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Thermal Addition Reactions of Monocyclic Phenols with Ethylene

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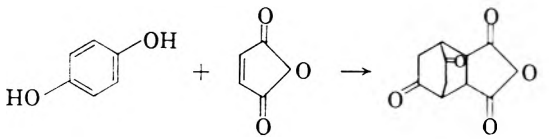
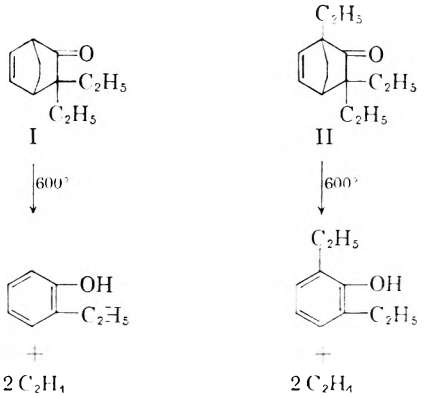
Ethyl-substituted bicyclooctenones have been obtained by the thermal addition of ethylene to monohydric phenols at high pressure. This ketone synthesis apparently involves *ortho* alkylation followed by the 1,4-addition of ethylene. Dihydric phenols react similarly to give cyclohexendiones and bicyclic ketones.

The first instance of a Diels-Alder reaction involving a monocyclic aromatic compound is that of hydroquinone with maleic anhydride to form 5,7 - dioxobicyclo[2.2.2]octane - 2,3 - dicarboxylic anhydride.[1] An analogous reaction has also been



reported for 2,5-dimethylhydroquinone.[2] We wish to report here the nature of the products formed in reactions of monohydric and dihydric phenols with ethylene at high temperature and pressure.

Reactions with monohydric phenols. Phenol and ethylene at 275° and 3000 atm. have given in 57% conversion a mixture of bicyclo[2.2.2]octenones I (10%) and II (90%) derived by the combination of phenol with 3 and 4 moles of ethylene, respectively. The major phenolic product was 2,6-diethylphenol. The structures 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I) and 1,3,3-triethylbicyclo[2.2.2]oct-5-en-2-one (II) are in agreement with the elemental composition of the products and with their infrared, ultraviolet, and nuclear magnetic resonance spectra. These structures were established further by transformations of the ketones. Thus, I and II absorbed one mole equivalent of hydrogen to yield the corresponding bicyclooctanones, and the pyrolysis of I and II to obtain ethylene along with *o*-ethylphenol and 2,6-diethylphenol, respectively, has defined the nature of the bridge and the position of the alkyl groups. Furthermore, I and II were synthesized directly from ethylene and *o*-ethylphenol.



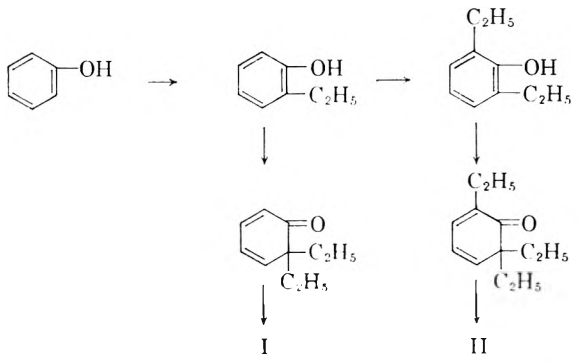
Other monohydric phenols reacted similarly. 2,6-Dimethylphenol and ethylene gave a single ketone believed to be 1,3-dimethyl-3-ethylbicyclo[2.2.2]-oct-5-en-2-one (III) (Fig. 1) as judged by its elemental composition, spectral properties, and pyrolysis to regenerate 2,6-dimethylphenol. *o*-Cresol formed two products, the composition and spectra of which conformed to the structures 3-ethyl - 3 - methylbicyclo[2.2.2]oct - 5 - en - 2 - one (IV) and either 1,3-diethyl-3-methylbicyclo[2.2.2]-oct-5-en-2-one (V) or the isomeric 3,3-diethyl-1-methylbicyclo[2.2.2]oct-5-en-2-one (VI).

In the conversion of monohydric phenols to bicyclooctenones by reaction with ethylene, it

(1) R. C. Cookson and N. S. Wariyar, *Chem. & Ind.*, 915 (1955); *J. Chem. Soc.*, 327 (1957).

(2) K. Takeda and K. Kitahonoti, *Ann.*, **606**, 153 (1957).

appears likely that *ortho* alkylation proceeded until one *ortho*-position had been alkylated twice, and the resulting cyclohexadienones then underwent Diels-Alder addition. Thus, the following scheme is proposed.



This scheme is in accord with the following considerations: (a) *o*-alkylphenols have been reported as the major product of the uncatalyzed reaction of phenol with olefins at 325° and 100–250 atm.[3] using an olefin/phenol mole ratio of approximately 2; (b) the bicyclooctenone II did not revert to a phenol when heated at its boiling point (270°). Thus, the formation of alkylphenols by decomposition of bicyclooctenones at the synthesis temperature (275°) is very unlikely; (c) the preponderance of ketone II over ketone I is in accord with the isolation of 2,6-diethylphenol as the major phenolic component.

Propylene with phenol at 275° and 3000 atm. afforded 2,6-diisopropylphenol as the major product (65% conversion to crude) with little other phenolic material. The infrared spectrum of the relatively small neutral fraction showed the absence of ketone. Similar results were obtained with isobutylene which afforded 2-*t*-butylphenol (29% conversion to crude) and 2,6-di-*t*-butylphenol (28% conversion to crude) and no ketone. The failure of propylene and isobutylene to give ketone products analogous to those obtained from ethylene is undoubtedly due to steric factors.

The aluminum phenoxide-catalyzed *ortho* and *diortho* alkylation of phenols has recently been reported.[4] Our results show that 2,6-dialkylphenols rather than the 2,4-isomers are preferentially formed even in the absence of a catalyst. In contrast to the catalyzed reaction, in which ethylene was found to be much less reactive than either propylene or isobutylene, the reactivity of these olefins under our conditions is of the same order of magnitude (with ethylene being unique in its ability to react further to form bicyclic ketones). In the uncatalyzed thermal alkylation of phenols reported earlier,[3] in which *o*-alkylphenols were the major product (olefin was not repressured into the system as the reaction proceeded), it was also found that the reactivity of ethylene was comparable to that of other olefins. However, in contrast to our results, the diethylphenol obtained from phenol and ethylene was reported to probably be the 2,4-isomer. The formation of bicyclooctenones from phenols and ethylene appears to be clearly the effect of high pressure since the temperatures used in our work and in the aluminum phenoxide-catalyzed reactions are comparable.

Reactions with dihydric phenols. Resorcinol gave in 55% yield a product $C_{16}H_{26}O_2$ which appeared to consist of three isomeric ketones. The major component (60% of the total) was a conjugated ketone for which the structure 1,1,3,3,5-pentaethyl-4-cyclohexen-2,6-dione (VII) (Fig. 1) is proposed. A second fraction, representing 30% of the ketone product, appeared on the basis of its analysis and infrared spectrum to be a mixture of an isomeric ($C_{16}H_{26}O_2$) diketone and hydroxy ketone for which the structures 1,3,3,5-tetraethylbicyclo[2.2.2]-octane-2,6-dione (VIII) and 1-hydroxy-2,2,4,6-tetraethylbicyclo[2.2.2]oct-5-en-3-one (IX) are proposed, respectively. The assignment of these structures is based on physical data and the assumption that alkylation occurs *ortho* to the hydroxyl groups as observed with monohydric phenols.

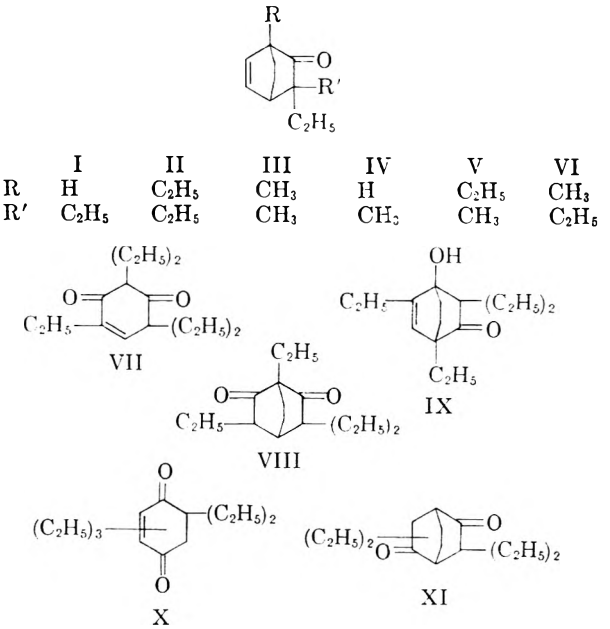


Fig. 1. Products from the reaction of monocyclic phenols with ethylene

The major products (in 55% yield) from hydroquinone and ethylene were largely isomeric $C_{16}H_{26}O_2$ ketones which were difficult to separate by distillation. The lower boiling C_{16} fractions were mostly conjugated ketones for which the partial structure pentaethyl-2-cyclohexen-1,4-dione (X) is proposed. The remaining C_{16} fractions were chiefly isomeric

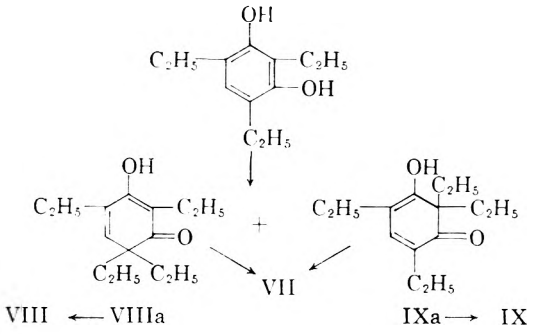
(3) E. A. Goldsmith, M. J. Schlatter, and W. G. Toland, *J. Org. Chem.*, **23**, 1871 (1958).

(4) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957). R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957).

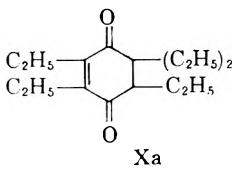
unconjugated ketones, which absorbed strongly in the infrared at 11.95 μ and for which the tetraethylbicyclo[2.2.2]octane-2,5-dione structure (XI) is proposed. A small proportion of $C_{18}H_{30}O_2$ ketone was also obtained. Although the C_{18} ketone was unconjugated, it did not appear to be bicyclic as judged from its infrared and ultraviolet spectra which were quite different from those of XI.

Catechol and ethylene formed ketone products (in 35% yield) which on distillation gave a constant boiling fraction (*ca.* 50% of total product) of the composition $C_{14}H_{22}O_2$. The infrared spectrum of this material showed absorption due to hydroxyl and to unconjugated and also conjugated carbonyl groups, indicating a mixture of at least two compounds. The presence in the product of a triethyl hydroxybicyclooctenone ($C_{14}H_{22}O_2$) would be consistent with the behavior of the simple phenols and with the spectroscopic data.

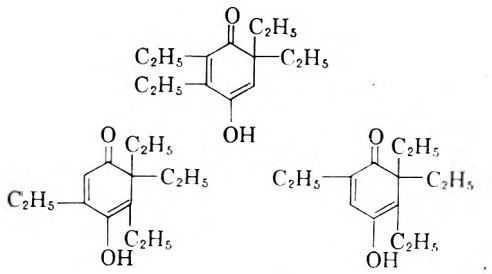
The reactions of dihydric phenols with ethylene can be rationalized in a manner very similar to that for the monohydric phenols. Thus, if one postulates in the case of resorcinol the preferential alkylation of all *ortho-* positions followed by the double alkylation of one *ortho-* position, the following scheme results, and the difference in the mode of reaction of resorcinol and of phenol involves only the ability of the proposed enol intermediates VIIIa and IXa either to undergo further *ortho* alkylation or to add ethylene.



Similarly, hydroquinone and ethylene might be expected to yield principally the pentaethylcyclohexendione Xa, with tetraethylhydroquinone as the intermediate. However, the presence of a substantial amount of isomeric C_{16} unconjugated ketones (bicyclooctanediones) in addition to pentaethylcyclohexendione suggests that such C_{14} intermediates as the following either undergo further *ortho* alkylation to give pentaethylcyclohexendiones (X) or add ethylene to give tetraethylbicyclooctanediones (XI).



Xa



EXPERIMENTAL

The preparation of bicyclooctenones[5] was carried out by heating the phenol with ethylene at high pressures in an oxygen-free system. The phenol was introduced into a 200 ml. pressure vessel which was equipped with a rocker mechanism and which was evacuated and purged with oxygen-free nitrogen. The vessel and its contents were shaken and heated while the ethylene was injected intermittently as required to maintain the pressure level for the duration of the reaction time (13–16 hr.). The reaction products were triturated with pentane, and the pentane solution was filtered and then extracted with four 200-ml. portions of aqueous methanolic potassium hydroxide.[6] After the pentane solution had been washed once with water, it was dried over anhydrous calcium sulfate and filtered. The residue obtained on removal of the pentane was then distilled under reduced pressure to obtain the ketonic products for fractionation. As an alternative, the crude product may first be distilled and then extracted with alkali.

The aqueous methanolic potassium hydroxide extracts were diluted with water, cooled, and strongly acidified. The phenolic products liberated were extracted with pentane, and the pentane solution was dried over anhydrous calcium sulfate, filtered and distilled to obtain the phenols.

Characterization of the products from phenol and ethylene. The crude product (251 g.) obtained by reaction of ethylene at 275° and 2600–3000 atm. with 120 g. of phenol (three runs of 40 g. each) afforded, after the removal of phenolic material, 124 g. (48% conversion[7]) of ketone product, b.p. 65–78° (0.3 mm.); n_D^{25} 1.4885. Fractionation of this product in a Podbielniak column gave 10 ml. of 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I); b.p. 130.5° (20 mm.); n_D^{25} 1.4935; d_{25} 0.9968; and 85 ml. of 1,3,3-triethylbicyclo[2.2.2]oct-5-en-2-one (II); b.p. 270° (760 mm.), 144.5° (20 mm.); n_D^{25} 1.4878–1.4882; d_{25} 0.9825. An additional 14 ml. of ketone II was obtained as a distillation residue; n_D^{25} 1.4883. These ketones have a camphoraceous odor.

Anal. Calcd. for $C_{12}H_{18}O$ (I): C, 80.85; H, 10.18. Found: C, 80.65; H, 10.18.

Anal. Calcd. for $C_{14}H_{22}O$ (II): C, 81.50; H, 10.75. Found: C, 81.63; H, 10.80.

Treatment of the crude ketone product with 2,4-dinitrophenylhydrazine in 95% alcohol containing a little sulfuric acid gave a crystalline derivative; m.p. 148–162°. After two recrystallizations from ethanol, the melting point was 165.5–168°. (The derivative obtained from a different sample gave the m.p. 170–170.5° after several recrystallizations.) This was the 2,4-dinitrophenylhydrazone of 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I).

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 59.90; H, 6.12; N, 15.86 (m.p. 165.5–168°).

The infrared, ultraviolet,[8] and nmr spectra of the pure

(5) Thomas J. Kealy, U. S. Patent 2,883,425, April 21, 1959.

(6) The alkali (Claisen's) was prepared as described by D. S. Tarbell, J. W. Wilson, and P. E. Fonta, *Org. Syntheses*, **Coll. Vol. III**, 269 (1955).

(7) Conversions to ketone were as high as 57%.

(8) The ultraviolet spectra of all the ketone products were measured in absolute ethyl alcohol, and the ultraviolet spectra of the phenols were measured in cyclohexane.

ketones were in accord with structure I and II; =CH 3.3 μ, unconjugated >C=O 5.8 μ (ketone I), 5.85 μ (ketone II), strained C=C 6.2 μ; λ_{max} 300 mμ, ϵ 98.1 (ketone I), λ_{max} 302 mμ, ϵ 103 (ketone II). The nmr spectrum of ketone I (measured at 56.4 Mc, relative to tetramethylsilane) showed doublets of equal area centered at −166 and −151 cps. assigned to the bridgehead hydrogens. Two sets of three peaks each were centered at −363 and −339 cps. These were assigned to the two non-equivalent olefinic hydrogens which interact with each other and with the bridgehead hydrogens. The area under the peaks of the bridgehead hydrogens equaled the area under the olefinic hydrogen peaks. Ketone II showed one doublet centered at −148 cps. assigned to the bridgehead hydrogen, the area of which was approximately one-half that of the olefinic hydrogen peaks.

A 2,4-dinitrophenylhydrazone was not formed by the triethyl ketone II, which suggested that this ketone was more hindered than the diethyl ketone I.

Ketones I and II did not react with ethyl nitrite in the presence of sodium ethoxide, indicating the absence of active hydrogen and suggesting the presence of a *gem*-diethyl group *alpha* to the carbonyl group.

Hydrogenation confirmed the presence of only one double bond in each ketone.

Hydrogenation of ketone I. A solution of 2 g. of crude 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I) (n_D^{25} 1.4900) in 75 ml. of absolute ethanol was hydrogenated at room temperature under 40 lb./sq. in. of hydrogen using a platinum oxide catalyst. The pressure quickly decreased to the calculated amount for the absorption of 1 mole equivalent of hydrogen. No further uptake of hydrogen was observed during 60 hr. shaking at approximately 60°. The alcohol was removed, and a 0.5-g. portion of the product was treated with 2,4-dinitrophenylhydrazine for 20 hr. The solution was filtered to obtain 0.24 g. of the dinitrophenylhydrazone of 3,3-diethylbicyclo[2.2.2]octan-2-one, m.p. 178–183°. After three recrystallizations from absolute ethanol, the product melted at 190–190.5.

Anal. Calcd. for $C_{18}H_{24}O_4N_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.55; H, 6.85; N, 14.98.

Hydrogenation of ketone II. 1,3,3-Triethylbicyclo[2.2.2]-oct-5-en-2-one (II) (20 g., n_D^{25} 1.4880) in 80 ml. of absolute ethanol was hydrogenated at room temperature using a 10% palladium-on-carbon catalyst and 40 lb./sq. in. hydrogen pressure. One mole equivalent of hydrogen was absorbed in about 15 min. After 3 hr., with no further absorption of hydrogen, the alcohol was removed under reduced pressure, and the 1,3,3-triethylbicyclo[2.2.2]octan-2-one was distilled; b.p. 73° (0.2 mm.); n_D^{25} 1.4839.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.18; H, 11.81.

Identification of phenolic products. The phenolic fraction (65 ml.) collected from several experiments afforded on distillation (a) 10 ml., b.p. 83–100° (15 mm.), n_D^{25} 1.5335–1.5249 probably containing phenol, *o*-ethylphenol and 2,6-diethylphenol,[9] (b) 37 ml. of 2,6-diethylphenol; b.p. 102° (15 mm.), m.p. 34.5–37°, λ_{max} 278, 271 mμ, ϵ 1770, 1725; and (c) 16 ml. of unidentified phenols; b.p. 111–127° (15 mm.), n_D^{25} 1.5149–1.5031. Fraction b was identified by analysis and by comparison of its infrared and ultraviolet spectra with those of authentic 2,6-diethylphenol,[10] m.p. 36–36.5°, λ_{max} 278, 271 mμ, ϵ 1815, 1755.

Pyrolysis of 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I). Ketone I (5 ml., n_D^{25} 1.4935) was passed through a tube 1 foot in length at 600° under 1 mm. pressure over a period of 20 min. The volatile pyrolysis product was shown by infrared inspection to consist chiefly of ethylene. The nonvolatile product was dissolved in pentane, and the solution was extracted with aqueous methanolic potassium hydroxide. After acidification of the alkaline extracts, the phenol was dissolved in pentane, and the solution was dried. Removal of the pentane gave *o*-ethylphenol which afforded a phenylurethan, m.p. 131.5–133°, having an infrared spectrum identical with that of the phenylurethan obtained from authentic *o*-ethylphenol, m.p. 136–138°.

Treatment of *o*-ethylphenol obtained as a pyrolysate with chloroacetic acid afforded *o*-ethylphenoxy acetic acid, m.p. 134–135°; the infrared spectrum of this derivative was identical with that of the derivative prepared from authentic o-ethylphenol, m.p. 136.5–138°.

Pyrolysis of 1,3,3-triethylbicyclo[2.2.2]oct-5-en-2-one (II). Ketone II (20 ml., n_D^{25} 1.4880) was passed through a tube 1 foot in length at 600° under 1 mm. pressure during a period of about 1 hr. Infrared analysis established that the volatile pyrolysis product was chiefly ethylene. The nonvolatile product was dissolved in pentane, and the solution was extracted with aqueous methanolic potassium hydroxide. The pentane on distillation left about 1 ml. of residue that was discarded. Acidification of the alkali solution gave a yellow oil which was extracted with pentane. The pentane solution was washed with water, dried, and evaporated on a steam bath to obtain an orange oil which on distillation gave 6.5 g. of colorless oil, b.p. 83–90° (5 mm.), n_D^{25} 1.5241–1.5231. A portion of the distilled product was dissolved in pentane. Cooling the solution in a solid carbon dioxide-acetone bath afforded 2,6-diethylphenol as white needles which were recrystallized several times by the same procedure; m.p. 36–36.5° alone or in admixture with authentic 2,6-diethylphenol. The identity of the product was further confirmed by a comparison of its infrared and ultraviolet spectra (λ_{max} 278, 271 mμ, ϵ 1770, 1710) with those of the authentic sample.

Synthesis of ketones I and II by reaction of o-ethylphenol with ethylene. *o*-Ethylphenol (23 g.) was heated with ethylene at 275° and 2700–3000 atm. for 13.5 hr. Separation of the phenolic material and distillation gave 12.5 g. (33% conversion) of ketone; b.p. 122–141° (17 mm.); n_D^{25} 1.4882. The infrared spectrum of this material showed that it consisted mostly of 1,3,3-triethylbicyclo[2.2.2]oct-5-en-2-one (II). Weak bands at 8.25 μ and at 11.7 μ indicated the presence of a small amount of 3,3-diethylbicyclo[2.2.2]oct-5-en-2-one (I) which was substantiated by the isolation of its 2,4-dinitrophenylhydrazone. One gram of the ketone product on treatment with 0.4 g. of reagent gave 0.05 g. of crude 2,4-dinitrophenylhydrazone; m.p. 159–161°. One recrystallization from ethanol raised the melting point to 166–168°.

Reaction of ethylene with 2,6-dimethylphenol. 2,6-Dimethylphenol (40 g.) was treated with ethylene at 275° and 2750–3000 atm. for 14 hr. After removal of grease and phenolic material, the product was distilled to obtain 30 g. (50% conversion) of water-white camphoraceous product, b.p. 42–43° (0.2 mm.); n_D^{25} 1.4829; d_{25} 0.9729. The infrared and ultraviolet spectra of the product (=CH 3.3 μ, >C=O 5.8 μ, C=C 6.2 μ, λ_{max} 298 mμ, ϵ 101) were consistent with the structure of 1,3-dimethyl-3-ethylbicyclo[2.2.2]oct-5-en-2-one (III).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.79; H, 10.36.

Pyrolysis of III at 600° (1 mm.) afforded 2,6-dimethylphenol, m.p. 41–43° after recrystallization, identified by analysis and by a comparison of its infrared and ultraviolet spectra (λ_{max} 278, 272 mμ, ϵ 1647, 1562) with those of an authentic sample of 2,6-dimethylphenol; m.p. 44–45°, λ_{max} 278, 272 mμ, ϵ 1610, 1549.

Reaction of ethylene with o-cresol. *o*-Cresol (80 g., two runs) and ethylene at 275° and 2600–3000 atm. for 13.5 hr. gave 57 g. (*ca.* 40% conversion) of ketone product boiling at 57–71° (0.4 mm.). Distillation gave 45 ml. boiling at 75° (1 mm.); n_D^{25} 1.4850; d_{25} 0.9723.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.37; H, 10.69.

(9) These phenols were identified as products obtained by the reaction of phenol with ethylene at 250° but their relative amounts were not determined.

(10) K. von Auwers and W. Mauss, *Ann.*, **460**, 240 (1928).

The infrared and ultraviolet spectra (=CH 3.25 μ, >C=O 5.8 μ, strained C=C 6.15 μ; λ_{max} 299 mμ, ϵ 99) were consistent with the alternative structures 1,3-diethyl-3-methylbicyclo[2.2.2]oct-5-en-2-one (V) or the position isomer 3,3-diethyl-1-methylbicyclo[2.2.2]oct-5-en-2-one (VI). The ketone V (or VI) failed to give a derivative with 2,4-dinitrophenylhydrazine.

The remainder of the distillate (13 ml.; b.p. 52–74° (1 mm.)) afforded with 2,4-dinitrophenylhydrazine the dinitrophenylhydrazone of 3-methyl-3-ethylbicyclo[2.2.2]oct-5-en-2-one (IV); m.p. 146–148°. After several recrystallizations from ethanol it melted at 154.5–155.5°.

Anal. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 58.98; H, 5.98; N, 16.44.

Characterization of the products from resorcinol. The product from the reaction of resorcinol (100 g., two runs) with ethylene at 250° and 2700–3000 atm. for 14.5 hr. was freed of grease and phenolic material. Distillation gave 138 g. (55% conversion) of light yellow liquid of the composition $C_{16}H_{26}O_2$; b.p. 76–100° (0.1 mm.); n_D^{25} 1.4871. This was combined with a previous product (b.p. 71–102° (0.1 mm.); n_D^{25} 1.4871–1.4933) to make a total of 180 g. which was fractionally distilled. After a forerun of 10 ml. (b.p. 74–97° (0.5 mm.)), 80 ml. of 1,1,3,3,5-pentaethyl-4-cyclohexen-2,6-dione (VII) was obtained; b.p. 97–98° (0.5 mm.); n_D^{25} 1.4849.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.80; H, 10.34.

The presence of conjugated and unconjugated carbonyl groups in the cyclohexenedione (VII) was apparent from the infrared (5.85 μ, 6.0 μ) and ultraviolet spectra λ_{max} (shoulder) 315 mμ, ϵ 75, λ_{max} 231 mμ, ϵ 8400. The nmr spectrum of the compound indicated the presence of olefinic hydrogen. Since the compound contained a conjugated carbonyl group, the possibility of a bicyclic system was eliminated. In view of the structure of the products from phenol, it seemed unlikely that alkylation *beta* to the hydroxyl groups would occur to any appreciable extent. Thus, the five ethyl groups were assigned the remaining three possible positions to give proposed structure VII.

Distillation did not effect the separation of the remaining two components (VIII and IX); however, the last material collected (40 ml., b.p. 106–111° (0.5 mm.); n_D^{25} 1.4928–1.4935) was free of the cyclohexendione, as shown by the absence of a 6.0 μ carbonyl band in the infrared spectrum of this fraction and also by the ultraviolet spectrum, λ_{max} 300 mμ, ϵ 120.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.70; H, 10.49.

In another experiment, a total boiling range of 85–125° (0.5 mm.) (n_D^{25} 1.4831–1.4952) was observed during fractionation of a similar resorcinol/ethylene product. A constant boiling fraction (b.p. 120° (0.5 mm.); n_D^{25} 1.4931) containing ketones VIII and IX was obtained.

Evidence for the presence of compounds VIII and IX ($C_{16}H_{26}O_2$) in the higher boiling fraction resides in the appearance of a hydroxyl band (2.8 μ) of moderate intensity and two unconjugated carbonyl bands (5.8 μ, 5.85 μ) in the infrared spectrum. That the hydroxyl was of the alcohol type (non-phenolic) was evidenced by the lack of absorption due to hydrogen bonding in this region of the spectrum and the absence of aromatic absorption in the 6–7 μ region. Accordingly, the diketone and isomeric hydroxy ketone structures VIII and IX are proposed.

Characterization of the products from hydroquinone. The product from the reaction of 275 g. of hydroquinone (five runs) and ethylene at 250° and 3000 atm. was distilled under reduced pressure. The distillate was dissolved in pentane, and the solution was extracted with five 200-ml. portions of Claisen's alkali. After the solution was dried over anhydrous calcium sulfate, the solvent was removed. Distillation of the residue afforded 352 g. (55%) of yellow oil, n_D^{25} 1.4885. This product was redistilled in a 13 mm.-diameter Podbielniak column.

TABLE I

DISTILLATION OF HYDROQUINONE-ETHYLENE PRODUCT

Fraction	Vol., ml.	B.P., °/20 mm.	n_D^{25}
1	10	93–149	1.4488
2–5	30	150–161	1.4871–1.4885
6–7	20	161–162	1.4899
8	5	162–163	1.4880
9–10	20	163	1.4909
11–13	41	163–164	1.4900–1.4886
14	6	164–172	1.4843
15	60	172–175	1.4894
16	15	175–185	1.4935
17–18	30	185–188	1.4922
19	15	188–189	1.4930
20–21	21	189–195	1.4937
22	4	195	1.4923
23–25	25	195–196	1.4955

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: Fraction 6–7: C, 76.59; H, 10.22. Fraction 9–10: C, 76.98; H, 10.12. Fraction 17–18: C, 76.92; H, 10.34. Fraction 20–21: C, 76.90; H, 10.32.

Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: Fraction 23–25: C, 77.47; H, 10.77.

Fractions 6–7 and 9–10 showed intense conjugated carbonyl absorption in the infrared at 5.95 μ with weaker unconjugated carbonyl absorption at 5.8 μ, and they absorbed in the ultraviolet at λ_{max} 253, 365 mμ, ϵ 10,000, 65. The infrared spectra of subsequent fractions indicated the presence of the same major component through fraction 11–13. Thus, these fractions appeared to contain conjugated ketone of the type X with lesser amounts of bicyclic ketone XI. The infrared spectrum of fraction 15 showed a preponderance of ketone with absorption at 5.8 μ and the presence of a much lesser amount of conjugated ketone (5.95 μ). Fraction 17–18 contained an even greater preponderance of unconjugated ketone which appeared to be an isomer of the main component of fraction 15 since other infrared absorption bands did not correspond (λ_{max} (inflection) 305 mμ, ϵ 8.75; λ_{max} (shoulder) 300 mμ, ϵ 75; λ_{max} 253, ϵ 1275). Fraction 20 also was comprised largely of unconjugated ketone. Intense absorption was noted at 11.95 μ in the infrared spectra of fractions 15–20 which was entirely lacking in fraction 23–25 even though this fraction showed intense carbonyl absorption at 5.8 μ with only a weak shoulder at 5.95 μ (λ_{max} 293, 251 mμ, ϵ 222, 1029).

Fraction 17–18 solidified to white crystals, m.p. 49–55°. Several recrystallizations from pentane at low temperature raised the melting point to 59–60° (>C=O 5.8 μ; λ_{max} 298 mμ, ϵ 50).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.77; H, 10.52.

On this basis fractions 15–20 appear to be predominantly a mixture of isomeric bicyclic $C_{16}H_{26}O_2$ ketones (XI). The simplicity of the infrared spectrum of fraction 23–25 and the absence of the 11.95 μ band together with the ultraviolet spectrum indicate that this material is not bicyclic and contains a minor amount of conjugated ketone.

Reaction of catechol with ethylene. The reaction of 120 g. of catechol (three runs) with ethylene at 250° and 3000 atm. for 13–16 hr. afforded 253 g. of yellow viscous oil. The product was triturated with pentane and filtered. After the removal of phenolic material by extraction of the pentane solution with Claisen's alkali, the dried solution was distilled to obtain 59 g. (37% conversion) of yellow oil, b.p. 84–110° (0.6 mm.), n_D^{25} 1.4976. This material was combined with a previous product obtained in the same manner (n_D^{25} 1.4972) to make a total of 104 g. of material for fractionation. Distillation in a 30" column afforded a large, constant boiling fraction (52 ml., b.p. 86° (0.4 mm.), n_D^{25} 1.4980)

apparently derived from the combination of catechol with four moles of ethylene.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.71; H, 9.95.

The infrared and ultraviolet spectra of this fraction, however, showed that it was a mixture; —OH 2.9 μ (nonphenolic), >C=O 5.8, 6.0 μ, C=C 6.1 μ (shoulder), λ_{max} 303, 239 mμ, ϵ 80, 5300.

Characterization of products from phenol and propylene. The product from the reaction of 80 g. of phenol (two runs) with propylene at 275° and 3000 atm. was dissolved in pentane and extracted with several portions of Claisen's alkali. The product (22 g.) obtained by distillation of the dried pentane solution appeared to consist of aromatic ether and nonaromatic hydrocarbon on the basis of its infrared spectrum. Distillation of the phenols obtained by acidification and extraction of the Claisen's alkali solution afforded (a) 11 g., b.p. 110–120° (17 mm.), n_D^{25} 1.5253; (b) 103 g. (65% conversion) of crude 2,6-diisopropylphenol, b.p. 120–126° (17 mm.) together with fractions b.p. 55–67° (0.2 mm.), n_D^{25} 1.5124–1.5063; and (c) a residue of 5 g. The analysis and the ultraviolet spectrum of a constant boiling fraction obtained in the above distillation were consistent with the values for 2,6-diisopropylphenol, 38 g., b.p. 126° (17 mm.), n_D^{25} 1.5111, λ_{max} 278, 271 mμ, ϵ 1890, 1870. Since the last cut obtained in the distillation had a very similar ultraviolet spectrum (λ_{max} 278, 271 mμ, ϵ 1744, 1707), it appears that the crude 2,6-diisopropylphenol was contaminated with a small amount of hydrocarbon.

Characterization of the products from phenol and isobutylene. The product from the reaction of phenol (120 g., three runs) and isobutylene at 275° and 3000 atm. for 14 hr., was dissolved in pentane and extracted with three 200-ml. portions of Claisen's alkali. After the pentane was removed from the dried solution, the residue (105 g.) was distilled to obtain 68 g. (28% conversion) of 2,6-di-*t*-butylphenol, b.p. 136–143° (21 mm.), n_D^{25} 1.4989–1.5001. The refractive index and infrared spectra of the lower (n_D^{25} 1.4719) and higher boiling fractions (n_D^{25} 1.48–1.46) indicated that these materials were largely hydrocarbons. The crude 2,6-di-*t*-butylphenol was redistilled in a 36″ column to obtain 51 ml. of pure 2,6-di-*t*-butylphenol, b.p. 133° (20 mm.), m.p. 34–37°, λ_{max} 278, 271 mμ, ϵ 1750, 1730.

Acidification and extraction of the Claisen's alkali solution afforded 55 g. (29% conversion) of 2-*t*-butylphenol, b.p. 96–107° (16 mm.), n_D^{25} 1.5211. Redistillation gave 37 g. of pure 2-*t*-butylphenol, b.p. 101–103.5° (13 mm.), n_D^{25} 1.5212, λ_{max} 278, 271 mμ, ϵ 2070, 2025, having the correct analysis.

WILMINGTON, DEL.

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

Some Applications of Isopropylidene Malonate and Its Derivatives to the Synthesis of Cyclic Compounds

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Diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate and its 3-methyl and 3-phenyl derivatives have been prepared by treating the sodium salts of diisopropylidene methylenedimalonate, diisopropylidene ethylidenedimalonate, and diisopropylidene benzylidenedimalonate, respectively, with iodine or bromine. By alkylation of the sodium salt of isopropylidene malonate in dimethylformamide at room temperature, isopropylidene 1,1-cyclohexanedicarboxylate and isopropylidene 1,1-cyclopentanedicarboxylate have been prepared.

Methylations of isopropylidene malonate (I) have yielded principally the dimethylmalonate derivative. The reactions have been carried out by treating the isolated silver salt, in ether suspension, with methyl iodide,[3] or, better, by treating isopropylidene malonate with silver oxide and methyl iodide in acetonitrile.[4] It has now been found that benzylation of this malonic acid derivative likewise has a strong tendency to proceed to the dialkylation product. Alkylation with benzyl chloride in methanol, ethanol or dimethylformamide (DMF) gave only isopropylidene dibenzylmalonate, as did also a reaction of the sodium salt of isopropylidene malonate with benzyldimethylphenylammonium chloride. Isopropylidene benzylmalonate was obtained by hydrogenation of the benzalmalonate.[5]

These observations suggested that the alkylation of isopropylidene malonate with methylene iodide be examined. The various products that might be expected from reaction between these reagents are diisopropylidene methylenedimalonate (IIa),[5] the cyclobutane derivative (IV) and isopropylidene methylenemalonate (V). When the reaction was carried out in acetonitrile with approximately equimolar quantities of the dihalide, the malonate and silver oxide, a product was obtained which proved to be none of these. The infrared spectrum of the substance was identical with that of a compound obtained earlier from diisopropylidene ethylenetetracarboxylate (VI)[6] and diazomethane, and the identity of the two samples was confirmed by a mixed melting point determination. Mild hydrolysis converted the compound to 1,1,2,2-cyclopropanetetracarboxylic acid. Thus the reaction product must be diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa).

The cyclopropane derivative (IIIa) was probably

(1) Sun Oil Co. Fellow, 1959–1960.

(2) Phillips Petroleum Co. Fellow, 1956–1957.

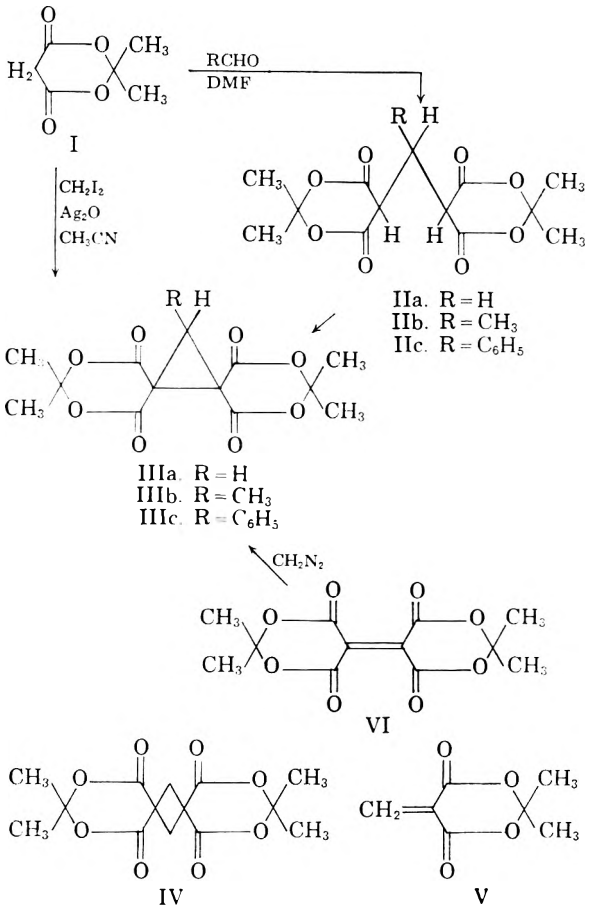
(3) E. Ott, *Ann.*, **401**, 159 (1913).

(4) D. Davidson and S. A. Bernhard, *J. Am. Chem. Soc.*, **70**, 3426 (1948).

(5) J. A. Hedge, C. W. Kruse, and H. R. Snyder, *J. Org. Chem.*, in press.

(6) H. R. Snyder and C. W. Kruse, *J. Am. Chem. Soc.*, **80**, 1942 (1958).

formed from diisopropylidene methylenedimalonate (IIa) through iodination and cyclization by silver oxide, the iodination occurring as the result of the formation of free iodine or its equivalent in the reaction mixture. Cyclization of IIa by treatment with dilute aqueous sodium hydroxide or sodium bicarbonate and solid iodine gave IIIa in yields of about 80%. Stirring a solution of IIa in acetonitrile with silver oxide did not bring about any reaction.

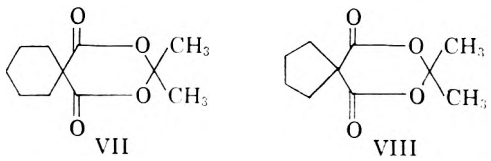


Cyclopropane derivatives were also prepared from diisopropylidene ethylidenedimalonate (IIb),[5] the condensation product of acetaldehyde and isopropylidene malonate, and from diisopropylidene benzylidenedimalonate (IIc),[5] the benzaldehyde condensation product. These cyclizations were most successful (yields 69% and 48%, respectively) when the sodium salts were prepared in methanol and treated with bromine. No exhaustive study of the effects of various reaction conditions on the yields was made, but cyclization of the former in dimethylformamide-aqueous sodium bicarbonate with solid iodine and of the latter in dimethylformamide by treatment with sodium methoxide and then with iodine occurred in yields of only about 15%. Dibenzylidene methylenedimalonate[5] was cyclized with dilute sodium hydroxide and solid iodine to form the dibenzylidene analog of IIa in 69% yield.

An attempt to prepare IV by the alkylation of IIa with methylene iodide in dimethylformamide containing sodium methoxide resulted only in the formation of a gel from which the sodium salt of IIa eventually precipitated.

Attempts to alkylate isopropylidene malonate in ethanolic sodium ethoxide solution resulted in the precipitation of the monosodium salt of isopropylidene malonate, which had been previously characterized by Meldrum.[7] Because of the insolubility of the sodium salt in ethanol, further alkylations were carried out in dimethylformamide, in which the sodium salt was more soluble.

When equimolar amounts of 1,5-dibromopentane and the monosodium salt of isopropylidene malonate (prepared from equimolar amounts of isopropylidene malonate and ethanolic sodium ethoxide) were allowed to react in dimethylformamide at room temperature, isopropylidene 1,1-cyclohexanedicarboxylate (VII) was obtained in 21% yield. The yield was doubled (41%) when a 2:1 ratio of monosodium salt to dihalide was employed. From this it was evident that a second mole of the monosodium salt or some other base was necessary if acceptable yields were to be obtained. However, when powdered sodium methoxide was added to supply the second mole of base, the expected product (VII) was obtained in a lower yield (11%) and, in addition, a small yield (6%) of 1,1-cyclohexanedicarboxylic acid was obtained. Evidently a portion of the methoxide had attacked the desired product (VII) to give 1,1-cyclohexanedicarboxylic acid, the methyl half-ester being a probable intermediate according to the work of Scheuer and Cohen.[8] Dimethylacetamide was found to be an equally suitable solvent for the preparation of VII.



The reaction of two moles of monosodium salt and one mole of 1,4-dibromobutane in dimethylformamide at room temperature afforded isopropylidene 1,1-cyclopentanedicarboxylate (VII) in 33% yield. 1,1-Cyclopentanedicarboxylic acid was formed in one experiment when dilute hydrochloric acid was added at the end of the reaction period and the mixture was allowed to stand at room temperature overnight. The benzylidene analog of VII, benzylidene 1,1-cyclopentanedicarboxylate, was prepared in low yield from equimolar amounts of benzylidene malonate, sodium methoxide and 1,4-dibromobutane. Attempts to prepare isopropylidene 1,1-cyclobutanedicarboxylate by similar methods were unsuccessful.

(7) A. N. Meldrum, *J. Chem. Soc.*, 598 (1908).

(8) P. J. Scheuer and S. G. Cohen, *J. Am. Chem. Soc.*, **80**, 4933 (1958).

EXPERIMENTAL[9,10,11]

Isopropylidene malonate was prepared according to the procedure of Davidson and Bernhard[4] and benzylidene malonate according to the procedure of Michael and Weiner.[12]

Isopropylidene dibenzylmalonate. A. *With methanol as solvent.* To 10 ml. of methanol in which 0.15 g. (6.5 mg.-atoms) of sodium had been dissolved were added 0.94 g. (6.5 mmoles) of isopropylidene malonate and 0.82 g. (6.5 mmoles) of benzyl chloride. Large crystals, which deposited during a 2-day period at room temperature, were collected and washed with methanol to yield 0.2 g. (19%) of isopropylidene dibenzylmalonate, m.p. 230–232°. An analytical sample, m.p. 231–232°, was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.06; H, 6.47.

B. *With ethanol as solvent.* A sodium ethoxide solution was prepared from 2.2 g. (0.096 g.-atom) of sodium and 100 ml. of absolute ethanol. Isopropylidene malonate, 6.9 g. (0.048 mole), was added to one-half of the sodium ethoxide solution and the mixture was heated to reflux. The remaining sodium ethoxide solution and 12.0 g. (0.096 mole) of benzyl chloride were added to the refluxing mixture over a 30-min. period. After the stirred reaction mixture was refluxed for 5 hr., the ethanol was evaporated *in vacuo* and the pasty residue was dissolved in water and extracted with 100 ml. of chloroform. The chloroform layer was concentrated *in vacuo* to a small volume and diluted with methanol to cause precipitation. Filtration afforded 2.5 g. (16%) of isopropylidene dibenzylmalonate, m.p. 227–230°.

C. *With dimethylformamide and sodium methoxide.* A mixture of 7.2 g. (0.05 mole) of isopropylidene malonate, 12.6 g. (0.1 mole) of benzyl chloride and 5.4 g. (0.1 mole) of sodium methoxide in 100 ml. of dimethylformamide was stirred at room temperature for 50 hr. The solid which had formed throughout the reaction period was collected and washed with water and a small amount of acetone to yield 4.7 g. of product. The filtrate from the reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was concentrated *in vacuo* and diluted with methanol to yield 0.9 g. of product. The total yield of isopropylidene dibenzylmalonate was 5.6 g. (35%).

D. *With dimethylformamide and the monosodium salt of isopropylidene malonate.* A solution of 0.83 g. (5 mmoles) of the monosodium salt of isopropylidene malonate (prepared as described in a later portion of this experimental section) and 0.63 g. (5 mmoles) of benzyl chloride in 60 ml. of dimethylformamide was left at room temperature for 6 days. A trace of insoluble material was removed by filtration, and 125 ml. of cold water was added to the filtrate to cause the precipitation of 0.45 g. of crude isopropylidene dibenzylmalonate, m.p. 190–230°. Recrystallization from acetone afforded 0.34 g. (42%) of nearly pure product, m.p. 232–233°.

E. *By alkylation with benzyldimethylphenylammonium chloride.* A solution of 1.0 g. (4 mmoles) of benzyldimethylphenylammonium chloride,[13] 0.58 g. (4 mmoles) of isopropylidene malonate and 0.34 g. (4 mmoles) of sodium bicarbonate in a minimum amount of water was concentrated *in vacuo* at 80°. The bath temperature was raised to 110–120° and a small amount of material, probably dimethylaniline, distilled at 75–80° (11 mm.). The residue was triturated first with methanol and then with water to yield 0.3 g. (46%) of reasonably pure product, m.p. 229–231°.

Isopropylidene benzylmalonate. The hydrogenation of 0.236 g. (1.01 mmoles) of isopropylidene benzalmalonate[5] in methanol over platinum at room temperature and atmospheric pressure afforded a nearly theoretical yield of isopropylidene benzylmalonate, m.p. 80–81°. The melting point was not changed by recrystallization from high-boiling petroleum ether.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.82; H, 6.15.

Diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa). A. *With silver oxide and acetonitrile.* To a magnetically stirred suspension of 6.5 g. (28 mmoles) of silver oxide and 6.7 g. (25 mmoles) of methylene iodide in 15 ml. of acetonitrile at 0° was added dropwise over a 10-min. period 3.6 g. (25 mmoles) of isopropylidene malonate in 12 ml. of acetonitrile. After the addition had been completed, stirring was continued at room temperature for 2 hr. At the end of this period the grey solids were removed by filtration and washed well with acetonitrile. The acetonitrile solution was concentrated *in vacuo* (bath temperature 45°) to a red oil. The addition of 30 ml. of cold water caused a mixture of oil and crystals to separate. The water-acetonitrile layer was decanted, and acetone was added to the oil and solid mixture. The solid remained undissolved. Upon filtration and washing with acetone, 0.35 g. of gray solid, m.p. 223–228° dec. with sublimation above 200°, was obtained. The combined acetone washes were concentrated to a red oil which yielded three successive crops (0.15 g.). These crops were obtained by adding acetone or ether to the concentrated red oil to cause precipitation, filtering, concentrating the filtrate and repeating the process. The total yield of diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa) was 0.50 g. (13%). The crude product was purified by dissolving in acetonitrile, filtering to remove any insoluble impurities and adding twice the volume of ether. Two such recrystallizations from acetonitrile-ether gave the analytical sample, m.p. 226–227° dec.

Anal. Calcd. for $C_{13}H_{14}O_8$: C, 52.35; H, 4.73. Found: C, 52.47; H, 4.80.

After a third recrystallization from acetonitrile alone, an even purer sample, m.p. 223.5–224° dec. in a capillary tube, was obtained. (*Anal.* Found: C, 52.35; H, 4.75.)

A mixed melting point of this pure material and the product (see part D) of the reaction of diazomethane with diisopropylidene ethylenetetracarboxylate (VI)[6] showed no depression (m.p. 225–227° dec.).

B. *With sodium hydroxide and iodine.* To a solution of 0.6 g. (2 mmoles) of diisopropylidene methylenedimalonate (IIa)[5] in 2 ml. (4 mmoles) of 2*N* sodium hydroxide solution and 23 ml. of water was added rapidly while stirring 1.04 g. (4 mmoles) of solid iodine. Stirring was continued at room temperature, and a white precipitate slowly formed over a 45-min. period. The precipitate was filtered, any remaining iodine crystals were mechanically separated and the filter cake was washed well with water to yield 0.47 g. (79%) of diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa), m.p. 226–227° dec.

C. *With sodium bicarbonate and iodine.* To a solution of 0.3 g. (1 mmole) of diisopropylidene methylenedimalonate (IIa)[5] in approximately 4 ml. of 5% sodium bicarbonate solution and 12 ml. of water at room temperature was added 0.25 g. (1 mmole) of solid iodine. A white precipitate formed slowly. Filtration and washing with cold water gave 0.23 g. (77%) of product (IIIa), m.p. 225–227° dec.

D. *With diazomethane.* A suspension of a few milligrams of diisopropylidene ethylenetetracarboxylate (VI)[6] in 10 ml. of ethereal diazomethane solution was allowed to stand at room temperature. After about 24 hr. the yellow color had vanished and compound IIIa, m.p. 226–227° dec., was col-

(9) All melting points were taken on a Kofler micro hot stage, unless otherwise specified.

(10) The infrared spectra were determined by P. E. McMahon and his associates. The spectra were obtained from a Perkin-Elmer Model 21 double beam recording spectrophotometer equipped with sodium chloride optics.

(11) The microanalyses were performed by J. Nemeth, Mrs. Ruby Ju, Miss Claire Higham, Mrs. A. S. Bay, and Miss Jane Liu.

(12) A. Michael and N. Weiner, *J. Am. Chem. Soc.*, **58**, 680 (1936).

(13) W. Michler and A. Gradmann, *Ber.*, **10**, 2078 (1877).

lected by filtration. Infrared spectra of this product and the product from part A were identical.

1,1,2,2-Cyclopropanetetracarboxylic acid. A. *By acid hydrolysis.* A mixture of 0.150 g. (0.5 mmole) of diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa) and 2.5 ml. of concentrated hydrochloric acid in 17.5 ml. of water was heated for 19 hr. on a steam bath. A small amount of undissolved material was removed by filtration. The filtrate was concentrated *in vacuo* to dryness to give the crude product, m.p. 175–185° dec. The crude product was stirred in 75 ml. of ether, filtered to remove any undissolved impurity, and the solution was concentrated to dryness to yield 0.069 g. (63%) of crude product, m.p. 180–187° dec.

B. *By basic hydrolysis.* To a hot solution of 0.3 g. of potassium hydroxide in 0.5 ml. of water was added in small portions with stirring 0.198 g. (0.67 mmole) of diisopropylidene 1,1,2,2-cyclopropanetetracarboxylate (IIIa). Stirring was continued until each portion had dissolved. The addition required about 30 min. The solution was allowed to cool and crystals formed. Water (5 ml.) was added to dissolve the crystals, and the solution was filtered to remove a small amount of remaining black solid. Acetic acid was added until the solution reached *p*H 6, and the solution was concentrated to dryness. Triturating the white solids in ether did not dissolve any material. This showed that the product was still present as the potassium salt. Anhydrous hydrobromic acid was bubbled into the ether suspension, and a fine white precipitate (potassium bromide) formed. The precipitate was collected and washed well with ether. Upon evaporation of the ether filtrate 0.101 g. (69%) of crude, pale yellow solid, m.p. 198–203° dec., was obtained. An acetone-carbon tetrachloride solution of the crude product was treated with Darco and allowed to evaporate. Evaporation yielded yellow needles, m.p. 210–214° dec., which were broken up, filtered and ether washed. A solution of this material in 4 ml. of concentrated hydrochloric acid was allowed to evaporate slowly to form large, colorless crystals, m.p. 217–218° dec. (lit., m.p. 218–220° dec.,[14] 210–212° dec.[15])

Anal. Calcd. for $C_7H_6O_8$: C, 38.54; H, 2.77. Found: C, 38.49; H, 3.02.

Diisopropylidene 3-methyl-1,1,2,2-cyclopropanetetracarboxylate (IIIb). A. *With sodium bicarbonate and iodine.* To a solution of 1.57 g. (5 mmoles) of diisopropylidene ethylidenedimalonate (IIb)[6] in 17 ml. of 5% sodium bicarbonate solution, 3 ml. of water and 10 ml. of dimethylformamide was added 1.27 g. (5 mmoles) of solid iodine. After 12 hr. at room temperature, a small amount of acetonitrile was added, and the mixture was heated on a steam bath for 15 min., cooled and filtered to yield 0.2 g. (13%) of white powdery product (IIIb), m.p. 216–217° dec. Recrystallization from acetonitrile, followed by recrystallization from acetone, gave the analytical sample, m.p. 208–210.5° dec. in a capillary tube.

Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.84; H, 5.16. Found: C, 53.58; H, 5.09.

B. *With sodium methoxide and bromine.* A sodium methoxide solution was prepared from 0.41 g. (17.8 mg.-atoms) of sodium and 25 ml. of commercial absolute methanol. To this sodium methoxide solution was added 2.79 g. (8.9 mmoles) of diisopropylidene ethylidenedimalonate (IIb).[6] A cloudy solution resulted. Bromine, 1.42 g. (8.9 mmoles), was added fairly rapidly to the cloudy solution. Heat was evolved and immediate precipitation resulted. The mixture was cooled for 5 min., filtered and washed with cold water to give 1.85 g. of powdery white product (IIIb), m.p. 208–209.5° dec. A second crop (0.05 g.) formed in the methanol-water filtrate. The total yield was 1.90 g. (69%).

Diisopropylidene 3-phenyl-1,1,2,2-cyclopropanetetracarboxylate (IIIc). A. *With sodium methoxide and bromine.* A sodium methoxide solution was prepared from 0.35 g. (15 mg.-atoms) of sodium and 25 ml. of commercial methanol. Diisopropylidene benzylidenedimalonate (IIc),[6] 2.82 g. (7.5 mmoles), was added to the sodium methoxide solution, not quite all dissolving. To this suspension was added 1.2 g. (7.5 mmoles) of bromine. A precipitate began to form within 15 min. at room temperature. After 20 min., 1.1 g. of crude product, m.p. 160–163° dec., was collected and washed with methanol. Addition of water to the methanol filtrate gave 0.25 g. of second-crop material. The total yield of crude product was 1.35 g. (48%). Treatment of the crude product with 5% potassium carbonate solution, followed by an acetone-water recrystallization, gave 1.2 g. (43%) of nearly pure product (IIIc), m.p. 185–187° dec. A second acetone-water recrystallization gave the analytically pure sample, m.p. 181–182.5° dec. in a capillary tube.

Anal. Calcd. for $C_{19}H_{16}O_8$: C, 60.96; H, 4.85. Found: C, 61.02; H, 4.75.

B. *With sodium methoxide and iodine.* To a solution of 1.88 g. (5 mmoles) of diisopropylidene benzylidenedimalonate (IIc)[6] in 60 ml. of dimethylformamide was added 0.54 g. (10 mmoles) of powdered sodium methoxide. Iodine, 1.27 g. (5 mmoles), was added to the clear, slightly yellow solution to give a red solution. After 5 hr. at room temperature, the mixture was poured into 300 ml. of ice water, but no precipitate resulted. Extraction of the dimethylformamide-water solution with ethyl acetate, followed by the addition of water to the concentrated ethyl acetate layer, gave 0.26 g. (14%) of crude product, m.p. 147–170° dec. The crude product was triturated in 5% potassium carbonate solution and recrystallized from acetone-ethanol-water to give white crystalline product (IIIc), m.p. 181–183° dec.

Dibenzylidene 1,1,2,2-cyclopropanetetracarboxylate. To a solution of 0.5 g. (1.26 mmoles) of dibenzylidene methylenedimalonate[6] in 1.25 ml. (2.5 mmoles) of 2*N* sodium hydroxide and 8 ml. of water was added 0.32 g. (1.26 mmoles) of solid iodine. The solution was agitated for a few minutes and left in an ice bath for 1 hr. Acetone was added to the mixture, and some gummy white precipitate, mixed with unchanged iodine, was collected. A second crop formed in the acetone-water filtrate. Filtration gave 0.23 g. of second crop material, m.p. 210–220° dec. The impure first crop was dissolved in acetone, carbon tetrachloride was added to remove the unchanged iodine, and water was added to give a fluffy white precipitate. The precipitate was collected and dried to yield 0.11 g. of product, m.p. 218–220° dec. The total yield of crude product was 0.34 g. (69%).

The crude material was stirred in 5% sodium bicarbonate solution, filtered and washed with water. Acidification of the filtrate gave a trace of crude dibenzylidene methylenedimalonate, m.p. 191–193° dec. Further purification was accomplished by dissolving the product in acetone and adding water to give, upon filtration and drying, 0.28 g. of dibenzylidene 1,1,2,2-cyclopropanetetracarboxylate, m.p. 222–225° dec.

The partially purified product was dissolved in acetonitrile and a small amount of petroleum ether (b.p. 30–60°) was added A trace of precipitate formed and was collected to give a white solid, m.p. 193–195° dec., which was soluble in 5% sodium bicarbonate solution. Apparently this material was dibenzylidene methylenedimalonate which had not been completely removed by the trituration in sodium bicarbonate solution. Evaporation of the petroleum ether and addition of water to the acetonitrile solution afforded, upon filtration and drying, the analytically pure material, m.p. 220–224.5° dec.

Anal. Calcd. for $C_{21}H_{14}O_8$: C, 63.96; H, 3.58. Found: C, 64.18; H, 3.53.

Unsuccessful attempts to prepare diisopropylidene 1,1,3,3-cyclobutanetetracarboxylate (IV). A. *From diisopropylidene methylenedimalonate and methylene iodide.* To a solution of 1.5 g. (5 mmoles) of diisopropylidene methylenedimalonate

(14) T. W. D. Gregory and W. H. Perkin, Jr., *J. Chem. Soc.*, 780 (1903).

(15) J. J. Lennon and W. H. Perkin, Jr., *J. Chem. Soc.*, 1513 (1928).

(IIa) in 40 ml. of dimethylformamide was added 0.54 g. (10 mmoles) of powdered sodium methoxide. The sodium methoxide did not dissolve completely, and additional solids appeared to form. To this mixture was added 1.4 g. (5.2 mmoles) of methylene iodide in 20 ml. of dimethylformamide. Solids continued to form. After 15 min., the mixture had started to gel, and more dimethylformamide (20 ml.) was added. After 2 hr., 30 ml. of dimethylformamide was added to the now solid gel and the mixture was warmed, but the gel became only slightly less viscous. After 1 day, the gel was less viscous. After 3 days, a white powder was removed by filtration. Dissolving a portion of this powder in water and acidifying gave crude diisopropylidene methylenedimalonate (IIa), m.p. 133–137° dec. The sodium salt was recombined with the dimethylformamide filtrate, more methylene iodide (1.4 g.) was added, and the mixture was heated at 80°for 70 min. The mixture was cooled and a small amount of sodium salt was collected and washed with acetone. An infrared spectrum of this fraction in Nujol was identical to a spectrum of the sodium salt taken before the mixture was heated. Both spectra were different from the spectrum of the monosodium salt of isopropylidene malonate in Nujol. Water was added to the dimethylformamide filtrate and the solution was extracted with ethyl acetate; however, evaporation of the ethyl acetate layer gave no solid product.

B. *From isopropylidene malonate and methylene iodide.* A sodium ethoxide solution was prepared from 2.3 g. (0.1 g.-atom) of sodium and 150 ml. of absolute ethanol. Solid isopropylidene malonate, 7.2 g. (0.05 mole), was added to the sodium ethoxide solution. The needles of isopropylidene malonate changed to white powder as the sodium salt formed. To this suspension was added 13.4 g. (0.05 mole) of methylene iodide. No heat of reaction was observed. After the mixture had stood at room temperature for about 16 hr., 4.0 g. of unchanged monosodium salt was removed by filtration. Further work-up yielded only more of the sodium salt of isopropylidene malonate.

C. *From diisopropylidene methylenedimalonate, methylene iodide and silver oxide.* A mixture of 1.5 g. (5 mmoles) of diisopropylidene methylenedimalonate (IIa),[5] 1.34 g. (5 mmoles) of methylene iodide and 1.16 g. (5 mmoles) of silver oxide in 60 ml. of acetonitrile was stirred magnetically at 0° for 5 hr. After standing in the refrigerator for 14 hr., the reaction mixture was filtered and the filtrate was concentrated to a small volume. The addition of water caused the formation of a precipitate which was filtered and dried to give 0.69 g. (46%) of diisopropylidene methylenedimalonate, m.p. 142–146° dec.

D. *From diisopropylidene methylenedimalonate and formaldehyde.* To a solution of 1.5 g. (5 mmoles) of diisopropylidene methylenedimalonate (IIa) and 0.41 g. (5 mmoles) of 37% aqueous formaldehyde in 35 ml. of dimethylformamide was added 0.95 g. (5 mmoles) of powdered *p*-toluenesulfonic acid. After standing at room temperature for 52 hr., the clear solution was poured into cold water; but only a clear solution resulted. No solid material was obtained from an ether extraction of the clear solution.

Monosodium salt of isopropylidene malonate. A sodium ethoxide solution was prepared from 3.85 g. (0.167 g.-atom) of sodium and 120 ml. of commercial absolute ethanol in a dried flask with a drying tube. A warm solution of 24.1 g. (0.167 mole) of dry isopropylidene malonate (dried in a desiccator over phosphorus pentoxide) in 200 ml. of absolute ethanol was added fairly rapidly to the sodium ethoxide solution. Monosodium salt began to precipitate immediately. The mixture was cooled for 20 min., filtered and washed with absolute ethanol and absolute ether to give 18.7 g. of monosodium salt. The filtrate was concentrated *in vacuo* to near dryness. The resulting precipitate, upon filtration, gave a second crop (7.8 g.) of monosodium salt. The total yield was 26.5 g. (95%). The solubility of the sodium salt in ethanol is approximately 2.4 g. per 100 ml. at 25°.

Isopropylidene 1,1-cyclohexanedicarboxylate (VII). A. *From equimolar amounts of monosodium salt and dihalide.* A mixture of 3.32 g. (20 mmoles) of the monosodium salt of isopropylidene malonate and 4.6 g. (20 mmoles) of 1,5-dibromopentane in 35 ml. of dimethylformamide was left at room temperature for 84 hr. All of the sodium salt dissolved within about 14 hr., and the color of the solution changed from colorless to yellow. At the end of the 84-hr. period the addition of water to the yellow solution caused precipitation. The mixture was cooled for 1 hr., filtered and pressed dry to give 0.9 g. (21%) of crude isopropylidene 1,1-cyclohexanedicarboxylate (VII), m.p. 114–118.5° with sublimation above 80°. The pure material, m.p. 119–119.5°, was obtained by dissolving the product in methanol and adding a small amount of water.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.21; H, 7.58.

B. *From a 2:1 ratio of monosodium salt and dihalide.* Conditions and amounts of the reactants for this reaction were the same as in part A except that only 2.3 g. (10 mmoles) of 1,5-dibromopentane was used. Work-up as in part A gave 1.1 g. of a mixture of VII and, probably, isopropylidene malonate. Trituration of this mixture in 5% sodium bicarbonate solution afforded 0.87 g. (41%) of crude VII.

C. *From equimolar amounts of monosodium salt, dihalide and sodium methoxide.* Conditions and amounts of the reactants for this reaction were the same as in part A except that 1.08 g. (20 mmoles) of powdered sodium methoxide was added after 25 hr. of the reaction. At the end of the 84-hr. period about 0.6 g. of light yellow powder was removed by filtration. This powder was dissolved in 3 ml. of water and the solution was acidified to yield 0.2 g. (6%) of 1,1-cyclohexanedicarboxylic acid, m.p. 177–178° dec. (lit., m.p. 176° dec.,[16] m.p. 179.5° dec.[17]). Work-up of the dimethylformamide filtrate as in part A yielded 0.09 g. of VII. Ether extraction of the dimethylformamide-water solution gave 0.37 g. of VII upon evaporation of the ether layer. The total yield of VII was 0.46 g. (11%).

D. *With dimethylacetamide as solvent.* Conditions and amounts of the reactants were the same as in part A except that dimethylacetamide was used instead of dimethylformamide as solvent. Work-up as in part A yielded 0.85 g. of VII. Extraction of the dimethylacetamide-water layer with ether and evaporation of the ether layer gave an additional 0.30 g. of VII. The total yield of VII was 1.15 g. (27%).

Isopropylidene 1,1-cyclopentanedicarboxylate (VIII). A mixture of 3.32 g. (20 mmoles) of the monosodium salt of isopropylidene malonate and 2.16 g. (10 mmoles) of 1,4-dibromobutane in 35 ml. of dimethylformamide was left at room temperature for 48 hr. The addition of cold water caused cloudiness but no precipitation. The dimethylformamide-water layer was extracted three times with ether, and the ether extract (undried) was allowed to evaporate slowly to a small volume of yellow oil (mostly dimethylformamide). The addition of a small amount of water caused the slow formation (1 or 2 days) of a precipitate which was filtered, washed with water and pressed dry. A second crop was obtained from the oil and water filtrate after 1 day. The total yield of crude isopropylidene 1,1-cyclopentanedicarboxylate (VIII), m.p. 75–84°, was 0.66 g. (33%). Recrystallization from ethanol-water gave a purer product, m.p. 85–87° with sublimation above 70°. A second recrystallization from ethanol-water, followed by a recrystallization from acetone-water, gave the analytically pure material, m.p. 86–87.5°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.81; H, 7.16.

1,1-Cyclopentanedicarboxylic acid. A mixture of 1.80 g. (10.8 mmole) of the monosodium salt of isopropylidene malonate and 2.34 g. (10.8 mmole) of 1,4-dibromobutane in 20 ml. of dimethylformamide was heated on a steam bath for 50 min. and left at room temperature for 4 days. At the

(16) W. A. Wightman, *J. Chem. Soc.*, 2541 (1926).
(17) A. I. Vogel, *J. Chem. Soc.*, 1487 (1929).

end of this period 60 ml. of water and 15 ml. of dilute hydrochloric acid were added. A cloudy solution resulted but no crystalline precipitate formed. After standing overnight, the now clear solution was extracted first with chloroform and then ether. Evaporation of the ether layer gave about 0.01 g. of long needles, which melted with decomposition at 173–182° with sublimation above 120°. The chloroform layer was evaporated to a red oil. Extraction of this red oil with ether gave, upon evaporation, a mixture of oil and crystals. This mixture was filtered and washed with a small amount of chloroform to give 0.25 g. of 1,1-cyclopentanedicarboxylic acid, m.p. 185–192° dec. (lit., m.p. 184–185° dec.,[18] m.p. 190° dec.[17]). The total yield of the diacid was 0.26 g. (15%).

Benzylidene 1,1-cyclopentanedicarboxylate. To a solution of 1.4 g. (7.3 mmoles) of benzylidene malonate and 1.57 g. (7.3 mmoles) of 1,4-dibromobutane in 50 ml. of dimethylformamide was added 0.39 g. (7.3 mmoles) of powdered sodium methoxide. After 53 hr. at room temperature, the clear yellow solution was poured into cold water. Precipitation resulted. Filtration gave 0.1 g. (6%) of benzylidene 1,1-cyclopentanedicarboxylate, m.p. 176–178° with sublimation above 120°. The product was insoluble in 5% sodium bicarbonate solution. Recrystallization from acetone-water and then from ethyl acetate gave the pure product, m.p. 177–178° in a capillary tube.

(18) E. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 86 (1894).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.96; H, 5.71.

Unsuccessful attempts to prepare isopropylidene 1,1-cyclobutanedicarboxylate. A. *With sodium methoxide in dimethylformamide.* To a mixture of 7.2 g. (0.05 mole) of isopropylidene malonate and 5.4 g. (0.10 mole) of sodium methoxide in 60 ml. of dimethylformamide at room temperature was added 10.1 g. (0.05 mole) of 1,3-dibromopropane. Heat was evolved and the mixture was cooled. After stirring for 11 hr., the mixture was allowed to stand for 48 hr. The addition of water caused no precipitation. Evaporation of ether and chloroform extracts gave no solid products. Concentration of the remaining water layer gave only the monosodium salt of isopropylidene malonate.

B. *With sodium ethoxide and ethanol.* A sodium ethoxide solution was prepared from 0.9 g. (40 mg.-atoms) of sodium and 80 ml. of absolute ethanol. To this sodium ethoxide solution at room temperature were added 2.9 g. (20 mmoles) of isopropylidene malonate and 4.0 g. (20 mmoles) of 1,3-dibromopropane in 80 ml. of absolute ethanol. No reaction was observed. Concentration of the ethanol gave only monosodium salt.

C. *With sodium ethoxide and refluxing ethanol.* The amounts of the reactants were the same as in part B. The 1,3-dibromopropane was added to the refluxing mixture and heating was continued for 5 hr. Work-up of the reaction mixture gave only malonic acid.

URBANA, ILL.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Epoxy Ketones. V.[1] Stereochemistry of 2-Benzal-4,4-dimethyl-1-tetralone Oxide. Diol Synthesis

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The boron trifluoride rearrangement of 2-benzal-4,4-dimethyl-1-tetralone oxide (I) gives 6-phenyl-9,9-dimethylbenzocycloheptane-5,7-dione which was isolated in a diketo and mixed enol form. The structures of the products resulting from the reaction of hydrogen chloride and methanol-sulfuric acid solutions with I have been shown to be 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone (VII) and 2-hydroxy-2-(α-methoxybenzyl)-4,4-dimethyl-1-tetralone (XI), respectively, by diagnostic chemical methods. The spiro-epoxy ketone I has been converted to various hydroxy ketones, epoxy alcohols and 1,2-diols through various hydrogenations or reaction with a Grignard reagent. A study of the infrared spectra, hydrogen bonding and the stereostructure of these hydroxy tetralin derivatives was investigated and tentative assignments of conformations and configurations have been made.

In a previously reported study[3] proton-donor, acid catalyzed reactions of 2-benzal-1-tetralone oxides were found to lead to cleavage of the epoxide ring and 2-hydroxy-1-tetralones were postulated as products, mainly on the basis of absorption spectra studies. As is discussed in detail later this has definitely now been shown to be the case.

When the spiroepoxy ketone, 2-benzal-4, 4-dimethyl-1-tetralone oxide[4] (I), was treated with the Lewis acid, boron trifluoride (see Chart 1), under the conditions described by House and Wasson for rearranging 2-benzalcyclohexanone-1 oxide,[5] an 85% yield of a product was obtained which has the analytical and spectral characteristics of the expected seven membered ring 1,3-diketone, 6-phenyl-9,9-dimethylbenzocycloheptane-5,7-dione (II). This product had none of the characteristics to be expected for the isomeric 1,2-diketone, 7-phenyl-9,9-dimethylbenzoheptane-5,6-dione. The diketo form II is readily converted to an enolic isomer IIA-C on recrystallization from acidified methanol. The enol structures IIA and IIB would be favored over IIC which does not allow for conjugation between the carbonyl oxygen and the hydroxyl

(1) *a.* For paper IV in this series see, N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang, *J. Am. Chem. Soc.* **83,** 974 (1961); *b.* Presented in part at the American Chemical Society Meeting, September 1960, New York, N. Y.

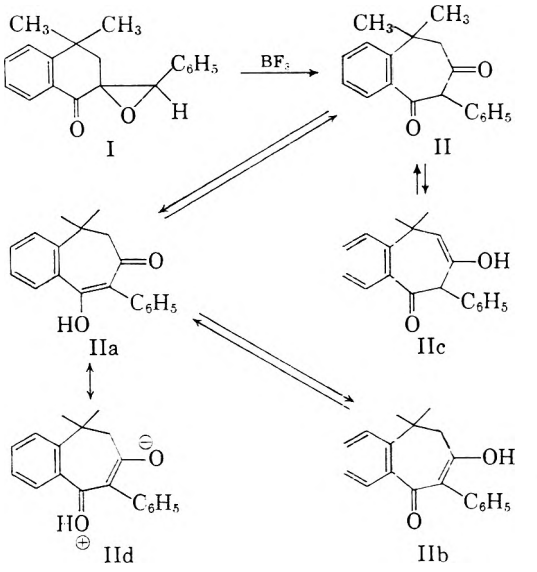
(2) Abstracted from the Ph.D. thesis of R. E. Bambury, University of Nebraska, January 1960.

(3) N. H. Cromwell, R. E. Bambury, and R. P. Barkley, *J. Am. Chem. Soc.*, **81,** 4294 (1959).

(4) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80,** 893 (1958).

(5) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.* **78,** 4394 (1956).

CHART 1



group. This is an important factor in the stabilization of enolized cyclic 1,3-diketones.[6] The presence of an infrared band (3500 cm.$^{-1}$) in the free or weakly hydrogen bonded O—H stretching region of the spectrum of the enol form, IIA and/or IIB, is expected since "conjugated chelation," as experienced[7] with open chain 1,3-diketones, is not possible. The enol IIA and/or IIB shows a broad double peak (1625 and 1635 cm.$^{-1}$) which indicates that in carbon tetrachloride solution the enol form of II exists as a mixture of two structures (*e.g.* IIA and IIB). House and Wasson[5] reported only a single peak in this region at 1615 cm.$^{-1}$ for the enol form of the symmetrical 2-phenyl-1,3-cyclohexanedione. Resonance of the type implied in IIA $\longleftrightarrow$ IID is mainly responsible for the great lowering of the carbonyl band in the β-hydroxy-α,β-unsaturated carbonyl structures.

The pure diketo form II showed no infrared absorption in the O—H stretching region of the spectrum and two carbonyl bands (γ C=O, aliphatic, 1731 cm.$^{-1}$ and γ C=O, aromatic, 1691 cm.$^{-1}$) in the expected regions. Dioxane solutions of the enol forms IIA,B and of the diketo form II show identical ultraviolet and infrared spectra indicating that they exist as tautomeric mixtures in this media.

The structures tentatively assigned in a previous report[3] to the hydrogen chloride and acid-catalyzed, methanol epoxide ring cleavage products of I have now been definitely established. Catalytic hydrogenation of the chlorohydrin VII in the presence of sodium bicarbonate gave an excellent yield of 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone (VIII). The structure of VIII was verified in several ways. Treatment of VIII with a sulfuric acid–acetic anhydride mixture at room temperature produced 2-benzyl-3,4-dimethyl-1-naphthol acetate (IX). Undoubtedly VIII undergoes a dehydration to 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene which has previously[4] been shown to give a dienone-phenol rearrangement to produce IX under these conditions. The α-hydroxy ketone VIII was shown to be stable to sodium methoxide or activated alumina.

The catalytic hydrogenation of the α-hydroxy ketone VIII gave 1,2-dihydroxy-2-benzyl-4,4-dimethyltetralin (IV), identical with the product obtained by the lithium aluminum hydride reduction of I. The 1,2-diol IV consumed 90% of the theoretical amount of periodate.

The structure of 2-hydroxy-2-(α-methoxybenzyl)-4,4-dimethyl-1-tetralone[4] (XI) has now been verified by catalytically reducing it to 1,2-dihydroxy-2-(α-methoxybenzyl)-4,4-dimethyltetralin (XII), which was shown to consume 91% of the theoretical amount of periodate expected for the 1,2-diol structural arrangement.

The conversion of the spiroepoxy ketone I to various epoxy alcohols and diols was carried out to study the stereochemistry of the reactions involved. An assignment of conformations and configurations for the various 1,2-diols involved in these synthetic studies is given in a special section.

The "reverse addition" of the methyl Grignard reagent to I gave a good yield of what at first appeared to be one isomer of 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide (III). However, the lithium aluminum hydride reduction of III gave a product, X, with a wide melting range but which was found to take up 99% of the theoretical amount of periodate. Chromatographing this mixed product on alumina resulted in the isolation of one pure diastereoisomer, m.p. 112–113°. It seems probable that the epoxy alcohol III is also a mixture of diastereoisomers since it has been shown repeatedly that lithium aluminum hydride reduction of epoxides is a stereospecific reaction.[8]

A widely melting product X from which the same diastereoisomer, m.p. 112–113°, was also obtained, resulted from the reaction of methylmagnesium bromide with 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone (VIII). This reaction of VIII to produce X would not necessarily be expected to be stereospecific but possibly stereoselective. Again the gross product X took up 96% of the expected amount of periodate in the cleavage experiment indicating that it probably is a mixture of the diastereoisomers.

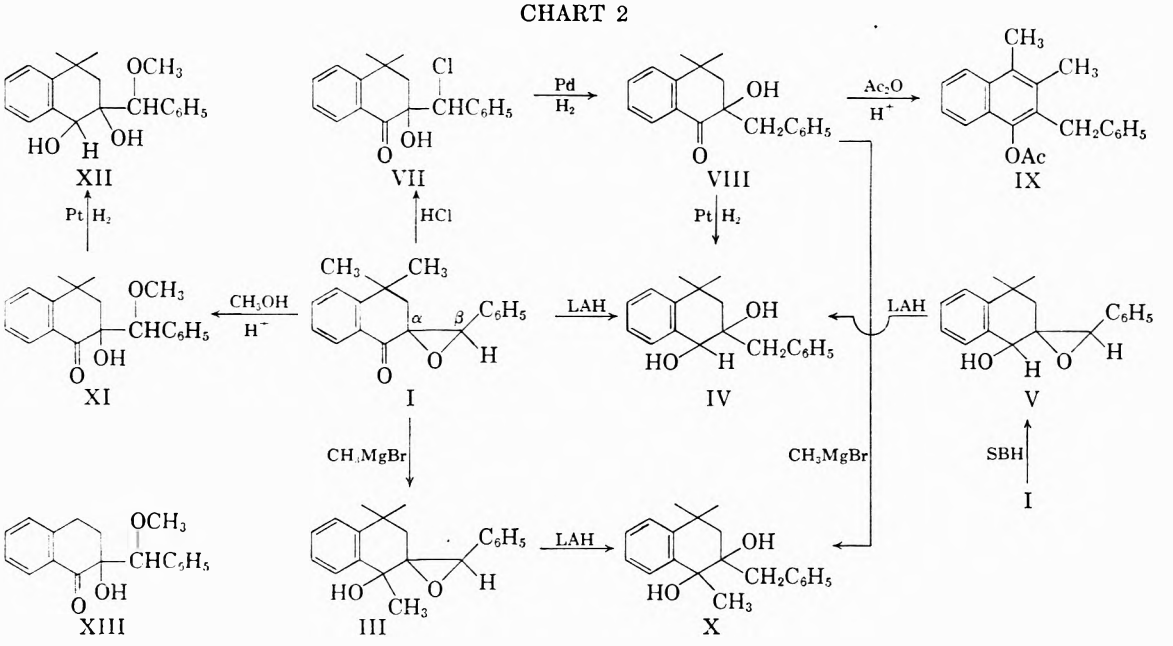
The reduction of the spiroepoxy ketone I with various reagents gave varying results. With sodium borohydride the only solid product isolated was 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (V) which was readily reduced by lithium aluminum

(6) *a.* N. H. Cromwell and R. D. Campbell, *J. Org. Chem.*, 22, 520 (1957); *b.* R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, 79, 3456 (1957).

(7) R. Rasmussen, D. Tunnicliff, and R. Brattain, *J. Am. Chem. Soc.*, 71, 1068 (1949).

(8) E. L. Eliel, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, M. S. Newman, ed., p. 106.

CHART 2



hydride to 1,2-dihydroxy-2-benzyl-4,4-dimethyltetralin (IV), identical with that obtained by the lithium aluminum hydride reduction of I, or the platinum oxide catalyzed hydrogenation of VIII.

The platinum catalyzed hydrogenation of I produced at least a 50% yield of V and a 29% yield of the unstable 2-(β-hydroxybenzyl)-4,4-dimethyl-1-tetralone (VI) which was readily dehydrated by alumina in the chromatographic separation to 2-benzal-4,4-dimethyl-1-tetralone.[4]

When the spiroepoxy ketone I was hydrogenated in benzene with a palladium-on-charcoal catalyst a mixed product resulted which calculations indicate was made up of 25% of the 1,2-diol IV (isolated) and 70% of VI which again was readily dehydrated on the chromatographic column of alumina to 2-benzal-4,4-dimethyl-1-tetralone (isolated). The unstable oil, which was mainly VI, was shown to have infrared bands in the expected locations (γOH, 3550 cm.$^{-1}$ and γC=O, 1695 cm.$^{-1}$) and no absorption at 1673 cm.$^{-1}$ as expected for 2-benzal-4,4-dimethyl-1-tetralone.[4] The aldol VI was shown to undergo readily a reverse aldol condensation to produce some benzaldehyde in the presence of potassium hydroxide.

These results from the catalytic hydrogenation of spiroepoxy ketone I are interesting in comparison with findings from comparable reductions of the less sterically restricted *trans*-chalcone oxide[9] which produces mainly the α-hydroxy ketone. Apparently the β-position in I is even less available than the α-position for hydrogen transfer by these catalysts. On the other hand lithium aluminum hydride attacks the spiroepoxy ketone I and/or 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (V) exclusively at the *beta* position. This is analogous to the behavior of *trans*-chalcone oxide with this reagent.[9]

VanderWerf has given[10] an excellent discussion of the factors effecting direction of ring opening for unsymmetrical epoxides. For the spiroepoxy ketone I the β-position would appear to be the center of lower electron density in contrast with the α-position but the position actually attacked obviously varies with the hydrogenation reagent employed.

In the prior study[3] the spiroepoxy ketone I was shown to be inert to reaction with amines. *Trans*-chalcone oxide has been found to undergo an SN2 attack by piperidine at the β-position, a reaction which undoubtedly involves a Walden inversion.[1a,11] As was pointed out in the previous report[3] the epoxide ring in I is readily cleaved with hydrogen chloride in a reaction which involves attack by a chloride ion at the β-carbon in a transition state involving inversion at this center.

Infrared absorption spectra, hydrogen bonding and stereostructure of hydroxy tetralin derivatives. In these studies a lithium fluoride prism was used in the spectrophotometer to increase its sensitivity in the O–H stretching region.

The infrared spectra of the α-hydroxy ketones studied in this investigation showed splitting. The band splitting effects in α-hydroxy ketones have been ascribed by Jones[12] and others[3] to intramolecular hydrogen bonding. This type of

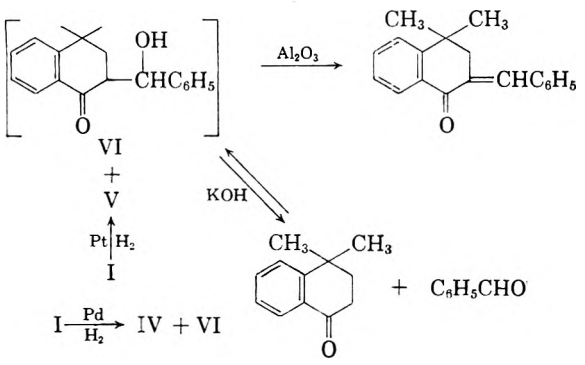
(9) W. Herz, *J. Am. Chem. Soc.*, **74**, 2928 (1952).

(10) A. Feldstein and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1626 (1954).

(11) N. G. Barker and N. H. Cromwell, *J. Am. Chem. Soc.*, **73**, 1051 (1951).

(12) R. N. Jones *et al. J. Am. Chem. Soc.*, **74**, 2820 (1952).

CHART 3



equilibrium would give rise to a free and a H-bonded O—H band and a free and H-bonded carbonyl band.

With 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone (VIII) the carbonyl region of the spectrum shows a non-bonded band at 1695 cm.$^{-1}$ and a shoulder at 1680 cm.$^{-1}$ ascribed to the presence of the H-bonded carbonyl form (H-bonding is expected to increase the ρ-character of the carbonyl bond resulting in a lowering of frequency). The hydroxyl region of the spectrum of VIII gave evidence of H-bonded (3512 cm.$^{-1}$) and free (3562 cm.$^{-1}$) O—H bands. It seems probable that the hydroxyl group is axial and the benzyl group equatorial.[4]

The introduction of α-electronegative groups in the benzyl group introduces an additional effect and it is indicated that the chlorohydrin (VII) and the two hydroxymethoxy ketones (XI) and 2-hydroxy-2-(α-methoxybenzyl)-1-tetralone (XIII)

show the following equilibrium in carbon tetrachloride. These compounds show a bifurcated carbonyl band indicating the presence of free and hydrogen bonded carbonyl groups. These compounds also show two hydroxyl peaks both in the hydrogen bonded region of the spectrum. A dilution study with VII, VIII, XI and XIII showed nearly the same relative intensities of the carbonyl and hydroxyl bands at high and low dilution, indicating the hydrogen bonding effects here are probably not intermolecular.

The infrared spectra of the two epoxy alcohols III and V prepared in this work showed a free O—H peak and an H-bonded OH peak at high concentrations. On dilution the lower H-bonded band disappeared, indicating that H-bonding in these cases is intermolecular in nature.[13] Another factor which must be taken into account in assigning the O—H bands for III and V is the knowledge that tertiary hydroxyl bonds absorb 10–15 cm.$^{-1}$ lower than the secondary O—H group. This type of lowering seems to be consistent for several types of secondary and tertiary alcohols.[14]

Kuhn[14] and Cole and Jefferies[15] have used infrared spectroscopy as a tool for assigning conformations to many cyclohexane-1,2-diols. The following generalizations have been found to be true: (1) secondary alcohols have a hydroxyl group stretching frequency 10–15 cm.$^{-1}$ higher than tertiary alcohols with the free hydroxyl group frequencies occurring between 3600–3640 cm.$^{-1}$ and the intramolecular H-bonded bands between 3580–3600 cm.$^{-1}$; (2) in cyclohexane *cis*-1,2-diols, where one group is equatorial and the other axial, the latter is involved in intramolecular H-bonding in preference to the former.

An examination of models of the 1,2-dihydroxytetralins prepared in this work (IV, X, XII) indicates that the cyclohexene ring of the tetralin nucleus is probably in a chair conformation. Therefore substituent groups on the cyclohexene ring will have near axial and equatorial conformations. In order that we may use the infrared spectral data to assign probable conformations and configurations to the 1,2-dihydroxytetralins, IV, X and XII, one basic and reasonable assumption must be made about the conformations of these compounds. This is that the bulky benzyl group in the 2-position of the three compounds takes an equatorial position in preference to the smaller 2-hydroxyl group. An examination of models of these compounds shows that if the benzyl group is forced into an axial position there is considerable interaction between it and one of the methyl groups at the 4-position. The benzyl group in 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone[4] was found to have an equatorial conformation. Also the isopropyl group takes an equatorial position in favor of a hydroxyl group in the cyclohexane diols.[15]

To make sure that the H-bonding observed with the tetralin-1,2-diols IV, X and XII was essentially intramolecular in nature, dilution studies were done. No significant change in the relative intensities of the hydroxyl bands were observed on changing from high to low concentrations.

The infrared spectrum of IV showed two hydroxyl peaks, a non-bonded one at 3620 cm.$^{-1}$ and a bonded one at 3579 cm^{-1}. Since both bonded and non-bonded bands occur, the "true *trans*" or diaxial conformation for the diol is eliminated. A molecule with a "true *trans*" conformation shows only a non-bonded hydroxyl band since intramolecular H-bonding is sterically impossible.[14,15] Therefore the hydroxyl groups in IV have either an equatorial, equatorial (e, e) conformation or an axial, equatorial (a, e) arrangement since the spectrum indi-

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1958, p. 96.

(14) L. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); *J. Am. Chem. Soc.*, **76**, 4323 (1954).

(15) A. Cole and P. Jefferies, *J. Chem. Soc.*, 4391 (1956).

cates intramolecular H-bonding does occur. The assignment of the benzyl group at the 2-position in IV to an equatorial conformation automatically assigns the hydroxyl group at the 2-position to an axial conformation. Thus the conformation of the hydroxyl group at the 1-position is apparently equatorial and the conformation of IV is a, e. This tentative assignment of the a, e conformation to the hydroxyl groups in IV suggests that they probably have a *cis* configuration since adjacent *trans* groups in cyclic compounds can have only e, e or a, a conformations.

The same considerations used in the assignment of the configuration of IV can also be used to assign the configuration of X. The spectrum of X also shows a bonded and non-bond hydroxyl peak and so 1,2-dihydroxy-2-benzyl-1,4,4-trimethyltetralin (X) has its hydroxyl groups in an a, e conformation in a *cis* configuration. The free hydroxyl stretching frequency is about 10 cm.$^{-1}$ lower than the free hydroxyl stretching frequency of IV as expected from the generalization (1) given above, since the free hydroxyl group of X is tertiary whereas the free hydroxyl group of IV is probably the secondary hydroxyl group in accord with generalization (2). It will be interesting to see the spectrum of the unknown diastereoisomer of X. The one studied here apparently has the *cis* configuration so the other isomer should have a *trans* arrangement of the hydroxyl groups and, therefore, show only one tertiary non-bonded hydroxyl peak.

The spectrum of 1,2-dihydroxy-2-(α-methoxybenzyl)-4,4-dimethyltetralin (XII) shows three hydroxyl peaks, two bonded and one non-bonded. The appearance of the third band in XII is undoubtedly due to H-bonding of one of the hydroxyls with the methoxy group. The low frequency of the band and its broad shape indicates that it is a very strong H-bond.[14] A methoxy group has been shown to be a better proton acceptor than a hydroxyl group.[16] Although the presence of the third band complicates the spectrum of XII it is still possible tentatively to assign an a, e conformation to the hydroxyls on the 2-position and 1-position, respectively, using the same reasoning as employed with IV and X. Thus 1,2-dihydroxy-2-(α-methoxybenzyl)-4,4-dimethyltetralin (XII) is assumed to be a *cis* diol.

EXPERIMENTAL[17]

Rearrangement of 2-benzal-4,4-dimethyl-1-tetralone oxide (I) *to 6-phenyl-9,9-dimethylbenzocycloheptane-5,7-dione* (II). House's[5] conditions for rearranging epoxy ketones were employed. A 2.2-g. sample of the epoxy ketone I produced 1.9 g. (86% yield) of a colorless product II, m.p. 100–105°. Several recrystallizations of II from acidified methanol and water produced IIA,B, m.p. 116–128°; λ_{max} 235 and 297 mμ (broad bands) (ε 10,000, 5800). The infrared spectrum with 10 mg./ml. in a 1.0-mm. cell using sodium chloride optics: γ_{OH}, 3500/25; $\gamma_{C=O}$, 1635/45 and 1625/50. The compound gave no isolable product with phenylhydrazine or *o*-phenylenediamine.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.98; H, 6.53.

When IIA,B was dissolved in benzene, washed with 20% potassium carbonate, the solution dried over anhydrous magnesium sulfate and recrystallized from the hot solution to which petroleum ether (b.p. 60–70°) was added, II, m.p. 100–105°, resulted. The infrared spectrum with 10 mg./ml. in a 1.0-mm. cell using sodium chloride optics showed: $\gamma_{C=O}$, aliphatic, 1731/85; $\gamma_{C=O}$, aromatic, 1691 broad/85; γphenyl, 1600/25.

In dioxane both IIA,B and II showed λ_{max} 285 mμ (broad) ε 4000; γ_{OH}, 3650/60, $\gamma_{C=O}$, 1730/40, 1690/70, 1625/50 (Perkin-Elmer Infracord).

Reaction of I *with methylmagnesium bromide.* From 4.4 g. (0.016 mole) of epoxy ketone I and 0.021 mole of commercial methylmagnesium bromide (Grignard reagent solution added slowly to ketone solution), 3.1 g. (66% yield) of 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide (III) was obtained, m.p. 165–167°, recrystallized from petroleum ether (b.p. 60–70°) and benzene; γOH, 3595/35 (5.0 mm. cell, 2.5 mg./ml.), 3595/20 (1.0 mm. cell, 7.5 mg./ml.), 3595/35 and 3474 (broad)/5 (1.0 mm. cell, 15 mg./ml.).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.31; H, 7.55.

Hydrogenation of I. A. *With lithium aluminum hydride.* A 4.4-g. sample of I in 250 ml. of dry ether was added to a well stirred slurry of 2.0 g. of lithium aluminum hydride in 100 ml. of dry ether over a period of 30 min. After stirring for an additional hour, working up the reaction mixture produced 3.8 g. (87% yield) of 1,2-dihydroxyl-2-benzyl-4,4-dimethyltetralin (IV), m.p. 140.5–142.5°, recrystallized from benzene and petroleum ether; γ_{OH}, 3620/45 and 3579/35; consumption of periodate, 90%.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.91; H, 7.85. Found: C, 80.88; H, 7.84.

B. *With sodium borohydride.* Reduction of 1.1 g. of I by boiling with 0.08 g. (1 molar equiv.) of sodium borohydride for a few minutes and then stirring for 1 hr. produced 0.45 g. of a solid product which after recrystallization from benzene and petroleum ether gave 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (V), m.p. 136–139°. A mixed melting point experiment with V obtained in the following experiment showed no depression and the infrared spectra were identical. Some unidentified oily material also resulted from the sodium borohydride reduction.

C. *With platinum oxide and hydrogen.* A 2.0-g. sample of I in 200 ml. of dry ether was shaken with 0.2 g. of platinum oxide under 35 lb./in.^{2} of hydrogen for 45 min. at room temperature. Recrystallization of the product from petroleum ether (b.p. 60–70°) produced 0.7 g. of 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (V), m.p. 139.5–141°; γOH, 3609/65 and 3475 (broad)/10 (20 mg./ml.), 3609/50 and 3475 (broad)/2 (10 mg./ml.), 3609/45 (2.5 mg./ml.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.55; H, 7.15.

The filtrate from the isolation of V was poured onto a 24 cm. × 2 cm. activated alumina (Merck) column which had previously been saturated with petroleum ether (b.p. 60–70°). The column was developed with petroleum ether-benzene mixtures and finally eluted with methanol-benzene

(16) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1955, p. 47.

(17) All melting points corrected. Ultraviolet absorption spectra were determined with a Cary Model 11-MS recording spectrophotometer employing matched 1 cm. fused silica cells and $10^{-4}M$ reagent grade methanol solutions over the range of 200–400 mμ. Infrared spectra were measured with a Perkin-Elmer Model 21 double-beam recording instrument over the frequency range of 4000–600 cm.$^{-1}$ using a sodium chloride or lithium fluoride prism and matched sodium chloride cells. Unless otherwise indicated lithium fluoride optics and 2.5 mg./ml. carbon tetrachloride solutions with 5 mm. cells were used.

mixtures. A yellow band which developed at the top of the column and moved down to be in the first eluates, produced 0.55 g. of 2-benzal-4,4-dimethyl-1-tetralone[4], m.p. 108–109°. The second eluate was found to contain 0.3 g. of V. Thus the total yield of isolated products from this reduction were 1.0 g. (50% yield) of V and 0.55 g. (29% yield) of 2-benzal-4,4-dimethyl-1-tetralone.

Attempted platinum oxide catalyzed hydrogenations of I in alcohol, dioxane or tetrahydrofuran were not successful and the starting material was recovered.

D. *With palladium-on-charcoal and hydrogen.* Hydrogenation of 2.0 g. of I in 100 ml. of benzene in the presence of 1.0 g. of 10% palladium-on-charcoal catalyst under 45 lb./in.^{2} after 2 hr. shaking produced an oily product. Crystallization from petroleum ether (b.p. 60–70°) gave 0.08 g. of IV, m.p. 140–143°. A mixed melting point experiment and its infrared spectrum showed this product to be identical with IV obtained from the lithium aluminum hydride reduction of I.

The filtrate from the isolation of IV contained 1.9 g. of a clear viscous oil; $\gamma_{C=O}$, 1695, γ_{OH}, 3550 cm.$^{-1}$. A chromatographic separation of a 0.3-g. sample of this oil on an alumina column, as described previously, produced 0.2 g. of 2-benzal-4,4-dimethyl-1-tetralone,[4] m.p. 106–108°, and 0.06 g. of IV, m.p. 140–142°.

A 0.1-g. sample of the viscous oil residue (1.9 g.) from the original isolation of IV was dissolved in 4% methanolic potassium hydroxide and allowed to stand 1 hr. The solution turned yellow and gave off a strong odor of benzaldehyde; 0.02 g. of IV was isolated from this mixture. These experiments indicate that this hydrogenation produces at least a 70% yield of *2-(α-hydroxybenzyl)-4,4-dimethyl-1-tetralone*, (VI) which is dehydrated by the basic alumina to 2-benzal-4,4-dimethyl-1-tetralone.

Reduction of 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone (VII) *to 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone* (VIII). The chlorohydrin[3] VII (5.9 g., 0.019 mole) dissolved in 250 ml. of benzene was shaken with 2.1 g. of 10% palladium on charcoal and 2.0 g. of sodium bicarbonate for 1.5 hr. at 45 lb./in.^{2} of hydrogen. The oily product was recrystallized from petroleum ether to give 5.0 g. (95% yield), m.p. 93.5–94.5°, of VIII; λ_{max}, 250 and 290 mμ (ε 11,800, 1600); with 1.0 mm. cell and 15 mg./ml.: γ_{OH}, 3560 (Sho.)/20 and 3510/30; $\gamma_{C=O}$, 1695/70 and 1680 (Sho.)/60; with 5.0 mm. cell and 2.5 mg./ml.: γ_{OH}, 3562/15 and 3512/25; $\gamma_{C=O}$, 1695/75 and 1680 (Sho.)/65.

Reduction of VIII *to* IV. A solution of 0.1 g. of VIII in 60 ml. of dry ether was shaken with 0.1 g. of platinum oxide catalyst for 2 hr. under 45 lb./in.^{2} of hydrogen. The oily product was crystallized from methanol and water, then benzene and petroleum ether to give 0.08 g. of 1,2-dihydroxy-2-benzyl-4,4-dimethyl-tetralin (IV), m.p. 141–142.5°, identical with the product obtained from the lithium aluminum hydride reduction of I.

Acid-catalyzed dehydration-rearrangement of VIII *to 2-benzyl-3,4-dimethyl-1-naphthol acetate* (IX). A 0.28-g. sample of VIII was allowed to stand at room temperature for 2 days in 20 ml. of acetic anhydride containing 1 ml. of coned. sulfuric acid. Dilution with water and neutralization with sodium hydroxide produced 0.2 g. of IX, m.p. 115–116°, recrystallized from methanol. The compound was identical with that previously prepared.[4]

2-Hydroxy-2-benzyl-4,4-dimethyl-1-tetralone (VIII) was stable to standing for 3 days in 4% methanolic sodium methoxide; it also was unchanged by activated alumina at 25–30°.

Reaction of VIII with methylmagnesium bromide. A 0.5-g. sample of VIII in 100 ml. of ether was treated with 7 ml. of commercial methylmagnesium bromide (excess) and stirred for 4 hr. The crude product, 0.55 g., m.p. 103–131° consumed 96% of the theoretical amount of periodate, indicating that it may be a mixture of the *erythro* and *threo* forms of 1,2-dihydroxy-2-benzyl-1,4,4-trimethyltetralin (X). This mixed product was chromatographed on alumina to produce only a low melting isomer of X in pure form, m.p. 112–113°; γOH, 3610/30 and 3587/50.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.21; H, 8.41.

Reduction of 2-hydroxy-2-(α-methoxybenzyl)-4,4-dimethyl-1-tetralone (XI). A solution of 0.5 g. of XI in 100 ml. of ether was shaken for 1 hr. with 0.1 g. of platinum oxide catalyst under 45 lb./in.^{2} of hydrogen. The resulting 1,2-dihydroxy-4,4-dimethyl-2-(α-methoxybenzyl)tetralin (XII), 0.46 g. (92% yield), m.p. 139–139.5°, was recrystallized from benzene and petroleum ether. This product, XII, used up 91% of the calculated amount of periodate in a cleavage experiment. The infrared spectrum showed: with 15 mg./ml. in a 0.1 mm. cell, γ_{OH}, 3618/5, 3582/5, 3480/2; with 7.5 mg./ml. in a 1.0 mm. cell, γ_{OH}, 3618/30, 3582/26, 3478/5; with 2.5 mg./ml. in a 5 mm. cell, γ_{OH}, 3618/47, 3582/40, 3480/9.

Anal. $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.98; H, 7.41.

Reduction of 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (V). A 0.84-g. sample of V in 100 ml. of dry ether was added slowly (2 hr.) with stirring to an ether slurry of 0.5 g. of lithium aluminum hydride. A 0.6-g. amount of 1,2-dihydroxy-2-benzyl-4,4-dimethyltetralin (IV), m.p. 140–143°, was isolated which was identical with that produced by the lithium aluminum hydride reduction of I.

Reduction of 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide (III). An attempted reduction of III with lithium aluminum hydride in dry ether returned only the starting material. A 0.5-g. sample of III dissolved in 50 ml. of dry tetrahydrofuran was added slowly to a stirred slurry of 0.6 g. of lithium aluminum hydride in 100 ml. of the same solvent. The mixture was refluxed for 8 hr. and allowed to stand at room temperature for 12 hr. Isolation gave 0.46 g. of a mixed product, m.p. 95–128°, which consumed 99% of the calculated amount of periodate for a mixture of the *erythro* and *threo* forms of the expected diol, 1,2-dihydroxy-2-benzyl-1,4,4-trimethyltetralin (X). Chromatographing on alumina produced 0.1 g. of the low melting isomer of X, m.p. 112–113°, identical with that prepared by the reaction of methylmagnesium bromide with 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone (VIII). Attempts to isolate a higher melting isomer of X in pure form were not successful.

Periodate cleavage of 1,2-diols. The procedure employed for cleaving the 1,2-diols prepared in this investigation was essentially the method outlined in *Organic Analysis*[18] for analyzing monoglycerides. Using this procedure, ethylene glycol consumed 97% of the calculated amount of periodate, benzoin 101%, 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide (III) 0%, 1-hydroxy-2-benzal-4,4-dimethyltetralin oxide (IV) 0%, 2-hydroxy-2-(α-methoxybenzyl)-4,4-dimethyl-1-tetralone (XI) 0%, 2-hydroxy-2-(α-methoxybenzyl)-1-tetralone[3] (XIII) 0%, 2-benzal-4,4-dimethyl-1-tetralone oxide[4] (I) 0%, and 2-hydroxy-2-benzal-4,4-dimethyl-1-tetralone (XIII) 0%. The results for the 1,2-diols prepared in this investigation are given with the description of the syntheses.

Infrared absorption spectra studies: A. *With 2-hydroxy-2-(α-methoxybenzyl)-1-tetralones* (XI) *and* (XIII). For 2.5 mg. of XI/ml. in a 5 mm. cell, γ_{OH}, 3555/30 and 3510/15, $\gamma_{C=O}$, 1692/65 and 1680/75; for 12 mg. of XI/ml. in a 1.0 mm. cell with sodium chloride optics, γ_{OH}, 3530/30 and 3480/20, $\gamma_{C=O}$, 1685 (shoulder)/80 and 1675/90; for 2.5 mg. of XIII/ml. in a 5 mm. cell, γ_{OH}, 3575/10 and 3510/27, $\gamma_{C=O}$, 1695/68 and 1682/70; for 15 mg. of XIII/ml. in a 1.0 mm. cell, γ_{OH}, 3573/15 and 3510/37, $\gamma_{C=O}$, 1694/78 and 1682/78.

(18) J. Mitchell, Jr., ed., *Organic Analysis*, Vol. I., Interscience Publishers, New York, 1953, pp. 44–46.

B. *With 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone* (VII). With 2.5 mg. of VII/ml. in a 5 mm. cell, γOH, 3545/20 and 3490/20; γC=O, 1696/70 and 1682/65; with 10 mg./ml. in a 1.0 mm. cell with sodium chloride optics, γOH, 3550/20 and 3500/23, γC=O, 1695–1683/80.

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LINCOLN, NEB.

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

An Indone to Naphthol Ring Expansion

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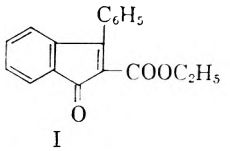
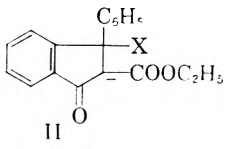
2-Carbethoxy-3-phenylindone (I) adds phenacyl chloride in a Michael reaction, and the resulting anion at once eliminates chloride forming a cyclopropane (III). This product is attacked further by bases, which cause it to rearrange into a naphthol (IV).

After 2-carbethoxy-3-phenylindone (I) was found to add certain anions forming II,[1] it became of interest to alkylate the products, but all attempts to do this failed. In explanation it may be noted first that anions II are weakly basic, the corresponding acids dissolving in carbonate, and second that C_2 in II is flanked by bulky groups on C_3, and it is well known that analogous mono-*tert*-alkylated malonic or acetoacetic esters are resistant to alkylation.

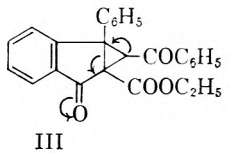


I

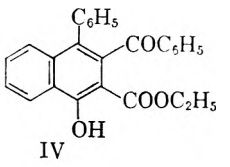


II

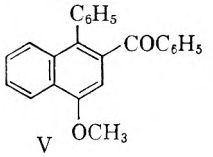
These inhibiting effects would be less important in an intramolecular reaction, and accordingly conditions were arranged so that a Michael reaction leading to II could be followed by an intramolecular alkylation. This was done by treating I with phenacyl chloride. In accordance with expectation, the cyclopropane III was formed smoothly.



III



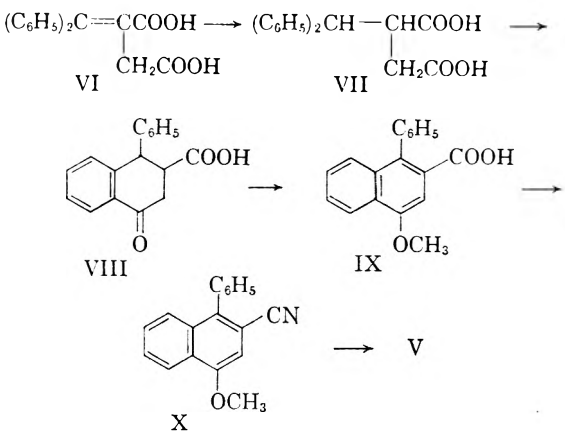
IV



V

Compound III was found to be quite sensitive to alkali. Although it could be isolated in good yield when proper conditions prevailed, use of excess base in the Michael reaction or treatment of isolated III with base led to formation of IV. The mechanism for the isomerization is indicated by arrows in formula III, and it is seen that the process is analogous to one studied recently by Wawzonek and Morreal.[2]

Structure IV for the rearrangement product was confirmed; hydrolysis, decarboxylation and methylation yielded V, and this substance was synthesized by the route indicated in formulas VI–X.



Diphenylitaconic acid (VI) was reduced by use of Raney alloy and sodium hydroxide[3] as recommended by Drake and Tuemmler[4] but the product was found to be not VII, but an aluminum complex of this acid, a fact which accounts for the low yield obtained by Drake and Tuemmler in their further use of the substance. The complex was remarkably stable; its clear solution in dilute bicarbonate deposited it unchanged on acidification; it was boiled with concentrated hydrochloric acid without change and it crystallized as described from ethyl acetate-benzene. Isolation of VII from the complex was accomplished by esterification (methanol-sulfuric acid) followed by saponification, or better by precipitation of the barium salt of VII directly from

(1) C. F. Koelsch, *J. Org. Chem.*, **25**, 2088 (1960).

(2) S. Wawzonek and C. E. Morreal, *J. Am. Chem. Soc.*, **82**, 439 (1960).

(3) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(4) N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.*, **77**, 1209 (1955).

the reduction mixture, the barium salt being subsequently freed of barium with hydrochloric acid.

EXPERIMENTAL

Compound III. A mixture of 2.5 g. of ethyl 3-phenylindone-2-carboxylate, 1.5 g. of phenacyl chloride and 12 ml. of *tert*-butyl alcohol was warmed, then cooled rapidly to 25° to give a fine suspension and treated with 0.75 g. of 85% potassium hydroxide in 1.5 ml. of water. After the mixture had been shaken for 15 min., it was evaporated at 95° under reduced pressure and then taken up in water and ether. The ether solution was washed with 5% sodium carbonate, then mixed with ligroin, giving 2.6 of nearly pure *ethyl 1-benzoyl-2-oxo-6b-phenyl-1a,6b-dihydrocycloprop[b]indene-1a-carboxylate*, III, colorless flat needles from dilute alcohol, m.p. 115–116°. The compound was insoluble in 10% sodium hydroxide and gave no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.8; H, 5.09. Found: C, 79.0; H, 5.21.

Compound IV. When 2.6 g. of III was added to a solution of 0.17 g. of sodium in 5 ml. of absolute alcohol, a deep yellow solution resulted that soon set to a solid crystalline magma. The mixture was heated for 15 min. on a water bath, then neutralized with acetic acid and taken up in water and ether. Crystallization from alcohol gave 2.4 g. of *ethyl 3-benzoyl-1-hydroxy-4-phenyl-2-naphthoate*, IV, faintly tan prisms, m.p. 120–121°. The compound gave a deep blue color with alcoholic ferric chloride; its yellow sodium salt was somewhat soluble in water.

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.8; H, 5.09. Found: C, 78.7; H, 5.11.

Saponification by boiling IV with excess 5% sodium hydroxide for 1 hr. gave *3-benzoyl-1-hydroxy-4-phenyl-2-naphthoic acid* in quantitative yield, nearly colorless needles from dilute acetic acid that sintered at 195° and melted at 215–217° with effervescence; alcoholic ferric chloride gave a deep green color that became blue on addition of water.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.2; H, 4.38. Found: C, 77.7; H, 4.47.

Compound V. When 0.4 g. of the above acid was heated at 220° for 5 min. it was converted into *3-benzoyl-4-phenyl-1-naphthol*, V, faintly yellow prisms from toluene, m.p. 226° with previous sintering. The sodium salt was bright yellow, difficultly soluble in cold water.

Anal. Calcd. for $C_{23}H_{16}O_2$: C, 85.2; H, 4.97. Found: C, 85.0; H, 5.01.

Methylation of the phenol was effected with methyl sulfate in 5% aqueous sodium hydroxide; the resulting *3-benzoyl-1-methoxy-4-phenylnaphthalene* formed coarse colorless plates from alcohol, m.p. 148–149°.

Anal. Calcd. for $C_{24}H_{18}O_2$: C, 85.2; H, 5.36. Found: C, 85.0; H, 5.37.

Compound VII. A solution of 15 g. of diphenylitaconic acid in 450 ml. of hot 10% sodium hydroxide was treated with 30 g. of Raney alloy in portions, then boiled for 30 min. and filtered. Addition of a concentrated solution of 20 g. of barium chloride dihydrate in hot water gave an easily filterable precipitate of the barium salt, less soluble in hot than cold water. This was removed and boiled for 15 min. with 150 ml. of water containing 25 ml. of hydrochloric acid. Cooling gave 14.9 g. of pure benzhydrylsuccinic acid, needles m.p. 180–183°; the product gave no color with concd. sulfuric acid (unreduced diphenylitaconic acid gives a deep green).

The aluminum complex which resulted when the reduction mixture from 10 g. of diphenylitaconic acid was poured into excess hot hydrochloric acid was dried and boiled for 1 hr. with 50 ml. of methanol containing 5 ml. of sulfuric acid. Water and ether were added, and the ether solution was extracted with dilute sodium carbonate. This gave 5.8 g. of *methyl hydrogen benzhydrylsuccinate*, needles from ethyl acetate-ligroin, m.p. 150–152°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.08. Found: C, 72.3; H, 6.11.

Methyl benzhydrylsuccinate remained in the ether, and separated from 60–68° ligroin (b.p. 60–68°) in the form of prisms (3.0 g.), m.p. 84–85°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.45. Found: C, 73.2; H, 6.70.

Saponification of both the acid ester and the neutral ester gave benzhydrylsuccinic acid.

Cyclization of 8.4 g. of benzhydrylsuccinic acid by the method of Hewitt[5] gave 7.3 g. of crude 1-phenyl-4-oxo-1,2,3,-4-tetrahydro-2-naphthoic acid (VIII), and when this was boiled for 1 hr. with 35 ml. of methanol containing 3 ml. of sulfuric acid it gave 4.5 g. of pure *methyl ester*, coarse needles from methanol, m.p. 115–117°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.1; H, 5.75. Found: C, 77.1; H, 5.77.

Compound IX. When a solution of 4.5 g. of the preceding ester in 10 ml. of benzene was treated with 2.6 g. of bromine, rapid reaction took place with evolution of hydrogen bromide. The solvent was removed and the crystalline residue was taken up in 30 ml. of collidine and boiled for 4 min. Collidine was then removed with dilute hydrochloric acid and the resulting *methyl 4-hydroxy-1-phenyl-2-naphthoate* was crystallized from methanol, giving 3.8 g. of hexagonal plates, m.p. 173–174°,[6] that fell to a powder on drying.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.07. Found: C, 77.7; H, 5.18.

Methylation of the above ester with excess methyl sulfate in aqueous alkali gave *methyl 4-methoxy-1-phenyl-2-naphthoate*, colorless needles from 80% acetic acid, m.p. 118–119°; yield 86%.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.0; H, 5.52. Found: C, 77.6; H, 5.48.

A solution of 1.5 g. of the methoxy ester and 0.7 g. of sodium hydroxide in 6 ml. of glycol was boiled for 1 min., then diluted with water and acidified. The resulting *4-methoxy-1-phenyl-2-naphthoic acid*, IX, formed colorless prisms from acetic acid, m.p. 217–219°; yield 1.4 g.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.07. Found: C, 77.9; H, 5.18.

Compound. X. When a suspension of 1.4 g. of the methoxy acid in 5 ml. of benzene containing 1.2 ml. of thionyl chloride was boiled for 5 min., a clear solution resulted. Benzene and excess thionyl chloride were then removed at 100° under reduced pressure, and the remaining crystalline acid chloride was redissolved in 10 ml. of benzene and shaken with 10 ml. of concd. ammonium hydroxide for 10 min. The product was removed by filtration and recrystallized from alcohol giving 1.35 g. of *4-methoxy-1-phenyl-2-naphthamide*, colorless needles, m.p. 210–212°.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 78.0; H, 5.45. Found: C, 77.8; H, 5.38.

The amide dissolved when it was boiled with thionyl chloride in benzene, but subsequent addition of water gave it back unchanged. In order to prepare *4-methoxy-1-phenyl-2-naphthonitrile* X, 1.1 g. of the amide was boiled with 5 ml. of phosphorus oxychloride for 10 min. Volatile materials were then removed at 100° under reduced pressure, and the residue was treated with water and benzene. A small amount of black amorphous substance was removed by filtration, and the product was crystallized from acetic acid, giving pink needles, m.p. 162°; yield 1 g.

Anal. Calcd. for $C_{19}H_{13}NO$: C, 83.4; H, 5.05. Found: C, 83.2; H, 5.12.

A solution of 0.9 g. of the nitrile in 5 ml. of benzene was added to ethereal phenylmagnesium bromide prepared from 0.5 g. of magnesium. No apparent reaction took place, but after the mixture had been boiled for 30 min. a dense white precipitate formed. The mixture was then shaken with iced

(5) C. L. Hewitt, *J. Chem. Soc.*, 596 (1936).

(6) Reported m.p. 174–175°, Borsche and Kettner, *Ann.*, **526**, 1 (1936).

hydrochloric acid, and the resulting *4-methoxy-1-phenyl-2-naphthylphenylketimine hydrochloride* was removed by filtration. To remove bromide anion, the salt was dissolved in alcohol and made basic with ammonium hydroxide. Addition of water then gave a colorless oil which was taken up in ether and reconverted to the hydrochloride by shaking with dilute hydrochloric acid. The salt was nearly insoluble in hot water, ethyl acetate, or benzene. It was easily soluble in chloroform and crystallized from a mixture of methanol and ether as deep yellow prisms, m.p. 235–240°; yield 1 g.

Anal. Calcd. for $C_{24}H_{20}ClNO + CH_3OH$: C, 74.0; H, 5.92. Found: C, 74.11; H, 5.37.

The ketimine salt was quite resistant to hydrolysis, but when 0.6 g. of it was boiled for 15 min. with 5 ml. of 50% acetic acid containing a few drops of hydrochloric acid, it gave 0.5 g. of 3-benzoyl-1-methoxy-4-phenylnaphthalene, identical (mixed melting point and infrared spectrum) with the compound obtained before.

Acknowledgment. The author thanks Mrs. O. Hamerston for analytical results.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Cleavage of 10-Substituted 1,2-Benzanthracenes[1-3]

FRANK A. VINGIELLO AND THOMAS J. DELIA

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The acid-catalyzed cleavage of 10-substituted 1,2-benzanthracenes has been observed and investigated.

Since a recent publication[4] noted the physiological activity of 10-phenyl-1,2-benzanthracene, and since 10-methyl-1,2-benzanthracene is a carcinogen, we thought it would be interesting to prepare 10-cyclohexyl-1,2-benzanthracene and have it screened for possible carcinogenic or carcinolytic activity. In view of the extensive use made of aromatic cyclodehydration reactions to prepare *meso*-substituted 1,2-benzanthracenes,[5] we chose to attempt the preparation of 10-cyclohexyl-1,2-benzanthracene (IIa) *via* the aromatic cyclodehydration of 2-(1-naphthylmethyl)phenyl cyclohexyl ketone (Ia). This ketone was prepared by the Grignard reaction between cyclohexylmagnesium bromide and 2-(1-naphthylmethyl)benzonitrile[6] followed by acid hydrolysis.[7] The first attempts at cyclization of the ketone involved the use of the often used boiling hydrobromic–acetic acid mixture. Although 14% of the expected 10-cyclohexyl-1,2-benzanthracene (IIa) was obtained, 32% of 1,2-benzanthracene (III) was also isolated. Apparently cleavage of the cyclohexyl group occurred during the course of the reaction. We also observed cleavage in the anthracene series. The acid-catalyzed cyclization of 2-benzylphenyl cyclohexyl ketone gave 29% of the expected hydrocarbon, 9-cyclohexylanthracene, and 23% of anthracene. Several instances of the loss of aromatic groups had been observed previously in this laboratory. Vingiello and Borkovec[8] reported cleavage during the attempted preparation of some di-*ortho* substituted *meso* phenyl-1,2-benzanthracenes and Vingiello and Stevens[4] reported loss of a methoxyphenyl group when 2-(1-naphthylmethyl)-4′-methoxy benzophenone or 2-(1-naphthylmethyl)-2′-methoxy diphenyl ketimine hydrochloride was treated with a strong acid. In either case, 1,2-benzanthracene was the only product isolated. Just recently Zajac[9] observed cleavage during the acid-catalyzed cyclization of 2-(2-naphthylmethyl)-2′-chloro-5′-methylbenzophenone which gave 1,2-benzanthracene. Bradsher and co-workers[10] reported the loss of an isopropyl group during the acid-catalyzed cyclization of ketones to give 9,10-dialkylphenanthrenes. They also showed that an olefin oxide which might be expected to yield 9-isopropyl-10-isobutylphenanthrene afforded instead 9-isobutylphenanthrene. They suggested that the loss of the isopropyl group in 9-isopropyl-10-alkylphenanthrenes was probably due to the strain introduced by crowding the two groups into the rather restricted space at the 9- and 10-positions. Our observations in

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(1) This paper has been abstracted in part from the Master's thesis of Thomas J. Delia presented to the Virginia Polytechnic Institute in 1959.

(2) This investigation was supported in part by a research grant (S-73) from the Bureau of State Services (Division of Sanitary Engineering Services and Division of Special Health Services) of the National Institutes of Health, Public Health Service.

(3) Presented before the Chemistry Section at the Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., November 1960.

(4) F. A. Vingiello and R. K. Stevens, *J. Am. Chem. Soc.*, **80**, 5256 (1958).

(5) See F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **78**, 1240 (1956), and references listed there.

(6) F. A. Vingiello, A. Borkovec, and J. Shulman, *J. Am. Chem. Soc.*, **77**, 2320 (1955).

(7) Again it was found that the yield of the ketone was 15–20% higher if the ketimine hydrochloride was not isolated; see Ref. 5.

(8) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **78**, 3205 (1956).

(9) W. W. Zajac, Jr., Ph.D. Dissertation, Virginia Polytechnic Institute, 1959.

(10) C. K. Bradsher and D. J. Beavers, *J. Am. Chem. Soc.*, **78**, 3193 (1956); C. K. Bradsher and W. J. Jackson, Jr., *J. Am. Chem. Soc.*, **76**, 4140 (1954); S. T. Amore, Ph.D. Dissertation, Duke University, 1944.

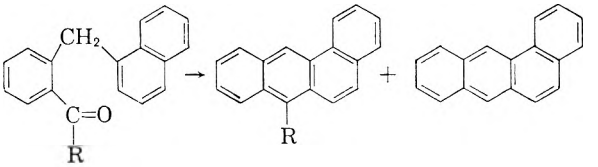
the benzanthracene series apparently involve steric strain resulting from interactions of the substituent in the 10- position with the 4- and 5-positions in the ring system itself rather than with another substituent. It is interesting to note that no cleavage was reported when 6- and 7-isopropyl-1,2-benzanthracenes were prepared by a method involving cyclization with concentrated sulfuric acid[11] nor was cleavage reported when 7-isopropenyl-1,2-benzanthracene was prepared by a method involving cyclization with hydrochloric and acetic acid.[12] This is in accord with the fact that the 6- and 7-positions are not as hindered as in the 10-position in 1,2-benzanthracene. Colonge and Bonnard[13] reported an interesting preparation of 9-isopropylanthracene which involved a variation of Bradsher's[14] original aromatic cyclodehydration reaction. They cyclodehydrated 6-isopropionyl-2,3,4,5-tetrahydrodiphenylmethane with the usual hydrobromic–acetic acid mixture and obtained 9 - isopropyl - 1,2,3,4 - tetrahydroanthracene which they dehydrogenated with sulfur to obtain the desired 9-isopropylanthracene. The geometry of the tetrahydro compounds is such as probably to afford less strain accounting for the lack of cleavage (loss of the isopropyl group). The sulfur is not acidic enough to cleave the 9-isopropylanthracene.

Although the mechanism of the loss of the cyclohexyl group during cyclization is not clear, it has been established that 10-cyclohexyl-1,2-benzanthracene is cleaved quantitatively to 1,2-benzanthracene when heated for twenty-four hours with the usual hydrobromic-acetic acid mixture. Similar treatment with only acetic acid results in recovery of the starting hydrocarbon.

Bradsher and Beavers[10] have mentioned that the acid-catalyzed dealkylation of an aromatic hydrocarbon appears to be a rare phenomenon. We sought therefore to gain further information regarding the cleavage by synthesizing a group of ketones the study of whose cyclization might give information regarding two factors thought to be important in the cleavage; namely, stability of the carbonium ion of the departing group and steric requirement of the departing group.

An interesting comparison was made regarding the stability of 10-cyclohexyl-1,2-benzanthracene (IIa), 10-phenyl-1,2-benzanthracene (IIc), and 9-benzylanthracene[15] towards a boiling mixture of hydrobromic and acetic acids. Although 10-cyclohexyl-1,2-benzanthracene was cleaved quantitatively to 1,2-benzanthracene, 10-phenyl-1,2-benzanthracene and 9-benzylanthracene were recovered unchanged. Since the cyclohexyl and phenyl groups impose essentially the same steric strain on the aforementioned 4- and 5-positions it may be that stability of the departing carbonium ion is important. Although we feel that the ability of the departing group to form a stable carbonium ion is important, it apparently is not a sufficient condition for cleavage since 9-benzylanthracene, which might be expected to form the very stable benzyl carbonium ion,[16] is not cleaved by the usual boiling hydrobromic–acetic acid mixture.

CHART I



Ia. R = Cyclohexyl
Ib. R = *n*-Propyl
Ic. R = *i*-Propyl
Id. R = *t*-Butyl

IIa. R = Cyclohexyl
IIb. R = *n*-Propyl
IIc. R = Phenyl

III

In an attempt to gain further information regarding the cleavage of 10-substituted 1,2-benzanthracenes we prepared the three ketones Ib–Id and studied their reaction with the usual hydrobromic–acetic acid mixture. The ketone Ib gave only 9-*n*-propyl-1,2-benzanthracene with no evidence of cleavage. The ketone Ic gave only cleavage product, 1,2-benzanthracene. The ketone Id gave a very small amount, *ca.* 3%, of cleavage product, 1,2-benzanthracene, accompanied by about half of the unchanged starting ketone. This last experiment is quite revealing. Although not constituting a proof, it suggests strongly that the hydrocarbon was cleaved and not the ketone.

Cleavage can be effected by other acids such as alumina and phenyl acid phosphate. The results of the cyclization experiments are summarized in Table I together with the results of the cleavage experiments.

These data indicate that both alkyl and aryl groups may be lost from aromatic polynuclear compounds as a result of an acid-catalyzed reaction and that the stability of the carbonium ion of the departing group as well as steric strain may facilitate the cleavage.

EXPERIMENTAL[17,18]

2-(1-Naphthylmethyl)phenyl cyclohexyl ketone (Ia). A Grignard reagent was prepared from 11.0 g. (0.45 mole)

(11) J. W. Cook, *J. Chem. Soc.*, 456 (1932).
(12) J. W. Cook, *J. Chem. Soc.*, 1408 (1933).
(13) J. Colonge and L. Bonnard, *Compt. rend.*, 240, 2540 (1955).
(14) C. K. Bradsher, *J. Am. Chem. Soc.*, 62, 486 (1940).
(15) The availability of this compound in our laboratory led us to use it rather than the corresponding benzanthracene. The steric situation regarding the 4- and 5-positions is identical in both compounds. See C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, 71, 1434 (1949) for the preparation of 9-benzylanthracene. When 9-cyclohexylanthracene was heated with the usual acid mixture only anthracene was recovered.
(16) E. A. Alexander, *Principles of Ionic Organic Reactions*, Wiley, New York, 1950, p. 42.
(17) All melting points are corrected.
(18) All analyses were carried out by Geller Microanalytical Laboratories, Bardonia, N. Y.

TABLE I

CYCLIZATION AND CLEAVAGE EXPERIMENTS

Starting Compound	Reaction Conditions	Product(s) (%)
Ia	HBr, HAc, reflux, 18 hr.	IIa (26); III (57)
Ia	Heated in Carius tube, 180°, 3 hr.	III (32)
Ia	Alumina,[a] 200° (1 mm.), 3 hr.	IIa (9); III (18)
Ia	Alumina,[b] 200° (1 mm.), 1 hr.	Ia (32)
Ia	Phenyl acid phosphate,[c] 130°, 2 hr.	III (5)
Ia	Polyphosphoric acid, 110°, 24 hr.	Ia (40)
Ib	HBr, HAc, reflux, 24 hr.	IIb (35)
Ic	HBr, HAc, reflux, 2 hr.	III (19)
Ic	HBr, HAc, reflux, 24 hr.	III (33)
Id	HBr, HAc, reflux, 48 hr.	III (3); Id (40)
2-Benzylphenyl cyclohexyl ketone	HBr, HAc, reflux, 24 hr.	9-Cyclohexylanthracene (29), Anthracene (23)
IIa	HBr, HAc, reflux, 24 hr.	III (quant.)
IIc	HBr, HAc, reflux, 24 hr.	IIc (quant.)
9-Cyclohexylanthracene	HBr, HAc, reflux, 24 hr.	Anthracene (47)
9-Benzylanthracene	HBr, HAc, reflux, 24 hr.	9-Benzylanthracene (quant.)

[a] Alcoa's activated alumina, H-151, mesh 1/8, dried at 225° (1 mm.) for 2 hr. before use. [b] Fisher's adsorption alumina, 80–200 mesh, dried at 225° (1 mm.) for 2 hr. before use. [c] This was kindly given to us by the Virginia-Carolina Chemical Corp., Richmond, Va. This material is a mixture of mono- and di-hydrogen phosphate esters containing varying amounts of polyphosphates.

of magnesium turnings and 84.4 g. (0.52 mole) of cyclohexyl bromide in 300 ml. of anhydrous ethyl ether. When the Grignard reagent was formed, the ether was removed by distillation and replaced with approximately 50 ml. of anhydrous toluene. Then 40.0 g. (0.16 mole) of 2-(1-naphthylmethyl)benzonitrile in 250 ml. of anhydrous toluene was added dropwise with stirring. The mixture was heated under reflux overnight. It was then decomposed with 86 ml. of an ice-cold 20% ammonium chloride solution. The organic layer was separated and heated under reflux for 24 hr. with 150 ml. of dilute sulfuric acid (1:2). After allowing the solution to cool, the organic layer was washed with water, 10% sodium carbonate, and again with water. The organic layer was then dried, concentrated, and distilled under reduced pressure. The fraction distilling between 248–250° at 2 mm. was collected as a colorless oil; yield 41 g. (76%).

An analytical sample was prepared by redistilling the oil and collecting the sample from the middle fraction; b.p. 223–224° at approximately 1 mm.

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.77; H, 7.37. Found: C, 87.97; H, 7.70.

The other new ketones of type I were prepared in a similar manner and are listed in Table II with their respective oiling ranges and analytical data.

TABLE II

NEW KETONES I

Ketone	Yield, %	B.P.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	76	223–224	1.0	87.77	87.97	7.37	7.70
Ib	65	195–196	1.5	87.48	87.81	6.99	7.46
Ic	75	182–184	1.0	87.48	87.67	6.99	7.11
Id	35	189–196	1.0	87.38	88.02	7.34	6.94

2-Benzylphenyl cyclohexyl ketone. (By F.A.V.). This compound was prepared using substantially the procedure given above for Ia. The reaction between cyclohexylmagnesium bromide and 2-benzylbenzonitrile[16] gave the desired product (70%), b.p. 194–197° (3 mm.).

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 85.92; H, 7.99.

Cyclization of 2-(1-naphthylmethyl)phenyl cyclohexyl ketone (Ia). A mixture of 10.0 g. of the ketone, Ia, 50 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was heated under reflux for 18 hr. On cooling white plates formed which were filtered and chromatographed on a column packed with alumina[19] using 30–60° petroleum ether as the eluent. This gave 3.98 g. (57%) of 1,2-benzanthracene identified by means of its ultraviolet spectrum, melting point, and melting point of the picrate.

The filtrate was neutralized with concd. sodium hydroxide and extracted with benzene. The benzene solution was washed with water, dried over calcium chloride, concentrated, and the resulting solid recrystallized from 95% ethanol giving 2.43 g. (26%) of 10-cyclohexyl-1,2-benzanthracene; m.p. 119–121°.

Anal. Calcd. for $C_{24}H_{22}$: C, 92.86; H, 7.14. Found: C, 93.01; H, 6.65.

Samples of pure 10-cyclohexyl-1,2-benzanthracene have been submitted to appropriate laboratories for screening for possible carcinogenic and/or carcinolytic activity.

The ultraviolet spectrum, recorded with a Perkin-Elmer Model 3000 Spectracord, 1 cm. path, of 10-cyclohexyl-1,2-benzanthracene in 95% ethanol was similar to the spectrum of 1,2-benzanthracene, as was to be expected, and does not appear worthy of further note.

Cyclization of 2-benzylphenyl cyclohexyl ketone. This experiment was conducted essentially as was the previous one. Two grams of the ketone gave 0.30 g. of anthacene and 0.55 g. of 9-cyclohexylanthracene.[20]

Anal.[21] Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 8.10.

As noted for the analogous situation regarding 10-cyclohexyl-1,2-benzanthracene, the ultraviolet spectrum of 9-cyclohexylanthracene[22] is similar to that of anthracene.

(19) The column was 18 mm. × 370 mm. and was packed with Fisher's adsorption alumina, 80–200 mesh.

(20) This compound was previously prepared by Willemart, *Compt. rend.*, **207**, 532 (1938) who reported neither a yield nor analytical data for the hydrocarbon. In our hands, his method, which involved the reaction between cyclohexylmagnesium bromide and anthrone gave an 8% yield of 9-cyclohexylanthracene.

(21) The analytical sample was prepared by Mr. H. H. Hannabass.

(22) The spectrum was recorded by Mr. J. Shulman.

The other acid-catalyzed cyclizations were carried out in a similar way. The results are summarized in Table I.

Cleavage of 10-cyclohexyl-1,2-benzanthracene (IIa). A mixture of 0.3 g. of the hydrocarbon, IIa, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 24 hr. On cooling, white plates formed which were filtered and recrystallized from 95% ethanol yielding white crystals, m.p. 157–160°, identified as 1,2-benzanthracene (100%).

The other acid-catalyzed cleavage experiments were carried out in a similar way. The results are summarized in Table I.

BLACKSBURG, VA.

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

Ionization Constants of Derivatives of Fluorene and Other Polycyclic Compounds[2]

PRESTON H. GRANTHAM, ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

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Potentiometric and spectrophotometric methods were applied to the determination of the apparent ionization constants, in 70% ethanol, of 120 polycyclic aromatic compounds. These were phenols, carboxylic acids, and chiefly amines derived from naphthalene, biphenyl, phenanthrene, chrysene, pyrene, dibenzofuran, dibenzothiophene, carbazole, diphenyl sulfide, diphenylmethane, and especially from fluorene. The effect of the substituent groups *N,N*-dimethyl-, nitro-, keto-, fluoro-, chloro-, bromo-, iodo-, acetamido-, methoxy-, hydroxy-, and amino- was established. The results are discussed in terms of inductive and steric interactions, resonance and hydrogen bonding in these molecules in relation to their structure.

Useful insight into the chemical and physical properties of molecules in the ground state can be derived from a comparative study of the ionization constants[3] of such molecules.[4,5] Relatively few compounds of the polynuclear aromatic type have been investigated in this regard. It is the purpose of this paper to present and discuss data in this field, especially in respect to derivatives of biphenyl, fluorene, and certain other tri- and tetracyclic compounds. The conclusions derived proved helpful in gaining a better understanding of the intimate molecular structure of the compounds, particularly in terms of inductive and resonance effects in the polynuclear systems. In addition, this study furnished information on the possible relationship of the ionization constants of some of these compounds to their carcinogenicity.[6] In a number of other cases a connection has been found between the pharmacologic activity in a series of related chemicals and their ionization constants.[7] In those instances the specific property assayed depended on whether the ionized or the nonionized species existed and was active at the *p*H of the living host, *i.e.* around *p*H 7.4.

The method used for the determination of the *p*K value involved the potentiometric measurement of the *p*H of a solution containing exactly equivalent amounts of a compound and its salt. This relatively simple procedure, while not of universal applicability,[7a] was found to be sufficiently accurate with the pure substances studied. The known literature values of some of the chemicals examined again in the present study (*cf.* footnotes to Tables) were reproduced without difficulty. In addition, the results obtained were corroborated in a number of cases by the spectrophotometric method. The values observed by this method were within the experimental error of those with the potentiometric procedure if the *p*K fell within the range of 3.50 to 11.80. The *p*K values of compounds outside this range were determined by the spectrophotometric method.

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

(2) Presented in part before the 125th Meeting of the American Association for the Advancement of Science, Washington, D. C., December 1958.

(3) In this paper all ionization constants refer to the apparent acid constant, pK_a'.

(4) In order to limit the references to a reasonable number, comprehensive reviews or monographs will be cited wherever possible. Similarly, references to the preparation of known compounds will generally not be given. J. H. W. will gladly supply information on particular compounds upon inquiry by interested readers.

(5) (a) H. C. Brown, D. H. McDaniel, and O. Häfliger in E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, New York, 1955, pp. 567–662. (b) L. N. Ferguson, *Electron Structures of Organic Molecules*, Prentice-Hall, New York, 1952, pp. 189–200. (c) A. Albert, *Heterocyclic Chemistry*, Oxford University Press, Oxford, England, 1959, pp. 336–346. (d) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956, pp. 46–80. (e) G. W. Wheland, *Resonance in Organic Chemistry*, Wiley, New York, 1955, pp. 337–376. (f) B. Pullman and A. Pullman, *Les Théories Électroniques de la Chimie Organique*, Masson et Companie, Paris, 1952, pp. 316–322. (g) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, Chapters VII and IX.

(6) For reasons of chemical stability the acetyl derivatives, such as *N*-2-fluorenylacetamide, are usually tested. However, animals possess enzyme systems capable of removing the acetyl group. In those cases where both amine and acetyl derivatives were examined the biological effects were usually similar. See E. K. Weisburger, and J. H. Weisburger, *Advances in Cancer Research*, **5**, 331 (1958).

(7) (a) A. Albert, *Pharmacol. Revs.*, **4**, 136 (1952); (b) D. Libermann, *Bull. soc. chim. biol.*, **34**, 1026 (1952); (c) T. C. Butler, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 367 (1955); (d) J. J. Burns, T. F. Yu, P. Dayton, L. Berger, A. B. Gutman, and B. B. Brodie, *Nature*, **182**, 1162 (1958).

Owing to the low solubility in water of most of the compounds, the data by the potentiometric procedure were obtained in 70% ethanol solution, usually at a concentration of 5.26×10^{-3} moles/l. Since the spectrophotometric method gave satisfactory results on more dilute solutions, both water and 70% ethanol were used as solvents in a comparative study involving some of the compounds.

EXPERIMENTAL[8]

Materials. Many of the compounds studied were available to us from previous work (shown as *W* in Tables). Others were kindly donated by Dr. F. E. Ray (shown as *R*), University of Florida, and by Drs. J. A. and E. C. Miller (*M*), University of Wisconsin, who also forwarded several of the compounds prepared by Dr. T. L. Fletcher (*F*), University of Washington, to all of whom we are greatly indebted. A few compounds were commercial (*C*) samples. Some of the amines were supplied as the acetyl derivatives. In these cases hydrolysis by 6–12*N* aqueous or ethanolic hydrochloric acid followed by isolation and recrystallization furnished the desired amines. Purity of the compounds was established by melting point determination, spectroscopy, and other appropriate methods.

Preparation of new compounds. N,N-Dimethylation of isomeric fluorenamines. This reaction was performed as described by Fletcher, *et al.*[9] Briefly, 5 mmoles of the fluorenamine and 6.7 mmoles (about 0.8 ml.) of trimethylphosphate (Aldrich Chemical Company, Milwaukee) were heated progressively in an oil bath at 195° and maintained thereat for 1 hr. Upon cooling to 100°, 6 ml. of 4.2*N* sodium hydroxide solution was added and the mixture refluxed another hour. After addition of 20 ml. of cold water the desired compound was isolated as described below for the various isomers.

N,N-Dimethyl-1-fluorenamine. The oily reaction mixture was extracted with ether. The ether solution was washed to neutrality, dried, and the solvent was distilled off. The residue was distilled *in vacuo* (3–5 mm.) yielding a yellowish liquid which turned to a glass at −80° but refused to crystallize at room temperature. However, conversion to the hydrochloride afforded 1.65 mmoles of white needles, which melted at 192.5–193.5° after four crystallizations from 6*N* hydrochloric acid.

Anal. Calcd. for $C_{15}H_{16}NCl$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.46; H, 6.51; N, 5.82.

N,N-Dimethyl-3-fluorenamine. Proceeding as with the 1-isomer, the vacuum distillation gave 2.95 mmoles of a yellowish solid, m.p. 59–62°. Four crystallizations from 2 ml. of petroleum ether (b.p. 30–60°) (in a freezer at −15°) left almost white crystals in clusters, m.p. 62–63°.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.19; H, 7.17; N, 6.66.

N,N-Dimethyl-4-fluorenamine. After the vacuum distillation, 3.1 mmoles of pale yellow liquid which crystallized on standing (m.p. about 30°) was obtained. This material was sublimed *in vacuo*. The sublimate, treated with Norit in dilute hydrochloric acid solution, furnished 2.5 mmoles of white powder, m.p. 34–36°, after neutralization with sodium bicarbonate solution. Four further crystallizations from 1–2 ml. of petroleum ether (at −15°) raised the m.p. to 37°.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.14; H, 7.16; N, 6.92.

4-Fluorenol. An ice-cold solution of 0.5 g. of 4-fluorenamine in 10 ml. of acetic acid, 10 ml. of water, and 5 ml. of concentrated sulfuric acid was diazotized with a solution of 0.3 g. of sodium nitrite in 3 ml. of water. After 0.5 hr., 0.7 g. of urea was added, and the mixture was stirred 15 min. longer. The solution of the diazonium salt was introduced dropwise into 110 ml. of refluxing 3.5*N* sulfuric acid. Upon cooling 0.15 g. (range 0.09–0.27 g. in various runs) of alkali-soluble material, m.p. 107–109° was obtained. Four crystallizations of 0.57 g. (combined material obtained in several experiments) from water afforded 0.12 g. of pale yellow crystals, m.p. 110–110.5°. The slight coloration was not removed by vacuum sublimation. $\lambda_{max}^{C_2H_5OH}$ 258.5 mμ (ε 18,200), 263.5 (16,400), 268.5 (21,000), 286.5 (7,600), 294 (8,700), and 306 (5,300): λ_{min} 241 (6,600), 262.5 (16,300), 265.5 (16,200), 279 (5,800), 290.5 (6,600), and 302.5 (4,900).

Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 86.00; H, 5.80.

4-Bromofluorene. Incidental to the preparation above, the diazonium solution from 0.73 g. of 4-fluorenamine was also decomposed in the presence of cuprous bromide in the usual manner. The resulting oil was taken up in benzene, washed with alkali and water, and percolated through an alumina column. The resulting waxy material was sublimed *in vacuo* (bath temperature 50°) and the sublimate crystallized from methanol-water to give 96 mg. of cream-colored crystals, m.p. 57–58°. Two further crystallizations from methanol left 15 mg. of white prisms, m.p. 60–61°, of 4-bromofluorene (Suzuki, *et al.*[10] reported m.p. 61°).

7-Nitro-2-fluorenecarboxylic acid. A solution of 3 g. of 2-fluorenecarboxylic acid in 40 ml. of glacial acetic acid was cooled to 40°, and 15 ml. of yellow fuming nitric acid (d = 1.49) was added. The mixture was stirred and heated to 100°. At 95° all dissolved and a reaction occurred at 100–105°. The temperature was kept at this level for 5 min., whereupon a precipitate began appearing. The pale yellow material, wt. 1 g., melted at 320–330° (Kofler block). Recrystallization from acetic acid (250 ml./g.) or better dimethylformamide-water (3:1) yielded small pale yellow

(8) Microanalyses were performed by the staff of the NIH Microanalytical Laboratory to whom we are grateful. Competent technical assistance was rendered by Mrs. A. Parker.

(9) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

(10) K. Suzuki, S. Kajigaeshi, and S. Kato, *Yuki Gosei Kagaku Kyōkai Shi*, **16**, 304 (1958). We are greatly indebted to Dr. Suzuki for valuable discussion and a sample of his material which showed no depression in melting point and identical infrared spectrum with the compound described here. The reason for repeating this particular experiment at this time was the controversy regarding the correct melting point of 4-bromofluorene. H. F. Miller and G. B. Bachman, *J. Am. Chem. Soc.*, **57**, 2447 (1935), reported a melting point of 165°. E. D. Bergmann and E. Loewenthal, *Bull. soc. chim. France*, 1952, 66, found 170°, and J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *J. Am. Chem. Soc.*, **74**, 4540 (1952), gave m.p. 112°. Suzuki, *et al.* established that the compound, m.p. 165°, in the hands of Miller and Bachman was really 2,7-dibromofluorene, m.p. 165°. Furthermore, it may be noted that Suzuki *et al.* observed a melting point of 167–168° for 4-bromo-9-fluorenol (although Miller and Bachman attributed a melting point of 149–150° to this compound). Thus, it is possible that Bergman and Loewenthal dealt with the 9-hydroxy derivative, considering the melting point of their sample and its method of preparation, a relatively short Clemmensen reduction giving a poor yield of product crystallizing from benzene.

Re-examination of our earlier preparation of the supposed 4-bromofluorene, m.p. 112°, revealed that it was really 2-bromofluorene (lit. m.p. 113°) by mixed melting point with an authentic sample[11] and identity of their infrared curves. Our starting material was obviously contaminated with 2-isomer, and in view of the much lower solubility of the 2-bromofluorene, it was the material isolated in the extensive crystallization procedures used earlier. Hence, 4-bromofluorene has a melting point of 61°, as described for the first time by Suzuki *et al.*

needles, m.p. 335° (Kofler) with some sublimation at 310°. $\lambda_{max}^{70\%C_2H_5OH}$ 257 mμ (ε 9,060), 328 (22,700); λ_{min} 228.5 (5,280), 276 (5,340).

Anal. Calcd. for $C_{14}H_9NO_4$: C, 65.88; H, 3.55. Found: C, 65.59; H, 3.81.

A Schmidt reaction in sulfuric acid–chloroform gave 7-nitro-2-fluorenamine, orange material, m.p. 230°, proving the location of the nitro group in the carboxylic acid.

7-Methoxy-3-nitro-2-fluorenamine. One gram of *N*-(7-methoxy-2-fluorenyl)acetamide in 100 ml. of acetic acid was nitrated by the dropwise addition, with efficient stirring, of 2 ml. of a 1:1 mixture of water and concentrated nitric acid at 20°. After continued stirring for 1 hr. the solution was poured on ice yielding 0.99 g. of a yellowish-orange precipitate, m.p. 158–160°. This material was hydrolyzed by refluxing in 20 ml. of a 1:1 mixture of ethanol and 6*N* hydrochloric acid for 0.5 hr. The product was extracted with 150 ml. of 0.3*N* hydrochloric acid, removing the compound nitrated *ortho* to the methoxy group which, however, was not isolated in pure form. The insoluble red residue (0.3 g.) of 7-methoxy-3-nitro-2-fluorenamine melted at 202°. Crystallizations from ethanol-water or benzene–petroleum ether mixtures gave long red needles of the same melting point.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.93. Found: C, 65.84; H, 4.94; N, 10.62.

Standard solutions. A 0.15*N* solution of potassium hydroxide was prepared with carbon dioxide-free redistilled water and standardized against reagent grade potassium hydrogen phthalate by accepted techniques. Dilution of reagent grade hydrochloric acid with redistilled water and standardization against the potassium hydroxide solution afforded 0.15*N* hydrochloric acid. The ethanol was a benzene-free, fermentation grade alcohol ("Pharmco" brand, 200 proof) obtained from Publicker Industries, Philadelphia.

Instruments. A Cambridge *p*H meter, model R, equipped with glass and saturated calomel electrode assemblies was used for *p*H measurements. The instrument was calibrated against standard buffers of *p*H 4, 7, and 9. The temperature of the solutions was maintained at 25° by partial submersion of the vessel in a thermostated bath.

Ultraviolet and visible spectra were recorded on a Cary spectrophotometer, model 14, employing 1-cm. quartz cells. The temperature of the cell compartment was kept constant at the desired temperature (*cf.* Table II) by circulating water from a bath.

Procedure for the potentiometric determination of the apparent ionization constant. The compound (15 micromoles, usually 2–4 mg.) was weighed accurately into the titration vessel, the top of a Parr style weighing bottle (Kimble Glass Co. weighing bottle stopper no. 15180, with a 24/12 standard joint). After solution in 2.0 ml. of ethanol, by gentle warming if required, 0.8 ml. of carbon dioxide-free redistilled water and 0.5 equivalent (50 microliters, micropipet) of 0.15*N* acid (for amino groups) or base (for carboxy, hydroxy, groups, or amine salts) was added, giving a 70% ethanol solution. The *p*H of this solution was accurately determined at 25°. Instrumental stability was checked by reading the appropriate standard buffers before and after each sample. Duplicate runs for each compound were performed and agreement was within 0.05 *p*H units. The ionic strength of the solutions was not taken into account, but little effect is anticipated with the dilute solutions used.[12]

A few compounds insoluble under these conditions were studied in more dilute solution (2.0–2.5 millimolar).

Ionization constants by the spectroscopic method. The method devised by Flexser, Hammett and Dingwall[13] and used recently in an extensive investigation of a series of azo dyes by Sawicki and Ray[cf. 14,15] was adapted to this study. Three spectra of the solutions of the ionized, nonionized, and a mixture of these forms of a compound were run sequentially on a Cary instrument so that the wave-length scale on the three curves coincided. In this manner the isosbestic points and the general suitability of the curves were readily apparent.[16] Calculations of the ionization constant based on the absorbance of the compound at the three hydrogen ion concentrations with the aid of the equations given by the pre-cited authors, were performed at a number of wave lengths but not near the maxima or minima. The results so obtained showed little scatter for any compound if the proper *p*H values were selected.

RESULTS AND DISCUSSION

The value of the apparent ionization constant obtained at a concentration of approximately 5 mmoles per liter is well within the reliable range of the simplified micromethod described. Indeed, the data for representative compounds with an amino, hydroxy, and carboxy group show little deviation until considerably higher dilutions are employed (Table I). The variation of the constant is more sensitive to the concentration factor with compounds at the extremes of validity of the method, as might be expected owing to the larger influence of hydrolytic phenomena with the weaker acids and bases.

Ionization constants of fluorenamines. Table II presents the *p*K values of the isomeric fluorena-

TABLE I

IONIZATION CONSTANTS OF A COMPOUND WITH AN AMINO, HYDROXY, AND CARBOXY GROUP IN SOLUTIONS OF VARYING CONCENTRATIONS

Compound	Concentration, Mmoles × 10^{-3}/Ml.	pK_a'
2-Fluorenamine	10	4.30
	5	4.31
	2.5	4.32
	1.0	4.44
N-(7-Hydroxy-2-fluorenyl)-acetamide	20	11.59
	10	11.58
	5	11.58
	2.5	11.35
	2.0	11.35
9-Oxo-4-fluorenecarboxylic acid	20	4.98
	10	5.00
	5	5.00
	2.5	5.01
	2.0	5.00
	1.0	5.15

(11) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, 80, 4327 (1958).

(12) T. V. Parke and W. W. Davis, *Anal. Chem.*, 26, 642 (1954).

(13) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, 57, 2103 (1935).

(14) E. Sawicki and F. E. Ray, *J. Org. Chem.*, 19, 1686 (1954).

(15) J. M. Vandenbelt, C. Henrich, and S. G. Vanden Berg, *Anal. Chem.*, 26, 726 (1954).

(16) A few preliminary experiments were required to select the optimal conditions with a compound of unknown *p*K value. Footnotes to the appropriate Tables show the hydrogen ion concentration so determined for each compound, and used in the calculations.

TABLE II

IONIZATION CONSTANTS OF ISOMERIC FLUORENAMINES AND AMINOFLUORENOLS IN 70% ETHANOL AND IN WATER

	pK_a' of Amino Group				pK_a' of Hydroxy Group
Method	Potentiom.	Spectroscopic			Potentiom.
Temperature	25°	25°	25°	40°	25°
Solvent	70% C_2H_5OH	70% C_2H_5OH	H_2O	H_2O	70% C_2H_5OH
Compound[a]					
1-Fluorenamine	3.60	3.57[b]	3.87[f]	3.67	—
2-Fluorenamine	4.30	4.27[c]	4.64[g]	4.42	—
3-Fluorenamine	4.37	4.39[d]	4.82[h]	4.57	—
4-Fluorenamine	3.4	3.15[e]	3.39[f]	3.52	—
9-Fluorenamine	7.56	—	—	—	—
2-Amino-1-fluorenol	4.54	—	4.82[i]	—	11.25
7-Amino-1-fluorenol	4.38	—	4.63[i]	—	11.66
2-Amino-3-fluorenol	4.50	—	—	—	11.60
7-Amino-3-fluorenol	4.32	—	4.63[i]	—	11.9
2-Amino-5-fluorenol	4.59	—	4.73[i]	—	11.9
2-Amino-7-fluorenol	4.60	—	4.88[i]	—	11.8
2-Amino-9-fluorenol	3.88	—	—	—	—

[a] The last compound was supplied by *M*; all others came from this laboratory (*W*). [b] Conditions for this determination were: Alkaline form (*1*), 0.2 ml. of 2.5 millimolar solution in ethanol, 6.8 ml. of ethanol, and 3 ml. of water; acid form (*2*) substitute 1 ml. of 0.107 *N* hydrochloric acid and 2 ml. of water for 3 ml. of water; buffered form (*3*), same but 0.1 ml. hydrochloric acid and 2.9 of water, pH measured in final solution 3.32. Conditions for other compounds will be listed in an abbreviated manner, giving the pH of *3*, and where necessary, solutions used for *1* or *2*. [c] *3*, pH 4.37. [d] *3*, pH 4.56. [e] *3*, pH 3.29. [f] *3*, pH 2.99. [g] *3*, pH 4.20. [h] *3*, pH 4.34. [i] *3*, pH 4.26.

mines and aminofluorenols obtained by two different methods in water and 70% ethanol. The potentiometric and the spectrophotometric methods give very similar results where the pK is above 3.50 for the amino group. The potentiometric method as used here is not suitable below this value; a pH reading of 3.3 to 3.4 is always found irrespective of the true value of the constant, as determined by the spectrophotometric method (*cf.* subsequent tables).

The ionization constants are 0.14–0.43 (average 0.28) units higher in water as compared to 70% ethanol. This slight effect of solvent on the pK of the amino group has also been reported by others.[17, cf. 5] On the other hand, acidic groups are weakened considerably when going from water to 70% ethanol solution, as evidenced by the relatively high pK values for the phenolic hydroxy group and the carboxylic acids (*see* Tables). This fact, likewise, has been observed in other series of compounds.[5]

A rise in temperature from 25 to 40° decreases the pK of 1-, 2-, and 3-fluorenamine by 0.20, 0.22, and 0.25 units, which corresponds to heats of ionization 5.7, 6.3, and 7.1 kcal./mole, respectively, values of the same order of magnitude as that reported by Elliot and Mason[18] for 2-fluorenamine (5.7) based on the temperature range of 0.2 to 20°. In contrast 4-fluorenamine exhibits an anomalous pattern in that the pK increased by 0.13 units in the 15° temperature interval.

Of the four isomeric fluorenamines, the order of decreasing basicity is the 3-, 2-, 1-, and 4- derivative. In turn, these four compounds can be assembled into two classes. On the one hand are the 3- and 2- derivatives, which have similar pK values of 4.39 and 4.27, and on the other the 1- and 4-isomers, which have lower pK values of 3.57 and 3.15, respectively. In the latter two compounds, the amine function is attached to carbon atoms *ortho* to the ring annelation, a *peri* position, suggesting that this location is responsible for their lower proton affinity. Such *ortho* effects have been reported in a number of other cases which are fully discussed in recent reviews[5] (*cf.* also the known examples of the naphthylamines, the pK values of which in 70% ethanol are listed in Table III). The slightly higher pK of 1-fluorenamine, as compared to the 4-isomer, may be attributed to the electron-releasing hyperconjugative action of the 9-methylene group, *ortho* to the 1-position, but *meta* to the 4-position. Likewise, the higher pK of 3-fluorenamine, can be explained by its location *para* to the 9-carbon, whereas the 2-derivative is *meta*. However, the 9-carbon does enhance the basicity even of the amino group located *meta* to the 9-position, since the 2- and 4-fluorenamines exhibit higher pK values than the comparable 4- and 2-biphenylamines (Table III).

The *N,N*-dimethyl derivatives of the hindered amines (2-biphenylamine, 1-, and 4-fluorenamine) are more basic than the corresponding unalkylated compounds (Table III), owing presumably to steric inhibition of resonance. The dimethylamino grouping is apparently deformed from a coplanar

(17) J. M. Vandenbelt, C. H. Spurlock, M. Giffels, and M. W. Eash, *Science*, 121, 646 (1955).

TABLE III

IONIZATION CONSTANTS OF VARIOUS AROMATIC AMINES IN 70% ETHANOL SOLUTION

Compound	Source	pK_a'	Method
1-Naphthylamine[i]	C	3.60	P
2-Naphthylamine[j]	C	3.85	P
1,2,3,4-Tetrahydro-2-naphthylamine	W	9.13	P
2-Biphenylamine[k]	M	2.94	S[a]
N,N-Dimethyl-2-biphenylamine	W	3.71	P
3-Biphenylamine[l]	M	3.89	P
3-Amino-4-phenylacetanilide	M	2.80	S[a]
4-Biphenylamine[m]	M	3.94	P
N,N-Dimethyl-4-biphenylamine	M	3.66	P
2-Methyl-4-biphenylamine	M	4.23	P
2′-Methyl-4-biphenylamine	M	4.03	P
4′-Methyl-4-biphenylamine	M	3.95	P
p-Terphenyl-4-amine	M	3.98	P
2′-Fluoro-4-biphenylamine	M	3.77	P
2-Phenanthrylamine[n]	M	3.74	P
3-Phenanthrylamine[n]	M	3.79	P
2-Chrysenamine	M	3.58	P
1-Pyrenamine[o]	M	2.77	S[a]
3-Dibenzofuranamine[p]	M	3.35	S[a]
2-Dibenzothiophenamine	M	3.94	P
3-Dibenzothiophenamine	M	3.52	P
4′-Amino-2-biphenylcarboxylic acid	R	3.92	P
4-Aminodiphenylsulfide	M	2.86	S[a]
3-Dibenzothiophenamine 5-oxide	M	2.57	S[a]
3-Dibenzothiophenamine 5-dioxide	M	1.25	S[b]
3-Aminocarbazole	M	5.75	P
N,N-Dimethyl-1-fluorenamine	W	4.41	P
N-Methyl-2-fluorenamine	R	4.02	P
N,N-Dimethyl-2-fluorenamine	W	3.99	P
N,N-Dimethyl-3-fluorenamine	W	4.43	P
N,N-Dimethyl-4-fluorenamine	W	3.59	P
7-Methoxy-2-fluorenamine	W	4.45	P
1-Aminofluorenone	W	−0.32	S[c]
2-Aminofluorenone	M	2.40	S[d]
3-Aminofluorenone	W	0.86	S[e]
4-Aminofluorenone	W	1.42	S[f]
7-Nitro-1-fluorenamine	W	3.50	P
3-Nitro-2-fluorenamine	W	−1.2	S[g]
7-Methoxy-3-nitro-2-fluorenamine	W	−0.9	S[g]
5-Nitro-2-fluorenamine	W	3.59	P
7-Nitro-2-fluorenamine	W	3.57	P
7-Nitro-3-fluorenamine	W	3.83	P
5-Nitro-4-fluorenamine	W	1.91	S[f]
7-Nitro-4-fluorenamine	W	2.19	S[d]
1-Fluoro-2-fluorenamine	W	2.59	S[h]
3-Fluoro-2-fluorenamine	W	2.69	S[a]
3-Iodo-2-fluorenamine	W	1.97	S[f]
4-Fluoro-2-fluorenamine	F	3.05	S[d]
5-Fluoro-2-fluorenamine	F	3.93	P
6-Fluoro-2-fluorenamine	W	3.71	S[a]
8-Fluoro-2-fluorenamine	W	3.54	S[h]
1-Fluoro-4-fluorenamine	W	2.95	S[h]
3-Fluoro-4-fluorenamine	W	2.71	S[a]
7-Fluoro-2-fluorenamine	M	3.53	S[h]
7-Chloro-2-fluorenamine	W	4.00	P
7-Bromo-2-fluorenamine	W	4.00	P
7-Iodo-2-fluorenamine	W	3.90	P
N-(7-Amino-2-fluorenyl)-acetamide	W	4.31	P
N-(7-Amino-3-fluorenyl)-acetamide	W	4.10	P

[a] Form *3*, *p*H 2.72. [b] *3*, *p*H 0.96. We are grateful to Dr. R. Bates, National Bureau of Standards, for discussions concerning the measurement of low *p*H values, which was performed by zero displacement of the *p*H meter with the appropriate buffers. [c] *3*, *p*H −0.25, obtained by the addition of 3 ml. of 6*N* H_2SO_4 to 7 ml. of ethanol solution; *2* was similarly made with 3 ml. of 25*N* H_2SO_4. [d] *3*, *p*H 2.50. [e] *3*, *p*H 0.75. [f] *3*, *p*H 1.45. [g] *3*, *p*H −0.73, obtained by using 3 ml. of 12.5*N* H_2SO_4, and *2* as under *c*. [h] *3*, *p*H 3.00. [i] In water *p*K is 3.92.[5a] [j] In water *p*K is 4.11[5a] (found in this study: 4.15). [k] *p*K is 3.78 in water,[5a] 3.03 in 50% ethanol[18a] at 20°. [l] *p*K is 4.18 in water,[5a] 3.82 in 50% ethanol.[18a] [m] *p*K is 4.27 in water,[5a] 3.81 in 50% ethanol.[18a] [n] *p*K values are 3.60 and 3.59, respectively, in 50% ethanol.[18a] [o] *p*K is 2.91 in 50% ethanol.[18a] [p] Sawicki and Ray[18c] reported a *p*K of 3.3.

position with the ring system by the adjacent hydrogen atoms, resulting in a decrease in the base-weakening resonance (*cf.* the excellent discussion of this phenomenon by Ferguson,[5b] and Brown, *et al.*[5a]). The *N,N*-dimethyl derivatives of the unhindered amines, such as 2- and 3-fluorenamine, and 4-biphenylamine show little change in the *p*K value, or a slight lowering.

9-Fluorenamine, in which the amine function is attached at the saturated 9-methylene carbon atom, is considerably more basic than its purely aromatic congeners, with a *p*K of 7.56. However, it is appreciably less proton-attracting than the corresponding open ring analog, benzylamine, with an estimated *p*K of about 9 in 70% ethanol (9.34 in water). Since the inductive effects in benzylamine and in 9-fluorenamine would tend to operate similarly, it would seem that the considerably lower proton affinity of the latter compound is due to hyperconjugative resonance phenomena between substituents at the 9-position and the remainder of the molecule. This concept is borne out by data with other 9-substituted derivatives, to be discussed later.

Ionization constants of other aromatic amines. The *p*K values of the naphthylamines in 70% ethanol are also about 0.30 units lower than the values in water (Table III). As discussed by Brown, *et al.*[5a] resonance as well as steric effects play a role in giving 1-substituted naphthalenes higher acidities than 2-substituted ones. Reduction of the ring bearing the amine function yields the strong base, 1,2,3,4-tetrahydro-2-naphthylamine, *p*K 9.13.

There is little difference between the constants of 3- and 4-biphenylamines. Substitution of an acetamino residue *ortho* to the 3-amino group is strongly base-weakening. 2-Methyl-4-biphenylamine has a *p*K quite similar to that of its analog, 2-fluoren-

(18) (a) J. J. Elliott and S. F. Mason, *J. Chem. Soc.*, 2352 (1959). (b) The values for the fluorenamines would appear to be somewhat higher than that observed in the precise and careful work of E. E. Sager and I. J. Siewers, *J. Research Natl. Bur. Standards*, **45**, 489 (1950) on the heat of dissociation of 4-aminobenzophenone in water, which was 19,000 joules deg.$^{-1}$ mole^{-1} or 4.54 kcal. mole^{-1} on the basis of determinations from 10 to 40° in 5-degree steps. (c) E. Sawicki and F. E. Ray, *J. Am. Chem. Soc.*, **75**, 2519 (1953).

amine. The base strengthening effect of the methyl group may, however, be somewhat more complex in this instance than that due to the 9-methylene in the fluorene derivative. In addition to its hyperconjugative inductive action, the methyl group also may force the unsubstituted phenyl ring out of the plane of the substituted ring, resulting in a reduced resonance interaction. This effect may well be measured in large part by the increased basicity of the 2′-methyl derivative over that of 4-biphenylamine itself, *i.e.*, by 0.09 units, since methyl, or carboxy, or phenyl groups in the 4′-position have little effect by themselves. Thus, inductive and resonance interactions between substituents in the two phenyl rings in biphenyl are rather weak, a conclusion also reached by Kreiter, *et al.*[19] On the other hand, such exchanges are somewhat more pronounced in the planar and more rigid fluorene molecule.

Just as 2- and 3-fluorenamine have similar *p*K values, the corresponding 2- and 3-phenanthrene derivatives showed the closely related constants of 3.74 and 3.79. Likewise, the 3-derivative has a higher *p*K owing to interaction with the electrons from 9,10 bond, *para* to the 3-carbon. 2-Aminochrysene has a lower *p*K than the phenanthrene derivative, because of the greater electron withdrawing power of the larger ring system. Elliott and Mason[15a] felt that "the conjugate acid of the larger amine had the smaller entropy of dissociation and less endothermic heat of dissociation." 1-Pyrenamine has the low constant of 2.77 not only because of the multiple ring system, but also because the amino group is in the *peri* position.

The oxygen and sulfur heterocyclic analogs of fluorenamine manifest lower *p*K values. The oxygen in 3-dibenzofuranamine, with the amino group in a *meta* relationship to the hetero atom, possesses a larger depressing effect than sulfur in 3-dibenzothiophenamine in accord with findings in other heterocyclic systems. 2-Dibenzothiophenamine, in which the sulfur is in a *para* position to the amine function, exhibits a higher *p*K than the 3-isomer, but the open analog 4-aminodiphenyl sulfide has an even lower *p*K. The 5-thio oxide and dioxide derivatives are much stronger acids than the thiophene derivatives. However, other things being equal, the sulfur to oxygen bond is less acid-strengthening than the carbon to oxygen bond in the corresponding fluorenone (see below), indicating that resonance phenomena are transmitted better through the carbon than through the sulfur atom. In contrast to the lowering of the proton affinity by oxygen and sulfur, a nitrogen atom *para* to the amino group as in 3-aminocarbazole is considerably base-strengthening. Carbazole itself is a very weak base,[20] so it would be logical to assume that the proton acceptor is the amino nitrogen rather than the ring nitrogen. However, it is also possible that the amino nitrogen increases the hydrogen ion affinity of the ring nitrogen. Thus, the position of the proton in 3-aminocarbazole is uncertain. Similar cases in other heterocyclic systems are on record.[5a,f]

Substituted fluorenamines. Derivatives of 2-fluorenamine monohydroxylated in any position except the 9-carbon are stronger bases than the parent compound (Table II). The base-strengthening effect on the amine function at carbon-2 is least with hydroxy groups at the 6- and 8-positions between which resonance interactions occur to the smallest extent. On the other hand, the strongest proton acceptor results when the hydroxy group is at the 7-position, an extended *para* position favoring exchanges of charges. A methoxy group at that carbon is not nearly as active, increasing the *p*K by only 0.15 units (Table III) as compared to 0.30 for the hydroxy group. If the electronegative hydroxy group is located at the 9-position, however, where it is not phenolic, it has a fairly large base-weakening effect on the amine function located at the 2-position. A keto group at the 9-position exerts an even larger effect, lowering the *p*K of the *meta* amino groups at the 2- and 4-positions by 1.90 and 1.73 units, respectively. Furthermore, the *p*K of the amino group at the 3-carbon, *para* to the keto function at the 9-position is reduced by over 3.5 units, presumably because of extensive resonance and inductive interactions. The amino group in 1-aminofluorenone is almost 10^4 times weaker than in the corresponding fluorene derivative, for the same reasons and with the additional attenuation due to hydrogen bonding across the *peri* locations of the functional groups. Except for the nitro group, the ketonic oxygen exhibits the highest base-weakening power.

The powerful electron-withdrawing ability of the unhindered nitro group serves as a sensitive indicator of resonance phenomena in the fluorene ring system. It exerts its most pronounced action in an *ortho* position. 3-Nitro-2-fluorenamine is the least basic of the amines studied in this series, with a *p*K of -1.2. The low value may be ascribed to a combination of factors, consisting of inductive and electronic withdrawal of electrons, hydrogen bonding, and possibly a steric inhibition of the approach of the proton. In this case a methoxy residue located at the extended *para* carbon, the 7-position, enhances the basicity by 0.3 units, a some-

(19) V. P. Kreiter, W. A. Bonner, and R. H. Eastman, *J. Am. Chem. Soc.*, **76**, 5770 (1954).

(20) Although the *p*K of carbazole has apparently not been measured (*cf.* Pullman and Pullman, *loc. cit.*[5f] p. 325) it seems to be very weakly basic indeed. Thus, the compound dissolves in 84% sulfuric acid, but the salt hydrolyzes to yield free carbazole upon dilution to about 25% sulfuric acid [*cf.* R. E. Glegg, *Anal. Chem.*, **28**, 532 (1956)]; T. Nakajima and B. Pullman, *Bull. soc. chim. France*, **1958**, 1502, and B. Pullman, *J. Chem. Soc.*, 1621 (1959), have discussed the basicity of the nitrogen atoms in purines and pyrimidines.

what larger effect than that seen in the absence of the nitro group. Advantage has been taken of the low basicity of 3-nitro-2-fluorenamine to separate this compound by virtue of its insolubility in dilute acid, from the more basic, soluble 7-nitro isomer.[21] As may be expected, a nitro group at the 7- and 5-positions lowers the proton affinity of an amino group at 2 and 4 quite appreciably. Moreover, in 5-nitro-4-fluorenamine, it is probably that hydrogen bonding can occur (extended *ortho* position) even though the 4- and 5-carbons of fluorene are rigidly held at a greater distance than the corresponding positions in biphenyl.[22] The comparatively smaller reduction in the ionization constant by a nitro group at the 7-position on amine functions at the 3- and 1-positions is a reflection of negligible resonance interactions between these positions. The diminution in *p*K observed can be attributed mainly to inductive effects.

The recent synthesis in three laboratories[23] of all the possible monofluoro-2-fluorenamines, as well as 1- and 3-fluoro-4-fluorenamine has permitted a study of the effect of fluorine on the basicity of the amine function. The largest base-weakening action is noted when the fluorine atom is in an *ortho* position, but the effect is not nearly as pronounced as in the nitro derivatives. The halogen in the same ring is a more effective depressant of the *p*K, even in a *meta* position, than in any position in the second ring.[23c,24] In this latter case, the pattern is not clear-cut in that it does not follow the expected behavior if resonance phenomena were of paramount importance. Thus, fluorine at the 8- and 7-positions has a larger base-weakening action than the halogen at the 6-carbon, but, curiously, substitution at the 5-carbon is least effective. It would seem that inductive effects are more significant in these cases, since halogen at the 5- and 7-position should lower the basicity of a 2-amino group more than halogen at the 6- and 8-carbons if resonance were to play any appreciable role. Moreover, 3-fluoro-4-fluorenamine has a lower *p*K value than the 1-fluoro derivative which is also consistent with this view.

The effect of halogens in the 7-position on the strength of the amino group at the 2-position was determined. Chlorine and bromine both depress the *p*K by 0.30 units, while iodine decreases it by 0.40 units. In contrast, fluorine has an appreciably larger action (0.77 units), although in other examples fluorine usually was the least effective of the halogens in lowering the proton affinity of an aromatic or heterocyclic amine.[5a] In an *ortho* position such as in 3-, however, iodine yields an amine with lower *p*K than fluorine does, presumably as a result of a larger steric inhibition by iodine to the approach of a hydrogen ion.

Diamino derivatives. An amino group in a suitable location of a multiple ring system can strengthen another amino group by inductive and resonance effects in addition to the operation of statistical factors.[5g] Thus, 1,2-naphthalenediamine exhibits a first ionization constant of 4.29 (Table IV), appreciably higher than that of 2-naphthylamine, 3.85. On the other hand, the 2,3-diamine has *p*K value of 3.99, only slightly larger than that of the monoamine. That localization of double bond character occurs in naphthalene derivatives between carbons 1 and 2, and of single bond properties between 2 and 3, is well known. The *p*K data reflect this condition whereby pronounced exchanges of charges occur between amino groups at 1 and 2, but not to the same extent between 2 and 3.

TABLE IV

FIRST AND SECOND[a] IONIZATION CONSTANTS OF AROMATIC DIAMINES IN 70% ETHANOL SOLUTION

Compound	Source	$pK_1'_a$	$pK_2'_a$
1,2-Naphthalenediamine	C	4.29	<3.5
2,3-Naphthalenediamine	C	3.99	<3.5
1,8-Naphthalenediamine	C	4.08	<3.5
2,2'-Biphenyldiamine	W	3.81	<3.5
Benzidine[b]	C	4.63	3.48
4,4'-Methylenedianiline	C	4.81	3.71
4,4'-Methylenebis(*N*,*N*-dimethyl)aniline	C	4.63	3.57
1,7-Fluorenediamine	W	4.47	<3.5
2,3-Fluorenediamine	W	4.49	<3.5
2,5-Fluorenediamine	W	4.52	<3.5
2,7-Fluorenediamine	W	4.97	3.5
4,5-Fluorenediamine	W	5.16	<3.5

[a] The value of pK_2' was not determined when it was less than 3.5, the limit of accuracy of the potentiometric method as used here. [b] pK_1 and pK_2 in water is 4.97 and 3.75 respectively.

Another type of influence is exemplified by 1,8-naphthalenediamine, with a *p*K of 4.08, as compared to a *p*K value of 3.60 for the corresponding monoamine. The two amino groups in the former compound are located at positions of low resonance or direct inductive interactions. Hence, the enhancement of the basicity caused by the introduction of the second amino group may be ascribable to a

(21) O. Diels, E. Schill, and S. Tolson, *Ber.*, **35**, 3284 (1902); A. Eckert and E. Langecker, *J. prakt. Chem.*, **118**, 263 (1928).

(22) (a) G. M. Brown and M. H. Bortner, *Acta Cryst.*, **7**, 139 (1954); D. M. Burns and J. Iball, *Nature*, **173**, 635 (1954); *Proc. Roy. Soc.* (*London*), A **227**, 200 (1955). (b) Fischer-Hirschfelder models suggest that nitro and amino, and nitro and carboxy groups at the 4- and 5-carbons overlap. Two amino groups are very close together but do not prevent free rotation, and obviously the same situation prevails for an amino group and a hydrogen atom.

(23) (a) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955). (b) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H.-L. Pan, *J. Am. Chem. Soc.*, **81**, 109 (1959). (c) K. Suzuki, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **24**, 1511 (1959).

(24) Advantage was taken recently of the larger base weakening effect of fluorine *ortho* to an amino group as compared to other positions to confirm the structure of a series of isomeric fluorofluorenamines.[23c]

favored steric location, whereby a single proton may be captured and shared by the two amino groups. A similar explanation may hold for the relatively high first ionization constant of 2,2′-biphenyldiamine, 3.81, in relation to that of 2-biphenylamine, 2.94.

Another compound of this type is 4,5-fluorenediamine, which as a result of this neighboring group participation is considerably stronger than the corresponding monoamine, 4-fluorenamine.[22b] Indeed, the 4,5-diamine has the highest pK of the diamines examined in this study, if exception is made of the heterocyclic 3-aminocarbazole.

The symmetrical 2,7-fluorenediamine possesses a higher first ionization constant (4.97) than the related monoamine, 2-fluorenamine (4.30). The second amino group exhibits a larger base-strengthening action in this system than in the open benzidine, wherein resonance effects would be the predominant factor, and in 4,4′-methylenedianiline (4,4′-diaminodiphenylmethane) in which inductive phenomena would be the more important. Hence, both of these mechanisms may be expected to contribute in the 2,7-fluorene derivative. Incidentally, *N*-methylation of the methylenedianiline gives a compound with a lower pK, since the amino groups are in an unhindered position. Resonance interactions are very weak between the 1- and 7-carbons of fluorene, so that the slightly higher pK of the 1,7-diamine as compared to 2-fluorenamine may be almost entirely related to inductive factors. An amino group at the 3- and at the 5-carbon has an unexpectedly low base-strengthening action on the amine function at 2, in view of the ease of transmission of both inductive and resonance effects between these positions. Incidentally, it is not too unreasonable to assume that it is the amino group at the 2- (or 7-) carbon which captures the first proton in the unsymmetrical 1,7 and 2,5-diamines, in view of the obvious differences in basic strength of amino groups in the unhindered 2- as compared to the hindered 1- and 4- (or 5-) positions. On the other hand, the situation is not as clear-cut with the 2,3-diamine, so that it is impossible to decide, with the data at hand, which of the two amino groups in this compound ionizes first. Actually, an equilibrium between the two forms may exist.

Isomeric fluorenols and derivatives. The ionization constant of the phenolic hydroxy group of the four isomeric fluorenols is relatively independent of structure. Thus, 1-, 2-, 3-, and 4-fluorenols have pK values of 11.39, 11.56, 11.76, and 11.71, respectively, in 70% ethanol (Table V).[25] It would appear that the electron cloud around the oxygen atom, which influences the ease of proton release is affected little by comparatively minor variations in the electron distribution of the polynuclear ring system in the ground state.[26] Moreover, the small size of the hydroxy group renders it rather insensitive to steric effects, which play such a prominent role in the case of the amines and of the carboxylic acids (see below). The slightly higher acidity of 1-fluorenol as compared to the 4-isomer suggests that hydrogen bonding might occur to a small extent from the 9- to the 1-position but not from the 5- to the 4-position. The lower acidity of the 3-derivative, relative to the 2-isomer, presumably results from the hyperconjugative action of the 9-methylene group in a *para* position.

TABLE V

IONIZATION CONSTANTS OF FLUORENOLS IN 70% ETHANOL SOLUTION

Compound[a]	pK_a'
1-Fluorenol	11.39
2-Fluorenol[b]	11.56
3-Fluorenol[c]	11.76
4-Fluorenol	11.71
N-(*N*-Hydroxy-2-fluorenyl)acetamide	10.96
N-(1-Hydroxy-2-fluorenyl)acetamide	10.40
N-(1-Hydroxy-4-fluorenyl)acetamide	11.12
N-(2-Hydroxy-3-fluorenyl)acetamide	10.43
N-(3-Hydroxy-2-fluorenyl)acetamide	10.58
N-(5-Hydroxy-2-fluorenyl)acetamide[d]	11.82
N-(6-Hydroxy-2-fluorenyl)acetamide	11.79
N-(7-Hydroxy-2-fluorenyl)acetamide	11.58
N-(8-Hydroxy-2-fluorenyl)acetamide	11.53
2-Nitro-1-fluorenol	8.69
4-Nitro-1-fluorenol	8.46
7-Nitro-1-fluorenol	10.74
3-Nitro-2-fluorenol	8.62
7-Nitro-2-fluorenol[e]	10.76
2-Nitro-3-fluorenol	9.12
7-Nitro-3-fluorenol	11.16
2,4-Dinitro-3-fluorenol	5.88
2-Nitro-3-hydroxyfluorenone	5.42
7-Nitro-4-fluorenol	10.98

[a] All but one of the compounds in this Table were prepared in this laboratory (*W*). We are grateful to Drs. Miller (*M*) for supplying a sample of *N*-(*N*-hydroxy-2-fluorenyl)acetamide.[27] [b] pK in water is 9.51.[19] [c] A pK value of 11.76 was also found by the spectroscopic method. [d] As under *c*, pK 11.93. [e] pK in water is 8.94.[19]

An amino group in an *ortho* position to the phenolic hydroxy group facilitates the proton release as a result of hydrogen bonding, while in all other positions the amino substituent acts in the opposite fashion (Table II). Likewise, an acetamino residue serves to increase the acidity of a phenol by about 1 pK unit when in an *ortho* position, also because of hydrogen bonding, but shows little effect in other positions (Table V). This difference could conceivably be employed in separating the *ortho* isomers of *N*-(hydroxyfluorenyl)acetamide from

(25) V. P. Kreiter *et al.*[19] also observed values in a narrow range, 9.40–9.51, for 3- and 4-hydroxybiphenyl, and 2-hydroxyfluorene. Their measurements were performed in water. The acid-weakening effect encountered when shifting from water to 70% ethanol, as in our determinations, is more than 2 units.

(26) In contrast, the spectra of the four fluorenols are markedly dissimilar, indicating appreciable differences in the structures of those molecules in the excited state.

the others by means of partition in suitably buffered solvent systems. *N*-Hydroxy-2-fluorenylacetamide is weaker than the *ortho*-derivatives, but stronger than the other isomers. All of these compounds are produced during the metabolism of *N*-2-fluorenylacetamide in animals.[6,27]

The nitro group has a powerful acid-strengthening effect and appears to accentuate the minor differences among the phenolic derivatives of fluorene. Thus, even though 2- and 3-fluorenol have quite similar *p*K values, 3-nitro-2-fluorenol has an appreciably higher acidity than the isomeric 2-nitro-3-fluorenol; in the latter compound the 9-methylene in the *para* position again functions to lessen the acid strength. On the other hand, a keto group in the 9-position results in a very considerable increase in the acidity. For this reason 3-hydroxy-2-nitro-9-fluorenone with a *p*K of 5.42 is soluble in aqueous bicarbonate solution. Indeed, the keto group in the *para* position is more potent in causing a proton release from the hydroxy group than a second nitro group in the *ortho* position. 2,4-Dinitro-3-fluorenol has a constant of 5.88. In general, a nitro group in an *ortho* or *para* position (in the same ring) decreases the *p*K of the phenols by about 3 units. A much smaller effect is observed when the nitro group is situated in a different ring from the hydroxy function. The least interaction occurs from the 7- to the 3-position, in which case resonance makes only an unimportant contribution.

Carboxylic acids. Biphenylcarboxylic acids are more acidic than benzoic acid (Table VI). In the 4-isomer, the increase in *p*K is rather small (0.09 units) resting mainly on differences in inductive and resonance effects between the biphenyl and phenyl residues. In the 2-derivative the additional factors of steric hindrance and nonplanarity enter, resulting in a somewhat more acidic compound. These differences in *p*K values are minimized in 70% ethanol. Thus, in water the drop in *p*K from benzoic to 2-biphenylcarboxylic acid is 0.74 units whereas in 70% ethanol it amounted to only 0.41 units.

An acetamino residue at the 4-carbon, *meta* to the carboxy in 2-biphenylcarboxylic acid is acid-strengthening. On the other hand, at the 4′-position in the other ring it is weakening, but an amino group at the same position results in a slightly more potent acid, perhaps because of some zwitterion participation.

The ionization constant of 2-fluorenecarboxylic acid is close to that of benzoic acid. It is slightly higher than that of 4-biphenylcarboxylic acid in which the carboxy function is in the same position relative to the second phenyl ring. In the fluorene derivative the acid-strengthening effect of the phenyl group is counterbalanced by the inductive weakening action due to the 9-methylene radical in a *meta* position. This latter effect is even more pronounced in the *para* and the *ortho* position making the 3- and 1- acids appreciably weaker than the 2-compound. In the 1-isomer, hydrogen bonding from the hydrogens at the 9-position may also play a role, since without these influences the carboxy group at a *peri* position would be expected to be stronger. Thus, the 4-derivative, less exposed to such moderating factors, is the strongest of the four fluorenecarboxylic acids.

Just as amines and phenols derived from fluorenone were stronger acids, the 9-keto function also facilitates proton release from the carboxylic acids. As might be predicted, the acid strength of a carboxy group increases most in the *ortho* position (1.35 units), somewhat less in the *para* position (1.06) and 0.87 units in the 4- and 0.56 units in the 2-position, both *meta* to the keto group.

Nitro groups in the ring not bearing the carboxy function likewise enhance the acidity, the effect being a fraction larger from the 7- to the 2- and 4-positions (some resonance contribution) than from the 7- to the 1- or 3-positions. Oddly, a nitro group at the 5-carbon weakens a carboxy at 4-, possibly because of steric considerations involving hydrogen bonding and attributable to interatomic distances of just the right order of magnitude.[22b,28] For like reasons, substituents at the 4-position of fluorene exhibit somewhat unusual properties,[29] and further physical-chemical investigations of such compounds are of considerable interest.

TABLE VI

IONIZATION CONSTANTS OF POLYNUCLEAR CARBOXYLIC ACIDS IN 70% ETHANOL SOLUTION

Compound	Source	pK_a'
Benzoic acid[a]	C	6.41
2-Biphenylcarboxylic acid[b]	W	6.00
4-Acetamino-2-biphenylcarboxylic acid	R	5.82
4′-Acetamino-2-biphenylcarboxylic acid	R	6.25
4′-Amino-2-biphenylcarboxylic acid	R	6.13
4-Biphenylcarboxylic acid	C	6.32
1-Fluorenecarboxylic acid	W	6.65
2-Fluorenecarboxylic acid	W	6.39
3-Fluorenecarboxylic acid	W	6.52
4-Fluorenecarboxylic acid	W	5.87
9-Oxo-1-fluorenecarboxylic acid	W	5.30
9-Oxo-2-fluorenecarboxylic acid	W	5.83
9-Oxo-3-fluorenecarboxylic acid	W	5.46
9-Oxo-4-fluorenecarboxylic acid	W	5.00
7-Nitro-1-fluorenecarboxylic acid	W	6.29
7-Nitro-2-fluorenecarboxylic acid	W	5.82
7-Nitro-3-fluorenecarboxylic acid	W	6.08
5-Nitro-4-fluorenecarboxylic acid	W	6.24
7-Nitro-4-fluorenecarboxylic acid	W	5.41

[a] *p*K in water and 50% ethanol is 4.20 (found in this study, 4.19) and 5.73,[5a] respectively; *cf.* also reference 17. [b] *p*K in water is 3.46.[5a]

(27) J. H. Weisburger, E. K. Weisburger, P. H. Grantham, and H. P. Morris, *J. Biol. Chem.*, **234**, 2138 (1959); J. W. Cramer, J. A. Miller, and E. C. Miller, *J. Biol. Chem.*, **235**, 250 (1960); J. A. Miller, J. W. Cramer, and E. C. Miller, *Cancer Research*, **20**, 950 (1960).

CONCLUSIONS

In addition to the relevant points already discussed this section will briefly comment on some of the salient factors derived from this study, especially in respect to fluorene. The ionization constants, reflecting conditions in the molecule in the ground state, suggest that interactions between rings are considerably less than might be expected on the basis of the profound alterations, as a function of structural changes, in the ultraviolet (and visible) spectra, which serve as indicators of molecules in the excited state.[30]

The substituent groups vary greatly in their ability to alter the ionization constants. The following order, arranged in decreasing proton-releasing power was observed, over-all, in the series of fluorene compounds studied: $-NO_2$, $-9-SO_2$, $9-CO$, $9-SO$, $-NH_3^+$, $9=O$, $-F$, $-I$, $-Cl$, $-Br$, $-NHCOCH_3$, $-H$, $-OCH_3$, $-OH$, $-NH_2$. A substituent in an *ortho* position exhibits, generally, a considerably larger effect than the same group in another position. Substituents in the same ring, even in a *meta* relationship for the most part are more effective than when they are located in different rings.

The ionization constants of the isomeric 1-, 2-, 3-, and 4-fluorenamines, 3.57, 4.27, 4.39, and 3.15, respectively, bear no relation to the carcinogenicity of these compounds in rats. Thus, the 2-isomer is carcinogenic, the 1- and 3-derivatives are considerably weaker, and 4-fluorenamine is inactive, according to the presently available data.[31,cf. 6] This lack of a correlation may mean that (1) the compounds examined themselves are not the substances directly involved in eliciting the carcinogenic action, (2) the differences in ionization constants play no role in allowing the penetration of the compounds at the physiological *p*H into the cells where metabolism and tumorigenesis take place. The latter point is quite likely since at *p*H of 7.4 all of the above compounds would be almost completely nonionized. Hence it would appear that point (1) is also a true statement. Other studies[cf. 6,27] suggest the same conclusion, namely that metabolism of the amines is required to elicit the carcinogenic intermediate.

BETHESDA 14, MD.

(28) However, an excellent study by E. Berliner and E. H. Winicov, *J. Am. Chem. Soc.*, **81**, 1630 (1959), suggests that factors other than hydrogen bonding may play a role in the relatively weak acid character of the 5-nitrofluorene-4-carboxylic acid. They noted that 7-nitro-1-naphthoic acid and the 8-nitro-2-isomer were the weakest of the respective nitronaphthoic acids, even though the substituents were in conjugated positions (as they are in our fluorene derivative). In the two exceptional acids of Berliner and Winicov, intramolecular hydrogen bonding cannot be implicated.

(29) For example, whereas 4-fluorenamine diazotizes in the normal manner, the yields of compounds resulting from the replacement of the diazonium derivative by hydroxy or bromine are as a rule quite poor. Likewise, the 4-substituted fluorenes are usually the lowest melting of any of the isomeric derivatives.

(30) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, Wiley, New York, 1957; R. A. Friedel, *Appl. Spectroscopy*, **2**, 13 (1956).

(31) H. R. Schinz, H. Fritz-Niggli, T. W. Campbell, and H. Schmid, *Oncologia*, **8**, 233 (1955); H. P. Morris, C. A. Velat, B. P. Wagner, M. Dahlgard, and F. E. Ray, *J. Natl. Cancer Inst.*, **24**, 149 (1960).

[CONTRIBUTION FROM THE FOOD MACHINERY AND CHEMICAL CORPORATION
CHEMICAL RESEARCH AND DEVELOPMENT CENTER]

Reaction of (4,5), (8,9)-Diepoxytricyclo[5.2.1.0^{2,6}]decane with Hydrogen Bromide in Glacial Acetic Acid[1]

A. J. DURBETAKI

Received June 9, 1960

Dicyclopentadiene dioxide was shown to react with hydrogen bromide in glacial acetic acid to give 5-bromotricyclo-[5.2.1.0^{2,6}]decane-4,9-dihydroxy-8-acetate[2] instead of the corresponding dibromohydrin. The structure of the product was inferred from infrared spectra and the formation of corresponding derivatives.

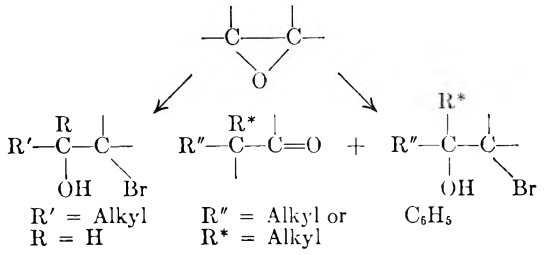
A series of epoxy derivatives with the tricyclo[5.2.1.0.^{2,6}]decane skeletal structure were synthesized and the characteristic position of bands attributable to the oxirane oxygen functional groups were studied. No absorption peaks in the 11.8 μ region were observed for compounds that had no epoxy group on the bicyclo [2.2.1.] heptane ring. Likewise, bands in the 12 μ region were absent for compounds with no oxirane oxygen on the cyclopentane ring. According to these results, assignment of the 852 cm.$^{-1}$ and 834 cm.$^{-1}$ bands of dicyclopentadiene dioxide to the oxirane oxygen of the bicyclo-[2.2.1.]heptane and the cyclopentane ring respectively was made.

The synthesis of dicyclopentadiene dioxide was first reported by Wieland and Bergel.[3] Recent commercial availability of this compound has focused attention on the reactivity of the oxirane oxygen groups and its corresponding assay by means of hydrohalogenation methods.[4,5]

When most epoxides are treated with hydro-

(1) This was presented before the 136th meeting of the American Chemical Society in Atlantic City, N. J., September 13, 1959.

halogen acids in glacial acetic acid, the corresponding halohydrins are formed rapidly and quantitatively. Certain epoxides which contain a tertiary carbon atom in the oxirane ring and other compounds which isomerize readily in acid media (*e.g.* styrene oxide), give the corresponding aldehyde or ketone with this reagent.[6] All hydrocarbon epoxides observed to date had given one of these two reactions. Therefore, we were surprised



to observe that the reaction of dicyclopentadiene dioxide with hydrogen bromide in glacial acetic acid consumed only one instead of two moles of hydrogen bromide per mole of compound.

This observation might be explained in several ways: (1) The possible isomerization of one epoxy group; (2) no reaction of one oxirane oxygen; (3) acetylation of one epoxy group of the dicyclopentadiene dioxide.

The infrared spectrum of dicyclopentadiene dioxide gives strong absorption bands related to the oxirane oxygen ring in the form of a doublet.[7] Since the two epoxy bands could be due to the respective oxirane oxygen of the dicyclopentadiene dioxide, it was felt that differentiation and specific assignment of frequencies will aid in the characterization of the reaction products and explanation of the observed reaction. With this in mind a series of epoxy derivatives with one epoxy group at one of the two possible positions on the tricyclo-[5.2.1.$0^{2,6}$]decane skeletal structure were prepared according to the procedures described in the experimental section and the characteristic position of bands attributable to the oxirane oxygen functional groups were studied. The frequencies of the oxirane oxygen ring bands are given in Table I.[8,9]

Compounds with oxirane oxygen on the bicyclo-[2.2.1]heptane ring gave a strong absorption in the 11.8 μ region. Compounds with oxirane oxygen on the cyclopentane ring gave strong absorption bands in the 12.0 μ region. In view of these results, the 852 cm.$^{-1}$ and 834 cm.$^{-1}$ bands of the dicyclopentadiene dioxide were assigned to the oxirane oxygen of the bicyclo[2.2.1]heptane and the cyclopentane ring, respectively.

TABLE I

FREQUENCY OF OXIRANE OXYGEN BANDS IN CM.$^{-1}$

Correlation of frequencies of oxirane oxygen bands of compounds with tricyclo[5.2.1.$0^{2,6}$]decane skeletal structure, bicyclo[2.2.1]-2,3-epoxyheptane, and 6-oxabicyclo[3.1.0]-hexane

Compound	Oxirane Oxygen at Bicyclo-[2.2.1]-heptane Ring	Oxirane Oxygen at Cyclo-pentane Ring
(8,9)-Epoxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]-dec-4-ene	850	
(4,5),(8,9)-Diepoxy-*endo*-tricyclo-[5.2.1.$0^{2,6}$]decane	852	834
(4,5)-Epoxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]-decane		838
(4,5)-Epoxy-*exo*-tricyclo[5.2.1.$0^{2,6}$]-decane-8-formate		838
(4,5)-Epoxy-*exo*-tricyclo[5.2.1.$0^{2,6}$]-decan-8-ol		837
(4,5)-Epoxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]-decane-8,9-diol		837
(2,3)-Epoxybicyclo[2.2.1]heptane	854	
6-Oxabicyclo[3.1.0]hexane		838

Dicyclopentadiene dioxide was allowed to react with hydrogen bromide in glacial acetic acid reagent at room temperature. The product formed was isolated after removal of the excess hydrogen bromide and acetic acid under vacuum at 0°. Infrared, functional group, and elemental analysis of the isolated product indicated the formation of the corresponding bromohydrin-hydroxyacetate (II).[2]

Alkaline hydrolysis of II with aqueous sodium carbonate resulted in the formation of III with an absorption band at 837 cm.$^{-1}$. The dihydroxy epoxide, III, reacted readily with hydrogen bromide in acetic acid to give V. The above experimental results established with no doubt that acetylation of the oxirane oxygen of the bicyclo[2.2.1]heptane ring occurs readily when dicyclopentadiene dioxide is allowed to react with hydrogen bromide in acetic acid. Attempts to treat I with acetic acid alone, under the same conditions utilized in the reaction with acetic acid–hydrogen bromide reagent, resulted in the quantitative recovery of I. The latter reaction suggested an acid catalyzed acetylation of the relatively basic epoxy group. This was substantiated by the fact that acetylation of the oxirane oxygen of the bicyclo[2.2.1]heptane ring proceeded readily and quantitatively in excess glacial acetic acid in the presence of catalytic amounts of perchloric acid. The isolated product after hydrolysis with aqueous sodium hydroxide had the same structure as III.

The acid catalyzed hydrolysis of I and III gave IV which reacted quantitatively with periodic

(2) For convenience only one of the two possible isomers is indicated throughout this paper. No experimental work to differentiate between 5-bromotricyclo[5.2.1.$0^{2,6}$]decane-4,9-dihydroxy-8-acetate and 5-bromotricyclo[5.2.1.$0^{2,6}$]decane-4,8-dihydroxy-9-acetate was undertaken.

(3) H. Wieland and F. Bergel, *Ann.*, 446, 13 (1925).

(4) A. J. Durbetaki, *Anal. Chem.*, 28, 2000 (1956).

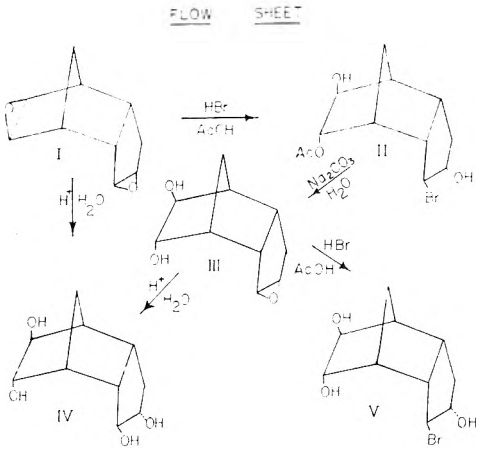
(5) A. J. Durbetaki, *Anal. Chem.*, 30, 2024 (1958).

(6) A. J. Durbetaki, *Anal. Chem.*, 29, 1666 (1957).

(7) J. Bomstein, *Anal. Chem.*, 30, 544 (1958).

(8) Determined in carbon disulfide solution.

(9) Determined as 1.5% solution.



acid according to the method of Pohle *et al.* for vicinal diols.[10] No apparent rearrangement of the type found for bicyclo[2.2.1]-2,3-epoxyheptane[11] was observed in the hydrolysis of I as is apparent from the positive periodic acid test.

The difference in reactivity between the oxirane oxygen of the bicyclo[2.2.1]heptane and that of the cyclopentane rings could not be readily explained by differences in group substituents and the donating or attracting nature of such groups. Flett[12] has shown that in some cases there is a correlation between the position of a characteristic absorption band and the reactivity of the group. The effect of steric strain on frequencies has been clearly demonstrated in small rings.[13–15] It is generally observed that analogous group structures with greater strain absorb about 20–35 cm.$^{-1}$ higher than those with lesser steric strain. The frequency of oxirane oxygen of the bicyclo[2.2.1]heptane ring appears 18 cm.$^{-1}$ higher than that of the corresponding epoxy of the cyclopentane ring (Table I). The behavior of dicyclopentadiene dioxide, resulting in the ring opening of one epoxy group by a weak acid while the other oxirane oxygen remains unaffected by it could therefore be attributed to steric strain.[16]

No apparent shift in oxirane band frequency was observed when the cyclopentane ring was *endo* or *exo* to the bicyclo[2.2.1]heptane ring (Table I). Furthermore, reaction with hydrogen bromide in acetic acid was quantitative in both isomeric forms as shown in the experimental section.

(10) W. D. Pohle, V. C. Mehlenbacker, and J. H. Cook, *Oil and Soap*, **22**, 115 (1945); *J. Am. Oil Chemists' Soc.*, **27**, 54 (1950).

(11) H. W. Kwart and W. G. Vosbrugh, *J. Am. Chem. Soc.*, **76**, 5400 (1954).

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

(13) J. LeComte, *J. phys. Radium*, **6**, 127 (1945); **6**, 257 (1945).

(14) S. L. Friess and P. E. Frankenburg, *J. Am. Chem. Soc.*, **74**, 2679 (1952).

(15) C. D. Gutsche, *J. Am. Chem. Soc.*, **73**, 786 (1951).

(16) It might be pointed out here that epoxides in general do not readily react with acetic acid under the experimental conditions described.[4,5]

EXPERIMENTAL

The dicyclopentadiene used in the preparation of the compounds described below was the *endo*-isomer, fractionally distilled, m.p. 33.6°. The *endo*-dicyclopentadiene dioxide was Food Machinery and Chemical Corporation Commercial product, recrystallized, m.p. 189.5–190.5°.

5-Bromotricyclo[5.2.1.0^{2,6}]decane-(4,9)-dihydroxy-8-acetate (II).[2] To dicyclopentadiene dioxide (0.5 g., 0.003 mole) dissolved in 5 ml. of chlorobenzene was added 0.006 mole of anhydrous hydrogen bromide in 50 ml. of glacial acetic acid. Upon complete addition of the reagent the solution was evaporated to dryness at 0–10° *in vacuo*. The residue was crystallized from acetonitrile to yield 0.89 g. (96%) of product. The infrared spectrum[17] of the product has bands at 3584 cm.$^{-1}$ (free —OH stretching), 3424 cm.$^{-1}$ (associated —OH stretching), 1724 cm.$^{-1}$ (ester C=O), 1245 cm.$^{-1}$ (acetate C=O) and 1076 cm.$^{-1}$ (—OH deformation). No bands at 834 and 852 cm.$^{-1}$ characteristic of oxirane oxygen are present.

Anal. Calcd. for $C_{12}H_{17}O_4Br$: C, 47.2; H, 5.7; Br, 26.2; CH_3COO, 19.3; OH, 11.2 Found: C, 47.0; H, 5.6; Br, 26.5; CH_3COO, 19.3; OH, 11.2.

Hydrolysis of II *to the (4,5)-epoxy-endo-tricyclo[5.2.1.0^{2,6}]-decane-8,9-diol* III. Compound II (0.7 g., 0.002 mole) was treated with 100 ml. of sodium carbonate solution (21.2 g. sodium carbonate in 100 ml. of distilled water) for 1.5 hr. while maintaining the temperature at about 98°. The alkaline solution was then extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was crystallized from petroleum ether (b.p. 30–60°) to yield 0.4 g. (95.4%) of III, m.p. 122–123°. The infrared spectrum of the crude product has bands at 3424 cm.$^{-1}$ (—OH stretching), 1080 cm.$^{-1}$ (—OH deformation), 837 cm.$^{-1}$ (C_5, oxirane oxygen). This material titrated with acetic acid–hydrobromic acid reagent and gave a positive periodic acid test for vicinal diol.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7; OH, 18.6; O(oxirane), 8.78. Found: C, 65.9; H, 7.6; OH, 18.7; O(oxirane), 8.6.

Hydrobromination of III *to 5-bromo-endo-tricyclo[5.2.1.0^{2,6}]-decane-4,8,9-triol* (V). To (4,5)-epoxy-*endo*-tricyclo[5.2.1.0^{2,6}]decane-8,9-diol (0.5 g., 0.003 mole) dissolved in 5 ml. of chlorobenzene was added 0.003 mole of anhydrous hydrogen bromide in 50 ml. of glacial acetic acid. Upon complete addition of the reagent the solution was evaporated to dryness at 0–10° *in vacuo*. The infrared spectrum of the product has bands at 3584 cm.$^{-1}$ (free —OH stretching), 3424 cm.$^{-1}$ (associated hydroxyl stretching), and 1076 cm.$^{-1}$ (—OH deformation). No bands at 837 cm.$^{-1}$ (C_5, oxirane oxygen) or 1724 cm.$^{-1}$ (ester C=O) are present.

Anal. Calcd. for $C_{10}H_{15}O_3Br$; C, 45.6; H, 5.7; Br, 30.4. Found: C, 45.5; H, 5.7; Br, 30.3.

endo-tricyclo[5.2.1.0^{2,6}]dec-4-ene.[18] To a solution of dicyclopentadiene (13.5 g., 0.10 mole) in 100 ml. of cyclohexane was added 2.2 g. of 5% palladium on barium sulfate. The mixture was shaken for 6 min. under 60 lbs. of hydrogen pressure in a Parr apparatus. After removal of the catalyst the solution was fractionally distilled *in vacuo* to yield 12.9 g. (94.3%) of a camphor-like crystalline solid m.p. 52–53° (lit.,[18] m.p. 52–53°). The infrared spectrum of the product has bands at 1613 cm.$^{-1}$ (C=C cyclopentane ring)[19]. No band at 992 cm.$^{-1}$ (C=C of the bicyclo[2.2.1]heptane ring[19]) is present.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.5, H, 10.5. Found: C, 89.4; H, 10.3.

(4,5)-Epoxy-endo-tricyclo[5.2.1.0^{2,6}]decane. To a solution of 10.2 g. (0.076 mole) of dihydrocyclopentadiene in 50 ml.

(17) Determined in chloroform solution.

(18) K. Alder and G. Stein, *Ann.*, **485**, 223 (1931).

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

of chloroform was added 16 g. of 41% peracetic acid and 2 g. of sodium acetate. During the addition of peracetic acid the temperature was not allowed to rise above 25°, and this temperature was maintained for 3 hr. after the addition had been completed. The reaction mixture was neutralized with 5% sodium hydroxide. The chloroform layer was separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue sublimed to yield 10.5 g. (92.3%) of product, m.p. 97–98° (lit.,[19] m.p. 98°). This material reacted with acetic acid–hydrobromic acid reagent. A discussion of the infrared spectra can be found in another section of this paper.

Anal. Calcd. for $C_{10}H_{14}O$: C, 80.0; H, 9.4; O(oxirane), 10.65. Found: C, 79.8; H, 9.4; O(oxirane), 10.65. Found, C, 79.8; H, 9.3; O(oxirane), 10.6.

(8,9)-Epoxy-endo-tricyclo[5.2.1.0^{2,6}]dec-4-ene. This compound, m.p. 79.5–80° (lit.,[18] m.p. 79–80°), was prepared as previously described.[18] The infrared spectrum of the product has bands at 992 cm.$^{-1}$ (C=C of the cyclopentane ring[19]) and 850 cm.$^{-1}$ (oxirane oxygen).

exo-tricyclo[5.2.1.0^{2,6}]dec-4-ene 8-formate (VI). This compound b.p. 136°/25 mm. (lit.[20] b.p. 136°/25 mm.) was prepared as previously described.[20] The infrared spectrum of the product has bands at 1721 cm.$^{-1}$ (ester C=O), 1179 cm.$^{-1}$ (formate C=O) and 1613 cm.$^{-1}$ (C=C of the cyclopentane ring[19]).

Epoxydation of VI to the (4,5)-Epoxy-exo-tricyclo[5.2.1.0^{2,6}]-decan 8-formate VII. To a solution of VI (36 g. 0.20 mole) in 150 ml. of chloroform was added 5 g. of sodium acetate and 52 g. of 41% peracetic acid. During the addition of peracetic acid the temperature was not allowed to rise above 25° and this temperature was maintained for 3 hr. after the addition had been completed. The reaction mixture was neutralized with 5% sodium bicarbonate. The chloroform layer was separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The residual oil was distilled to yield 38.1 g. (97.1%) of the epoxide, b.p. 111° (1 mm.), n^{21} 1.5042. The infrared spectrum of the product has bands at 1720 cm.$^{-1}$ (ester C=O), 1179 cm.$^{-1}$ (formate C=O), and 838 cm.$^{-1}$ (oxirane oxygen).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 68.0; H, 7.3; O(oxirane), 8.2. Found: C, 68.0; H, 7.2; O(oxirane), 8.1.

Hydrolysis of VII to the (4,5)-epoxy-exo-tricyclo[5.2.1.0^{2,6}]-decan-8-ol VIII. Compound VII (3.0 g., 0.015 mole) was treated with 100 ml. of sodium carbonate solution (21.2 g. sodium carbonate in 100 ml. of distilled water) for 1.5 hr. while maintaining the temperature at about 98°. The alkaline solution was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The highly viscous oil residue was crystallized from petroleum ether (b.p. 30–60°) to yield 2.4 g. (96.1%) of pure product. The infrared spectrum of the oily product has bands at 3380 cm.$^{-1}$ (—OH stretching) 1080 cm.$^{-1}$ (—OH deformation), 838 cm.$^{-1}$ (cyclopentane ring oxirane oxygen).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5; O(oxirane), 9.6. Found: C, 72.2; H, 8.4; O(oxirane), 9.5.

Acetylation of I to III. To dicyclopentadiene dioxide (1 g.) dissolved in 50 ml. of glacial acetic acid was added 2 drops of 72% perchloric acid. The solution was kept at 50° for 15 min. The acetic acid solution was made alkaline with 25% sodium hydroxide. The alkaline solution was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was crystallized from petroleum ether to yield 1.09 g. (98.4%) of glycol, m.p. 122–123°. The infrared spectrum of the crude product was identical with that obtained from the alkaline hydrolysis of II.

Acetylation of I. To a solution of I, 0.5 g. in chloroform, was added 50 ml. of glacial acetic acid. The acetic acid was removed *in vacuo* at 10°. The residue, m.p. 189.5–190.5°, had an infrared spectrum identical with I and gave a negative periodic acid test for vicinal diol.

Hydrolysis of I.[21] Dicyclopentadiene dioxide 1 g. and 100 ml. of distilled water containing 2 drops of 72% perchloric acid was maintained at 85° for 8 hrs. The water solution was extracted with chloroform. The chloroform extract dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. The residue was a hygroscopic resin and could not be recrystallized.[18] The infrared spectrum was characteristic of that of a glycol and 1 mole of the compound reacted quantitatively with 2 moles of periodic acid as expected for a tetrol.

6-Oxabicyclo[3.1.0]hexane. To a solution of 10.2 g. (0.015 mole) of cyclopentene in 50 ml. of chloroform was added 24 g. of 40% peracetic acid and 2 g. of sodium acetate. During the addition of peracetic acid the temperature was not allowed to rise above 25°, and this temperature was maintained for 3 hr. after the addition had been completed. The reaction mixture was neutralized with 5% sodium hydroxide. The chloroform layer was separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residual liquid was distilled to yield 12.2 g. (97%) of the epoxide, b.p. 99–100° (lit.,[22] b.p. 98.5–100°). The infrared spectrum of the product has a band at 838 cm.$^{-1}$ (C_5, oxirane oxygen). No bands at 904 cm.$^{-1}$ and 1619 cm.$^{-1}$ (C=C of the cyclopentene ring) are present.

(2,3)-Epoxybicyclo[2.2.1]heptane. This compound m.p. 125–126° (lit.,[23] m.p. 125–127°) was prepared as previously described. The infrared spectrum of the product has a band at 854 cm.$^{-1}$.

Analytical methods. 1. Acetoxy: E. P. Clark, *Ind. Eng. Chem. Anal. Ed.*, **8**, 487 (1936). 2. Hydroxyl (lithium aluminum hydride method): R. E. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947). 3. Oxirane oxygen (acetic acid–hydrobromic acid method).[3] 4. Glycol (periodic acid).[9]

Acknowledgments. The author wishes to express his appreciation to Food Machinery and Chemical Corporation for permission to publish this work, to Dr. H. K. Latourette for his valuable review criticism of this work, and to Dr. S. Linder for supplying the dicyclopentadiene dioxide.

PRINCETON, N. J.

(20) P. D. Bartlett and A. Schneider, *J. Am. Chem. Soc.*, **68**, 6 (1946).

(21) The hydrolysis of I on a micro scale followed by an *in situ* periodic acid oxidation in chloroform–acetic solution was adapted for the quantitative analysis of dicyclopentadiene dioxide by the author (unpublished data).

(22) J. Böeseken, *Rec. Trav. Chim.*, **47**, 689 (1928).

(23) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5396 (1954).

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

The Synthesis and Dehydration of 7-Hydroxyspiro[5.6]dodecane, a Neopentyl System

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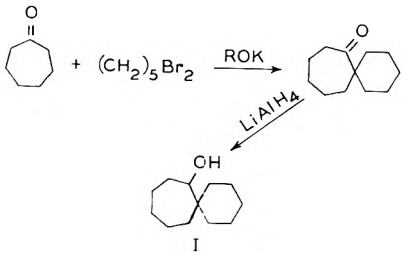
Received August 16, 1960

Rearrangements of α-hydroxyspiranols must lead to changes in ring size. The preparation of 7-hydroxyspiro[5.6]dodecane has been improved and its dehydration with four typical dehydration catalysts has been studied. In all cases the two major products were shown to be cyclohexylcyclohexene and spiro[5.6]-7-dodecene (or a position isomer thereof). Conformational analysis suggests that the course of the reaction is determined solely on steric grounds and that it can be rationalized by a comparison of the free energies of the various transition states.

Dehydrations of α-hydroxyspiranes are of interest for two reasons. First, these spiranols are unique in that they contain neopentyl systems which are completely incorporated into two fused alicyclic rings. Any rearrangements which occur must therefore result in changes of ring size. Consequently, dehydrations of these systems, unlike aliphatic neopentyl alcohols, afford an opportunity to study the effect of ring size and conformation of the resulting rearrangements. Second, the rearrangements of these compounds might provide new synthetic routes to otherwise difficultly obtainable fused ring systems. The few studies which have been made have been briefly reviewed.[3]

The dehydration of 7-hydroxyspiro[5.6]dodecane (I) has previously been attempted by Jacquier and Christol[4] and Christol, Jacquier, and Mousseron.[5] These workers treated the spiranol with polyphosphoric acid and obtained only a small amount of cyclohexylcyclohexene (IX) and unchanged alcohol. In addition, the spiranol was reported to be unaffected by twice its weight of zinc chloride at 140°. In contrast to these observations, Laber[6] has reported that the spiranol I is easily dehydrated by zinc chloride, giving an 80% yield of IX. Because of these surprising results and because of the aforementioned possible application of the dehydrations of such spiranols to the synthesis of otherwise difficultly obtainable fused ring systems, it appeared desirable to study the preparation and dehydration of 7-hydroxyspiro[5.6]dodecane.

The spiranol was prepared as follows:



I

7-Ketospiro[5.6]dodecane was prepared in approximately 45% yield by a modification of the method of Mousseron.[7] However, the spiranone could not be purified by fractional distillation. Analysis of the middle fractions by both infrared spectrophotometry and vapor phase chromatography indicated that olefinic and ketonic impurities on the order of 15–20% were present. Attempts to isolate and characterize these impurities were unsuccessful due to the complexity of the reaction product.

The crude ketone was purified both by elution chromatography and by regeneration from the semicarbazone (45% yield). The latter method proved to be the more convenient for the purification of large amounts of the crude ketone. Even though the semicarbazone could not be obtained in high purity because of contamination by isomeric ketones, the regenerated material was easily purified by fractional distillation. This purification technique, together with modifications described in the Experimental, constitute what is probably the best available procedure for the preparation of this compound.

The crude ketone was reduced directly to the desired spiranol with lithium aluminum hydride. Only 28.4% of high purity spiranol was obtained, the remainder being contaminated by olefinic impurities.

The spiranol was dehydrated using four catalysts: anhydrous alumina, concentrated sulfuric acid, zinc chloride, and boron trifluoride etherate. The olefins were distilled and analyzed by vapor phase chromatography. The results are summarized in Table I.

(1) American Petroleum Institute Fellow, 1956–1958; Esso Research and Engineering Company Fellow, 1958–1959. Present address, Paulsboro Laboratory, Socony Mobil Oil Co., Inc., Paulsboro, N. J.

(2) Taken in part from the dissertation submitted by P. A. Naro in partial fulfillment of the requirements for the Ph.D. degree at The Pennsylvania State University.

(3) P. A. Naro and J. A. Dixon, *J. Am. Chem. Soc.*, **81**, 1681 (1959).

(4) R. Jacquier and H. Christol, *Bull. soc. chim. France*, 556 (1954).

(5) H. Christol, R. Jacquier, and M. Mousseron, *Bull. soc. chim. France*, 346 (1957).

(6) G. Laber, *Ann.*, **588**, 79 (1954).

(7) M. Mousseron, R. Jacquier, and H. Christol, *Bull. soc. chim. France*, 346 (1957).

TABLE I

RESULTS OF THE DEHYDRATIONS OF 7-HYDROXYSPIRO[5.6]DODECANE

Catalyst	Reaction Temp.	Percentage Yield: Olefin product	Component A, cyclohexylcyclohexene	Component B, spiro[5.6]-7-dodecene (VIII)	Component C	Other
Boron trifluoride	25	90	83.4	14.2	1.0	1.4
Sulfuric acid	100	92	61.3	37.9	0.8	0
Zinc chloride	130	93	77.7	21.5	0	0.8
Alumina	350	84	51.1	42.9	4.7	1.3

The olefins from these dehydrations could not be separated by fractional distillation. However, A and B, the two main components, were isolated in high purity in a preparatory vapor-phase chromatography apparatus similar to one described by Anderson.[8]

Component A was the principal product in all of the dehydrations. It was found to be identical in all respects to an authentic sample of cyclohexylcyclohexene prepared by the method of Signaigo and Cramer.[9]

Component B, the only other major component, was hydrogenated to a compound whose infrared spectrum was identical to that of spiro[5.6]dodecane, prepared by Wolff-Kishner reduction of the corresponding ketone. The olefin was therefore spiro[5.6]-7-dodecene (VIII) or a position isomer thereof.

Component C could not be isolated and was therefore not identified. Laber,[6] who also dehydrated the spiranol I, observed a transitory blue color while preparing the nitrosochloride of his product. He attributed this color to the presence of traces of bicyclo[0.5.5]-1(7)-dodecene (VI). Although a blue color was also noted in this research, the same effect was observed when the nitrosochloride of pure cyclohexylcyclohexene was prepared. There is therefore no real evidence that component C might be VI.

Trace amounts of other components of shorter retention times were sometimes observed in the chromatography traces but these could not be isolated or identified.

The products and intermediates which might reasonably be expected from the dehydration are illustrated in Fig. 1. The fact that only two major products were actually found suggested that the transition state conformation of the spiranol might be important. Accordingly, the relative energies of the axial and equatorial isomers of the spiranol in all of its four possible ring conformations have been estimated. Results indicate that the hydroxyl group in the axial isomer is not always more hindered than the equatorial since the latter en-

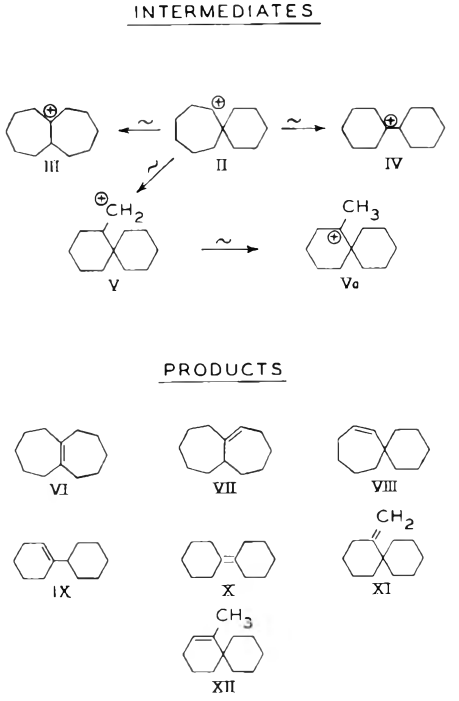


Figure 1

counter skew interactions with the cyclohexane ring. In all cases the energy differences between the two were within the range 0.8–2.4 kcal. Such a small energy difference will not be important in determining the course of a reaction provided that the barrier to interconversion is small compared to the energy of activation.

Examination of molecular models suggests that at least two transition states are possible for each isomer (Fig. 2). Thus, the axial may yield A and B while the equatorial may lead to C and D. (In these figures the rear atom is the C_7-atom and the R-groups refer to the rest of the ring involved.) Transition state C generates the unlikely intermediate V which involves a change from a secondary carbonium ion to a primary one. State A, which leads to VIII, would therefore be expected to predominate. On the other hand, any energy differences between B and D are not immediately obvious. Although both would lead to intermediates involving tertiary carbonium ions,

(8) B. C. Anderson, E. I. du Pont de Nemours and Company, private communication.

(9) F. K. Signaigo and P. L. Cramer, *J. Am. Chem. Soc.*, 55, 3326 (1933).

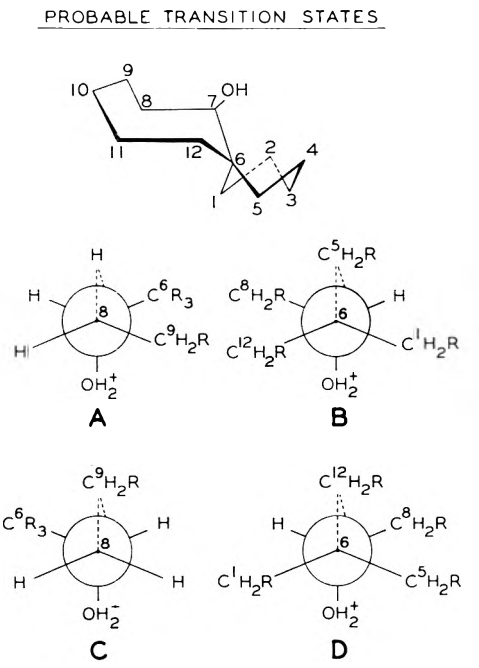


FIGURE 2

the intermediate generated by B (III) would be much less stable than that generated by D (IV) because of the great distortion of the two seven-membered rings caused by the necessary planar sp^2 state of the bridgehead atom. Because of this strain, transition state D would be expected to predominate and to yield cyclohexylcyclohexene (IX), which is observed.

In view of the foregoing it is not surprising that the predominant products in the dehydration are VIII and IX. However, it is interesting to note that the product distribution in the sulfuric acid-catalyzed dehydration very closely approaches that found in the alumina dehydration. In a previous study[3] involving the dehydration of 6-hydroxyspiro[4.5]decane, no normal product was found in the sulfuric acid-catalyzed dehydration while the use of alumina gave 42% of the normal olefin. As the same experimental techniques were used in both studies, the results suggest that for 6-hydroxyspiro[4.5]decane the transition state free energy for the axial isomer is less than that of the equatorial isomer ($F\ddagger_{ax} < F\ddagger_{eq}$), while for the present case the reverse is true ($F\ddagger_{eq} \leqq F\ddagger_{ax}$).

It is noteworthy that the dehydrations of both 7-hydroxyspiro[5.6]dodecane and 6-hydroxyspiro-[4.5]decane[3] represent examples of reaction courses determined purely on steric grounds. Further work is planned in which it will be determined whether or not these reaction courses are sensitive to temperature.

EXPERIMENTAL[10]

Preparation of 7-ketospiro[5.6]dodecane. Into a carefully dried, nitrogen-filled flask equipped with a stirrer and condenser were placed 1 kg. (13.5 moles) of anhydrous *t*-butyl alcohol and 82.1 g. (2.1 moles) of potassium.[11] The mixture was stirred for 8 hr. under nitrogen and the resulting clear water-white solution was distilled to dryness under reduced pressure. To the resulting white salt were added 2 l. of anhydrous toluene, 112 g. (1 mole) of cycloheptanone, and 230 g. (1 mole) of 1,5-dibromopentane. The mixture was refluxed for 73 hr. The resulting brown solution was treated with 200 ml. of water and 400 ml. of a 10% hydrochloric acid solution and cooled to room temperature. The organic layer was separated and the aqueous layer extracted three times with ether. The original layer and the extracts were combined, washed with 5% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Removal of the ether followed by distillation of the dark residue yielded 133 g. of crude product, b.p. 83° (3 mm.), n_D^{25} 1.4749–1.4880. Attempts to purify the crude spiranone by fractional distillation through a spinning band column[12] were unsuccessful. Fortunately, the crude product could be used directly in the synthesis of 7-hydroxyspiro[5.6]dodecane as described below.

Analyses of the crude ketone by vapor phase chromatography and by infrared spectroscopy indicated that it contained 15–20% of olefinic impurities. The material was purified by regeneration from the semicarbazone. From 250 g. of the crude product there was obtained 161 g. (47%) of the semicarbazone, m.p. 186–204°. All attempts to purify the derivative further by recrystallization failed. Hydrolysis with 10% hydrochloric acid followed by fractional distillation yielded 112.1 g. (96%) of high purity spiranone, b.p. 100° (2.3 mm.), n_D^{25} 1.4922, n_D^{20} 1.4939, d_4^{20} 0.9897, M_D 53.25 (calcd.), 53.02 (found).

The 2,4-dinitrophenylhydrazone was prepared in the usual way,[13a] m.p. 117–118°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: N, 15.55. Found: N, 15.54.

Preparation of 7-Hydroxyspiro[5.6]dodecane. A solution of 105 g. of crude 7-ketospiro[5.6]dodecane in 500 ml. of anhydrous ether was slowly added to a refluxing slurry of 11.0 g. (0.29 mole) of lithium aluminum hydride in 1 l. of anhydrous ether (nitrogen atmosphere). After addition was complete the mixture was refluxed for 1 hr. and the excess hydride was decomposed by dropwise addition of 58.2 g. (0.61 mole) of ethyl acetate. The resulting mixture was hydrolyzed with 10% sodium hydroxide solution and the ethereal solution was decanted. The solid residue was extracted three times with ether and the combined material was dried over anhydrous sodium sulfate. Removal of the ether followed by fractional distillation of the residue through a spinning band column[12] yielded 29.8 g. (28.4%) of high purity spiranol, b.p. 151° (20 mm.), n_D^{25} 1.5082, n_D^{20} 1.5103, d_4^{20} 1.0059, M_D 54.77 (calcd.), 54.23 (found). The 3,5-dinitrobenzoate was prepared,[13b] m.p. 104.3–105.2°.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found: C, 78.63; H, 11.90.

Dehydration over alumina. The apparatus used consisted of a horizontal 36-inch, 30 mm. i.d. Pyrex tube with three separately controlled heating sections. The alumina (4–8 mesh, Alorco) was activated by heating overnight at 450° in a stream of nitrogen. The spiranol (20 g., 0.11 mole) was added to the tube at a rate of about 20 drops/min. while maintaining the three sections at 250, 300, and 350°,

(10) All melting points are uncorrected. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) W. S. Johnson and G. H. Daub, *Organic Reactions*, Wiley, New York, 1951, Vol. VI, p. 42.

(12) This column is manufactured by the Nester-Faust Co., Exton, Pa. The packed section is 36 inches long with an internal diameter of 11 mm. The band is a spiral of 300 mesh stainless steel screen.

(13a) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, Wiley, New York, 1954, p. 171. (b) p. 165.

respectively. After all of the material had been added to the tube, a slow stream of nitrogen was passed through to sweep out any remaining olefins and water. A total of 17.6 g. (88%) of material was collected. The remainder of the products remained on the alumina as a black deposit. The organic material was taken up in ether and dried over anhydrous copper sulfate. Distillation yielded 15.2 g. (84%) of olefins, b.p. 40–43° (0.2 mm.), n_D^{25} 1.4955.

Dehydration with sulfuric acid. A solution of 5.00 g. (0.027 mole) of 7-hydroxyspiro[5.6]dodecane and 1 drop of concentrated sulfuric acid was heated to 100°, at which point the olefins and water distilled. The distillate was taken up in ether and dried over anhydrous copper sulfate. The ether and then the olefins were distilled to yield 4.13 g. (92%) of product, b.p. 50–60° (0.5 mm.), n_D^{25} 1.4948.

The nitroso chloride[3] was prepared and crystallized as pale blue crystals, but three recrystallizations from large volumes of acetone yielded only white needles, m.p. 141.5–142.5°. A mixed melting point taken with a sample of the nitroso chloride of cyclohexylcyclohexene, prepared by the method of Signaigo and Cramer,[9] was not depressed.

Dehydration with zinc chloride. A mixture of 5.00 g. (0.037 mole) of freshly fused zinc chloride and 5.00 g. (0.027 mole) of 7-hydroxyspiro[5.6]dodecane was heated at 135° for 1 hr. at 130 mm. pressure. The resulting paste was treated with 5 ml. of water and extracted three times with ether. The combined extracts were dried over anhydrous copper sulfate and distilled to yield 4.20 g. (93%) of olefin product, b.p. 78–80° (1 mm.), n_D^{25} 1.4942.

Dehydration with boron trifluoride etherate. A solution of 5.00 g. (0.027 mole) of 7-hydroxyspiro[5.6]dodecane and 10 ml. of boron trifluoride etherate was stirred at room temperature for 4.5 hr. The reaction mixture was treated with 50 ml. of water and the yellow upper layer was separated. The aqueous layer was extracted three times with hexane and the combined material was washed with dilute bicarbonate solution and dried over anhydrous copper sulfate. Distillation yielded 1.20 g. (25.2%) of unchanged spiranol and 3.00 g. (90%, based on spiranol actually dehydrated) of olefins, b.p. 70–80° (1 mm.), n_D^{25} 1.4941.

Analyses. All olefin analyses were made in an Aerograph instrument[14] at 150° using a helium flow rate of 90 ml./min. The column consisted of a 12-foot length of 0.25-inch o.d. copper tubing packed with 30% 1,2,3-tris(β-cyanoethoxy)-propane[15] on 30–60 mesh firebrick. This absorbent, suggested by Anderson,[8] had excellent selectivity for these olefin mixtures.

Acknowledgment. The authors express their appreciation to the American Petroleum Institute and to the Esso Research and Engineering Company for the funds which helped to support this research.

UNIVERSITY PARK, PA.

(14) Obtained from Wilkens Instrument and Research, Inc., Berkeley, Calif.

(15) H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, **65**, 27 (1943); H. A. Bruson, U. S. Patent **2,401,607** (*Chem. Abstr.*, **40**, 5450 (1946)).

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH STATION[1]]

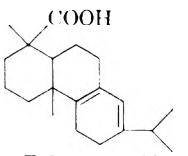
The Thermal Isomerization of Palustric Acid

N. MASON JOYE, JR., AND RAY V. LAWRENCE

Received July 8, 1960

The thermal isomerization of palustric acid was studied at 170 and 200°. Spectrographic and chromatographic examination of the isomerizates showed that abietic and neoabietic acid accounted for all of the detectable products. The formation of abietic acid was favored in this isomerization over the formation of neoabietic acid. The isomerization was found to be a first-order reaction with respect to the palustric acid. Palustric acid was shown to be more stable to heat than levopimaric acid and less stable than neoabietic acid. Methyl palustrate underwent only a slight change on prolonged heating at 200°.

A series of thermal and acid isomerizations was started in this Laboratory on the abietic-type acids in oleoresin and rosin—namely, levopimaric acid,[2,3] neoabietic acid,[4] and palustric acid. Palustric acid, the most recently isolated acid, is one of the major constituents of pine oleoresin and rosin[5]. The structure of this acid was recently established by Schuller, *et al.*[6]:



Palustric acid

This paper describes a study of the thermal isomerization of pure palustric acid at 170 and 200°. Samples of palustric acid were heated in sealed evacuated tubes over a period of twenty-four hours and the progress of the isomerization followed by obtaining the specific rotation, ultraviolet absorption spectrum and chromatographic analysis of each sample. At both temperatures the isomerization product seemed to approach an equilibrium mixture of approximately 13% palustric acid, 80% abietic acid, and 7% neoabietic acid. Palustric acid has a half-life of about four hours at 170°.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) V. M. Loeblich, D. E. Baldwin, R. T. O'Connor, and R. V. Lawrence, *J. Am. Chem. Soc.*, **77**, 6311 (1955).

(3) D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *J. Am. Chem. Soc.*, **78**, 2015 (1956).

(4) V. M. Loeblich and R. V. Lawrence, *J. Am. Chem.*, **79**, 1497 (1957).

(5) V. M. Loeblich, D. E. Baldwin, and R. V. Lawrence, *J. Am. Chem. Soc.*, **77**, 2823 (1955).

(6) W. H. Schuller, R. N. Moore, and R. V. Lawrence, *J. Am. Chem. Soc.*, **82**, 1734 (1960).

TABLE I

SUMMARY OF DATA ON THE THERMAL ISOMERIZATION OF PALUSTRIC ACID AT 170°

Time, Hr.	$[\alpha]_D$, 2% C_2H_5OH	α at 241 mμ	Palustric, %	Abietic, %	Neoabietic, %	Calcd., $[\alpha]_D$	Calcd., α at 241 mμ
0	+71		99+				
.50	+51	19	86	11	2	+53	21
1	+43	21	78	18	2	+40	25
2	+23	30	[a]				
4	−13	41	48	49	5	−9	47
8	−32	53	31	63	6	−34	57
24	−65	68	13	80	7	−63	67

[a] Sample lost on a poor chromatographic column.

In comparing the isomerization of palustric acid with those of levopimaric acid[2] and neoabietic acid,[4] these observations were made. (1) Palustric acid is more stable to heat than levopimaric acid and less stable to heat than neoabietic acid. After thirty minutes at 200° levopimaric acid was completely isomerized to other acids. Under the same conditions about half of the palustric acid and only 16% of the neoabietic acid was isomerized.

	Time, Hr.	Palustric, %	Abietic, %	Neoabietic, %
Levopimaric acid[2,3]	1/2	34	52	14
Neoabietic acid[4]	1/2	5	11	84
Palustric acid	1/2	54	42	4

(2) The logarithm of the concentration of palustric acid plotted against the time gives a straight line characteristic of first-order reactions. Levopimaric acid also gave a first-order reaction but neoabietic acid does not give a reaction curve characteristic of first- or second-order reactions. This is probably due to a back-reaction in the neoabietic acid isomerization with more neoabietic acid being formed from the original isomerization product, palustric acid. This back-reaction results in a progressive retardation of the reaction rate causing the reaction to fail to exhibit overall first-order kinetics. The same back-reaction effect probably occurs in the palustric acid isomerization from the neoabietic acid formed; however, the isomerization of the neoabietic acid to palustric acid is too slow to have any significant effect on the overall rate.

Thermodynamically heterannular dienes are more stable than homoannular dienes; therefore, palustric acid would be expected to form neoabietic acid more readily than neoabietic acid would form palustric acid.

The rate of isomerization of palustric acid at 200° was found to be approximately eight times as fast as the isomerization at 170°. Chromatographic analysis of the products of the isomerization at 170 and 200° showed that the composition of the eight-hour and the one-hour samples were essentially the same.

Temp.	Time, Hr.	Palustric, %	Abietic, %	Neoabietic, %
170	8	31	63	6
200	1	34	61	6

The isomerization products were shown to consist of abietic acid, neoabietic acid, and palustric acid. The peaks from the chromatographic analysis were checked by ultraviolet absorption analysis and showed only the presence of the three suspected acids. No levopimaric acid was detected in any of the isomerization products. The ultraviolet absorption spectrum and the specific rotation gave no indication that levopimaric acid was present in any of the products.

The rate of isomerization of methyl palustrate was also measured by change in specific rotation and specific extinction coefficient. The ester showed marked stability to heat like methyl neoabietate[4] and methyl levopimarate.[2] It was estimated from the specific rotations that the rate of isomerization of the acid was about 2,000 times as fast as that of the ester.

EXPERIMENTAL

The palustric acid used for the thermal isomerization studies was prepared by the method of Loeblich, Baldwin, and Lawrence.[5] It had an $[\alpha]_D$ +71° (2% in ethanol, m.p. 162–167°), and was shown by chromatographic and ultraviolet absorption analysis to contain more than 99% palustric acid.

One-tenth gram samples of palustric acid were placed in glass tubes and the air replaced with nitrogen by thorough flushing and repeated evacuation. The tubes were sealed off under high vacuum and heated in an oil bath for specified lengths of time.

Analysis of the 170° thermally isomerized palustric acid. The data obtained on each sample included the specific rotation, ultraviolet absorption analysis and chromatographic analysis. The chromatographic procedure and the values used to calculate the specific rotations and specific extinction coefficients are described by Loeblich, Baldwin, O'Connor, and Lawrence.[2] A summary of the data on the thermal isomerization of palustric acid at 170° is given in Table I.

TABLE II

SUMMARY OF DATA ON THE THERMAL ISOMERIZATION OF PALUSTRIC ACID AT 200°

Time (Hr.)	$[\alpha]_D$ 2% C_2H_5OH	α at 241 mμ	Palustric, %	Abietic, %	Neoabietic, %	Calcd. $[\alpha]_D$	Calcd. α at 241 mμ
0	+71		99+				
0.25	+19	27	72	27	2	+26	31
0.50	−3	37	54	42	4	0	42
0.75	−26	45	40	54	6	−21	51
1	−35	51	34	61	6	−31	56
1.5	−48	56	26	67	6	−42	60
2	−53	61	19	72	7	−51	63
4	−63	62	15	77	7	−59	66
8	−68	68	11	80	7	−66	68

The identity of the palustric, abietic and neoabietic acids was confirmed by checking the ultraviolet absorption spectrum of the peaks from a chromatographic analysis.

Thermal isomerization of palustric acid at 200°. The isomerization of palustric acid at 200° was observed by the same method as at 170°. A summary of the data on the thermal isomerization of palustric acid at 200° is given in Table II.

Thermal isomerization of methyl palustrate at 200°. Methyl palustrate was prepared by treating an ether solution of palustric acid with an excess of an ether solution of diazomethane. The solution was extracted with dilute alkali, washed neutral with water and the ether removed by distillation. The ester crystallized from methanol, m.p. 24–27°, $[\alpha]_D$ + 67.0°, α 26.5 at 265–266 mμ. The ester was sealed in an evacuated tube and after heating at 200° for 72 hr. had the following constants; $[\alpha]_D$ + 62.9°, α 22.4 at 265–266 mμ.

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[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH LABORATORY, THE DOW CHEMICAL CO., TEXAS DIVISION]

Hydrogenolysis of Ketals

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Hydrogenolysis of ketals in the presence of acid and rhodium or palladium yields ethers and alcohols. Ketals of secondary alcohols react faster than those of primary alcohols. A mechanism is suggested.

The literature contains several references to the hydrogenolysis of aldehyde acetals to ethers and alcohols, usually under conditions of rather high temperature and pressure.[1] Hydrogenolysis of aldehyde and ketone acetals to hydrocarbons has also been reported,[2] but in each of these cases the $-C(OR)_2-$ group was a substituent on an aromatic nucleus. By hydrogenation Gorin[3] opened the ring of some cyclic ketals of sugars and obtained ether derivatives of the sugars. Bond scission occurred at the oxygen attached to the secondary carbon atoms of the sugars, indicating that secondary alkoxyl groups are more labile than primary ones in this reaction. Staff[1] stated that ketals could be hydrogenated to ethers and alcohols but gave no experimental data.

We have found that hydrogenation of acidified ketals gives high yields of saturated ethers and alcohols under mild conditions (Reaction 1). The reaction

$$R_2C(OR')_2 + H_2 \xrightarrow{H^+,\ Rh} R_2CHOR' + R'OH \quad (1)$$

has been demonstrated with the dimethyl, dibutyl, diisopropyl, and dicyclohexyl ketals of acetone and with cyclohexanone diisopropyl ketal. With ketals of secondary alcohols the hydrogenation proceeds rapidly to completion at room temperature, and with ketals of primary alcohols appreciable rates are obtained at 50 to 80°. Yields of isolated products, based on conversions calculated from the hydrogen uptake, ranged from 70% to nearly 100%. Recovery of starting materials, absence of by-products, and infrared analyses indicate that actual yields were approximately quantitative.

Tests of several platinum metal catalysts for the hydrogenation of isopropenyl methyl ether showed rhodium the most active. Platinum and ruthenium were almost inactive, and palladium was about half as active as rhodium. As these metals had the same

(1) F. Sigmund and G. Marchart, *Monatsh.*, **48**, 267 (1927); M. Cabanac, *Compt. rend.*, **188**, 1257 (1929); C. E. Staff (to Carbide and Carbon Chemicals Corp.), U. S. Patent **2,397,514** (April 2, 1946); N. V. Polak and Schwarz's Essencefabrieken, Dutch Patent 68,125 (June 15, 1951); J. W. Copenhaver (to General Aniline and Film Corp.), U. S. Patent **2,590,598** (March 25, 1952) and U. S. Patent **2,604,493** (July 22, 1952).

(2) T. Kariyone and Y. Kimura, *J. Pharm. Soc. Japan*, No. 500, 746 (1923); P. E. Papadakis, *J. Am. Chem. Soc.*, **58**, 665 (1936); T. Kariyone, T. Kajiura, A. Ueno, and N. Suzuki, *J. Pharm. Soc. Japan*, **73**, 493 (1953).

(3) P. A. J. Gorin, *J. Org. Chem.*, **24**, 49 (1959).

TABLE I

HYDROGENOLYSIS OF KETALS $R_2C(OR')_2$ TO ETHERS R_2CHOR' AND ALCOHOLS R'OH

Ketal R	Ketal R'	Moles	Time, Hr.	Temp.	H_2 Consumed, % of Theory	Material Balance, Moles: Ether	Alcohol	Recovered ketal	Properties of Ether: B.P.°	Mm.	n_D(T)	Density, g./ml. (T)
CH_3	n-C_4H_9	0.20	4	25	34							
			23	60	47	0.16	0.14	—[a]	103[b]	760	1.3853(25)	0.754(25)
CH_3	CH_3	2.00	17	25	5							
			73	50–80	24	0.47	—[a]	1.42	32[c,d]	760	1.3490(24)	0.722(24)
CH_3	i-C_3H_7	0.20	1	25	97	0.15	0.19	—[a]	69	760	1.3664(24)	0.724(24)
—[e]	i-C_3H_7	0.10	2.5	25	100	0.09	0.10	—[a]	155–156[f,g]	760	1.4283(25)	0.846(25)
CH_3	cyclo-C_6H_{11}	0.116	3	25	90	0.12[h]	0.11[h]	0[h]	155	760	1.4305(25)	—
						0.07[i]	—[a]	—[a]				

[a] Recovery not attempted. [b] Lit.[8] b.p. 108°(738), d_{15} 0.7594, $n_{5461}^{24.9}$ 1.3889. [c] Lit.[9] b.p. 32.5° (777), d_{20}^{20} 0.735, n_D^{20} 1.3576. [d] Purity determined by gas chromatography 98%. [e] R_2C = cyclohexyliden. [f] Lit.[6] b.p. 168–169° (716), n_D^{20} 1.4833, d_4^{20} 0.9285. [g] Purity determined by gas chromatography 98%. *Anal.* Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 75.97, 76.13; H, 12.82, 12.88. [h] Determined by infrared spectroscopy. [i] Isolated by distillation after conversion of the cyclohexanol to an acid ester.

order of activity with acetone diisopropyl ketal, rhodium was selected for use with the other ketals.

There is considerable evidence[4] that acidification of ketals results in the establishment of an equilibrium whose components are ketal, unsaturated ether, and alcohol (Equation 2). If R'' is a primary alkyl radical, the concentration of

$$R_2CH—CR'(OR'')_2 \overset{H^+}{\rightleftharpoons} R_2C{=}CR'(OR'') + R''OH \quad (2)$$

unsaturated ether is usually very small at room temperature but is large enough at elevated temperatures for the ether to be distilled from the mixture. Reichle[5] noted the ease with which ketals of secondary alcohols are decomposed by acids to unsaturated ethers, and this corresponds with our experience. We have also found that the infrared spectrum at room temperature of an acidified solution of acetone diisopropyl ketal in nine volumes of isopropyl alcohol contains a distinct absorption band at 6.05 μ, due to the unsaturated ether, which completely disappears when one volume of methanol is added. Evidently ketals of secondary alcohols are much more dissociated in this manner than are those of primary alcohols.

The dissociation of the ketal to unsaturated ether and alcohol probably constitutes the first step in the apparent hydrogenolysis of ketals. Hydrogenation then removes the unsaturated ether and this allows further conversion of the ketal. Accumulation of the alcohol opposes this dissociation and with the depletion of the ketal there finally results such a small concentration of unsaturated ether that hydrogenation virtually stops. Several experimental facts support this hypothesis. First, hydrogenolysis requires acid. It fails in neutral or alkaline media, even at 100°. Second, rates are in accord with the effects predicted from other reactions. They are in the same order as we have observed qualitatively for the ease of the acid-catalyzed splitting of ketals to unsaturated ethers and alcohols. Third, conversions of ketals of primary alcohols are less complete than those of secondary alcohols, probably because the equilibrium of Reaction 2 is less favorable to formation of unsaturated ether when the alkoxyl groups are primary. Fourth, the activity of catalysts is in the same order for both the ketals and unsaturated ethers.

Waser and co-workers[6] reported properties for cyclohexyl isopropyl ether which are abnormal among the properties of a series of related compounds which they prepared. The values we obtained fit well in Waser's series and together with other characterization data indicate that they are the properties of cyclohexyl isopropyl ether. Waser probably obtained a mixture of this ether and his starting material.

EXPERIMENTAL

Materials. Acetone dimethyl ketal (2,2-dimethoxypropane) was commercial material used as received from The Dow Chemical Company. The other ketals were specially prepared.[7] Electrolytic hydrogen was used in a Parr hydrogenation apparatus, Model No. 3911. The hydrogenation catalysts were obtained from Baker and Co., Incorporated.

(4) F. Sigmund and R. Uchann, *Monatsh.*, **51**, 234 (1929); A. Johannissian and E. Akunian, *Bull. univ. état R. S. S. Arménie*, No. 5, 245 (1930); D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **57**, 544 (1935); C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.*, **60**, 1905 (1938); W. H. Carothers and H. B. Dykstra, U. S. Patent 2,124,686, July 26, 1938; H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, 1955, 2052; W. L. Howard and N. B. Lorette, *J. Org. Chem.*, **25**, 525 (1960).

(5) W. T. Reichle, dissertation, The Ohio State University, 1958.

(6) E. Waser, H. Sommer, C. Landweer, and C. Gaza, *Helv. Chim. Acta*, **12**, 418 (1929).

(7) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521, 525 (1960).

(8) H. Henstock, *J. Chem. Soc.*, 1931, 372.

(9) *Handbook of Chemistry*, 8th ed., N. A. Lange, Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 592, 1374.

Hydrogenolysis of ketals. The ketal was placed in the hydrogenation vessel and 0.2 g. of rhodium (5%) on alumina and 1 drop of concentrated hydrochloric acid were added (0.5 g. of rhodium catalyst and 0.5 ml. of acid were used with the acetone dimethyl ketal). The mixture was then shaken with hydrogen at 35–60 p.s.i.g. for the time and at the temperature shown in Table I. If the alcohol produced were soluble in water, the mixture was extracted with water and the alcohol and ether isolated from the separated phases by distillation. To facilitate separation of the ethers from butanol and cyclohexanol, these alcohols were converted respectively to their acid malcate and phthalate esters by refluxing the product mixture with the anhydride. The acid esters were then extracted into aqueous bicarbonate solution, and the ethers were obtained by distillation. The butanol was recovered by distillation after saponification of its acid ester. The hydrogenation of the dimethyl and dibutyl ketals was started at room temperature, then conducted at a higher temperature until no change in hydrogen pressure could be detected in a 2-hr. interval. The amount of hydrogen consumed at each temperature, the material balance for the total hydrogenation, and other pertinent data are given in Table I.

FREEPORT, TEX.

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

Formylation of Pyrones in the Presence of Trifluoroacetic Acid

L. L. WOODS[1] AND P. A. DIX

Received May 19, 1960

This paper describes a new method of formylating pyrones through the use of carbon monoxide-hydrogen chloride mixture in the presence of trifluoroacetic acid as a catalyst.

Mononuclear pyrones, particularly the 4-pyrones which are our primary interest have, so far, resisted all our efforts to oxidize the appended alkyl or hydroxyalkyl groups to aldehydes or acids. Therefore, it was decided to devise a method to formylate these compounds without oxidation.

The method worked remarkably well for the formation of aldehydes from kojic acid, α-chloro-α-deoxy kojic acid and 2-hydroxymethyl-5-methoxy-4-pyrone to produce compounds of the I_{A-C} series given in Table I.

failure of methone to react in the expected way and because no consistent results could be obtained with any of the usual nitrogenous reagents commonly used to characterize carbonyl-containing compounds. All efforts to oxidize the pyrone aldehydes to the corresponding acids were failures.

It was visualized that the malonic acid derivatives resulting in the formation of a pyrone–acrylic acid (Table II) would serve the dual purpose of demonstrating the presence of the formyl group and also indicate the position of its attachment on

TABLE I

FORMYL DERIVATIVES OF PYRONES

No.	Pyrone	Yield, %	M.P.	Formula	Carbon		Hydrogen		Chlorine	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
I_A	2-Hydroxymethyl-5-methoxy-4-pyrone	82	165–166	$C_8H_8O_5$	52.17	52.53	4.37	4.64		
I_B	α-Chloro-α-deoxy-kojic acid	100	168–170	$C_7H_5ClO_4$	44.58	44.29	2.67	2.89	18.80	19.11
I_C	Kojic acid	67	159–160	$C_7H_6O_5$	49.42	49.54	3.55	3.82		
I_D	6-Methyl-2-pyrononc	72	193.5–194	$C_7H_6O_4$	54.55	55.09	3.92	4.09		
I_E	Coumarin	94	70–71.5	$C_{10}H_6O_3$	68.96	68.72	3.47	3.29		

Compounds I_{D-E} were subsequently prepared merely to ascertain if the method was effective on 2-pyrones. 2,6-Dimethyl-4-pyrone for some unaccountable reason failed to form more than a water insoluble oil which could not be crystallized and could not be distilled, and benzodihydro-4-pyrone was so reactive that the monoformyl derivative was never isolated.

The malonic acid derivatives of most of the formylated pyrones were prepared because of the the pyrone ring. This latter premise would be effectively demonstrated if the aldehyde group were in position of 6 of kojic acid or α-chloro-α-deoxykojic acid since the resultant pyrone–acrylic acid would spontaneously cyclize to form coumaropyrones similar to those prepared previously.[2]

However, not only did the compounds fail to cyclize, spontaneously they also failed to cyclize when heated with 100% phosphoric acid at 120–

(1) To whom communications regarding this contribution should be addressed.

(2) L. L. Woods and P. A. Dix, *J. Org. Chem.*, 24, 1148 (1959).

TABLE II

ACRYLIC ACID DERIVATIVE

Pyrone Aldehyde	Yield, %	M.P.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
II_A	40	157.5	$C_9H_8O_6$	50.95	50.49	3.80	3.62		
II_B	54	166–167.5	$C_9H_7ClO_5$	46.87	46.39	4.36	4.08	15.37	15.68
II_C	46	167.5–169.5	$C_{10}H_{10}O_6$	53.10	53.19	4.45	4.68		
II_D	51	189–190	$C_9H_8O_5$	55.10	55.42	4.11	4.21		

130° and with concentrated sulfuric acid when heated at 90° for one hour.

The failure to obtain coumaropyrones proves unequivocally that the formyl group must be on position 3, as it is the only other position available for such attachment and the only position in which a formyl group would be sufficiently stable to form a pyrone–acrylic acid derivative.

Proof of the validity of the previous statement was obtained by producing the bisaldehyde of α-chloro-α-deoxy-kojic acid which when converted into the pyrone acrylic acid derivative gave the same melting point and mixed melting point of the pyrone–acrylic acid derivative of the mono-formylated I_B, indicating the instability of the formyl group in position 6.

The orientation of substituents on a pyrone ring is not surprising if consideration is given to the fact that trifluoroacetic acid is a powerful solvating agent[3] and that the compound acted upon by a substituent is no longer a pyrone but an activated complex of the pyrone hydrogenchloride salt. This, of course, now makes reasonable an assumption that the 3-position is activated due to the conversion of the nuclear oxygen to a positive pole created by co-ordination with the solvating trifluoroacetic acid.

Infrared data (Table III) did not give what we considered to be conclusive proof of formylation in compounds I_{A-C}; other physical means of demonstration were sought. An effort to determine molecular weights of these compounds was attempted by mass spectrographic means but the compound would not volatilize, so NMR studies were made to give the desired evidence.

The NMR spectra for compounds I_{A-C} are given in Table IV using 2,6-dimethyl-4-pyrone as a reference substance. The resonances appear at about the positions predicted by the Chamberlain[4] chemical shift charts except for the hydrogen of the formyl group. Any conjecture by the author, at this time, as to why the formyl group gives a peak at −0.7 would be valueless. The hydrogen of the hydroxyl group does not appear because rapid exchange broadens the peak beyond detection.

TABLE III

INFRARED ABSORPTION BANDS IN CM.$^{-1}$ (KBr Pellet)

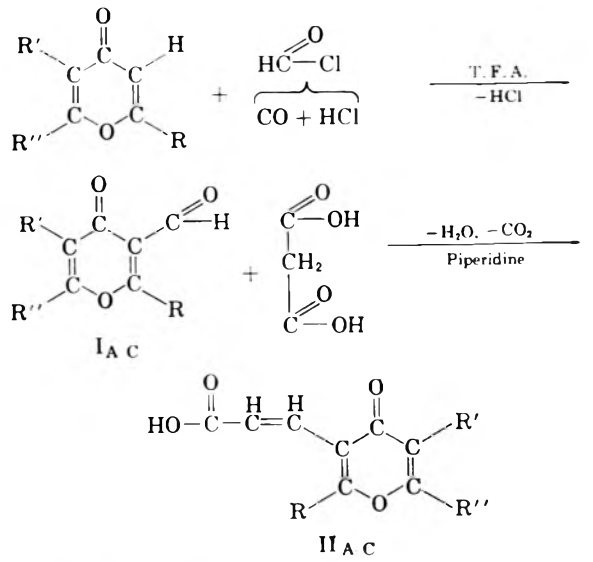
I_A	3125, 2857 shoulder, 1653, 1626, 1610, 1600, 1471, 1389, 1284, 1227, 1143, 1078, 943, 854
I_B	3125, 1653, 1618, 1587, 1453, 1374, 1282, 1225, 1166, 1117, 865, 8000
I_C	3125, 1631, 1603, 1266, 1221, 1152, 1092, 1005, 9615, 877

(3) L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 3059 (1960).

TABLE IV

DELTA (δ) VALUE OF NMR SPECTRA IN DIMETHYL SULFOXIDE

I_A	H, 1; $-CH_2OH$, 3.2; $-C(=O)-H$, −0.7; $-OCH_3$, 3.7
I_B	H, 0.7; $-CH_2Cl$, 2.8; $-C(=O)-H$, −0.7
I_C	H, 1; $-CH_2OH$, 3.2; $-C(=O)-H$, −0.7
2,6-Dimethyl-4-pyrone	H (nuclear), 1; H (methyl), 4.7



$I_{A\,C}$

$II_{A\,C}$

I_A. R = CH_2OH, R′ = OH, R″ = H
[2-Hydroxymethyl-3-formyl-5-hydroxy-4-pyrone]
I_B. R = CH_2Cl, R′ = OH, R″ = H
[2-Chloromethyl-3-formyl-5-hydroxy-4-pyrone]
I_C. R = CH_2OH, R′ = OCH_3, R″ = H
[2-Hydroxymethyl-3-formyl-5-methoxy-4-pyrone]
II_A = β—[2-Hydroxymethyl-5-hydroxy-4-pyrone-3] acrylic acid
II_B = β—[2-Chloromethyl-5-hydroxy-4-pyrone-3] acrylic acid
II_C = β—[2-Hydroxymethyl-5-methoxy-4-pyrone-3] acrylic acid

(4) N. F. Chamberlain, *Anal. Chem.*, **31**, 56 (1959).

EXPERIMENTAL[5]

Compounds of I_{A-E} *series.* In a wash bottle—tall form—fitted with a fritted aspirator plate was placed 0.15 mole of the pyrone with 30 ml. of trifluoroacetic acid. A 50–50 mixture of carbon monoxide and dry hydrogen chloride from a tank was bubbled fairly rapidly through the solution at room temperature for not less than 3 hr. Usually during the initial portion of the reaction period the mixture warmed up somewhat but as the pyrone dissolved the temperature decreased and the viscosity of the material increased to a thick sirup. At the termination of the reaction period the product was diluted with 100 ml. of water and chilled overnight in the freezing compartment of the refrigerator. The precipitate was suctioned off and dried in air. With compounds I_{A-C} the crude material was recrystallized twice from absolute ethanol. However, for I_D three recrystallizations from distilled water was necessary and I_E was purified by recrystallizing it twice from heptane.

Compounds of II_{A-D} *series.* A mixture consisting of 0.01 mole of the pyrone aldehyde, 0.01 mole of malonic acid, 5 drops of piperidine in 30 ml. of absolute ethanol was placed in a flask, protected from moisture, then immersed in a water bath at 80° for at least 5 hr. The solutions were then acidified with 10–15 drops of concentrated hydrochloric acid and chilled. The precipitates were recrystallized once from absolute ethanol. In the case of sample II_D the alcoholic solution was acidified, 50 ml. of water added, and then heated to drive off some of the ethanol. Upon chilling, a chocolate-colored precipitate was obtained which was taken up in distilled water, decolorized with Norite, and then chilled to give colorless crystals.

(5) All analyses were by Dr. Carl Tiedcke and all melting points were determined on a Fisher-Johns melting point assembly.

Reduction of I_C. Two grams of I_C was dissolved in 50 ml. of ethanol and 4 g. of potassium borohydride was added. The reaction flask was stoppered with cotton and allowed to stand overnight, following which 10 ml. of concentrated hydrochloric acid was added and an additional 40 ml. of ethanol. The solution was heated, filtered while warm, and the solution evaporated to dryness over a steam bath to give a brown compound which was 2,3-bis(hydroxy-methyl)-5-hydroxy-4-pyrone, crude yield 1.4 g.

The material was recrystallized twice from ethanol; it softened above 164° and melted at 167°.

Anal. Calcd. for $C_8H_{10}O_5$: C, 51.61; H, 5.42. Found: C, 51.90; 5.19.

Bisformylation of α-chloro-α-deoxykojic acid. To 30 g. of α-chloro-α-deoxy kojic acid in a wash bottle, described previously, 40 ml. of trifluoroacetic acid was added and the mixture of carbon monoxide–hydrogen chloride was bubbled in at a rapid rate for 6.5 hr. The solution was diluted with 200 ml. of water and chilled as previously stated; crude yield 21.3 g. Recrystallization of the compound three times from absolute ethanol gave a tan substance m.p. 165–166.5°.

Anal. Calcd. for $C_8H_5ClO_5$: C, 44.65; H, 2.32; Cl, 16.37. Found: C, 44.82; H, 2.52; Cl. 16.22.

Acknowledgment. The authors acknowledge with gratitude the financial assistance of the Robert A. Welch Foundation which made this study possible. We also wish to express our thanks to Drs. T. J. Greaney, Jr., and F. C. Stehling of the Humble Oil and Refining Company of Baytown, Tex., who obtained the NMR and infrared data.

HOUSTON 4, TEX.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Acylations of Bisacetylferrocene with Esters by Potassium Amide to Form Bis-β-diketones. Consideration of Mechanism[1]

CHARLES E. CAIN,[2] T. ARTHUR MASHBURN, JR., AND CHARLES R. HAUSER

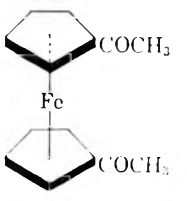
Received June 10, 1960

Acylations at both of the methyl groups of bisacetylferrocene with esters by potassium amide in liquid ammonia to form bis-β-diketones appears to be quite general. Unsuccessful attempts were made to isolate the corresponding mono-β-diketones, which might be expected as intermediates. The bis-β-diketones were allowed to react with an excess of hydrazine to form bis-pyrazoles. A mechanism for the diacylations is suggested.

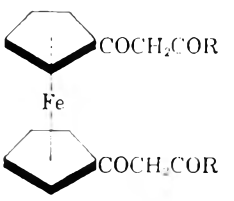
It has recently been observed[3] that both of the methyl groups of bisacetylferrocene (I) can be benzoylated readily with methyl benzoate by means of potassium amide to form the bis-β-diketone II in good yield.

It has now been found that I can similarly be acylated with ethyl acetate and ethyl propionate to form the bis-β-diketones III and IV respectively.

Although mono-β-diketones of type V might be expected to be formed as intermediates, no such compound could be isolated either in the previous work or in the present investigation.



I



II. R = C_6H_5
III. R = CH_3
IV. R = C_2H_5

That the products isolated were the bis-β-diketones II, III, and IV was supported not only by their analyses and molecular weight (for II),[4] but also by their infrared spectra, which showed

(1) Supported in part by the Office of Ordnance Research, U. S. Army.

(2) Esso Research and Engineering Company Fellow, 1957–1958.

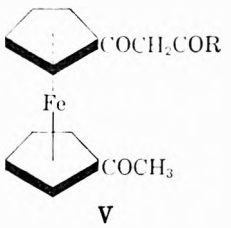
(3) C. R. Hauser and C. E. Cain, *J. Org. Chem.*, **23**, 1142 (1958).

TABLE I

YIELDS OF β-DIKETONES FROM BIS- AND MONOACETYLFERROCENES WITH ESTERS BY VARIOUS EQUIVALENTS OF POTASSIUM AMIDE

Expt. No.	Acetyl Ferrocene	KNH_2 Equiv.	Ester	Equiv.	Medium	Time, hr.	β-Diketone	Yield, %	Recov., I or IX, %
1	Bis (I)	1	Methyl benzoate	1	Liq. NH_3, then ether	5.5[a]	II	0	95
2	Bis (I)	1	Ethyl acetate	1	Liq. NH_3 then ether	3.5[a]	III	0	88
3	Bis (I)	2	Methyl benzoate	1	Liq. NH_3, then ether	8.5[a,d]	II	20	67
4	Bis (I)	2	Methyl benzoate	2	Liq. NH_3, then ether	6.5[a,d]	II	46	45
5	Bis (I)	2	Methyl benzoate	2	Liq. NH_3	0.33	II	—	83
6	Bis (I)	2	Ethyl acetate	1	Liq. NH_3, then ether[b]	4.5[a]	III	45–50	—
7	Bis (I)	4	Methyl benzoate	4	Liq. NH_3	0.33	II	10	82
8	Bis (I)	4	Methyl benzoate	4	Liq. NH_3	1.0	II	35	39
9	Bis (I)	4	Methyl benzoate	4	Liq. NH_3	5.0	II	72	—
10	Bis (I)	4	Methyl benzoate	4	Liq. NH_3, then ether	4.5[a,d]	II	62	20
11	Bis (I)	4	Ethyl acetate	4	Liq. NH_3	0.33	III	—	85
12	Bis (I)	4	Ethyl acetate	4	Liq. NH_3, then ether	1.25[a,c]	III	72	9
13	Bis (I)	4	Ethyl propionate	4	Liq. NH_3, then ether	1.25[a,c]	IV	50	23
14	Mono (IX)	1	Methyl benzoate	1	Liq. NH_3	—	X	29	—
15	Mono (IX)	1	Ethyl acetate	1	Liq. NH_3	1.5	XI	25	—
16	Mono (IX)	2	Methyl benzoate	2	Liq. NH_3, then ether	1.5[a,e]	X	58–63	—
17	Mono (IX)	2	Ethyl acetate	2	Liq. NH_3, then ether	1.5[a]	XI	54–66	—
18	Mono (IX)	2	Methyl benzoate	2	Liq. NH_3	1.0	X	45	—

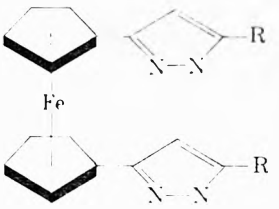
[a] The time in liquid ammonia was about 45 min., the remainder being in ether. [b] Ether at reflux for 4 hr. [c] Ether at reflux for 0.25 hr. [d] Ref. 3. [e] Ref. 10.



V

strong, broad bands in the region of 6.2–6.6 μ for their conjugate-chelate structures.[5] None of them gave a band in the region of 5.88–5.96 μ for a free carbonyl group,[6] which should have been present had the products been the mono-β-diketones of type V. Bisacetylferrocene (I) shows such a band at 6.0 μ. Only II exhibited a band at 14.5 μ attributable to the monosubstituted benzene ring.[7]

Further support for the structures of the bis-β-diketones II, III, and IV was their conversion to bispyrazoles VI, VII, and VIII respectively. The analyses of these products showed no oxygen, some of which would have been present had they been pyrazoles of mono-β-diketones of type V.



VI. R = C_6H_5
VII. R = CH_3
VIII. R = C_2H_3

The infrared spectra of these products were very similar to one another. They showed bands in the regions considered characteristic of the pyrazole ring[8] except in the region of 10.7 μ.[9]

In Table I are summarized the yields of bis-β-diketones II, III, and IV obtained from I under various conditions. Also in this table are given, for comparison, some results on the benzoylation and acetylation of mono-acetylferrocene (IX) to form mono-β-diketones X and XI respectively. While the benzoylation of IX with potassium amide has

(4) This molecular weight, which was not reported in Ref. 3, was determined by Dr. Carl Tiedcke, Laboratory of Microchemistry, Teaneck, N. J. Calcd. for $C_{28}H_{22}FeO_4$, 478. Found: 440, 464, 458, 447. Average 452 ± 10%.

(5) See L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley and Sons, New York, 1958, p. 142.

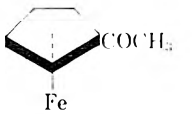
(6) See Ref. 5, page 137.

(7) See Ref. 8, page 76.

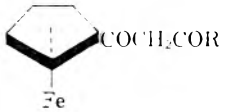
(8) See C. S. Rondestvedt and P. K. Chang, *J. Am. Chem. Soc.*, **77**, 6532 (1955).

(9) See P. Mirone and M. Vampiri, *Atti. acad. nazl. Lincie., Rend., Classe sci. fis., mat. e nat.*, **12**, 583 (1952); *Chem. Abstr.*, **46**, 9423 (1952).

previously been described[10] the acetylation with this reagent has apparently not been reported earlier.



IX



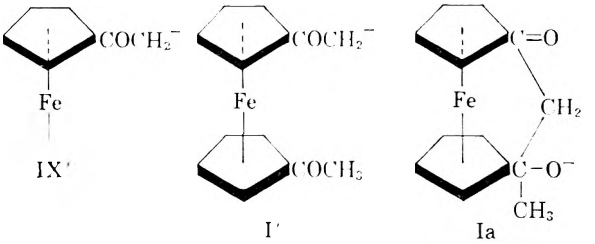
X, R = C_6H_5
XI, R = CH_3

It can be seen from Table I that the best yields of bis-β-diketones II, III, and IV were obtained employing four molecular equivalents each of potassium amide and appropriate ester to one of bisacetylferrocene (I) (Experiments 8, 10, 12, and 13). These proportions of reactants correspond to the use of two molecular equivalents each of an alkali amide and ester to one of a monoketone such as IX as recommended when the yield is to be based on the ketone.[11]

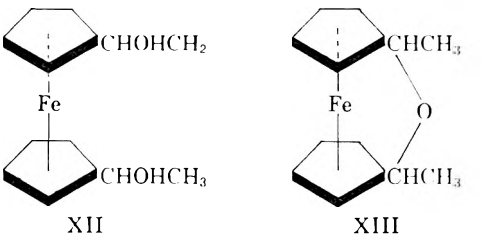
Whereas the acylation of ordinary monoketones have generally been effected in ether,[11] those of bis- and monoacetylferrocenes were initiated in a mixture of liquid ammonia and ether, and completed either in this medium or in ether after replacing the ammonia by the latter solvent (see Table I).

Attempts to stop the benzoylation and acetylation of bisacetylferrocene (I) at the monoacylation stage V were unsuccessful. These attempts included the neutralization of the reaction mixture before the acylation was complete and the use of less of the alkali amide and ester than that required for maximum yield. In all such experiments, only the bis-β-diketone was isolated and/or the starting bisacetylferrocene was recovered (see experiments 1,2,3,4,5,6,7,9, and 11). For example, when the reaction of I with four equivalents each of potassium amide and methyl benzoate in liquid ammonia was stopped after twenty minutes or one hour (experiments 7 and 8) the only product that could be isolated was the bis-β-diketone II and much of the starting bisacetylferrocene (I) was recovered. Moreover, in experiment 8 the crude, recovered I appeared not to be contaminated with any β-diketone as determined by an infrared spectrum (no band in the 6.1–6.5 μ region). Similarly when the benzoylation of I was effected with two equivalents of the alkali amide and one or two equivalents of the methyl benzoate (experiments 3 and 4), the only product isolated was II, much of I being recovered. From these results it may be concluded that the second acyl group is introduced into the molecule more readily than the first.

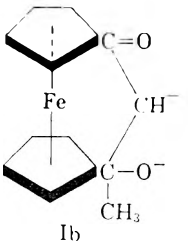
It can further be seen from Table I that one equivalent of potassium amide failed to effect the benzoylation or acetylation of the bisketone I (experiments 1 and 2), whereas this amount of reagent brought about considerable acylation of the monoketone IX (experiments 14 and 15). Even an excess of sodium methoxide has failed to effect the benzoylation of I[3], although this reagent has been reported to bring about the acetylation of IX to form XI in 29% yield.[12] As the reactive intermediate of IX is presumably monocarbanion IX′, the failure of I to be acylated by an equivalent of the alkali amide indicates that the corresponding monocarbanion I′ is not present in appreciable concentration. Instead I′ is suggested to undergo intramolecular cyclization to form the anion Ia, which might not be expected to be acylated under the conditions employed.



There is evidence that the two groups of certain bis derivatives of ferrocene have a "*cis*" configuration[13] as would be required for the formation of Ia. Moreover there is only a low energy barrier to rotation in this type of molecule.[14,15] In this connection, we have observed that the bisglycol XII readily undergoes an acid-catalyzed dehydration in refluxing ethanol-water to form cyclic ether XIII.[16]



As two or more equivalents of potassium amide effects the acylation of I (see Table I), this amount of reagent evidently produces an intermediate carbanion which, on the assumption that the monoanion has cyclic structure Ia, would presumably be Ib.



Ib

(10) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 482 (1957).

(11) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 114, 122 (1954).

(12) V. Weinmayr, *Naturwiss*, **45**, 311 (1958).

(13) See D. A. Semenov and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 2741 (1957).

(14) See M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

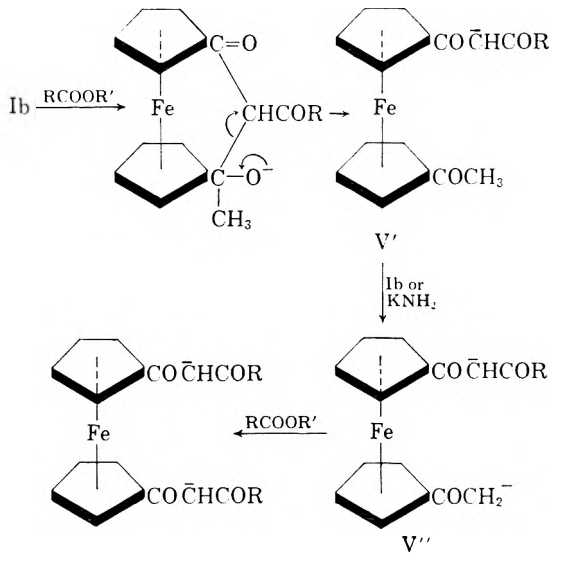
(15) See Yu. T. Struchkov, *Zhur. Obschchei Khim.*, **27**, 2039 (1957).

(16) The details of this reaction will be published later.

Some support for the formation of such a carbanion with two equivalents of the reagent but not with one is the observation that the addition of one equivalent of the reagent to an orange-red suspension of I in liquid ammonia produced no color change, whereas the addition of a second equivalent gave a dark, brown-red mixture. Step-wise neutralization of the reaction mixture with ammonium chloride reversed these color changes, and 88% of I was recovered. On the other hand, the addition of one equivalent of the reagent to a brown-red solution of monoacetylferrocene (IX) in liquid ammonia produced a brown-yellow mixture indicating the formation of a carbanion. This color change was reversed on adding an equivalent of ammonium chloride.

The acylation of carbanion Ib with an ester to form the dianion of bis-β-diketone II, III, or IV is suggested to follow the course outlined in Scheme A.

SCHEME A



According to Scheme A, the first acylation occurs at a carbanion of a methylene ketone (Ib) and the second acylation, at the carbanion of a methyl ketone (V''). As methyl ketones are known to undergo acylation more readily than similar methylene ketones,[17] Scheme A is in line with the conclusion drawn above that the second acyl group is introduced into the bisacetylferrocene molecule more readily than the first. The more rapid introduction of the second acyl group might be favored by a greater solubility of the dipotassio salt of dicarbanion V'' compared to that of the dipotassio salt of dianion Ib and possibly also by the isomerization of "*cis*" dianion V'' to the "*trans*" configuration because of repulsion between the negative charges on the two side-chains.

(17) See Ref. 11, p. 69.

EXPERIMENTAL[18]

Acylations of bisacetylferrocene (I) *to form bis-β-diketones.* The results under various conditions are summarized in Table I, the yields of products being based on essentially pure compounds. The experiments employing 4 equivalents each of the reagent and ester, which produced the best yields, are described below.

A. *With methyl benzoate to form* II. This reaction has previously been initiated in a mixture of liquid ammonia and ether but completed in ether alone. It has now been effected entirely in a mixture of liquid ammonia and ether as described below.

To a stirred solution of 0.1 mole of potassium amide in 300 ml. of liquid ammonia[19] was added 6.8 g. (0.025 mole) of bisacetylferrocene (I). The resulting yellow suspension was stirred for 30 min., and 13.6 g. (0.1 mole) of methyl benzoate in 100 ml. of dry ether was added dropwise. The resulting red-brown suspension was stirred in liquid ammonia for 5 hr. and then neutralized with an excess of ammonium chloride. The ammonia was replaced with ether on the steam bath, and the resulting ethereal suspension was filtered. The dark red bis-β-diketone II on the funnel was washed thoroughly with ether followed by water. It melted at 208–210° and, after recrystallization from acetone at 212–214°; reported m.p. 213.5–214°.[3] The yield was 8.7 g. (72%). Some infrared bands occurred at 6.2, 6.35, 6.75, 7.75, and 14.5 μ.

B. *With ethyl acetate to form* III. To a rapidly stirred solution of 0.1 mole of potassium amide in 250 ml. of liquid ammonia[19] was added 6.8 g. (0.025 mole) of I, followed after 30 min., by 8.8 (0.1 mole) of ethyl acetate in 150 ml. of anhydrous ether. The resulting red suspension was stirred for 1 hr., and the ammonia was then evaporated as 300 ml. of anhydrous ether was added. After stirring for about 25 min., the ethereal suspension was filtered, and the red solid on the funnel was washed thoroughly with ether. The solid (presumably the dipotassio salt of bis-β-diketone III) was dissolved in 150 ml. of water, and the solution was acidified with concentrated hydrochloric acid to *p*H 4. The resulting precipitate was collected and recrystallized from chloroform-hexane to give 6.3 g. (72%) of bis-acetyl-β-diketone III as small red crystals, m.p. 142.5–144°. Some infrared bands occurred at 6.2, 6.4, 6.5, 6.8, 7.4, and 7.75 μ.

Anal. Calcd. for $C_{18}H_{18}Fe$: C, 61.04; H, 5.12; Fe, 15.77. Found: C, 60.94; H, 4.87; Fe, 15.99.

C. *With ethyl propionate to form* IV. This acylation was effected essentially as described above for III, employing 0.2 mole of potassium amide[19] in 250 ml. of liquid ammonia, 0.05 mole of I, and 0.2 mole of ethyl propionate in 100 ml. of ether. There was obtained 9.5 g. (50%) of bis-propionyl-β-diketone IV as fine, red crystals, m.p. 114–115.5°. Some infrared bands occurred at 6.3, 6.6, 6.8, and 7.4 μ.

Anal. Calcd. for $C_{20}H_{22}O_4Fe$: C, 62.84; H, 5.80; Fe, 14.62. Found: C, 62.89; H, 5.82; Fe, 15.37.

Acylations of monoacetylferrocene (IX) *to form mono-β-diketones.* The results of the benzoylation are reported in Table I. The acetylation was carried out as described below.

To a rapidly stirred solution of 0.11 mole of potassium amide[19] in 300 ml. of liquid ammonia was added 12.5 g. (0.055 mole) of monoacetylferrocene. The resulting yellow suspension was stirred for 15 minutes and 9.7 g. (0.11 mole) of ethyl acetate in 150 ml. of dry ether was added dropwise to produce a red suspension. After 1 hr. an excess of ammonium chloride was added, and the ammonia replaced with dry ether. The mixture was filtered and the ethereal filtrate was shaken with an excess of saturated copper acetate solution to produce an orange-red solid. The mixture was

(18) Melting points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained on a Perkin-Elmer Model 21 recording spectrophotometer.

(19) See C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

filtered, and the solid was washed well with water followed by ether. This solid was shaken with 15% hydrochloric acid to give 9.6 g. (60%) of monoacetyl-β-diketone XI as red crystals; after recrystallization from hexane the compound melted at 97–97.5°, reported[12,20] m.p. 96–97°.

Anal. Calcd. for $C_{14}H_{14}FeO_2$: C, 62.25; H, 5.22. Found: C, 62.67; H, 5.30.

Cyclizations of bis-β-diketones with hydrazine to form pyrazoles. Pyrazole VI was prepared as previously described.[3]

To a solution of 1 g. of bis-β-diketones III or IV in 200 ml. of absolute ethanol was added 10 g. of 95% hydrazine in 20 ml. of absolute ethanol to produce a deep red color. After adding 1 drop of glacial acetic acid, the solution was boiled for a few minutes. The resulting bright-red solution was cooled overnight in the refrigerator.

Pyrazole VII was obtained in 89% yield as a pink powder, m.p. 300° dec. Some infrared bands occurred at 6.3, 6.85, 7.28, 7.7, and 8.65 μ.

Anal. Calcd. for $C_{18}H_{18}N_4Fe$: C, 62.44; H, 5.24; N, 16.18; Fe, 16.13. Found: C, 62.04; H, 5.41; N, 16.16; Fe, 16.38.

Pyrazole VIII was obtained in 99% yield as a pink powder, m.p. 300° dec. Some infrared bands occurred at 6.25, 6.35, 6.85, 7.25, 7.7, and 8.62 μ.

Anal. Calcd. for $C_{20}H_{22}N_4Fe$: C, 64.18; H, 5.93; N, 14.97; Fe, 14.92. Found: C, 64.18; N, 15.01; Fe, 14.96.

DURHAM, N. C.

(20) See L. Wolf and M. Beer, *Naturwiss.*, **44**, 442 (1957).

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

Ferrocenyl and 1,1′-Ferrocenylene Grignard Reagents[1a]

HAROLD SHECHTER AND JOHN F. HELLING[1b]

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Grignard reagents have been prepared by controlled reactions of magnesium with chloroferrocene, bromoferrocene, iodoferrocene, and 1,1′-dibromoferrocene, respectively, in tetrahydrofuran. Advantageous techniques involving methyl iodide and ethylene bromide have been developed. Ferrocenyl Grignard reagents decompose at elevated temperatures to give ferrocene and biferrocenyl; in the presence of cobaltous chloride, ferrocenylmagnesium bromide gives biferrocenyl in 80% conversion. These abnormal Grignard reactions apparently involve ferrocenyl radicals.

Lithio and sodioferrocenes are obtained by exchange of ferrocene with butyllithium[2] and phenyl- or amyl sodium,[3] respectively. These preparations often have disadvantages that mixtures of mono and dimetalloferrocenes are formed, and the excess metal alkyls or aryls required compete undesirably in many preparative sequences. Ferrocenyl Grignard reagents have not been previously described; efforts to prepare ferrocenylmagnesium iodide from iodoferrocene and magnesium in ethyl ether have been unsuccessful.[4] It is now reported that chloroferrocene, bromoferrocene, and iodoferrocene (Table I) react with magnesium powder in tetrahydrofuran under controlled conditions to give Grignard reagents in satisfactory yields. 1,1′-Dibromoferrocene has been converted to its di-Grignard reagent (59%). The yields of these reagents were determined by carbonation and isolation of the resultant carboxylic acids. The potential utility of ferrocenyl Grignard reagents in synthesis is indicated by the present results in conjunction with the elegant methods for preparing bromo- and chloroferrocenes from lithioferrocenes and butyl borate and subsequent reaction of ferrocenylboronic acids with cupric halides.[5]

Reactions of haloferrocenes and magnesium to give Grignard reagents occur under oxygen-free nitrogen when initiated with methyl iodide; an attempt to use iodine as an initiator was unsuccessful. The relative reactivities of haloferrocenes are typical: iodo> bromo> chloro. The rates of reaction and conversions to Grignard reagents are increased by use of methyl iodide or ethylene bromide as entrainers (Table I). Methylmagnesium iodide does not undergo exchange with bromoferrocene under conditions for preparing the ferrocenyl Grignard reagent.

Haloferrocenes also react with magnesium in tetrahydrofuran to give biferrocenyl and ferrocene. Thus, reaction of iodoferrocene and magnesium at 25–30° for three hours in the presence of ethylene

(1)(a) Abstracted from a portion of the Ph.D. Dissertation of J. F. Helling, The Ohio State University, 1960. (b) DuPont Company Fellow, 1958–1959; National Science Foundation Cooperative Fellow, 1959–1960. Present address, Chemistry Department, Massachusetts Institute of Technology, Cambridge, Mass.

(2)(a) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954). (b) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954).

(3)(a) A. N. Nesmeyanov, E. G. Perevalova, and Z. A. Beinoravichute, *Doklady Akad. Nauk S.S.S.R.*, **112**, 439 (1957). (b) A. N. Nesmeyanov, E. G. Perevalova, Z. A. Beinoravichute, and I. L. Malygina, *Doklady Akad. Nauk S.S.S.R.*, **120**, 1263 (1958).

(4) A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **100**, 1099 (1955).

(5)(a) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Doklady Akad. Nauk S.S.S.R.*, **126**, 1004 (1959). (b) In the present research (see Experimental) preparation of lithioferrocenes in 1:1 tetrahydrofuran–ethyl ether and subsequent reaction with butyl borate in ethyl ether resulted in 44% conversion to ferrocenylboronic acid and 18% conversion to 1,1′-ferrocenylenediboronic acid; 29% ferrocene was recovered. (c) Iodoferrocene is prepared by reaction of chloromercuriferrocene and iodine (see Experimental).

TABLE I

REACTIONS OF HALOFERROCENES AND MAGNESIUM

Haloferrocene[a]	Reactant Ratio, Mole			Temp., °	Time,[b] Hr.	Conv.,[c,d] %	Recovery, %; Haloferrocene[e]
	Haloferrocene	Mg	CH_3I				
Chloro	1	4	1	46–48[f]	4.0	15	79
Bromo	1	3	–[g]	38–42[f]	3.5	49[h]	34
Bromo	1	4	1	37–39[f]	2.0	84	11
Iodo	1	3	–[g]	11–12	2.5	47	44
Iodo	1	4	1	11–12	1.0	65	27
1,1′-Dibromo	1	5	2	33–34[f]	5.25	59[i]	Trace

[a] Reactions were performed with 0.5–1.0 g. of the haloferrocene and 15–20 ml. of tetrahydrofuran. [b] Time after dropwise addition of halide. [c] Conversion of haloferrocene to Grignard reagent; determined by addition of Dry Ice to give the carboxylic acid. [d] Optimum conditions for preparing the Grignard reagents were not determined. [e] The recovered haloferrocene, on the basis of melting points and infrared spectra, contained ferrocene. [f] The halides in tetrahydrofuran were added at room temperature. [g] Methyl iodide in trace amounts was used as the initiator. [h] Biferrocenyl was formed in 9% conversion. [i] Conversion to 1,1′-ferrocenedicarboxylic acid; ferrocenecarboxylic acid was also obtained in 16% conversion.

bromide as an entrainer yielded ferrocene (62%) and biferrocenyl (34%). Bromoferrocene, magnesium, and methyl iodide at 38–42° for three and a half hours gave biferrocenyl (9%), ferrocene, and the ferrocenyl Grignard reagent. At elevated temperatures the yields of Grignard reagents are substantially reduced by formation of ferrocene and biferrocenyl. Analogously, reaction of butyllithium and iodoferrocene in ethyl ether at 0° and subsequent carbonation gave biferrocenyl (20%), ferrocene (60%), and ferrocenecarboxylic acid (17%). Reaction of ferrocenylmagnesium bromide with cobaltous chloride gave biferrocenyl in 80% conversion.[6]

Formation of biferrocenyl and ferrocene in the present systems may indicate that ferrocenyl radicals are generated readily[6] (Equation 1); dimerization of ferrocenyl radicals (Equation 2) or exchange with the solvent (Equation 3) may thus give biferrocenyl and ferrocene.[7] The incursion

$$C_5H_5—Fe—C_5H_4—MgX \longrightarrow C_5H_5—Fe—C_5H_4\cdot + \cdot MgX \quad (1)$$

$$2C_5H_5—Fe—C_5H_4\cdot \longrightarrow C_5H_5—Fe—C_5H_4—C_5H_4—Fe—C_5H_5 \quad (2)$$

$$C_5H_5—Fe—C_5H_4\cdot + H—R \longrightarrow C_5H_5—Fe—C_5H_5 + \cdot R \quad (3)$$

of these abnormal Grignard reactions under relatively mild conditions to yield biferrocenyl and ferrocene appears to have much in common with reactions of diferrocenylmercury and silver[8] or palladium black,[9] iodoferrocene and copper bronze,[8] and ferrocenylboronic acid and ammoniacal silver oxide[5a] to give analogous products.[10]

EXPERIMENTAL

Iodoferrocene. Iodoferrocene[4] was prepared advantageously in the present study by reaction of chloromercuriferrocene and iodine in partial solution in methylene chloride. After the mixture had been stirred 30 min. at room temperature, methylene chloride was evaporated and the iodine complexes destroyed with aqueous sodium thiosulfate. The product was dissolved in petroleum ether, passed through an alumina column, and concentrated. Vacuum sublimation[11] of the red oily residue gave iodoferrocene (70% conversion), m.p. 43–45°; lit.[4] m.p. 44–45°.

Ferrocenylboronic acid and 1,1′-ferrocenylenediboronic acid. Ferrocenylboronic acid and 1,1′-ferrocenylenediboronic acid were obtained by an improved modification of a previous procedure.[5a] Ferrocenyllithium was prepared in tetrahydrofuran–ethyl ether[12] (1:1 by volume, 220 ml.) from butyllithium (~0.27 mole) and ferrocene (16.7 g., 0.09 mole). The mixture was filtered through glass wool and then added dropwise in 2 hr. to butyl borate (72.5 g., 0.315 mole) in ethyl ether (50 ml.) at −70°. A solid formed. The mixture was warmed to room temperature (1.5 hr.), decomposed with 10% aqueous sodium hydroxide (100 ml.) and filtered. The ether solution was extracted nine times with 10% aqueous sodium hydroxide (total vol., 400 ml.). Acidification of the basic solution with 10% sulfuric acid at 0° gave a yellow precipitate which was washed with water. Soxhlet extraction of the precipitate with ethyl ether for 4 days removed ferrocenylboronic acid (9.02 g., 0.039 mole, 44%)

(6) Related homolytic decomposition reactions of Grignard reagents are summarized and discussed by M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, pp. 116–137.

(7) Reaction of iodoferrocene and magnesium at room temperature (see Experimental) and subsequent carbonation of the mixture gave only biferrocenyl and ferrocene. The absence of ferrocenecarboxylic acid indicated that the Grignard reagent had been completely destroyed before carbonation and hydrolysis, and thus ferrocene was formed by radical exchange with the solvent rather than by hydrolysis. As stringent precautions were always taken to avoid hydrolysis of the Grignard reagents before carbonation, formation of ferrocene by radical-exchange with the solvent appears to be a general competitive process.

(8) M. D. Rausch, *J. Am. Chem. Soc.*, 82, 2080 (1960).

(9) O. A. Nesmeyanova and E. G. Perevalova, *Doklady Akad. Nauk S.S.S.R.*, 126, 1007 (1959).

(10)(a) Other reactions of ferrocenyl Grignard reagents are being investigated. (b) Lithioferrocene and dinitrogen tetroxide in ethyl ether at −70° give nitroferrocene, m.p. 124–125°, in 2% yield. The melting point of nitroferrocene was previously reported incorrectly (96–97°); J. F. Helling and H. Shechter, *Chem. & Ind.*, 1157 (1959). Reaction of ferrocenylmagnesium bromide and dinitrogen tetroxide in ethyl ether–tetrahydrofuran at −70° does not yield nitroferrocene.

(11) Vacuum sublimation is a convenient method for purifying iodoferrocene, bromoferrocene, and chloroferrocene.

(12) D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. & Ind.*, 1388 (1957).

which was obtained as a yellow powder after evaporation of solvent, m.p. 136–140° dec.; lit.[6a] m.p. 143–148°. Remaining as an insoluble yellow powder from the Soxhlet extraction was 1,1′-ferrocenylenediboronic acid (4.42 g., 0.016 mole, 18%), dec. ~200°; lit.,[5a] dec. 180°.

The ether solution which had been washed with alkali was concentrated; filtration and vacuum sublimation of the precipitate gave crude ferrocene (4.93 g., 29%).

Ferrocenylmagnesium bromide (Methyl iodide as entrainer). Anhydrous tetrahydrofuran (5 ml.) was added to magnesium powder (0.36 g., 0.0148 g.-atom, 80–200 mesh) flamed briefly under oxygen-free dry nitrogen.[13] After the magnesium had been activated with a drop of methyl iodide, a solution of bromoferrocene (1.00 g., 0.0038 mole) and methyl iodide (0.53 g., 0.0037 mole) in tetrahydrofuran (10 ml.) was added dropwise with stirring at 31–33°. The mixture was then stirred at 37–39° for 2 hr. under nitrogen, cooled to 0°, and Dry Ice was added.[14] After the mixture had been acidified with hydrochloric acid and diluted with ether, the organic layer was extracted with excess aqueous sodium hydroxide (10%). The orange basic solution was cooled to 0° and neutralized with cold hydrochloric acid. A voluminous yellow precipitate formed which was extracted with ether. After the ether solution had been evaporated to dryness, ferrocenecarboxylic acid (0.73 g., 0.0032 mole, 84%) was obtained, m.p. 194–197° dec. after crystallization from ether–petroleum ether (b.p. 30–60°). lit.[2b] m.p. 192–205° dec.; lit.[15] m.p. 219–225° dec. The infrared spectrum of the acid was identical with that of an authentic sample.

The initial organic layer, after the extraction with sodium hydroxide, was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. Vacuum sublimation of the residue gave a mixture of bromoferrocene and ferrocene (0.11 g., 11% calculated as bromoferrocene, 15% calculated as ferrocene),[16] m.p. 75–125°.

Ferrocenylmagnesium bromide (Methyl iodide as initiator). Ferrocenylmagnesium bromide was prepared as previously described with the exceptions that no entrainer was used and the reaction was effected at 38–42° for 3.5 hr. Bromoferrocene (0.96 g., 0.0036 mole), magnesium powder (0.26 g., 0.0108 g.-atom) and initiator amounts of methyl iodide in tetrahydrofuran (15 ml.) gave ferrocenecarboxylic acid (0.41 g., 0.0018 mole, 49%), m.p. 194–197° dec. after crystallization from ether–petroleum ether.

Vacuum sublimation of the nonacidic products gave a mixture of ferrocene and bromoferrocene (0.33 g., 34% calculated as bromoferrocene). Remaining as a nonsublimable residue was biferrocenyl (0.06 g., 0.00016 mole, 9%), m.p. 233–237° after recrystallization from benzene-ligroin; lit.[8] m.p. 239–240° dec. Identification of biferrocenyl was confirmed by its infrared spectrum.[17]

Attempted reaction of bromoferrocene and methylmagnesium iodide. Methylmagnesium iodide was prepared under oxygen-free, dry nitrogen from methyl iodide (0.88 g., 0.0062 mole) and magnesium powder (0.13 g., 0.0056 g.-atom) in tetrahydrofuran (15 ml.) at 27° for 1.5 hr.; only traces of magnesium remained. Bromoferrocene (0.50 g., 0.00187 mole) in tetrahydrofuran (5 ml.) was added dropwise with stirring at 27°. The mixture was stirred at 37–40° for 2 hr., cooled to 0°, and Dry Ice was added. Isolation of products by methods previously described gave bromoferrocene (0.38 g., 76%) m.p. 29–30°; no ferrocenecarboxylic acid was detected.

Reaction of iodoferrocene and magnesium (Reduction and coupling). Magnesium turnings (0.57 g., 0.0233 g.-atom) in tetrahydrofuran (10 ml.) were activated with a small quantity of ethylene bromide. Iodoferrocene (2.34 g., 0.0075 mole) in tetrahydrofuran (20 ml.) was added dropwise with stirring under oxygen-free, dry nitrogen at room temperature. After ethylene bromide (2.82 g., 0.0150 mole) in tetrahydrofuran (25 ml.) had been added slowly, the mixture was stirred 3 hr., cooled to 0°, and Dry Ice added.

Following treatment of the mixture with hydrochloric acid, dilution with ether, and filtration, the organic layer was extracted with excess aqueous sodium hydroxide. The colorless alkaline extract contained no ferrocene derivatives. The ether solution was washed with water, dried, and evaporated. Vacuum sublimation of the residue gave ferrocene (0.86 g., 0.0045 mole, 62%), m.p. 168–174°; lit.[18] m.p. 173–174°. Remaining as a nonsublimable residue was biferrocenyl (0.47 g., 0.0012 mole, 34%), m.p. 236.5–237.5° after recrystallization from benzene-ethanol; lit.[8] m.p. 239–240°.

Reaction of ferrocenylmagnesium bromide and cobaltous chloride. Magnesium powder (0.33 g., 0.0135 g.-atom) under oxygen-free, dry nitrogen was activated with a drop of methyl iodide. A solution of bromoferrocene (0.72 g., 0.0027 mole) and ethylene bromide (0.51 g., 0.0027 mole)[19] in tetrahydrofuran (10 ml.) was added in 30 min. at 29–30°. After the mixture had been stirred for 2.5 hr. at 37–39°, anhydrous cobaltous chloride (0.23 g., 0.0018 mole)[20] was added all at once at 0°.

The mixture was warmed to room temperature, allowed to stand overnight, decomposed with hydrochloric acid, and worked up in the usual manner. Vacuum sublimation of the residue gave a mixture of ferrocene and bromoferrocene (0.13 g., 18% calculated as bromoferrocene[16]), m.p. 35–95°. Remaining as a red-orange residue was biferrocenyl (0.40 g., 0.0011 mole, 80%) which melted at 230–234° after recrystallization from benzene-ethanol.

Reaction of butyllithium and iodoferrocene. Butyllithium was prepared under nitrogen from butyl bromide (0.96 g., 0.007 mole) and lithium wire (0.0972 g., 0.014 g.-atom) in ethyl ether (10 ml.). Iodoferrocene (1.09 g., 0.0035 mole) in ethyl ether (15 ml.) was added dropwise with stirring at 0°. The mixture was stirred 1 hr. at 0° and then Dry Ice was added. After having been washed with hydrochloric acid, the mixture was extracted with aqueous sodium hydroxide. The ether layer was washed with water, dried, and evaporated. Vacuum sublimation of the residue gave impure ferrocene (0.39 g., 0.0021 mole, 60%), m.p. 140–165°; lit.[18] m.p. 173–174°. Biferrocenyl (0.13 g., 0.00035 mole, 20%) remained as a red-orange residue, m.p. 236–237° from benzene–petroleum ether; lit.[8] m.p. 239–240°.

Acidification of the basic extract gave a yellow precipitate which was extracted with ether. After the extract had been dried, ferrocenecarboxylic acid (0.14 g., 0.00060 mole, 17%) crystallized upon addition of petroleum ether, m.p. 194–197° dec.

Reaction of 1,1′-dibromoferrocene and magnesium. A solution of 1,1′-dibromoferrocene (0.55 g., 0.0016 mole) and methyl iodide (0.45 g., 0.0032 mole) in tetrahydrofuran (10 ml.) was added dropwise to stirred magnesium powder (0.20 g., 0.0080 g.-atom; activated with a drop of methyl iodide) in tetrahydrofuran (5 ml.) at 29–32° under nitrogen. The mixture was stirred at 33–34° for 5.25 hr. and cooled to 0°;

(13) L. F. Fieser, *Experiments in Organic Chemistry*, Third Edition, D. C. Heath and Co., Boston, Mass., 1957, p. 299.

(14) The techniques in preparing ferrocenylmagnesium chloride and iodide were similar to those presently described.

(15) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

(16) The percentage composition was not determined because of the difficulty in separating ferrocene from haloferrocenes.

(17) S. I. Goldberg and D. W. Mayo, *Chem. & Ind.*, 671 (1959).

(18) T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

(19) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

(20)(a) A. R. Pray, *Inorganic Syntheses*, Vol. V, McGraw-Hill, New York, 1957, p. 153. (b) M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.*, **63**, 2316 (1941).

Dry Ice was added. After the mixture had been treated with hydrochloric acid and diluted with ether and tetrahydrofuran, the organic layer was extracted with excess aqueous sodium hydroxide. The basic solution was cooled to 0° and neutralized with cold hydrochloric acid. The yellow precipitate which formed was extracted with tetrahydrofuran with the aid of added saturated aqueous sodium chloride and then recrystallized by addition of petroleum ether. The solid obtained was filtered and washed with ether. Evaporation of the ether washings and recrystallization of the residue from benzene and ether–petroleum ether gave ferrocenecarboxylic acid (0.06 g., 0.00026 mole, 16%) which was identified by comparison with an authentic sample.

Remaining as a residue from the ether washing was 1,1′-ferrocenedicarboxylic acid (0.26 g., 0.0016 mole, 59%) which did not melt or decompose below 280°; lit.,[2b] no melting or decomposition below 250°. The infrared spectrum of the 1,1′-ferrocenedicarboxylic acid obtained was identical with an authentic sample. The identity of the dicarboxylic acid was confirmed by esterification with methanol catalyzed by hydrochloric acid; chromatography on alumina and vacuum sublimation of the product gave dimethyl 1,1′-ferrocenedicarboxylate (73% conversion), m.p. 112–113°; lit.[2b] m.p. 114–115°.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE DOW CORNING CORP.]

Reaction of 3,3,3-Trifluoropropylmagnesium Bromide with Carbonyl Compounds

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Received August 18, 1960

The reaction of 3,3,3-trifluoropropylmagnesium bromide with methyl trifluoroacetate and 1,1,1,5,5,5-hexafluoro-2-pentanone in both ether and tetrahydrofuran has shown the Grignard to be only a weak reducing agent. In the case of methyl trifluoroacetate, the principal product was a solid which on hydrolysis yielded the hydrate of 1,1,1,5,5,5-hexafluoro-2-pentanone. Evidence for the structure of this solid intermediate, $CF_3CH_2CH_2C(OCH_3)(OMgBr)CF_3$, and a reaction mechanism involving this intermediate are presented.

Fluorine-containing Grignard reagents have been studied extensively and, in particular, the preparation and reactions of the perfluoroalkylmagnesium halides have received much attention.[1] However, derivatives of the type $R_fCH_2CH_2MgX$ (R_f = CF_3, C_2F_5, etc.) have been studied only briefly in reactions of limited scope.[2,3] In this laboratory a study was undertaken to ascertain the differences between a Grignard of the above type and a nonhalogenated Grignard in reactions in which reduction by the Grignard reagent generally occurs. For this purpose, the reaction of 3,3,3-trifluoropropylmagnesium bromide (I) with fluorine-containing carbonyl compounds was chosen.

The tendency of fluorine-containing esters to undergo reduction in preference to addition with certain Grignard reagents has been extensively discussed.[2,4–8] In this study, the reaction of I with methyl trifluoroacetate in ether solution formed an insoluble material which on hydrolysis and further treatment with phosphorus pentoxide gave 1,1,1,5,5,5-hexafluoro-2-pentanone (II). No reduction was observed. A similar reaction conducted in tetrahydrofuran indicated no formation of a solid precipitate and yielded II as well as 1,1,1,7,7,7-hexafluoro - 4 - (trifluoromethyl) - 4-heptanol (III) and 1,1,1,5,5,5-hexafluoro-2-pentanol (IV). The last compound, resulting from reduction by the Grignard, was formed in only 12% yield. In an effort to increase the yield of reduction product (IV), the reaction was conducted in the presence of an excess of isopropylmagnesium bromide in ether solution.[8] The principal product of this reaction was 1,1,1-trifluoro-3-methyl-2-butanol (V) as well as lesser amounts of II, III and IV. In contrast to the poor reducing action of I, the reaction of methyl trifluoroacetate with *n*-propylmagnesium bromide in ether was found to give only 1,1,1-trifluoro-2-pentanol (VI), the reduction product.

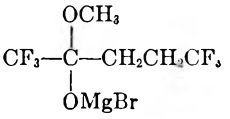
Addition of magnesium bromide to the methyl trifluoroacetate prior to the addition of I in tetrahydrofuran solution changed the product distribution markedly. The principal product was the ketone (II) with only trace amounts of III and IV. A similar reaction conducted in ether solution gave only II, as was the case in the absence of magnesium bromide.

The reaction of II with trifluoropropyl Grignard in ether formed the addition product (III) in good yield together with a small yield of the reduction product (IV). Addition of magnesium

(1) J. J. Lagowski, *Quart. Rev.*, **Vol. XIII**, No. 3, 233 (1959).
(2) O. R. Pierce, E. T. McBee, and R. E. Cline, *J. Am. Chem. Soc.*, **75**, 5618 (1958).
(3) E. T. McBee and A. Truchan, *J. Am. Chem. Soc.*, **70**, 2910 (1948).
(4) K. N. Campbell, J. O. Knoblock and Barbara K. Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950).
(5) E. T. McBee, J. F. Higgins, and O. R. Pierce, *J. Am. Chem. Soc.*, **74**, 1387 (1952).
(6) E. T. McBee, O. R. Pierce, and J. F. Higgins, *J. Am. Chem. Soc.*, **74**, 1736 (1952).
(7) E. T. McBee, O. R. Pierce, and M. C. Chen, *J. Am. Chem. Soc.*, **75**, 2324 (1953).
(8) O. R. Pierce, J. C. Siegle, and E. T. McBee, *J. Am. Chem. Soc.*, **75**, 6324 (1953).

bromide to the solution decreased the amount of reduction as would be expected.[9,10] However, a corresponding increase in addition product was not obtained.

The nature of the solid obtained in reactions conducted in ether solution was briefly examined. Hydrolysis gave a mixture of the hydrate of II, methanol and ether. No 1,1,1-trifluoropropane, arising from the hydrolysis of the Grignard, could be detected. These facts together with elemental analysis suggest the material is the ether solvated form of the following:



EXPERIMENTAL

Starting materials. 1,1,1-Trifluoro-3-bromopropane[11] was available in research quantities. Trifluoroacetic acid was purchased from the Minnesota Mining and Manufacturing Co. and esterified by conventional methods.

Technique. The reactions were conducted in three necked flasks equipped with a condenser, mercury-sealed stirrer and additional funnel. A Dry Ice-cooled trap was connected to the condenser. The Grignard reagent was prepared separately in a conventional manner and filtered through a glass wool plug under a nitrogen atmosphere into the reaction flask. In most cases, the carbonyl compound was added to the Grignard. All reactions were cooled by an ice bath.

After reaction was complete (usually a 2-hr. period), the mixture was hydrolyzed by adding 10% sulfuric acid. The organic layer was washed three times with water and the combined aqueous phases were extracted with three 50 ml. portions of ether. The various solvent solutions were combined, dried with Drierite, and distilled using a Todd fractional distillation apparatus.

Reaction of I *with methyl trifluoroacetate* (a) *Ether solution.* Methyl trifluoroacetate (64 g., 0.5 mole) was added with stirring to a solution of I prepared from 1,1,1-trifluoro-3-bromopropane (194.7 g., 1.1 moles) and magnesium (24.3 g., 1.0 g.-atom) in 600 ml. of diethyl ether. A heavy precipitate was noted at the end of the addition. Hydrolysis and fractionation of the reaction mixture gave an impure product containing water and boiling at 74–76° in approximately 70% yield. A small amount of 1,1,1-trifluoropropane, formed by the hydrolysis of I, was observed in the cold trap.

The product from several experiments was combined (392.0 g.) and cooled to 0°C. in a flask. Phosphorus pentoxide (339.0 g., 2.3 moles) was added in small portions with shaking to form a smooth paste. The flask was fitted with a Vigreux column, condenser, and receiver and the mixture heated slowly to 120° at which point a material distilled smoothly. Fractional distillation of this material gave 1,1,1,5,5,5-hexafluoro-2-pentanone (II) (374.0 g., 1.93 moles).[12]

(b) *Tetrahydrofuran solution.* Methyl trifluoroacetate (384.0 g., 3.0 moles) was added to a solution of I prepared from 1,1,1-trifluoro-3-bromopropane (1080 g., 6.1 moles) and magnesium (145.8 g., 6.1 g.-atoms) in 3600 ml. of tetrahydrofuran. Much less precipitate was noted than in the case of an ether solvent. Hydrolysis and fractionation gave impure II (132 g.), b.p. 74–82° (approximately 23% yield), 1,1,1,5,5,5-hexafluoro-2-pentanol (IV) (72 g., 0.37 mole, 12% yield), b.p. 118°, n_D^{25} 1.3518, and 1,1,1,7,7,7-hexafluoro-4-(trifluoromethyl)-4-heptanol (III), b.p. 77° at 30 mm. n_D^{25} 1.3328 (464 g., 1.59 moles, 53% yield).

Anal. Calcd. for $C_5H_6F_6O$: C, 30.6; F, 58.2. Found: C, 31.1; F, 57.9. Calcd. for $C_8H_9F_9O$: C, 32.8; H, 3.3; F, 58.5. Found: C, 33.1; H, 3.8; F, 58.3.

Reaction of methyl trifluoroacetate with I *and isopropylmagnesium bromide.* A mixture of I and isopropylmagnesium bromide was prepared from 1,1,1-trifluoro-3-bromopropane (194.7 g., 1.1 moles), 2-bromopropane (170 g., 1.5 moles) and magnesium (60 g., 2.5 g.-atoms) in 2 l. of ether. Methyl trifluoroacetate (128 g., 1.0 mole) was added with stirring. Hydrolysis and fractionation gave 1,1,1-trifluoro-3-methyl-2-butanol[8] (70 g., 0.5 mole, n_D^{25} 1.3518, 50% yield), IV (10 g., 0.05 mole, 5% yield), III (48 g., 0.18 mole, 18% yield) and impure II (approximately 30% yield). Propene (24 g., 0.55 mole) and 1,1,1-trifluoropropane (29 g., 0.3 mole) were found in the cold trap.

Reaction of methyl trifluoroacetate with n-propylmagnesium bromide. Methyl trifluoroacetate (64.0 g., 0.5 mole) was added to a solution of *n*-propylmagnesium bromide prepared from *n*-propyl bromide (135.3 g., 1.1 moles) and magnesium (24.3 g., 1.0 g.-atom) in 600 ml. of ether. Hydrolysis and fractional distillation gave 1,1,1-trifluoro-2-pentanol (50.0 g., 0.36 mole, b.p. 110°, 72% yield).[13] Propene (13 g., 0.32 mole) was recovered from the trap.

Reaction of II *with trifluoropropylmagnesium bromide.* II (194.0 g., 1.0 mole) was added to a solution of Grignard reagent prepared from trifluorobromopropane (194.7 g., 1.1 moles) and magnesium in 600 ml. of ether. Hydrolysis and fractional distillation gave the impure II, yield *ca.* 15%, IV in 31% yield and III in 45% yield. Trifluoropropene (17 g., 0.18 mole) and trifluoropropane (7 g., 0.08 mole) were recovered from the trap.

Reactions in the presence of magnesium bromide (a) Methyl trifluoroacetate (64 g., 0.5 mole) was mixed with magnesium bromide (prepared from 0.6 mole of magnesium and 0.6 mole of bromine in tetrahydrofuran solvent[9]) and added to a tetrahydrofuran solution of I (194.7 g., 1.1 moles of $CF_3CH_2CH_2Br$, and 24 g., 1.0 mole of magnesium in 500 ml. of tetrahydrofuran). After hydrolysis and fractionation there was obtained impure II (about 61% yield), unchanged methyl trifluoroacetate (10% yield), trifluoroacetic acid (28%) and trace amounts of III and IV.

(b) An ether solution of I (97 g., 0.55 mole of 3-bromo-1,1,1-trifluoropropane, magnesium, 12 g., 0.5 g.-atom, and 350 ml. of diethyl ether) was added to an ether solution of II (97 g., 0.5 mole) and magnesium bromide (92 g., 0.5 mole). Hydrolysis and fractionation gave impure II (approximately 52% recovery) and III (54 g., 0.18 mole, 36% yield). No 3,3,3-trifluoro-1-propene was observed.

Studies of Grignard-ester complex. The solid formed on reaction of methyl trifluoroacetate with I in diethyl ether was treated as follows:

(a) The reaction mixture was hydrolyzed and the major part of the ether was removed by distillation. Phosphorus pentoxide (50.0 g.) was added and the fractionation was continued. II (167 g., 0.86 mole) was isolated in 86% yield.

(b) As soon as addition was complete, the solid was removed by filtration, rinsed with fresh ether, dried *in vacuo* for 30 min. at room temperature and analyzed immediately.

(c) After drying, the solid was suspended in fresh ether and hydrolyzed. No trifluoropropane or trifluoropropene was recovered. Fractional distillation gave impure II in approximately 62% yield. The ether solution remaining after

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

(10) E. T. McBee, O. R. Pierce, and D. D. Meyer, *J. Am. Chem. Soc.*, **77**, 83 (1955).

(11) O. W. Steward and O. R. Pierce, *J. Am. Chem. Soc.*, **81**, 1983 (1959).

(12) E. T. McBee, A. E. Kelly, and E. Rapkin, *J. Am. Chem. Soc.*, **72**, 5071 (1950).

(13) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

the solid had been removed was hydrolyzed. A trace of trifluoropropane was evolved. Fractional distillation yielded a trace of II.

When a similar run was made using a 2:1 ratio of trifluoropropylmagnesium bromide to methyl trifluoroacetate, hydrolysis of the solid gave equivalent results. Hydrolysis of the ether phase gave trifluoropropane in an amount corresponding to the excess Grignard reagent.

(d) After drying, the solid was hydrolyzed in the absence of solvent. Fractional distillation of the hydrolysis mixture gave ether (21 g., 0.28 mole) and methanol, isolated as an azeotropic mixture with II in low (15–20%) yield.

The analysis of the solid complex is given subsequently.

DISCUSSION

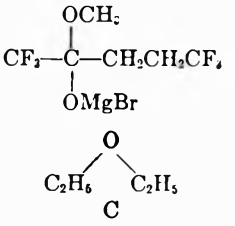
In the following discussion the structure of the Grignard reagent is written as RMgX, although it has been shown[14,15] that the composition of a Grignard solution is probably closer to $R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX$. However, it has been pointed out[16] that all forms of the Grignard reagent show the same reactivity and that the structure RMgX adequately describes the average composition of the mixture. All species are assumed to be solvated, but no attempt has been made to show the nature of the bonding between the Grignard reagent and the solvent molecule.

The mechanism of the reduction of a carbonyl compound by a Grignard has been well defined[17] and probably applies in this case. The low amount of reduction obtained can be explained by the inability of I to release a pair of electrons due to the inductive effect of the trifluoromethyl grouping. As a consequence, the effect of magnesium bromide on the relative amounts of addition and reduction products was small in the case of II. However, in the case of methyl trifluoroacetate, magnesium bromide can interfere with the formation of a complex between the ester and I. Thus the subsequent intermolecular shift involved in the formation of the tertiary alcohol (III) would be minimized, accounting for the change in the product distribution.

The mechanism of the addition of a Grignard reagent to a carbonyl group is less clear, particularly in reactions involving an ester. It appears that the reaction sequence proposed by Grignard[18] and supported by others[19,20] is applicable to the reaction of I with methyl trifluoroacetate.

The alternate mechanism involving a free ketone intermediate[21–23] is less attractive since the ketone (II) was found to react normally with I in both the free state and when complexed with magnesium bromide.

Further evidence for an intermediate similar to that proposed by Grignard, *i.e.*,



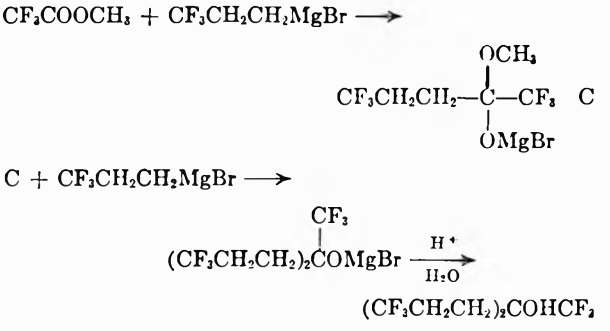
was found in the analysis of the solid. A complex such as this, when isolated from a reaction mixture and analyzed without further purification would not be expected to be a pure species. This is indicated by the analytical data.

Anal. Calcd. for C: C, 29.7; H, 4.2; F, 28.3; Mg, 5.9; Br, 19.9; Or — see text. Found: C, 26.3; F, 25.6; H, 4.3; Mg, 5.5; Br, 22.0; OR, 23.8.

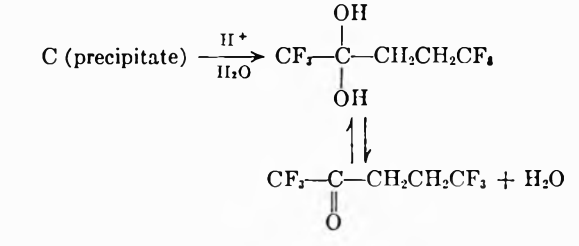
The theoretical methoxy content of C is 7.6%. However, the ether would also react with the reagents used in this determination. If the ether is assumed to react quantitatively, the value would be approximately three times this figure. A more precise calculation would not be valid and was not attempted.

In view of the evidence for an intermediate such as C, together with the semi-quantitative analytical data presented, the following scheme for the reaction of I with methyl trifluoroacetate is offered:

(1) in tetrahydrofuran



(2) in ether



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(14) Abegg, *Ber.*, **38**, 4112 (1905).

(15) Schlenk and Schlenk, *Ber.*, **62B**, 920 (1929).

(16) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, New York, 1954, p. 681.

(17) F. S. Whitmore, paper presented at 105th National Meeting, Amer. Chem. Soc., April, 1943, Atlantic City, N. J.

(18) V. Grignard, *Compt. rend.*, **132**, 336 (1901).

(19) A. A. Morton and L. V. Peakes, Jr., *J. Am. Chem. Soc.*, **55**, 2110 (1933).

(20) M. S. Kharash and O. Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice-Hall, New York, 1954, p. 550.

(21) Reformatsky, *J. Russ. Phys. Chem.*, **37**, 1905, 881.

(22) D. R. Boyd and H. H. Hatt, *J. Chem. Soc.*, 898 (1927).

(23) K. N. Campbell, J. O. Knoblock, and Barbara K. Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950).

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

Infrared Spectra of *cis*- and *trans*-Propenyllithium. Stereochemistry of the Reaction of Vinyl Chlorides with Lithium Metal

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The *cis*- and *trans*-propenyl chlorides have been converted to propenyllithiums. An examination of the infrared spectra of the propenyllithiums permitted assignment of geometric structure to them, and showed that the chlorides were converted to lithium derivatives with retention of configuration.

Vinyl halides react to form vinyllithiums which in turn react with various reagents, such as carbon dioxide or benzaldehyde, to form the corresponding vinyl adducts. It is known that the geometrical isomer of the acid or alcohol obtained in these examples is such that the two reaction steps together have yielded over-all retention of configuration.[2] *A priori* this means that either both of the reaction steps have proceeded with retention of configuration, or else both have proceeded with inversion.[3] It is known that certain vinylic halides, for example bromobenzene, must undergo these reactions with retention in both steps, since if the first step went with inversion, phenyl-lithium would contain a *trans* double bond. From this evidence though, it can only be concluded that a vinyl halide can react to form a vinyllithium with retention. It does not prove that the reaction will proceed with retention when there is no geometrical constraint on the system.

This problem has been long recognized. Nesmeyanov and Borisov[4] have claimed that various halides, and in particular the 1-bromopropenes, have been shown to react to form the lithium derivatives with retention of configuration by what they call the "method of even and odd cycles." With regards to the application of the method to the present case, it can be seen that if formation and reaction of the propenyllithium always proceeds with the same stereochemistry, no matter what that stereochemistry is, the experimental results obtained necessarily follow. There is no way by the method of even and odd cycles to tell whether there have been two retentions or two inversions, except by analogy. Such an analogy can never be considered a proof. The only apparent way to determine the configuration of the vinyllithium intermediate is to examine the vinyllithium itself.

DISCUSSION

In the present work it was desired to prepare geometrically pure isomers of a vinyllithium, and to establish their structures by infrared spectra. The 1-propenyl system was chosen as most convenient. The *cis* and *trans* isomers of 1-chloropropene have had their structures established by dipole moment measurements.[5] The isomeric bromo compounds have been studied with regards to their stereochemical transformation by earlier workers, but they are not easy to work with as they equilibrate at a significant rate at room temperature.[6] The chloro compounds, which are stable to 135°, were therefore used.

It was established that under the conditions used in the present work the *cis*-1-chloropropene could be converted to a 1-propenyllithium, which in turn reacted with benzaldehyde to give the known[7] *cis*-1-phenyl-2-butene-1-ol, while the *trans* chloride led similarly to the *trans* alcohol.

The *cis*- and *trans*-propenyllithiums were prepared by the reaction of lithium metal and the chloride in ether solution. The solid propenyllithium was isolated under a nitrogen atmosphere, and a Nujol mull was prepared of it. The spectra of the two isomers were quite different, and the important features are recorded in Table I.

The out-of-plane hydrogen bending frequencies have been among the most useful for assignment of geometrical structure to olefins.[8] Almost all disubstituted olefins having a *trans* arrangement of hydrogens show this band at from 865 to 990

(1) This research was supported by a grant from the Alfred P. Sloan Foundation.

(2) (a) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951); (b) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, **76**, 1902 (1954); (c) D. Y. Curtin and E. E. Harris, *J. Am. Chem. Soc.*, **73**, 2716 (1951); (d) D. Y. Curtin, H. W. Johnson, Jr., and E. G. Steiner, *J. Am. Chem. Soc.*, **77**, 4566 (1955).

(3) Various workers (a) D. Y. Curtin and W. J. Koeal, Jr., *Chem. & Ind. (London)*, 262 (1960); (b) H. M. Walborsky and F. J. Impastato, *J. Am. Chem. Soc.*, **81**, 5835 (1959); (c) R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 4842 (1950); (d) D. E. Applequist, private communication, have recently shown that alkyl lithiums are formed and react with retention of configuration under certain circumstances.

(4) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, 1, 158 (1957).

(5) N. B. Hannay and C. P. Smyth, *J. Am. Chem. Soc.*, **68**, 1005 (1946).

(6) K. E. Harwell and L. F. Hatch, *J. Am. Chem. Soc.*, **77**, 1682 (1955).

(7) D. Y. Curtin and J. W. Crump, *J. Am. Chem. Soc.*, **80**, 1922 (1958).

(8) For considerable discussion and a list of references, see L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1954, p. 31.

TABLE I

INFRARED SPECTRA OF 1-PROPENYLLITHIUMS PREPARED FROM THE CHLORIDES OF INDICATED CONFIGURATION[a]

cis	*trans*
2760 (W)	2725 (W)
2050 (W)	2070 (W)
1540 (S)	1555 (S)
1127 (W)	1230 (M)
1035 (S)	1045 (S)
	1030 (M)

[a] Most of the C—H bending and stretching frequencies are obscured by the Nujol, and they are not indicated.

cm.$^{-1}$ The presence of a highly electronegative atom on the double bond, such as in *trans*-propenyl chloride, lowers this frequency by some 30 cm.$^{-1}$, and it is expected that the electropositive lithium should increase the frequency by a similar amount.[9] In the present case neither isomer shows absorption in the range 965–990 cm.$^{-1}$ The strong absorption near 1040 cm.$^{-1}$ of each isomer is probably due to the C—Li stretching vibration.[10] This leaves the medium band at 1030 cm.$^{-1}$ in the isomer obtained from the *trans* chloride as the best candidate for the *trans*-out-of-plane bending frequency.[11] The other isomer shows only the C—Li band in this region. On this basis the *trans* structure can be assigned to the lithium derivative obtained from the *trans* halide.

It seems to be rather generally true that the C=C stretching frequency is higher for a *trans* disubstituted ethylene than it is for its *cis* isomer, regardless of whether the attached groups are electropositive or electronegative. For example, simple alkenes show this band at 1673 and 1657 cm.$^{-1}$ for *trans* and *cis* isomers respectively.[8] The propenyl chlorides absorb at 1681, 1648 (doublet), and 1639, 1605 (doublet) cm.$^{-1}$, respectively, while for the bromomercury propenes the frequencies are 1625 cm.$^{-1}$ and 1510, 1600 cm.$^{-1}$ (doublet). The *trans*- and *cis*-propenyllithiums (as assigned from the out-of-plane bending frequencies) have C = C stretching frequencies at 1555 and 1540 cm.$^{-1}$ respectively, and this is consistent with the assignment made.

The infrared spectra of *cis*- and *trans*-propenyllithium have also been reported by Nesmeyanov, Borisov and Novikova.[4,12] Their spectra bear little resemblance to those obtained in the present work. In particular they report absorption for the *trans* and *cis* isomers respectively at 1645 and 1623 cm.$^{-1}$ for the C = C stretching modes (under unspecified conditions) and at 975 and 700 cm.$^{-1}$ for the out-of-plane bending. These values are similar to those of the starting materials and propenyl derivatives such as might be obtained from various side reactions.

According to Walsh,[13] the C = C stretching frequency is increased by the joining of an electronegative atom to one of the carbons. The electronegative atom tends to pull electrons out toward it, and since p electrons are further from the carbon than s electrons, the result is to increase the p character of the bond toward the electronegative atom. The p character of the σ component of the C = C bond is consequently decreased, which increases the C = C bond strength and raises the frequency. It can therefore be concluded that the reverse should occur when an electropositive atom is attached to carbon. According to this view, a decrease in this frequency is expected when an electropositive atom replaces a hydrogen atom on the double bond. The low C = C frequencies observed for the propenyllithiums are qualitatively as expected, and it is difficult to imagine to what other kind of structure they could be assigned. Samples of the solid alkenyl lithiums which were isolated were seen to blacken, smoke, generate considerable heat, and sometimes ignite when exposed to air, and there seems to be no question but that the spectral bands listed in Table I actually are of the propenyllithiums. It is not clear to what compounds the spectra reported by Nesmeyanov and coworkers[12] are to be attributed.

On the basis of the infrared spectra of the propenyllithiums it can be concluded that they are formed and react exclusively with retention of configuration under the conditions used. It therefore seems likely that in the general case vinyllithiums are formed and react preferentially with retention of configuration.

EXPERIMENTAL[14]

cis and *trans*-Propenyl chloride. One liter of commercial 1,2-dichloropropane was purified by washing it with concentrated sulfuric acid, followed by distillation. This material was then added dropwise to a refluxing solution of alcoholic potassium hydroxide. Material boiling below 60° was continuously removed by distillation. The distillate was washed with water, dried over calcium chloride, and then fractionally distilled through a 4-foot helix-packed column. The low and high boiling fractions were separately refractionated and gave respectively the *cis* isomer, b.p. 30.8–31.3°, and *trans* isomer, b.p. 37.9°. The infrared spectra indicated that neither isomer contained more than 2% of the other. About 100 g. of each was obtained. The isomers

(9) (a) N. Sheppard and G. B. B. M. Sutherland, *Proc. Roy. Soc.*, **196A**, 195 (1949); (b) R. E. Kitson, *Anal. Chem.*, **25**, 1470 (1953); (c) W. J. Potts and R. A. Nyquist, *Spectrochim. Acta*, **14**, 679 (1959).

(10) (a) T. L. Brown and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 1859 (1957); (b) A. N. Rodionov, D. N. Shigorin, T. W. Talalaeva, and K. A. Kocheshkov, *Doklady Akad. Nauk. (SSSR)*, **123**, 113 (1958).

(11) The bands at 1030 and 1045 cm.$^{-1}$ are given the indicated assignments on the basis of their relative intensities. These two assignments could be reversed without affecting the present conclusions.

(12) A. N. Nesmayanov, A. E. Borisov, and N. V. Novikova, *Doklady Akad. Nauk.*, **119**, 504 (1958).

(13) A. D. Walsh, *Disc. Faraday Soc.*, **2**, 18 (1947).

(14) The authors are indebted to Miss B. Bach for determining the infrared spectra described.

were identified by boiling point,[15] and by the presence of an intense hydrogen out-of-plane bending band at 924 cm.$^{-1}$ in the infrared spectrum of the *trans* compound.

cis and *trans*-Propenyllithium. This procedure is representative. A solution of 4 g. of *cis*-propenyl chloride in 15 ml. of ether was stirred vigorously under nitrogen with a two-fold excess of lithium metal[16] for 3 hr.

The reaction mixture was then filtered (in a dry box under nitrogen) to remove lithium metal and some salts. The filtrate was then evaporated under vacuum, and the residue was used to prepare a mull in Nujol. This mull was placed in an infrared cell, which could then be handled in air.

A modification of this procedure eliminated the filtration above. The pieces of lithium metal were picked out by hand, and after evaporation of the volatile material, the remainder of the solid was used for the mull. The principal bands obtained and assigned to the propenyllithium were the same in either method. Some small variable bands were also obtained, and since they were not consistently present in samples prepared in different runs, they were clearly due to impurities and were not further considered. The infrared spectra were recorded on both a Beckman IR-4 and a Baird Spectrophotometer.

trans- and *cis*-1-Phenyl-2-butenol-1. The reaction mixture containing propenyllithium from the *trans* chloride was cooled to 5° and 2 g. of benzaldehyde was added dropwise with stirring. After stirring the mixture an additional 20 min. at 5° the solution was filtered to remove excess lithium, and a cold saturated solution of ammonium chloride was added to the filtrate. The phases were separated, and the aqueous phase was extracted with ether. The combined ether layers were dried over potassium carbonate, and the ether was evaporated. Distillation furnished 2 g. of material, b.p. 103–110° (0.25 mm.). The infrared spectrum showed a strong band at 965 cm.$^{-1}$ which is characteristic of the *trans* isomer, and it was not detectably contaminated by the *cis*, which absorbs at 980 cm.$^{-1}$

The *cis* chloride similarly yielded the *cis* alcohol, which showed strong absorption at 980 cm.$^{-1}$, and was not detectably contaminated with the *trans*.

DETROIT 2, MICH.

(15) E. H. Huntress, *Organic Chlorine Compounds*, Wiley, New York, 1948, p. 947.

(16) It was found that lithium from some batches consistently reacted very well, while that from other batches consistently failed to react. J. A. Beel, W. G. Koch, G. E. Tomasi, D. E. Hermansen, and P. Fleetwood, *J. Org. Chem.*, 24, 2036 (1959) have shown that the sodium content of the lithium can greatly affect its reactivity toward halides. The quality of the lithium used in the present work is not known.

[CONTRIBUTION FROM THE WILLIAM ALBERT NOYES LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

1,6-Reductive Coupling of Hindered *o*-Vinyl Diaryl Ketones[1]

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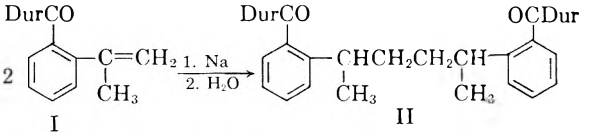
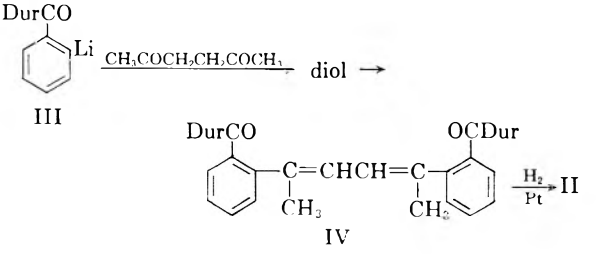
Received July 25, 1960

Mesityl *o*-vinylphenyl ketone, duryl *o*-vinylphenyl ketone, and duryl *o*-isopropenylphenyl ketone have been reduced with metallic sodium, the products being the corresponding butanes to be expected from 1,6-reductive coupling involving the side chain. The reductive coupling product of the isopropenyl compound was isolated in the expected two diastereoisomeric forms. These compounds were synthesized independently from *o*-duroylphenyllithium and acetonylacetone. The diol was dehydrated, and the resulting diene was hydrogenated catalytically.

1,6-Addition of Grignard reagents to hindered ketones is well known, and in the reaction of *t*-butylmagnesium chloride with duryl *o*-isopropenylphenyl ketone was shown to involve the *p*-position rather than the side chain.[4] The formation of *p,p'*-diduroylbiphenyl from duryl *p*-hydroxyphenyl ketone[5] depends on a 1,6-coupling. It has now been found that a similar coupling involving the side chain can be realized by treating hindered *o*-vinylphenyl ketones with sodium. The hexane derivatives II produced in this way from duryl *o*-isopropenylphenyl ketone (I) correspond to the two diastereoisomeric forms to be expected.



Their structure was established by an independent synthesis beginning with the condensation of *o*-duroylphenyllithium (III)[6] with acetonylacetone. The crude diol was dehydrated with dilute sulfuric acid to give 1,4-di (*o*-duroylphenyl)-1,4-dimethylbutadiene (IV). Hydrogenation of the diene produced a mixture of the two diastereoisomeric hexane derivatives. When isolated in pure form they were found, by reference to mixture melting point deter-



(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) Socony-Vacuum Oil Company Fellow, 1954–55.

(3) Deputationist of the Government of the Union of Burma.

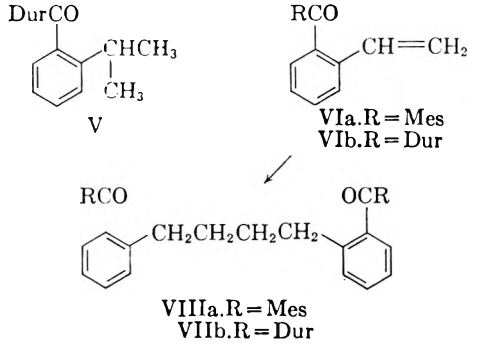
(4) R. C. Fuson, W. D. Emmons, and S. G. Smith, Jr., *J. Am. Chem. Soc.*, 77, 2503 (1955).

(5) R. C. Fuson and G. W. Parshall, *J. Am. Chem. Soc.*, 76, 5561 (1954).

(6) R. C. Fuson, W. C. Hammann, and W. E. Smith, *J. Org. Chem.*, 19, 674 (1954).

minations, and by comparison of infrared spectra to be identical to the products obtained by the sodium reduction.

In the reaction of the isopropenyl ketone I with sodium, duryl *o*-isopropylphenyl ketone (V), a 1,6-reduction product, was also isolated in a small yield. Mesityl *o*-vinylphenyl ketone (VIa) and duryl *o*-vinylphenyl ketone (VIb) were found to behave similarly. The butane derivatives were isolated each in a single form as expected.



EXPERIMENTAL[7]

Treatment of duryl o-isopropenylphenyl ketone with sodium. To 1 g. of powdered metallic sodium in 100 ml. of absolute ether was added with stirring a portion of 1.4 g. (0.005 mole) of duryl *o*-isopropenylphenyl ketone (I)[8] dissolved in 50 ml. of dried benzene. After the mixture had attained a black color the rest of the ketone solution was added over 20 min. The mixture was heated under reflux, with stirring, for 6 hr. and treated with water. Chromatographic separation of the products on a column of 100 g. of alumina with large volumes of eluents yielded 267 mg. (18.9%) of duryl *o*-isopropylphenyl ketone (V), m.p. 148.5–149.5°, identified by a mixture melting point determination and comparison of the infrared spectrum[9] with that of an authentic sample. Also isolated were 55 mg. (3.9%) of the original ketone I and 340 mg. (24%) of one of the 2,5-di(*o*-duroylphenyl)hexanes II, colorless crystals from benzene-ethanol, m.p. 232–232.5°.

Anal.[10] Calcd. for $C_{40}H_{46}O_2$: C, 85.97; H, 8.30. Found: C, 85.90; H, 8.30.

A third product, the diastereoisomeric hexane, when recrystallized from the same solvents, melted at 211.5–212.5°, yield 400 mg. (28.5%).

Anal. Calcd. for $C_{40}H_{46}O_2$: C, 85.97; H, 8.30. Found: C, 85.89; H, 8.26.

The infrared spectra of the two diastereoisomeric products are nearly identical. They contain bands at 1668 cm.$^{-1}$, assignable to a carbonyl group, at 760 cm.$^{-1}$, assignable to a 1,2-disubstituted phenyl ring, and at 717 and 1485 cm.$^{-1}$, assignable to chained methylene groups.

Condensation of o-duroylphenyllithium (III) *with acetonylacetone.* A solution of 1 g. (0.009 mole) of freshly redistilled acetonylacetone in 15 ml. of anhydrous ether was added over 5 min. to *o*-duroylphenyllithium made at −78° from 6.34 g. (0.02 mole) of duryl *o*-bromophenyl ketone, 50 ml. of ether, and 25 ml. of 0.82*N* solution (0.02 mole) of *n*-butyllithium in ether. The cold bath was removed; the reaction mixture was allowed to warm up slowly with stirring to room temperature in the course of 1 hr. and then heated under reflux for 30 min. longer. The mixture was cooled and treated with 30 ml. of cold 5% sulfuric acid. The resultant slurry was stirred at room temperature for 10 min. The ether layer was washed and dried. Removal of ether and crystallization of the residual oil from chloroform-ethanol gave 266 mg. of 1,4-di(*o*-duroylphenyl)-1,4-dimethylbutadiene (IV), yellow crystals, m.p. 277–279°. The crystallization filtrates were concentrated and subjected to chromatography; an additional 200 mg. of the product was isolated. Its infrared spectrum has absorption bands assignable to the carbonyl groups (1675 cm.$^{-1}$), to the duryl group (818, 865, and 945 cm.$^{-1}$), and to conjugated olefinic double bonds (1635 cm.$^{-1}$). The ultraviolet spectrum[11] has two absorption maxima at 203 mμ and 250 mμ with log ε equal to 5.8451 and 5.7404, respectively. Duryl *o*-isopropenylphenyl ketone shows similar absorption maxima at 203 mμ and 250 mμ with log ε equal to 3.6324 and 3.3053, respectively.

Hydrogenation of 1,4-di-(o-duroylphenyl)-1,4-dimethylbutadiene. A solution of 130 mg. (2.34×10^{-4} mole) of the diene in 20 ml. of 1:1 chloroform-ethanol mixture was treated with hydrogen in the presence of 30 mg. of Adams catalyst at room temperature and pressure. The theoretical uptake of hydrogen (10.5 ml., 4.68×10^{-4} mole) was complete in 1 hr. The mixture was stirred, however, for an additional 4 hr. and allowed to stand under hydrogen for 42 hr. to ensure ketonization of the product.[12] The catalyst was removed and the organic solution concentrated to give 85 mg. of colorless crystals, m.p. 182–213°. The infrared spectrum of this mixture was superimposable on those of the diastereoisomeric 2,5-di(*o*-duroylphenyl)hexanes. Chromatographic separation of 50 mg. of the mixture gave 20 mg. of the isomer melting at 232–232.5° and 18 mg. of the isomer melting at 211.5–212.5°. The identity of the compounds was established by mixture melting points and by comparison of infrared spectra.

Treatment of mesityl o-vinylphenyl ketone with sodium. The procedure was similar to that described for the isopropenyl compound. A solution of 2 g. of the ketone[8] in 50 ml. of sodium-dried, thiophene-free benzene was added in part to a slurry of 1 g. of freshly powdered sodium in 100 ml. of anhydrous ether which had been blanketed with dry nitrogen. The addition was accompanied with stirring, the stirrer being pushed down in order to cut fresh surfaces on sodium. A dark red color diffused throughout the solution in 3 min. The rest of the ketone solution was then added over a 15-min. interval, and the reaction mixture was heated under reflux with stirring for 6 hr. The mixture was allowed to cool slowly to 0° and treated cautiously with 50 ml. of 4% dilute hydrochloric acid; the resulting mixture was stirred under nitrogen for 20 min. The organic layer was washed and dried over anhydrous sodium sulfate. The solvent was removed by low-pressure distillation, and the residual oil was chromatographed on 120 g. of Merck acid-washed aluminum oxide. From the chromatogram 86 mg. (4.3%) of mesityl *o*-ethylphenyl ketone[8] and 1.22 g. (60.7%) of 1,4-di(*o*-mesitoylphenyl)butane (VIIa), colorless crystals from benzene-ethanol, m.p. 182–182.5°, were obtained.

Anal. Calcd. for $C_{36}H_{38}O_2$: C, 86.01; H, 7.62. Found: C, 85.95; H, 7.62.

The infrared spectrum of the reductive coupling product has bands assignable to a conjugated carbonyl group (1670 cm.$^{-1}$), a 1,2-disubstituted phenyl ring (760 cm.$^{-1}$), a mesityl group (852 cm.$^{-1}$), and chained methylene groups (730, 1233, and 1483 cm.$^{-1}$). The nuclear magnetic resonance spectrum[13] has values of 2.74, attributed to the phenyl hydrogen atoms, 3.26, attributed to the mesitylene hydrogen

(7) All melting points are corrected.

(8) R. C. Fuson and M. T. Mon, *J. Org. Chem.*, **26**, 756 (1961).

(9) The infrared spectra were determined by Mr. Paul McMahon, Mrs. Mary Verkade, Miss Charlene Leubke, Mr. D. H. Johnson, and Mr. William Dalton.

(10) The microanalyses were performed by Mr. Josef Nemeth, Mrs. A. S. Bay, and Miss Jane Liu.

(11) The ultraviolet spectra were obtained from a Cary Model 14 recording spectrophotometer by Miss Cynthia Juan.

(12) R. C. Fuson and R. E. Foster, *J. Am. Chem. Soc.*, **65**, 913 (1943).

atoms, and 6.91, attributed to the methylene hydrogen atoms. The values of 7.74 and 7.98 were attributed to the hydrogen atoms on the methyl groups *para* and *ortho* to the carbonyl functions, respectively. The spectrum peaks were identified by the relative areas under their curves as compared to the number of the hydrogen atoms.

Treatment of duryl o-vinylphenyl ketone[8] *with sodium.* This experiment was performed in the manner just described. The products, however, offered great difficulty in purification. This might be the main reason for the relatively low yields. Duryl *o*-ethylphenyl ketone[8] was obtained in 2.2% yield and the reductive coupling product, colorless crystals from chloroform-ethanol, m.p. 242–244°, in 30.8% yield. The infrared and the nuclear magnetic resonance spectra of 1,4-di(*o*-duroylphenyl)butane (VIIb) were similar to those of its mesityl analog.

Anal. Calcd. for $C_{38}H_{42}O_2$: C, 85.99; H, 7.98. Found: C, 85.55; H, 8.18.

URBANA, ILL.

(13) The nuclear magnetic resonance spectra were determined by Mr. O. W. Norton at 60 mc. with a Varian Model V-4300 B high-resolution spectrometer.

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

Oxidation of Methyl-*t*-butylcarbinol with Lead Tetraacetate

WILLIAM A. MOSHER, CLIFTON L. KEHR, AND LEON W. WRIGHT

Received March 30, 1960

The oxidation of methyl-*t*-butylcarbinol with lead tetraacetate yields the expected ketone along with *t*-butyl acetate, isobutylene, and acetaldehyde. The relative yields of ketone and cleavage products may be varied by changing the conditions of oxidation with either the ketone or oxidative cleavage products becoming the major product. These products are consistent with an ionic mechanism.

The oxidation of benzpinacolyl alcohol with lead tetraacetate has been reported by Mosher and Neidig[1] to give 70% triphenylcarbinol as a result of oxidative cleavage. Because this represents the highest yield of such a cleavage yet reported, the reaction of the analogous aliphatic alcohol has now been carried out; methyl-*t*-butylcarbinol also yields cleavage products with lead tetraacetate under a variety of conditions.

The results of this study are summarized in Table I. Several individual reactions were carried out under the general conditions reported for the various runs. Carbon dioxide was invariably a product indicating secondary oxidations and considerable unchanged alcohol and its acetate were found. Material balances varied from 60% to nearly theoretical. With a 1:1 molar ratio of alcohol to lead tetraacetate the cleavage was 6% at 50–65° while it was almost 50% at 95–100° working in acetic acid solution. In nitrobenzene solution more esterification occurred and cleavage at 65–75° was 30%. Previous studies with this alcohol and chromic acid yielded 4% cleavage in acetic acid–water at 30°.[2]

EXPERIMENTAL

Preparation of reagents. Methyl-*t*-butylcarbinol was prepared in 31% yield by the reaction of *t*-butylmagnesium chloride and acetaldehyde, and in 68% yield by the reduction of pinacolone with aluminum isopropoxide in isopropyl alcohol. Distillation of the crude alcohol through a Whitmore-Lux[3] total condensation, partial take-off column packed with a single turn glass helices, and equivalent to twenty theoretical plates, resulted in a product boiling at 120–121° at 760 mm., n_D^{20} 1.4152. The procedure used for lead tetraacetate has been previously described.[4]

Oxidation. The data given in Table I indicate the mole quantities of alcohol, oxidizing agent, and solvent used in each experiment. In the usual case, the alcohol and oxidizing agent were mixed at room temperature with the indicated solvent in a 3-l., three-necked, round bottomed flask equipped with a thermometer, a mercury-sealed stirrer, and a reflux condenser to which was attached a Dry Ice trap, two Ascarite tubes, and a gas-collecting bottle. In Runs 1, 4, and 5, Table I, the Dry Ice trap was omitted and the acetaldehyde was absorbed by the Ascarite (with polymerization). In Run No. 2, Table I, the oxidizing agent was added, in small portions, to the stirred acetic acid–alcohol solution at reaction temperature in order to maintain a large excess of alcohol. After tetravalent lead was no longer present (negative potassium iodide test) in the reaction mixture, the product was diluted with water and steam distilled. The combined oil layers were separated, washed with bicarbonate solution, dried over anhydrous potassium carbonate, and fractionated through a column of twenty theoretical plates. In a typical experiment, from the distillation charge of 70.0 g., Run No. 1, Table I, the following cuts were obtained: I. *t*-Butyl acetate (3.8 g., 3.3%), acetanilide derivative by the method of Hardy[5] gave m.p. and mixed m.p. with an authentic sample of acetanilide, 113–115°; the ester was refluxed with hydrochloric acid (6N) to give *t*-butyl chloride (b.p. 54–56°, n_D^{20} 1.3850), which then was converted through Grignard reagent and phenyl isocyanate to trimethylacetanilide, m.p. 127–129°. II. Pinacolone (9.2 g., 9.2%), 2,4-dinitrophenylhydrazone m.p. and mixed m.p. 126–128°. III. Unchanged carbinol (46.0 g.; 45.1%). IV. Pinacolyl acetate (5.7 g.; 4.0%), acetanilide derivative obtained by the method of Hardy[5] gave m.p. and mixed m.p. 113–114°; the ester was also hydrolyzed in basic diethylene glycol and the liberated alcohol converted to the 3,5-dinitrobenzoate ester, m.p. and mixed m.p. 105–106°. The pot residue consisted of 2.3 g. of slightly charred

(1) W. A. Mosher and H. A. Neidig, *J. Am. Chem. Soc.*, **72**, 4452 (1950).

(2) W. A. Mosher and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 2544 (1948).

(3) F. C. Whitmore and A. R. Lux, *J. Am. Chem. Soc.*, **54**, 3448 (1932).

(4) W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.*, **75**, 3172 (1953).

(5) D. V. N. Hardy, *J. Chem. Soc.*, 398 (1936).

TABLE I

LEAD TETRAACETATE OXIDATION OF METHYL-*t*-BUTYLCARBINOL

Run No.	1	2	3	4	5		
Solvent	HOAc	HOAc	HOAc	$C_6H_5NO_2$	HOAc	HOAc–Acetone	
Moles solvent	3.3	4.1	4.0	4.0	3.3	1	3
Moles $Pb(OAc)_4$	1	1	1	1	1	1	
Moles alcohol	1	1	2	1	0.4	1	
Temperature	50–60	95–100	95–100	65–75	75–85	45–50	
Products (Moles/100 moles alcohol allowed to react)							
Pinacolone	17	3	3	5	13	25	
Pinacolyl acetate	8	14	15	31	22	10	
t-Butyl acetate	6	31	30	16	8	13	
Isobutylene	—	20	22	—	—	—	
Acetaldehyde	—	20	18	32	23	10	
% cleavage	6	51	52	32	23	13	

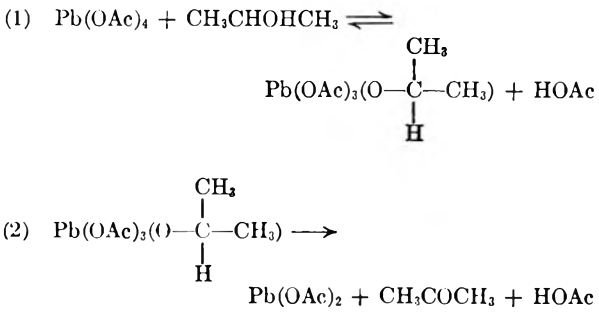
liquid. In Run No. 2, Table I, the isobutylene was characterized by distilling into a series of three cold traps containing pure bromine. A second Dry Ice trap in the series immediately after the bromine traps did not contain any liquid, indicating the absence of isobutane. Hydrolysis of the isobutylene dibromide[6] gave isobutyraldehyde, 2,4-dinitrophenylhydrazone m.p. and mixed m.p., 185–186°.

DISCUSSION

The data in Table I indicate that lead tetraacetate is a very unusual oxidizing agent for methyl-*t*-butylcarbinol because the ratio of normal product, ketone, to cleavage product, *t*-butyl alcohol or isobutylene, may be varied within limits by changing temperature and reactant concentrations. The highest yields of cleavage are obtained when a large excess of alcohol is maintained throughout the reaction. In nitrobenzene solution or in the presence of moderate amounts of acetic acid, lead tetraacetate is an effective acetylating agent.

The ability of lead tetraacetate to cleave glycols discovered and so successfully developed by Criegee[7] is well known and is believed to proceed through an ionic mechanism involving electron transfer between the tetravalent lead atom and the glycol oxygen in a cyclic ester intermediate.[8] This mechanism is considerably strengthened by the work on chromate ester intermediates in chromic acid oxidations by Westheimer and his students.[9]

The formation of cyclic esters is not possible in the present case but the probability of the formation of simple esters is very good. Criegee[8] has isolated from methanol solution such species as $Pb(OAc)_3(OCH_3)$ and $Pb(OAc)_2(OCH_3)(OH)$. These compounds were unstable and decomposed readily to formaldehyde and lead diacetate. Presumably such intermediates are formed in all monohydric alcohol oxidations with lead tetraacetate although we have not been able to isolate such compounds in the present study. Kharasch, *et al.*[10] explain the oxidation of monohydric alcohols by the following scheme:



(1) $Pb(OAc)_4 + CH_3CHOHCH_3 \rightleftharpoons Pb(OAc)_3(O-\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}-CH_3) + HOAc$

(2) $Pb(OAc)_3(O-\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}-CH_3) \longrightarrow Pb(OAc)_2 + CH_3COCH_3 + HOAc$

These reactions cannot be the only steps involved, however, for equation 1 illustrates an equilibrium which will probably be initiated when the reagents (in the ratios shown) are mixed in acetic acid as solvent.[8] Yet the reaction mixture can be heated at reflux for many hours until the lead tetraacetate decomposes completely to lead diacetate without even a trace of carbonyl compound being formed. It has been demonstrated,[11] however, that if the alcohol is added in considerable excess over the oxidizing agent, *e.g.* 15:1, the reaction proceeds quite rapidly below 100° C. One can conclude from these observations that a third equilibrium, Equation 3, may be involved before oxidation proceeds:

(3) $Pb(OAc)_3(OR) + HOR \rightleftharpoons Pb(OAc)_2(OR)_2 + HOAc$

(4) $Pb(OAc)_2(OR)_2 \longrightarrow Pb(OAc)_2 + RO^- + RO^{+}$[12]

Evidence for a reaction such as (4) has been previously presented.[4]

(6) W. L. Evers, *et al.*, *J. Chem. Soc.*, **55**, 1136 (1933).

(7) R. Criegee, *Ber.*, **64**, 260 (1931).

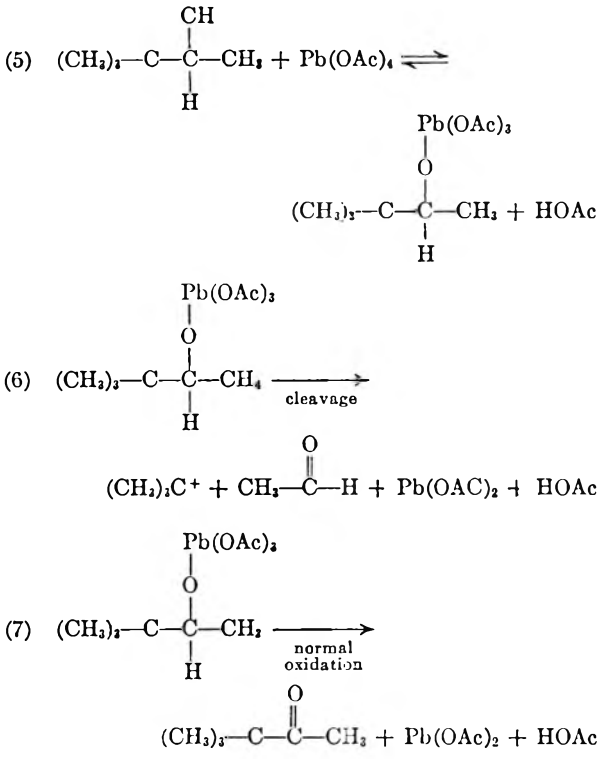
(8) R. Criegee, L. Kraft, and B. Rank, *Ann.*, **507**, 159 (1933).

(9) A. Leo and F. H. Westheimer, *J. Am. Chem. Soc.* **74**, 4383 (1952).

(10) M. S. Kharasch, H. N. Freidlander, and W. H. Urry, *J. Org. Chem.*, **16**, 533 (1951).

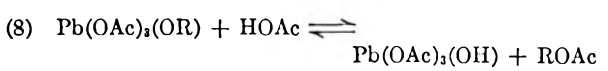
(11) C. L. Kehr, Ph.D. Dissertation, University of Delaware (1952).

(12) RO^+ will, of course, have only a transitory existence and is probably involved as a polarized part of the $Pb(OAc)_2(OH)_2$ molecule in concerted reactions. The formulation is for simplicity.



The formulations used for the decomposition of alkoxy lead triacetate result in the development of positive polarity on the hydroxyl oxygen and are, therefore, essentially equal to our previous formulations with positive character on oxygen atoms in alcohol oxidations.[2]

The high yield of pinacolyl acetate (Run No. 3, Table I) is probably due to the decomposition of the monoester of tetravalent lead, *i.e.* $Pb(OAc)_3(OR)$, *via* Equation 8.



The resulting tetravalent lead salt equilibrates with the other tetravalent lead compounds or reacts with solvent (acetic acid) to reform lead tetraacetate.

Kharasch, *et al.*[10] have shown that lead tetraacetate reacts, when heated to 120° in acetic acid solution, to give carbon dioxide (42%), methane (30%), acetoxyacetic acid (40%), and methylene diacetate (6%). These workers propose a radical type mechanism involving triacetoxy lead radicals to account for the observed reaction products. Mosher and Kehr[4] reinvestigated and extended the work of Kharasch, *et al.* to a variety of organic acids in an attempt to elucidate the type of mechanism involved. Mosher and Kehr concluded that the decomposition of lead tetraacetate in acetic and similar organic acids occurred *via* an ionic mechanism even at the high temperature (100–135°) used in their study.

The results of the present oxidation study are also best explained by an ionic mechanism. Any attempt to explain the cleavage products by a free radical mechanism falls short because of the absence of isobutane and hexamethylethane in the product mixture. It is known, for example, that *t*-butyl free radicals, when formed in solution at the same temperature employed in this study disproportionate quantitatively to isobutane and isobutene.[13] At low temperatures the *t*-butyl free radical is known to dimerize to give hexamethylethane (in the preparation of branched chain carbinols with *t*-butyl Grignard reagents, some hexamethylethane is always found as a by-product). In the oxidation of methyl-*t*-butylcarbinol, neither isobutane nor hexamethylethane was found in the product mixture.

NEWARK, DEL.

(13) H. C. McBay Ph.D. Dissertation, University of Chicago (1945).

[CONTRIBUTION FROM UNION CARBIDE PLASTICS CO., DIVISION OF UNION CARBIDE CORP.]

Aromatic Aldehydes from Benzyl Alcohols *via* Inorganic Hypochlorite Oxidation[1]

CAL Y. MEYERS[2]

Received June 14, 1960

The action of aqueous inorganic hypochlorite on several benzyl alcohols has been studied. Benzaldehyde and *o*-methoxybenzaldehyde were thus obtained in good yield from their respective alcohols. Under the conditions employed there was no evidence of reaction between the hypochlorite and these aldehydes. *o*-Hydroxybenzyl alcohol, under identical conditions, provided no aromatic aldehyde but was chlorinated in the nucleus with a concurrent elimination of formaldehyde. Possible mechanisms are considered.

The potential stock of variously substituted hydroxybenzyl alcohols is apparent from the recent compilations by Martin[3] and Megson.[4] This particular type of benzyl alcohol is simply prepared from the phenol and formaldehyde and

(1) Presented before the Meeting-in-Miniature, North Jersey Section, American Chemical Society, Jan. 28, 1957.

(2) Present address and that to which inquiries should be directed: Istituto di Chimica Industriale, Università di Bologna, Viale Risorgimento, 4, Bologna, Italy.

thus may be a future economical source of many corresponding derivatives. This communication is concerned with the use of aqueous inorganic hypochlorite with benzyl alcohols as a possible simple and economical means of preparing the corresponding aromatic aldehydes.

The transformation of an alcohol to its aldehyde may be regarded as dehydrogenation and usually is initiated by an oxidation process.[5] The latter, however, may have deleterious effects upon the sensitive nucleus of these phenolic systems: Ring-fission[6] and polyhydroxylation[7] are often observed. A variety of oxidation schemes have, on occasion, afforded aldehydes from phenol alcohols.[8] The success of any one method is very much dependent upon the nature of ring substituents. If the latter is nitro, for example, a strong oxidant like permanganate works well and does not destroy the ring. Weak reagents, such as cupric sulfate, are successful when the phenol alcohol has an additional hydroxyl or methoxyl in the nucleus. Saligenin (*o*-hydroxybenzyl alcohol) in *anhydrous* ether or hexane is transformed into salicylaldehyde by a suspension of manganese dioxide.[9] Organic agents have been used, but they are expensive and often are difficult to remove from the desired aldehyde. In most instances oxidants tend to react with the sensitive aldehydes formed, yielding acids. To diminish the sensitivity of the ring and that of the resulting aldehyde, it is advisable to block the phenolic hydroxyl group prior to oxidation. Permanganate or dichromate then may be used with general success in obtaining the corresponding blocked aldehydes.[8]

A general method was still desired which would transform phenol alcohols directly into their aldehydes, in good yield. The application of an indirect oxidation approach seemed reasonable. Halogenation-dehydrohalogenation schemes have been generally successful in preparing ketones and some aldehydes from the corresponding alcohols, *tert*-butyl hypochlorite being the most widely reported agent.[10] These reactions probably involve the formation of corresponding hypohalite of the alcohol, which readily is dehydrohalogenated yielding the desired carbonyl product (Equation 1). However,

$$\text{R—CHOH} \xrightarrow{\text{alkyl—O—X}} \text{R—CHOX} \xrightarrow[-\text{HX}]{} \text{R—C=O} \quad (1)$$

R=alkyl, aryl, or H; X=halogen

organic hypohalites (and, presumably, similar reagents such as *N*-halosuccinimides, -acetamides, etc.) can function as ionic or free radical halogenating agents, depending on the solvent used and the reactions involved.[11a] Thus, methoxy- and hydroxybenzaldehydes may react promptly with these reagents to form the corresponding ring-halogenated aldehyde (ionic, free radical) or benzoyl halide (free radical).[11b] With phenol alcohols, then, any advantage of this scheme with these reagents over ordinary oxidation methods seemed defeated.

The haloform reaction[12] as applied to methylalkylcarbinols involves initial transformation to the ketone by inorganic hypohalite,[12,13] generally in aqueous solutions. The α-methylene functions are then rapidly halogenated, however, through an ionic mechanism.[13] Under the polar conditions necessarily used with inorganic hypohalites, the latter do not function *via* free radical mechanisms.[11] Thus, primary alcohols should yield the corresponding aldehydes; if the latter have no α-hydrogens they should be quite stable to further reaction: —CHO groups are halogenated by a free radical sequence, not ionic; furthermore, mildly alkaline hypochlorite apparently is no better an oxygen source than is molecular oxygen dissolved in water.[14] The only reactive agent in inorganic hypohalite solutions is the free hypohalous acid, not hypohalite ion; and hypohalous acids are weaker halogenating agents than the corresponding free halogens.[11a] It seemed quite possible, therefore, that mildly alkaline solutions of these hypohalites, maintained at moderate temperatures, would not attack the nuclei of hydroxy- or methoxybenzaldehydes.

Few accounts could be found describing the preparation of corresponding aldehydes by treatment of alcohols with aqueous halogenating solutions. In one, chlorine-water was utilized.[15] In another, aqueous hypochlorite, sodium hydroxide, and temperatures exceeding 100° were employed.[16] These conditions differed from those hypothesized above as being optimum for the direct preparation of alde-

(3) R. W. Martin, *The Chemistry of Phenolic Resins*, John Wiley, New York, 1956.

(4) N. J. L. Megson, *Phenolic Resin Chemistry*, Academic Press, New York, 1958.

(5) For provocative discussions the following are noted: P. D. Bartlett, *Organic Chemistry*, Vol. III, H. Gilman, ed., John Wiley, New York, 1953, pp. 75–78; and W. A. Waters, *Organic Chemistry*, Vol. IV, H. Gilman, ed., John Wiley, New York, 1953, p. 1207.

(6) C. K. Ingold, *Chemistry of Carbon Compounds*, Vol. IIIA, E. H. Rodd, ed., Elsevier Publishing Co., Princeton, N. J., 1954, p. 78.

(7) H. D. Dakin, *Am. Chem. J.*, **42**, 477 (1909); H. D. Dakin, *Org. Syntheses*, Coll. Vol. I, 149 (1947).

(8) These are reviewed by Martin, Ref. 3, pp. 225 ff.

(9) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(10) M. Anbar and D. Ginsburg, *Chem. Revs.*, **54**, 925 (1954); note especially Table V, p. 937.

(11)(a) Ref. 10, pp. 943–953; (b) Ref. 10, Table VI, p. 938.

(12) R. C. Fuson and B. A. Bull, *Chem. Revs.*, **15**, 275 (1934).

(13) E. R. Alexander, *Ionic Organic Reactions*, John Wiley, New York, 1950, pp. 206 ff.

(14) G. Holst, *Chem. Revs.*, **54**, 179 (1954).

(15) F. D. Chattaway and O. G. Backeburg, *J. Chem. Soc.*, **123**, 2999 (1923). The intention of this study was to isolate benzyl hypochlorite by treating benzyl alcohol with Cl_2—H_2O. Instead, benzaldehyde was identified in the product and the desired hypochlorite was postulated as the unisolable intermediate (*cf.* Equation 1).

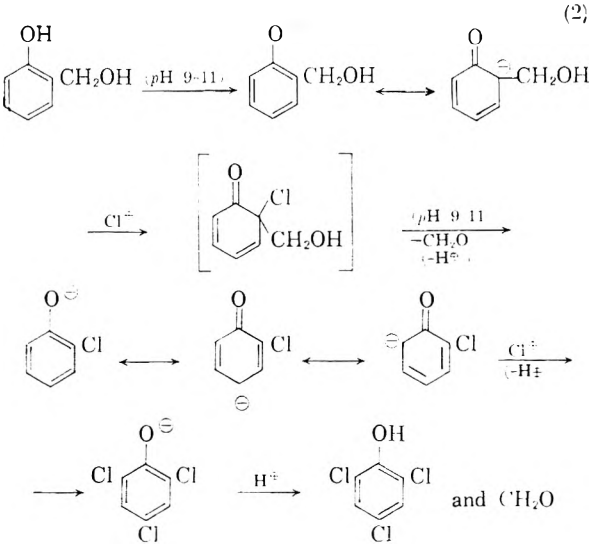
hydes in aqueous media.[17] Moreover, and more important, the effects of these conditions on the sensitive hydroxy- and methoxy- substituted nuclei were not reported.

DISCUSSION

In this study, commercial "bleaching powder" (calcium chloride–calcium hypochlorite mixture) was converted to the more water-soluble potassium hypochlorite. Aqueous solutions of the latter were then standardized and used in all of the reactions studied. The transformation of benzyl alcohol to benzaldehyde was examined first. In the course of several reactions, experimentally optimum conditions of alcohol reaction and aldehyde stability were determined: (1) The use of slightly more than equivalent amounts of hypochlorite. (2) The addition of methanol to aid solution of the benzyl alcohol. (Pure methanol is stable to aqueous hypochlorite solutions.[18]) (3) The maintenance of *p*H 9–11 by adjusting the amount of potassium carbonate in the hypochlorite solution prepared. (4) Mechanical agitation of the reaction mixture at room temperature for at least twelve to fourteen hours. Under such conditions the reactions proceeded smoothly and yields close to eighty per cent of benzaldehyde were realized in single-pass experiments. No benzoic acid or halogenated derivatives were detected in these preparations.

The next reaction studied involved saligenin, the type of alcohol obtained from phenol and formaldehyde.[3,4] Unlike benzyl alcohol, this phenol alcohol possesses reactive ring positions. Under the mild reaction conditions outlined above, it was hoped that only salicylaldehyde would result; the reactive nucleus and —CHO of the latter, it is recalled, are vulnerable to attack by organic hypohalites.[11b] The results, however, were disappointing, but interesting. Not only was the ring chlorinated in the open positions (4- and 6-) but the 2-hydroxymethyl group was eliminated as formaldehyde and replaced by chlorine, 2,4,6-trichlorophenol being a product isolated. This result may be explained. At *p*H 9–11 the phenoxy anion would be present as its several resonance forms whose negative centers would be the *primary* targets of the electrophilic positive chlorine of the hypochlorite.[19] When the 2-position is so attacked the resulting system is stabilized (benzenoid formation) by the elimination of formaldehyde, and subsequent ring halogenation may follow (Equation 2).[20]

(2)



Final products identified[20]

Similar displacement of formaldehyde during bromination of such phenols has been previously recognized.[21] It has been found, in fact, that diazonium coupling reactions on the *ortho*-position of these phenols occur with the preferential displacement of the hydroxymethyl group rather than a hydrogen atom.[22] This was originally believed true also in *para* reactions,[23] but the converse was proved in these cases.[22] Chelation of the *o*-methylol with the phenolic oxygen has been recognized[24,25] and may account for the easy displacement of the former. On this basis Equation 2 depicts the hydroxymethyl group being displaced before the 4- and 6-hydrogen atoms. The postulate of a semiquinoid intermediate (following initial chlorination and before loss of

(16) C. O. Benedetti, A. P. Vanselow, and W. Vanselow, U. S. Patent No. 1,405,261, Jan. 31, 1922. This is sparsely detailed but describes an industrial scheme whereby the production of benzaldehyde is made possible by " . . . the great difference in volatility with steam of benzyl alcohol and benzaldehyde." It is implied that if the aldehyde is not removed "as formed," great amounts of benzoic acid result. However, as the solutions contained free sodium hydroxide and the reaction temperatures exceeded 100°, there is little doubt that these drastic conditions, independent of hypochlorite effect, would readily permit acid formation from the aldehyde by atmospheric oxidation and *via* the Cannizzaro reaction. The present study verifies the stability of such aldehydes to aqueous hypochlorite under more moderate conditions.

(17) Organic hypohalites are sparingly soluble in water. They are used mainly in chloroform, carbon tetrachloride, acetic acid, etc. In contact with water, moreover, they are readily hydrolyzed into hypohalous acids, the latter being the actual halogenating agents for substrates in the solution.[11a]

(18) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley, New York, 1948, p. 138.

(19) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N. Y., 1940, pp. 149–150, 204–205.

(20) Formaldehyde was the only aldehyde formed. Trichlorophenol, though in minor amounts, was the only other product isolated. The other chlorophenols, obviously the major products, are much more water soluble and were apparently removed by the too-thorough washing process.

(21) Ref. 3, p. 218.

(22) J. H. Freeman and C. E. Scott, *J. Am. Chem. Soc.*, **77**, 3384 (1955).

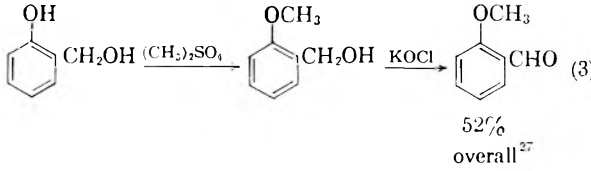
(23) E. Ziegler and G. Zigeuner, *Monatsh.*, **79**, 26, 89 and 158 (1948).

(24) G. R. Sprengling and C. W. Lewis, *J. Am. Chem. Soc.*, **75**, 5709 (1953).

(25) J. H. Freeman and C. W. Lewis, *J. Am. Chem. Soc.*, **76**, 2080 (1954).

formaldehyde) closely parallels that reported in analogous bromodesulfonation studies.[26]

While anisole is intermediate between benzene and phenoxy ion in nuclear reactivity to electrophilic agents[19] it remained to be determined whether this reactivity would predominate over that of the carbinol group in the reaction of *o*-methoxybenzyl alcohol with this hypochlorite reagent. Under conditions virtually identical with those described above, this alcohol followed the oxidation pattern of benzyl alcohol rather than that of ring chlorination-formaldehyde loss suffered by saligenin. The overall yield[27] of *o*-methoxybenzaldehyde, based on the original charge of saligenin, was about fifty-two per cent. The reaction sequence is noted in Equation 3.



(3)

Neither formaldehyde nor *o*-methoxybenzoic acid was detected in the final reaction mass. Rather vigorous treatment of this methoxybenzaldehyde with hydriodic acid in acetic acid failed to generate salicylaldehyde.[28]

CONCLUSION

(1) Nonphenolic aromatic aldehydes may be simply prepared from the parent alcohols by treating the latter essentially with aqueous solutions of "bleaching powder." Methoxy derivatives are included. (2) Phenol alcohols, under these conditions, may lose the alcohol side chain and are ring-halogenated, as indicated by the reactions of saligenin. (3) Aldehyde groups are apparently stable in aqueous hypochlorite solutions of *p*H 9–11 at room temperature. (4) Aqueous inorganic hypohalite may be more specific in these aldehyde syntheses, and certainly more economical, than organic hypohalites. The latter, moreover, necessarily are used in organic solvents.[17]

EXPERIMENTAL[29]

Preparation of hypochlorite solution. Commercial bleaching powder containing 24% "available chlorine" was found satisfactory but "H.T.H." (Monsanto) containing 35% "available chlorine" was preferable. This was treated with aqueous potassium carbonate solution to a final *p*H 9–11 and the precipitated calcium carbonate was removed by filtration. The precipitate was washed thoroughly with water and the combined washings plus original filtrate then diluted so that 100 ml. contained 0.1 mole of potassium hypochlorite. In these experiments 100 g. of "H.T.H." was accordingly treated so that 1000 ml. of final solution was virtually of this concentration.

Benzyl alcohol–hypochlorite reaction. A solution was prepared containing 112 ml. (0.112 mole) of potassium hypochlorite and 10.8 g. (0.1 mole) of distilled benzyl alcohol (b.p. 204–205°) dissolved in 60 ml. of methanol. The solution was diluted with 250 ml. of water and shaken for several minutes. The almond odor of benzaldehyde was detected almost immediately and the reaction temperature rose to 46° during these first minutes. Automatic shaking was continued overnight at room temperature (36–40°, in this laboratory). Finally, the turbid solution (*p*H remained 9–11) was extracted four times with benzene and the combined extracts were dried over anhydrous sodium sulfate then concentrated under reduced pressure. The slightly yellow oily residue was fractionally distilled, the main cut boiling at 178–180°, which is correct for benzaldehyde. The 2,4-dinitrophenylhydrazone prepared from several drops of distillate melted sharply at 236.5–237°; lit.,[30] m.p. 237°. A Tollens test produced a brilliant silver mirror within several minutes in a warm water bath. The 8.4 g. of pure benzaldehyde represents a 77% yield. The alkaline aqueous residue from the benzene extracts was acidified with cold hydrochloric acid but no benzoic acid was detected.

o-Hydroxybenzyl alcohol–hypochlorite reaction. The method used here was virtually identical with that described for benzyl alcohol, but the latter was replaced with 12.4 g. (0.1 mole) of *o*-hydroxybenzyl alcohol (saligenin) melting sharply at 84–85° (recrystallized from toluene). However, in this case the solution darkened immediately and the odor of formaldehyde was detected as quickly. The identity of the latter was confirmed *in situ* by its 2,4-dinitrophenylhydrazone which, when purified, melted at 165–166° (lit. value[30] is the same). A mixture of this derivative from pure formaldehyde and from the reaction mass also melted sharply at 165–166°. The dark mixture was adjusted to *p*H 4 with dilute hydrochloric acid and extracted several times with ether. The combined ethereal solutions were dried over anhydrous sodium sulfate and then concentrated under reduced pressure. There resulted a mass of slightly yellow crystals which, after being washed thoroughly with water and dried (*in vacuo*), melted at 66–68°. 2,4,6-Trichlorophenol melts at 67–68°[30] and a mixture of pure sample and isolated crystals also melted at 66–68°.[20]

Preparation of o-methoxybenzyl alcohol. Sodium saligenin monohydrate was prepared by the treatment of saligenin with an equivalent of sodium hydroxide in aqueous solution. The crystalline salt was precipitated from acetone, washed with the latter, and desiccated *in vacuo* at room temperature. The monohydrated salt was identified by its neutralization equivalent (titrated to bromphenol blue), by its water content (Karl Fischer method) and by its weight loss after 2 hr. at 150°.

To 16.4 g. (0.1 mole) of sodium saligenate monohydrate in 100 ml. of dry methanol was added slowly 12.6 g. (0.1 mole) of dimethyl sulfate in 50 ml. of dry methanol. The mixture was agitated vigorously and kept below 35° by the intermittant use of an ice bath. The original orange color slowly disappeared and after being agitated overnight at room temperature the mixture was only slightly yellow and the *p*H was 6–7. These indicated that the saligenate had been completely utilized. The mixture was diluted with ether and the sodium methyl sulfate was removed by filtration. The filtrate was dried over anhydrous sodium sulfate, the solvents removed *in vacuo*, and the residue fractionally distilled. The

(26) L. G. Cannell, *Abstracts of Papers*, American Chemical Society, 130th Meeting, Sept., 1956, p. 57O.

(27) The use of bisulfite, while affording an excellent purification-isolation scheme for the aldehyde, no doubt reduced its yield considerably.

(28) Methoxy groups in similar structures are also only difficultly removed with this and other hydrolytic agents (L. I. Smith, H. E. Ungnade, J. W. Opie, W. W. Prichard, R. B. Carbin, and E. W. Kaiser, *J. Org. Chem.*, **4**, 323 (1939).

(29) All melting points are uncorrected.

(30) E. H. Huntress and S. A. Mulliken, *Identification of Pure Organic Compounds*, Order I, John Wiley, New York, 1941.

main cut, a colorless oil, was taken at 111–112°/8–10 mm.; lit. value[30] for *o*-methoxybenzyl alcohol, b.p. 104°/5 mm.

o-Methoxybenzyl alcohol-hypochlorite reaction. The total pure cut of the above distillate was dissolved in 15 ml. of methanol and this solution was diluted with 100 ml. of water. This solution was then added to 100 ml. (0.1 mole) of potassium hypochlorite solution and then diluted with 100 ml. of water. At this point the solution had *p*H 11. The system was mechanically shaken overnight at room temperature which was attained shortly after the initial exotherm (to 51°) on mixing the reactants. The organic constituents were then removed by ether extraction (to negative 2,4-dinitrophenylhydrazone test of aqueous residue) and the aldehyde removed from the combined ether portions by extraction with aqueous sodium bisulfite solution (to negative 2,4-dinitrophenylhydrazone test of ethereal layer). These combined aqueous extracts were acidified to *p*H 2 with dilute cold hydrochloric acid, then extracted with ether until no aldehyde remained in the aqueous portion (negative 2,4-dinitrophenylhydrazone test). The combined ether extracts were dried over anhydrous sodium sulfate, the ether was removed under reduced pressure, and 7 g. of water-white oil remained. Several drops of the oil were used to make derivatives: *2,4-dinitrophenylhydrazone*, dark orange crystals, m.p. 249–252° (lit.[30] m.p., 253° for this derivative of *o*-methoxybenzaldehyde); *oxime*, white needles, m.p. 89–91° (lit.[30] m.p., 92° for this derivative of *o*-methoxybenzaldehyde). The 7 g. of pure *o*-methoxybenzaldehyde obtained represented a 51.5% yield[27] (overall reaction, based on sodium saligenate). No methoxybenzoic acid was found.

BOUND BROOK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, PURDUE UNIVERSITY]

Further Application of the Hypochlorite Method of Chain Shortening in the Carbohydrate Series[1]

ROY L. WHISTLER AND K. YAGI

Received July 15, 1960

D-Arabinose from D-mannonic acid and D-lyxose from D-galactonic acid are prepared in yields of 35.3% and 40.7%, respectively. β-Maltose monohydrate is converted to 3-*O*-α-D-glucopyranosyl-α-D-arabinose in 32.6% yield and α-lactose monohydrate is converted to 3-*O*-β-D-galactopyranosyl-α-D-arabinose in 38.1% yield. This convenient chain shortening procedure is thus, apparently, well suited to oligosaccharides. The glycosylpentoses are obtained in crystalline form and as crystalline osazones. The galactosylarabinose is also obtained as its crystalline anilide.

Recently Whistler and Schweiger[2] described the preparation of D-arabinose from D-glucose by a two-stage, but single batch, hypochlorite oxidation. D-Arabinose was obtained in 35% crystalline yield. Work is here undertaken to determine the applicability of this convenient chain shortening procedure to two hexoglyconic acids and to two reducing disaccharides.

General usefulness of the oxidation reaction to glyconic acid is indicated by application to D-mannonic acid and D-galactonic acid with the production of D-arabinose and D-lyxose in crystalline yields of 35.3% and 40.7%, respectively. The yields thus approximate those obtained through use of the Ruff degradation.[3]

A very useful extension of the procedure appears to be to the reducing oligosaccharides where other chain shortening procedures are cumbrous or lead to low over-all yields. The hypochlorite procedure when applied to β-maltose monohydrate produces 3-*O*-α-D-glucopyranosyl-α-D-arabinose in a yield of 32.6%, and when applied to α-lactose monohydrate produces 3-*O*-β-D-galactopyranosyl-α-D-arabinose in 38.1% yield. Both disaccharides are obtained crystalline and as the crystalline phenylosazones. The second disaccharide is also obtained as the crystalline anilide, *N*-phenyl-(3-*O*-β-D-galactopyranosyl) - D - arabinosylamine monohydrate.

EXPERIMENTAL

Oxidation of maltose. Ten grams of β-maltose monohydrate were dissolved in 200 ml. of water and the *p*H was adjusted to 11 with sodium hydroxide. To this was added 500 ml. of 0.334*N* sodium hypochlorite (3 moles of oxidant per mole of maltose) which was adjusted to *p*H 11 with sodium hydroxide and sodium carbonate. The mixture was kept at 25° in the dark and the *p*H was frequently checked and corrected by addition of sodium hydroxide solution. In 22 hr. when about 2.4 moles of sodium hypochlorite per mole of maltose were consumed, the solution was brought to *p*H 5.0 by the addition of hydrochloric acid. To this was added 300 ml. of 0.266*N* sodium hypochlorite: 1.4 moles per mole of original maltose. The mixture was kept at 25° in the dark and the *p*H was maintained at *p*H 4.5–5.0 by the addition of sodium hydroxide solution. After 12 hr. when the oxidant was consumed, the solution was neutralized and concentrated under reduced pressure until sodium chloride crystallized in large amounts. After addition of three volumes of methanol, the salt crystals were removed by filtration. The filtrate was then further desalted by passage through Amberlite IR-120(H) and IR-45(OH) exchange resins.[4] The solution was filtered through a thin layer of activated carbon[5] and concentrated to a sirup under reduced pressure.

(1) This is paper No. 8 in a series concerning "Action of Oxidants on Carbohydrates." The previous paper is R. L. Whistler and A. M. Belfort, *TAPPI*, in press. Journal Paper No. 1640 of the Purdue Agricultural Experiment Station, Lafayette, Ind.

(2) R. L. Whistler and R. Schweiger, *J. Am. Chem. Soc.*, 81, 5190 (1959).

(3) See: H. G. Fletcher, Jr., H. W. Diehl, and C. S. Hudson, *J. Am. Chem. Soc.*, 72, 4546 (1950).

(4) Products of Rohm & Haas, Philadelphia.

(5) Darco G-60, a product of the Matheson Company, Inc., East Rutherford, N. J.

Paper chromatograms using ethyl acetate:acetic acid:formic acid:water (18:3:1:4 v./v.) as irrigant and silver nitrate[6] as spray reagent showed the presence of a principal component, $R_{glucose}$ 0.52, which gave only D-glucose and D-arabinose on hydrolysis. The sirup also contained small amounts of D-glucose and D-arabinose ($R_{glucose}$, 1.43) and a trace amount of unoxidized maltose ($R_{glucose}$, 0.36).

The amount of the disaccharide ($R_{glucose}$, 0.52) present in the sirup was determined by quantitative[7] paper chromatographic measurement of the increase in D-arabinose which was obtained on hydrolysis. The yield thus calculated was 32.7% of the theoretical amount.

Isolation and identification of 3-O-α-D-glucopyranosyl-α-D-arabinose. Ten grams of β-maltose monohydrate was treated as above except that the crude product was chromatographed on a carbon-Celite[8] column[9] (30 × 170 mm.). The 5% ethanol eluate which contained only the disaccharide was evaporated under reduced pressure to a sirup and triturated with absolute ethanol to give 2.83 g. or 32.6% yield of amorphous disaccharide, $R_{glucose}$ 0.52.

A 1.50-g. sample of this crude, amorphous disaccharide was repurified on a carbon-Celite column[9] (48 × 17 cm.) which was washed successively with 3 l. of water, 4 l. of 1.5% ethanol, 3 l. of 4% ethanol and 3 l. of 6% ethanol. Since paper chromatographic examination showed that the 1.5% and 4% ethanol effluents contained most of the disaccharide, these two were combined and evaporated under reduced pressure to dryness; yield 1.33 g. This material was dissolved in a few drops of water, 20 ml. of methanol was added, and a small amount of insoluble material removed by filtration. The filtrate was evaporated under reduced pressure to about 3 ml., seeded with an authentic sample provided by H. S. Isbell and allowed to stand at room temperature for 2 weeks. Crystals which formed were filtered, washed with methanol, and dried; m.p. 114–117°, yield 0.86 g. Two recrystallizations from 95% methanol afforded pure 3-*O*-α-D-glucopyranosyl-α-D-arabinose monohydrate; m.p. 119–121°, undepressed on admixture with an authentic sample, $[\alpha]_D^{25}$ +56.9° → +47.0° (constant after 15 hr.) (*c*, 1.0 in water). The observed values are in agreement with the m.p. 121° and $[\alpha]_D$ +47° (water), reported for the α-monohydrate by Moyer and Isbell,[10] but are in disagreement with the m.p. 172° and $[\alpha]_D^{20}$ +16.5° (water), reported by Gakhokidze[11] and with the optical rotation, $[\alpha]_D^{20}$ +72.0° (water), reported for the amorphous disaccharide by Zemplén.[12]

To prepare the phenylosazone, 0.4 g. of the disaccharide and 0.8 g. of phenylhydrazine hydrochloride with 1.5 g. of sodium acetate trihydrate were dissolved in 10 ml. of water and the mixture was heated on a steam bath for 60 min. On cooling and stirring, crystals separated and were recrystallized from 30% ethanol and dried at 70° in vacuum. They decomposed at 195–200°; reported[11] m.p. 195–200°.

Oxidation of lactose. Ten grams of α-lactose monohydrate were oxidized as described for maltose. Paper chromatography of the products showed the presence of a major component at $R_{glucose}$ 0.46. This substance gave D-galactose and D-arabinose on hydrolysis. The amount of the disaccharide present in the sirup as measured by quantitative chromatographic determination of the increase in D-arabinose on hydrolysis showed it present in 36.5% yield.

Another similar oxidation of 10 g. of α-lactose monohydrate gave 3.30 g. of the amorphous disaccharide; yield 38.1%.

Isolation and identification of 3-O-β-D-galactopyranosyl-α-D-arabinose. A 0.60-g. sample of the amorphous disaccharide was dissolved in 3 ml. of methanol, filtered, and the filtrate seeded with an authentic sample provided by H. S. Isbell. On standing at room temperature crystallization proceeded gradually for 2 weeks, at which time the crystals were filtered, washed with methanol, and dried; m.p. 160–163°, yield 0.25 g. Recrystallization was effected by dissolving the crude crystals in a few drops of water, adding 20 ml. of methanol, filtering the resulting solution, concentrating the filtrate to about 3 ml. under reduced pressure, and allowing the solution to stand at room temperature for a week. The pure sample of 3-*O*-β-D-galactopyranosyl-α-D-arabinose was obtained after two recrystallizations; m.p. 166–168°, undepressed on admixture with an authentic sample, $[\alpha]_D^{25}$ −50.2° → −63.0° (constant after 15 hr.) (c, 1 in water). Reported values for the disaccharide are: m.p. 166–168°,[13] 165°,[14] 165–166°,[15] and 162–169°[16]; $[\alpha]_D^{19}$ −50.3° → −63.1°,[13] $[\alpha]_D^{20}$ −55.1°,[14] $[\alpha]_D^{23}$ −54.5° → −62°[16] and $[\alpha]_D^{20}$ −62.5°,[17] in water.

For further identification, a crystalline aniline derivative of the disaccharide was prepared after Kuhn and Kirschenlohr.[16] The mother liquor separated from the crude crystals of the disaccharide was evaporated to dryness. The resulting residue weighing 0.30 g. was dissolved in 2 ml. of methanol; 0.10 g. of aniline was added, and the mixture was heated under reflux for 1.5 hr. After cooling, *N*-phenyl(3-*O*-β-D-galactopyranosyl)-D-arabinosylamine monohydrate was collected on a fritted glass funnel; yield 0.31 g., m.p. 169–170°. On recrystallization from 80% aqueous ethanol it melted at 170–171° and showed $[\alpha]_D^{25}$ +34.0° (*c*, 0.50 in pyridine); $[\alpha]_D^{25}$ +2.6° → 10.5° (after 1 hr.) → −44.3° (constant after 10 hr.) (*c*, 0.42 in water) and $[\alpha]_D^{25}$ +37.0° → +25.0° (after 4 days) → +16.5° (after 14 days) (*c*, 0.60 in dimethylformamide). Kuhn and Kirschenlohr[16] reported m.p. 170–171°, $[\alpha]_D^{22}$ +34.7° (pyridine), $[\alpha]_D^{22}$ −16° → −42° (after 1 hr. in water) and $[\alpha]_D^{25}$ +36° → +7.5° (after 4 days in dimethylformamide). The phenylosazone prepared as described above decomposed at 236°; reported m.p. 236–238°,[18] 242°.[19]

Oxidation of maltobionic acid. β-Maltose monohydrate was oxidized by bromine in the presence of calcium benzoate[20] and the resulting calcium maltobionate solution was deionized with Amberlite IR-120(H). After neutralization with lithium hydroxide, the solution was concentrated to a thick sirup and mixed with 2-propanol. On cooling the mixture, fine crystals of lithium maltobionate trihydrate were obtained; $[\alpha]_D^{25}$ +96.8° (*c*, 5.0 in water), reported[21] $[\alpha]_D^{20}$ +97.3° (*c*, 8.7 in water).

A 4.28-g. portion of lithium maltobionate trihydrate (0.01 mole) was dissolved in 200 ml. of water and was mixed with 200 ml. of 0.222*N* sodium hypochlorite (2 moles per mole of maltobionate) at *p*H 5. The mixture was held at 25° in the dark and the *p*H maintained at 4.5–5.0 by the addition of

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sodium hydroxide when necessary. After 28 hr. when the oxidant was consumed, the mixture was deionized by means of both cation and anion exchange resins in the manner described above and was concentrated to 100 ml. A 50-ml. aliquot was concentrated further and chromatographed on a carbon-Celite column. The first 300 ml. of aqueous effluent contained both D-glucose and D-arabinose in small amounts. The next 100 ml. contained a very small amount of D-glucose and some disaccharide. The remaining disaccharide was then removed from the column with 700 ml. of 5% ethanol. This fraction was concentrated to a sirup and triturated with absolute ethanol to give 0.260 g. (16.6% of the theoretical amount) of amorphous powder ($R_{glucose}$ 0.52) which yielded only D-glucose and D-arabinose on hydrolysis. The phenylosazone, m.p. 196–200°, showed no change in melting point on admixture with 3-*O*-α-D-glucopyranosyl-α-D-arabinose obtained by the oxidation of maltose.

Oxidation of D-*mannonic acid.* D-Mannono-γ-lactone was prepared from D-mannose by oxidation with bromine,[22] m.p. 151°. After hydrolysis of 1.78 g. (0.01 mole) of D-mannono-γ-lactone by boiling with 100 ml. of 0.1*N* sodium hydroxide solution for 10 min., the solution was adjusted to *p*H 5 with hydrochloric acid, and 100 ml. of 0.418*N* sodium hypochlorite (2 moles per mole of D-mannonic acid) at *p*H 5 were added. The solution was kept at 25° in the dark and the *p*H was maintained at 4.5–5.0 by the addition of sodium hydroxide solution. After about 30 hr. when the oxidant was consumed, the reaction mixture was deionized with ion exchange resins and found to contain D-arabinose in 48.7% of the theoretical amount when analyzed by the Willstätter-Schudel method.[23] Crystalline β-D-arabinose was obtained in the yield of 0.53 g. (35.3% of the theoretical amount); $[\alpha]_D^{25}$ −175° → −105° (*c*, 1.0 in water), m.p. 156–157°, undepressed on admixture with authentic D-arabinose.

Oxidation of D-*galactonic acid.* After hydrolysis of 1.78 g. (0.01 mole) of D-galactono-γ-lactone by boiling with 100 ml. of 0.1*N* sodium hydroxide solution for 10 min., the solution was adjusted to *p*H 5 with hydrochloric acid and mixed with 100 ml. of 0.401*N* sodium hypochlorite solution (2 moles per mole of D-galactonate) at *p*H 5. The oxidation was completed in about 24 hr. at the *p*H range of 4.0–5.0 in the dark at 25°. Determination of D-lyxose by Willstätter-Schudel titration of the deionized sirup indicated that there was present 50.1% of the theoretical amount. The yield of crystalline α-D-lyxose, $[\alpha]_D^{25}$ −14° → +5.3° (c, 1.0 in water) obtained from the final solution was 0.61 g. (40.7% of the theoretical amount); m.p. 103–106°, undepressed on admixture with authentic D-lyxose.

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[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Alumina: Catalyst and Support. VI.[1] Aromatization of 1,1-Dimethylcyclohexane, Methylcycloheptane, and Related Hydrocarbons over Platinum-Alumina Catalysts[2,2a]

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The aromatization of 1,1-dimethylcyclohexane (I), 4,4-dimethylcyclohexene (II), methylcycloheptane (III), and 5,5-dimethylcyclohexadiene (IV) over platinum-alumina catalysts has been investigated. The catalysts were prepared by impregnating aluminas of various intrinsic acidities with a solution of dinitrodiammine platinum, $Pt(NH_3.NO_2)_2$.

The relative acidities of the aluminas and the method of platinizing them were found to have a profound effect on the composition of the aromatized product. The aromatization of I and II was accompanied by isomerization and the extent of isomerization could be related to the intrinsic acidity of the alumina. The product of the isomerization was mainly *o*-xylene admixed with *m*- and *p*-xylene and in the presence of a catalyst having high intrinsic acidity, alkylcyclopentanes were also produced.

The aromatization of methylcycloheptane formed ethylbenzene and xylenes; the distribution of the various aromatic compounds depended upon the acidity of the alumina used.

Recent publications of this laboratory have stated that aluminas have intrinsic acidic properties and that the relative acidities of the aluminas depend upon the method of their preparation.[4] It was demonstrated that alumina prepared from aluminum isopropoxide is more acidic than that prepared from potassium aluminate. The relative acidities of the aluminas were determined by the ease with which they brought about the isomerization of various olefins.[4,5] Recently it has been shown

(1) For paper V of this series see: H. Pines and C. N. Pillai, *J. Am. Chem. Soc.*, **82**, 2401 (1960).

(2) Paper III of the series of Aromatization of Hydrocarbons. For paper II see: H. Pines and C. T. Chen, *J. Am. Chem. Soc.*, **82**, 3562 (1960).

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(3) Postdoctoral Fellow, 1958–1959.

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that the catalytic behavior of molybdena-alumina[6] and chromia-alumina[2,7] is greatly influenced by the relative intrinsic acidities of the aluminas used in the preparation of these catalysts.

The use of platinum-alumina catalysts for the conversion of hydrocarbons has found wide application in industry.[8] The UOP Platforming catalyst has been reported to be composed of platinum, alumina and halogen.[9]

It has been reported that 1,1,3-trimethylcyclohexane yielded *m*-xylene when passed over a platinum-alumina catalyst prepared from a commercial alumina; however, in the presence of added hydrogen chloride (arising from an alkyl chloride) the aromatization was accompanied by isomerization resulting in the formation of trimethylbenzenes.[10]

The purpose of the present study was to determine the effect of aluminas of various intrinsic acidities upon the behavior of the respective platinum-alumina catalysts toward the aromatization of 1,1-dimethylcyclohexane (I), 4,4-dimethylcyclohexene (II), methylcycloheptane (III) and 5,5-dimethyl-1,3-cyclohexadiene (IV). It was of particular interest to determine whether there is a correlation between the dehydroisomerization reaction of I and II and the intrinsic acidities of the aluminas used in the preparation of the catalysts.

The aluminas used were of known composition and could be prepared reproducibly.[4] The aluminas were platinized by impregnation with hot aqueous solutions of dinitrodiammine platinum. Care was exercised to avoid the introduction of halide ions as it is known that hydrogen halide increases the catalytic acidic properties of aluminas[11] and sodium chloride reduces such acidity.[4] Two commercial platinum-alumina reforming catalysts were compared with our platinum-alumina.

EXPERIMENTAL

Preparation of catalysts (a) Alumina *ex* isopropoxide was prepared by hydrolysis of aluminum isopropoxide. The alumina was filtered and dried at 120° for 2 days. The alumina was screened to collect particles of 60–100 mesh, mixed with 4% of 60–100 mesh stearic acid and made into $1/8 \times 1/8$ inch pills. The pills were heated at 500° for 4 hr. in a stream of air and finally calcined at 700° for 4 hr. in a stream of air.

(b) Alumina *ex* potassium aluminate was prepared according to the detailed description given previously.[2] The precipitated alumina was washed five times by decantation and centrifugation.

(c) Platinum-alumina catalysts. The platinum complex dinitrodiammine platinum was prepared as described in the literature.[12] Calcined alumina pellets (10 cc., 7.1 g.) were treated with a hot aqueous solution containing dinitrodiammine platinum to give the desired platinum content. The minimum amount of water was used to dissolve the dinitrodiammine platinum. The pellets were dried under a heat lamp and heated to 500° in an air stream to decompose the complex.

A list of the various platinum-alumina catalysts which were prepared, and their designations are given in Table I.

TABLE I

PLATINUM-ALUMINA CATALYSTS

Designation	Source of Aluminas	% Pt	Remarks[a]
A	$Al(OC_3H_7)_3$	1	—
B	$KAlO_2$	1	Washed five times, 0.09% K (estimated)[4]
C	$KAlO_2$	1	Washed seven times, 0.06% K (estimated)[4]
AA	$Al(OC_3H_7)_3$	1	Al_2O_3 equilibrated with $Pt(NH_3.NO_2)_2$ solution 24 hr. at 100°
D	$Al(OC_3H_7)_3$	5	—
E	$Al(OC_3H_7)_3$	1	Al_2O_3 equilibrated with water at 100° for 24 hr. before platinizing
Harshaw	Commercial	1	Commercial alumina platinized in this laboratory
X	Commercial	0.6	"Reforming Catalyst"
Y	Commercial	?	"Platinum reforming catalyst/gamma alumina/precipitated from acid medium with NH_4OH"

[a] Details of catalyst preparation are found in the Experimental section.

Catalyst A was prepared by impregnating alumina *ex* aluminum isopropoxide with 1% platinum.

Catalyst B was prepared by impregnating alumina *ex* potassium aluminate with 1% platinum.

Catalyst C differs from Catalyst B only in that its alumina had been washed seven times instead of five.

Catalyst D was prepared from the same alumina as that used for Catalyst A and was impregnated with 5% platinum.

Catalyst E was prepared by keeping the calcined but unplatinized alumina used for Catalyst A in contact with water at 100° for 24 hr. The alumina was then dried and platinized with 1% platinum.

Catalyst AA was made by keeping calcined but unplatinized alumina in contact with platinizing solution (1% platinum) at 100° for 24 hr. The resulting material was decomposed as described above.

Harshaw catalyst was prepared by impregnating the commercial alumina with the platinum complex (1% platinum). The intrinsic acidity of this alumina was less than that of the alumina which was used for the preparation of Catalyst B. The evaluation of the acidic properties of the Harshaw alumina has been described previously.[4]

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Platinum-alumina reforming Catalysts X and Y were obtained from commercial sources. The details of their preparation were not revealed; they contained 0.6 to 1% platinum.

Synthesis of hydrocarbons. 1,1-Dimethylcyclohexane (I), *4,4-dimethylcyclohexene* (II) and methylcycloheptane (III) were obtained by methods previously reported.[1]

5,5-Dimethylcyclohexadiene (IV) was synthesized from II as previously described.[13]

Experimental procedure. Samples of the platinum-alumina catalysts (5 or 10 cc.) were placed in Pyrex reaction tubes (1 cm. diameter). The space above the catalyst was filled with glass beads to act as a preheater. The tubes so prepared were heated overnight in a vertical furnace at 350° in an air stream. Before each reaction the catalyst was purged with nitrogen and reduced at 350° for 30–60 min. in a stream of hydrogen.

The delivery pump and product recovery apparatus have been described previously.[2] Liquid products were condensed at 0° and noncondensable gasses were collected over saturated aqueous sodium chloride solution.

During the experiments listed in Table II consecutive 1- and 2- ml. samples were collected and analyzed separately. The averages of such determinations are reported. Usually the first sample collected would show an anomalously high degree of isomerization and was, therefore, ignored in computing the average. From three to eight samples were collected during experiments lasting from 45 min. to 3 hr.

To obtain samples from the experiments listed in Table IV, the first milliliter collected at each space velocity was discarded and the next retained for analysis. The delivery rate of the pump was then changed and the process repeated. These experiments were always performed in order of increasing space velocity, *i.e.*, of decreasing contact time.

Identification and estimation of products made use of a gas-liquid partition chromatographic column of dipropyl tetrachlorophthalate.[2] The identities of products were established by comparing their retention times with those of authentic specimens. Infrared spectroscopy confirmed the presence of major constituents. Ultraviolet spectroscopy was used to detect and estimate the conjugated cyclic dienes produced.

The relative retention times for the various hydrocarbons using dipropyl tetrachlorophthalate at 102° were: Compound (relative time); unknown (3.9): 1,1-Dimethylcyclohexane (I) [8.0]; 4,4-Dimethylcyclohexene (II) [8.8]; Toluene and methylcycloheptane [11.0]; 5,5-Dimethyl-1,3-cyclohexadiene (IV) [12.5]; ethylbenzene (17.3); *m*- and *p*-Xylene (19.5); *o*-xylene (24.3).

Silicone column was used to determine the fractions containing toluene, methylcycloheptane and 1,1-dimethylcyclohexane. The relative retentions were: methylcycloheptane and 1,1-dimethylcyclohexane 20.5, and toluene 31.5.

DISCUSSION OF RESULTS

Experiments 1, 2 and 6 (Table II) show that in the aromatization of 1,1-dimethylcyclohexane (I), the yield of the *o*-xylene, product of skeletal isomerization, increases in the order of Harshaw < B < A. The same order of increasing acidity has been noted in cyclohexene isomerization over the corresponding aluminas.[4] Catalyst A, which was prepared from the most acidic alumina, catalyzed the formation of isopropylcyclopentane and of some isomeric cyclopentanes, while progressively smaller amounts of these compounds were produced with the less acidic catalyst. It is interesting to note that *m*- and *p*-xylene, amounting to 6–7% of the total aromatics, were produced even in the presence of the less acidic catalyst; in addition, about 1% of ethylbenzene was also present in the aromatic product.

Experiments 1, 3, and 4 illustrate vividly the effect of platinizing procedure on catalyst acidity. The three catalysts (A, AA, and E) contain the same amount of platinum and were prepared from alumina of the same batch. Catalyst A, prepared by rapid absorption of the platinizing solution, exhibits high acidity as shown by its high *o*-xylene and low toluene yields. Catalyst AA was prepared by keeping the alumina in prolonged contact with the platinizing solution. Maatman and Prater[14] have found that when *alpha* alumina pellets (3 mm.) are placed in contact with chloroplatinic acid solution, equilibration of platinum content throughout the pellets requires some 23 hours. Experiment 3 shows Catalyst AA to be considerably less acidic than Catalyst A. The acidity decrease is probably due to an extensive neutralization of acid sites by preferential absorption of the platinum complex. However, the possibility remains that the acidity decrease is due to partial hydration of the aluminas. To distinguish between these alternatives a sample from the same batch of alumina was kept in contact with hot water for 24 hours and then was platinized by rapid absorption of the complex. Experiment 4 shows the catalyst so prepared to be less acidic than Catalyst A but more acidic than Catalyst AA. This might indicate that the diffusion of the dinitrodiammine platinum on a partially hydrated alumina is more rapid and that the platinum was able to penetrate to the center of the alumina pill and, hence, to neutralize more uniformly the stronger acid sites.

The present results indicate that platinum-alumina catalysts having acidic properties and capable of causing skeletal isomerization during aromatization of saturated hydrocarbons may be prepared even in the absence of halogen acids as previously indicated.[10]

The olefinic *gem*-dimethylcyclohexenes are known to be more susceptible to skeletal isomerization during the aromatization than the corresponding saturated hydrocarbons.[10] This was also confirmed by the present study (Exp. 9 and 10). Even the weakly acidic Catalyst B caused extensive isomerization (Exp. 2 *vs.* 9). Catalyst C (Exp. 10) differed from Catalyst B only in having been more thoroughly washed and hence slightly more acidic.[4] The data (Exp. 9 *vs.* 10) seem to bear out this observation so far as the formation of *o*-xylene is concerned. However, the difference is small and may not be significant.

In this connection it is important to indicate that

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TABLE II

AROMATIZATION OF 1,1-DIMETHYLCYCLOHEXANE(I) AND OF 4,4-DIMETHYLCYCLOHEXENE(II)

Exp.	Substrate	Cat.	% Conv.[b]	Reaction Products, %					
				$C_6H_5CH_3$	$C_6H_5C_2H_5$	*o*-Xylene	*m*- + *p*-Xylene[c]	IPCP[d]	Other[e]
1	I	A	65	18	1	60	7	6	9
2	I	B	49	54	1	32	6	Trace	7
3	I	AA	67	60	1	29	6	Trace	4
4	I	E	63	39	1	48	6	Trace	5
5	I	D	76	69	1	19	6	Trace	6
6	I	Harshaw	62	80	1	13	6	Trace	Traces
7	I	X	80	33	1	54	10	2	[g]
8	I	Y	73	18	1	70	4	3	4
9	II[f]	B	62	7	1	82	1	5	6
10	II[f]	C	67	5	1	79	5	6	6
11	*cis*-1,2-DMCH[h]	A	98	—	0.1	97.5	0.2	—	2[i]

The experiments were made at 350° and at HLSV[a] = 0.5.

[a] Vol. liquid passed per hour per vol. catalyst used. [b] Moles reaction products per total moles in isomerate. [c] Infrared spectroscopy showed *meta/para* ratio = 2.2–3.5. [d] Isopropylcyclopentane. [e] Complex mixture of low-boiling compounds including 1,1,3-trimethylcyclopentane. [f] In these reactions I in the isomerate is calculated as starting material. [g] A mixture of some 16 low-boiling compounds. [h] Dimethylcyclohexane. [i] Various dimethylcyclohexanes.

cis-1,2-dimethylcyclohexane yielded 97.5% *o*-xylene when passed over the most acidic catalyst. The extent of skeletal isomerization was less than 3% (Exp. 11). Thus, it might be concluded that 1,2-dimethylcyclohexyl species once formed does not undergo skeletal rearrangement.

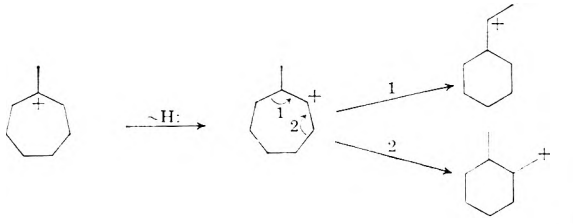
The sensitivity of *o*-xylene formation to catalyst acidity suggests that it arises chiefly *via* 1,2-methyl migration of the 2,2-dimethylcyclohexyl carbonium ion, followed by dehydrogenation. Formation of such an ion from II *via* protonation of a carbon-carbon double bond would be expected to occur more readily than its formation from I, a process requiring either hydride ion abstraction or previous dehydrogenation to an olefin. Experiments 9 and 10 show that indeed II is more readily isomerized.

It was shown that compound I forms predominantly toluene and compound II forms *o*-xylene when passed over Catalyst B (Table II). It could therefore be concluded that during aromatization the olefinic hydrocarbons II and IV which presumably precede the formation of the aromatic compounds are not desorbed from the dehydrogenation sites of the catalyst prior to demethanation. In the presence of the more acidic Catalyst A, however, the protonation of the adsorbed species II and IV can probably occur, leading to an isomerization reaction.

The increase in platinum concentration from 1% to 5% decreases the isomerization properties of the catalyst (Exp. 5 *vs.* 1). This can be explained by a more thorough neutralization of the stronger acid sites on the alumina used in the preparation of the catalyst. It is, however, not excluded that the relative rate of protonation of the adsorbed species decreases with the increase of platinum concentration.

The presence of *m*- and *p*-xylene and of small amounts of ethylbenzene is difficult to explain by means of a carbonium ion mechanism. The presence of the *m*-xylene could be explained by the thermal decomposition of 5,5-dimethylcyclohexadiene (IV)[13]; this, however, would not explain the formation of *p*-xylene or ethylbenzene.

The formation of *m*- and *p*-xylene and ethylbenzene could best be explained by a ring expansion of I or II to form a seven-membered ring intermediate. It was found that methylcycloheptane (IV) on aromatization forms toluene, xylenes, ethylbenzene and 1,1-dimethylcyclohexane (Table III). The yield of ethylbenzene increased and the yield of I decreased with the acidity of alumina. This increase in ethylbenzene formation can be explained by an ionic mechanism by which the formation of methylcycloheptyl carbonium ion can be assumed to be one of the intermediate steps. Ring contraction of this carbonium ion would lead to the formation of *sec*-cyclohexylethyl carbonium ion rather than to methylcyclohexylmethyl carbonium ion inasmuch as the formation of the former would involve the participation of secondary and tertiary carbonium ions without the formation of the less stable primary carbonium ions.



The aromatization of methylcycloheptane seems to proceed preferentially through an intermediate

TABLE III

AROMATIZATION OF METHYLCYCLOHEPTANE (III) AND OF 5,5-DIMETHYLCYCLOHEXADIENE (IV). T = 350°

Exp.	Substrate	Cat.	HLSV[a]	% Conv.[b]	Products, % $C_6H_5CH_3$	$C_6H_5C_2H_5$	*o*-Xylene	m- + *p*-Xylene	I	[illegible]	IPCP[d]	Other[e]
12	IV	A	0.6	87[g]	3	—	84	10[f]	[g]	—	—	3
13	IV	A	2.0	86[g]	7	—	82	5[f]	[g]	6	—	1
14	IV	B	0.6	60[g]	15	—	74	2[f]	[g]	9	—	Trace
15	III	A	0.5	95	11	22	32	29	7	—	Trace	Trace
16	III	A	4.0	26	8	18	26	24	9	—	8	7
17	III	AA	0.5	89	21	11	24	29	15	—	Trace	—
18	III	B	0.5	36	32	8	18	27	15	—	—	—
19	III	D	0.5	97	29	6	22	27	16	—	—	—

[a] See Table II, footnote [a]. [b] See Table II, footnote [b]. [c] Probably cycloheptane or cycloheptadiene. [d] Isopropylcyclopentane. [e] See Table II, footnote [e]. [f] Infrared examination showed *meta* ≫ *para*. [g] Only traces of IV found in isomerate. I and II calculated as starting material.

TABLE IV

EFFECT OF CONTACT TIME ON THE AROMATIZATION OF 1,1-DIMETHYLCYCLOHEXANE

Exp.	$HLSV^{-1}$[a]	Cat.	% Conv.[b]	Reaction Products: c	d	e	Toluene	*o*-Xylene	*m*- + *p*-Xylene	Ethylbenzene	[illegible]	Others[f]
20	2.0	A	65				8	80	5	1	1	5
21	1.0	A	41			Trace	5	82	6	1	2	5
22	0.5	A	18			1	2	78	8	1	1	10
23	0.25	A	3			11	5	64	12	—	Trace	9
24	2.0	B	33	—	7	—	52	34	6	1	—	
25	1.0	B	15	1	12	Trace	38	46	3	1	—	
26	0.5	B	9	1	20	6	29	40	4	—	—	
27	0.25	B	4	1	48	7	21	23	—	—	—	

[a] See Table II, footnote [a]. [b] See Table II, footnote [b]. [c] Identified by ultraviolet spectroscopy, λ_{max} = 234–235 mμ and gas chromatography. [d] 3,3- and/or 4,4-Dimethylcyclohexene. [e] Identified by λ_{max} = 257 mμ. [f] Table II, footnote [c].

formation of 1,1-dimethylcyclohexyl species. This is indicated by the high yield of toluene and of compound I formed when a catalyst of lower acidity is used (Table III).

The formation of isopropylcyclopentane from compound I in the presence of the more acidic catalyst (Table III) can be explained by a ring contraction of 2,2-dimethylcyclohexyl carbonium ion.

The amount of *o*-xylene formed is higher in the case of Catalyst A than B, 32% *vs.* 18% (Exps. 15 and 18). This is not too surprising because in the presence of the more acidic catalyst 1,1-dimethylcyclohexane aromatizes preferentially to *o*-xylene rather than to toluene.

The effect of contact time upon the aromatization of I over Catalyst A (having an alumina of high intrinsic acidity) was studied (Table IV). The composition of the aromatic fraction was almost constant with the conversion changing from about 65% to 18% (Exps. 20–22). When the contact time was reduced still further, so as to obtain only 3% conversion, 11% of 5,5-dimethyl-1,3-cyclohexadiene (IV) was present in the reaction product.

Compound IV when passed over Catalyst A yielded mainly xylenes. (Table III) and only 3–7% of toluene (Exps. 12 and 13). In the presence of the less acidic Catalyst B, the yield of toluene was 15% (Exp. 14). Since the reaction product contained also compounds I and II it can not be excluded that toluene might have been produced preferentially from compound I.

The effect of contact time upon the aromatization of 1,1-dimethylcyclohexane over the less acidic Catalyst B has been studied also (Table IV) and the composition of the product examined by a combination of gas chromatography and ultraviolet spectroscopy. It was observed that at the longest contact time, the main products of reaction were toluene, *o*-xylene, and smaller amounts of *gem*-dimethylcyclohexene. As the contact time decreases, the concentration of the *gem*-dimethylcyclohexene and that of *gem*-dimethylcyclohexadiene increases, while the amount of *o*-xylene decreases. The concentration of toluene decreases with decrease in contact time. It is interesting to note that according to the ultraviolet spectroscopy about 1% of product corresponding to conjugated methylenecyclohexene or to 3-methylene-4-methyl-

cyclohexene were also present; the first compound may be the precursor of toluene. The absorptivity value used for this calculation was reported previously.[13]

The experimental results summarized in Table IV suggest that the aromatization of 1,1-dimethylcyclohexane to *o*-xylene proceeds stepwise, *via* the formation of *gem*-dimethylcyclohexene and cyclohexadiene and that the latter then undergoes a dehydroisomerization reaction as indicated in Table IV.

SUMMARY

(1) The effect of aluminas in the platinum-alumina catalysts have been investigated in regard to the aromatization of 1,1-dimethylcyclohexane (I) and 4,4-dimethylcyclohexene (II).

(2) The aromatization of I and II can be used as a measuring stick for the determination of acidic properties of platinum-alumina catalysts; for catalysts with weak acidic properties, compound II is recommended.

(3) High activity dehydroisomerization catalysts were prepared, even in the absence of halogen acids, when aluminas of high intrinsic acidity were used.

(4) Platinum seems to neutralize the acidic sites of aluminas.

(5) The dehydroisomerization reaction can be explained by a carbonium ion mechanism.

(6) The demethanation reaction to form toluene seems to proceed through a stepwise dehydrogenation to II and IV. The dehydrogenated species are not desorbed from the catalyst prior to demethanation. In the presence of catalyst having acidic properties the adsorbed species are probably protonated before they are aromatized.

(7) The aromatization of I and II seems to proceed in part through a ring expansion, followed by a ring contraction. This would explain the presence of *m*- and *p*-xylene and of ethylbenzene in the reaction product. The aromatization of methylcycloheptane gives data in accordance with this hypothesis.

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[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Alumina: Catalyst and Support. VII.[1] Aromatization of *n*-Heptane-1-C^{14} Over Chromia-Alumina Catalysts[2,3]

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The aromatization of *n*-heptane-1-C^{14} over chromia alone and chromia-alumina catalysts having different intrinsic acidities was studied. The catalysts exhibited specific activity decrease patterns and the C^{14} distribution in the product toluene was found to depend on the nature of the catalysts and change with time. The results were interpreted by mechanisms involving five-, six-, and seven-membered ring intermediates of which the relative contributions depend on the nature of the catalyst and change of time. Cycloheptane was aromatized over chromia-alumina catalysts in good yields. Ethylcyclopentane was aromatized over chromia-alumina catalyst having high intrinsic acidity but not over chromia-alumina catalyst in which the alumina had low intrinsic acidity.

The mechanism of catalytic aromatization of alkanes has been the subject of considerable interest for the last twenty-five years.[4a-c] Chromia-alumina was found to be one of the best catalysts for this reaction. The mechanisms of Twigg,[5] Herington and Rideal,[6] Pitkethly and Steiner,[7] and Wheatcroft[8] would all predict 50% methyl labeled toluene from *n*-heptane-1-C^{14}. Recently Mitchell[9] has reported values of 27–29% in disagreement with the prediction and postulated three mechanisms to account for the low value of methyl label. These include an intermediate formation of a transanular bridge,[6] rapid five- to six-membered

(1) For Paper VI of this series see: H. Pines and T. W. Greenlee, *J. Org. Chem.*, **26**, 1052 (1961).

(2) Paper IV of the series of aromatization of hydrocarbons. For Paper III see Ref. 1.

(3) 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.

(4) (a) For a review of the literature see: A. H. Steiner, "Catalytic Cyclization and Aromatization of Hydrocarbons," in *Catalysis*, Vol. IV, pp. 529–560, edited by P. H. Emmett, Reinhold, New York, 1956. (b) G. F. Ciapetta, R. M. Dobres, and R. W. Baker, "Catalytic Reforming of Pure Hydrocarbons and Petroleum Naphthas," in *Catalysis*, Vol. VI, pp. 492–692, edited by P. H. Emmett, Reinhold, New York, 1958. (c) C. Hansch, *Chem. Revs.*, **353** (1953).

(5) G. H. Twigg, *Trans. Far. Soc.*, **34**, 1006 (1939).

(6) E. F. G. Herington and E. K. Rideal, *Proc. Roy. Soc.*, **184A**, 434, 447 (1945).

(7) R. C. Pitkethly and A. H. Steiner, *Trans. Far. Soc.*, **35**, 979 (1939).

(8) R. W. Wheatcroft, dissertation, University of California, August 1, 1949.

(9) J. J. Mitchell, *J. Am. Chem. Soc.*, **80**, 5848 (1958).

ring interconversion,[10] and intermediate formation of cycloheptane species.

In none of the published papers dealing with the aromatization catalyzed by chromia-alumina is there suggestion that alumina might exert an effect upon the catalytic properties of chromia-alumina and thereby alter the consequences of the reaction.

Recent studies in our laboratory have disclosed that alumina has intrinsic acidic properties and that the strength of the acid sites depends on the methods used for the preparation of the alumina.[11] Alumina obtained by hydrolysis from aluminum isopropoxide catalyzed the isomerization of cyclohexene to methylcyclopentenes, whereas alumina prepared from potassium aluminate did not effect such isomerization. It has also been shown that aluminas of different intrinsic acidities influence the catalytic properties of chromia-alumina catalysts in aromatization reactions.[12]

The present study was undertaken to determine the effect of different chromia-alumina catalysts on the aromatization of *n*-heptane-1-C^{14} and gain a better understanding of the mechanism of aromatization reaction.

EXPERIMENTAL

Hydrocarbons. a. n-Heptane-1-C^{14} was synthesized in 70% overall yield by the carbonation of *n*-hexylmagnesium bromide with carbon dioxide-C^{14}, the lithium aluminum hydride reduction of the resulting *n*-heptanoic acid-1-C^{14}, and finally the hydrogenolysis of the resulting *n*-heptanol-1-C^{14}. A synthetic sequence of this type was described previously.[14]

b. Ethylcyclopentane, b.p. 102–103.7°, n_D^{20} 1.4192, was synthesized in 76% overall yield, by the iodine catalyzed dehydration of 1-ethylcyclopentanol followed by hydrogenation.

c. Cycloheptane, b.p. 117–118°, n_D^{20} 1.4432, was prepared by the conventional Wolf-Kishner reduction of cycloheptanone in 72% yield.

Catalysts. The catalysts used in this study were: chromia alone (20 ml., 24.2 g.); chromia-alumina A (20 ml., 17.0 g.) in which the alumina was prepared by hydrolysis of aluminum isopropoxide and is considered to have strong intrinsic acidic properties; and chromia-alumina B (15 ml., 11.0 g.), in which the alumina was prepared by precipitation from potassium aluminate and is considered to have very weak intrinsic acidic properties. The chromia-alumina catalysts were prepared by impregnation; a more detailed description of the catalysts was given in a previous paper.[13]

Apparatus and procedure. The apparatus used was that described previously.[13] The hydrocarbons were passed over the catalysts at 500°, atmospheric pressure, and hourly liquid space velocity of 0.32. The liquid products were withdrawn periodically and analyzed by infrared spectroscopy and gas chromatography using a 6-foot tricresyl phosphate on fire brick column.

The liquid product obtained from *n*-heptane-1-C^{14} was[8] diluted with inactive toluene and chromatographed on silica gel.[14] The toluene fraction thus obtained was oxidized with alkaline potassium permanganate to benzoic acid. The weight percent of toluene in the original sample was calculated by the isotope dilution method.[14] The benzoic acid was decarboxylated by heating in quinoline with copper oxide at 265° for 3 hr. Both carbon dioxide and benzene were assayed for C^{14} to obtain the isotope distribution.

All the samples assayed were converted to gaseous carbon dioxide. The organic samples were burned by wet combustion according to the procedure of Van Slyke,[15a,b] in which the carbon dioxide produced was 100 ± 0.5% for all aromatic substances assayed. For compounds such as *n*-heptane-1-C^{14} dry combustion was preferred.[14]

The radioactivity assay was performed in a 250 ml. ionization chamber, connected to a vibrating reed electrometer. The commercially available instrument used was a Dynacon model 6000,[16] equipped with a 10 millivolt variable chart speed recorder.

DISCUSSION

The experimental results obtained from the aromatization of *n*-heptane-1-C^{14} are summarized in Table 1.

Toluene formation. Over chromia alone the toluene content starts at a high value of 70% and falls rapidly to 10%. Over chromia-alumina A (having alumina of high intrinsic acidity) the conversion to toluene starts at 45% and decreases almost linearly with the smallest slope of the three experiments. Over chromia-alumina B (prepared from potassium aluminate and having an alumina of very weak intrinsic acidity) the toluene content starts at about the same value as in Experiment 2 but decreases with a greater slope and ends with the lowest value of all. Not much may be concluded from these data concerning the mechanism, but these patterns indicate that incorporation of different aluminas in chromia-alumina produces different catalytic effects.

Distribution of C^{14}. a. Chromia. Chromia alone gave 47% methyl-labeled toluene. Mitchell[9] has found that the catalytic dehydrocyclization showed no isotope discrimination within experimental error, but that the assay of the methyl carbon involved an overall 10% isotope discrimination. As the present decarboxylation method was conducted at 265°—much higher than the temperature at which Mitchell carried out the Hunsdiecker reaction—it is expected that the isotope discrimination attending our assay of the methyl carbon is absent or at least much lower than 10%. In the present experiments benzene resulting from the decarboxylation was also assayed, and the largest deviation from 100% radioactivity recovery was 2.7%. In any event, therefore, an uncertainty of 3% may be allowed for the assay data.

It follows that the dehydrocyclization over chromia alone may be interpreted by any one of

(10) H. Pines and R. W. Myerholtz, *J. Am. Chem. Soc.*, **77**, 5392 (1955).

(11) H. Pines and W. O. Haag, *J. Am. Chem. Soc.*, **82**, 2471 (1960).

(12) C. T. Chen, W. O. Haag, H. Pines, *Chem. & Ind.*, 1379 (1959).

(13) H. Pines and C. T. Chen, *J. Am. Chem. Soc.*, **82**, 3562 (1960).

(14) H. Pines and A. W. Shaw, *J. Am. Chem. Soc.*, **79**, 1474 (1957).

(15) (a) D. D. Van Slyke, J. Folch, *J. Biol. Chem.*, **136**, 509 (1940). (b) D. D. Van Slyke, J. Plazin, and T. R. Weisiger, *J. Biol. Chem.*, 191, 299 (1951).

(16) Nuclear-Chicago Corp.

TABLE I

TOLUENE CONTENT OF DEHYDROCYCLIZATION PRODUCT FROM *n*-HEPTANE-1-C^{14} AND DILUTION DATA. C^{14} DISTRIBUTION IN TOLUENE

Expt.	Catalyst	Activity of *n*-Heptane, μc./Mmole	Cut[a]	Product, G.	Toluene Added, G.	Toluene,[b] Wt. %	C^{14} Distribution in Toluene[b] Methyl, %	Ring, %	Difference,[c] %
1	Chromia alone	2.86	1	1.293	3.644	70.2	44.7	56.9	+1.6
			3	1.594	2.190	27.2	47.3	52.3	−0.4
			5	2.019	2.017	10.3	47.4	52.3	−0.3
2	Chromia-Alumina A	2.74	1	1.283	2.635	44.5	38.7	60.7	−0.6
			3	1.592	2.716	29.8	39.8	60.0	−0.2
			6	1.877	2.354	20.3	41.7	59.3	+1.0
3	Chromia-Alumina B	2.74	1	1.583	2.551	44.1	17.5	81.0	−1.5
			3	1.787	2.419	22.3	21.7	77.0	−1.3
			5	2.089	2.603	4.1	32.1	70.6	+2.7

[a] Cuts were taken at 3-ml. intervals. [b] Calculated by isotope dilution method. Activities of benzoic acids derived from toluene samples are given in Table II. [c] Difference between 100% activity recovery and experimental value.

TABLE II

DATA ON DECARBOXYLATION OF BENZOIC ACID DERIVED FROM TOLUENE

Benzoic Acid from Expt.	Cut	Activity, μc./Mmole	Carbon Dioxide, μc./Mmole	Benzene, μc./Mmole
1	1	0.570	0.255	0.324
	3	0.472	0.223	0.247
	5	0.266	0.126	0.139
2	1	0.488	0.189	0.296
	3	0.407	0.162	0.244
	6	0.381	0.159	0.266
3	1	0.589	0.103	0.477
	3	0.387	0.0841	0.298
	5	0.0865	0.0284	0.0611

the mechanisms[5-8] which predicted 50% methyl label. However, there is another mechanism which would also give 50% methyl label. It involves the process: formation of absorbed cyclopentene by 1,5-closure of adsorbed 1- or 2-heptene and ring expansion to absorbed methylcyclohexene. Actually this is 1,6-closure carried out in two steps, but it is nonetheless different from the second postulated mechanism of Mitchell in that the cyclopentane species is formed from heptene directly but not from adsorbed methylcyclohexene. Twigg's opinion[5] that 3-heptene must isomerize to 1- or 2-heptene before undergoing cyclization may not be absolute, because 3-heptene may also undergo 1,5-closure directly, followed by ring expansion and aromatization. The relatively slow rate of toluene formation from 3-heptene may be attributed to the slow rate of the aromatization of the cyclopentene intermediate or, as Twigg has pointed out, to the necessity of first isomerizing to other heptenes, or both.

It was shown previously that chromia has intrinsic acidity as noted by its ability to cause some skeletal isomerization accompanying the aromatization of 1,1-dimethylcyclohexane.[13] The acidities, however, were considered to be insufficient to cause a deep-seated isomerization such as five- to six-membered ring interconversion, and the isomerization was explained as proceeding mainly in terms of methyl migration through a carbonium ion mechanism. In the dehydrocyclization of *n*-heptane over chromia alone methyl migration in the intermediate methylcyclohexane species is likely to be involved although the methyl label would not thereby be affected. The slightly lower methyl label of 45% for cut 1 might, therefore, be due to an involvement of a cycloheptane intermediate to be mentioned later.

The increase in methyl label with time is explained as due to the deactivation of dehydrogenation sites, which probably are responsible for the formation of seven carbon ring intermediates. The preferred deactivation of the dehydrogenation sites was observed previously.[13]

b. Chromia-Alumina A. That alumina modified or changes the nature of chromia and thereby alters the consequences of the reaction is revealed by the data on chromia-alumina A. The methyl label of about 40% is obviously different from 50% and must be accounted for by contribution of some side reactions which give less methyl label. These side reactions may involve those speculated by Mitchell. However, the first postulate of bicyclic intermediate may be excluded on the grounds already mentioned[12] and to be discussed in detail in a following paper of this series.[17]

The second postulate of Mitchell concerning five- to six-membered ring interconversion may not be excluded entirely if it is assumed that the olefinic species were involved and not the saturated hydrocarbons. Chromia-alumina A was able to dehydroisomerize 1,1-dimethylcyclohexane to a greater extent than chromia alone did, indicating that it possesses stronger acidic sites than the latter. The acidities were, however, considered to be still insufficient to cause six- to five-membered ring

(17) H. Pines and C. T. Chen, paper presented before the Second International Congress on Catalysis, July 4-9, 1960, Paris, France.

interconversion in 1,1-dimethylcyclohexane but not in 4,4-dimethylcyclohexene.[15] The adsorbed cyclopentane species as intermediate could be involved to an appreciable extent at first because ethylcyclopentane over chromia-alumina A gave 20% toluene. The toluene yield decreased rapidly to 3%. The formation of alkylcyclopentanes from alkanes having five carbon atom chains were reported in the literature.[18]

The formation of cycloheptane intermediate is, however, not excluded as responsible for the less than 50% C^{14} methyl label.

c. *Chromia-Alumina B.* Remarkably different results were obtained with the less acidic chromia-alumina B which gave methyl label values ranging from 17.5% to 32%. Cyclopentanes were not involved in the reaction since ethylcyclopentane was not aromatized over this catalyst. Mitchell's value of 28% falls in the range of our values, although it is not known whether or not his value was a constant throughout his dehydrocyclization experiment, as he analyzed a gross sample of the product. It is inadequate to restrict oneself to those mechanisms which give 25% methyl label. It is now apparent that mechanisms which would predict an even lower value are necessary to explain the 17.5%. A methyl label value of 14.3% will result if one assumes the following processes: formation of adsorbedcycloheptene species from adsorbed 1-heptene, rapid rolling around of the adsorbed cycloheptene, and ring contraction to adsorbed methylcyclohexene. This differs from the third speculation of Mitchell in that the seven-membered ring intermediate is formed not from the absorbed methylcyclohexene but directly from adsorbed 1-heptene, and that it rolls around the catalyst surface so much more rapidly than the subsequent ring contraction that isotopic equivalency of all of the seven carbon atoms is acquired. Although this process is necessary to account for the 17.5% methyl label, a concurrent operation of Mitchell's cycloheptene mechanism may not be excluded.

Cycloheptane gave toluene in 95% and 65% yield over chromia-alumina A and B, respectively, providing proof that the seven-membered ring compounds could be intermediates in the dehydrocyclization reaction. One may argue that chromia-alumina B gave a smaller yield of toluene from cycloheptane than chromia-alumina A, while the radiochemical data suggest a much greater contribution of the seven-membered ring intermediate over chromia-alumina B. It seems that the ability to form the adsorbed cycloheptene intermediate is a more important factor in this reaction than is the ability to destroy it. An alternative way of acquiring isotopic equivalency of the seven carbon atoms may involve simultaneous desorption and hydrogenation to cycloheptane. However, distinction between the two can not definitely be made at present.

The data obtained from the competitive aromatization of *n*-heptane and cycloheptane seem to indicate that desorbed cycloheptane is not involved in dehydrocyclization of *n*-heptane. The data in Table III show that cycloheptane disappeared faster than *n*-heptane, but the two chromia-alumina catalysts gave the same relative rate of reaction of these hydrocarbons. Decrease in mole ratio cycloheptane/*n*-heptane of starting mixture decreased the relative rate, suggesting that the two hydrocarbons were competing for the same catalyst sites. The rather small relative rate of 2:3 seems to predict a possible survival of the cycloheptane intermediate in the dehydrocyclization of *n*-heptane. Vapor phase chromatography revealed a trace of a compound having retention time intermediate between those of *n*-heptane and toluene but not exactly the same as that of cycloheptane.

TABLE III

COMPETITIVE AROMATIZATION OF *n*-HEPTANE AND CYCLOHEPTANE AT 500°

	Chromia-Alumina A	Chromia-Alumina B
Mole ratio[a]	1.01	1.01
H.L.S.V.	1.02	0.84
Rel. ratio[b]	2.6	2.7
Mole ratio[a]	0.39	0.39
H.L.S.V.	1.04	0.84
Rel. rate[b]	2.0	2.1

[a] Mole ratio cycloheptane/*n*-heptane of the charging stock. [b] Relative rate of disappearing, cycloheptane/*n*-heptane, as calculated from the mole ratio of remaining hydrocarbons.

The absence of cycloheptane in the products from the reaction of *n*-heptane is not necessarily an indication that cycloheptene species were not involved in the aromatization reaction. It is probable that adsorbed cycloheptene species were present but their relative rates of aromatization to toluene is much faster than that of cycloheptane.

CONCLUSION

The present study has added a new mechanism involving the intermediate formation of adsorbed cycloheptene. It may be concluded that the formation of toluene from *n*-heptane over a chromia catalyst may involve five-, six-, and seven-membered ring intermediates the relative contributions of which depend on the nature of the catalyst and change with time. It has been demonstrated that aluminas of different intrinsic acidities influence the behavior of chromia-alumina catalysts. The C^{14} distribution data suggest that a

(18) A. L. Liberman, G. V. Loza, G. Min-Nan, and B. A. Kazanskii, *Proc. Acad. Sci., U.S.S.R.*, 120, 113 (1958).

larger ring is more readily formed over chromia-alumina B having low intrinsic acidity. It appears that the catalyst sites leading to the specific ring closures are plural in kind and different in number from one catalyst to another. Besides the acidic properties, the arrangement of chromia on alumina surface may be a more important factor in the dehydrocyclization reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Michael Type Additions with Nitroparaffins.[1] A Convenient Route to Nitrocyclohexanols

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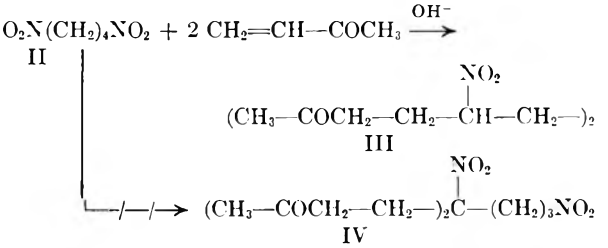
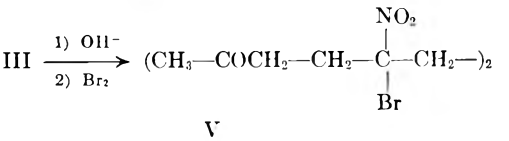
Primary nitroparaffins condense with phenyl vinyl ketone to afford monoaddition adducts. Treatment of these products with an additional equivalent of phenyl vinyl ketone yields predominantly the expected diadducts. Strong bases such as ethoxide and hydroxide cause cyclization of the initial reaction products to form substituted cyclohexanols providing a convenient synthetic route to these structures. When this Michael type reaction is applied to methyl vinyl ketone, the initial diaddition compounds cannot be isolated. Instead, cyclization occurs with the formation of cyclohexanols. The reaction of 2 equivalents of methyl vinyl ketone with α,ω-dinitroalkanes gives the symmetrical addition compound. Four equivalents of methyl vinyl ketone give the tetraaddition product. However, here also cyclization occurs concurrently with reaction so that dicyclohexanol derivatives are obtained. Dehydration of these cyclohexanols, followed by hydrogenation, opens a new route for the preparation of substituted nitrocyclohexanes.

Although the Michael type addition employing primary and secondary nitroparaffins as donors has been investigated by many workers,[2] little attention has been given to the use of α,ω-dinitroparaffins in this reaction. Only two reports[3] dealing with the Michael addition to dinitro compounds have appeared in the literature. Feuer and Leston found that disodium 2,2-dimethyl-1,3-propanedinitronate reacted in an unusual way with methyl acrylate to afford 4,4-dimethyl-5-(2′-carboxyethylidene)isoxazoline oxide, while 1,5-dinitropentane gave a 34% yield of the expected Michael adduct 5,9-dinitro-2,12-tridecanedione (I) when treated with two equivalents of methyl vinyl ketone.[3b]

α,ω-Dinitroparaffins. The present investigation was initiated by studying the reaction between 1,4-dinitrobutane (II) and two equivalents of methyl vinyl ketone. When this reaction was carried out in ethanol and in the presence of a catalytic amount of sodium hydroxide, two products, m.p. 91.5–92.5° and 61–62° were obtained. The same two compounds were secured when the full salt of compound II was employed. As the elemental analyses



of both products corresponded to $C_{12}H_{20}O_6N_2$ and as their infrared spectra were very similar, they were considered to be the *meso* and *dl* forms of 5,8-dinitro-2,11-dodecanedione (III). However, the possibility that one compound was the unsymmetrical adduct IV could not be ruled out *a priori*. Evidence rendering structure IV untenable was obtained by converting both isomers into the same dibromo derivative (V) in almost quantitative



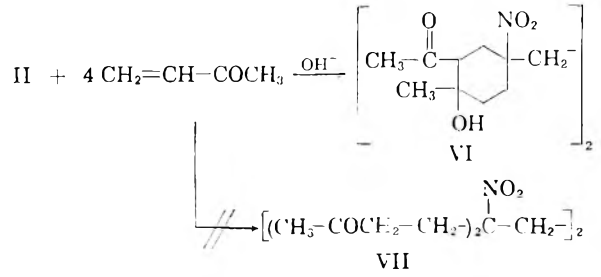
yield on treatment with two equivalents of base and excess bromine. The infrared spectra of compound V, obtained in both reactions were superimposable and a mixed melting point determination showed no depression.

(1)(a) From the Ph.D. thesis of Ronald Harmetz, Purdue University, 1959; (b) presented before the Division of Organic Chemistry at the Cleveland Meeting of the American Chemical Society, April 1960.

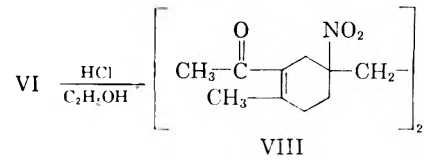
(2)(a) M. C. Kloetzel, *J. Am. Chem. Soc.*, **69**, 2271 (1947); (b) D. E. Worrall, and C. J. Bradway, *J. Am. Chem. Soc.*, **58**, 1607 (1936); (c) E. P. Kohler, *J. Am. Chem. Soc.*, **38**, 889 (1916); (d) F. Villani and F. Nord, *J. Am. Chem. Soc.*, **69**, 2608 (1947); (e) E. P. Kohler and H. Engelbrecht, *J. Am. Chem. Soc.*, **41**, 764, 1379 (1919); (f) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **65**, 23 (1943); (g) G. D. Buckley, T. J. Elliott, F. G. Hunt, and A. Lowe, *J. Chem. Soc.*, 1505 (1947); (h) G. D. Buckley, J. L. Charlish, and J. D. Rose, *J. Chem. Soc.*, 1514 (1947); (i) A. Lambert and H. A. Piggott, *J. Chem. Soc.*, **1947**, 1489; (j) for a thorough survey of the literature, reference is made to *The Michael Reaction* by E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(3)(a) H. Feuer and G. Leston, Abstract of Papers presented at the International Congress of Pure and Applied Chemistry, Paris, July 1957, p. 24; (b) H. Feuer and C. N. Aguilar, *J. Org. Chem.*, **23**, 607 (1958).

When 1,4-dinitrobutane was treated with four equivalents of 85% aqueous methyl vinyl ketone (inhibitor free), an 86% yield of a tetraaddition adduct was secured. Recrystallization of this material from methanol or acetonitrile afforded several fractions, the decomposition point of which ranged from 200–237°. The infrared spectra of the several fractions were similar and all showed a hydroxyl band in the 2.9 μ region. The elemental analyses of two samples, m.p. 223–229° dec. and 236–237° dec., corresponded to a tetraaddition adduct. The presence of a hydroxyl band in the infrared spectrum indicated that the product was not the expected tetraadduct VII but rather the cyclic compound 1,2-bis(1′-nitro-3′-acetyl-4′-hydroxy-4′-methylcyclohexyl)ethane (VI), which probably arose from compound VII *via* an intramolecular aldol condensation.



Compound VI was converted into a dioxime in an 88% yield; this further established its structure. Treatment of the crude derivative with boiling methanol afforded a soluble material, m.p. 248° dec. and an insoluble material, m.p. 254–256° dec. The elemental analyses of both corresponded to that calculated for the dioxime of compound VI and their infrared spectra were void of a carbonyl band, indicating complete reaction of the keto groups. The difference in melting point can be ascribed to the presence of diastereoisomers. Chemical evidence for the presence of a hydroxyl group in compound VI was obtained by dehydrating it to compound VIII. The ultraviolet spectrum



of the olefin possessed a band at 232 mμ, indicating that the product was an α,β-unsaturated ketone.[4]

It was observed that when the preparation of compound VI was carried out with 100% methyl vinyl ketone, containing 0.06 g. of hydroquinone, the yield decreased by about 30%. In order to ascertain whether the absence of water or the presence of hydroquinone in the methyl vinyl ketone was the cause of the lower yield, a series of experiments were performed which are summarized in Table I.

TABLE I

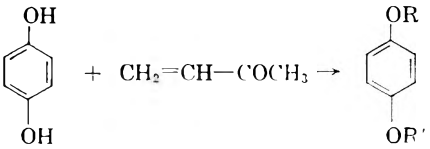
REACTION OF 1,4-DINITROBUTANE WITH FOUR EQUIVALENTS OF METHYL VINYL KETONE[a]

Expt.	Hydroquinone	Catalyst	Added Water[b]	Yield, %
1	None	3 drops of 20% aq. NaOH	3.0 g.	86
2	None	3 drops of 20% aq. NaOH	None	82
3	0.06 g.	3 drops of 20% aq. NaOH	None	59
4	0.06 g.	11 drops of 20% aq. NaOH	None	75
5	0.06 g.	3 drops of 20% aq. NaOH	3.0 g.	56

[a] All experiments were carried out in 95% ethanol at 40° for 24 hours. [b] The water present in the 95% ethanol is not included.

It is seen from the data in Table I that the addition of water did not alter the yield significantly and that the presence of hydroquinone (experiments 3 and 5) had a very detrimental effect on the yield. This effect was largely eliminated when a greater amount of base was employed (Expt. 4). It was obvious then that the hydroquinone or a reaction product between hydroquinone and methyl vinyl ketone, neutralized the base which was necessary to catalyze the desired Michael addition.

In a preliminary investigation it was found that hydroquinone reacted with methyl vinyl ketone to give a product, the elemental analysis of which agreed with both the mono- and diaddition adducts (IXa and IXb). However, the presence of infrared



IXa. R = CH_2—CH_2—$COCH_3$; R′ = H
IXb. R = R′ = CH_2—CH_2—$COCH_3$

absorption bands at 3.10 and 8.13 μ (aromatic hydroxyl) and 9.02 μ (aromatic ether) established that the product was the monoaddition adduct IXa.

The reaction of 1,5-dinitropentane (X) with two and four equivalents of methyl vinyl ketone, under conditions which gave good yields in the case of 1,4-dinitrobutane, resulted only in 31–34% yield of the diaddition adduct (I) but gave no tetraaddition product. The crude yield of compound I was increased to 40% when dioxane and "Triton B" were substituted for ethanol and sodium hydroxide. However, this solvent catalyst combination did not give any tetraaddition adduct when four equivalents of methyl vinyl ketone were employed. The tetraaddition adduct, 1,3-bis(1′-nitro-3′-acetyl-4′-hydroxy-4′-methylcyclohexyl)propane (XI), was finally obtained in a 50% yield when the reaction employing ethanol and sodium hydroxide was repeated with compound X which was washed with an aqueous sodium bicarbonate solution. These

(4) A. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold Ltd., London, 1954, p. 94.

TABLE II

REACTION OF 1,4-DINITROBUTANE WITH METHYL ACRYLATE

Expt.	Solvent	Temp.	Catalyst	Ratio 1,4 D.N.B.[a] / M.A.	Inhibitor	Time in Hours	Yield of XIV, %
1	Abs. CH_3OH	40°	$NaOCH_3$	1/2	None	72	8
2	Abs. CH_3OH	40°	$NaOCH_3$	1/2	Hydroquinone	8	0
3	Abs. CH_3OH	40°	$NaOCH_3$	1/2	Hydroquinone	18	11
4	Abs. CH_3OH	40°	$NaOCH_3$	1/6	*p*-Methoxyphenol	26	34
5	Abs. CH_3OH	40°	Full Na salt	1/2	None	8	0
6	T.H.F.[b]	40°	$NaOCH_3$	1/2	Hydroquinone	8	*ca.* 5
7	T.H.F.	40°	"Triton B"	1/2	Hydroquinone	36	66
8	T.H.F.	28°	Full Na salt	1/2	None	48	0
9	T.H.F.	40°	"Triton B"	1/2	Hydroquinone	8	63–66
10	Abs. CH_3OH	40°	"Triton B"	1/2	Hydroquinone	8	*ca.* 3

[a] $\frac{\text{1,4 D.N.B.}}{\text{M.A.}} = \frac{\text{equivalents of 1,4-dinitrobutane}}{\text{equivalents of methyl acrylate}}$. [b] T.H.F. = tetrahydrofuran.

data indicated that X contained an acidic impurity which neutralized the base necessary to catalyze the desired Michael addition.

Compound XI was also secured in a 50% yield by treating the diaddition adduct I with two equivalents of methyl vinyl ketone.

The infrared spectrum of the tetraaddition adduct possessed a hydroxyl band a 2.86 μ indicating that cyclization had taken place, resulting in the formation of compound XI. Additional proof for the cyclic structure was obtained by converting compound XI in 71% yield to a dioxime, the infrared spectrum of which was void of a carbonyl absorption.

Treatment of an ethanolic solution of 1,6-dinitrohexane (XII) containing a catalytic amount of sodium hydroxide, with four equivalents of methyl vinyl ketone afforded a 38% yield of 1,4-bis(1′-nitro - 3′ - acetyl - 4′ - hydroxy - 4′ - methylcyclohexyl)butane (XIII). The yield of compound XIII was not increased when the solvent and catalyst were dioxane and Triton B, respectively; treating compound XII with sodium bicarbonate also had no effect on the yield.

The crude product was separated, with isopropyl alcohol, into a higher and lower melting fraction, m.p. 221–221.5° dec., and 180.5–182° dec., the elemental analyses of which were in agreement with structure XIII. The cyclic structure was indicated by their infrared spectra which were similar and showed a hydroxyl band at 2.90 μ. The oximino derivatives of both materials analyzed correctly for the dioxime of compound XIII, indicating that they were diastereoisomers.

The reaction of compound II with two equivalents of methyl acrylate gave the expected product dimethyl 4,7-dinitrodecanedioate (XIV).

$$\text{II} + 2CH_2{=}CHCO_2CH_3 \xrightarrow{OH^-} \left[CH_3O_2C(CH_2)_2\overset{NO_2}{\overset{|}{C}}H{-}CH_2{-} \right]_2$$

XIV

The highest yield (66%) of compound XIV was obtained when compound II was treated with two equivalents of methyl acrylate for thirty-eight hours at 40° employing tetrahydrofuran and Triton B as solvent and catalyst, respectively. When the reaction was conducted in methanol with the full sodium salt of compound II or with Triton B or sodium methoxide as catalyst, the yields of compound XIV were 0–34%, (Table II).

Two solids, m.p. 60–62° and 91.5–92.5°, were separated from the crude reaction product which represented the diastereomers of compound XIV. The elemental analyses were in agreement with structure XIV and their infrared spectra were very similar.

The tetraaddition adducts dimethyl 4,7-bis-(2′ - carbomethoxyethyl) - 4,7 - dinitrodecanedioate (XV) and 4,7-bis(2′-cyanoethyl)-4,7-dinitrodecanedinitrile (XVI) were prepared in excellent yields by treating a solution of compound II in tetrahydrofuran containing a small quantity of Triton B, with four equivalents of methyl acrylate and acrylonitrile, respectively.

$$\text{II} + 4CH_2{=}CHR \xrightarrow{OH^-} [(R{-}CH_2{-}CH_2{-})_2\overset{NO_2}{\overset{|}{C}}{-}CH_2{-}]_2$$

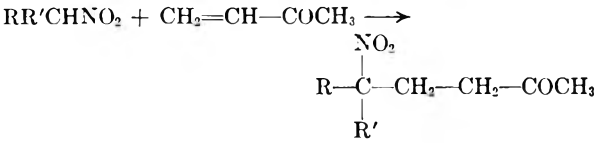
XV. R = CO_2CH_3
XVI. R = CN

By subjecting compound XV to acid hydrolysis a 92% yield of the corresponding tetraacid, 4,7-bis(2′-carboxyethyl)-4,7-dinitrodecanedioic acid was secured.

Mononitroparaffins. In view of the fact that cyclic products were obtained from the reaction of α,ω-dinitroparaffins with four equivalents of methyl vinyl ketone, it appeared desirable to determine the structure of the methyl vinyl ketone diaddition adducts (and triaddition adduct in the case of nitromethane) of primary mononitro paraffins; Shechter, Ley, and Zeldin[5] prepared and

(5) H. Shechter, D. E. Ley, and L. Zeldin, *J. Am. Chem. Soc.*, 74, 3664 (1952).

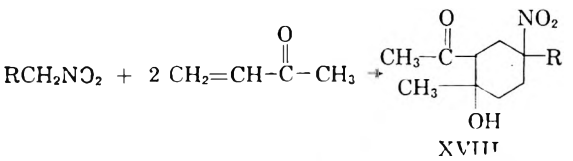
characterized the monoaddition adducts XVIIa and XVIIb. These authors stated that besides



XVIIa. R = R′ = H
XVIIb. R = H; R′ = CH_3
XVIIc. R = H; R′ = CH_3—CH_2—CH_2

these products "... nitroethane and nitromethane also yield 1:2 and 1:2 and 1:3 adducts respectively ...." However, no attempts to isolate and characterize these materials were reported.

When nitromethane, nitroethane, 1-nitropropane, and 1-nitrobutane were treated with two equivalents of methyl vinyl ketone (three equivalents in the case of nitromethane), cyclization of the Michael adducts took place with the formation of 1-methyl 2-acetyl-4-alkyl-4-nitro-1-cyclohexanols (XVIII).



XVIIIa. R = CH_3; XVIIIb. R = CH_2—CH_3; XVIIIc. R = CH_2—CH_2—CH_3; XVIIId. R = CH_2—CH_2—$COCH_3$; XVIIIe. R = H.

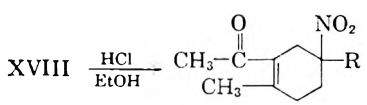
The structure of these products was established by (1) elemental analyses, (2) infrared data, (3) oxime and/or semicarbazone formations, and (4) dehydration to cyclic olefins (XIX). In Table III are summarized the yields of the cyclic alcohols (XVIII) and their derivatives.

TABLE III

Compound	Yield, %	Oxime, Yield, %	Olefin, Yield, %
XVIIIa	93	92	85
XVIIIb	65	90	73
XVIIIc	73	80, 97[a]	86
XVIIId	64	85	—
XVIIIe	5	—	—

[a] Semicarbazone.

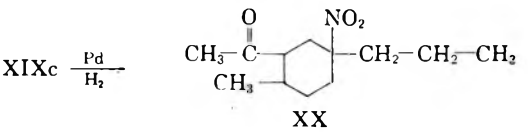
The infrared spectra of compounds XVIII possessed hydroxyl bands in the region of 2.85–3.0 μ and their oxime derivatives showed the correct analysis for monoximes, except compound XVIIId which showed the correct analysis for a dioxime. Complete oximation was established by the absence of a carbonyl band in the infrared spectra of these derivatives.



XIXa. R = CH_3
XIXb. R = CH_2—CH_3
XIXc. R = CH_2—CH_2—CH_3

The dehydration of compounds XVIII to XIX was carried out in refluxing ethanol saturated with hydrogen chloride. The olefins were shown to be α,β-unsaturated ketones by the presence of a peak in the 242–243 mμ region of their ultraviolet spectra.

Catalytic hydrogenation of compound XIXc with palladium chloride gave an 89% yield of compound XX, b.p. 90–120° (0.2 mm). The wide boiling point range can be ascribed to the presence



XX

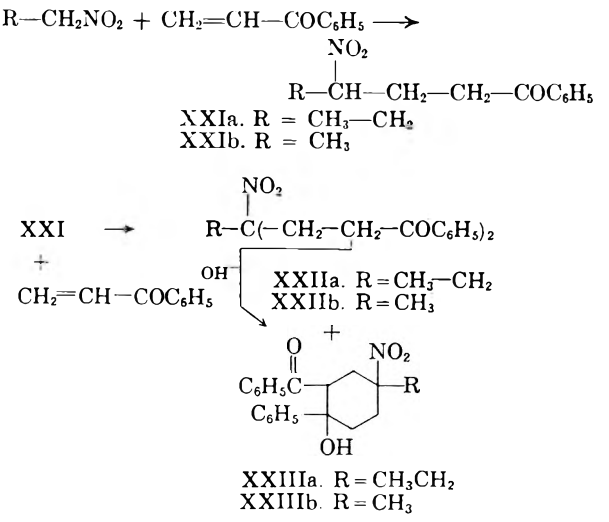
of diastereoisomers since the infrared spectra of the several fractions obtained were all very similar. The isomers were partially separated by dissolving the distillate in hexane and cooling the resulting solution to −78°. Filtration afforded a solid isomer, which after several recrystallizations from hexane melted at 54–55°. The hexane filtrate was distilled and a fraction boiling at 90–95° (0.2 mm.) as well as the above solid, were subjected to elemental analyses. Both samples showed the correct analysis for $C_{12}H_{21}O_3N$ which was in agreement with structure XX.

It is interesting to note that the diaddition adduct XVIIIa prepared from nitroethane and two equivalents of methyl vinyl ketone was not obtained unless the nitroparaffin was washed with an aqueous sodium bicarbonate solution. This indicated that an acidic impurity was present in the nitroethane which neutralized the catalytic amount of sodium hydroxide employed. These results are analogous to those obtained in the reaction of compound X with methyl vinyl ketone (*vide supra*). The product XVIIIa consisted of a solid and a liquid. As the infrared spectra of both were very similar, it was surmised that the liquid was either very crude or a product of a mixture of diastereoisomers of compound XVIIIa. The latter assumption was verified by dehydrating the oil in 77% yield to the same olefin (XIXa) which was also obtained from the solid product.

During the course of this investigation the monoaddition adduct, 5-nitro-2-octanone (XVIIc), which has not been previously reported, was prepared in 83% yield by treating 1-nitrobutane with one equivalent of methyl vinyl ketone.

In view of the cyclic products resulting from the Michael addition with methyl vinyl ketone and primary nitroparaffins, it was interesting to extend the investigation to phenyl vinyl ketone.

The monoaddition adducts XXIa and XXIb were prepared in 92% yield by treating nitropropane and nitroethane with one equivalent of phenyl vinyl ketone, prepared *in situ* from β-chloropropiophenone and the salt of the nitroparaffin. The diaddition adducts were prepared in almost quantitative yield by treating compounds XXIa and



XXIb with another equivalent of phenyl vinyl ketone.

The infrared spectrum of the crude reaction product obtained by treating XXIa, at 0–5°, with phenyl vinyl ketone, possessed a hydroxyl band at 2.90 μ, two carbonyl bands of similar intensity at 5.97 and 6.02 μ and aromatic absorption bands at 13.16, 13.45, 14.32, and 14.42 μ. Fractional recrystallization of this material from isopropyl ether afforded several fractions the infrared spectra of which were similar to that of the crude product. However, two fractions were obtained which possessed only one carbonyl band. One of these, m.p. 132–132.5°, had absorption peaks at 2.90 (hydroxyl), 6.02 (aromatic ketone), 13.16 and 14.32 μ (aromatic), while the other, m.p. 128–129°, had bands at 5.97 μ (aromatic ketone), 13.45 and 14.42 μ (aromatic), but was void of a hydroxyl band. Both showed correct analyses for a diaddition adduct. As the infrared spectrum of the higher melting material possessed a hydroxyl band, it was assigned the cyclic structure XXIIIa while the lower melting product, which did not contain a hydroxyl band, was assigned structure XXIIa. To verify this assignment, compound XXIIa was converted to its corresponding oximino derivative, in 95% yield. The elemental analysis of this material was in agreement with that calculated for the dioxime of compound XXIIa. In addition, compound XXIIa gave compound XXIIIa in almost quantitative yield, by refluxing in ethanol containing a catalytic amount of sodium hydroxide.

The yield of compound XXIIIa from the monoaddition adduct XXIa was increased to 90% by refluxing for five hours an aqueous ethanolic solution of XXIa with phenyl vinyl ketone.

When an attempt was made to convert compound XXIIIa to its corresponding oximino derivative, 93% of the starting material was recovered. The resistance to oximation might be rationalized from a study of the Fisher-Taylor-Hirschfelder model of XXIIIa, which showed that the carbonyl carbon is shielded by the substituents on the cyclohexane ring.

The phenyl vinyl ketone diaddition adduct of nitroethane was obtained in a 99% yield by treating an aqueous ethanolic solution of the sodium salt of compound XXIb with β-chloropropiophenone at 40° for four hours. The infrared spectrum of the product possessed a hydroxyl band at 2.90 μ and a strong carbonyl band at 6.01 μ with a weak shoulder at 5.95 μ, indicating that the product was predominantly compound XXIIIb containing a small amount of compound XXIIb. This assumption was based on the presence of the hydroxyl band and the fact that it was previously found (*vide supra*) that compound XXIIIa possessed a carbonyl band at 6.01 μ while its open chain structural isomer XXIIa showed a carbonyl band at a lower wave length (5.97 μ).

The small amount of compound XXIIb in the crude product was converted to the cyclic structure XXIIIb by refluxing it for eleven hours in ethanol containing a catalytic amount of sodium hydroxide. The total yield of compound XXIIIb was 93%. The infrared spectrum contained a hydroxyl band at 2.90 μ and only one carbonyl band at 6.01 μ. Attempted reaction of this compound with hydroxylamine was fruitless and only starting material (92% recovery) was obtained. The unreactivity of the carbonyl group is analogous to the results obtained with compound XXIIIa and again can be attributed to shielding of the carbonyl carbon.

When the reaction with compound XXIb and β-chloropropiophenone was carried out under anhydrous conditions, by replacing the aqueous ethanol with dry methanol and the sodium hydroxide with sodium methoxide, a 97% crude yield of product was obtained which consisted mostly of the noncyclic product XXIIb (weak hydroxyl band at 2.90 μ and a strong carbonyl band at 5.95 μ with a shoulder at 6.01 μ). By treating the crude product with hot ethanol, followed by recrystallization of the insoluble material from acetonitrile a solid, m.p. 153.5–154°, was secured. This material was identified as compound XXIIb by (1) its elemental analysis which corresponded to $C_{20}H_{21}O_4N$ (2) its infrared spectrum, which was void of a hydroxyl band but contained a carbonyl band at 5.95 μ, and (3) the elemental analysis of its dioximino derivative which agreed with that calculated for compound XXIIb.

The previous experiments indicated that the formation of the cyclic product XXIIIb was favored when aqueous ethanol was employed as the solvent, while mostly noncyclic material (XXIIb) resulted when dry methanol was used. These results may be explained on the basis of the strength of the base present in the reaction mixture. Hine and Hine[6] have reported that the relative base strength of methoxide, ethoxide, and hydroxide

ion increases in the order given. Thus, in the reaction employing dry methanol the base, methoxide ion, did not catalyze the internal aldol condensation as well as ethoxide or hydroxide, which were present in the experiment performed in aqueous ethanol.

The investigation of the reaction of mononitroparaffins with phenyl vinyl ketone was extended to nitromethane by treating an aqueous methanolic solution containing 0.2 mole of sodium methanenitronate with 0.19 mole of β-chloropropiophenone at 0–20° for an hour and a half. Two products, m.p. 131–132° and 62.5–63.5°, were obtained, the infrared spectra of which were void of a hydroxyl absorption, indicating that neither compound was cyclic in structure. The elemental analysis of the

$$CH_3NO_2 + CH_2{=}CH{-}COC_6H_5 \longrightarrow$$
$$H_2C(NO_2){-}CH_2{-}CH_2{-}COC_6H_5 \text{ (XXIV)} + HC(NO_2)(CH_2{-}CH_2{-}COC_6H_5)_2 \text{ (XXV)}$$

lower melting product and its corresponding semicarbazone, prepared in 96% yield, agreed with that calculated for the monoaddition adduct, γ-nitrobutyrophenone (XXIV). Sonn[7] who had prepared this compound by a similar procedure, reported a melting point of 102° dec. The yield of compound XXIV was increased to 78% by employing a 10:1 ratio of nitromethane to phenyl vinyl ketone.

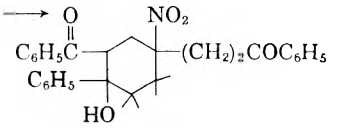
The elemental analysis of the higher melting product, m.p. 131–132°, corresponded only to that calculated for the diaddition adduct (XXV). Its structure was established by its conversion to a mono-bromo product, 1,5-dibenzoyl-3-bromo-3-nitropentane,[8] which in its turn showed the correct analysis.

As Allen and Bell[9] had reported the preparation of the triaddition adduct (XXVI) of phenyl vinyl ketone to nitromethane by treating β-chloropropiophenone and nitromethane in the presence of potassium acetate and a sufficient quantity of sodium methoxide to keep the reaction medium basic, we duplicated their reaction conditions. A product, m.p. 131–132° was obtained which was not XXVI but was identical with the diadduct XXV.

$$O_2NC[(CH_2)_2CO]_3$$
XXVI

Treatment[8] of the sodium salt of XXV with β-chloropropiophenone in dimethyl sulfoxide gave the cyclic triadduct XXVII. The structure assignment was based on (1) its elemental analysis, (2) its infrared spectrum, which possessed a hydroxyl band at 2.91 μ and a carbonyl band at 6.05 μ with a shoulder at 5.98 μ, and (3) the elemental analysis of its monooxime derivative. The infrared spectrum of this derivative showed a hydroxyl band at 2.90 μ and a carbonyl band at 6.08 μ. The failure of compound XXVII to give a dioxime can be again attributed (*vide supra* compound XXIIIa) to the highly hindered carbonyl group attached to the cyclohexane ring.

$$[O_2N{=}C(CH_2)_2COC_6H_5]^-\ Na^+ + ClCH_2CH_2COC_6H_5 \longrightarrow$$



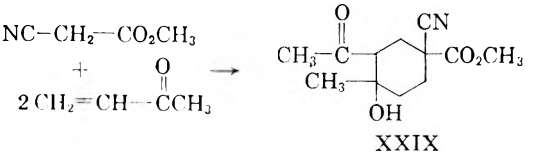
XXVII

The reaction between methyl cyanoacetate and phenyl vinyl ketone was also investigated because Allen and Bell[9] claimed that the product was the open chain diaddition adduct XXVIII. Our findings

$$NC{-}CH_2{-}CO_2CH_3 + CH_2{=}CH{-}COC_6H_5 \longrightarrow NC{-}C(CO_2CH_3)(CH_2{-}CH_2{-}COC_6H_5)_2$$
XXVIII

were in agreement with their structure assignment, as the elemental analysis of the product corresponded to $C_{22}H_{21}O_4N$ and its infrared spectrum was void of a hydroxyl absorption.

It is interesting to note that the reaction between methyl cyanoacetate and two equivalents of methyl vinyl ketone, in the presence of a catalytic amount of sodium methoxide gave the cyclic product XXIX. The structure assignment was based on



XXIX

(1) the elemental analysis which corresponded to $C_{12}H_{17}O_4N$, (2) its infrared spectrum which possessed a hydroxyl band at 2.89 μ, and (3) its corresponding semicarbazone, prepared in 90% yield which showed the correct analysis for structure XXIX.

EXPERIMENTAL

Reagents and solvents. Methyl vinyl ketone (85% water azeotrope), b.p. 76°, was obtained from Monomer and Polymers. Methyl vinyl ketone (100%), b.p. 79.5–81°, n_D^{20} 1.4108 was secured by rectification of technical grade methyl vinyl ketone produced by Matheson, Coleman and Bell. Unless otherwise specified the methyl vinyl ketone employed in this investigation did not contain any inhibitor. Methyl acrylate was Eastman yellow label, distilled prior to use, b.p. 80°, n_D^{20} 1.4018. Acrylonitrile, b.p. 78–79°, n_D^{20} 1.3908, was an American Cyanamid product. Methyl cyanoacetate, b.p. 115–116° (35 mm.), n_D^{20} 1.4182 was obtained from Matheson, Coleman and Bell.

(6) J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).

(7) A. Sonn, *Chem. Ber.*, **68**, 150 (1935).

(8) We are indebted to Maria L. G. Limson, Purdue University, for carrying out this experiment.

(9) C. F. H. Allen and A. B. Bell, *Can. J. Research*, 11, 40 (1934).

Mononitroparaffins were secured from Commercial Solvents Corporation and distilled over boric acid prior to use. The α,ω-dinitroparaffins were prepared according to the procedure of Feuer and Leston.[10]

Tetrahydrofuran was DuPont's technical grade, purified according to the procedure of Feuer and Savides.[11] Purified dioxane and absolute methanol were prepared according to the procedure of Fieser.[12]

Spectral measurements. All ultraviolet spectral measurements were carried out with a Cary Model 10-11 spectrophotometer. The solvent employed was commercial 95% ethanol.

All infrared spectral-measurements were performed with a Perkin-Elmer Recording Infrared Spectrophotometer Model 21. The solid compounds were measured in a Nujol mull.

5,8-Dinitro-2,11-dodecanedione (III). A solution of 14.8 g. (0.1 mole) of 1,4-dinitrobutane, 100 ml. of 95% ethanol, 3 drops of 20% aqueous sodium hydroxide, and 16.5 g. (0.2 mole) of 85% aqueous methyl vinyl ketone, contained in a 200 ml. round bottom flask equipped with a mechanical stirrer and thermometer, was heated at 40° for 24 hr. After cooling the solution to 0–5°, 3 drops of glacial acetic acid was added. Further cooling to −78° and subsequent filtration afforded 24.2 g. (83% yield) of 5,8-dinitro-2,11-dodecanedione (III), m.p. 56–85°. After three recrystallizations from 95% ethanol the melting point rose to 91.5–92.5°. The filtrates from these recrystallizations were combined and evaporated to dryness. The residue was triturated with a small quantity (*ca.* 75 ml.) of methanol at room temperature and the insoluble material, high melting isomer, removed by filtration. Cooling the filtrate to −15° afforded a solid enriched with the low melting isomer. After repeating this procedure three times the melting point, 61–62°, remained constant.

The infrared spectra of the two isomers were very similar. The high melting isomer possessed a carbonyl band at 5.85 μ and nitro bands at 6.48 and 7.32 μ, while the lower melting diastereoisomer showed a carbonyl absorption at 5.83 μ and nitro bands at 6.48 and 7.32 μ.

Anal. Calcd. for $C_{12}H_{20}O_6N_2$: C, 49.99; H, 6.99; N, 9.72. Found for higher melting solid: C, 50.02; H, 7.17; N, 9.96. Found for lower melting solid: C, 49.88; H, 7.00; N, 9.53.

5,8-Dibromo-5,8-dinitro-2,11-dodecanedione (V). To a mixture of 8.64 g. (0.03 mole) of compound III, m.p. 61–62° and 70 ml. of methanol was added dropwise, with stirring, a solution of 2.48 g. (0.06 mole) 97% sodium hydroxide dissolved in 20 ml. of water. The addition was regulated so that the temperature did not exceed 9°. The ice bath was then removed and the solution warmed to 25° and stirred until a *p*H of 8–9 was attained (*ca.* 20 min.). After cooling to 0–5°, 11.5 g. (0.072 mole) of bromine was added dropwise at such a rate that the temperature did not exceed 9°. Stirring for an additional 0.5 hr. at room temperature, followed by filtration and washing of the precipitate with 100 ml. of distilled water gave 13.5 g. (100% yield) of product, m.p. 120–121°. Recrystallization from aqueous methanol yielded 12.4 g. (92% yield) of pure *5,8-dibromo-5,8-dinitro-2,11-dodecanedione* (V), m.p. 121–122°.

The infrared spectrum possessed a carbonyl band at 5.85 μ and nitro bands at 6.46 and 7.46 μ.

Anal. Calcd. for $C_{12}H_{18}O_6N_2Br_2$: C, 32.28; H, 4.04; N, 6.28; Br, 35.87. Found: C, 32.18; H, 3.96; N, 6.10; Br, 36.15.

When the previous experiment was repeated employing 8.64 g. (0.03 mole) of the higher melting diastereoisomer of compound III a 97% yield of the same dibromo derivative (V) was obtained.

1,2-Bis(1'-nitro-3'-acetyl-4'-hydroxy-4'-methylcyclohexyl)ethane (VI). In a 200-ml. round bottom flask equipped with a mechanical stirrer and thermometer were placed 7.4 g. (0.05 mole) of 1,4-dinitrobutane, 125 ml. of 95% ethanol, 3 drops of 20% aqueous sodium hydroxide, and 19.8 g. (0.24 mole) of 85% aqueous methyl vinyl ketone. The solution was stirred at room temperature for 1 hr. and then heated at 40° for an additional 24 hr. After cooling to 0–5°, 3 drops of glacial acetic acid was added. Filtration afforded 18.6 g. (86% yield) of a mixture of diastereoisomers possessing the structure, *1,2-bis(1'-nitro-3'-acetyl-4'-hydroxy-4'-methylcyclohexyl)ethane* (VI), m.p. 200–203° dec. Two recrystallizations from methanol raised the melting point to 223–229° dec., while several recrystallizations from acetonitrile afforded a solid, melting at 236–237° dec.

The infrared spectra of the high and low melting samples were very similar. The high melting solid possessed a hydroxyl band at 2.92 μ, a carbonyl band at 5.94 μ, and a nitro band at 6.52 μ, while the lower melting solid showed absorptions for these groups at 2.90, 5.92, and 6.51 μ, respectively.

Anal. Calcd. for $C_{20}H_{32}O_8N_2$: C, 56.06; H, 7.53; N, 6.54. Found for higher melting solid: C, 56.11; H, 7.75; N, 6.51. Found for lower melting solid: C, 56.50; H, 7.92; N, 6.20.

The dioxime of compound VI was prepared in the usual manner[13] except that the reaction mixture was refluxed for 17 hr. An 88% yield of product was obtained which on treatment with boiling methanol afforded an insoluble material, m.p. 254–256° dec., and a soluble material, m.p. 244–245° dec., which precipitated from the filtrate on the addition of water. Recrystallization of the lower melting material from 50% aqueous methanol raised the melting point to 248° dec.

Anal. Calcd. for $C_{20}H_{34}O_8N_4$: C, 52.39; H, 7.47; N, 12.22. Found for lower melting solid: C, 52.32; H, 7.75; N, 12.22. Found for higher melting solid: C, 52.69; H, 7.53; N, 12.33.

1,2-Bis(1'-nitro-3'-acetyl-4'-methyl-1'-cyclohexenyl)ethane (VIII). A mixture of 8.56 g. (0.02 mole) of compound VI, m.p. 230–231°, and 175 ml. of absolute ethanol was cooled in an ice bath at 0–5°, while 41.5 g. (1.13 moles) of gaseous hydrogen chloride was bubbled into the reaction mixture. The flask was fitted with a condenser, refluxed for 24 hr., and then cooled to 0–5°. Filtration afforded 3.57 g. (46% yield) of compound VIII, m.p. 167–169°. Recrystallization from isopropyl alcohol afforded pure *1,2-bis(1'-nitro-3'-acetyl-4'-methyl-1'-cyclohexenyl)ethane* (VIII), m.p. 173.5–174.5°.

The infrared spectrum possessed an olefinic band at 6.02 μ, a shoulder at 5.94 μ (carbonyl), and nitro bands at 6.54 and 7.42 μ while the ultraviolet spectrum showed a peak at 232 mμ, log ϵ 4.02.

Anal. Calcd. for $C_{20}H_{28}O_6N_2$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.12; H, 7.21; N, 7.24.

p-(1'-Oxa-4'-oxopentyl)phenol (IXa). In a 200-ml. round bottom flask were placed 11.0 g. (0.1 mole) of hydroquinone, 100 ml. of 95% ethanol, 3 drops of 20% aqueous sodium hydroxide, and 19.8 g. (0.24 mole) of 85% aqueous methyl vinyl ketone. The mixture was heated at 40° with stirring for 24 hr., cooled to 0–5°, and acidified with 3 drops of glacial acetic acid. Evaporation of the solution to dryness, *in vacuo*, and recrystallization of the residue from water afforded 8.3 g. of product, m.p. 115–119°. Subsequent recrystallization from carbon tetrachloride raised the melting point to 124.5–125.5°.

The infrared spectrum contained a carbonyl band at 5.92 μ, an ether band at 9.02 μ, and aromatic hydroxyl bands at 3.10 and 8.13 μ.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.89; H, 6.71.

5,9-Dinitro-2,12-tridecanedione (I). The procedure em-

(10) H. Feuer and G. Leston, *Org. Syntheses*, **34**, 37 (1954).

(11) H. Feuer and C. Savides, *J. Am. Chem. Soc.*, **81**, 5826 (1959).

(12) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath, New York, 1941, pp. 359 and 368.

(13) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, Third Ed., Wiley, New York, 1948, pp. 202 and 170.

ployed was similar to that used for the preparation of compound III except that 16.2 g. (0.1 mole) 1,5-dinitropentane was employed, which was mixed with 10 ml. of a 6.5% aqueous sodium bicarbonate solution.

Filtration of the cooled (−78°) reaction mixture afforded an oily solid which on treatment with a small quantity of 95% ethanol at room temperature afforded a 40–50% yield of 5,9-dinitro-2,12-tridecanedione (I), m.p. 75–76° (lit. value,[3b] m.p. 77.5–78.5°).

1,3-Bis(1'-nitro-3'-acetyl-4'-hydroxy-4'-methylcyclohexyl)-propane (XI). (a) *From 1,5-dinitropentane.* The procedure employed was similar to that used for the preparation of compound VI except that 8.1 g. (0.05 mole) 1,5-dinitropentane was employed which had been washed with an aqueous sodium bicarbonate solution and dried by filtering through anhydrous sodium sulfate. A 50% yield (11.0 g.) of a mixture of diastereoisomers of compound XI, m.p. 153–160° was obtained. Recrystallization from isopropyl alcohol afforded a solid, m.p. 167–177°, the infrared spectrum of which possessed a hydroxyl band at 2.86 μ, a carbonyl band at 5.90 μ, and a nitro band at 6.50 μ.

Anal. Calcd. for $C_{21}H_{34}O_8N_2$: C, 57.00; H, 7.75; N, 6.33. Found: C, 56.85; H, 7.59; N, 6.27.

(b) *From compound I.* A mixture consisting of 9.06 g. (0.03 mole) of compound I, 150 ml. of 95% ethanol, 2 drops of 20% aqueous sodium hydroxide, and 4.62 g. (0.066 mole) of 85% aqueous methyl vinyl ketone was mechanically stirred at 40° for 24 hr. Cooling to 0–5° followed by acidification with 3 drops of glacial acetic acid and subsequent filtration afforded 6.5 g. (50% yield) of compound XI, m.p. 165–175°.

The dioxime of compound XI was prepared in the usual manner[13] except that the reaction mixture was refluxed for 24 hr. A 71% yield of product, m.p. 168–171°, was obtained. Recrystallization from aqueous methanol raised the melting point to 180–187°.

Anal. Calcd. for $C_{21}H_{36}O_8N_4$: C, 53.38; H, 7.68; N, 11.86. Found: C, 53.09; H, 7.79; N, 12.05.

1,4-Bis(1'-nitro-3'-acetyl-4'-hydroxy-4'-methylcyclohexyl)-butane (XIII). The procedure employed was similar to that used for the preparation of compound VI except that 8.80 g. (0.05 mole) of 1,6-dinitrohexane was employed. A 39% yield (8.90 g.) of 1,4-bis(1'nitro-3'-acetyl-4'-hydroxy-4'-methylcyclohexyl)butane (XIII), m.p. 188–198° dec., was obtained. The diastereoisomers of compound XIII were partially separated by treating the product with 300 ml. of boiling isopropyl alcohol. The insoluble material melted at 219–221° dec. Concentration and cooling of the filtrate to −15° afforded a lower melting solid, m.p. 170–174° dec. Recrystallization of the higher melting solid from acetonitrile and the lower from isopropyl alcohol raised the melting points to 221–221.5° dec. and 180.5–182° dec., respectively.

The infrared spectra of both materials were similar and possessed a strong hydroxyl band at 2.90 μ.

Anal. Calcd. for $C_{22}H_{36}O_8N_2$: C, 57.88; H, 7.95; N, 6.14. Found for lower melting solid: C, 57.79; H, 7.89; N, 6.16. Found for higher melting solid: C, 57.84; H, 8.10; N, 6.16.

The *dioxime* of the lower melting mixture of the diastereoisomers of compound XIII was prepared in the usual manner[13] except that the reaction mixture was refluxed for 27 hr. A 90% yield of product was obtained, which after recrystallization from acetonitrile melted at 190–193°. The infrared spectrum of this material was void of a carbonyl absorption.

Anal. Calcd. for $C_{22}H_{38}O_8N_4$: C, 54.30; 7.87; N, 11.52. Found: C, 54.48; H, 7.98; N, 11.23.

The *dioxime* of the higher melting mixture of diastereoisomers of compound XIII was obtained in a 92% yield. Recrystallization from isopropyl alcohol raised the melting point to 239.5–240°.

Anal. Calcd. for $C_{22}H_{38}O_8N_4$: C, 54.30; H, 7.87; N, 11.52. Found: C, 54.41; H, 8.12; N, 11.69.

Dimethyl 4,7-dinitrodecanedioate (XIV). In a 200-ml. round bottom flask, equipped with a mechanical stirrer, dropping funnel, and thermometer were placed 120 ml. of tetrahydrofuran, 14.8 g. (0.1 mole) of 1,4-dinitrobutane and 2 ml. of an 85% methanolic solution of Triton B. The flask was placed in an ice bath and 17.2 g. (0.2 mole) of methyl acrylate, containing 0.05 g. of hydroquinone, was added dropwise, so that the temperature did not exceed 35°. After stirring the solution at 40° for 36 hr. it was cooled to 0–5° and acidified with 7*N* hydrochloric acid. Evaporation *in vacuo* afforded an oil. Dissolution of the oil in a mixture containing 125 ml. of diethyl ether and 50 ml. of purified tetrahydrofuran and subsequent cooling to −78° gave on filtration 21.2 g. (66% yield) of a mixture of the two diastereoisomers of dimethyl 4,7-dinitrodecanedioate (XIV), m.p. 65–75°.

The isomers were separated by dissolving the product in hot methanol and allowing the resulting solution to cool to room temperature. Filtration afforded a solid enriched with the high melting isomer, m.p. 70–89°. Several recrystallizations from methanol raised the melting point to 91.5°–92.5°. The filtrates from the above recrystallizations were combined, evaporated *in vacuo* to one quarter of the original volume, frozen in Dry Ice, and filtered. The solid obtained was treated with warm methanol (30–35°) and filtered to remove the undissolved high melting isomer. Slow cooling of the filtrate to −15° and subsequent filtration yielded material enriched with the low melting isomer, m.p. 59–71°. After several recrystallizations in this manner a solid melting at 60–62° was secured.

The infrared spectra of the high and low melting isomers were similar and possessed a carbonyl band at 5.80 μ and a nitro band at 6.46 μ.

Anal. Calcd. for $C_{12}H_{20}O_8N_2$: C, 45.00; H, 6.29; N, 8.75. Found for higher melting solid: C, 45.34; H, 6.60; N, 8.64. Found for lower melting solid: C, 44.79; H, 6.32; N, 8.81.

Dimethyl 4,7-bis(2'-carbomethoxyethyl)-4,7-dinitrodecanedioate (XV). The procedure employed was similar to that used in the preparation of compound XIV except that 7.4 g. (0.05 mole) of 1,4-dinitrobutane and a reaction time of 60 hr. was employed. After acidification, the reaction mixture was filtered and afforded 22.9 g. (93% yield) of dimethyl 4,7-bis(2'-carbomethoxyethyl)-4,7-dinitrodecanedioate (XV), m.p. 120–122°. Recrystallization from acetonitrile raised the melting point to 122.5–123.5°.

The infrared spectrum possessed an ester carbonyl band at 5.74 μ and nitro bands at 6.48 and 7.37 μ.

Anal. Calcd. for $C_{20}H_{32}O_{12}N_2$: C, 48.77; H, 6.55; N, 5.69. Found: C, 48.91; H, 6.34; N, 5.62.

4,7-Bis(2'-carboxyethyl)-4,7-dinitrodecanedioic acid. In a 500-ml. round bottom flask were placed 18.4 g. (0.0374 mole) of compound XV and 300 ml. of 6*N* hydrochloric acid. The flask was fitted with a condenser and the mixture refluxed for 24 hr. Cooling to 5° and filtration afforded 15.1 g. (92% yield) of 4,7-bis(2'-carboxyethyl)-4,7-dinitrodecanedioic acid, m.p. 219.5°. Recrystallization from water did not raise the melting point.

The infrared spectrum possessed a carbonyl band at 5.88 μ and a nitro band at 6.52 μ.

Anal. Calcd. for $C_{16}H_{24}O_{12}N_2$: C, 44.03; H, 5.54; N, 6.42. Found: C, 43.90; H, 5.66; N, 6.40.

4,7-Bis(2'-cyanoethyl)-4,7-dinitrodecanedinitrile (XVI). The procedure employed was similar to that used for the preparation of compound XV except that the methyl acrylate was replaced with 11.7 g. (0.22 mole) of acrylonitrile and the reaction time was decreased to 24 hr. A 68% yield of compound XVI, m.p. 153–156°, was obtained. Recrystallization from acetonitrile raised the melting point to 162–164°.

The infrared spectrum possessed a nitrile band at 4.46 μ and nitro bands at 6.47 and 7.36 μ.

Anal. Calcd. for $C_{16}H_{20}O_4N_6$: C, 53.32; H, 5.59; N, 23.32. Found: C, 53.20; H, 5.81; N, 23.65.

5-Nitro-2-octanone (XVIIc). In a 300-ml. round bottom flask, equipped with a mechanical stirrer and thermometer, were placed 20.6 g. (0.2 mole) of freshly distilled 1-nitrobutane, 150 ml. of 95% ethanol, and 4 drops of 20% aqueous sodium hydroxide. The mixture was cooled to 0–5° and 14.0

g. (0.2 mole) of methyl vinyl ketone (containing 0.05 g. of hydroquinone) was added. After heating the mixture with stirring at 40° for 24 hr., it was cooled to 0–5° and acidified with 3 drops of glacial acetic acid. The ethanol was removed *in vacuo* and the residue distilled to afford 28.8 g. (83% yield) of product, b.p. 67–71° (0.2 mm.); n_D^{20} 1.4414–1.4428. Redistillation afforded pure *5-nitro-2-octanone* (XVIIc), b.p. 62° (0.12 mm.); n_D^{20} 1.4418.

The infrared spectrum possessed a ketone band at 5.82 μ and nitro bands at 6.46 and 7.36 μ.,

Anal. Calcd. for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.80; H, 8.69; N, 8.43.

The semicarbazone of compound XVIIc was prepared in 88% yield by the usual method[13] and recrystallized from 25% aqueous ethanol, m.p. 112–112.5°.

Anal. Calcd. for $C_9H_{18}O_3N_4$: C, 46.94; H, 7.88; N, 24.33. Found: C, 46.77; H, 7.88; N, 24.40.

1,4-Dimethyl-2-acetyl-4-nitro-1-cyclohexanol (XVIIIa). A 300-ml. round bottom flask, equipped with a mechanical stirrer was charged with 150 ml. 95% ethanol, 15.0 g. (0.2 mole) freshly distilled nitroethane (which had been washed with a 6% aqueous sodium bicarbonate solution and dried by filtering through anhydrous sodium sulfate) and 4 drops of 20% aqueous sodium hydroxide. The mixture was cooled to 0–5° and 36.2 g. (0.44 mole) of 85% aqueous methyl vinyl ketone was added. The mixture was then stirred at room temperature (28°) for 1 hr. and at 40° for an additional 24 hr. After cooling the solution to 0–5°, acidification with 3 drops of glacial acetic acid, and evaporation of the solvent *in vacuo* a semisolid was obtained which upon dissolution in warm (60°) 40% aqueous methanol and slow cooling to −15° afforded 25.3 g. of crude product (XVIIIa), m.p. 66–76°. Removing the methanol, *in vacuo*, extracting with three 100-ml. portions of ether, drying with magnesium sulfate followed by filtration and distillation gave 14.5 g., b.p. 70–140° (0.2 mm.) of liquid, the infrared spectrum of which was similar to the solid previously obtained. Thus the total crude yield of 1,4-dimethyl-2-acetyl-4-nitro-1-cyclohexanol (XVIIIa) was 93%.

Recrystallization of the solid product from hexane raised the melting point to 78–79°.

The infrared spectrum showed bands at 2.89 (hydroxyl), 5.88 (carbonyl), 6.53 and 7.46 μ (nitro).

Anal. Calcd. for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.70; H, 8.06; N, 6.46.

The *monoöxime of compound* XVIIIa was prepared in 92% yield by the usual method.[13] Recrystallization from aqueous ethanol raised the melting point to 165.5–166°.

Anal. Calcd. for $C_{10}H_{18}O_4N_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.01; H, 8.14; N, 12.28.

1,4-Dimethyl-2-acetyl-4-nitro-1-cyclohexene (XIXa). A mixture of 21.5 g. (0.1 mole) of solid 1,4-dimethyl-2-acetyl-4-nitro-1-cyclohexanol (XVIIIa) and 300 ml. of absolute ethanol, contained in a 500 ml. round bottom flask, was cooled in an ice bath to 0–5°, while 50 g. (1.4 moles) gaseous hydrogen chloride was bubbled into the mixture. The flask was fitted with a condenser and the reaction mixture refluxed for 24 hr. Removing the ethanol *in vacuo*, diluting the residue with 100 ml. of water, extracting with four 100-ml. portions of ether, washing the combined extracts with 100 ml. of a saturated sodium bicarbonate solution, drying over magnesium sulfate, filtering and distilling gave 16.8 g. (85% yield) of product, b.p. 100–104° (0.3 mm.). Redistillation afforded pure 1,4-dimethyl-2-acetyl-4-nitro-1-cyclohexene (XIXa), b.p. 82° (0.1 mm.), n_D^{20} 1.4998.

The infrared spectrum possessed a ketone band at 5.92 μ, an olefinic band at 6.15 μ, and nitro bands at 6.50 and 7.41 μ, while the ultraviolet spectrum showed a peak at 242 mμ, log ϵ 3.72.

Anal. Calcd. for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10: Found: C, 61.08; H, 7.64; N, 7.27.

When the liquid fraction, b.p. 70–140° (0.2 mm.), of 1,4-dimethyl-2-acetyl-1-cyclohexanol (XVIIIa) was dehydrated, a 77% yield of compound XIXa was obtained.

1-Methyl-2-acetyl-4-ethyl-4-nitro-1-cyclohexanol (XVIIIb). The procedure employed was similar to that used for the preparation of compound XVIIIa except that 17.8 g. (0.2 mole) of 1-nitropropane was employed.

After evaporation of the solvent *in vacuo*, a heavy oil was obtained which partially solidified when cooled to −78°. Filtration afforded 13.2 g. of crude product (XVIIIb), m.p. 49–55°. Distillation of the filtrate afforded three fractions. The first, 3.43 g., b.p. 103–108° (5 mm.), n_D^{20} 1.4418 was identified as 5-nitro-2-heptanone [lit. value[14] b.p. 102° (4.8 mm.), n_D^{20} 1.4410]. Fraction two, 6.80 g. b.p. 80–110° (0.1 mm.) consisted of a solid suspended in a liquid. Filtration gave 1.35 g. of product (XVIIIb), m.p. 53–56°. The filtrate consisted of crude 5-nitro-2-heptanone (XVIIc) as indicated by comparison of its infrared spectrum with that of an authentic sample of compound XVIIc. Fraction three, solidified completely affording 15.1 g. of compound XVIIIb, m.p. 50–56°. Thus the total crude yield of 1-methyl-2-acetyl-4-nitro-4-ethyl-1-cyclohexanone (XVIIIb) was 65%. Recrystallization from 40% aqueous ethanol raised the melting point to 58–58.5°.

The infrared spectrum possessed bands at 2.97 (hydroxyl), 5.92 (carbonyl), 6.52 and 7.37 μ (nitro).

Anal. Calcd. for $C_{11}H_{19}O_4N$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.79; H, 8.36; N, 6.18.

The *monoöxime of compound* XVIIIb which was prepared by the usual manner[13] in 90% yield and recrystallized from aqueous ethanol, melted at 169–169.5°.

Anal. Calcd. for $C_{11}H_{20}O_4N_2$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.34; H, 8.36; N, 11.44.

1-Methyl-2-acetyl-4-ethyl-4-nitro-1-cyclohexene (XIXb). The procedure employed was similar to that used in the preparation of compound XIXa except that 22.9 g. (0.1 mole) of compound XVIIIb was employed.

Distillation afforded 18.8 g. (86% crude yield) of liquid product, b.p. 110–115° (0.5 mm.). Dissolving this liquid in 95% ethanol and cooling to −78°, gave 15.4 g. (73% yield) of 1-methyl-2-acetyl-4-ethyl-4-nitro-1-cyclohexene (XIXb), m.p. 41–44°. Dissolving XIXb in isopropyl ether at room temperature and slow cooling to 10° raised the melting point to 44.5–46°.

The infrared spectrum possessed a ketone band at 5.95 μ, an olefinic band at 6.13 μ, nitro bands at 6.53 and 7.37 μ, while the ultraviolet spectrum showed a peak at 242 mμ, log ϵ 3.47.

Anal. Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.65. Found: C, 62.37; H, 8.27; N, 6.59.

1-Methyl-2-acetyl-4-propyl-4-nitro-1-cyclohexanol (XVIIIc). In a 300-ml. round bottom flask, equipped with a mechanical stirrer and thermometer, were placed 20.6 g. (0.2 mole) of freshly distilled 1-nitrobutane, 150 ml. of purified dioxane, and 2 ml. of a 35% methanolic solution of Triton B. The flask was immersed in a cold water bath (18°) and 36.3 g. (0.44 mole) of 85% aqueous methyl vinyl ketone (containing 0.1 g. of hydroquinone) was added dropwise so that the temperature did not exceed 30°. The solution was stirred at 40° for an additional 15 hr., cooled to 0–5°, acidified with dilute hydrochloric acid, diluted with 900 ml. of water, and extracted with three 250-ml. portions of ether. The ether extracts were combined, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to afford a semisolid. Recrystallization of this material from 50% aqueous methanol afforded 29.1 g. of product (XVIIIc), m.p. 89.5–90.5°. By warming the filtrate, from the recrystallization, to 60° followed by the addition of 100 ml. of water and slow cooling to 10°, an additional 6.8 g. of product (XVIIIc), m.p. 74–84° was obtained. Thus the total yield of 1-methyl-2-acetyl-4-propyl-4-nitro-1-cyclohexanol (XVIIIc) was 73%. Recrystallization from 50% aqueous ethanol or hexane raised the melting point to 89.5–90°.

(14) Unpublished data from the Ph.D. thesis of R. Miller, Purdue University, January 1959

The infrared spectrum showed bands at 2.92 (hydroxyl), 5.93 (carbonyl), 6.51 and 7.41 μ (nitro).

Anal. Calcd. for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.18; H, 8.74; N, 5.73.

The monoöxime, m.p. 153–154°, and *monosemicarbazone*, m.p. 190.5–191.5° of compound XVIIIc were prepared by the usual method[13] in 80% and 97% yields, respectively. Both compounds were purified by recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{12}H_{24}O_4N_4$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.64; H, 8.83; N, 10.99.

Anal. Calcd. for $C_{13}H_{24}O_4N_3$: C, 51.98; H, 8.05; N, 18.66: Found: C, 52.11; H, 8.14; N, 18.66.

1-Methyl-2-acetyl-4-nitro-4-propyl-1-cyclohexene (XIXc). The procedure employed was similar to that used in the preparation of compound XIXa except that 31.6 g. (0.13 mole) of compound XVIIIc was employed.

Distillation afforded 25.3 g. (86% yield) of liquid product, b.p. 124° (1.0 mm.). Dissolving the distillate in methanol at room temperature and cooling the solution to −78°, gave 24.1 g. (81% yield) of 1-methyl-2-acetyl-4-nitro-4-propyl-1-cyclohexene (XIXc), m.p. 55.5–56.5°. Dissolving XIXc in methanol and slowly cooling to −15°, raised the melting point to 57.5–58.5°.

The infrared spectrum possessed a ketone band at 5.90 μ, an olefinic band at 6.10 μ and nitro bands at 6.49 and 7.39 μ while the ultraviolet spectrum showed a peak at 243 mμ, log ϵ 3.75.

Anal. Calcd. for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.98; H, 8.71; N, 5.97.

1-Methyl-2-acetyl-4-nitro-4-(3′-oxobutyl)-1-cyclohexanol (XVIIId). The procedure employed was similar to that used for the preparation of compound XVIIIa except that 6.1 g. (0.1 mole) of nitromethane and 27.2 g. (0.33 mole) of 85% aqueous methyl vinyl ketone were used.

After acidification, the reaction mixture was cooled to −78° and filtered to afford 14.0 g. of compound XVIIId, m.p. 104–105°. Distillation of the filtrate at 0.001 mm. afforded several fractions boiling at 80–160°. By dissolving the distillates in 95% ethanol and slowly cooling to −15° an additional 3.45 g. of product (XVIIId), m.p. 102–104°, was obtained. The total yield of 1-methyl-2-acetyl-4-nitro-4-(3′-oxobutyl)-1-cyclohexanol (XVIIId) was 94%. Recrystallization from isopropyl alcohol raised the melting point to 107–108°.

The infrared spectrum possessed a hydroxyl band at 2.89 μ, a carbonyl band at 5.88 μ with a shoulder at 5.82 μ and nitro bands at 6.50 and 7.36μ.

Anal. Calcd. for $C_{13}H_{21}O_5N$: C, 57.55; H, 7.80; N, 5.16. Found; C, 57.52; H, 7.81; N, 5.18.

The *dioxime* of compound XVIIId was prepared in 85% yield by the usual method.[13] It melted at 95–97° after recrystallization from water and drying on a clay plate. Drying it for 4 days at 28° and 0.1 mm. increased the melting point to 155–156°, but the analysis indicated that water of crystallization was still present.

Anal. Calcd. for $C_{13}H_{23}O_5N_3 \cdot {}^3/_4H_2O$: C, 49.60; H, 7.80; N, 13.35. Found: C, 49.65; H, 8.15; N, 13.43.

Drying the compound for 36 hr. at about 1.0 mm. removed all the water.

Anal. Calcd. for $C_{13}H_{23}O_5N_3$: C, 51.81; N, 7.69; N, 13.95. Found: C, 51.47; H, 7.72; N, 14.32.

1-Methyl-2-ethyl-4-nitro-1-cyclohexanol (XVIIIe). In a 200-ml. round bottom flask, equipped with a mechanical stirrer and thermometer, were placed 100 ml. of methanol and 16.6 g. (0.2 mole) of sodium methanenitronate. The reaction mixture was cooled in an ice bath and 50 ml. of water and 28.0 g. (0.4 mole) of methyl vinyl ketone were added dropwise, not allowing the temperature to exceed 10°. After stirring at 0–5° for 0.5 hr. the solution was acidified with 13.4 g. (0.26 mole) of glacial acetic acid, evaporated *in vacuo* to remove the methanol and the aqueous residue diluted with 100 ml. of water and extracted with four 100-ml. portions of ether. Drying the combined extracts with magnesium sulfate, filtering, and distilling gave 6.8 g. (27% yield), b.p. 67–73° (0.25 mm.), n_D^{20} 1.4442–1.4463 of crude 5-nitro-2-pentanone (XIa) [lit. value,[5] b.p. 117–120° (10 mm.), n_D^{20} 1.4441] and 14.7 g., b.p. 93–150° (0.001 mm.) of a heavy oil. By dissolving the oil in 95% ethanol and cooling to −78° a 5% yield (3.3 g.) of crude 1-methyl-2-acetyl-4-nitro-1-cyclohexanol (XVIIIe) was obtained. Recrystallization from isopropyl ether afforded pure product, m.p. 85–85.5°.

The infrared spectrum possessed bands at 2.89 (hydroxyl), 5.91 (carbonyl), 6.45 and 7.43 μ (nitro).

Anal. Calcd. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.89; H, 7.75; 7.02.

2-Acetyl-4-nitro-4-propyl-1-methylcyclohexane (XX). A solution of 38.3 g. (0.17 mole) of compound XIXc in 175 ml. of 95% ethanol was placed in a low pressure Parr Hydrogenator and shaken with 3 g. of 5% palladium chloride on Darco G-60,[15] at an initial hydrogen pressure of 30 p.s.i. A total of 14.3 lbs. (0.17 mole) of hydrogen was absorbed in 3 hr. The solution was filtered and the filtrate evaporated *in vacuo*. Vacuum distillation of the residue afforded 34.2 g. (89% yield) of product (XX), b.p. 90–120° (0.2 mm.), which consisted of a mixture of solid and liquid isomers. Partial separation of the isomers was achieved by dissolving the distillate at room temperature in hexane and cooling the resulting solution to −78°. Filtration gave a small amount of solid which was recrystallized by dissolving it in a minimum amount of hexane at room temperature and slowly cooling to −15°. In this manner a solid isomer of 2-acetyl-4-nitro-4-propyl-1-methylcyclohexane (XX), m.p. 54–55° was secured.

Anal. Calcd. for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.15; H, 9.35; N, 6.05.

The filtrate from the original separation of isomers was redistilled and a fraction boiling at 90–95° (0.2 mm.) was subjected to elemental analysis.

Anal. Calcd. for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.65; H, 9.10; N, 6.38.

γ-Nitrocaprophenone (XXIa). To a cold (0–5°) solution of 21.1 g. (0.19 mole) sodium 1-propanenitronate in 220 ml. of 85% aqueous methanol, was added 30.42 g. (0.18 mole) of β-chloropropiophenone prepared according to the procedure of Allen and Barker.[16] The mixture was stirred at room temperature 30 min. and then at 40° for an additional 24 hr. After cooling to 0–5° it was acidified with 11 drops of glacial acetic acid, evaporated *in vacuo* to remove the methanol, diluted with 400 ml. of water, and extracted with four 100-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated. The residue (38 g.) was dissolved in a minimum amount of 95% ethanol and slowly cooled to −15°. Filtration afforded 32.5 g. of product (XXIa), m.p. 33–34°. An additional 4.0 g. of compound XXIa, m.p. 32–33°, was secured by cooling the filtrate to −78°. Thus the total yield of γ-nitrocaprophenone (XXIa) was 92%. Dissolving the product in a minimum amount of 95% ethanol at room temperature and slowly cooling to −15°, raised the melting point to 33.5–34.5°.

The infrared spectrum of this material possessed a carbonyl band at 5.92 μ, nitro bands at 6.47 and 7.35 μ, and aromatic bands at 6.27, 6.33, 13.27, and 14.49 μ.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.88; H, 6.84; N, 6.34.

The *bromo-derivative of compound* XXIa was prepared in 95% yield by treating XXIa with one equivalent of base and excess bromine. Recrystallization of the product from 95% ethanol raised the melting point to 59–60°.

Anal. Calcd. for $C_{12}H_{14}O_3NBr$: C, 48.00; H, 4.67; N, 4.67; Br, 26.67. Found: C, 47.93; H, 4.67; N, 4.61; Br, 26.92.

γ-Nitrovalerophenone (XXIb). The procedure employed

(15) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 685 (1955).

(16) C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.*, 54, 736 (1932).

was similar to that used for the preparation of compound XXIa except that 19.4 g. (0.2 mole) of sodium ethanenitronate was employed.

The reaction mixture was heated 4 hr. at 40°, cooled to 0–5°, acidified with glacial acetic acid, diluted with 1700 ml. of water, and kept at 10° for 10 hr. Filtration afforded 36.1 g. (93% yield) of product, m.p. 54.5–56.5°, which was readily recrystallized from warm (50°) isopropyl ether or 85% aqueous methanol to yield pure γ-nitrovalerophenone (XXIb), m.p. 58.5–59°.

The infrared spectrum possessed a carbonyl band at 5.95 μ, nitro bands at 6.52 and 7.40 μ, and aromatic bands at 6.26, 6.31, 13.40, and 14.46 μ.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 64.01; H, 6.37; N, 6.70.

3-Ethyl-3-nitro-1,5-dibenzoylpentane (XXIIa) *and 1-phenyl-2-benzoyl-4-ethyl-4-nitro-1-cyclohexanol* (XXIIIa). In a 300 ml. round bottom flask, equipped with a mechanical stirrer and thermometer, were placed 24.3 g. (0.11 mole) of γ-nitrocaprophenone (XXIa) and 170 ml. of methanol. The flask was cooled in an ice bath while a solution of 4.52 g. (0.11 mole) 97% sodium hydroxide, dissolved in 30 ml. of water was added dropwise, with stirring, so that the temperature did not exceed 9°. After complete addition, the ice bath was removed and the solution stirred until a *p*H of 8–9 (Hydrion paper) was attained (*ca.* 0.5 hr.). The flask was again immersed in an ice bath and 16.9 g. (0.10 mole) of β-chloropropiophenone was added. Within 5 min. the reaction mixture set into a solid cake. The contents of the flask were diluted with 1800 ml. of water and manually stirred for approximately 10 min. Filtration afforded 34.3 g. (94% yield) of a mixture, m.p. 118–120°, of compounds XXIIa and XXIIIa. The infrared spectrum of this mixture possessed two carbonyl bands (5.97 μ and 6.02 μ) and a hydroxyl band (2.90 μ). Separation of the structural isomers was accomplished by fractional recrystallization from isopropyl ether, compound XXIIa being more soluble. A 31 and 46% yield of compounds XXIIa, m.p. 128–129°, and XXIIIa, m.p. 128–132°, respectively, were obtained. Recrystallization of compound XXIIIa from hexane raised the melting point to 132–132.5°.

The infrared spectrum of compound XXIIa possessed bands at 5.97 (carbonyl), 6.55 (nitro), 6.26, 6.34, 13.45, and 14.42 μ (aromatic), but was void of a hydroxyl band. The spectrum of compound XXIIIa possessed bands at 2.90 (hydroxyl), 6.02 (carbonyl), 6.53 and 7.45 (nitro), 6.26, 6.34, 13.16, and 14.32 μ (aromatic).

Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.37; H, 6.56; N, 3.96. Found for XXIIa: C, 71.27; H, 6.45; N, 3.83. Found for XXIIIa: C, 71.15; H, 6.74; N, 4.22.

When the previous reaction was repeated with the following modifications, 500 ml. of 95% ethanol and a reflux time of 5 hr., a 90% yield of compound XXIIIa was obtained.

The *dioxime* of compound XXIIa was prepared in 95% yield by the usual method.[13] The product, m.p. 139.5–140° was purified by recrystallization from 50% aqueous ethanol.

Anal. Calcd. for $C_{21}H_{25}O_4N_3$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.82; H, 6.65; N, 11.02.

1-Phenyl-2-benzoyl-4-methyl-4-nitro-1-cyclohexanol (XXIIIb). A 500-ml. round bottom flask, immersed in an ice bath and equipped with a mechanical stirrer, dropping funnel, and thermometer, was charged with 10.4 g. (0.05 mole) of γ-nitropentanophenone (XXIb) and 250 ml. of 95% ethanol. A solution of 2.05 g. (0.05 mole) of 97% sodium hydroxide dissolved in 25 ml. of water was added dropwise with stirring at such a rate that the temperature did not exceed 9°. The ice bath was removed and the solution stirred until a *p*H of 8–9 (Hydrion paper) was attained (*ca.* 20 min.). The solution was again cooled to 0–5° and 7.61 g. (0.045 mole) of β-chloropropiophenone was added. The mixture was then heated with stirring at 40° for 4 hr., cooled to 0–5°, acidified with glacial acetic acid, and poured into 1500 ml. of water. Filtration afforded 15.0 g. of product, m.p. 127–137°, the infrared spectrum of which showed that it was mostly XXIIIb containing a small amount of noncyclic product XXIIb. To cyclize the product completely it was refluxed further for 11 hr. in ethanol containing 4 drops of 20% aqueous sodium hydroxide. Slow cooling to −78° and subsequent filtration afforded 14.2 g. (93% yield) of 1-phenyl-2-benzoyl-4-methyl-4-nitrocyclohexanol (XXIIIb), m.p. 138–142°. Recrystallization from 95% ethanol raised the melting point to 139–143°.

The infrared spectrum possessed bands at 2.89 (hydroxyl), 6.01 (carbonyl), 6.52, 7.41 (nitro), 6.25, 6.31, 13.14, and 13.33 μ (aromatic).

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78, H, 6.24; N, 4.13. Found: C, 70.64; H, 6.37; N, 4.05.

1,5-Dibenzoyl-3-methyl-3-nitropentane (XXIIb). The procedure employed was similar to that used for the preparation of XXIIIb except that the ethanol and sodium hydroxide were replaced with absolute methanol and 1.15 g. (0.05 mole) of sodium dissolved in 100 ml. of absolute methanol. After acidification, the reaction mixture was poured into 1500 ml. of cold distilled water. Filtration afforded 14.8 g. (97% yield) of product, m.p. 131–141°, the infrared spectrum of which indicated by the presence of a weak hydroxyl band at 2.89 μ and a strong carbonyl band at 5.95 μ with a shoulder at 6.01 μ that it was mostly the open chain compound XXIIb containing a small amount of the cyclic compound XXIIIb. Partial separation of these structural isomers was accomplished by triturating the crude product with 200 ml. of boiling 95% ethanol and filtering. The infrared spectrum of the insoluble material (10.0 g.), m.p. 150–151°, did not contain a hydroxyl band and had only a single carbonyl absorption at 5.95 μ. Recrystallization of this material from acetonitrile afforded pure 1,5-dibenzoyl-3-methyl-3-nitropentane (XXIIb), m.p. 153.5–154°.

Cooling of the ethanol filtrate to −10°, and subsequent filtration afforded 4.5 g. of a mixture, m.p. 132–140°, of compounds XXIIb and XXIIIb.

The infrared spectrum of compound XXIIb possessed bands at 5.95 (carbonyl), 6.54, 7.40 (nitro), 6.26, 6.32, 13.45, and 14.48 μ (aromatic).

Anal. Calcd. for $C_{20}H_{21}O_4N$ (XXIIb): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.86; H, 6.05; N, 4.02.

The *dioxime* of compound XXIIb was prepared by the usual method.[13] A 98% yield of product, m.p. 157.5–158.5°, was obtained. Recrystallization from aqueous methanol or benzene did not change the melting point.

Anal. Calcd. for $C_{20}H_{23}O_4N_3$: C, 65.02; H, 6.28; N, 11.38. Found: C, 64.92; H, 6.31; N, 11.05.

1,5-Dibenzoyl-3-nitropentane (XXV) *and γ-nitrobutyrophenone* (XXIV). A 500-ml. round bottom flask, immersed in an ice bath and equipped with a mechanical stirrer, thermometer, and dropping funnel, was charged with 12.2 g. (0.2 mole) of freshly distilled nitromethane and 200 ml. of methanol. A solution of 8.24 g. (0.2 mole) of 97% sodium hydroxide dissolved in 90 ml. of water was added dropwise, not allowing the temperature to exceed 8°. The reaction mixture was stirred for 20 min., followed by the addition of 32.1 g. (0.19 mole) of β-chloropropiophenone. After the initial exothermic reaction had subsided, the ice bath was removed and the mixture was stirred for an additional 1.5 hr. The mixture was again cooled to 0–5°, acidified with glacial acetic acid and poured into 600 ml. of cold distilled water. Filtration afforded 29.4 g. of product, m.p. 98–114°, which was dissolved in 2100 ml. of boiling methanol. The resulting solution was slowly cooled to 10° and kept at this temperature for 10 hr. Filtration afforded 18.7 g. (61% yield) of 1,5-dibenzoyl-3-nitropentane (XXV) m.p. 131–132°. Evaporation of the filtrate *in vacuo* afforded a semisolid residue which was dissolved in a minimum amount of boiling methanol and slowly cooled to room temperature. Filtration gave 7.3 g. (20% yield) of γ-nitrobutyrophenone (XXIV), m.p. 57–61°.

Recrystallization of compounds XXIV and XXV from acetonitrile and 95% ethanol respectively, raised the melt-

ing point of the former compound to 62.5–63.5° and that of the latter compound to 132.5–133.5°.

The infrared spectrum of compound XXIV possessed a carbonyl band at 5.95 μ, a nitro band at 6.46 μ and aromatic bands at 13.44 and 14.44 μ. The spectrum of compound XXV showed these bands at 5.95, 6.47, 13.24, and 14.49 μ.

Anal. Calcd. for $C_{10}H_{11}O_3N$ (XXIV): C, 62.16; H, 5.74; N, 7.25. Found: C, 62.51; H, 5.70; N, 7.17.

Anal. Calcd. for $C_{19}H_{19}O_4N$ (XXV): C, 70.14; H, 5.89; N, 4.31. Found: C, 70.35; H, 6.05; N, 4.31.

The yield of compound XXIV was increased to 78% by repeating the above reaction using 122 g. (2.0 moles) of nitromethane and reducing the reaction time to 0.5 hr. at 10–15°.

The *semicarbazone of* compound XXIV was prepared by the usual method.[13] A 96% yield of product, m.p. 150–152° dec., was obtained. Recrystallization from isopropyl alcohol raised the melting point to 155.5–156° dec.

Anal. Calcd. for $C_{10}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.07; H, 5.74; N, 22.38.

1,5-Dibenzoyl-3-bromo-3-nitropentane.[8] A solution of 12 g. (0.037 mole) of compound XXV in 100 ml. of dimethyl sulfoxide was cooled to 0–5°. To this solution was added 1.53 g. (0.037 mole) of sodium hydroxide (97% assay) dissolved in 25 ml. of water. The reaction mixture was stirred at room temperature until a *p*H of 8–9 was obtained. Bromine (6.5 g., 0.041 mole) was then added dropwise below 9° and the mixture was stirred at room temperature for 1.5 hr. Suction filtration afforded 6.08 g. (40.7% yield), m.p. 143–157°. This crude material was recrystallized by dissolving it in acetonitrile and reprecipitating with water. After four recrystallizations, 1,5-dibenzoyl-3-bromo-3-nitropentane melted at 166°.

Anal. Calcd. for $C_{19}H_{18}O_4NBr$: C, 56.43; H, 4.45; N, 3.47; Br, 19.80. Found: C, 56.57; H, 4.61; N, 3.56; Br, 19.58.

1-Phenyl-2-benzoyl-4-(2′-benzoylethyl)-4-nitro-1-cyclohexanol (XXVII). In a 200-ml. round bottom flask, equipped with a mechanical stirrer and reflux condenser, were placed 14.6 g. (0.045 mole) of compound XXV and 100 ml. of dimethyl sulfoxide. The flask was immersed in an ice bath at 0–5° and a solution of 1.85 g. (0.045 mole) of 97% sodium hydroxide, dissolved in 75 ml. of water was added dropwise with stirring at such a rate that the temperature did not exceed 9°. The ice bath was removed and the solution stirred until a *p*H of 8–9 (Hydrion paper) was attained (in *ca.* 20 min.). The solution was again cooled to 0–5° and 6.72 g. (0.040 mole) of β-chloropropiophenone was added. The mixture was heated with stirring for 2 hr. at 60–70°, then cooled to 0–5°, acidified with glacial acetic acid and diluted with 600 ml. of water. Filtration afforded 17.6 g. (97% yield) of crude 1-phenyl-2-benzoyl-4-(2′-benzoylethyl)-4-nitro-1-cyclohexanol (XXVII), m.p. 135–143°, which on recrystallization from aqueous acetonitrile melted at 151–151.5°.

The infrared spectrum possessed a hydroxyl band at 2.91 μ, a carbonyl band at 6.05 μ with a shoulder at 5.98 μ and nitro bands at 6.55 and 7.43 μ.

Anal. Calcd. for $C_{28}H_{27}O_4N$: C, 73.50; H, 5.95; N, 3.06. Found: C, 73.72; H, 5.82; N, 3.09.

The *monoöxime* of compound XXVII was prepared in 88.6% yield by the usual method.[13] The product, m.p. 182–183° was purified by dissolving it in hot 95% ethanol and reprecipitating it with water.

Anal. Calcd. for $C_{28}H_{28}O_5N_2$: C, 71.17; H, 5.97; H, 5.93. Found: C, 71.46; H, 6.00; N, 5.95.

3-Carbomethoxy-3-cyano-1,5-dibenzoylpentane (XXVIII). The procedure employed was similar to that used for the preparation of compound XXIIIb except that the following solvent and reagents were used: 19.8 g. (0.2 mole) of methyl cyanoacetate, 150 ml. of absolute methanol, 4.6 g. (0.2 mole) of sodium dissolved in 200 ml. of absolute methanol, and 32.1 g. (0.19 mole) of β-chloropropiophenone.

A 96% yield (33.2 g.) of compound XXVIII, m.p. 132.5–138°, was obtained. Recrystallization from acetonitrile raised the melting point to 145–146° (lit. value,[9] m.p. 144°).

The infrared spectrum possessed an ester carbonyl band at 5.74 μ, a cyano band at 4.45 μ, a ketone carbonyl band at 5.95 μ and aromatic absorptions at 6.26, 6.32, and 14.47 μ.

Anal. Calcd. for $C_{29}H_{31}O_4N$: C, 72.71; H, 5.82; N, 3.85: Found: C, 72.50; H, 6.04; N, 3.88.

1-Methyl-2-acetyl-4-carbomethoxy-4-cyano-1-cyclohexanol (XXIX). In a 300-ml. round bottom flask, fitted with a mechanical stirrer, thermometer and drying tube were placed 17 ml. of absolute methanol and 0.15 g. (6.52 mmoles) of sodium. After dissolution was complete, 14.85 g. (0.15 mole) of methyl cyanoacetate was added. The solution was cooled to 0–5° and 23.1 g. (0.33 mole) of methyl vinyl ketone was added portionwise with stirring so that the temperature did not exceed 10°. The mixture was then heated at 40° for 11 hr. After cooling to 0–5° and neutralization with 0.39 g. of glacial acetic acid, the solution was evaporated *in vacuo* to afford an oil which on dissolution in 65 ml. of isopropyl alcohol and cooling to −10° gave 15.5 g. (46% yield) of 1-methyl-2-acetyl-4-carbomethoxy-4-cyano-1-cyclohexanol (XXIX), m.p. 75–80°. Recrystallization from isopropyl alcohol raised the melting point to 84–85°.

The infrared spectrum possessed bands at 2.89 μ (hydroxyl), 4.48 (cyano), 5.74 (ester carbonyl) and 5.90 μ (ketone carbonyl).

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.30; H, 7.07; N, 6.02.

The *monosemicarbazone* of compound XXIX, m.p. 197–197.5°, was obtained by the usual method.[13]

Anal. Calcd. for $C_{13}H_{20}O_4N_4$: C, 52.69; H, 6.80; N, 18.91. Found: C, 52.68; H, 6.79; N, 19.26.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Some Reactions of α-t-Acetylenic-t-amines[1]

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The reactions of two α-t-acetylenic-t-amines, $(CH_3)_2C(NR_2)$—C≡CH, were studied in detail. These compounds, 3-dimethylamino-3-methyl-1-butyne and 3-pyrrolidino-3-methyl-1-butyne, were found to undergo the typical reactions of the triple bond and of the ethynyl hydrogen. From the two model compounds, twenty-six new substances of the following classes were prepared: acetylenic-1,4-amino alcohols, C-alkylated acetylenic amines, acetylenic-1,4-diamines, 2,7-diamino-3,5-diacetylenes, 2-amino-7-hydroxy-3,5-diacetylenes, 1,2-amino ketones, 1,2-amino alcohols, acetylenic amino acids, allylic amines, and saturated amines. These compounds were characterized by the formation of methiodide and hydrochloride salts.

A previous paper[3] described the synthesis of acetylenic secondary and tertiary amines through the interaction of acetylenic chlorides of the type RR'C(Cl)—C≡CH with primary and secondary amines. Recently,[4] this method was studied in detail and shown to constitute a valuable new synthetic technique. Furthermore, it has been found[5] earlier that the acetylenic primary amines underwent alkylation, acylation, hydrogenation, and addition to carbonyl compounds in the expected manner. Since the properties of the tertiary amines had not been studied systematically and since these compounds constitute a new class of sterically hindered amines, an investigation of the reactions of α-t-acetylenic-t-amines for possible exploitation of the products as pharmaceutical agents[6] was considered to be of interest.

The transformations discussed below are shown in Fig. 1.

Each of the acetylenic-t-amines, 3-dimethylamino-3-methyl-1-butyne (II), and 3-pyrrolidino-3-methyl-1-butyne (III), gave with ammoniacal silver nitrate solution, curdy white precipitates typical of compounds possessing a terminal ethynyl group.

Treatment of II and III with ethylmagnesium bromide gave the Grignard but with somewhat surprising results. The rate of formation of the organometallic was much slower than anticipated and several hours of reflux were generally needed for complete reaction (stoichiometric evolution of ethane). It had been reported[7,8] that the addition of amines increased the rate of reaction between alkylacetylenes and ethylmagnesium bromide. The decreased basicity[9] of the amine function coupled with a decrease in the acidity of the ethynyl hydrogen may explain the pronounced decrease in rate exhibited by II and III.

Additions of carbonyl compounds (aldehyde or ketone) to an ethereal suspension of the Grignards of II and III, followed by hydrolysis, resulted, in several cases, in the formation of acetylenic-1,4-amino alcohols (IV, V, VI, VII). The Grignard reagents were sensitive to enolizable ketones and when cyclohexanone, desoxybenzoin, acetophenone or propiophenone was employed, no amino alcohol was isolated. When the lithium salt of III was condensed with acetophenone in liquid ammonia,[10] however, VIII could be obtained in low yield.

Esterification of IV with acetic anhydride or propionic anhydride and pyridine failed. This is in agreement with Huggil and Rose.[11]

The reaction between the sodium salts of II and III, in liquid ammonia, and ethyl and butyl bromides gave the C-alkylated derivatives,[12] IX, X, XI and XII.

By employing the Mannich reaction[13] with formaldehyde and diethylamine or pyrrolidine on II and III, the acetylenic 1,4-diamines XIII, XIV, XV and XVI were prepared in good to excellent yields.

Oxidative coupling of II and III to 2,7-bis(dimethylamino) - 2,7 - dimethyl - 3,5 - octadiyne (XVII) and 2,7-bis(pyrrolidino)-2,7-dimethyl-3,5-octadiyne (XVIII), respectively, was accomplished by two techniques. In one method the reaction mixture was heated at 50–55° at atmospheric pres-

(1) Paper no. 74 on substituted acetylenes; previous paper, G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, **26**, 725 (1961).

(2) Eli Lilly Company Fellow, 1957–1959. Abstracted from the Ph.D. Dissertation of A. C. P., 1960.

(3) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, **79**, 2142 (1957).

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(5) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 4297 (1953).

(6) Pharmacological testing is in progress in the Lilly Research Laboratories, Indianapolis, Indiana.

(7) J. H. Wotiz, C. A. Hollingsworth, and R. Dessy, *J. Am. Chem. Soc.*, **77**, 103 (1955).

(8) J. H. Wotiz, C. A. Hollingsworth, and A. W. Simon, *J. Org. Chem.*, **24**, 1202 (1959).

(9) K. N. Campbell, F. C. Fatora, and B. K. Campbell, *J. Org. Chem.*, **17**, 1141 (1952).

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(11) H. P. W. Huggil and J. D. Rose, *J. Chem. Soc.*, 335 (1950).

(12) R. F. Parcell and C. B. Pollard, *J. Am. Chem. Soc.*, **72**, 2385 (1950).

(13) J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, 782 (1949).

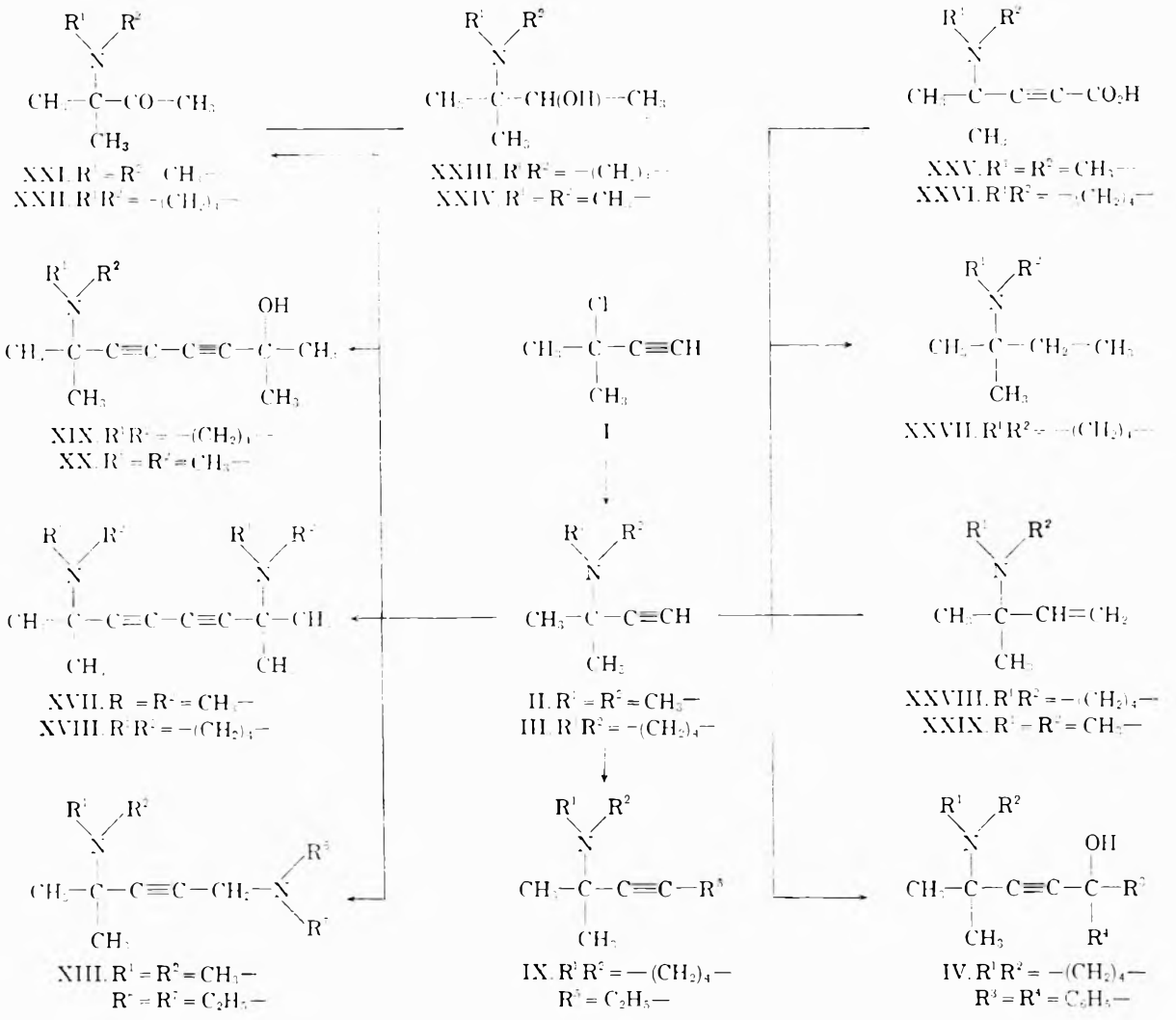

Fig. 1. Reactions of α-*t*-acetylenic-*t*-amines

sure with passage of air.[13] The other method entailed the shaking of the reaction mixture under a slight oxygen pressure (2–4 *p.s.i.g.*). The latter method consistently gave the diamines in better yield and higher purity.

Treatment of II and III with 3-methyl-1-butyne-3-ol under oxidative coupling conditions produced moderate yields of the oxidative cross-coupled products XIX and XX, as well as the symmetrical diamines and diacetylenic glycol. This appears to be the first reported use of this technique with acetylenic amines.

Hydration of II and III in the presence of mercuric oxide and sulfuric acid afforded the amino ketones XXI and XXII. These ketones did not undergo the haloform reaction. By reduction with sodium borohydride in methanol[14] the corresponding 1,2-amino alcohols, XXIII and XXIV, were prepared.

Passage of dry carbon dioxide gas through a suspension of the sodium salts of II and III in ether[15] produced, after neutralization, the acetylenic

(14) J. H. Biel and F. DiPierro, *J. Am. Chem. Soc.*, **80**, 4614 (1958).

amino acids, XXV and XXVI, respectively. As with many acetylenic acids, these compounds decarboxylated upon heating. The isolation and purification entailed the extraction and recrystallization of the amino acids from glacial acetic acid. 4 - Dimethylamino - 4 - methyl - 2 - pentynoic acid (XXV) was obtained as the amino acid in the zwitterion form. 4-Pyrrolidino-4-methyl-2-pentynoic acid (XXVI), on the other hand, could only be isolated containing one molecule of acetic acid per molecule of amino acid (elemental analysis and infrared spectrum). Attempts to prepare amides by the reaction of these acids with thionyl chloride or acetyl chloride, followed by addition of cold ammonium hydroxide, were unsuccessful.

Low pressure hydrogenation of III, employing either Raney nickel or 10% palladium on activated charcoal as catalysts, yielded 2-pyrrolidino-2-methylbutane (XXVII). With II under the same reaction conditions, extensive hydrogenolysis of the carbon-nitrogen bond was encountered. This is consistent with previous results.[5,16] If the hydrogenation of II and III was terminated after the absorption of one mole of hydrogen, the allylic amines, XXVIII and XXIX, were isolated in good yield. This indicated that the hydrogenolysis of the dimethylamine function upon attempted saturation of II occurred after the allylic compound was formed and can be attributed, at least in part, to the known fragility of such bonds.

Bromination of III gave somewhat unexpected results. Upon addition of bromine to a solution of III in carbon tetrachloride at 0°, a light yellow solid precipitated instantaneously. The infrared spectrum and physical properties indicated that this material was not a simple addition product. The only identifiable compound isolated was 3-pyrrolidino-3-methyl-1-butyne hydrobromide.

An attempt to prepare 1-bromo-3-pyrrolidino-3-methyl-1-butyne through the interaction of bromine and the Grignard reagent derived from III resulted in the coupled product, XVIII.

The compounds listed in Fig. 1 were characterized by the formation of methiodide and/or hydrochloride salts.

EXPERIMENTAL[17]

3-Chloro-3-methyl-1-butyne (I) was prepared as previously described.[18]

3-Dimethylamino-3-methyl-1-butyne (II) was prepared by a modification of the earlier procedure.[3] 3-Chloro-3-methyl-1-butyne (255 g., 2.5 moles) at 0–5°, was added to 710 g. (6.3 moles) of a 40% aqueous solution of dimethylamine at 0–5°, in a 2-l., round bottom flask fitted with a mechanical stirrer. The reaction mixture was stirred for 4 days while the temperature was maintained near 15°. The dark orange precipitate was collected, washed with cold water and dissolved in cold 3*N* hydrochloric acid. The acidic solution was extracted with two 150-ml. portions of ether (discarded) and treated three times with decolorizing charcoal. The resulting light yellow solution was cooled and made strongly alkaline with cold concentrated ammonium hydroxide solution. The white precipitate was collected, washed with cold concentrated ammonium hydroxide solution and finally with water. After dissolving the wet solid in ether, the ether layer was separated, dried overnight with anhydrous potassium carbonate and then for five additional hours over potassium hydroxide pellets. The ether was removed by distillation through a 25-cm. helix-packed column to yield 148.3 g. (53%) of white solid, m.p. 99–101° (lit. (3), m.p. 99–102°).

3-Pyrrolidino-3-methyl-1-butyne (III) was prepared in a similar manner from 300 g. (2.92 moles) of 3-chloro-3-methyl-1-butyne, 639 g. (9.0 moles) of pyrrolidine and 240 ml. of water. The reaction mixture was allowed to stand at 15° for 3 days and then worked up as described above. A 55% yield of white solid with m.p. 74–76° was obtained.

1,1-Diphenyl-4-pyrrolidino-4-methyl-2-pentyne-1-ol (IV). Magnesium turnings (1.6 g., 0.066 g.-atom), covered with 75 ml. of anhydrous ether, were converted to ethylmagnesium bromide in the usual way with 7.4 g. (0.068 mole) of ethyl bromide diluted with 100 ml. of anhydrous ether in a 1-l., three-necked, round bottom flask fitted with a water-cooled Allihn condenser, mercury sealed stirrer and dropping funnel. Drying tubes containing calcium chloride were attached to the condenser and dropping funnel. 3-Pyrrolidino-3-methyl-1-butyne (6.85 g., 0.05 mole) in 100 ml. of anhydrous ether was added dropwise with stirring. After 4 hr. of reflux a curdy white precipitate appeared and the reaction mixture was refluxed for an additional 4 hr., during which time precipitation was complete. Benzophenone (9.4 g., 0.05 mole) in 100 ml. of anhydrous ether was added dropwise with stirring (10 min.) and the reaction mixture was stirred overnight and then boiled for 4 hr. Hydrolysis was effected with ammonium chloride solution and the ether layer was separated, washed with two 200-ml. portions of cold water and dried over anhydrous potassium carbonate. Distillation of the ether left a light yellow solid. The product was washed with cold petroleum ether (b.p. 35–60°) and crystallized twice from benzene-petroleum ether to yield colorless crystals, weight 8.6 g. (54%), m.p. 138–139°.

The infrared spectrum revealed bands at 2.8, 8.5 and 4.5 μ assigned[19] to —OH, tertiary —C—O and —C≡C—, respectively.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 81.84; H, 7.85; N, 4.17.

The *hydrochloride* was prepared by addition of ethereal hydrogen chloride to a cooled solution of the amino alcohol (10.0 g., 0.031 mole) in 150 ml. of anhydrous ether. The precipitate was collected and crystallized from absolute ethanol; yield 9.0 g. (81%); m.p. 200–205° dec.

Anal. Calcd. for $C_{22}H_{26}ClNO$: C, 74.24; H, 7.36; N, 3.94. Found: C, 73.57; H, 7.33; N, 3.71.

The other hydrochlorides named below were prepared by a similar procedure unless otherwise stated.

The *methiodide* was prepared from 7.3 g. (0.023 mole) of amino alcohol and 5 g. (0.035 mole) of methyl iodide in 100 ml. of benzene. After standing for 48 hr., the precipitate was collected and crystallized from absolute ethanol; yield 9.5 g. (91%); m.p. 203–204° dec.

Anal. Calcd. for $C_{23}H_{28}INO$: N, 3.04. Found: N, 2.81. The other methiodides described were prepared by the same procedure unless otherwise stated.

1-Phenyl-4-pyrrolidino-4-methyl-2-pentyne-1-ol (V) was prepared in the same way from 1.6 g. (0.066 g.-atom) of magnesium turnings, 7.4 g. (0.068 mole) of ethyl bromide, 6.85 g. (0.05 mole) of 3-pyrrolidino-3-methyl-1-butyne and

(15) M. Olomucki and I. Marszak, *Compt. rend.*, 242, 1338 (1956).

(16) E. R. H. Jones, R. N. Lacey, and P. Smith, *J. Chem. Soc.*, 940 (1946).

(17) All melting and boiling points are uncorrected.

(18) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Am. Chem. Soc.*, 72, 3542 (1950).

(19) L. H. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, Inc., New York, 1954.

5.3 g. (0.05 mole) of freshly distilled benzaldehyde. The product was crystallized from benzene-petroleum ether; yield 8.3 g. (68%), m.p. 102–105°.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.69; H, 8.71; N, 5.85.

The *hydrochloride* had m.p. 180–183°

Anal. Calcd. for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.58; H, 7.95; N, 4.92.

1-Phenyl-1-(4-pyridyl)-4-pyrrolidino-4-methyl-2-pentyne-1-ol (VI) was prepared by the same procedure from 1.6 g. (0.066 g.-atom) of magnesium turnings, 7.4 g. (0.068 mole) of ethyl bromide, 6.85 g. (0.05 mole) of 3-pyrrolidino-3-methyl-1-butyne and 10.0 g. (0.055 mole) of 4-benzoylpyridine. The yellow solid was crystallized from ethyl acetate-petroleum ether and then from ethanol-water; yield 5.2 g. (32%), m.p. 135–137°.

Anal. Calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 77.11; H, 7.56; N, 8.14.

1-Phenyl-1-cyclohexyl-4-dimethylamino-4-methyl-2-pentyne-1-ol (VII) was similarly prepared from 4.37 g. (0.18 g.-atom) of magnesium turnings, 22.2 g. (0.24 mole) of ethyl bromide, 16.7 g. (0.15 mole) of 3-dimethylamino-3-methyl-1-butyne and 29.0 g. (0.15 mole) of phenyl cyclohexyl ketone. The yellow, semi-solid material was washed with pentane and crystallized from petroleum ether; yield 10.0 g. (22%), m.p. 139.5–140°.

Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22, H, 9.76; N, 4.68. Found: C, 80.74; H, 10.02; N, 4.53.

The *hydrochloride* had m.p. 192–193° dec.

Anal. Calcd. for $C_{20}H_{30}ClNO$: C, 71.51; H, 9.00; N, 4.17. Found: C, 71.51; H, 9.18; N, 4.03.

2-Phenyl-5-pyrrolidino-5-methyl-3-hexyne-2-ol (VIII). Lithiumamide (0.12 mole) was prepared from 0.84 g. (0.12 g.-atom) of lithium metal, 300 ml. of liquid ammonia and 0.10 g. of ferric nitrate nonahydrate in a 1-l., three-necked, round bottom flask fitted with a Dry Ice condenser, mercury sealed stirrer, and dropping funnel. 3-Pyrrolidino-3-methyl-1-butyne (13.7 g., 0.10 mole) in 100 ml. of anhydrous ether was added dropwise with stirring (20 min.) and the mixture was stirred for an additional 90 min. Twelve grams (0.10 mole) of freshly distilled acetophenone in 100 ml. of anhydrous ether was added dropwise. The mixture was then stirred for 6 hr. and allowed to stand overnight (ammonia evaporated). Ether (100 ml.) was added and hydrolysis was effected with 5 ml. of methanol followed by 50 g. of crushed ice and 150 ml. of water. The ether layer was separated, washed with two 150-ml. portions of water and dried over anhydrous potassium carbonate. The ether was removed by distillation and the residue allowed to stand for 1 week in an evaporating dish. The yellow solid was then dissolved in anhydrous ether and the hydrochloride precipitated by addition of ethereal hydrogen chloride. The precipitate was crystallized twice from absolute ethanol-anhydrous ether; yield 1.5 g. (5.0%), m.p. 188–189°.

Anal. Calcd. for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.62; H, 8.23; N, 4.85.

This *hydrochloride* (0.15 g.) was dissolved in water and the solution was filtered and made strongly alkaline with concd. ammonium hydroxide solution. The precipitate was washed with water and recrystallized from ethanol-water; m.p. 127–129°.

2-Pyrrolidino-2-methyl-3-hexyne (IX). Sodium amide was prepared in the usual manner[20] from sodium metal (6.0 g., 0.26 g.-atom) and 350 ml. of liquid ammonia in a 1-l., three-necked, round bottom flask fitted with a Dry Ice condenser, mercury sealed stirrer and dropping funnel. 3-Pyrrolidino-3-methyl-1-butyne (27.4 g., 0.20 mole) in 200 ml. of anhydrous ether was added dropwise with stirring (30 min.) and the reaction mixture was stirred an additional 90 min. Thirty-three grams (0.31 mole) of ethyl bromide in 100 ml. of anhydrous ether was added dropwise (30 min.). The reaction mixture was then stirred for 4 hr. and allowed to stand overnight for evaporation of the ammonia. One hundred milliliters of ether was added, followed by 5 ml. of methanol and 250 ml. of crushed ice and water. The ether layer was separated, washed with 150 ml. of water and dried over anhydrous potassium carbonate. Distillation through a modified Claisen flask with a 25-cm. Vigreux section gave 27.8 g. (84% yield) of fractions boiling between 88–90° (19 mm.) and 91–92° (21 mm.), n_D^{25} 1.4632–1.4641. Redistillation gave a colorless liquid, b.p. 92° at 21 mm., n_D^{25} 1.4645.

The infrared spectrum exhibited a band at 4.5 μ, characteristic of an unsymmetrically disubstituted acetylene.

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.94; H, 11.59. Found: C, 79.98; H, 11.04.

The hydrochloride, recrystallized from absolute ethanol-anhydrous ether, had m.p. 176–178°.

Anal. Calcd. for $C_{11}H_{20}ClN$: N, 6.94. Found: N, 6.98. The methiodide, recrystallized from absolute ethanol-ethyl acetate, melted at 140–141°.

Anal. Calcd. for $C_{12}H_{22}NI$: N, 4.56. Found: N, 4.51.

2-Pyrrolidino-2-methyl-3-octyne (X) was prepared in the same way from 3.0 g. (0.13 g.-atom) of sodium, 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne and 17.8 g. (0.13 mole) of *n*-butyl bromide. The product distilled at 120° (18 mm.), n_D^{25} 1.4638, weight 15.3 g. (78% yield). Redistillation gave a colorless liquid, b.p. 75° at 1 mm., n_D^{25} 1.4640.

Anal. Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 81.12; H, 12.03; N, 7.47.

The *hydrochloride* had m.p. 127–129°.

Anal. Calcd. for $C_{13}H_{24}ClN$: N, 6.10. Found: N, 6.16.

The *methiodide* melted at 159–160°.

Anal. Calcd. for $C_{14}H_{26}NI$: N, 4.18. Found: N, 4.12.

2-Dimethylamino-2-methyl-3-hexyne (XI) was prepared in the same way from 6.0 g. (0.26 g.-atom) of sodium, 22.2 g. (0.20 mole) of 3-dimethylamino-3-methyl-1-butyne and 32.7 g. (0.30 mole) of ethyl bromide. The fractions boiling between 70–71° (36 mm.), n_D^{25} 1.4378–1.4380, were collected: weight 23.7 g. (85% yield).

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.54; H, 11.91; N, 9.93.

The *hydrochloride* had m.p. 224–225° dec.

Anal. Calcd. for $C_9H_{18}ClN$: N, 7.97. Found: N, 8.07.

The *methiodide* melted at 187–188° dec.

Anal. Calcd. for $C_{10}H_{20}NI$: N, 4.98; Found: N, 4.99.

2-Dimethylamino-2-methyl-3-octyne (XII) was prepared in the same way from 6.0 g. (0.26 g.-atom) of sodium, 22.2 g. (0.20 mole) of 3-dimethylamino-3-methyl-1-butyne and 35.5 g. (0.26 mole) of *n*-butyl bromide. Fractions boiling between 87–88° (21 mm.), n_D^{25} 1.4418–1.4428, were collected; weight 25.5 g. (76% yield). Redistillation gave a colorless liquid, b.p. 84° at 16 mm., n_D^{25} 1.4425.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65. Found: C, 79.10; H, 12.57.

The *hydrochloride* had m.p. 146–148°.

Anal. Calcd. for $C_{11}H_{22}ClN$: N, 6.87. Found: N, 6.97.

The *methiodide* melted at 184–186°.

Anal. Calcd. for $C_{12}H_{24}NI$: N, 4.53. Found: N, 4.87.

1-Diethylamino-4-methyl-4-dimethylamino-2-pentyne (XIII). To a solution of 8.0 g. (0.11 mole) of diethylamine and 30 ml. of purified dioxane in a 100-ml., round bottom flask fitted with a water-cooled condenser was added 11.1 g. (0.10 mole) of 3-dimethylamino-3-methyl-1-butyne and 6.0 g. (0.20 mole) of paraformaldehyde. The reaction mixture was heated at reflux for 13 hr. and then distilled through a modified Claisen flask with a 25-cm. Vigreux column. Fractions boiling at 75–76.5° (1.5 mm.) weighed 18.1 g. (93% yield), n_D^{25} 1.4536–1.4539. Redistillation gave a colorless liquid, b.p. 53° (0.2 mm.), n_D^{25} 1.4540.

Anal. Calcd. for $C_{12}H_{24}N_2$: N, 14.27. Found: N, 14.50.

The *dihydrochloride*, recrystallized from absolute ethanol-ethyl acetate, had m.p. 203–206°.

(20) T. H. Vaughn, R. R. Vogt, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

Anal. Calcd. for $C_{12}H_{26}Cl_2N_2$: C, 53.52; H, 9.73; N, 10.41. Found: C, 53.68; H, 9.87; N, 10.22.

The *dimethiodide* melted at 213° dec.

Anal. Calcd. for $C_{14}H_{30}N_2I_2$: C, 35.01; H, 6.30; N, 5.83. Found: C, 35.07; H, 6.36; N, 5.86.

1-Pyrrolidino-4-methyl-4-dimethylamino-2-pentyne (XIV) was prepared from 11.0 g. (0.10 mole) of 3-dimethylamino-3-methyl-1-butyne, 7.81 g. (0.11 mole) of pyrrolidine and 6.0 g. (0.20 mole) of paraformaldehyde. The reaction mixture was refluxed for 24 hr. Distillation gave 15.9 g. (82% yield) of material collected in three fractions boiling at 79–80° (0.6 mm.), n_D^{25} 1.4749–1.4750. Redistillation gave b.p. 74° at 0.4 mm., n_D^{25} 1.4748.

Anal. Calcd. for $C_{12}H_{22}N_2$: N, 14.42. Found: N, 14.60.

The *dihydrochloride* had m.p. 133–137°.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2$: C, 53.93; H, 9.05; N, 10.48. Found: C, 53.89; H, 8.94; N, 10.49.

The *dimethiodide* was prepared as follows. Seventeen grams (0.12 mole) of methyl iodide was added to 8.0 g. (0.04 mole) of the diamine in 50 ml. of absolute ethanol and the reaction mixture was allowed to stand at room temperature for 8 hr. A yellow solid was collected and dissolved in a minimum quantity of water. Addition of acetone effected the formation of a colorless oil. The aqueous layer was decanted and acetone was then added to the oil which subsequently solidified upon cooling. This solid was dissolved in a solution of anhydrous methanol and 5.7 g. (0.04 mole) of methyl iodide. After 1 hr., the salt was precipitated by the addition of anhydrous ether. Recrystallization from absolute ethanol-anhydrous methanol gave 14.9 g. (76% yield) of crystals; m.p. 222–223° dec.

Anal. Calcd. for $C_{14}H_{28}I_2N_2$: N, 5.86. Found: N, 5.87.

1-Diethylamino-4-methyl-4-pyrrolidino-2-pentyne (XV) was prepared from 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne, 8.0 g. (0.11 mole) of diethylamine and 6.0 g. (0.20 mole) of paraformaldehyde. The reaction mixture was refluxed for 48 hr. Distillation gave 14.4 g. (65% yield) collected in three fractions boiling at 135–136° (20 mm.), n_D^{25} 1.4710–1.4713. Redistillation gave a colorless liquid, b.p. 76.5° (0.4 mm.), n_D^{25} 1.4710.

Anal. Calcd. for $C_{14}H_{26}N_2$: N, 12.60. Found: N, 12.64.

The *dihydrochloride* had m.p. 185–188°.

Anal. Calcd. for $C_{14}H_{28}Cl_2N_2$: C, 56.94; H, 9.56; N, 9.49. Found: C, 57.00; H, 9.65; N, 9.48.

The *dimethiodide* was prepared by adding methyl iodide to a solution of the diamine in absolute ethanol. After 6 hr. at room temperature, the salt was precipitated with ether; m.p. 192–194° dec.

Anal. Calcd. for $C_{16}H_{32}N_2I_2$: C, 37.96; H, 6.37; N, 5.53. Found: C, 38.14; H, 6.54; N, 5.61.

1,4-Bis(pyrrolidino)-4-methyl-2-pentyne (XVI) was prepared from 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne, 7.81 g. (0.11 mole) of pyrrolidine and 6.0 g. (0.20 mole) of paraformaldehyde. Distillation gave 18.2 g. (83% yield) collected in three fractions boiling at 94–95° (0.3 mm.), n_D^{25} 1.4910–1.4915. Redistillation gave a colorless liquid, b.p. 140° at 0.8 mm., n_D^{25} 1.4915.

Anal. Calcd. for $C_{14}H_{24}N_2$: N, 12.71. Found: N, 12.87.

The *dihydrochloride* had m.p. 221–222° dec.

Anal. Calcd. for $C_{14}H_{26}Cl_2N_2$: C, 57.33; H, 8.94; N, 9.55. Found: C, 57.27; H, 9.04; N, 9.61.

The *dimethiodide* melted at 200–202° dec.

Anal. Calcd. for $C_{16}H_{30}I_2N_2$: C, 38.11; H, 6.27; N, 5.56. Found: C, 38.04; H, 6.27; N, 5.52.

2,7-Bis(dimethylamino)-2,7-dimethyl-3,5-octadiyne (XVII). Ten grams (0.11 mole) of cuprous chloride, 7.5 g. of ammonium chloride and 9 ml. of water were added to a solution of 11.1 g. (0.10 mole) of 3-dimethylamino-3-methyl-1-butyne and 50 ml. of 2*N* hydrochloric acid in a 150 ml. flask fitted with a mechanical stirrer and gas dispersion tube. The reaction mixture was heated at 50–55° with stirring and passage of air for 10 hr. The resulting mixture was then cooled and made strongly alkaline with cold concd. ammonium hydroxide. A solid precipitated and the suspension was extracted with three 200-ml. and two 150-ml. portions of ether. The ether extracts were combined and dried over anhydrous potassium carbonate. The ether was then distilled and the solid residue allowed to stand overnight to remove volatile impurities. Crystallization from ethanol-water gave 6.5 g. (59% yield), m.p. 181–184°.

Anal. Calcd. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.40; H, 10.90; N, 12.85.

The *dihydrochloride*, recrystallized from ethanol-water, had m.p. 240–241°.

Anal. Calcd. for $C_{14}H_{26}Cl_2N_2$: C, 57.33; H, 8.94; N, 9.55. Found: C, 56.96; H, 9.06; N, 9.47.

The *dimethiodide* melted at 210° dec.

Anal. Calcd. for $C_{16}H_{30}I_2N_2$: C, 38.11; H, 6.00; N, 5.55. Found: C, 38.66; H, 6.19; N, 5.95.

2,7-Bis(pyrrolidino)-2,7-dimethyl-3,5-octadiyne (XVIII). Thirteen grams (0.13 mole) of cuprous chloride, 7.5 g. of ammonium chloride and 15 ml. of water were added to a solution of 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne and 50 ml. of 2*N* hydrochloric acid in a thick-walled bottle. The resulting mixture was shaken under an oxygen pressure of 2–4 *p.s.i.g.* The reaction mixture became warm and after 2 hr. 15 ml. of water was added and shaking with oxygen was continued for an additional 2 hr. Addition of cold concd. ammonium hydroxide effected the precipitation of a solid and the resulting slurry was extracted with a 300-ml., a 200-ml. and two 100-ml. portions of ether. The ether extracts were combined and dried over anhydrous potassium carbonate. Distillation of the ether gave a solid residue which was crystallized from ethanol-water; yield 11.0 g. (80%); m.p. 142–144°.

When the procedure described above for the preparation of XVII was employed, a 52% yield was obtained.

Anal. Calcd. for $C_{18}H_{28}N_2$: C, 79.36; H, 10.36; N, 10.28. Found: C, 79.15; H, 9.94; N, 10.31.

The *dihydrochloride* had m.p. 195–208° dec.

Anal. Calcd. for $C_{18}H_{30}Cl_2N_2$: N, 8.11; Found: N, 7.99.

7-Pyrrolidino-2,7-dimethyl-3,5-octadiyne-2-ol (XIX). A mixture of 6.85 g. (0.05 mole) of 3-pyrrolidino-3-methyl-1-butyne, 25 ml. of 2*N* hydrochloric acid, 25 g. (0.25 mole) of 3-methyl-1-butyne-3-ol, 7.5 g. of ammonium chloride, 12.0 g. (0.12 mole) of cuprous chloride and 75 ml. of water in a thick-walled bottle was shaken under an oxygen pressure of 1–2 *p.s.i.g.* The resulting mixture became warm and a solid precipitated. After 3 hr., an additional 3 g. of cuprous chloride and 25 ml. of water were added and shaking with oxygen was continued for 1 hr. After addition of cold concd. ammonium hydroxide solution (until the mixture was strongly alkaline) a brown precipitate was collected, washed with cold dilute ammonium hydroxide and finally with water. This solid was extracted with a 50-ml. and a 25-ml. portion of 2*N* hydrochloric acid. The acidic solution was decolorized with charcoal, cooled and made strongly alkaline with cold concd. ammonium hydroxide. A yellow, oily layer formed which subsequently solidified upon standing at room temperature. Crystallization from ethanol-water and then from petroleum ether (b.p. 35–60°) yielded 5.7 g. (52%) of white needles, m.p. 125–127°.

The infrared spectrum exhibited the expected bands at 2.8 and 4.5 μ.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.66; H, 9.71; N, 6.42.

The *hydrochloride* had m.p. 193–195°.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 64.05; H, 9.10; N, 5.75. Found: C, 63.99; H, 8.66; N, 5.85.

7-Dimethylamino-2,7-dimethyl-3,5-octadiyne-2-ol (XX) was prepared similarly from 5.6 g. (0.05 mole) of 3-dimethylamino-3-methyl-1-butyne, 27 ml. of 2*N* hydrochloric acid, 25 g. (0.25 mole) of 3-methyl-1-butyne-3-ol, 12.0 g. (0.12 mole) of cuprous chloride, 7.5 g. of ammonium chloride and 75 ml. of water. After shaking with oxygen maintained at 1–2 *p.s.i.g.* for 3 hr., an additional 6 g. of cuprous chloride and 25 ml. of water were added and the reaction mixture was shaken with oxygen for 1 hr. The amino alcohol was re-

crystallized twice from benzene-petroleum ether and then from ethanol-water; yield 3.0 g. (31%) of white plates, m.p. 149.5–152.5°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.81; H, 10.03; N, 7.12.

The *hydrochloride* had m.p. 242–243° dec.

Anal. Calcd. for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77; N, 6.10. Found: C, 62.63; H, 8.54; N, 5.92.

3-Dimethylamino-3-methyl-2-butanone (XXI). Mercuric oxide (1.5 g.) was added to a solution of 18.2 g. of 96% sulfuric acid, 35 g. of water, 11.1 g. (0.10 mole) of 3-dimethylamino-3-methyl-1-butyne and 15 ml. of methanol. The reaction mixture was heated at 80–90° for 3 hr., cooled and made strongly alkaline by dropwise addition of cold concd. sodium hydroxide solution. After extraction of the oil with two 75-ml. portions of ether, the ether extracts were combined and dried over anhydrous potassium carbonate. Removal of the ether at atmospheric pressure and distillation of the residue through a semi-micro Vigreux column gave 6.9 g. (54% yield) of a fraction with b.p. 78° (68 mm.), n_D^{20} 1.4278. Redistillation gave a colorless liquid, b.p. 72° at 52 mm., n_D^{20} 1.4280.

A strong band at 5.89 μ in the infrared spectrum clearly indicated the presence of a carbonyl function.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.87; H, 12.06; N, 10.70.

The *hydrochloride* had m.p. 145–149°.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.75; H, 9.74; N, 8.46. Found: C, 50.14; H, 10.28; N, 8.07.

The *methiodide* melted at 213–214° dec.

Anal. Calcd. for $C_8H_{18}INO$: C, 35.43; H, 6.69; N, 5.17. Found: C, 35.72; H, 6.80; N, 5.37.

3-Pyrrolidino-3-methyl-2-butanone (XXII) was prepared by a similar procedure with 2.5 g. of mercuric oxide, 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne, 18.2 g. of 96% sulfuric acid, 20 ml. of methanol and 20 ml. of water. The reaction mixture was heated at 75–80° on a steam bath for 3 hr. Distillation of the product gave a fraction with b.p. 90° (18 mm.), n_D^{21} 1.4581, weight 8.0 g. (52% yield). Redistillation gave b.p. 87.5–88° at 16 mm., n_D^{20} 1.4588.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.61; H, 10.77; N, 8.89.

The *methiodide* melted at 169–187° dec.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71. Found: C, 40.62; H, 6.92; N, 4.68.

3-Pyrrolidino-3-methyl-2-butanol (XXIII). To 7.2 g. (0.047 mole) of 3-pyrrolidino-3-methyl-2-butanone in 50 ml. of methanol was added, in small portions, 3.0 g. (0.24 mole) of sodium borohydride. The ensuing reaction was quite exothermic. After addition was complete, the mixture was heated on a steam bath for 2 hr., cooled, added to 60 g. of ice and then acidified by dropwise addition of 60 ml. of cold 5*N* hydrochloric acid. The mixture was concentrated to near dryness at room temperature and the residue diluted with water to a total volume of 100 ml. Potassium hydroxide pellets (30 g.) were added in small portions to the cooled mixture. An oil separated and was extracted with four 50-ml. portions of ether. Sodium chloride (10 g.) was added to the aqueous layer followed by further extraction with two 50-ml. portions of ether. The ethereal extracts were combined, dried superficially with anhydrous potassium carbonate and finally with anhydrous magnesium sulfate. The ether was removed by distillation and the residue distilled through a semi-micro Vigreux column; yield 6.0 g. (81%) of fractions with b.p. 99–100° (17 mm.), $n_D^{20.4}$ 1.4670–1.4674. Redistillation of the product gave b.p. 99° at 18 mm., n_D^{25} 1.4653.

The infrared spectrum showed the expected —OH band at 2.95 μ.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.88; H, 11.93; N, 9.04.

The *methiodide* melted at 188–189°.

Anal. Calcd. for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68. Found: C, 40.18; H, 7.49; N, 4.70.

3-Dimethylamino-3-methyl-2-butanol (XXIV) was prepared in a similar manner from 8.0 g. (0.62 mole) of 3-dimethylamino-3-methyl-2-butanone and 11.3 g. (0.31 mole) of sodium borohydride. The yield was 6.6 g. (88%) of fractions boiling at 90° (60 mm.), n_D^{25} 1.4375–1.4400. Redistillation gave b.p. 90° at 60 mm., n_D^{25} 1.4400.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.02; H, 13.36; N, 10.55.

The *methiodide* decrepitated at 166–169° and melted with decomposition at 248–252° (preheated block).

Anal. Calcd. for $C_8H_{20}INO$: N, 5.13; Found: N, 5.00.

4-Dimethylamino-4-methyl-2-pentynoic acid (XXV). Sodium metal (3.0 g., 0.13 g.-atom) was converted to the amide in the usual manner[20] with 300 ml. of liquid ammonia in a 1-l., three-necked, round bottom flask fitted with a mercury sealed stirrer, gas outlet tube and dropping funnel. 3-Dimethylamino-3-methyl-1-butyne (11.1 g., 0.10 mole) dissolved in 100 ml. of anhydrous ether was added dropwise with stirring (20 min.). After evaporation of the ammonia at room temperature the gas outlet tube was replaced with an Allihn condenser and attached drying tube (soda lime) and a gas inlet tube replaced the dropping funnel. The mixture was then boiled on a steam bath for 6 hr. to remove remaining ammonia. During this period, 200 ml. of anhydrous ether was added. The reaction mixture was cooled to room temperature and diluted with ether to a total volume of 500 ml. Dry carbon dioxide gas was then bubbled through the mixture for eleven hours. Cold water (200 ml.) was added and the mixture was shaken until there were two clear layers. The aqueous layer was separated, extracted with 100 ml. of ether (discarded), filtered and acidified to *p*H 3 with 50% sulfuric acid. Evaporation of this solution to dryness at room temperature gave 23.0 g. of a solid residue. This solid was extracted with two 75-ml. portions (A and B, respectively) of warm (75°) glacial acetic acid. On cooling to room temperature, a solid crystallized from A; weight 6.1 g. Upon addition of ether, 4.2 g. of solid precipitated from B. These fractions were combined, dissolved in warm (80°) glacial acetic acid and the solution allowed to cool to room temperature. The product was collected and washed with ether. The yield was 8.0 g. (52%) of colorless crystals which decarboxylated cleanly to 3-dimethylamino-3-methyl-1-butyne on heating.

The infrared spectrum revealed a band at 6.2 μ (assigned to —CO_2—) and the absence of any band assigned to O—H stretching vibrations. This is consistent with the zwitterion form of the amino acid. In contrast, the spectrum of 4-pyrrolidino-4-methyl-2-pentynoic acid (XXVI) contained not only the band at 6.3 μ but also a band at 5.85 μ (assigned to C=O stretching vibration of —CO_2H) and at 2.9 μ (stretching vibration of bonded OH). This is to be expected if XXVI is an acetic acid salt or is solvated by one molecule of acetic acid per molecule of amino acid.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.16; H, 8.63; N, 8.94.

4-Pyrrolidino-4-methyl-2-pentynoic acid (XXVI) was prepared in a similar manner from 3.0 g. (0.13 g.-atom) of metallic sodium, 300 ml. of liquid ammonia and 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne dissolved in 100 ml. of anhydrous ether. The solid residue obtained from evaporation of the acidified aqueous solution was extracted with two 60-ml. portions of glacial acetic acid at 80°, and the solutions allowed to cool at room temperature. The solid was collected and recrystallized from glacial acetic acid as described above. The yield was 9.6 g. (40%) of material which decarboxylated on heating.

Anal. Calcd. for $C_{12}H_{19}NO_4$ ($C_{10}H_{15}NO_2 \cdot CH_3CO_2H$): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.65; H, 7.85; N, 5.90.

2-Pyrrolidino-2-methylbutane (XXVII). 3-Pyrrolidino-3-methyl-1-butyne (13.7 g., 0.10 mole) was dissolved in 75 ml. of absolute ethanol in a thick-walled bottle and 2–3 g. of Raney nickel (wet with alcohol) was added. The mixture was shaken with hydrogen at an initial pressure of 50 *p.s.i.g.* until the pressure drop indicated absorption of 0.2 mole of

hydrogen (5 hr.). The catalyst was filtered off, the ethanol removed at atmospheric pressure and the residue distilled through a modified Claisen flask with a 25-cm. Vigreux column. The fractions boiling at 80–81° (39 mm.), n_D^{25} 1.4479, weighed 9.0 g. (64% yield). Redistillation yielded 8.2 g. of a colorless liquid, b.p. 80° (38 mm.), n_D^{25} 1.4482.

The infrared spectrum exhibited no absorption bands usually assigned to carbon-carbon unsaturation.

When the preparation was repeated using 1.0 g. of 10% palladium on activated charcoal as the catalyst, a 50% yield was realized.

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.94; H, 13.59; N, 9.63.

The *hydrochloride* had m.p. 137–142°.

Anal. Calcd. for $C_9H_{20}ClN$: C, 60.82; H, 11.34; N, 7.88. Found: C, 60.20; H, 11.03; N, 7.90.

3-Pyrrolidino-3-methyl-1-butene (XXVIII). To 13.7 g. (0.10 mole) of 3-pyrrolidino-3-methyl-1-butyne and 60 ml. of petroleum ether in a thick-walled bottle was added 0.07 g. of 10% palladium on activated charcoal. The mixture was shaken with hydrogen at an initial pressure of 50 *p.s.i.g.* until the pressure drop indicated absorption of 0.1 mole of hydrogen (1 hr.). The catalyst was filtered off, the petroleum ether removed by distillation at atmospheric pressure and the residue distilled through a modified Claisen with a 25-cm. Vigreux column. The fractions boiling between 74–74.5° (36 mm.), n_D^{25} 1.4560–1.4571 were collected; weight 12.8 g. Redistillation gave b.p. 56° at 16 mm., n_D^{25} 1.4571, weight 12.0 g. (86% yield).

The infrared spectrum showed bands at 3.28, 6.14, 7.07, 9.98, 10.99 and 14.55 μ.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 76.99; H, 12.52.

The *methiodide* had m.p. 152–158° dec.

Anal. Calcd. for $C_{10}H_{20}NI$: N, 4.98. Found: N, 5.00.

3-Dimethylamino-3-methyl-1-butene (XXIX) was prepared by the same procedure with 11.1 g. (0.10 mole) of dimethylamino-3-methyl-1-butyne, 0.065 g. of 10% palladium on activated charcoal and 60 ml. of petroleum ether. The hydrogenation time was 10.5 hr. The fractions boiling between 110–114°, n_D^{25} 1.4225–1.4230 were collected; weight 7.3 g. (63% yield). Redistillation gave material with b.p. 113°, n_D^{25} 1.4231.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36. Found: C, 74.78; H, 13.06.

The *methiodide* had m.p. 155–158° dec.

Anal. Calcd. for $C_8H_{18}N$: N, 5.49. Found: N, 5.75.

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NOTRE DAME, IND.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, ORGANIC CHEMICALS DIVISION, AMERICAN CYANAMID CO.]

The Chlorination of N,N-Dimethylaniline

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The chlorination of *N,N*-dimethylaniline with molecular chlorine gives 2-chloro- and 2,4-dichloro-*N,N*-dimethylaniline as the chief products. The chlorination with *N*-chlorosuccinimide, however, yields 39% 4-chloro- and 43% 2-chloro-*N,N*-dimethylaniline. This 4-chloro derivative has been found more reactive than the 2-chloro isomer in a competitive reaction with chlorine at about 40°, but the two have been found to react at about the same rate with *N*-chlorosuccinimide in the kinetic studies made.

Chlorination of *N,N*-dimethylaniline was reported by Krell[1] in 1872 to give an undefined mixture of monochlorodimethylanilines as well as 2,4-dichloro- and 2,4,6-trichloro-*N,N*-dimethylaniline. The nature of the mixture of the monosubstituted products was elucidated by Tishchenko[2] who reported that equal quantities of 2- and 4-chloro-*N,N*-dimethylanilines were formed on treatment of a suspension of *N,N*-dimethylaniline in aqueous sodium carbonate with chlorine. More recently Danilov and Koz'mina[3] have stated that chlorination with *N*-chloroacetanilide gave rise to both 2- and 4-chloro derivatives while Carpmael[4] found that the use of chlorine gave only 2-chloro-*N,N*-dimethylaniline as the monosubstituted product. These results are in marked contrast with the bromination and nitrosation of *N,N*-dimethylaniline which give principally the 4-substituted product. The present work was undertaken to investigate the apparent anomaly of this chlorination reaction.

It was found that chlorination of *N,N*-dimethylaniline with chlorine in various solvents, sulfuryl chloride in chlorobenzene, dichlorine oxide in carbon tetrachloride, and sodium hypochlorite in acid and basic solutions all gave 2-chloro- and 2,4 dichloro-*N,N*-dimethylaniline. The 4-chloro-*N,N*-dimethylaniline was found only in small or trace quantities. Chlorination with *N*-chloro reagents such as *N*-chlorosuccinimide, 1,3-dichloro-5,5-di-

(1) G. Krell, Ber., **5**, 878 (1872).

(2) D. V. Tishchenko, *J. der Russ. Phys. Chem. Gessell.*, **60**, 161 (1928).

(3) S. N. Danilov and O. P. Koz'mina, *Zhur. Obschei Khim.* (*J. Gen. Chem.*), **19**, 309–317 (1949).

(4) W. Carpmael, Br. Pat. **288,665**; Ger. Pat. **453,427**, Fr. Pat. **634,255**.

methyl hydantoin, and hexachloromelamine, on the other hand, definitely gives an appreciable yield of 4-chloro-*N*,*N*-dimethylaniline. The use of *t*-butyl hypochlorite also yields some 4-isomer, but to a lesser extent. Chlorination of dimethylaniline with purified *N*-chlorosuccinimide in dimethylformamide yielded a mixture containing 43% 2-chloro- and 39% 4-chloro isomers; interestingly in this reaction the formation of 2,4-dichlorodimethylaniline was practically nil. In fact, all the data seem to indicate an inverse relationship between the yields of 4-chloro- and 2,4-dichlorodimethylaniline. In the cases where *N*-chloro reagents were used the yield of the 4-chloro derivative was appreciable and the yield of the 2,4-dichloro compound was low. When chlorine was used, the reverse was true. This observation suggested that the 2,4-dichloro compound was formed from the 4-chloro isomer.

In the reaction with *N*-chlorosuccinimide there appeared to be an induction period which is suggestive of a free-radical process. However, the introduction of free-radical initiators such as azobisisobutyronitrile or the use of light failed to affect the reaction as observed or to increase the yield of the 4-chloro isomer when chlorine was used. It is unfortunate that not all the starting *N*,*N*-dimethylaniline could be accounted for in these reactions because of the inevitable accompanying oxidation reactions, but in no case was there any 3-chloro isomer found in the gas-chromatographical analyses.

The chlorination with *N*-chlorosuccinimide is strongly influenced by the reaction medium. In dimethylformamide the reaction gave the best yield of the 4-chloro isomer, while in dimethylformamide with 37% hydrochloric acid, water, or lithium chloride added, the yields approached those obtained with free chlorine as shown in Table II.

An explanation of the difference between the *N*-chlorochlorinating agents and chlorine is suggested by the competitive chlorination of a mixture of the anilines by molecular chlorine at 38° in chlorobenzene. The solution was saturated with gaseous hydrogen chloride in order to approximate the conditions of a normal experiment at halfway mark.

	Starting Mixture, Mole	After Chlorination, Mole[a]
N,*N*-Dimethylaniline	0.11	0.032
2-Chlorodimethylaniline	0.04	0.058
4-Chlorodimethylaniline	0.04	0.012
2,4-Dichlorodimethylaniline	0.00	0.022
Total	0.19	0.124

[a] Chlorine usage = 0.095 moles (one-half of the molecular quantities of the anilines present). Time equals one hour.

As the reaction is attended by considerable oxidation, the system does not lend itself to kinetic study. However, the results of the competitive study indicate that both *N*,*N*-dimethylaniline and its 4-chloro derivative are attacked under the reaction conditions and it would appear reasonable to assume that the low yield of 4-chloro-*N*,*N*-dimethylaniline is due to its ready conversion to the 2,4-dichloro compound. This view is in agreement with the inverse relationship of the yields of these two products already mentioned.

Kinetic studies of the chlorination with *N*-chlorosuccinimide in dimethylformamide further support this view. The reaction was milder and more easily controlled. The rate constants for this reaction are shown in Table I:

TABLE I

REACTION CONSTANTS (L./MOLE/MIN.)

Temp.	*N*,*N*-Dimethylaniline	2-Chloro-	4-Chloro-
0°	5.27×10^{-5}	5.49×10^{-10}	6.84×10^{-13}
25°	4.29×10^{-4}	3.64×10^{-6}	1.13×10^{-7}
50°	3.23×10^{-2}	6.02×10^{-3}	2.92×10^{-3}
75°	4.01×10^{-1}	3.48	17.53

It is interesting to note that with *N*-chlorosuccinimide the reaction rates at temperatures up to and including 50° were higher for *N*,*N*-dimethylaniline and for the 2-chloro derivative. It was under these conditions that an appreciable amount of the 4-chloro-*N*,*N*-dimethylaniline was isolated.

Thus it would appear that it is essential to have a positive chlorine-type reagent for the direct chlorination of *N*,*N*-dimethylaniline to produce any appreciable amount of 4-chloro-*N*,*N*-dimethylaniline. The yield of the 4-chloro isomer is dependent upon the nature of the solvent and upon the temperature. The data are consistent with the notion that molecular chlorine reacts much more rapidly with 4-chloro-*N*,*N*-dimethylaniline than with the 2-chloro isomer, while *N*-chlorosuccinimide reacts with both species at approximately the same rate at about 40°. Consequently the 4-chloro isomer can be obtained by direct chlorination only with the use of positive-chlorine reagents.

EXPERIMENTAL

General procedure. *N*,*N*-Dimethylaniline was dissolved in enough solvent to give a 20% solution which was then brought to the temperature indicated by using external heating or cooling. An equal molar amount of chlorine was slowly bubbled through the solution by means of a dispersion tube. After the chlorine addition, the solution was stirred for the desired length of time after which it was drowned in water and the amine hydrochloride was neutralized with sodium carbonate. The product was then separated from the aqueous layer along with the solvent which was then distilled at atmospheric pressure, and the crude product was then vacuum distilled.

In cases where a positive-chlorine chlorinating agent was used, it was slowly added to the solution of the *N*,*N*-dimethylaniline. As there was no amine hydrochloride formed

TABLE II

CHLORINATION OF ONE MOLE OF *N,N*-DIMETHYLANILINE (DMA)

Chlorinating Agent, One Mole	Solvent[a]	Material Added	Temp.	Time, Hr.	DMA Recovered Mole	2-Chloro-DMA, Mole	4-Chloro-DMA, Mole	2,4-Dichloro-DMA, Mole
Chlorine	CCl_4	—	−15	6.0	0.485	0.173	0.017	0.132
"	CCl_4	4 g. benzoyl peroxide, light	20–25	7.0	0.487	0.264	0.028	0.104
"	Chlorobenzene	—	10–40	5.0	0.374	0.286	0.036	0.159
"	Chlorobenzene	12.1 g. iodine	10–15	4.0	0.450	0.274	0.011	0.119
"	DMF	—	15–20	4.0	0.538	0.202	0	0.122
"	Pyridine	—	5–10	16.0	0.342	0.258	0.026	0.092
"	Liq. SO_2	—	−10	4.5	0.319	0.290	0.066	0.043
"	20% NaOH	—	10–12	4.0	0.330	0.190	0.050	0.14
"	37% HCl	—	30–50	4.0	0.160	0.470	0	0.117
12% NaOCl	Acetic acid	—	10–40	7.0	0.09	0.13	0	0.24
Cl_2O	CCl_4	—	5–15	6.0	0.505	0.189	0.032	0.012
Pyridinedichloride	CCl_4	—	20	21.0	0.688	0.118	0.015	0.002
SO_2Cl_2	Chlorobenzene	—	10–15	4.5	0.372	0.364	0.034	0.095
Purified *N*-chloro-succinimide[b]	DMF	None	40–50	22.0	0	0.43	0.39	0
N-Chlorosuccinimide	DMF	None	65–70	7.5	0.033	0.393	0.309	0.01
N-Chlorosuccinimide	DMF	160 g. H_2O	40–60	5.0	0.033	0.507	0.191	0.02
"	DMF	100 g. LiCl	40–60	5.0	0.068	0.551	0.138	0.044
"	DMF	238 g., 37% Aq HCl	40–60	5.0	0.302	0.45	0.07	0.088
"	CCl_4	None	50–70	20.0	0.10	0.485	0.280	0.021
"	Acetic acid	None	10	20.0	0.035	0.236	0.124	0.01
1,3-Dichloro-5,5-dimethyl hydantoin[c]	CCl_4	None	10–30	20.0	0.10	0.36	0.193	0.01
Hexachloromelamine[d]	CCl_4	None	10–17	20.0	0.08	0.29	0.09	0.01
t-Butyl hypochlorite	CCl_4	None	10–18	7.0	0.29	0.27	0.15	0.11
t-Butyl hypochlorite	CCl_4	[e]	20–40	5.0	0.36	0.248	0.074	0.06
t-Butyl hypochlorite	*t*-C_4H_9OH	None	20–40	4.0	0.44	0.196	0.047	0.09

[a] DMA in solvent as 20% solution. [b] Recrystallized from water, dried; other *N*-chlorosuccinimide samples are pure grade materials as supplied by laboratory supply houses, m.p. 147–149°. [c] One-half mole. [d] One-sixth mole. [e] Added 8 g. azobisisobutyronitrile.

when using the *N*-chlorinating agents or *t*-butyl hypochlorite, the neutralization with sodium carbonate was omitted.

Method of analysis. The mole figures presented were obtained by vapor phase chromatography of the simply distilled reaction products. In the distillation of the crude products, no attempt was made to separate the isomers, but simply to distill all the volatile matters from the tarry residue. This distilled mixture was then analyzed, and the residue from this distillation is considered in the over-all yield of components. The accuracy of this analytical method, employing vapor phase chromatography, was checked by actual fractionation of several large-scale chlorination reactions. As the boiling points of 4-chloro- and 2,4-dichlorodimethylaniline are practically identical, chlorine analyses were made to determine the proportions of the components in these fractions. In general, good agreements were obtained.

Kinetic studies. The kinetics of the chlorination of *N,N*-dimethylanilines were studied by a Differential Thermal Analysis apparatus similar to that described by Borchardt and Daniels.[5] Solutions of 0.5*M* *N*-chlorosuccinimide and 0.5*M* *N,N*-dimethylaniline in dimethylformamide were allowed to react and dimethylformamide was used as reference material. Second order rate constants were calculated by equations of Borchardt and Daniels.[5] Infrared analyses were made to ascertain that the products were actually chlorinated dimethylanilines.

The gas chromatography instrument used was the Model 124 from F & M Scientific Glassware Company. The separation was achieved by using a 6-ft. Apiezon L column.

Acknowledgment. The authors are extremely indebted to Dr. E. C. Vieira for his valuable work on the kinetic studies presented in this paper.

BOUND BROOK, N. J.

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[CONTRIBUTION FROM THE NORWICH PHARMACAL CO.]

The Thermal Decomposition of 2-Hydrazinoethanol and 1-Hydrazino-2-propanol

JOHN C. HOWARD, GABRIEL GEVER, ALEXANDER B. NEILL, AND PETER H. L. WEI

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The thermal decomposition of the title compounds formed methylhydrazine in 20–30% yield.

In an earlier paper we reported our interest in hydrazino alcohols and their use in the synthesis of 3-amino-2-oxazolidones.[1]

During the attempted distillation of 2-hydrazinoethanol, brisk gas evolution occurred at about 215° and a liquid, b.p. 80–150°, distilled. The residue then charred with some violence. Purification of the liquid gave methylhydrazine in 25% yield, identified by its boiling point, acid sulfate and acid oxalate. In this and subsequent decompositions, the presence of 2-aminoethanol was established, and ammonia and hydrazine were identified in the gaseous effluent. Neutral gases were also evolved but not identified.

These results were considered to be of sufficient synthetic interest to justify a serious effort to improve the rather low yield of methylhydrazine (Table I). However, neither a nitrogen atmosphere during the decomposition, nor the addition of powdered glass (recently used with success by Newman and Caflisch[2] in the McFayden-Stevens aldehyde synthesis) had a significant effect on the yield. A free radical initiator, benzoyl peroxide, was used in an effort to lower the decomposition temperature. This was also unsuccessful; good results were achieved, however, in moderating the occasionally violent decompositions by the use of polyethylene glycol-400, although this had little effect on the yield.

TABLE I

EFFECT OF ADDITIVES ON METHYLHYDRAZINE YIELD

Additive	2-Hydrazinoethanol, g.	% Yield of Methylhydrazine
None	116	25
Nitrogen	200	31
Powdered glass, 4 g.	10	30
Benzoyl Peroxide, 105 mg.	30	21
Polyethylene Glycol-400, 300 g.	200	30

We next turned our attention to the thermal decomposition of 1-hydrazino-2-propanol, $NH_2NHCH_2CHOHCH_3$. This reaction proceeded more smoothly than with 2-hydrazinoethanol, little gas was evolved and no violent decompositions occurred. The crude volatile liquid product was distilled, and the distillate, b.p. 95–108°, was dried over sodium hydroxide and redistilled. Two main fractions were obtained. Fraction A was identical with methylhydrazine in boiling point and infrared spectrum. Fraction B, b.p. 92–97°, showed more intense absorption at 7.25 μ (methyl deformation) and weaker absorption at 6.2 μ (NH deformation) than methylhydrazine. The preparation of methylhydrazine acid oxalate, and acetaldehyde 2,4-dinitrophenylhydrazone from Fraction B indicated that it might be acetaldehyde methylhydrazone. Several attempts to synthesize this compound from acetaldehyde and methylhydrazine in ether solution yielded an unstable liquid very similar to Fraction B. Satisfactory analytical data could not be obtained. That the substance was mainly acetaldehyde methylhydrazone was indicated by its conversion to acetaldehyde 2,4-dinitrophenylhydrazone and methylhydrazine oxalate.

The corrected yield of methylhydrazine from 1-hydrazino-2-propanol based on the amount isolated by distillation plus the methylhydrazine acid oxalate from Fraction B was 20%. Infrared analysis of the crude volatile product in chloroform solution indicated a total yield of 30–40%.

Although the main reaction leading to methylhydrazine may be simply described (Eq. 1), its mechanism probably involves several steps and possibly proceeds through free radical intermediates.

$$\text{(1)}\quad NH_2NHCH_2\underset{\displaystyle R}{\underset{|}{C}}HOH \longrightarrow CH_3NHNH_2 + RCHO$$

R=H, CH_3

EXPERIMENTAL[3]

Thermal decomposition of 2-hydrazinoethanol. (This describes Run 1, Table I; other runs summarized there were

(1)(a) G. Gever, *J. Am. Chem. Soc.*, **76**, 1283 (1954); (b) G. Gever, C. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. J. Hayes, *J. Am. Chem. Soc.*, **77**, 2277 (1955).

(2) M. S. Newman and E. G. Caflisch, Jr., *J. Am. Chem. Soc.*, **80**, 862 (1958).

(3) The melting points were determined on a calibrated Fisher-Johns block and the infrared spectra were determined on the Perkin-Elmer Model 21 equipped with sodium chloride optics. The elemental analyses were performed by Mr. Gordon Ginther and associates of these Laboratories.

carried out by the same general method and are not individually described.) In a 200-ml. flask set up for distillation and equipped with a gas outlet tube connected to a dilute hydrochloric acid trap was placed 116 g. (1.53 moles) of 2-hydrazinoethanol, b.p. 91–98° (0.8–1.5 mm.). The flask was heated to 215–220° with an oil bath. At about 200° moderate bubbling began and gases evolved. After 1 hr. a total of 75.5 g. of distillate had collected. An attempt was made to fractionate 61.7 g. of this material at reduced pressure. At room temperature 39.2 g. distilled at 14 mm. Continued heating of the residue gave 2.3 g., b.p. 50° (3.5 mm.). This liquid was refluxed with 6.6 g. of oxalic acid dihydrate in 50 ml. of ethanol, filtered, cooled, and the crystalline precipitate recrystallized from 100 ml. of 80% ethanol. This gave 0.7 g. of ethanolamine oxalate, melting point and mixed melting point with authentic material 191–192°. Redistillation of the 39.2 g. at normal pressure gave 35.1 g., b.p. 81–104°. That this was mainly methylhydrazine was indicated by preparation of the oxalate. One gram of the distillate was refluxed with 3 g. of oxalic acid dihydrate in 85 ml. of 80% ethanol; cooling separated 1.1 g. (37%) of crystals, m.p. 162–164° (lit.[4] m.p. 166°). Preparation of authentic methylhydrazine oxalate under these conditions resulted in a 51% yield (m.p. 167–168°) after recrystallization from 80% ethanol. The boiling range for the distillate indicated it to be wet. (It is known that methylhydrazine forms a high-boiling (104°) azeotrope[5, 6]). The distillate (33.8 g.) was therefore dried on the steam bath over 35 g. of sodium hydroxide. Distillation through a Vigreux column gave 13.9 g. of methylhydrazine, b.p. 86–87° (lit. b.p. 87°). The yield corresponded to a total of 17.8 g. (25%) of methylhydrazine in the 75.5 g. of crude distillate. (The infrared spectrum of this sample was not recorded, but in other runs (Table I) the distillate gave a infrared spectrum in chloroform identical with authentic methylhydrazine). One gram of the distillate was added to 35 ml. of ethanol containing 2 g. of sulfuric acid. Cooling separated 2.2 g. (70%) of crystals, m.p. 141–142°, mixed melting point with authentic methylhydrazine acid sulfate (m.p. 141–142°) was undepressed. Titration of the dilute hydrochloric acid solution showed that 2.73 g. of alkaline gases (calculated as ammonia) were evolved. Ammonia was identified in one run by condensation of the alkaline gases, including some water, in a trap cooled with a Dry Ice–acetone mixture. Treatment with benzoyl chloride yielded benzamide, m.p. 129–130°. Mixed melting point with authentic benzamide was undepressed. Evidence proving the presence of a small quantity of hydrazine in these gases was obtained in another run by treatment of the acid solution with ethanolic 5-nitro-2-furaldehyde. A small amount of yellow solid separated; it was identified by m.p. (245–248°) and infrared spectrum as 5-nitro-2-furalazine.[7]

Thermal decomposition of 1-hydrazino-2-propanol. In a 500-ml. flask equipped with stirrer, thermometer, gas outlet tube leading through an acid trap, and a variable take-off distillation assembly, was placed 301 g. (3.34 moles) of hydrazino-2-propanol[1a]. The flask was heated to 210° with a mantle. After 5.5 hr. 187 g., b.p. 125–145°, had distilled. A reflux ratio of 3 to 1 was used. Near the end of the reaction some gas evolved and a yellow liquid began to distil. This fraction, b.p. 145–193°, (27 g.) showed an infrared band at 6.0 μ. It was not investigated further. The bulk (164 g.) of the distillate was redistilled through a Vigreux column. The first fraction (112 g.), b.p. 95–108°, was dried over 50 g. of sodium hydroxide at room temperature for 8 hr. The organic layer was decanted and dried again over 14 g. of sodium hydroxide overnight in the refrigerator. The organic layer was then filtered through glass wool and distilled through a Vigreux column. Two fractions, A, 9.5 g., b.p. 85–86°, and B, 31.0 g., b.p. 92–97°, were collected. Fraction A was identical in boiling point and infrared spectrum with authentic methylhydrazine.

A solution of 2.0 g. of Fraction B in 10 ml. of ethanol was added to a warm solution of 5.0 g. of oxalic acid in 20 ml. of ethanol. Colorless crystals immediately separated; after cooling, these were collected, 2.83 g., m.p. 167–169°, undepressed with authentic methylhydrazine acid oxalate.

A solution of 2.0 g. of Fraction B in 10 ml. of methanol was slowly added with cooling to a solution of 6.0 g. of 2,4-dinitrophenylhydrazine prepared by dissolving the hydrazine in 10 ml. of concentrated sulfuric acid and subsequent dilution with 100 ml. of methanol. Orange crystals separated and were collected, washed with methanol and water, 3.09 g., m.p. 150–152°. Recrystallization from 50 ml. of ethanol and 10 ml. of nitromethane gave 2.2 g., m.p. 164–165° (lit.[8] m.p. 164°). Mixed melting point with authentic acetaldehyde 2,4-dinitrophenylhydrazone was undepressed.

Attempted preparation of acetaldehyde methylhydrazone. To 164 g. (3.57 moles) of freshly distilled methylhydrazine in 500 ml. of ether was dropwise added, with stirring and cooling, 157 g. (3.57 moles) of acetaldehyde in 200 ml. of ether. The flask was protected from carbon dioxide by a soda-lime tube, and maintained at about 20° by an ice bath. The reaction mixture consisted of two phases at the end of the addition. These were separated, and the aqueous phase was extracted with 200 ml. of ether. The combined ether extracts were dried over 100 g. of sodium hydroxide for 2 days. After removal of the drying agent the ether was distilled through a 1-ft. Vigreux column. The residue was distilled in the same way, and the distillate, b.p. 97–108°, was collected. The distillate was twice fractionated through an 8-inch Vigreux column and the fraction b.p. 105–106° (33 g.) was collected.

Anal. Calcd. for $C_3H_8N_2$: C, 49.97; H, 11.18. Found: C, 47.13; H, 11.03.

When exposed to the air this material quickly formed a solid (m.p. 50–60°) which slowly turned yellow even in the refrigerator. This material yielded methylhydrazine oxalate in 31% yield (m.p. 168–170°) and acetaldehyde 2,4-dinitrophenylhydrazone in 43% yield (m.p. 164–165°) after treatment with oxalic acid and 2,4-dinitrophenylhydrazine in the usual manner.

2-Aminoethanol oxalate. A solution of 1 g. of 2-aminoethanol, 3 g. of oxalic acid dihydrate and 100 ml. of ethanol was heated to boiling then cooled and the crystalline product collected (m.p. 134–135°) and recrystallized from 37 ml. of 75% ethanol. The yield was 0.3 g., m.p. 190–192°.

Anal. Calcd. for $C_6H_{16}N_2O_6$: C, 33.95; H, 7.60; N, 13.20. Found: C, 34.06; H, 7.96; N, 13.39.

Acknowledgment. We wish to thank Dr. J. Meinwald of Cornell University for helpful advice.

NORWICH, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ST. JOHN'S UNIVERSITY AND INSTITUTE OF ORGANIC CHEMISTRY, UNIVERSITY OF BUDAPEST]

Chemical Studies of Polyaspartic Acids[1]

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The thermal polycondensation of aspartic acid (I) yields anhydropolyaspartic acid (IV). Various steps in an assumed mechanism, I ⟶ II ⟶ III ⟶ IV, were investigated. On heating, acetyl aspartic acid gave anhydropolyaspartic acid instead of the monomer anhydride. L-Aspartic anhydride (II) was polymerized to poly-α,β-L-aspartic acid (III) which formed IV under the same conditions as I. Partial hydrolysis of IV reformed III. The conversion of poly-α-L-aspartic acid (V) into IV was carried out by various methods. The ease of formation of the imide ring was demonstrated by the conversion of both α- and β-anilide of acetyl aspartic acid into the same succinimide derivative. Partial hydrolysis of the succinimide derivative gave mainly the β-anilide.

In preliminary communications,[3-6] we reported briefly investigations of the structure of anhydropolyaspartic acid and of α, β-polyaspartic acid. We now report additional experiments concerning the mechanism of the polycondensation of aspartic acid and rearrangement of asparagine derivatives into isoasparagine derivatives and vice versa.

Polycondensation of aspartic acid was carried out either by heating it *in vacuo* or removing the water formed by azeotropic distillation.[7] The polymeric material, referred to as anhydropolyaspartic acid (IV), was formed by the loss of two molecules of water during condensation.

Partial hydrolysis of IV in alkaline medium yielded α,β-polyaspartic acid (III). The purified free acid (III) when dried at 60–70° *in vacuo* gave analytical data in agreement with III. Like β-poly-DL-asparatic acid,[8a] γ-polyglutamic acid[8b] and α, γ-polyglutamic acid,[8c] III is also very soluble in water contrasting with α-polyaspartic acid and α-polyglutamic acid which are insoluble. It gives a strong biuret reaction which α,γ-polyglutamic acid[8c] does not.

On the basis of amino nitrogen determination (van Slyke) the molecular weights of different preparations of III were between 6000 and 12,000. Molecular weights determined by this method can be misleading because of the possibility of cyclization. However, Fox and co-workers reported that molecular weights of polyaspartic acid calculated from sedimentation constants agreed with values obtained by end-group analysis.[9]

The approximate amounts of the α- and β-linkages in III were determined by a degradation procedure similar to that used in the proof of structure of native polyglutamic acid.[10]

Anhydropolyaspartic acid (IV) was hydrolyzed to the sodium salt of III which was then converted directly to polyaspartic acid polymethyl ester (VI) using methanol–hydrochloric acid solution. The methoxyl content of the ester indicated about 90% esterification of the carboxyl groups. The polyamide (VIIa) was readily prepared by direct ammonolysis of VI after dialysis. The amidation of VI was nearly quantitative producing a polyamide in which about 90% of the carboxyl groups were in the amide form.

As expected every α-aspartyl amide residue (VIII) gave the intermediate IX by Hofmann degradation and α,β-diaminopropionic acid on subsequent acid hydrolysis. Similarly β-aspartyl amide residues (X) gave acetaldehyde *via* the intermediate XI. Acetaldehyde present in the acidic hydrolyzate of the degraded polyaspartic acid polyamide, was separated as the 2,4-dinitrophenylhydrazone, and any α,β-diaminopropionic acid isolated as the flavianate. Control experiments indicated the approximate loss of acetaldehyde (32%) and of diaminopropionic acid (40%) during the isolation procedure. The corrected amount of acetaldehyde-dinitrophenylhydrazone, obtained from degraded polyamide preparation, showed that at least 33% of the aspartic acid was incorporated with β-peptide bonds. Similarly, from the weight of α,β-diaminopropionic acid diflavianate at least 25% of the aspartyl residues had α-peptide bonds. Therefore, the ratio of α- and β-aspartyl residues in polyaspar-

(1) This work was supported in part by a research grant (RG 6579) from the National Institutes of Health, Public Health Service.

(2) Visiting scientist from Institute für Katalyseforschung, Rostock, Germany.

(3) J. Kovacs, I. Könyves, and Á. Pusztai, *Experientia*, 9, 459 (1953).

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(7) In a private communication E. Katchalski had made it known that A. Berger had successfully converted aspartic acid hydrochloride into anhydropolyaspartic acid using this procedure.

(8)(a) V. Bruckner, T. Vajda, and J. Kovacs, *Naturwiss.*, **41**, 449 (1954); *Acta Chim. Hung.*, **6**, 209 (1955); (b) V. Bruckner and J. Kovacs, *Acta Chim. Hung.*, **12**, 363–404 (1957). Summarizing review; (c) V. Bruckner, M. Szekerke, and J. Kovacs, *Naturwiss.*, **43**, 107 (1956); *Z. physiol. Chem.*, **309**, 25 (1957).

(9) A. Vegotsky, K. Harada, and S. W. Fox, *J. Am. Chem. Soc.*, **80**, 3361 (1958).

(10) J. Kovacs and V. Bruckner, *J. Chem. Soc.*, 4255 (1952); V. Bruckner, J. Kovacs, and H. Nagy, *J. Chem. Soc.*, 148 (1953).

tic acid was found to be about 1:1.3, assuming that no intramolecular transpeptidation[5] took place during the esterification, amidation, or Hofmann degradation. It was further assumed that the remaining 42% of the aspartyl residues were similarly bound, that is in the ratio of about 1:1.3.

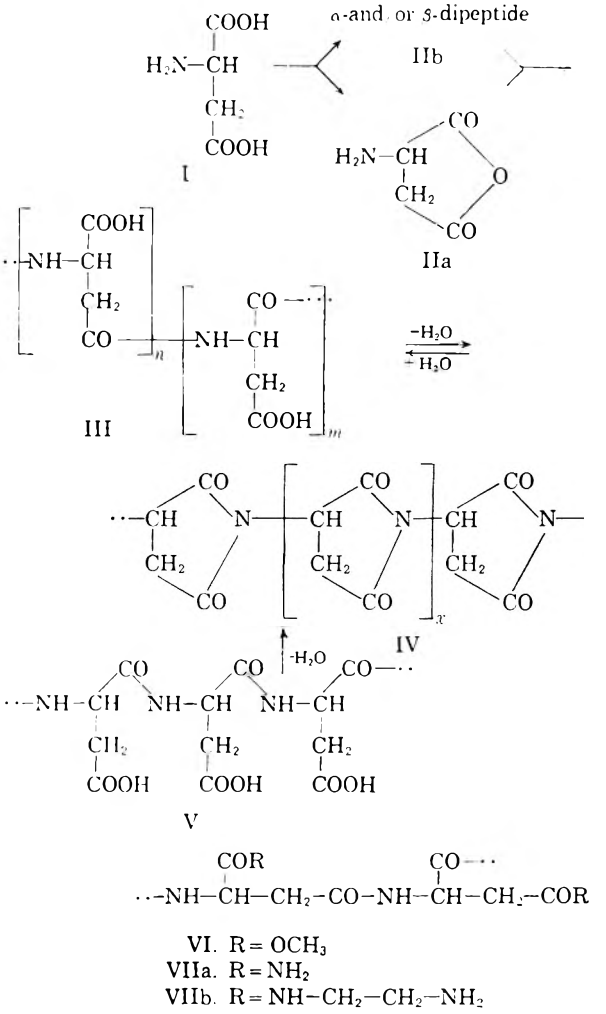
Anhydropolyaspartic acid was easily converted directly to polyamide (VIIa) and a substituted polyamide (VIIb) with liquid ammonia and ethylenediamine respectively. Hofmann degradation of the polyamide (VIIa) gave approximately the same amount of asparaginyl as of isoasparaginyl residues. A sample of anhydropolyaspartic acid, prepared by heating α,β-polyaspartic acid, when carried through the same procedure showed an excess of isoasparaginyl residues.

DISCUSSION

On the basis of the experimental work reported here the initial reaction in the polycondensation of aspartic acid may be the formation of either aspartic anhydride (IIa) or dipeptide(s) (IIb). The former would be followed by intermolecular polyacylation and the latter by polycondensation with aspartic acid or peptides. Whichever is assumed, the next product is α,β-polyaspartic acid (III).[11] However, under the reaction conditions this material is unstable and undergoes intramolecular dehydration producing IV, a polymer composed of succinimide units.[3,5,6,12]

Reaction I → II. Acetylaspartic acid was selected as a model compound to test the formation of the anhydride. However on being heated (145°, 200°) it did not form anhydride but lost water and acetic acid and was converted into a glassy polymeric material. The infrared spectrum with a double band at 5.6 and 5.86 μ, and the biuret reaction indicated that the product had a structure similar to IV. The formation of the acetylaspartic anhydride as an intermediate was suspected; however acetylaspartic anhydride did not polymerize under these reaction conditions. Raising the temperature decomposed it with the formation of acetamide. Therefore an intermolecular transacylation reaction was indicated with the formation of a polypeptide chain. This polymerization of acetylaspartic acid is unique among the acylamino acids.

On the basis of these results reaction I → IIb by direct intermolecular acylation can be expected but reaction I → IIa can not be excluded. Apparently polycondensation of aspartic acid to III through intermediate IIa or IIb is a fast reaction while III to IV is slow. On heating, aspartic acid in boiling tetralin lost the first molecule of water within seventeen hours, while the second molecule was obtained only after several days. It seems to be significant that the dehydration of α,β-polyaspartic acid (III) to anhydropolyaspartic acid (IV) under similar conditions also required several days.



Reaction II → III. The hydrobromide of L-aspartic acid anhydride (II) was polymerized in pyridine to α,β-L-polyaspartic acid (III). It was prepared from carbonbenzoxy-L-aspartic anhydride by decarbobenzoxylation in hydrobromic-acetic acid solution. Its structure was verified by the reaction with aniline which yielded α- and β-aspartic acid anilides.[13]

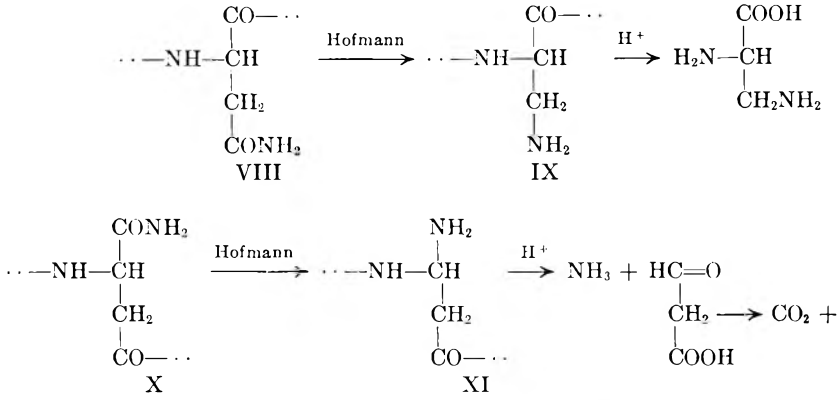
Furthermore, treatment of hydrobromide with ammonia produced L-isoasparagine together with a small amount of asparagine. One recrystallization gave chromatographically pure L-isoasparagine. With methanol, the hydrobromide gave L-aspartic acid α-methyl ester. The homogeneity of the re-

(11) In addition to these routes diketopiperazine, formed from α-dipeptide, could undergo various reactions leading to polyaspartic acid. Such possibilities are discussed in general by E. Katchalski, in *Advances in Protein Chemistry*, **13**, 333–5 (1958). The anhydride formed at the C terminal of a peptide could also participate in the polymerization.

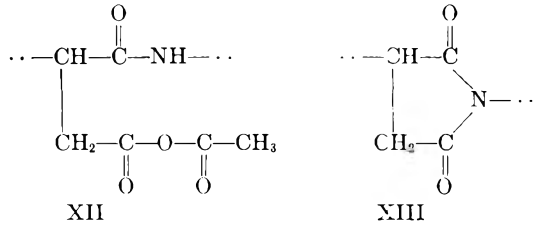
(12) J. Kovacs, I. Könyves, and Á. Pusztai, *Vegyipari Kutató Intézetek Közleményei*, **4**, 120 (1954).

(13) L-Aspartic acid β-anilide was first reported by F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 2976 (1951). It was prepared from phthalyl-L-aspartic acid β-anilide giving m.p. 251–252°. Aspartic acid β-anilide reported in this paper gave m.p. 241–242° and $[\alpha]_D^{24}$ 33.4°; the presence of the free α-carboxyl group was confirmed by the ninhydrin reaction.

crystallized ester was established by conversion to L-isoasparagine. The structure of polymerized product was established by the degradation method employed for the proof of structure of DL-polyaspartic acid.



Reaction III → IV and V → IV. Both poly- α, β-aspartic acid (III) and poly α-L-aspartic acid (V) were converted into anhydropolyaspartic acid (IV) under the same experimental conditions used for the pyrocondensation of aspartic acid. In addition, it was found that treatment of the latter (V) with acetic anhydride also produced IV.[14] This last reaction was accompanied by only a slight degree of racemization as determined by the [α] value of the aspartic acid obtained by the total hydrolysis of the product. The reaction probably involves the activation of the carboxyl group by a mixed anhydride formation (XII). Intramolecular elimination of acetate ion gives the polyimide (XIII).



The conversion of α,β-polyaspartic acid (III) into anhydropolyaspartic acid (IV) was followed by infrared spectroscopy[15]; the characteristic absorption bands of polyaspartic acid such as amide I at 6.01 (in potassium bromide, 6.05 is oil paste) and NH stretching near 3 μ disappeared or nearly completely disappeared; the strong amide II in polyaspartic acid appeared as a weak band in spectrum of anhydropolyaspartic acid.

The anhydropolyaspartic acids prepared from all of the above sources had the same properties; (a) they were insoluble in water and in diluted sodium bicarbonate solution, (b) they gave α,β-polyaspartic acid on partial hydrolysis, the structure of which was established by degradation described previously.

In connection with step I → II it is to be noted that Harada[16] recently suggested that aspartic anhydride is not a necessary intermediate in the free aspartic acid condensation and proposed an alternate hypothetical route involving the formation of α-aspartylaspartic acid, which had been proposed earlier by the present author.[12] Also with reference to steps IIa → III and III → IV, Harada explained polyimide formation from the anhydride through an amide intermediate by analogy, using the reaction of γ-butyrolactone with ammonia as an example. However, the formation of the polyimide (IV) through the intermediate amide (III) from the anhydride IIa or dipeptide IIb had already been reported.[5,6,12] These were apparently overlooked by Harada.

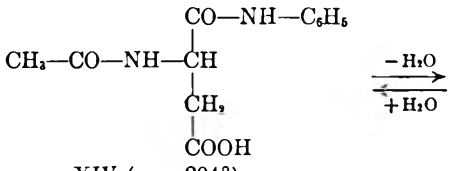
Analogous reactions which demonstrate the ease of formation of aminosuccinimide and whose probable mechanism is the same as that proposed, XII → XIII, were investigated. Both *N*-acetyl-DL-aspartic acid α-anilide (XIV), m.p. 204°, and *N*-acetyl-DL-aspartic acid β-anilide, (XV) m.p. 179°, were converted by acetic anhydride into the same imide (XVI), m.p. 162°. The higher melting anilide (XIV) was considered by Barker[17] to be the β-anilide and its dehydrated product to be the oxazolone derivative (XVII). In view of the fact that both α- and β-anilide yielded the same compound upon treatment with acetic anhydride, structure XVII must be discarded in favor of XVI as representing the dehydrated product. Moreover, the infrared spectrum of the compound XVI contained a double band at 5.60 and 5.86 μ characteristic of succinimides. Both α- and β-anilide were converted to the corresponding amides using the mixed anhydride method. The amide, m.p. 216°, obtained from the lower melting anilide (XV) when subjected to the Hofmann degradation yielded acetaldehyde while amide of the isomer, m.p. 229°, did not. Therefore the structures of the anilides must be those assigned above.

(14) Acetylation of the terminal amino groups is expected.

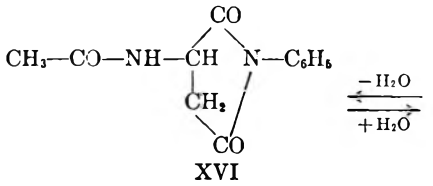
(15) We are indebted to Miss Florence D. Stefano for infrared spectra.

(16) K. Harada, *J. Org. Chem.*, **24**, 1662 (1959).

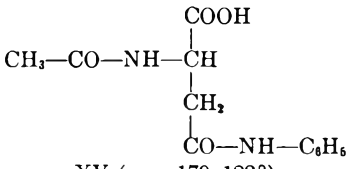
(17) C. C. Barker, *J. Chem. Soc.*, 453 (1953).



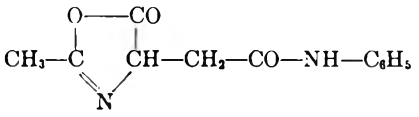
XIV (m.p. 204°)



XVI



XV (m.p. 179–182°)



XVII

Partial hydrolysis of the imide (XVI) provided a mixture of the α- and β-anilides in a ratio of about 1:8. The relative amounts of α- and β-anilide and peptides obtained from the imide derivative must be governed, at least in part, by the electrophilic character of the two carbonyl groups in the ring; attack at the α-carbonyl, corresponding to the stronger acid is favored. These experiments demonstrate that the α-amide bond in an aspartylpeptide or polypeptide can be converted to β-amide bond through the imide, and vice-versa. It appears that aspartyl peptides may give imide derivatives during manipulation elsewhere in the chain.

Ammonolysis of imide gave a mixture of asparagine and isoasparagine derivatives. The mixture contained 81% pure *N*-acetyl-isoasparagine, determined by direct isolation. It was estimated that at least 10% *N*-acetylasparagine anilide was present, from the amount of α, β-diaminopropionic acid produced in the Hofmann degradation of the mixture.

The formation of aminosuccinimide derivatives from esters of aspartic acid derivatives was reported recently by Sondheimer and Holley,[18] Battersby and Robinson.[19] Lockhart and Abraham[20] have observed a similar cyclization during the acid hydrolysis of Bacitracin A. The formation of glutarimide derivatives from acylated glutamyl peptides[21] represents an analogous reaction.

(18) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, 76, 2467 (1954).

(19) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).

(20) I. M. Lockhart and E. P. Abraham, *Biochem. J.*, 62, 645 (1956).

EXPERIMENTAL

*Preparation of anhydro-poly-*DL*-aspartic acid* (IV). (a) *By direct heating.* Thirty grams of finely powdered DL-aspartic acid was heated at 200° *in vacuo* (0.1 mm.) for 120 hr. The resulting tawny product was triturated with three 100-ml. portions of saturated sodium bicarbonate solution. The granular product was filtered, or separated by centrifugation, washed with water, 1% hydrochloric acid solution and with water until the filtrate was salt free. The yield of yellowish powder obtained after drying over phosphorus pentoxide at 100° and 15 mm. was 18 g. The sample for analysis was further dried at 180° for 200 hr.

Anal. Calcd. for $(C_4H_3O_2N)_\infty$: C, 49.5; H, 3.1; N, 14.4. Found: C, 48.6; H, 4.2; N, 14.6.

(b) *By heating in tetralin.* A suspension of 10 g. of dry finely powdered DL-aspartic acid in tetralin was refluxed for 100 hr. The water formed was removed by azeotropic distillation. After the crude product was filtered and washed with ether the polymer was further purified as described in (a). Drying was accomplished under vacuum by heating the material at 100° over phosphorus pentoxide for 12 hr.[22] The yield of light yellow anhydropolyaspartic acid was 7 g.

Anal. Calcd. for $(C_4H_3O_2N)_\infty$: C, 49.5; H, 3.1; N, 14.4. Found: C, 48.6; H, 3.7; N, 14.3.

Poly-α,β*-*DL*-aspartic acid* (III). After a solution of 9.7 g. (0.1 mole) of anhydropolyaspartic acid (IV) in 1500 ml. of 0.1*N* sodium hydroxide was allowed to stand at room temperature for 1 hr. the excess base was neutralized with 0.1*N* hydrochloric acid solution. The resulting solution was adjusted to *p*H 5.5 with 20% acetic acid and after heating to 40–50° a saturated solution of cupric acetate was added with stirring until precipitation occurred. Under these conditions the copper salt was granular and was easily collected and washed with water. The *copper salt of polyaspartic acid,* dried over phosphorus pentoxide, was obtained in 96% yield.

Anal. Calcd. for $(C_4H_4O_3N)_2Cu_\infty$: Cu, 21.8. Found: Cu, 21.5.

The copper salt from above (14.9 g.) was suspended in 50 ml. of water and hydrogen sulfide was added until a colorless solution was obtained. Following filtration the resulting solution was concentrated to 10 ml. under vacuum and dialyzed against ten 200-ml. portions of water over a period of 90 hr. At this point the material within the membrane did not give movable low molecular weight components upon paper chromatography. The solution within the dialyzing sac was concentrated to 5 ml., lyophilized and further dried under vacuum at 60°, providing 0.8 g. of polyaspartic acid (III) as a fluffy powder. This material was very soluble in water, slightly soluble in methanol and ethanol, soluble in warm dimethylformamide and gave a strong lilac biuret reaction. The R_f values for polyaspartic acid with a butanol–water–acetic acid solvent system was zero using ninhydrin as an indicator.

Anal. Calcd. for $(C_4H_3O_3N)_\infty$: C, 41.7; H, 4.4; N, 12.2. Found: C, 41.6; H, 4.8; N, 12.3.

Van Slyke amino-nitrogen determination of III using four different preparations gave molecular weights of 6100 (53 residues), 8200 (71 residues), 10,800 (93 residues) and 12,100 (105 residues).

Amino-nitrogen analysis (van Slyke) of aliquots taken at various times from a solution of anhydropolyaspartic acid (IV) in 0.1*N* sodium hydroxide (3 mg. of IV/ml. of base) gave molecular weights as 42,700, 18,680, and 12,740 at times of 0.0, 20.8, and 140 min. respectively. In another

(21) J. Kovacs, K. Medzihradszky, and V. Bruckner, *Naturwiss.*, 41, 45 (1954). *Acta Chim. Hung.*, 6, 183 (1955); V. Bruckner and J. Kovacs, *A. Magyar Tud. Akad. Kémiai Tud. Oszt. Közl.*, 3, 105 (1952).

(22) Anhydropolyaspartic acid prepared by Fox[9] is material reported to have approximately one molecule of water per residue after vacuum drying at 80°.

determination, after IV was allowed to stand at room temperature for 2 days in 0.05*N* sodium hydroxide (4 mg. of IV/ml. of base), the molecular weight was 11,670.

Preparation of anhydropoly-DL-aspartic acid (IV) *from poly-α,β-DL-aspartic acid.* Polyaspartic acid (III), (317 mg., molecular weight 12,100), was heated at 200° over phosphorus pentoxide for 5 days. The loss of water was quantitative assuming the loss of a molecule per residue of aspartic acid. As expected the material remaining was found to be insoluble in water and dilute sodium bicarbonate solution and was soluble in sodium hydroxide and warm saturated sodium bicarbonate solution.

Anal. Calcd. for $(C_4H_3O_2N)_\infty$: C, 49.5; H, 3.1; N, 14.4. Found: C, 48.8; H, 3.4; N, 14.1.

Poly-α,β-DL-aspartic acid methyl ester (VI). A solution of 0.97 g. of anhydropolyaspartic acid in 20 ml. of *N* sodium hydroxide was allowed to stand at room temperature for 1 hr. The excess sodium hydroxide was neutralized with 10 ml. of *N* hydrochloric acid and the solution was evaporated to dryness *in vacuo*. The sodium salt of the polyaspartic acid was treated with methanol-hydrochloric acid solution, prepared from 250 ml. of anhydrous methanol and 1.5 ml. of acetyl chloride. After shaking for 30 min. the clear solution was allowed to stand at room temperature for 70 hr. The solution was then filtered and evaporated to dryness *in vacuo*. The residue was triturated with 20 ml. of anhydrous methanol and the solvent was removed under reduced pressure. This manipulation was repeated five times. The hydrochloric acid free residue was treated with 30 ml. of methanol and after removal of the sodium chloride by filtration the solution was evaporated to dryness. The residue polyaspartic acid methyl ester was dissolved in 5 ml. of hot water, lyophilized, and dried at 56° for 2 hr. over phosphorus pentoxide. The yield of powdery solid, containing 3.1% ash and 19.4% methoxyl, was 950 mg. Further purification was achieved by dialyzing a solution of the polyester in 15 ml. of water against six 500-ml. portions of distilled water. The dialyzed solution provided 500 mg. of VI after lyophilization and desiccation over phosphorus pentoxide for 2 hr. at 56°.

Anal. Calcd. for $(C_5H_7O_3N)_\infty$: C, 46.5; H, 5.42; N, 10.85; CH_3O, 24.0. Found: C, 44.6; H, 5.6; N, 11.05; CH_3O, 21.7; ash, 0.2.

Poly-α,β-DL-aspartic acid amide (VIIa). The above polyaspartic acid methyl ester (CH_3O = 21.7) was treated with 60 ml. of liquid ammonia for 50 hr. in a sealed tube at room temperature. The polyaspartic acid amide obtained after evaporation of the ammonia was dissolved in 12.5 ml. of water and lyophilized. The yellow powdery polyamide gave a positive biuret test and paper chromatography indicated the absence of low molecular weight components (solvent, butanol: acetic acid: water 4:1:1; development, ninhydrin).

Anal. Calcd. for $(C_4H_6O_2N_2)_\infty$: C, 42.1; H, 5.27; N, 24.5. Found: C, 39.7; H, 5.8; N, 23.7; CH_3O, 0.33%; ash, 0.1%.

Ammonolysis of anhydropolyaspartic acid. A solution of 1.5 g. of anhydropolyaspartic acid in 40 ml. of liquid ammonia was allowed to stand at room temperature in a sealed tube for 70 hr. After 10–12 hr. the heavier yellow, viscous anhydropolyaspartic acid–ammonia phase was separated. The ammonia was evaporated and the resulting glass was allowed to stand over sulfuric acid in a vacuum desiccator. The material was then dissolved in 5 ml. of water and lyophilized. The yield of powdery yellow polyamide, containing 23.12% nitrogen, was 1 g. Five hundred milligrams of the polyamide was further purified by dialyzing against ten 100-ml. portions of water during a period of 90 hr. The dialyzed solution provided 250 mg. of amide (VIIa) after lyophilization. This polyamide gave a positive biuret reaction and a zero R_f value using butanol:acetic acid:water solvent system.

Anal. Calcd. for $(C_4H_6O_2N_2)_\infty$: C, 42.1; H, 5.27; N, 24.5. Found: C, 40.12; H, 6.06; N, 22.7; ash 0.2%.

Hofmann degradation of poly-α,β-DL-aspartic acid amides. (A) A sample of 114 mg. of polyaspartic acid polyamide (prepared from anhydropolyaspartic acid by ammonolysis) was dissolved in 2.5 ml. of 0.4*N* sodium hypochlorite solution prepared from 10% sodium hydroxide solution. After standing at room temperature for 2 hr. the reaction mixture was treated with 4 ml. of *N* hydrochloric acid. The distillate from the neutral solution was bubbled into 30 ml. of 2*N* hydrochloric acid solution saturated with 2,4-dinitrophenylhydrazine. Twenty-one milligrams of acetaldehyde-2,4-dinitrophenylhydrazone was obtained. An additional amount of acetaldehyde-2,4-dinitrophenylhydrazone was obtained by hydrolysis of the residual solution with 10 ml. of 1.5*N* hydrochloric acid followed by further distillation for 15 min. The total yield of 2,4-dinitrophenylhydrazone was 52 mg., m.p. 140–145°, which represents 23.2% of the aspartyl residues in polyaspartic acid. Control experiments indicated a 32% loss of acetaldehyde during the isolation procedure which raised the amount of β-aspartyl residues to 34.1%. The m.p. of the acetaldehyde-2,4-dinitrophenylhydrazone was 146–147° after crystallization from alcohol and this material gave no depression with an authentic sample.

The residue after distillation was further hydrolyzed by boiling with 10 ml. of concd. hydrochloric acid for 4 hr. This solution was evaporated *in vacuo* and the residue was treated with 2 ml. of concd. hydrochloric acid. After removal of the sodium chloride by filtration the solution was evaporated to dryness and the hydrochloric acid treatment was repeated twice. The residue was repeatedly dissolved in 2 ml. of water and evaporated to dryness. The hydrochloric acid-free, brown residue was dissolved in 2 ml. of water and added to a saturated aqueous solution of 500 mg. of flavianic acid. After 1 day the α,β-diaminopropionic acid diflavianate was collected by filtration and washed twice with cold water. After drying *in vacuo* at 100°, over phosphorus pentoxide, the yield was 165 mg. This represents 22.5% of the α-aspartyl residues, and 37.7%, after corrections for losses. The crude diflavianate, m.p. 222–223°, melted at 224° after crystallization from water.

Additional samples of polyaspartic acid polyamide prepared from anhydropolyaspartic acid, were submitted to Hofmann degradation and the corrected values for β-aspartyl residues were 40.8% and 30.6% and for α-aspartyl residues the values were 15.6% and 28.4%.

(B) Anhydropolyaspartic acid obtained from α,β-polyaspartic acid was also converted to polyamide and Hofmann degradation indicated this material contained 45% β- and 18% α-peptide bonds.

(C) Similarly Hofmann degradation of the polyamide obtained from α,β-polyaspartic acid polymethyl ester gave corrected values of 33% for the 6-peptide bonds and 26.4% for the α-peptide bonds.

α,β-Diaminopropionic acid diflavianate. A solution of 124 mg. of α,β-diaminopropionic acid hydrobromide[23] in 3 ml. of water was added to a saturated solution containing 1 g. of flavianic acid. After 40 hr. the diflavianate was filtered and washed with two 2-ml. portions of cold water. After drying *in vacuo* at 100° over phosphorus pentoxide the average yield was 266 mg., 60%, m.p. 223°. This material gave no depression on admixture with the diflavianate obtained from Hofmann degradation of the polyamide. An analytical sample of diflavianate was prepared by crystallization from water, m.p. 223°.

Anal. Calcd. for $C_{23}H_{20}O_{18}N_6S_2$: C, 37.7; H, 2.75; N, 11.47. Found: C, 37.41; H, 2.92; N, 11.34.

In order to determine the loss of acetaldehyde during the isolation procedure 10 ml. of a 0.503%. acetaldehyde water solution was treated with 10 ml. of 0.1*N* hydrochloric acid and after standing 15 min. the acetaldehyde was distilled into acidic dinitrophenylhydrazine reagent. The average yield of dinitrophenylhydrazone was 173 mg. (68%), m.p. 147°. The yield was unchanged when 1.5*N* hydrochloric acid was used.

Acetaldehyde was not obtained when anhydropolyaspartic acid or polyaspartic acid polymethyl ester was treated with

sodium hypochlorite solution under the conditions used for the Hofmann degradation of polyaspartic acid polyamide.

Pyrolysis of DL-*acetylaspartic acid.* DL-Acetylaspartic acid (6.176 g., m.p. 142–144°) was heated *in vacuo* at 200°. Acetic acid and water which were formed during the pyrolysis were collected in a Dry Ice trap. After 6 hr. the loss of weight was 2.365 g. (85.92%) and 2.503 g. (90.93%) after 11 hr.; the calculated loss for 1 molecule of acetic acid, and water is 2.752 g. The trap content contained 1.878 g. (88.21%) acetic acid. Infrared spectrum of the glassy polymeric material was identical with that of anhydropolyaspartic acid obtained from aspartic acid.

Anal. Calcd. for $(C_4H_3O_2N)_\infty$: N, 14.4. Found: 13.32.

Another sample of DL-acetylaspartic acid (175 mg.) was heated the same way at 148° for 4 hr. The loss of weight was 55 mg. (70.5%) and 44.5 mg. (65.4%) acetic acid was obtained from the Dry Ice trap.

DL-Acetylaspartic anhydride was recovered unchanged after heating at 148° for 4 hr.; however acetamide as a decomposition product was isolated when it was heated at 200°.

*Poly-α,β-*DL-*aspartic-(β-aminoethyl)amide* (VIIb). Anhydropolyaspartic acid (100 mg.), prepared from α,β-poly-DL-aspartic acid (molecular weight 12,100), was added in small portions to 5 ml. of anhydrous ethylenediamine. The yellow solution stood at room temperature for 20 hr. and was then refluxed for 1.5 hr. After the ethylendiamine had been distilled *in vacuo* the residue was dissolved in water and dialyzed against ten 200-ml. portions of water for 3 hr. The solution within the dialyzing sack was lyophilized; the residue was triturated with an alcohol-ether mixture, then with ether and dried under vacuum at 78° yielding 60 mg. of yellowish hygroscopic powder. The biological activity of this basic polypeptide derivative is under examination.

Anal. Calcd. for $(C_6H_{11}O_2N_3)_n$: N, 26.7. Found: N, 22.0.

The equivalent weight obtained by potentiometric titration using 0.01*N* hydrochloric acid was 167.5; calculated mean residue weight is 157.

L-*Aspartic anhydride hydrobromide.* Carbobenzoxy-L-aspartic anhydride (1.25 g., 0.005 mole) was treated with 7 g. of 15% hydrogen bromide in acetic acid at room temperature for 1 hr. Crystalline L-aspartic anhydride hydrobromide deposited. The precipitation was brought to completion by the addition of absolute ether at 0°. The precipitate was filtered with the exclusion of moisture then washed with a mixture of absolute ether and acetic anhydride, finally with absoluble ether and dried over phosphorus pentoxide. It was soluble in acetone and dimethylformamide; yield 0.85 g., 86.7%, m.p. 166–169° dec., $[\alpha]_D^{22}$ −21.26° (c 2.3, in dimethylformamide).

Anal. Calcd. for $C_4H_3O_3N{\cdot}HBr$: C, 24.49; H, 3.09; N, 7.14. Found: C, 24.36; H, 3.44; N, 7.11.

L-*Aspartic acid α- and β-anilide.* L-Aspartic anhydride hydrobromide was heated with an excess of aniline at 100° until a clear solution was obtained. The reaction mixture was treated with dilute sodium hydroxide solution, the aniline was extracted with ether and the slightly basic solution was acidified with dilute hydrochloric acid, to a *p*H 1.5, which precipitated the mixture of α-, and β-anilides. The yield was nearly quantitative. This mixture of anilides was dissolved in small amount of hot water and then five volumes of methanol was added to the filtered solution. After standing overnight at 2° nearly pure β-anilide separated. Recrystallization from water yielded needles of the β-anilide, m.p. 235–236° dec., $[\alpha]_D^{24}$ +33.4° (*c* 1.0, 0.1*N* hydrochloric acid). Several recrystallizations raised the m.p. to 241–242°; the mixed m.p. with a large amount of α-anilide was 220–230°.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.42; H, 5.84; N, 13.50.

The mother liquor from β-anilide was evaporated to one fifth of its volume and the α-anilide separated as needles. After recrystallization from water the m.p. was 212° dec. Mixtures of this product with large amount of β-anilide melted over a wide range at *ca.* 200°, $[\alpha]_D^{24}$ +62.5° (*c* 0.1, 0.1*N* hydrochloric acid).

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.34; H, 5.86; N, 13.20.

The α-anilide gave a brown color and the β-anilide a violet color when paper chromatograms were developed with ninhydrin.

L-*Isoasparagine.* A solution of L-aspartic anhydride hydrobromide in dimethylformamide was added to a large excess of liquid ammonia. The ammonia was allowed to evaporate and the remaining solvent was removed by evaporation at low pressure. The residue was treated with water and then evaporated *in vacuo;* the addition of water, and evaporation were repeated. Paper chromatogram of this crude material (phenol:water) indicated the presence of isoasparagine contaminated with a very small amount of asparagine. After recrystallization from alcohol-water chromatographically pure isoasparagine was obtained. A sample which was dried over phosphorus pentoxide *in vacuo* at 78° melted at 185–188° and had a specific rotation identical with that of isoasparagine prepared by Bergmann and Zervas.[24]

α-*Methyl-*L-*aspartate.* L-Aspartic anhydride hydrobromide was moistened with small amount of acetic anhydride and then dissolved in large excess of absolute methanol. The solvent was removed *in vacuo,* and the residue dissolved in water. An excess of silver oxide was added to the water solution to remove the bromide. The reaction mixture was filtered, the filtrate was treated with hydrogen sulfide, filtered again and evaporated to dryness. The recrystallization of the solid residue was from an alcohol-water solution, yielded L-aspartic acid α-methyl ester, m.p. 167°; $[\alpha]_D^{28}$ +37.60 (*c.* 0.5, water).

Anal. Calcd. for $C_5H_9O_4N$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.56; H, 6.21; N, 9.53.

A sample of the ester was dissolved in liquid ammonia and kept at room temperature in a sealed tube. Chromatographically pure isoasparagine was obtained which gave no depression on admixture with an authentic sample.

*Poly-α,β-*L-*aspartic acid.* L-Aspartic anhydride hydrobromide (980 mg.) was added to 2 ml. of dry pyridine (dried over barium oxide). Polymer began to form in addition to crystalline pyridine hydrobromide. After heating for an hour at 70° the pyridine was removed *in vacuo.* The residue was dissolved in 10 ml. of water and evaporated to dryness under reduced pressure. This procedure was repeated five times. The residue was dissolved in 5 ml. of water and dialyzed against five 50-ml. portions of 0.005*N* hydrochloric acid over a period of 10 hr. The dialysis was continued against twenty 1000-ml. portions of distilled water over a period of 144 hr. The solution within the dialyzing sack was lyophilized then dried at 58° *in vacuo* over phosphorus pentoxide; a total of 338 mg. (58.8%) α,β-poly-L-aspartic acid was obtained.

Anal. Calcd. for $C_4H_5O_3N$: C, 41.7; H, 4.4; N, 12.2. Found: C, 41.5; H, 4.5; N, 12.0.

Van Slyke amino-nitrogen determination gave a molecular weight of 7200 (61 residues).

Poly-α,β-L-aspartic acid (250 mg.) was hydrolyzed with 2.5 ml. of 6*N* hydrochloric acid in a sealed tube at 110° for 24 hr. The reaction mixture was evaporated to dryness, and the residue was neutralized with dilute sodium hydroxide to precipitate aspartic acid: $[\alpha]_D^{22}$ +25.4° (*c* 1, 2.5*N* hydrochloric acid).

*Methyl poly-α,β-*L-*aspartate.* This polyester was prepared according to the procedure described above. The dialyzed and lyophilized product was dried at 58° *in vacuo* over phosphorus pentoxide providing a polyester in which 93% of the carboxyl groups were esterified.

Anal. Calcd. for $(C_5H_7O_3N)_\infty$: C, 46.5; H, 5.42; N, 10.85; CH_3O, 24.0. Found: C, 45.0; H, 5.8; N, 11.0; CH_3O, 22.4; ash, 0.3.

*Poly-α,β-*L-*aspartic acid amide.* The polyester was con-

(23) E. Frankland, *J. Chem. Soc.,* 97, 1318 (1910).

(24) M. Bergmann and L. Zervas, *Ber.,* 65B, 1192 (1932).

verted into the polyamide using liquid ammonia at room temperature. Analysis of the dialyzed and dried product indicated that 92% of the carboxyl groups were converted into amide groups.

Anal. Calcd. for $(C_4H_5O_2N_2)_\infty$: C, 42.1; H, 5.3; N, 24.5. Found: C, 40.7; H, 5.9; N, 23.5; ash, 0.2.

Hofmann degradation of poly-α,β-L-aspartic acid amide. Two samples of polyamide prepared above was submitted to Hofmann degradation, and the corrected value for β-aspartyl residues was 40.2% and for α-aspartyl residues the value was 25.7%.

Preparation of anhydropolyaspartic acid from poly-α-L-aspartic acid. A. *By direct heating.* Poly-α-L-aspartic acid (90 mg.) was converted into anhydropolyaspartic acid according to the procedure described previously.

Anal. Calcd. for $(C_4H_3O_2N)_\infty$: N, 14.4. Found: N, 14.3; ash, 0.1. Anhydropolyaspartic acid was also prepared by heating poly-α-L-aspartic acid in tetralin and removing the water formed by azeotropic distillation.

B. *By heating with acetic anhydride.* To a solution of 50 mg. of poly-α-L-aspartic acid in 1 ml. of dimethylformamide was added 2 ml. of acetic anhydride. The mixture was heated at 100° for 3 hr. After half an hour heating anhydropolyaspartic acid slowly separated. Ten milliliters of ether was added to the cold reaction mixture and the precipitate was centrifuged, washed twice with 10 ml. of ether, and dried. Yield of tawny anhydropolyaspartic acid was 38 mg.

Anhydropolyaspartic acid obtained by procedure A or B is insoluble in sodium bicarbonate solution and gives a strong biuret reaction.

Anhydropolyaspartic acid (38 mg.) prepared by procedure B, was hydrolyzed with 10 ml. of 6*N* hydrochloric acid for 10 hr. The solution was evaporated *in vacuo* and the residue dissolved in 10 ml. of *N* hydrochloric acid; $[\alpha]_D^{20}$ +21.9° (c, 4.56, 5.64*N* hydrochloric acid).

Partial hydrolysis of anhydropolyaspartic acid obtained from poly-α-L-aspartic acid. Anhydropolyaspartic acid (75 mg.) prepared by direct heating of poly-α-L-aspartic acid was hydrolyzed according to the procedure described previously; yield was 38 mg. after drying at 65° for 6 hr.

Anal. Calcd. for $(C_4H_5NO_3)_\infty$: N, 12.2. Found: N, 11.8; ash, 1.1.

Hofmann degradation of poly-α,β-aspartic acid obtained from poly-α-L-aspartic acid. Poly-α,β-aspartic acid methyl ester was prepared from polyaspartic acid obtained above, by the procedure described previously. Purification was achieved by dialyzing the solution of the ester. After lyophilization and drying *in vacuo* at 65°, 86 mg. of product was obtained containing 21.2% methoxyl group (Calcd., OCH_3, 24%).

By a procedure similar to that described previously, poly-α,β-aspartic acid methyl ester was converted into poly-α,β-aspartic acid amide. This polyamide after purification by dialysis contained 21.4% nitrogen and 0.2% methoxyl group which indicated that about 74% of the carboxyl groups are amidated.

Hofmann degradation of this poly-α,β-aspartic acid amide gave corrected values of 44.8% for the β-peptide bonds and 40.8% for the α-peptide bonds.

N-Acetyl-DL-asparagine α-anilide. *N*-acetyl-DL-aspartic α-anilide (XIV) (5 g., 0.02 mole) was dissolved in a mixture of 250 ml. of dry dioxane, 50 ml. of dry chloroform, 77 ml. of dry dimethylformamide, 75 ml. of dry tetrahydrofuran and 2.8 ml. of triethylamine. The solution was cooled to 0° and 3 ml. (0.02 mole) of ethyl chloroformate was added dropwise with vigorous stirring. After 20 min., 5 ml. of concd. ammonium hydroxide was added. Stirring was continued for 7 hr. at room temperature and 200 ml. of water was added to reaction mixture. The *p*H was then adjusted to 7 by addition of hydrochloric acid. The solution was evaporated to dryness, the residue was suspended in a small amount of water, filtered, and the crystalline material was successively washed with sodium bicarbonate solution, dilute hydrochloric acid, and water. The residue, 3.5 g. (70%) melted at 223–225°. Recrystallization from alcohol then from water raised m.p. to 226–229° dec. This substance did not yield acetaldehyde when treated with sodium hypochlorite and then hydrolyzed with 5*N* hydrochloric acid.

Anal. Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.81; H, 6.06; N, 16.86. Found: C, 57.63; H, 6.30; N, 16.82.

N-Acetyl-DL-isoasparagine β-anilide. The preparation of *N*-acetyl-DL-isoasparagine β-anilide was similar to that of *N*-acetyl-DL-asparagine α-anilide. Yield was 44.4%, m.p. 208–210°. The compound was recrystallized from alcohol, m.p. 214–216°, mixed melting point with a sample of the compound obtained from DL-acetamidosuccinoyl anilide with ammonia gave no depression.

N-Acetyl-DL-isoasparagine β-anilide (53 mg.) was treated with 3.3 ml. of 0.48% sodium hypochlorite solution at 0° for 5 min. and allowed to stand at room temperature for 10 min. and finally raised to 80° for 15 min. The clear solution was acidified with 5 ml. of 5*N* hydrochloric acid and distilled into a saturated solution of 2,4-dinitrophenylhydrazine in 20 ml. 2*N* hydrochloric acid. Acetaldehyde 2,4-dinitrophenylhydrazone (10.6 mg.) was precipitated, melted at 147° alone, and admixed with authentic material.

N-Phenyl-DL-acetamidosuccinimide (XVI). *A. From N-Acetyl-DL-aspartic β-anilide.* *N*-Acetyl-DL-aspartic β-anilide (XV), m.p. 177–178°, (200 mg., 0.0008 mole) and 2 ml. of acetic anhydride were heated at 95° for 1 hr. The solvent was removed *in vacuo* and the crystallization of the resulting sirup was induced by the addition of benzene. The crystals were filtered and washed with benzene. The crude imide weighed 139 mg., (70.5%), m.p. 160–162°. Recrystallization from absolute ethyl alcohol raised the m.p. to 162–164°. The infrared spectrum contained a double band at 5.60 and 5.86 μ.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21. Found: C, 61.76; H, 5.13.

B. *From N-Acetyl-DL-aspartic α-anilide.* *N*-Acetyl-DL-aspartic α-anilide (XIV) (1.00 g., 0.004 mole, m.p. 203–204°) was converted into the imide as described above. This material was identical (mixed melting point and infrared) with the material obtained from *N*-acetyl-DL-aspartic β-anilide; yield 0.79 g., 85%.

Partial hydrolysis of N-phenyl-DL-acetamidosuccinimide. *N*-Phenyl-DL-acetamidosuccinimide (XVI) (5 g., 0.02 mole) was dissolved with stirring at 0° in 5 ml. 0.5*N* sodium hydroxide (0.025 mole). After 30 min. the clear solution was put into an icebox for an hour. The filtered solution was acidified with 3.4 ml. of 5.1*N* hydrochloric acid. The precipitate that appeared was filtered and washed with a small volume of water giving 4.7 g. (88%) mixture of *N*-acetyl-DL-aspartic anilides, m.p. 178–180°. Addition of 1 ml. of 5.1*N* hydrochloric acid to the filtrate gave a second crop of white needles, 0.45 g. (9%), m.p. 179–182°; total yield 5.15 g. (97%). This mixture of the α- and β-anilides was then treated with 30 ml. of hot alcohol and filtered. *N*-Acetyl-DL-aspartic β-anilide (750 mg., m.p. 177–178°) separated as white needles from the cooled filtrate. The undissolved material was then extracted with 80 ml. of hot dry acetone. From the filtrate a second crop of 980 mg. of β-anilide was obtained, m.p. 176–178°. The acetone-insoluble material, m.p. 191–192°, was treated again with 20 ml. of hot alcohol and filtered. The alcohol insoluble *N*-acetyl-DL-aspartic α-anilide (300 mg. 5.6%) melted at 202–204°. One crystallization of this material from water raised the melting point to 204–205°. This substance had no depression on mixed melting point with the sample prepared from *N*-acetyl-DL-aspartic anhydride and aniline; the infrared spectra showed identical bands at 5.9, 6.0, 6.1, 6.3, 6.6 μ. All the mother liquors were combined and evaporated to dryness. The residue was treated with 10 ml. of 5% sodium bicarbonate solution, filtered, and the filtrate was acidified with hydrochloric acid. The precipitate (610 mg.) which melted at 178–179° was mixed with the other crops and the combined mixture melted at 176–178°; total yield 2.34 g., 44%. This *N*-acetyl-DL-aspartic β-anilide had no depression on

mixed melting point with a sample prepared from *N*-acetyl-DL-aspartic anhydride and aniline. Infrared spectra showed identical bands at 5.8, 6.0, 6.25, 6.45, 6.7 μ.

Action of ammonia on N-phenylacetamidosuccinimide. *N*-Phenylacetamidosuccinimide (XVI) (0.75 g., 0.00324 mole) was treated with 4 ml. of concd. aqueous ammonia for 12 hr. The resulting solid was filtered and washed with water. Recrystallization from 80 ml. of alcohol gave 0.61 g. (81.2%) of *N*-acetyl-DL-aspartic α-amide β-anilide, m.p. 214–216°. This product gave no depression on admixture with a sample of the compound obtained from *N*-acetyl-DL-aspartic β-anilide by the mixed anhydride method. Hofmann degradation of 50 mg. of this substance with 3.5 ml. of 0.48% sodium hypochlorite solution gave 10 mg. of acetaldehyde-dinitrophenylhydrazone m.p. 147° alone and admixed with authentic material. A paper chromatographic analysis of the hydrolyzed mother liquor failed to indicate the presence of α,β-diaminopropionic acid. In second experiment 2.039 g. (0.0088 mole) of the imide (XVI) was treated with 30 ml. of concd., aqueous ammonia at room temperature for 16 hr. and finally evaporated to dryness. Sodium hypochlorite solution (23 ml., 30.83 mg. sodium hypochlorite per ml.) was added to the residue at 0° with stirring. The stirring was continued at room temperature for 40 min. and then at 80° for 15 min. The clear solution was acidified with 15 ml. of 6*N* hydrochloric acid and distilled into 2,4-dinitrophenylhydrazine hydrochloride solution until acetaldehyde 2,4-dinitrophenylhydrazone (87.6 mg.) was formed. The remaining solution was refluxed for 5 hr. and then evaporated to dryness. The residue was treated with 5 ml. of concd. hydrochloric acid. The undissolved sodium chloride was filtered off and the filtrate was evaporated and dried over sodium hydroxide. Semiquantitative paper chromatography (butanol, acetic acid, water; 4:1:5) indicated the presence of about 150 mg. of α,β-diaminopropionic acid (10%) in addition to aspartic acid.

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[CONTRIBUTION FROM THE NEUROSURGICAL SERVICE OF THE MASSACHUSETTS GENERAL HOSPITAL AND THE DEPARTMENT OF SURGERY OF HARVARD MEDICAL SCHOOL]

Synthesis of p-[Di(2-C14-chloroethyl)amino]-L-phenylalanine. A Study of Bis(β-hydroxyethylation) of Arylamines[1]

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A study is carried out of various methods for the bis(β-hydroxyethylation) of aryl amines with a view toward synthesizing C14-labelled nitrogen mustards of high specific activity. The label would be in the biologically-active portion of the molecule. The synthesis of p-[di(2-C14-chloroethyl)amino]-L-phenylalanine was carried out.

The assumption that the effectiveness of cytotoxic agents in the treatment of cancer is greatest if they preferentially concentrate in neoplastic tissue would seem to be a rational hypothesis. On this basis, the treatment of brain tumors by these compounds offers a distinct advantage over such therapy for neoplasms in other regions of the body. Tumors of the brain have a considerably altered permeability to many substances relative to adjacent normal areas[2] and consequently, it seems feasible to devise cancerocidal substances which, by cerebral perfusion, would concentrate selectively in the tumor. Work in this laboratory with aromatic boron compounds[3,4] has yielded information as to types of structures and substituents which aid or restrict the passage of organic compounds into the brain. Lipid solubility has been observed to be an important criterion in determining this rate and ease of penetration of the brain by such substances.[3,4]

Previous work with P^{32}-labelled triethylene thiophosphoramide (thio-TEPA) showed[5] that alkylating agent had a high lipid solubility and penetrated normal brain more readily and accumulated in higher concentration than in the corresponding neoplastic tissue. Based on our initial hypothesis, this would be considered an undesirable compound. On the other hand, p-[di(2-chloroethyl)amino]-L-phenylalanine had a low lipid solubility[6] as determined by the standard partitioning procedure.[3] From this consideration and the known high biological activity of melphalan,[7] the preparation of this compound with a C^{14}-label was undertaken to study its localization in brain and brain tumor as a function of its lipid solubility. The radioactive DL-compound with the label in the phenylalanine position of the molecule had been prepared[8] from carboxy-labelled benzoic acid. A synthesis incorporating C^{14} in high yield in the mustard group, however, would offer two important advantages: (1) a general method for preparing most nitrogen and sulfur mustards with a C^{14} label and (2) the label would be in the alkyl-

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ating portion of the molecule and consequently, its site of action could be determined. For this purpose, several different methods for synthesizing di(2-hydroxyethyl)arylamines were investigated. Such substances would be converted readily into the corresponding di(2-chloroethyl)- or di[2-(*p*-toluenesulfonoxy)ethyl]amines.

Several methods have been described in the literature relating to the formation of di(2-hydroxyethyl)arylamines. They are: (1) the condensation of the amine with ethylenechlorhydrin in refluxing aqueous suspensions of calcium carbonate,[9] (2) the reaction of a labile aromatic halogen with diethanolamine,[10] (3) reaction of an aromatic amine with ethylene oxide in sealed tubes with or without an inert solvent,[11,12] and (4) the acid-catalyzed reaction of ethylene oxide with the amine in an aqueous solution.[9,13–15] The first method even at these high temperatures resulted in mixtures of mono- and dialkylated amines. Consequently based on the alkylating agent the yield of the di(2-hydroxyethyl)amine was low. The second procedure required an aromatic halogen activated by electron-withdrawing groups on the aromatic nucleus. Such an approach is limited to certain specific compounds and is obviously not one of general utility. The third method required high temperatures and pressures together with long reaction times and even under these forcing conditions, appreciable amounts of the monohydroxyethylated product occurred. Only by use of the fourth procedure did the preparation of an optically-active amino acid containing a C^{14} label in the mustard group appear feasible as well as a general synthetic scheme. However, even in this approach, previous workers had added a large excess of ethylene oxide to an aqueous acetic acid solution of amine. Of course, such conditions could not be used if one were to attain a good utilization of ethylene-1,2-C^{14} oxide and consequently a high specific activity of the nitrogen mustard. This necessitated an investigation of several possible methods and conditions in which the hydroxyethylating agent is the limiting component.

For the purpose of the study, ethyl *p*-aminobenzoate was used as a model compound and attempts were made to oxyethylate the amine under a variety of conditions and with different agents. The only substances which were isolated and characterized were the unchanged starting material and ethyl *p*-[di(2-hydroxyethyl)amino]benzoate. The latter was recrystallized to a constant melting point, 71°–73°, and its yields with respect to the utilization of the hydroxyethylating agent are recorded in Table I. No attempts were made to determine the amount of the monohydroxyethylamino compound present in the reaction mixture since, for the purpose of this study, the bis compound was the only one of interest.

In one series of reactions, alkylation with ethylene oxide in different molar amounts was carried out in formic, acetic, and propionic acids with varying percentages of water. Hydroxyethylation of the model amine with ethylene oxide was also attempted under anhydrous conditions in ethanol, diethyleneglycol dimethyl ether, benzene, and dioxane with and without acidic catalysts such as boron trifluoride, acetic, and *p*-toluenesulfonic acids. Basic solvents and catalysts were avoided in this study since their utilization was negated by the need for preparing a nitrogen mustard containing an optically-active amino acid.

In addition to ethylene oxide as the hydroxyethylating agent, ethylene carbonate was also used. This reagent has proved useful in the hydroxyethylation of phenols,[16,17] thiophenols, alcohols, thiols, carboxylic acids and amines.[18] The possibility of using C^{14} labelled ethylene carbonate would offer two distinct advantages: (1) its ready synthesis from ethylene-1,2-C^{14} glycol and (2) a greater ease in handling relative to low boiling ethylene oxide. As with the reactions involving ethylene oxide, only ethyl *p*-[di(2-hydroxyethyl)-amino]benzoate was isolated. In Table I the yields and conditions are recorded.

A third approach to the synthesis of bis(2-hydroxyethyl)arylamines was the attempt at catalytic reductive alkylation of the corresponding nitro compound in the presence of glycolaldehyde. This method has been utilized in the synthesis of dialkylanilines from nitrobenzene in the presence of aliphatic aldehyde.[19] However, no examples with glycolaldehyde have been reported.

DISCUSSION

As seen from Table I, the more successful incorporations of ethylene oxide occurred when the reaction was carried out in glacial acetic and propionic acids. The addition of water appreciably decreased the utilization of the alkylating agent. However when formic acid was used as the solvent only ethyl *p*-formamidobenzoate could be isolated, indicating a more rapid rate for this step relative to hydroxyethylating. Kinetic studies on the ring

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TABLE I

HYDROXYETHYLATION OF ETHYL p-AMINOBENZOATE

Solvent and Conditions[a]	% Excess of the Oxyalkylating Agent	Yield of the Ethyl di(2-Hydroxyethyl)-aminobenzoate	% Utilization of the Oxyalkylating Agent
	ETHYLENE OXIDE		
50% Aqueous acetic acid	50	38	25
	100	53	27
	300	76	19
Glacial acetic acid	0	67	67
	50	80	53
	100	79	40
Propionic acid	0	46	46
	100	73	37
	ETHYLENE CARBONATE		
Ethylene carbonate 95°–100°	100	0	0
160°–163°	100	8	4
185°–190°	100	17	9
2-Methyl-2-butanol, 102°	100	0	0

[a] Where temperatures are not listed, the reaction was carried out at room temperature.

opening of substituted ethylene oxides in aqueous solutions showed[20,21] that the hydrolytic cleavage of the epoxide is acid-catalyzed readily forming the glycols. On this basis, competitive reactions between water and the aromatic amine for the conjugate acid of the oxide can be expected. In the concentrated acids this competition could obviously not occur. Swain[22] observed that the ring opening reaction of iodide ion with a substituted epoxide occurred appreciably faster in glacial acetic acid relative to aqueous solutions. This, in addition to the fact that the acetate ion did not compete with iodide for the oxide, would suggest that glacial acetic acid would be preferable to an aqueous acetic acid solution as a hydroxyethylating medium. The results in Table I confirm this.

All other attempts in various nonaqueous solvents with and without acid catalysts were singularly unsuccessful. This includes use of ethanol, diethyleneglycol dimethyl ether, diglyme–acetic acid (1:1), diglyme–boron trifluoride, boron trifluoride etherate, and several of these solvents with catalytic amounts of acetic or p-toluenesulfonic acids. Also the amine hydrochloride of ethyl p-aminobenzoate failed to yield more than insignificant amounts of ethyl p-[di(2-hydroxyethyl)-amino]benzoate when treated in benzene, dioxane, or a benzene-ethanol (1:1) mixture with ethylene oxide. Reductive alkylation with glycolaldehyde did not succeed and the reactions with ethylene carbonate, as shown in Table I, gave poor yields of the bis compound.

On this basis the preparation of p-[di(2-hydroxy-C^{14}ethyl)amino]-L-phenylalanine was carried out by incorporating C^{14}-labelled ethylene oxide into p-amino-*N*-phthaloyl-L-phenylalanine ethyl ester in glacial acetic acid. The dihydroxyethyl derivative of the amine was not isolated but converted directly into the nitrogen mustard. The yield of the product isolated, based on the amine, was 43% and calculated on the utilization of C^{14}-ethylene oxide was 41%.

This method for preparing C^{14}-labelled nitrogen mustards with the label in the alkylating portion of the molecule would appear to offer general utility. Use of such compounds will permit correlation of the incorporation of the agent in the tumor tissue with biological effectiveness of the antimitotic compound. At the same time, further information will be available as to whether lipid solubility of an organic compound is an important criterion in determining the penetration of brain and brain tumor. Partition studies of C^{14}-labelled melphalan in order to determine lipid solubility were carried out as previously described.[3] The coefficients for the aqueous/benzene and aqueous/chloroform partitions were 103 and 116 respectively. Values in this range indicate that such a compound has a very low lipid solubility and should be a desirable compound based on our initial hypothesis.

EXPERIMENTAL[23]

General. In all the hydroxyethylation experiments performed with ethyl p-aminobenzoate as a model compound, the only substances which were isolated and characterized were the starting material and the ethyl p-[di(2-hydroxyethyl)amino]benzoate. For reasons mentioned earlier, no attempts were made to determine the extent of formation of the monohydroxyethylated product.

Reactions with ethylene oxide. A. *In acetic acid and propionic acids.* In order to obtain comparable results 4.12 g. of ethyl p-aminobenzoate (0.025 mole) was dissolved in 25 ml. of the concentrated acid or in 50 ml. of the 50% aqueous acid. To the solution cooled to about 4° was added with shaking the chosen amount of ethylene oxide. After standing in a stoppered flask at room temperature for 24 hr., the reaction mixture was diluted with water to about 100 ml. and neutralized by saturation with solid sodium bicarbonate. The precipitates formed were collected, washed with small amounts of cold water, dried, and recrystallized from 70 ml. of benzene. The ethyl p-[di(2-hydroxyethyl)amino]benzoate (m.p., 71°–73°) was filtered after 24 hr. Yields and utilization of the oxyalkylating agent under different conditions are shown in Table I.

B. *In formic acid.* The conditions of the attempted hydroxyethylation and the processing of the reaction mixture using formic acid as a solvent were the same as described previously in section A. Even in the presence of a large excess of ethylene oxide, no ethyl p-[di(2-hydroxyethyl)-amino]benzoate was isolated. The only compound identified was ethyl p-formamidobenzoate which, after successive recrystallizations from benzene and water, melted at 150°–151°. The same compound was readily synthesized from the amine and formic acid in the absence of ethylene oxide.

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(23) All melting points are uncorrected.

Anal. Calcd. for $C_{10}H_{11}NO_3$: N, 7.25. Found: N, 7.31.

Reactions with ethylene carbonate. A stirred mixture of 17.6 g. (0.2 mole) of ethylene carbonate and 8.25 g. (0.05 mole) of ethyl *p*-aminobenzoate was heated for 6 hr. at temperatures ranging from 95° to 190° as shown in Table I. After being cooled to room temperature the solidified melt was extracted with three 50-ml. portions of warm benzene. The combined extracts were allowed to cool to room temperature and after 24 hr., the crystallized products were filtered, washed with a small volume of benzene, and dried.

In another experiment the same proportions of the reactants were refluxed in 40 ml. of 2-methyl-2-butanol for 6 hr. The solution was evaporated to an oily residue *in vacuo* and worked up as described above.

Attempts at reductive hydroxyethylations. A solution of 1.80 g. of glycolaldehyde (0.03 mole) in 15 ml. of 95% ethanol containing 1.95 g. of ethyl *p*-nitrobenzoate with 1.0 ml. of glacial acetic acid as a condensing agent was hydrogenated at room temperature in the presence of 0.1 g. of platinum oxide catalyst. In a similar manner the reaction was attempted only using 1.65 g. of ethyl *p*-aminobenzoate instead of the nitro compound with 120 mg. of anhydrous sodium acetate as the condensing substance. In both cases only ethyl *p*-aminobenzoate could be isolated.

Preparation of p-[di(2-chloro-C^{14}-ethyl)amino]-L-phenylalanine. *p*-Amino-*N*-phthaloyl-L-phenylalanine ethyl ester (I) prepared according to the method of Bergel and Stock[9] was used as starting material. All subsequent chemical transformations leading to the crude C^{14}-labelled phenylalanine mustard were performed in the same tared flask to avoid possible losses in material transfers.

In a 100-ml. one neck flask a solution of 3.073 g. (I) (9.1 mmoles m.p., 108°–109°) in 15 ml. of glacial acetic acid was maintained nearly at its freezing point. The long shaped ampule, containing 0.434 g. of ethylene-1,2-C^{14} oxide[24] (10 mmoles, specific activity 0.203 millicurie/mmole) in its bulb, was inserted in a one hole rubber stopper in such a position that the top of it would be submerged about 5 mm. under the surface of the acetic acid solution if the stopper were placed into the neck of the flask. Keeping the oxyalkylating agent in the bulb in solid state with liquid nitrogen the top of the ampule was opened. Then the ampule, by means of the stopper, was placed into position in the flask. The ethylene oxide was quantitatively transferred into the cold acetic acid solution by allowing the bulb to warm up slowly to room temperature. The ampule was rinsed by controlled warming and subsequent cooling of the flask. After completing this transfer, the solution was kept stoppered at room temperature for 18 hr. with occasional shaking. Then under the same conditions, the solution was treated with an additional 10 ml. of inactive ethylene oxide (0.2 mole) for 24 hr. in order to complete the hydroxyethylation. Finally, the mixture was concentrated and dried as a sirup in vacuo.

Without any further purification, the hydroxyethylated amine ester was dissolved in 50 ml. of benzene and the solution distilled until about 15 ml. of distillate was collected. The residual benzene solution was gently refluxed with 12 ml. of freshly distilled phosphorus oxychloride for 25 min. and then concentrated to an orange brown gum *in vacuo*. The gum was dissolved in 40 ml. of a benzene-ethanol mixture (1:1) and the solution evaporated to dryness at low temperatures. This procedure was repeated again to remove residual phosphorus oxychloride.

The residue obtained in the chlorination was dried over sodium hydroxide *in vacuo* and subsequently refluxed in 40 ml. of 6*N* hydrochloric acid for 3 hr. The hydrolysis mixture was cooled for several hours, filtered on a tared fritted glass funnel, and dried. The weight of the precipitated phthalic acid was determined in order to check the completeness of the hydrolysis. Then 100 ml. of a saturated sodium acetate solution was added in small portions to the cold filtrate. The precipitated crude L-phenylalanine mustard was collected, washed with a small amount of cold saturated sodium acetate solution, and dried, yielding 2.172 g. (73% based on the amount of I) of the impure compound. The crude substance was recrystallized from methanol by concentrating a 250 ml. alcoholic solution to a volume of 50 ml. 1.190 g. (43% yield) of *p*-[di(2-chloro-C^{14} ethyl)amino]-L-phenylalanine (m.p. 181°–184°, $[\alpha]_D^{25}$ +9.5 ± 0.6°, c, 0.93 g./100 ml. in 1*N* hydrochloric acid) having a specific activity of 0.213 mc./mmole was obtained. Based on the specific activity of the oxyalkylating agent, the utilization of ethylene-1,2-C^{14} oxide was 41%.

Distribution of C^{14}-labelled melphalan between aqueous and lipid phases. Approximately 2 mg. of the C^{14}-labelled L-phenylalanine mustard was partitioned between 50 ml. of an aqueous potassium dihydrogen phosphate buffer (*p*H 7.18) and 50 ml. of benzene or chloroform. After separation of the two phases, several 0.05 ml. quantities of each layer were plated and counted. Distribution coefficients found are 103 for aqueous/benzene and 116 for aqueous/chloroform.

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

Reaction of Ammonia with an Aromatic Aldehyde in Dilute Solution

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The reaction of *p*-dimethylaminobenzaldehyde, at very low concentrations, with ammonia in methanol is similar in many respects to its reaction with primary amines to yield Schiff bases. The rate of the reaction is determined at 0° and 25° and the energy and entropy of activation calculated. The formation of a simple imine is inferred.

The action of ammonia on aromatic aldehydes is generally complex and usually results in the formation of hydrobenzamides,[1] the kinetics of which were investigated by Dobler[2] as early as 1922. By passing gaseous hydrogen chloride into a solution of hydrobenzamide in ethanol, Busch[3] was able to

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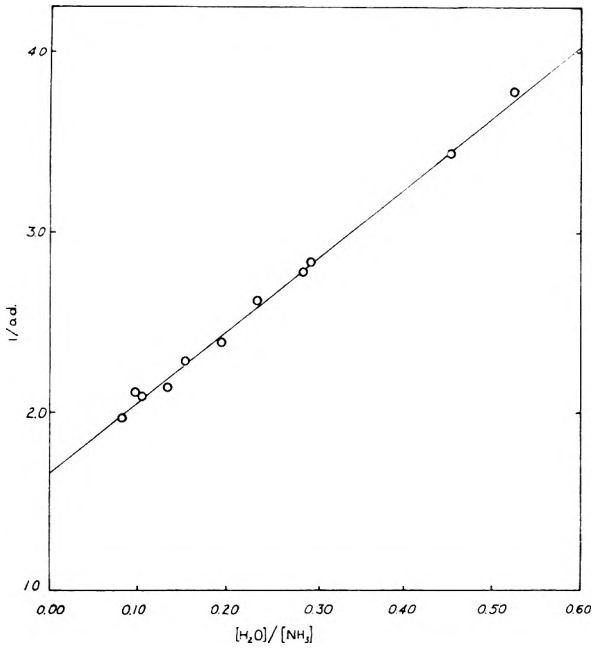


Fig. 1. Reciprocal of optical density of equilibrium mixture plotted against $[H_2O]/[NH_3]$

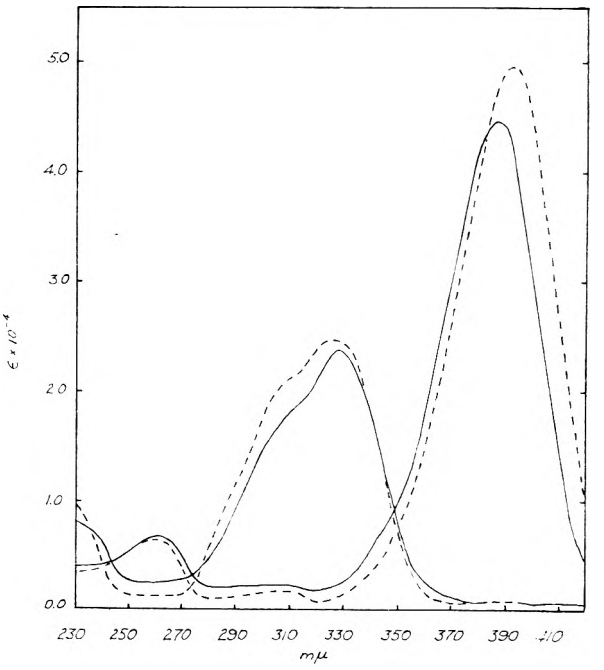


Fig. 2. Extinction coefficients *vs.* wave length for *p*-dimethylaminobenzylidenimine (solid line) and *N*-(*p*-dimethylaminobenzylidene)-*n*-butylamine (broken line). The curves with maxima near 330 mμ are for the pure compounds; those with maxima near 390 mμ are for the conjugate acids

isolate the hydrochloride of benzylidenimine. This unstable imine was itself isolated from a solution of hydrobenzamide in liquid ammonia[4] and also as a product of the catalytic reduction of benzonitrile under vacuum.[5] No rate studies have been made of the formation of this imine or its analogs.

p-Dimethylaminobenzaldehyde was chosen as a reactant because of its particular suitability for spectrophotometric study. Since the rate of formation of products resulting from the combination of two or more aldehyde molecules with ammonia should be very small at low aldehyde concentrations, it seemed possible that the reaction might go no farther than the formation of *p*-dimethylaminobenzylidenimine. We therefore sought evidence for the reaction,

$$ArCHO + NH_3 \rightleftharpoons ArCH{=}NH + H_2O \qquad (1)$$

by employing the spectrophotometric techniques already used for the investigation of Schiff base formation.[6]

EXPERIMENTAL

Materials. Eastman white label *p*-dimethylaminobenzaldehyde was recrystallized twice from water. A methanolic ammonia solution was prepared by passing ammonia, evolved from boiling ammonium hydroxide, through a drying column and into methanol. The solvent for the kinetic runs was reagent grade methanol.

Rate measurements. For each group of runs, a standard solution of *p*-dimethylaminobenzaldehyde was pipetted into 50-ml. volumetric flasks containing solutions of methanolic ammonia. After dilution to the mark, samples were periodically withdrawn and diluted 1:25 into a solution of hydrochloric acid in methanol. The acid served to convert the *p*-dimethylaminobenzylidenimine to its conjugate acid and the unchanged aldehyde to the acetal. The imine concentration was then determined from the ultraviolet absorption peak of the imine conjugate acid at 386 mμ, the absorption of the acetal being negligible at this wave length. The imine conjugate acid was found to undergo rapid decomposition which necessitated extrapolation of a plot of optical density *vs.* time in order to determine the value at the moment of dilution.

Determination of extinction coefficient and equilibrium constant. The extinction coefficient, ϵ, of the conjugate acid of the imine at 386 mμ and the equilibrium constant for the reaction 1 were obtained at 24.85° from equilibrium determinations of the water and ammonia concentrations and measurements of the optical density at the conjugate acid peak. The failure of the reaction to go 100% to completion at feasible ammonia concentrations precluded obtaining the extinction coefficient directly from the spectrum after complete reaction.

From the equilibrium expression, $K = [ArCH{=}NH][H_2O]/[ArCHO][NH_3]$, the following equation may be derived:

$$\frac{1}{(o.d.)} = \frac{25}{Ka\epsilon} \cdot \frac{[H_2O]}{[NH_3]} + \frac{25}{a\epsilon} \qquad (2)$$

where (o.d.) is the optical density of the acidified equilibrium mixture, K is the equilibrium constant, a is the initial aldehyde concentration, and 25 is the dilution factor. The intercept and slope of a plot of $1/(o.d.)$ against $[H_2O]/[NH_3]$ gave ϵ and K, as shown in Fig. 1, after correction for slightly unequal aldehyde concentrations. The values obtained were $\epsilon_{386} = 4.46 \times 10^4$ and $K_{25} = 0.416$.

The water concentrations in the reaction flasks were determined by titration with Karl Fischer reagent and the ammonia concentrations by titration with standard hydrochloric acid to a methyl red end point.

A solution of *N*-(*p*-dimethylaminobenzylidene)-*n*-butyla-

(4) H. H. Strain, *J. Am. Chem. Soc.*, **49**, 1558 (1927).

(5) R. Escourreau, *Bull. soc. chim. France*, **45**, 735 (1929).

(6)(a) T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953). (b) G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *J. Am. Chem. Soc.*, **80**, 1254 (1958).

TABLE I

[ArCHO] M	[NH_3] M	[H_2O] M	10^5k_2 L. Mole^{-1}. Sec^{-1}	K
		TEMPERATURE 24.85°		
3.31×10^{-4}	0.504	0.118	4.45	0.416[a]
	0.500	0.049	4.53	
	1.003	0.083	4.00	
	1.005	0.104	4.12	
6.63×10^{-4}	1.007	0.048	4.13	
3.38×10^{-4}	0.248	0.112	4.60[b]	
	0.494	0.096	4.58[b]	
	0.495	0.066	4.55[b]	
3.38×10^{-4}	0.250		4.17[c]	
	0.497		4.17[c]	
	0.992		3.78[c]	
3.29×10^{-4}	0.247		4.55	
	0.494		4.58	
	0.971		4.38	
			Av. 4.41 ± .18	
		TEMPERATURE 0.00°		
3.29×10^{-4}	0.247	0.078	0.862	0.644[d]
	0.486	0.120	0.825	0.688[d]
	0.978	0.179	0.767	0.720[d]
6.57×10^{-4}	0.479	0.170	0.830	0.693[d]
			Av. 0.831 ± .027	0.686 ± .021

[a] The equilibrium constant at 25° was determined graphically. [b] Measured in 0.0074M sodium methoxide. [c] Measured in 0.1374M sodium methoxide. These values were not considered in the average. [d] Obtained directly from spectrophotometric and titrimetric measurements of the different species present at equilibrium.

mine was prepared by allowing *p*-dimethylaminobenzaldehyde to react with excess *n*-butylamine in methanol.[6b]

RESULTS AND DISCUSSION

The reaction of *p*-dimethylaminobenzaldehyde with ammonia shows second-order kinetics as previously observed in the reaction of this and other aldehydes with amines.[6,7] The reaction was carried out in a large excess of ammonia and the resulting data treated as a pseudo first-order reversible reaction. The sum of the forward and reverse first-order rate constants, $k_1 + k_{-1}$, was easily obtained from the slope, λ, of the line resulting from the usual plot of such data. Since the water and ammonia concentrations remained essentially constant throughout the reaction, the forward and reverse second-order rate constants, k_2 and k_{-2}, may be expressed as $k_2 = k_1/[NH_3]$ and $k_{-2} = k_{-1}/[H_2O]$. Since $k_1 + k_{-1} = 2.303\,\lambda$ and $k_{-2}\,[H_2O] = k_2[H_2O]/K$, where K is the equilibrium constant, the expression for the forward second-order rate constant becomes

$$k_2 = \frac{2.303\lambda}{[NH_3] + [H_2O]/K} \qquad (3)$$

or

$$k_2 = \frac{2.303\lambda}{[NH_3] + [ArCHO]_e[NH_3]/[ArCH{=}NH]_e} \qquad (4)$$

The values of k_2 listed in Table I were calculated by means of equation 4. Each k_2 is the result of from five to eight kinetic measurements; the average deviation from the mean is 4% for the rate constants obtained at 25° and 3% for those obtained at 0°.

The results shown in Table II are typical. This was one of six runs to which sodium methoxide was added in order to rule out the possibility of base catalysis or catalysis by traces of acid.

TABLE II

REACTION OF *p*-DIMETHYLAMINOBENZALDEHYDE WITH AMMONIA AT 25°

($a = 3.38 \times 10^{-4}M$, [NH_3] = 0.495M, [$NaOCH_3$] = 0.0074M, [H_2O] = 0.0657M)

t, Sec.	10^4x, M	Log $\frac{x_0-x_e}{x-x_e}$	$10^5\,(k_1 + k_{-1})$, Sec.$^{-1}$	$10^5\,k_2$, L./Mole^{-1} Sec.$^{-1}$
2880	0.207	0.0358	2.86	4.48
6540	.462	.0842	2.96	4.64
10260	.675	.129	2.90	4.54
14100	.874	.176	2.88	4.51
17580	1.05	.222	2.91	4.55
23580	1.29	.297	2.90	4.53
27600	1.45	.349	2.91	4.56
∞	2.62	—	—	—

Average k_2: 4.54 × 10^{-5} l. mole^{-1} sec.$^{-1}$

The spectrum of the conjugate acid of the imine was obtained with a Beckman recording spectrophotometer. Although the conjugate acid decomposed at a measurable rate, a medium scanning speed reproduced the spectrum with an error of no more than 1%. In an acidified solution of the reaction mixture, the only absorbing species was the conjugate acid; in the basic solution, however, two absorbing species were present: the imine and the aldehyde. Since the concentration of the imine present was known from the ab-

(7) R. L. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284, 6425 (1956).

sorption of its conjugate acid, the absorption of the aldehyde remaining in the basic solution could be calculated and subtracted from the spectrum of the aldehyde-imine mixture, leaving the spectrum of the imine. The conclusion that the imine is obtained as the product of the reaction of ammonia with a very dilute aldehyde solution appears further borne out by the comparison of these spectra with the spectra of *N*-(*p*-dimethylaminobenzylidene)-*n*-butylamine and its conjugate acid as shown in Fig. 2.

The mean values of k_2 at 0° and 25°, given in Table I, were used in calculating the energy and entropy of activation for the reaction, with the result that E_a = 10.9 kcal./mole and $\Delta S^{\ddagger}$ = −43.7 e.u. The close correspondence with the values for the reaction of this same aldehyde with *n*-butylamine (8.0 kcal./mole and −41.9 e.u.)[6b] and *t*-butylamine (10.3 kcal./mole and −41.7 e.u.)[8] is one more indication that imine formation is taking place.

Acknowledgment. We are grateful for the support of the National Science Foundation.

CHARLOTTESVILLE, VA.

(8) Unpublished work by C. E. Bell, Jr., and T. I. Crowell.

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

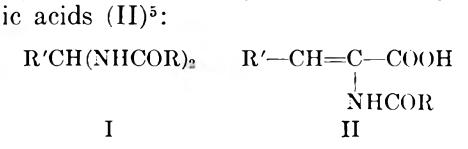
The Reactions of Carbobenzoxyamino Acid Amides with Carbonyl Compounds

URI ZEHAVI[2] AND DOV BEN-ISHAI

Received August 4, 1960

Amides of carbobenzoxyglycine, carbobenzoxyalanine, and carbobenzoxyphenylalanine have been found to react with carbonyl compounds (isobutyraldehyde, benzaldehyde, and cyclohexanone), in the presence of a sulfonic acid catalyst, to give two types of products: 1-carbobenzoxy-4-imidazolidinones (III) and carbobenzoxyamino acid 1-isobutenylamides (IV). The structure of the products is predetermined by the structure of the amide and that of the carbonyl component.

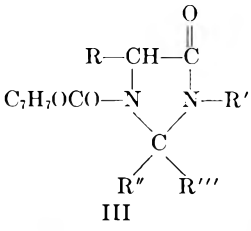
Primary amides and primary urethanes are known to react with aldehydes under acidic conditions to give alkylidenebisamides[3] (I) and alkylidenebisurethans (I,R = OR').[4] In the case of α-keto acids two types of reaction products are known, the bis-adduct (type I) and α-acylaminoacrylic acids (II)[5]:



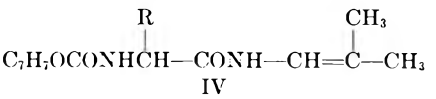
I II

If additional functional groups are present in the amide or urethan component, intramolecular cyclization may occur, leading to cyclic products. Thus, asparagine affords upon treatment with formaldehyde, 6-hydroxytetrahydropyrimidine-4-carboxylic acid,[6] and carbobenzoxyamino acids,[7] or β-hydroxyalkylcarbamates[8] afford on reacting with carbonyl compounds oxazolidine derivatives.

In the present paper the reactions of primary and secondary carbobenzoxyamino acid amides with isobutyraldehyde, benzaldehyde, and cyclohexanone are described. Refluxing benzene solutions of carbobenzoxyglycineamide, carbobenzoxyalanineamide, and carbobenzoxyphenylalanineamide with benzaldehyde or cyclohexanone in the presence of a sulfonic acid catalyst affords crystalline 1-carbobenzoxy-4-imidazolidinone (III. R' = H) under identical experimental conditions the same primary amides react with isobutyraldehyde to give open chain products of the ene-amide type, *i.e.* carbobenzoxyamino acid 1-isobutenylamides (IV):



III



IV

Carbobenzoxyamino acid methylamides (secondary amides) do not react with cyclohexanone and their reactions with isobutyraldehyde and benzaldehyde are much slower than those of the corresponding primary amides. With the methylamides only 1-carbobenzoxy-4-imidazolidinones (III. R' = CH_3) were obtained even with isobutyraldehyde.

The structures assigned to the reaction products are based upon their infrared spectra and chemical behavior. The carbobenzoxyimidazolidinones lack the NH absorptions of the starting materials in the 1500–1600 cm.$^{-1}$ region (cyclic lactams). The two

(1) Presented at the 26th meeting of the Israel Chemical Society, Jerusalem, April, 1960.

(2) From a thesis submitted for the M.Sc. degree by U. Zehavi, Israel Institute of Technology, Haifa, 1960.

(3) W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933).

(4) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

(5) A. E. Martel and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941).

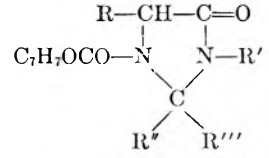
(6) D. French and J. T. Edsall, *Advances in Protein Chemistry*, **2**, 306 (1945).

(7) D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 5736 (1957). F. Micheel and W. Meckstroth, *Ber.*, **92**, 1675 (1959).

(8) M. Lamin and D. Ben-Ishai, *J. Org. Chem.*, submitted for publication.

TABLE I

CARBOBENZOXYIMIDAZOLIDINONES

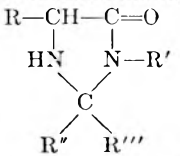


R	R′	R″	R‴	Time of Reaction, Hr.	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	H	H	C_6H_5	1	81	172[d]	$C_{17}H_{16}O_3N_2$	68.90	68.84	5.44	5.46	9.45	9.60
H	H		$(CH_2)_5$	3.5	69	222[d]	$C_{16}H_{20}O_3N_2$	66.64	66.44	6.99	7.05	9.72	9.89
H	CH_3	H	$(CH_3)_2CH$	8.0	64	89[d]	$C_{17}H_{20}O_3N_2$	65.19	65.01	7.30	7.21	10.14	10.33
H	CH_3	H	C_6H_5	48.0	68	116[d]	$C_{18}H_{18}O_3N_2$	69.66	69.56	5.85	5.87	9.03	9.21
CH_3[a]	H		$(CH_2)_5$	2.0	70	236[c]	$C_{17}H_{22}O_3N_2$	67.52	67.49	7.33	7.18	9.25	9.48
C_7H_7[a]	H	H	C_6H_5		22[e]	186[e]	$C_{24}H_{22}O_3N_2$	74.59	74.45	5.74	5.72	7.25	7.28
C_7H_7[a]	H	H	C_6H_5	4.5	34[c]	84[f]	$C_{27}H_{26}O_3N_2$[h]	76.15	75.93	5.88	5.90	6.10	6.38
C_7H_7[a]	H		$(CH_2)_5$	12.0	80	164[f]	$C_{23}H_{26}O_3N_2$	72.99	73.13	6.93	6.95	7.40	7.67
C_7H_7[b]	H		$(CH_2)_5$	11.0	71	146[g]	$C_{23}H_{26}O_3N_2$	72.99	73.03	6.93	6.75	7.40	7.52

[a] *d,l*-Isomer. [b] *l*-Isomer, $[\alpha]_D^{25}$ +169° (*c*, 0.5 in chloroform). [c] One of two isomers obtained in the same reaction. [d] Crystallized from ethyl acetate–hexane. [e] Crystallized from benzene. [f] Crystallized from benzene-methylcyclohexane. [g] Crystallized from methylcyclohexane. [h] This isomer crystallized with benzene in a 2:1 ratio.

TABLE II

4-IMIDAZOLIDINONES



R	R′	R″	R‴	Yield, %	M.P.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
H	H	H	C_6H_5	61	105[d]	$C_9H_{10}ON_2$	66.65	66.40	6.22	6.21	17.27	17.10		
H	H		$(CH_2)_5$	84	121[d]	$C_8H_{14}ON_2$	62.30	62.16	9.15	9.00	18.17	17.99		
H	CH_3	H	$(CH_3)_2CH$	74	[c]	$C_7H_{14}ON_2$	59.12	58.87	9.92	9.72	19.70	19.90		
H	CH_3	H	C_6H_5	73	159–162	$C_{10}H_{13}ON_2Cl$					13.18	12.94	16.69	16.56
CH_3[a]	H		$(CH_2)_5$	76	103[e]	$C_9H_{16}ON_2$	64.25	64.42	9.59	9.73	16.65	16.73		
CH_3[a]	CH_3	H	$(CH_3)_2CH$	60	157–160	$C_8H_{17}ON_2Cl$					14.55	14.42	18.44	18.62
C_7H_7[a]	H		$(CH_2)_5$	77	113[e]	$C_{15}H_{20}ON_2$	73.73	73.61	8.25	8.44	11.47	11.35		
C_7H_7[b]	H		$(CH_2)_5$	85	102[f]	$C_{15}H_{20}ON_2$	73.73	73.78	8.25	8.18	11.47	11.16		
C_7H_7[a]	CH_3	H	$(CH_3)_2CH$	45	142–143	$C_{14}H_{21}ON_2Br$					8.95	8.79	25.56	25.36

[a] *d,l*-Isomer. [b] *l*-Isomer, $[\alpha]_D^{25}$ −63° (*c*, 0.5 in chloroform.) [c] B.p. 66°/0.01 mm. [d] Crystallized from benzene-hexane. [e] Crystallized from ethyl acetate–hexane. [f] Crystallized from methylcyclohexane.

carbonyl absorptions of the carbobenzoxyamino acid amides at 1675–1690 (amide) and 1710–1720 cm.$^{-1}$ (carbamate)[9] merge to one carbonyl absorption at 1700–1715 cm.$^{-1}$ in the carbobenzoxyimidazolidinones. These displacements are due to a rise in the amide carbonyl frequency due to incorporation into a five-membered lactam ring and to a lowering of the carbamate carbonyl frequency, the secondary carbamate having been converted into a tertiary carbamate.[9] The 1-carbobenzoxy-3-methyl-4-imidazolidinones (III. R′ = CH_3) lack NH absorptions both in the 3420–3460 cm.$^{-1}$ and 1500–1530 cm.$^{-1}$ regions. The imidazolidinones show a strong band in the C—H bonding region (1400–1420 cm.$^{-1}$) which is either absent or very weak in the starting materials.

The carbobenzoxyimidazolidinones (Table I) were converted by catalytic hydrogenation into the free 4-imidazolidinones (Table II). These compounds show carbonyl absorptions at 1690–1710 cm.$^{-1}$, a strong band at 1400–1420 cm.$^{-1}$ and lack the NH absorption band in the 1500–1600 cm.$^{-1}$ region.

The 4-imidazolidinones reported in the literature were prepared by desulfurization of thiohydantoins[10] or by the condensation of α-aminonitriles with carbonyl compounds.[11]

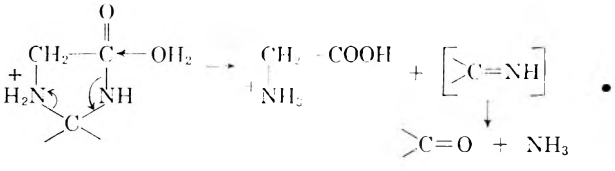
The carbobenzoxyamino acid 1-isobutenylamides (IV) show two carbonyl absorptions at 1670–1690 cm.$^{-1}$ (amide) and 1710–1725 cm.$^{-1}$ (carbamate) and NH absorptions at 3300–3460 cm.$^{-1}$ and 1500–1550 cm.$^{-1}$ They lack the strong band in the 1400 cm.$^{-1}$ region which is present in all the imidazolidinone derivatives. The C=C bands could not be observed probably because of masking by the amide carbonyl absorptions.

Carbobenzoxyglycine 1-isobutenylamide (IV. R = H) decolorizes bromine solution and gives a positive dinitrophenylhydrazone test for isobutyraldehyde. On catalytic hydrogenation it affords glycine isobutylamide which was found to be, after recarbobenzoxylation, identical with carbobenzoxyglycine isobutylamide. Glycine 1-isobutenylamide was obtained by removing the carbobenzoxy group with hydrogen bromide in acetic acid.[12] The hydrobromide could be recarbobenzoxylated to afford the starting materials.

In order to obtain further information concerning formation of the ene-amides, the reaction of phenylacetamide with isobutyraldehyde, benzaldehyde, and cyclohexanone was also investigated. Under the same experimental conditions (boiling benzene) phenylacetamide reacts with benzaldehyde to give benzylidenebisphenylacetamide. Isobutyraldehyde affords in addition to the bis-adduct also *N*-(1-isobutenyl)phenylacetamide in about 50% yield. The latter compound shows NH absorptions at 3410 cm.$^{-1}$ and 1510 cm.$^{-1}$ and a carbonyl absorption at 1660 cm.$^{-1}$ It absorbs one mole of hydrogen and is converted into *N*-isobutylphenylacetamide. Phenylacetamide reacts with cyclohexanone in boiling toluene to give exclusively *N*-(1-cyclohexenyl)phenylacetamide. The properties of these ene-amides are similar to those described above, they decolorize bromine solution and give a positive dinitrophenylhydrazone test for the corresponding carbonyl component.

Carbobenzoxy-*d,l*-phenylalanineamide, on treatment with benzaldehyde, affords two products which can be separated by fractional crystallization. One product melts at 186° and the other at 84°. Their infrared spectra, which are almost identical, suggest that they are isomeric 1-carbobenzoxy-4-imidazolidinones. The lower melting isomer crystallize with benzene in a 2:1 ratio. It loses the solvent upon drying above its melting point and the melt, which solidifies on cooling (m.p. 55–58°), analyses well for the imidazolidinone derivative. A mixed melting point of these isomers is depressed.

The acid hydrolysis of the free imidazolidinones was studied qualitatively and compared with the rate of hydrolysis of α-benzylideneaminoacetamide,[11] glycine 1-isobutenylamide, and glycineamide itself. The hydrolysis was followed by paper chromatography. In 5*N* hydrochloric acid at room temperature both α-benzylideneaminoacetamide and glycine 1-isobutenylamide hydrolyze completely after twelve hours to give glycineamide and glycine. Under the same conditions glycineamide is partly hydrolyzed to glycine. 2-Phenyl-4-imidazolidinone and 2-spirocyclohexano-4-imidazolidinone are much more stable to hydrolysis. After 100 hours spots of the unhydrolyzed imidazolidinones could be observed on the chromatogram. The only hydrolytic product detected was glycine; no glycineamide was observed at any time during the hydrolysis. 2-(*p*-Nitrophenyl)-4-imidazolidinone hydrolyzes to give glycine much faster (twenty-four hours) than 2-phenyl-4-imidazolidinone or glycineamide itself. These observations suggest that under acidic conditions (5*N* hydrochloric acid) a *direct* hydrolysis of the imidazolidinone to the amino acid, without passing through the amino acid amide, occurs:



(9) S. Pinchas and D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 4099 (1957).

(10) J. T. Eduards and E. F. Matlem, *Chemistry and Industry*, 193 (1954), K. Freter, J. Rabinowitz, and B. Witkop, *Ann.*, **607**, 174 (1957).

(11) A. C. Davis and A. L. Levy, *J. Chem. Soc.*, 3479 (1951).

(12) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

TABLE III

CARBOBENZOXYAMINO ACID AMINES

$$C_7H_7OCONHCHCONHR'$$
(with R on the CH)

R	R'	M.P.	Yield, %	Formula	Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
H	CH_3	105	47	$C_{11}H_{14}O_3N$	59.45	59.63	6.35	6.16	12.60	12.80
CH_3[a]	H	123	51	$C_{11}H_{14}O_3N$	59.45	59.69	6.35	6.57	12.60	12.45
CH_3[a]	CH_3	114	48	$C_{12}H_{16}O_3N$	61.00	60.95	6.83	6.64	11.86	11.79
C_7H_7[a]	H	183	48	$C_{17}H_{18}O_3N$	68.44	68.28	6.08	5.95	9.39	9.33
C_7H_7[a]	CH_3	152	53	$C_{18}H_{20}O_3N$	69.21	69.27	6.45	6.43	8.97	8.95
C_7H_7[b]	H	167	71							

[a] *d,l*-Isomer. [b] *l*-Isomer, Ref. 7, m.p. 167°.

In neutral solutions (*p*H = 7) at room temperature, 2-phenyl- and 2-spirocyclohexano-4-imidazolidinones hydrolyze slowly to give glycineamide. In boiling water hydrolysis to glycineamide of the above imidazolidinones is completed within twenty minutes.

EXPERIMENTAL[13]

Carbobenzoxyamino acid amides. A solution of carbobenzoxyamino acid (0.25 mole), methanol (30 ml.), and concentrated sulfuric acid (2.5 ml.) in 1,2-dichloroethane was refluxed for 12 hr. according to the procedure of Clinton and Laskowski.[14] The oily methyl ester obtained was dissolved in 250 ml. of ethanol saturated with ammonia[15] or methylamine and the solution was left at room temperature for 5 days. The ethanol was removed *in vacuo* and the solid amide obtained was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and 5% hydrochloric acid and dried over sodium sulfate. The carbobenzoxyamino acid amide crystallized on concentration of the ethyl acetate solution (Table III).

Reaction of carbobenzoxyamino acid amides with carbonyl compounds. General procedure. A solution of the amide (0.025 mole), carbonyl compound (0.050 mole), and β-naphthalene sulfonic acid (0.25 g.) in benzene (200 ml.) was refluxed and the water was distilled and collected in a water separator as soon as it was formed. The reaction time is recorded in Table I. Ethyl acetate (200 ml.) was added and the combined benzene–ethyl acetate solution was washed with 10% aqueous sodium carbonate solution and water and dried over sodium sulfate. The product obtained after the removal of the organic solvent *in vacuo* was crystallized from a suitable solvent (Table I). The oily products which did not crystallize were hydrogenated catalytically without further purification and were characterized as the imidazolidinone hydrochlorides (Table II).

1-Carbobenzoxy-2-(p-nitrophenyl)-4-imidazolidinone. A mixture of carbobenzoxy-glycineamide (5.2 g., 0.025 mole), *p*-nitrobenzaldehyde (3.78 g., 0.025 mole), and β-naphthalenesulfonic acid (0.2 g.) in benzene (200 ml.) was refluxed for 2 hr. as described above (general procedure). After cooling to room temperature the solid material was filtered and crystallized from methanol–ethyl acetate. The yield was 4.14 g. (48%), m.p. 222°.

Anal. Calcd. for $C_{17}H_{15}O_5N_3$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.69; H, 4.33; N, 12.20.

1-Carbobenzoxy-2-phenyl-5-benzyl-4-imidazolidinone. A solution of carbobenzoxy-*d,l*-phenylalanine (3.75 g., 0.0125 mole), benzaldehyde (2.5 ml.) and β-naphthalene sulfonic acid (0.1 g.) in benzene (100 ml.) was refluxed as described above (general procedure). The residue obtained after removal of the solvent was crystallized from benzene-methylcyclohexane to give a product (1.4 g.) which melted at 170–174°. The addition of hexane to the mother liquor precipitated a second product (2.3 g.) which melted at 79–81°. The melting points of the products were raised to 186° and 84°, respectively, after recrystallization (Table I) and a mixed melting point was depressed. The infrared spectra of the two products which were almost identical showed carbonyl absorptions at 1710–1720 cm.$^{-1}$, NH absorptions at 3420 cm.$^{-1}$, and a strong band at 1400 cm.$^{-1}$ They lack the NH absorptions of the starting material in the 1500–1600 cm.$^{-1}$ region. The lower melting isomer crystallizes with benzene in a 2:1 ratio. It loses 10% of its weight on drying at 140°/0.01 mm. for 3 hr. and the melt which solidifies on cooling (m.p. 55–58°) has an analysis which agrees well for 1-carbobenzoxy-2-phenyl-5-benzyl-4-imidazolidinones.

Anal. Calcd. for $C_{24}H_{22}O_3N_2$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.29; H, 5.66; N, 7.35.

4-Imidazolidinones. 1-Carbobenzoxy-4-imidazolidinone (0.01 mole) was hydrogenated catalytically in ethanol (100 ml.) under 4 atm. pressure and in the presence of 5% palladized charcoal (0.1 g.). After 5 hr. the solution was filtered from the catalyst and evaporated *in vacuo* to dryness. The solid 4-imidazolidinone thus obtained was crystallized from a suitable solvent (Table II). The oily imidazolidinones were dissolved in dry ether and the solution was saturated with dry hydrogen chloride. The hydrochlorides were filtered and crystallized from absolute ethanol and dry ether (Table II).

2-p-Nitrophenyl-4-imidazolidinone hydrobromide. 1-Carbobenzoxy-2-*p*-nitrophenyl-4-imidazolidinone (1.7 g.) was dissolved in a solution of hydrogen bromide in glacial acetic acid (25%; 4 g.). After 1 hr., dry ether (50 ml.) was added and the hygroscopic hydrobromide which precipitated was washed three times with 50-ml. portions of dry ether. The hydrobromide was then suspended in ethyl acetate (100 ml.) and anhydrous potassium carbonate (3 g.) was added. After stirring for 3 hr. the solution was filtered and evaporated to dryness *in vacuo*. The free imidazolidinone thus obtained was crystallized from ethyl acetate–hexane. The yield was 0.34 g. (33%), m.p. 127°.

Anal. Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.40; H, 4.53; N, 20.29.

Carbobenzoxyglycine-1-isobutenylamide. A mixture of carbobenzoxyglycineamide (0.025 mole), isobutyraldehyde (0.050 mole), and β-naphthalenesulfonic acid in benzene (200 ml.) was refluxed for 2 hr. as described above (general procedure). The product obtained after the evaporation of the solvent *in vacuo* was crystallized from ethyl acetate. The yield was 73%; m.p. 136°.

(13) Melting points were taken on a Fisher-Johns block and are uncorrected.

(14) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(15) S. W. Fox and H. Wax, *J. Am. Chem. Soc.*, **73**, 2936 (1951).

Anal. Calcd. for $C_{14}H_{18}O_3N_2$: C, 64.10; H, 6.92; N, 10.68; mol. wt., 262. Found: C, 63.91; H, 6.71; N, 10.75; mol. wt., 242.

Carbobenzoxyglycineisobutylamide. Carbobenzoxyglycine-1-isobutenylamide (0.15 g.) was catalytically hydrogenated in ethanol (50 ml.) under 4 atm. pressure in the presence of 5% palladized charcoal (0.1 g.). After 4 hr. the solution was filtered from the catalyst and evaporated *in vacuo* to dryness. The glycine isobutylamide thus obtained was dissolved in 10% sodium bicarbonate solution (10 ml.) and carbobenzoxylated in an ice water bath with carbobenzoxy chloride (0.5 g.). The product was extracted with ether (100 ml.) and the ethereal solution was washed with water and 10% hydrochloric acid and dried over sodium sulfate. The residue obtained after the evaporation of the ether was crystallized from ethyl acetate–hexane. The yield was 0.42 g. (64%), m.p. 71°.

Anal. Calcd. for $C_{14}H_{20}O_3N_2$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.78; H, 7.72; N, 10.49.

This compound was found to be identical, through infrared spectra and mixed melting point, with carbobenzoxyglycineisobutylamide prepared from carbobenzoxyglycine and isobutylamide in the presence of dicyclohexylcarbodiimide.[16]

Glycine 1-isobutenylamide hydrobromide. Carbobenzoxyglycine-1-isobutenylamide (1.3 g.) was dissolved in a 25% solution of hydrogen bromide in glacial acetic acid (4.0 g.).[12] After 30 min. dry ether (50 ml.) was added and the solid precipitate was filtered and washed with dry ether. The hydrobromide melted at 173–175° after crystallization from absolute ethanol and dry ether; yield 1.0 g. (96%).

Anal. Calcd. for $C_6H_{13}ON_2Br$: N, 13.41; Br, 38.22. Found: N, 13.21; Br, 38.10.

Carbobenzoxy-d,l-alanine 1-isobutenylamide. A mixture of carbobenzoxy-*d,l*-alanineamide (0.025 mole), isobutyraldehyde (0.050 mole), and β-naphthalenesulfonic acid (0.2 g.) in benzene (200 ml.) was refluxed for 1 hr. as described above (general procedure). The product obtained after the evaporation of the solvent *in vacuo* was crystallized from ethyl acetate–hexane and melted at 113°; yield 80%.

Anal. Calcd. for $C_{15}H_{20}O_3N_2$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.36; H, 7.11; N, 9.95.

Carbobenzoxy-d,l-phenylalanine 1-isobutenylamide. A mixture of carbobenzoxy-*d,l*-phenylalanineamide (0.025 mole), isobutyraldehyde (0.050 mole), and β-naphthalenesulfonic acid (0.2 g.) in benzene (200 ml.) was refluxed for 1 hr. as described above (general procedure). The product melted at 127° after crystallization from benzene; yield 93%.

Anal. Calcd. for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.56; H, 6.67; N, 8.07.

Reaction of phenylacetamide with isobutyraldehyde. A mixture of phenylacetamide (3.4 g., 0.025 mole), isobutyraldehyde (2.8 g., 0.050 mole), and β-naphthalenesulfonic acid (0.25 g.) in benzene (250 ml.) was refluxed for 1.5 hr. as described above (general procedure). The solvent was removed *in vacuo* and the residue was chromatographed over 100 g. of basic aluminum oxide (Merck). The *N*-(1-isobutenyl)phenylacetamide was eluted first with benzene-chloroform (1:2) followed by isobutylenebisphenylacetamide. The *N*-(1-isobutenyl)phenylacetamide melted at 102° after crystallization from ethyl acetate–hexane; yield 2.54 g. (52%).

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.35; H, 7.96; N, 7.37.

The isobutylenebisphenylacetamide melted at 223° after crystallization from aqueous ethanol; yield 1.80 g. (43%).

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.21; H, 7.24; N, 8.62.

N-Isobutylphenylacetamide. *N*-(1-Isobutenyl)phenylacetamide (0.79 g.) was hydrogenated catalytically in ethanol (20 ml.) under atmospheric pressure and in the presence of 5% pallidized charcoal (0.1 g.). After 1 mole of hydrogen was absorbed (7 hr.) the solution was filtered from the catalyst and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate–hexane and melted at 76°; yield 0.67 g. (84%).

Anal. Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.39. Found: C, 75.53; H, 8.76; N, 7.30.

This compound was found to be identical, through mixed melting point and infrared spectra, with *N*-isobutylphenylacetamide prepared from phenylacetyl chloride and isobutylamine by the Schotten-Baumann procedure.

N-(1-Cyclohexenyl)phenylacetamide. A mixture of phenylacetamide (3.4 g., 0.025 mole), cyclohexanone (4.0 g., 0.050 mole and β-naphthalenesulfonic acid (0.2 g.) in toluene (250 ml.) was refluxed for 24 hr. as described above (general procedure). The product melted at 106° after crystallization from benzene–hexane; yield 3.19 g. (59%).

Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.22; H, 7.70; N, 6.62.

N-Cyclohexylphenylacetamide. *N*-(1-Cyclohexenyl)phenylacetamide (2.15 g.) was hydrogenated catalytically in ethanol (20 ml.) under atmospheric pressure in the presence of 5% palladized charcoal (0.2 g.). After 1 mole of hydrogen was absorbed (8 hr.) the solution was filtered from the catalyst and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate and melted at 139°; yield 1.79 g. (82%).

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.29; H, 8.65; N, 6.49.

This compound was found to be identical, through mixed melting point and infrared spectra, with *N*-cyclohexylphenylacetamide prepared from phenylacetyl chloride and cyclohexylamine by the Schotten-Baumann procedure.

Benzylidenebisphenylacetamide. A mixture of phenylacetamide (3.4 g., 0.025 mole), benzaldehyde (5.3 g., 0.050 mole), and β-naphthalenesulfonic acid (0.25 g.) in benzene (300 ml.) was refluxed for 5 hr. as described above (general procedure). The solution was cooled to room temperature and the product which had precipitated was filtered and crystallized from ethanolwater. The yield was 4.3 g. (94%), m.p. 238°.

Anal. Calcd. for $C_{23}H_{22}O_2N_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.15; H, 6.16; N, 7.86.

Acid hydrolysis of 4-imidazolidinones. 4-Imidazolidinone (5×10^{-5} mole) was dissolved in 5*N* hydrochloric acid (1 ml.) and the solution was left at room temperature. Samples were taken out at various intervals of time and were put on the chromatogram. The paper chromatograms (ascending) were run overnight on Whatman No. 1 paper, with *n*-propyl alcohol–acetic acid–water (10:1:9) or methanol-pyridine-water (80:40:20) as developing solvent systems. Spots were detected with ninhydrin.

HAIFA, ISRAEL

(16) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

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

Synthesis of Pyrrole-3-carboxylic Acids

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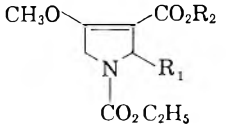
When 3-carbethoxy-4-methoxy-Δ^3-pyrrolines are heated under reflux with alkali, elimination of the methoxyl group occurs and pyrrole-3-carboxylic acids are formed. Since a variety of the requisite pyrrolines are readily available, this procedure is a convenient one for the synthesis of such acids.

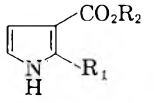
While engaged in the preparation of some 3-methoxypyrroles, we unexpectedly discovered a new synthesis of pyrrole 3-carboxylic acid (I), which proceeded in good yield from readily available starting materials. Since the present method is considerably more convenient for the preparation of I than those given in the literature,[2-4] we pursued several instances of the same reaction in order to gain some insight into its mechanism and generality.

In an effort to convert the pyrroline diester (III) to the pyrroline amino acid (II) without shifting the double bond, mild hydrolytic conditions were employed (60°, *p*H 11). The double bond was indeed stable under these conditions, as shown by the ultraviolet spectra of aliquots as the hydrolysis proceeded. The original maximum absorption of II was at 248 mμ. At the conclusion of the hydrolysis, this β-methoxyacrylic ester absorption of II had been shifted to the β-methoxyacrylic acid anion absorption at 237 mμ. Acidification of the aliquot returned the absorption to 248 mμ, a further indication that the -methoxyacrylic acid chromophore had been preserved.

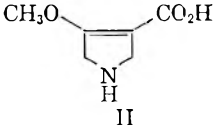
However, only 100 mole % of alkali was consumed over a nine-hour period, and no more was taken up during an additional twelve hours at 60° and pH 11. Furthermore, after diazomethane esterification of the reaction products, the pyrroline diester (IV) was isolated in good yield, showing conclusively that the hydrolysis has been completely selective, leaving the carbamate ester group untouched.



	R_1	R_2
III	H	C_2H_5
IV	H	CH_3
VI	CH_3	C_2H_5
IX	$CO_2C_2H_5$	C_2H_5



	R_1	R_2
I	H	H
V	H	CH_3
VII	CH_3	H
VIII	CH_3	CH_3
X	CO_2H	H
XI	CO_2CH_3	H

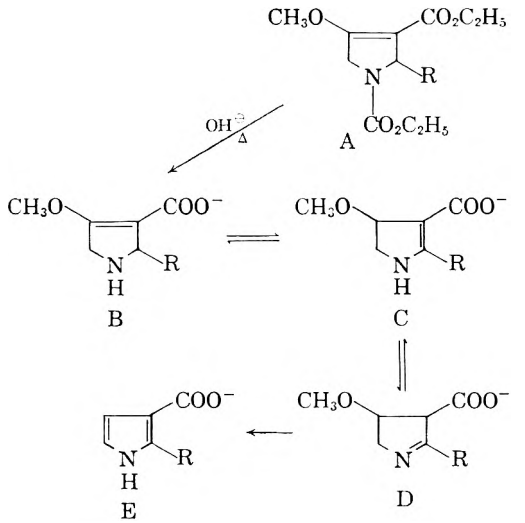


II

We therefore turned to a more vigorous hydrolysis, boiling the pyrroline diester (III) with aqueous barium hydroxide. The only product obtained under these conditions was an acid (I), isolated in 60% yield. This acid (I) could be converted to its methyl ester (V) with diazomethane; I and V were identified as pyrrole-3-carboxylic acid and methyl pyrrole-3-carboxylate, respectively.

The same vigorous hydrolytic conditions, when applied to the pyrrole VI, resulted in a similarly good yield of the corresponding pyrrole acid VII, but when applied to the pyrroline triester IX, gave only a poor yield of the pyrrole diacid X.

A reasonable path by which the β-methoxy-Δ^3-pyrrolines may be converted to the pyrrole-3-carboxylic acids is shown in the following scheme:



Strong alkaline hydrolysis of the ester removes the *N*-carbethoxyl group as well, and the resulting pyrroline may equilibrate among the Δ^3, Δ^2, and Δ^1 forms, B, C, and D. Elimination of the β-methoxyl group from isomer D now takes place readily because of the increased acidity of the hydrogen[5] alpha to the carboxyl.

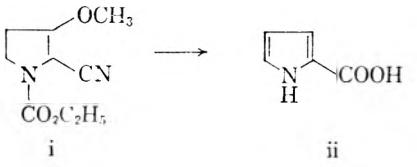
(1) Public Health Service Predoctoral Research Fellow of the National Institute of Mental Health.

(2) I. J. Rinkes, *Rec. trav. chim.*, **56**, 1224 (1937).

(3) I. J. Rinkes, *Rec. trav. chim.*, **57**, 426 (1938).

(4) R. A. Nicolaus and L. Mangoni, *Gazz. chim. ital.*, **86**, 358 (1956).

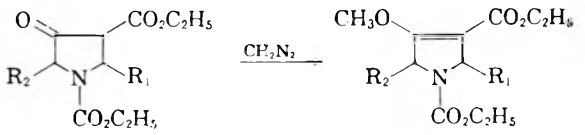
(5) A similar reaction which appears to proceed by the same type of mechanism is the conversion of the pyrroline (i) to the pyrrole acid (ii) by a vigorous alkaline hydrolysis. This reaction will be described in a forthcoming publication.



i ii

In the case where R is carboxyl, isomer C would be the most stable, hence the poor yield of pyrrole-2,3-carboxylic acid on hydrolysis of the triester IX.

By the nature of the reaction, this new synthesis may be employed only in the preparation of pyrrole-3-carboxylic acids unsubstituted at the 1- and 4-positions, since these are the positions from which the carbethoxyl and methoxyl groups, respectively, are eliminated. Otherwise, its application appears to be quite broad. The starting materials are the corresponding 3-pyrrolidones (XII) which are available in variety and in excellent yield by condensation of an *N*-carbethoxy-α-amino acid ester and an α,β-unsaturated ester.[6] Treatment with diazomethane then gives the enol methyl ether XIII.



XII XIII

EXPERIMENTAL[7]

1,3-Dicarbethoxy-4-methoxy-Δ^3-pyrroline (III). To an ethereal solution of 1,3-dicarbethoxy-4-pyrrolidone[6] (69.0 g., 0.3 mole) was added a large excess of ethereal diazomethane. The reaction was carried out at 0°, the diazomethane being added over a period of 15 min. After standing for 3 hr. at room temperature, the reaction mixture was evaporated to a residue which was dissolved in fresh ether and shaken once with 1*N* sodium hydroxide. The ether phase was distilled through a 1-meter Podbielniak column to yield, after a forerun at 104–140°/2.3 mm., 60 g. (83%) of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III), m.p. 65–66°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7400); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s), 6.08 (s).

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.3; H, 7.0; N, 5.8; OR, 3.00/243. Found: C, 54.0; H, 7.2; N, 5.9; OR, 3.02/243.

1,3-Dicarbethoxy-2-methyl-4-methoxy-Δ^3-pyrroline (VI). Treatment of 1,3-dicarbethoxy-2-methyl-4-pyrrolidone[6] (9.7 g., 0.04 mole) with diazomethane was carried out exactly as described above. Distillation of the ether phase at 123–125°/1.0 mm. gave 9.8 g. (94%) of a clear liquid, 1,3-dicarbethoxy-2-methyl-4-methoxy-3-pyrroline (VI); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 4100); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s), 6.07 (s).

Anal. Calcd. for $C_{12}H_{19}O_5N$: C, 56.0; H, 7.4; OR, 3.00/257. Found: C, 55.8; H, 7.5; OR, 2.95/257.

1,2,3-Tricarbethoxy-4-methoxy-Δ^3-pyrroline (IX). This was prepared from 1,2,3-tricarbethoxy-4-pyrrolidone by the procedure of Kuhn and Osswald;[6] ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7010); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.80–6.00 μ (s), 6.07 (m).

1-Carbethoxy-3-carbomethoxy-4-methoxy-Δ^3-pyrroline (IV). A solution of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III) (5.0 g., 0.0205 mole) in 60% aqueous methanol was stirred at 60°, while a sodium hydroxide solution was added to bring the *p*H to 11. As the *p*H dropped to *p*H 10 or less, more sodium hydroxide was added to return the *p*H to 11. After 9 hr., 100 mole % of alkali had been consumed, and the *p*H remained constant under these conditions for an additional 12 hrs. In contrast to the starting material, which has ultraviolet absorption at 248 mμ, this solution now absorbed at 237 mμ, but on acidification, the λ_{max} returned to 248 mμ. This dark brown alkaline solution was acidified to *p*H 5 with phosphoric acid and extracted with 1-butanol (6 × 50 ml.). The combined butanol extracts were evaporated *in vacuo*, and the residue was dissolved in ether and treated with a large excess of ethereal diazomethane. After standing for 3 hr. at room temperature, the reaction mixture was evaporated to a residue which was dissolved in fresh ether and washed once with aqueous sodium carbonate, and the ether phase was evaporated to a crystalline residue. Crystallization from hexane and resublimation at 85°/0.1 mm. gave 3.1 g. (66%) of 1-carbethoxy-3-carbomethoxy-4-methoxy-Δ^3-pyrroline (IV), m.p. 90–93°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7450); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s); 6.08 (s).

Anal. Calcd. for $C_{10}H_{15}O_5N$: C, 52.4; H, 6.6; N, 6.1; OR, 3.00/229. Found: C, 52.8; H, 6.3; N, 6.0; OR, 2.95/229.

The alkyl iodides resulting from the alkoxyl determination were trapped in toluene and examined by gas phase chromatography, giving a ratio of ethyl iodide to methyl iodide of 1:2.

Pyrrole-3-carboxylic acid (I). A heterogeneous mixture of 12.2 g. (0.05 mole) of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III) and 50 g. (0.11 mole) of barium hydroxide octahydrate in 250 ml. of water was boiled for 4 hr. The light yellow suspension was filtered, the filtrate was extracted with ether (2 × 100 ml.), and the aqueous phase was acidified to *p*H 1 with 12*N* sulfuric acid. The precipitated barium sulfate was removed, the filtrate was extracted with chloroform (5 × 50 ml.), and the combined chloroform extracts were evaporated to a crystalline residue, which was sublimed at 100°/0.1 mm. to yield 3.0 g. (60%) of pyrrole-3-carboxylic acid (I), m.p. 150–150.5° (reported m.p. 148°,[2] and 146–147°[8]); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 222.5 mμ (ϵ 7,725), 245 (5,165); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.92 μ (m), 5.97 (s); pK_a' 5.07 (reported pK_a 4.95[9]).

Methyl pyrrole-3-carboxylate (V). To an ethereal solution of pyrrole-3-carboxylic acid (I) was added a large excess of ethereal diazomethane at room temperature over a period of 5 min. After standing at room temperature for 3 hr., the solution was evaporated, and the residue was dissolved in fresh ether which was washed with 1*N* sodium hydroxide. Evaporation of the ether phase left a crystalline residue, which was sublimed at 60°/1.0 mm. to yield 90% of methyl pyrrole-3-carboxylate (V), m.p. 86–87° (reported m.p. 87°,[2] 88–89°[3]); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ϵ 7966), 247 (5310); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.82 μ (s), 3.55 (w), 5.82 sh (m), 5.90 (s).

2-Methylpyrrole-3-carboxylic acid (VII). A mixture of 1.0 g. (3.9 mmoles) of 1,3-dicarbethoxy-2-methyl-4-methoxy-Δ^3-pyrroline (VI) and 5.0 g. (11.0 mmoles) of barium hydroxide octahydrate in 100 ml. of water was boiled for 4 hr. The suspension was filtered, the filtrate was extracted with ether (2 × 50 ml.), the aqueous phase was acidified to *p*H 1 with 12*N* sulfuric acid, and the precipitated barium sulfate was removed by filtration. The filtrate was extracted with ether (5 × 50 ml.), and the combined ether extracts were evaporated to a crystalline residue which was sublimed at 100°/0.1 mm. to yield 310 mg. (60%) of 2-methylpyrrole-3-

(6) R. Kuhn and G. Osswald, *Ber.*, **89**, 1423 (1956).

(7) All melting points are corrected; boiling points are not corrected. Microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley.

(8) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, **20**, 795 (1956).

(9) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, **22**, 311 (1957).

carboxylic acid (VII), decomposing sharply at 178–179° (reported[10] m.p. 168° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 222 mμ (ε 7297), 254 (6014); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.91 μ (w), 3.07 (m), 6.02 (s); pK_a' 5.75 (reported pK_a 5.80[9]).

Methyl 2-methylpyrrole-3-carboxylate (VIII). To an ethereal solution of 2-methylpyrrole-3-carboxylic acid (VII) was added a large excess of ethereal diazomethane at room temperature, over a period of 5 min. After standing at room temperature for 3 hr., the solution was evaporated to a residue, which was dissolved in fresh ether, and washed once with 1*N* sodium hydroxide. The ether phase was evaporated to a crystalline residue, which was sublimed at 40°/0.1 mm. to yield 95% of methyl 2-methylpyrrole-3-carboxylate (VIII), m.p. 67–68°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 223 mμ (ε 7398); 255 (6341); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.92 μ (m), 3.07 (w), 5.88 sh (m), 5.93 (s).

Pyrrole-2,3-dicarboxylic acid (X). A mixture of 7.0 g. (0.022 mole) of 1,2,3-tricarbethoxy-4-methoxy-Δ³-pyrroline (IX) and 30 g. (0.066 mole) of barium hydroxide octahydrate in 100 ml. of water was boiled for 4 hr. The acidic fraction was isolated as above, and the combined ether extracts were evaporated to a solid residue which was sublimed at 180°/0.1 mm.; yield, 170 mg. (5%) of pyrrole-2,3-dicarboxylic acid (X), m.p. 220° dec., sintering at 150° (reported[8] m.p. 225° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 2,450), 276 (4,200).

Dimethyl pyrrole-2,3-dicarboxylate (XI). An ethereal solution of pyrrole-2,3-dicarboxylic acid (X) was treated with a large excess of ethereal diazomethane, and the neutral fraction was isolated as above, yielding, after sublimation at 50°/0.1 mm., 36 mg. of dimethyl pyrrole-2,3-dicarboxylate (XI), m.p. 69–71° (reported[11] m.p. 72–73°); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ε 2580), 278 (4422); infrared absorption: $\lambda_{max}^{CHCl_3}$ 3.00 μ (m), 5.84 (s), 5.94 (s).

BERKELEY, CALIF.

(10) E. Benary, *Ber.*, **44**, 495 (1911).

(11) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, **22**, 500 (1957).

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

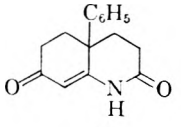
Synthesis of Angularly Substituted Octa- and Decahydroquinolines[1]

C. F. KOELSCH AND D. L. OSTERCAMP[2]

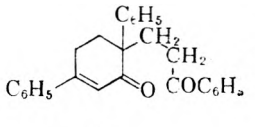
Received July 5, 1960

4a-Phenyl-Δ⁸-octahydro-2,7-quinolinedione (I) and its *N*-methyl derivative have been reduced with hydrogen and palladium, hydrogen and nickel, and with lithium aluminum hydride. The ultimate reduction product is 4a-phenyldecahydroquinoline or its *N*-methyl derivative, but selection of an appropriate reducing agent enables one to obtain various intermediates in good yield.

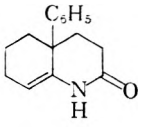
Some time ago it was found that 4a-phenyl-Δ⁸-octahydro-2,7-quinoline-dione could be obtained in quantity from readily available materials.[3] The presence of a quaternary carbon in I made it desirable to convert the substance into basic derivatives, for these might have interesting pharmacological properties. Results of experiments in this direction are now reported.



I



II

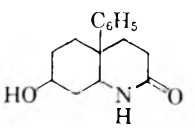


III

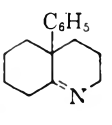
With Grignard reagents, I formed insoluble complexes whose hydrolysis gave back I unchanged. The *N*-methyl derivative of I reacted with phenylmagnesium bromide at both carbonyl groups, but the product lost nitrogen when it was treated with water, and only II was isolated. The structure of this substance was established by synthesis through base-catalyzed reaction of phenylacetone with two equivalents of acrylophenone.

With hydrogen in presence of palladium-charcoal, I lost the ketonic oxygen, forming III. The *N*-methyl derivative of I behaved similarly, forming the *N*-methyl derivative of III. Both of these substances gave the same hydrolysis product, 2-phenylcyclohexanone-2-propionic acid.

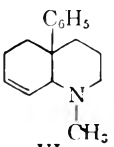
With hydrogen in presence of Raney nickel, I gave a mixture, m.p. 170–205°, in contrast to the previously claimed[3] quantitative formation of IV, erroneously reported to have m.p. 117–119°. The mixture furnished only 48% of IV, m.p. 227–229°, together with 6% of III, and no other pure product could be isolated.



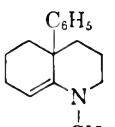
IV



V



VI



VII

With lithium aluminum hydride, I gave V, a deoxidation similar to those discussed by Gaylord.[4] The product (V) was further reduced, using Raney nickel, to known 4a-phenyldecahydroquinoline,

(1) From the Ph.D. Thesis of D. L. Ostercamp, September 1959.

(2) National Science Fellow, 1958–59.

(3) C. F. Koelsch and H. M. Walker, *J. Am. Chem. Soc.*, **72**, 346 (1950).

(4) N. G. Gaylord, Experientia, **10**, 166 (1954). In agreement with structural deductions based on Gaylord's mechanism, the compound showed no NH absorption, and a strong band at 1650 cm.$^{-1}$, corresponding to the 1658 cm.$^{-1}$ C=N band of Δ^{1,8a}-octahydroquinoline assigned by Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

characterized as its *N*-benzoyl and *N*-phenylacetyl derivatives. The latter was reduced again (lithium aluminum hydride) forming *N*-phenethyl-4a-phenyldecahydroquinoline.

When the *N*-methyl derivative of I was reduced with lithium aluminum hydride, the unsaturated amine VI was formed, and not enamine VII. The nature of the product was established by the method of Leonard and Gash[5]; the absorption at 1645 cm.$^{-1}$ of the free base was not shifted in salt formation. Confirmation of this method was obtained by applying it to VII, synthesized both by action of mercuric acetate[6] on 1-methyl-4a-phenyldecahydroquinoline and by reduction of the *N*-methyl derivative of III with lithium aluminum hydride.[7] Here the expected shift in absorption with salt formation was observed; the free base absorbed at 1638 cm.$^{-1}$ (>C=C—N<), the perchlorate at 1671 cm.$^{-1}$ (>C=$\overset{+}{\text{N}}$<).

EXPERIMENTAL

Reaction with phenylmagnesium bromide. A solution of 5 g. of the *N*-methyl derivative of I[3] in 75 ml. of warm benzene was added to ethereal phenylmagnesium bromide prepared from 1.7 g. of magnesium. The mixture was boiled until it became clear (1–2 hr.) and then decomposed with saturated ammonium chloride solution. Removal of solvents left a gum which was dissolved in hot acetic acid containing dilute hydrochloric acid. The solution deposited 1.1 g. of crude product, and 2.2 g. more was obtained by working over the mother liquors. Recrystallization from acetic acid gave 3.0 g. of *1,4-diphenyl-3-oxo-4(β-benzoylethyl)cyclohexene* (II), m.p. 193–195°.

Anal. Calcd. for $C_{27}H_{24}O_2$: C, 85.2; H, 6.36. Found: C, 85.2; H, 6.50.

The same compound was obtained (crude yield 46%) when a suspension of 6 g. of β-chloropropiophenone and 2 g. of phenylacetone in 35 ml. of *tert*-butyl alcohol was treated dropwise with 5*N* methanolic potassium hydroxide to strongly basic reaction and then kept for 12 hr. When less β-chloropropiophenone was used in this synthesis, the product was 1,4-diphenyl-3-oxocyclohexene (yield 37%, m.p. 145–146°) as reported previously.[8]

When 1 g. of II was treated with 1.2 g. of chromic anhydride in acetic acid at 80° it was partly (0.6 g.) recovered and partly converted into an acid, probably *3-(β-benzoylethyl)-2,6-dioxo-3,6-diphenylcaproic acid*, prisms from acetic acid, m.p. 256–259° dec.; absorption at 1715, 1690, and 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{24}O_5$: C, 75.7; H, 5.65. Found: C, 76.2; H, 5.92.

Hydrogenation using palladium. A suspension of 0.5 g. of I in 30 ml. of alcohol absorbed 2 equivalents of hydrogen when it was shaken with 10% palladium on charcoal for 20 hr. The resulting 4a-phenyl-Δ^8-octahydro-2-quinolone (III) formed needles from ethyl acetate (0.31 g.) m.p. 211–214° (reported[9] m.p. 208–210°); $\lambda_{max}^{C_2H_5OH}$ 231 mμ, ε 10,300.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.3; H, 7.56; N, 6.17. Found: C, 79.0; H, 7.34; N, 6.21.

The *N*-methyl derivative of I (6 g.) in 180 ml. of alcohol similarly absorbed 2 equivalents of hydrogen during 2 days. The resulting *1-methyl-4a-phenyl-Δ^8-octahydro-2-quinolone* formed needles (4.7 g.) from dilute methanol, m.p. 112–114°; $\lambda_{max}^{C_2H_5OH}$ 233, ε 10,200.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.6; H, 7.94; N, 5.81. Found: C, 79.8; H, 8.13; N, 5.95.

Acid hydrolysis[9] gave 71% of 2-phenylcyclohexanone-2-propionic acid, m.p. 110–112° (reported[9] m.p. 113–115°).

Hydrogenation with nickel. Hydrogenation of I according to the published directions gave a nearly quantitative yield of a mixture m.p. 170–205°. When 12.1 g. of this mixture was extracted with three successive portions (100, 75, 75 ml.) of boiling ethyl propionate, there was left 5.6 g. of nearly pure *4a-phenyl-7-hydroxydecahydro-2-quinolone*, m.p. 224–227°. Crystallization from nitromethane gave plates, m.p. 227–229°; the infrared spectrum was consistent with structure IV.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.80; N, 5.71. Found: C, 73.5; H, 7.58; N, 5.77.

When the crude reduction product (6 g.) was boiled for 10 min. with 60 ml. of acetic anhydride containing 0.2 g. of sulfuric acid, *7-acetoxy-1-acetyl-4a-phenyldecahydro-2-quinolone* (3.8 g.) was obtained. Crystallization from 100° ligroin and then methanol gave prisms m.p. 151–152°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04; N, 4.25. Found: C, 69.6; H, 7.11; N, 4.51.

Boiling the acetyl derivative with 1.5*N* alcoholic potassium hydroxide for 5 min. gave back 43% of IV.

Oxidation of pure IV (3.5 g.) to *4a-phenyldecahydro-2,7-quinolinedione* was accomplished by use of chromium trioxide (1.4 g.) in 1.5 ml. of water and 20 ml. of acetic acid. An excess of chromate was removed by dilution with water and addition of lead acetate, and the organic product was extracted with chloroform. Crystallization from ethyl acetate gave colorless plates (2 g.) which showed a proper infrared spectrum but which could not be obtained in a sharp-melting form; m.p. 184–213°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.04; N, 5.76. Found: C, 73.8; H, 7.08; N, 5.93.

Reduction with lithium aluminum hydride. A mixture of 10 g. of I and 9 g. of lithium aluminum hydride in 300 ml. of ether was boiled for 21 hr. and then decomposed with 10% sodium hydroxide. Fractional distillation gave 7.4 g. of nearly pure *4a-phenyl-Δ^{8a}-octahydroquinoline* (V), b.p. 182–184° at 26 mm. For analysis this was converted to its *picrate*, yellow plates from alcohol, m.p. 96-99°.

Anal. Calcd. for $C_{15}H_{19}N + C_6H_3N_3O_7 + C_2H_5OH$: C, 56.6; H, 5.78; N, 11.47; C_2H_5OH, 9.43. Found: C, 57.0; H, 6.03; N, 10.96; C_2H_5OH (loss in weight at 110° at 2 mm.), 9.26.

The solvent-free picrate had m.p. 188–190°.

Anal. Calcd. for $C_{15}H_{19}N + C_6H_3N_3O_7$: C, 57.0; H, 5.01; N, 12.6. Found: C, 58.0; H, 5.08; N, 12.4.

Regenerated from its picrate, the free base had b.p. 168° at 15 mm., $n_D^{25.1}$ 1.5708.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.5; H, 8.98; N, 6.57. Found: C, 84.6; H, 9.11; N, 6.76.

Hydrogenation of 4 g. of V in alcohol using Raney nickel and hydrogen at 30 lbs. required 13 days and gave 3.2 g. of 4a-phenyldecahydroquinoline, b.p. 175–178° at 16 mm. that still contained a small amount of V. The *benzoyl derivative* of the decahydro compound, obtained in 95% yield using Schotten-Baumann conditions, formed plates from alcohol, m.p. 156–157°.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.7; H, 7.89; N, 4.39. Found: C, 82.9; H, 7.73; N, 4.39.

Regenerated from the benzoyl derivative by hydrolysis with hydrobromic–acetic acid, the decahydro compound gave a picrate m.p. 115–116° (alcohol solvate) and 154–156° (reported[10] 118° and 155–157°).

(5) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(6) N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

(7) L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6599 (1955).

(8) S. Fujise and K. Tiba, *Bull. Chem. Soc. Japan*, **14**, 480 (1939).

(9) D. Elad and D. Ginsberg, *J. Chem. Soc.*, 4137 (1953).

(10) V. Boekelheide, *J. Am. Chem. Soc.*, **69**, 790 (1947).

With 3.2 g. of phenylacetyl chloride in ether and aqueous sodium bicarbonate, 3.2 g. of the decahydro compound gave 4.4 g. of *4a-phenyl-1-phenylacetyldecahydroquinoline*, plates from ligroin, m.p. 106–107°.

Anal. Calcd. for $C_{23}H_{27}NO$: C, 82.8; H, 8.16; N, 4.2. Found: C, 83.0; H, 8.05; N, 4.4.

Reduction of the phenylacetyl derivative (3.3 g.) was effected with 1.75 g. of lithium aluminum hydride in 30 ml. of ether by boiling 20 hr. *4a-Phenyl-1-phenethyldecahydroquinoline* was isolated by decomposition with 10% sodium hydroxide. The *hydrobromide* formed colorless crystals (3.6 g.) from ethyl acetate–alcohol, m.p. 243–244°.

Anal. Calcd. for $C_{23}H_{29}N$ + HBr: C, 69.0; H, 7.55; N, 3.50. Found: C, 69.3; H, 7.50; N, 3.48.

The *hydrochloride* had m.p. 228–230°.

Anal. Calcd. for $C_{23}H_{29}N$ + HCl: C, 77.6; H, 8.5; N, 3.94. Found: C, 77.9; H, 8.78, N, 3.97.

1-Methyl-4a-phenyl-Δ^8-octahydro-2,7-quinolinedione (10 g.) reduced with 8.7 g. of lithium aluminum hydride (8.7 g.) gave 7.93 g. of crude product. This was purified through its *picrate*, yellow needles (12.3 g.) from alcohol, m.p. 182–184°.

Anal. Calcd. for $C_{16}H_{21}N$ + $C_6H_3NO_7$: C, 57.9; H, 5.3; N, 12.3. Found: C, 58.8; H, 5.43; N, 12.3.

Regenerated from its picrate, *1-methyl-4a-phenyl-Δ^7-octahydroquinoline* (VI, 87% yield) had b.p. 172–173° at 13 mm., n_D^{25} 1.5653 (supercooled); m.p. 57–59°; weak absorption at 1642 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.5; H, 9.31. Found: C, 84.4; H, 8.91.

The *hydroiodide* formed crystals from water, m.p. 256–258° dec.; weak absorption at 1645 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{21}N$ + HI: C, 54.1; H, 6.24; N, 3.94. Found: C, 54.4; H, 6.19; N, 4.02.

The *perchlorate* formed crystals from alcohol, m.p. 253–255° dec.; weak absorption at 1645 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{21}N$ + $HClO_4$: C, 58.6; H, 6.77; N, 4.27. Found: C, 58.8; H, 6.73; N, 4.22.

When VI (5.5 g.) was shaken with Raney nickel in alcohol under hydrogen at 30 lbs., one equivalent of the gas was absorbed and 5.14 g. of 1-methyl-4a-phenyldecahydroquinoline was obtained, b.p. 160–161° at 8 mm., $n_D^{25.5}$ 1.5541; reported[11] 126–128° at 3 mm. Its hydrochloride had m.p. 224–226°, reported,[11] 225–226°. Its perchlorate formed crystals from alcohol m.p. 210–211°.

Anal. Calcd. for $C_{16}H_{23}N$ + $HClO_4$: C, 58.3; H, 7.33; N, 4.25. Found: C, 58.5; H, 7.38; N, 4.11.

Oxidation of 3.1 g. of 1-methyl-4a-phenyldecahydroquinoline was effected by heating it with 16.7 g. of mercuric acetate in 135 ml. of 5% acetic acid for 1 hr. at 95°. Mercurous acetate (99–100% yield) was then removed by filtration, and the remainder of the mercury was precipitated with hydrogen sulfide. The resulting crude enamine (VII), a pale yellow oil, showed strong absorption at 1638 cm.$^{-1}$. Treatment with perchloric acid in alcohol gave 2.3 g. of *1-methyl-4a-phenyl-Δ^8-octahydroquinoline perchlorate*, prisms m.p. 134–136°; strong absorption at 1671 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{21}N$ + $HClO_4$: C, 58.6; H, 6.77; N, 4.27. Found: C, 58.9; H, 6.75; N, 4.21.

The same perchlorate was obtained in 70% yield from the base obtained from 3 g. of 1-methyl-4a-phenyl-Δ^8-octahydro-2-quinolone by treatment with 1.4 g. of lithium aluminum hydride in 100 ml. of ether for 10 hr.

Regenerated from its perchlorate, *1-methyl-4a-phenyl-Δ^8-octahydroquinoline* (VII) formed an oil that darkened on exposure to air; b.p. 125–127° at 3 mm.; n_D^{25} 1.5718.

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.5; H, 9.31. Found: C, 84.7; H, 9.25.

Acknowledgment. The authors thank Mrs. O. Hamerston and Mr. W. C. Kuryla for analytical results.

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(11) N. Sugimoto, H. Kugita, and T. Fujita, *J. Pharm. Soc. Japan*, **75**, 177 (1955); *Chem. Abstr.* **50**, 1814 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

The Synthesis of *trans*-2,4-Dioxo-3-hydroxydecahydroquinazoline[1]

LUDWIG BAUER AND C. N. V. NAMBURY

Received August 1, 1960

The synthesis of *trans*-hexahydrophthalo(benzoylhydroxamic) and 5-norbornene-*endo-trans*-2,3-dicarbo(benzoylhydroxamic) acids, III and IV, is described. Various rearrangements of these hydroxamic acids are discussed.

The synthesis of 3-hydroxy-[2] and 3-benzenesulfonyloxy-5,6-dihydrouracil[3] was extended to a synthesis of 2,4-dioxo-3-hydroxydecahydroquinazoline, V, and to several of its derivatives. Our original intention was to prepare both the *cis* and *trans* isomers of V by unequivocal syntheses from the corresponding *cis* and *trans* methyl hexahydrophthalates.

To avoid isomerization during the synthesis of methyl *cis*-hexahydrophthalate, *cis*-hexahydrophthalic anhydride was refluxed with methanol to afford methyl hydrogen *cis*-hexahydrophthalate[4] which in turn was treated with diazomethane. The *cis* ester so obtained was identical with that made more conveniently by the esterification of the anhydride with methanol in the presence of sulfuric acid.[5] Isomerization of the *cis* ester by sodium ethoxide in methanol at 100° according to the method of Hückel[6] yielded the *trans* ester.

(1) The authors would like to express their appreciation for the support of this work through Grant CY-4661 from the National Cancer Institute of the National Institute of Health, United States Public Health Service.

(2) C. D. Hurd, C. M. Buess, and L. Bauer, *J. Org. Chem.*, 19, 1140 (1954).

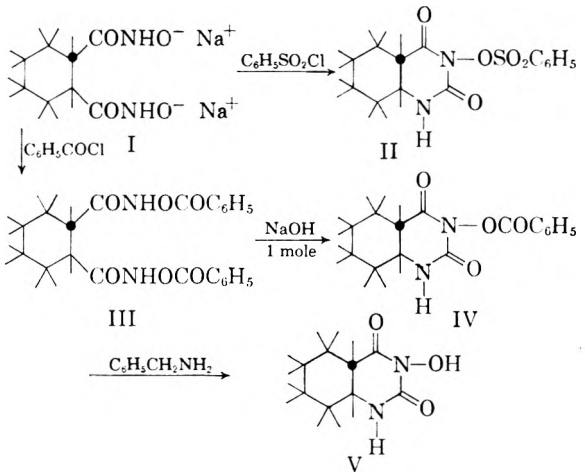
(3) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954).

(4) C. G. Overberger and P. Kabasakalian, *J. Org. Chem.*, **21**, 1124 (1956).

(5) H. A. Smith and T. Fort, *J. Am. Chem. Soc.*, **78**, 4000 (1956).

(6) W. Hückel and E. Groth, *Ber.*, **58**, 449 (1925).

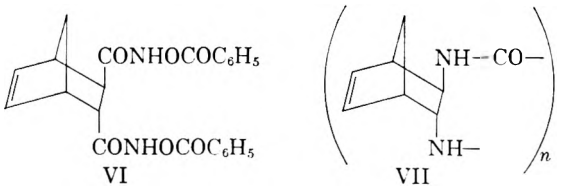
The reactions of hydroxylamine and sodium methoxide with either the *cis* or the *trans* ester gave a sodium hydroxamate, I, which on benzoylation afforded only *one* benzoylhydroxamic acid, III, m.p. 188°. However, the notable difference was the yield of III: 6% from the *cis* and 45% from the *trans* ester. Furthermore, acidification of the sodium hydroxamate from the *cis* ester yielded no crystalline product, while that from the *trans* ester gave *trans*-hexahydrophthalohydroxamic acid, m.p. 191–192°. We feel that this hydroxamic acid is identical to one previously described[7] as "cis"-hexahydrophthalohydroxamic acid, m.p. 191–193°, which was prepared by heating methyl *cis*-hexahydrophthalate with hydroxylamine and sodium methoxide at 100° for half an hour, followed by acidification. During that preparation, the *cis* ester isomerized to the *trans* ester (*vide et supra*) and the product subsequently isolated was *trans*-hexahydrophthalohydroxamic acid.



Rearrangement of III with *one* mole of sodium hydroxide afforded IV, presumably *via* an intermediate isocyanatobenzoylhydroxamic acid, which cyclized spontaneously. Excess sodium hydroxide on III yielded a mixture from which a small amount of V could be isolated. Ammonolysis with benzylamine smoothly removed the benzoyl group in IV to give V. Attempted hydrolysis of the benzoyl group of IV with sodium hydroxide led to a mixture thus indicating that more deep-seated changes had occurred.

The action of benzenesulfonyl chloride on I according to the method previously described[3] afforded the sulfonate ester II. Nucleophilic attack[8] on II by hydroxide ion followed by hydrolysis yielded the expected *trans*-1,2-cyclohexanediamine while attack by sodium ethoxide gave *trans*-1,2-di(carboethoxyamino)cyclohexane.

This series of reactions was applied to 5-norbornene-*endo*-2,3-dicarboxylic anhydride. Treatment of this anhydride with methanol and *p*-toluenesulfonic acid afforded the *cis* ester which was isomerized with sodium methoxide to the *trans* ester. The latter was converted by hydroxylamine and sodium ethoxide to sodium 5-norbornene-*endo*-*trans*-2,3-dicarbohydroxamate, from which we could not obtain a cyrstalline hydroxamic acid, nor would the reaction with benzenesulfonyl chloride yield a crystalline analog of II. However, benzoylation of this sodium salt afforded the benzoylhydroxamic acid, VI. However, the attempt to rearrange one hydroxamic acid grouping in VI followed by ring closure to an analog of IV failed. The only product of the reaction with one or preferably two moles of sodium hydroxide was the polymeric urea (VII). The structure of VII was established by the



following criteria: (a) Its elemental analysis indicated an empirical formula $C_8H_{10}N_2O$. (b) Its infrared spectrum exhibited two broad absorption peaks between 1520 and 1660 cm.$^{-1}$ [in potassium bromide] which resembled those shown between 1520 and 1680 cm.$^{-1}$ [in potassium bromide] by the polymeric urea, $[—NH(CH_2)_4NHCO—]_n$. The latter was prepared by the rearrangement of adipo(benzoylhydroxamic) acid.[9] When cyclization of the intermediate β-isocyanatobenzoylhydroxamic acid is impossible, rearrangements of the second benzoylhydroxamic group occurs to yield polyureas.[9]

In a recent paper,[10] a benzoylhydroxamic acid, m.p. 178–179°, is described, whose gross structure resembles VI, but neither its exact preparation nor its stereochemistry were reported.

EXPERIMENTAL[11]

Methyl cis- and trans-hexahydrophthalates. The *cis* ester b.p. 82° (0.5 mm.), n_D^{23} 1.4580 was prepared[5] in 85% yield from the *cis*-hexahydrophthalic anhydride[12] and converted in 82% yield to *trans* ester,[6] b.p. 72–75° (0.5–0.75 mm.) n_D^{24} 1.4539. The infrared spectra (Beckman IR-4; 10% chloroform solution) of the two esters showed the following bands:

cis Ester (in cm.$^{-1}$): 3050 (m); 2960 (s); 2880 (m); 1725 (vs); 1445 (s); 1430 (m); 1370 (inflection); 1335 (w); 1300 (m); broad absorption 1250–1170 (s); 1128 (s); 1098 (w); 1070 (w); 1038 (s); 1000 (m); 915 (vvw); 895 (w); 880 (w).

(7) M. A. Stolberg, W. A. Mosher, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, 79, 2617 (1957).

(8) For the mode of action see C. M. Buess and L. Bauer, *J. Org. Chem.*, 20, 34 (1955).

(9) C. D. Hurd and D. G. Botteron, *J. Org. Chem.*, 11, 207 (1946).

(10) F. Winternitz and C. Wlotzka, *Bull. soc. chim., France*, 511 (1960).

(11) All melting points are uncorrected. Microanalyses were carried out by Dr. Kurt Eder, Geneva, Switzerland, and Micro-Tech Laboratories, Skokie, Ill.

(12) Kindly supplied by the National Aniline Division of the Allied Chemical and Dye Corp.

trans Ester (in cm.$^{-1}$): 3050 (m); 2960 (s); 2880 (m); 1725 (vs); 1445 (s); 1432 (s); 1370 (w); 1350 (w); 1320 (s); 1300 (inflection); 1252 (s); 1215 (s); 1170 (s); 1112 (m); 1067 (w); 1042 (s); 1010 (w); 975 (w); 910 (w); 903 (w).

Sodium trans-hexahydrophthalohydroamate. Methyl *trans*-hexahydrophthalate (20.0 g.; 0.1 mole) was added to an ethanolic solution of hydroxylamine (prepared from 15.4 g. hydroxylamine hydrochloride and an equivalent amount of sodium ethoxide). This solution was stirred at 25° with a solution of sodium ethoxide (from 5.0 g. of sodium in 150 ml. ethanol). After 0.5 hr. the salt was collected and dried *in vacuo*. It weighed 24 g. and was used without further purification for the reactions described below.

trans-Hexahydrophthalohydroxamic acid. An aqueous solution of the sodium *trans*-hexahydrophthalohydroxamate (6.0 g. in 8 ml. of water) was cooled to 10° and 5% hydrochloric acid added dropwise until the solution was neutral. The hydroxamic acid (1.5 g.; 30%) crystallized and melted at 191–192°. Recrystallization from dioxane-water yielded colorless tufts, m.p. 192°.

Anal. Calcd. for $C_8H_{14}N_2O_4$ (202.2): C, 47.52; H, 6.93; N, 13.86. Found: C, 47.65; H, 6.89; N, 13.80.

trans-Hexahydrophthalo(benzoylhydroxamic) acid. Sodium *trans*-hexahydrophthalohydroxamate (7.4 g.; 0.03 mole) was dissolved in an aqueous solution of sodium acetate trihydrate (8.1 g. in 60 ml. water) and a trace of saponin was added. This solution was stirred and cooled to about 0°. Benzoyl chloride (9 ml.) was then added dropwise, the temperature of the mixture being kept between 0 and 5°. After 0.25 hr., more benzoyl chloride (3 ml.) was added and the mixture stirred for another 0.75 hr. Acidification with concentrated hydrochloric acid (7.5 ml.) yielded a solid which was filtered and was washed with 1:1 mixture of benzene-ligroin (b.p. 60–90°). The crude solid was recrystallized from dioxane and was obtained as shining plates, m.p. 188°.

Anal. Calcd. for $C_{22}H_{22}N_2O_6$ (410.4): C, 64.39; H, 5.37; N, 6.83. Found: C, 64.44; H, 5.44; N, 6.92.

The yield was 5.5 g. or 45%, based on methyl *trans*-hexahydrophthalate.

trans-2,4-Dioxo-3-benzoyloxydecahydroquinazoline. trans-Hexahydrophthalo(benzoylhydroxamic) acid (6.15 g.; 0.015 mole) was suspended in a sodium hydroxide solution (0.6 g.; 0.015 mole in 50 ml. water) and the mixture was stirred and heated on the steam bath for 1 hr. A light voluminous solid (3.5 g.; 81%) was formed which crystallized from ethanol in shining needles, m.p. 210–211°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$ (288.2): C, 62.55; H, 5.55; N, 9.75. Found: C, 62.63; H, 5.67; N, 9.69.

trans-2,4-Dioxo-3-hydroxydecahydroquinazoline. A solution of *trans*-2,4-dioxo-3-benzoyloxydecahydroquinazoline (2.88 g.; 0.01 mole) in benzylamine (1.08 g.; 0.01 mole) was heated at 150° for 40 min. The solution was cooled and triturated with 5*N* acetic acid (25 ml.). A solid (2.0 g.; m.p. 100–107°) which separated, was filtered and crystallized from benzene–petroleum ether (b.p. 60–90°) and was identified as *N*-benzylbenzamide, m.p. 105–107°, lit.,[13] m.p. 105–106°.

The aqueous filtrate was evaporated to dryness and the residue boiled with benzene (125 ml.) and this residue (1.15 g.; 62.5%), m.p. 201–203°, was recrystallized from chloroform-cyclohexane to form colorless rhombs, m.p. 204–205°.

Anal. Calcd. for $C_8H_{12}N_2O_3$ (184.1): C, 52.17; H, 6.52; N, 15.21. Found: C, 52.39; H, 6.47, N, 15.44.

An aqueous solution of this compound gave an intense red color with feric chloride.

trans-2,4-Dioxo-3-benzenesulfonyloxydecahydroquinazoline. A suspension of sodium *trans*-hexahydrophthalohydroxamate (24.0 g.; 0.1 mole) in tetrahydrofuran was stirred vigorously at 20° while a solution of benzenesulfonyl chloride (28 ml.; 0.22 mole) in tetrahydrofuran (65 ml.) was added dropwise (20 min.) so that the temperature of the reaction mixture remained at 25°. After 30 min., sodium acetate trihydrate (10.4 g.) was added to the mixture and stirring continued for another 45 min. The reaction mixture was filtered and the filtrate concentrated to one third of its volume and allowed to crystallize. The product (8.1 g.; 25%) crystallized, m.p. 203–205°. One recrystallization from tetrahydrofuran raised the m.p. to 208–209.°

Anal. Calcd. for $C_{14}H_{16}N_2O_5S$ (324.1): C, 51.86; H, 4.95; N, 8.67; S, 9.91. Found: C, 52.21; H, 4.96; N, 9.00; S, 10.22.

Rearrangement of trans-2,4-dioxo-3-benzenesulfonyloxydecahydroquinazoline (a) *With sodium ethoxide.* To a suspension of *trans*-2,4-dioxo-3-benzenesulfonyloxydecahydroquinazoline (2.4 g; 0.0075 mole) in boiling ethanol (115 ml.) was added dropwise sodium ethoxide solution (0.2 g.; sodium in 8. ml. ethanol) over a period of 10 min. The solution was then boiled another 5 min. Ethanol was removed *in vacuo* and the residue extracted with boiling benzene (160 ml.). Evaporation of the benzene solution left a residue which crystallized from benzene–petroleum ether (b.p. 60–90°) to give *trans*-1,2,-di(carbethoxyamino)-cyclohexane, (1.3 g.; 67%) m.p. 142° lit.,[14] m.p. 145°.

Hydrolysis of the urethan with concentrated hydrochloric acid according to the method of Wieland gave *trans*-1,2-diaminocyclohexane dihydrochloride in 80% yield, m.p. 300–303°, lit. m.p. 303°.[14]

(b) *With sodium hydroxide. trans*-3-Benzenesulfonyloxydecahydroquinazoline (2.43 g.) was dissolved in aqueous sodium hydroxide solution (0.3 g. in 10 ml. water) and was boiled for 45 min. A small amount of solid was filtered and the filtrates concentrated to a very small volume. Concentrated hydrochloric acid (20 ml.) was added and the solution refluxed for 6 hr. The solution was made alkaline with sodium hydroxide and benzoyl chloride (4 ml.) were added. The derivative (1.1 g.; 46%) which formed crystallized from acetic acid, m.p. 350°.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.2): C, 74.50; H, 6.88; N, 8.69. Found: C, 74.55; H, 6.93; N, 8.59.

In an experiment similar to that above, benzenesulfonyl chloride (3.0 ml.) was added instead of benzoyl chloride. On acidification of the basic medium *trans*-1,2-di(phenylsulfonamido)cyclohexane (1.0 g.; 35%) was obtained, which recrystallized from benzene–petroleum ether (b.p. 60–90°), m.p. 155–156°, lit.[15] m.p. 153–155°.

trans-1,2-Diaminocyclohexane dihydrochloride was made recently by the reduction of 1,2-cyclohexanedionedioxime by sodium in ethanol[16] but no melting point of this salt was recorded. These authors characterized the free bases by its boiling point. The over-all yield of the base from ethyl 2-oxocyclohexanecarboxylate was stated to be 0–20%. In another recent attempt to prepare *trans*-1,2-diaminocyclohexane, the product of the catalytic hydrogenation of methyl phthalate was subjected to the Curtius rearrangement.[17] The base was obtained by these authors in unspecified yield and was characterized by a hydrochloride, m.p. 322–326°, a benzoyl derivative, m.p. 340–343°, and a benzenesulfonyl derivative, m.p. 153–154°.

Methyl 5-norbornene-endo-cis-2,3-dicarboxylate. This ester was prepared in 76% yield according to the method of Morgan, *et al.*,[18] b.p. 71–73° (0.25 mm.) n_D^{22} 1.4846.

Isomerization of the cis to the trans ester. The *cis* ester (26.25 g.; 0.125 mole) was refluxed in methanol containing sodium methoxide (0.6 g. sodium in 20 ml. methanol). After

(13) E. Beckmann, *Ber.*, **23**, 3334 (1890).

(14) H. Wieland, O. Schlichting, and W. v. Langsdorff, *Z. physiol. Chem.*, **161**, 74 (1926).

(15) F. M. Jaeger and L. Bijkerk, *Proc. Acad. Sci. Amsterdam*, **40**, 12 (1937).

(16) H. S. Broadbent *et al.*, *J. Am. Chem. Soc.*, **82**, 189 (1960).

(17) V. G. Iashunskil and M. N. Shchukina, *J. Gen. Chem., USSR, Engl. Transl.*, **28**, 230 (1958).

(18) M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *J. Am. Chem. Soc.*, **66**, 404 (1944).

1.25 hr., the solution was cooled, diluted with water (150 ml.), and the ester extracted into a benzene-ether (1:1) mixture (100 ml.). The organic layer was washed with water, with dilute sulfuric acid, and then again with water. Distillation of the organic layer afforded the *trans* ester (23.0 g.; 87%), b.p. 68–69° at 0.2 mm. On cooling, the distillate solidified m.p. 29.5–30°, lit.[19] b.p. 119–120° at 4 mm., m.p. 37–39°. The infrared spectra (10% chloroform solution) of the *cis* and *trans* esters showed notable differences:

cis Ester (in cm.$^{-1}$): 3000 (s); 1742 (vs); 1430 (s); 1358 (m); 1335 (s); 1250 (s); 1195 (s); 1165 (s); 1118 (w); 1092 (w); 1075 (m); 1040 (m); 942 (w); 908 (m); 848 (w).

trans Ester (in cm.$^{-1}$): 3000 (s); 1732 (vs); 1430 (s); 1368 (m); 1310 (s); 1260 (s); 1242 (w); broad absorption between 1210–1170 (s); 1110 (s); 1070 (w); 1022 (s); 990 (w); 910 (m); 878 (w); 862 (m).

5-Norbornene-endo-trans-2,3-dicarbo(benzoylhydroxamic) acid. The *trans* ester (21.0 g.; 0.1 mole) was treated with hydroxylamine and sodium ethoxide as described above. As the salt did not precipitate after 3 hr., the solvents were removed *in vacuo*. The residual sodium salt was dissolved in water (200 ml.) containing sodium acetate trihydrate (16.2 g.) and treated dropwise with benzoyl chloride (40 ml.) at 0°. After 2.0 hr. the mixture was acidified, with concentrated hydrochloric acid (20 ml.) and the solid filtered, washed with water, then with benzene (100 ml.) and then with ether (20 ml.). The crude solid (22.5 g.) was recrystallized from 80% ethanol (250 ml.) and it formed fine needles which weighed 21.0 g. (50%) m.p. 187° with dec.

Anal. Calcd. for $C_{23}H_{20}N_2O_6$ (420.2): C, 65.71; H, 4.77; N, 6.67. Found: C, 65.32; H, 4.78, N, 6.98.

The *cis* ester when carried through this reaction sequence afforded only 30% of the *trans*-benzoylhydroxamic acid.

Rearrangement of trans-benzoylhydroxamic acid, VI. The hydroxamic acid (4.2 g.; 0.01 mole) was dissolved in potassium hydroxide solution (1.12 g. in 26.4 ml. of water). The solution was warmed on a steam bath and within 5 min. a solid commenced to precipitate. After 1 hr. the product (2.25 g.) was collected, washed with water. It decomposed above 300°. The product was boiled with methanol (100 ml.) and refiltered. The solid decomposed above 340°.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 64.00; H, 6.66; N, 18.66. Found: C, 63.71; H, 6.87; N, 18.32.

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(19) The *trans* ester was prepared by refluxing the anhydride in methanol in the presence of dry hydrogen chloride. A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, 10, 149 (1945).

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

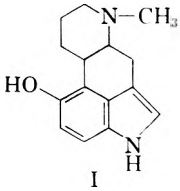
The Synthesis of 6-Hydroxy-1,3,4,5-tetrahydrobenz [cd] indole[1]

JAMES A. MOORE AND MICHAEL RAHM

Received July 25, 1960

5,8-Dimethoxy-1-tetralone (IV) was converted to the aminomethyltetralin (VIII) *via* the cyanohydrin (V) and nitrile (VII). Demethylation and ferricyanide oxidation led to the 6-hydroxytetrahydrobenzindole (IX).

The importance of both 5-hydroxytryptamine (serotonin) and of lysergic acid derivatives in pyschopharmacology, and the biochemical interactions of these substances,[2] suggest that derivatives of 12-hydroxyergoline (I) might be of considerable pharmacological interest. This possibility has prompted us to undertake synthetic efforts designed to furnish access to the 12-hydroxyergoline system.



I

Most of the previous synthetic approaches to reduced benz[*cd*]indole or ergoline derivatives have involved the elaboration of rings C and D on a preformed indole nucleus[3]; an exception has very recently been described by Walker and Weaver.[4] The presence of the 12-hydroxy group in II, however, lends a rather broader scope to the synthetic possibilities. One attractive approach permitted by this substituent is embodied in the elegant synthesis of 5-hydroxyindole, described by Cromartie and Harley-Mason,[5] in which β-(2,5-dihydroxyphenyl)ethylamine is cyclized directly to the indole by mild oxidation. As an initial stage in the adaptation of this route to the ergoline system I, the preparation of the model tricyclic compound IX has been accomplished and is described in the present paper.

The required aminomethyltetralin was obtained from 5,8-dimethoxy-1-tetralone (IV)[6] by the reaction sequence shown in Fig. 1. In the preparation of the ketone IV, the procedure of Momose *et*

(1) Supported by a grant from the Geschickter Fund for Medical Research.

(2) For a review, *cf. Ann. N. Y. Acad. Sci.*, 66, 417–480 (1957).

(3) *Inter alia:* F. C. Uhle and W. A. Jacobs, *J. Org. Chem.* 10, 76 (1945); A. Stoll and J. Rutschmann, *Helv. Chim. Acta* 33, 67 (1950); E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.* 78, 3087 (1956); H. Plieninger, M. Schach v. Wittenau and B. Kiefer, *Chem. Ber.* 91, 2095 (1958).

(4) G. N. Walker and B. N. Weaver, *J. Org. Chem.* 35, 484 (1960).

(5) R. J. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.* 2525 (1952).

(6) T. Momose, H. Oya, Y. Ohkura, and M. Iwasaki, *Pharm. Bull.* (Tokyo), 2, 119 (1954); *Chem. Abstr.* 50, 911 (1956).

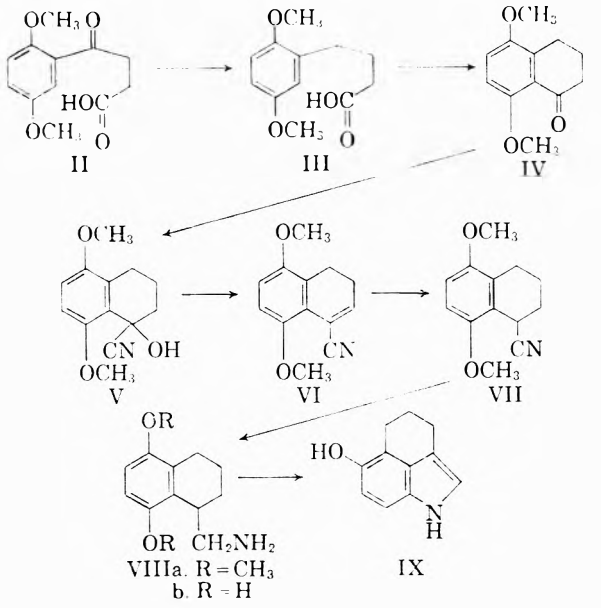


Fig. 1 Preparation of the aminomethyltetralin, IX

al.[6] starting with β-(2,5-dimethoxybenzoyl)propionic acid was followed with two modifications. Instead of a two-stage sequence of electrolytic reduction to the lactone and subsequent hydrogenolysis, the arylbutyric acid (III) was obtained directly in 66% yield by Wolff-Kishner reduction. Cyclization of III was accomplished with polyphosphoric acid. The crystalline cyanohydrin V was obtained in the usual way in 75% yield and was then dehydrated with thionyl chloride in pyridine. Although catalytic reduction of the unsaturated nitrile in the presence of acid furnished the amine VIIIa in moderate yield, hydrogenation to the saturated nitrile followed by hydride reduction was more satisfactory for larger-scale preparations of VIIIa. Demethylation was effected with constant-boiling hydrobromic acid, giving the hydrobromide of VIIIb in 70% yield.

The oxidation of the dihydroxyamine, as the hydrochloride, was carried out according to the procedure described for the phenethylamine.[5] The crude indole could be crystallized directly after extraction with ether, but was very unstable until purified by passage over a column of alumina. The material was then sublimed and recrystallized to give a colorless product in 52% yield. The ultraviolet spectrum was very similar to that of 5-hydroxyindole.

The 6-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole formulation for the oxidation product is quite firmly established by this straightforward reaction sequence. It seemed desirable, nevertheless, to confirm the structure by conversion to the known 1,3,4,5-tetrahydrobenz[*cd*]indole,[7] particularly since it was anticipated that such a transformation would be required in the structure proof of more complex tetracyclic members of the series which are currently in preparation. The similar removal of a hydroxyl group in the indole benzenoid ring was accomplished in the structure proof of 6-hydroxyyohimbyrine by Raney nickel detosylation,[8] and an attempt was made to apply this procedure to IX. The tosylate was obtained in good yield, but neither this compound nor 5-tosyloxyindole could be converted to the corresponding unsubstituted indole, the unchanged tosylates being recovered after vigorous treatment with Raney nickel.

(7) W. A. Jacobs and G. Gould, *J. Biol. Chem.*, **120**, 141 (1937); F. C. Uhle, C. G. Vernick, and G. L. Schmir, *J. Am. Chem. Soc.* **77**, 3334 (1955).

EXPERIMENTAL[9]

β-(2,5-Dimethoxybenzoyl)propionic acid[6] was prepared from 125 g. of succinic anhydride, 333 g. of aluminum chloride and 155 g. of *p*-dimethoxybenzene in 2 l. of nitrobenzene. The mixture was allowed to warm from 5° to 29° during 3.5 hr. at which time the color changed from orange to green, and the solution was then promptly poured into iced hydrochloric acid. After extraction with bicarbonate and reacidification, 218 g. (81%) of colorless product, m.p. 101–102°, was obtained.

α-(2,5-Dimethoxyphenyl)butyric acid (III). A solution of 17.6 g. of the keto acid II in 200 ml. of triethylene glycol containing 10 g. of sodium hydroxide, 10 ml. of 85% hydrazine hydrate and 10 ml of water was refluxed for 3 hr. and then was heated further without a condenser until the temperature rose to 210°. After another hour sufficient water was added to lower the temperature to 190° and heating was continued for 4 more hours. The solution was then cooled and poured into a mixture of 50 ml. of concd. hydrochloric acid and 500 g of ice. The precipitated acid was washed and dried, 11.0 g. (66%), m.p. 64–65°; after recrystallization from ether, m.p. 68–69°.

5,8-Dimethoxy-1-tetralone (IV). To polyphosphoric acid prepared from 500 g. of 85% phosphoric acid and 455 g. of phosphoric anhydride was added 22.9 g. of III. After warming on the steam bath for 1.5 hr. the orange solution was poured onto ice and the ketone extracted with ether. The ether solution was washed with base, dried, and evaporated. Two crops of colorless prisms were obtained, total 15 g., m.p. 58–62°.

The *2,4-dinitrophenylhydrazone* was obtained as orange-red needles from ethyl acetate, m.p. 245–246°.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: C, 55.95; H, 4.70; N, 14.50. Found: C, 56.14; H, 4.73; N, 14.24.

5,8-Dimethoxy-1-tetralone cyanohydrin (V). Solutions of 3.74 g. of the ketone IV in 300 ml. of ether and 60 g. of sodium cyanide in 300 ml. of water were stirred and treated dropwise with a solution of 34 ml. of concd. sulfuric acid in 80 ml. of water. After 1 hr. the ether layer was washed with water, dried with sodium sulfate, decolorized with charcoal, and concentrated to a syrup. The cyanohydrin crystallized as colorless prisms, m.p. 97–98°. Recrystallization from ethanol furnished 3.1 g., m.p. 103–104°, λ^{KBr} 2.86 μ, 4.48 μ (weak).

4-Cyano-5,8-dimethoxy-1,2-dihydronaphthalene (VI). To a solution of 38 g. of the cyanohydrin V in 19 ml. of pyridine at 0° was added 10 ml. of thionyl chloride. The yellow solution was then heated for 1 hr. on the steam bath, cooled

(8) L. Dorfman, A. Furlenmaier, C. F. Huebner, R. Lucas, H. B. Mac Phillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. Andre, *Helv. Chim. Acta* **37**, 59 (1954).

(9) Infrared spectra were obtained in potassium bromide discs for all new compounds; selected bands are recorded for the more important compounds.

and treated with ice water. The product separated as a yellow solid, m.p. 81–86°. Recrystallization from ethanol gave 28 g. (80%) of colorless needles, m.p. 85–86°, λ^{KBr} 4.49 μ (med.).

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.82; H, 6.15; N, 6.31.

1-Cyano-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VII). A solution of 28 g. of the unsaturated nitrile VI in 100 ml. of methanol was shaken with 1 g. of 10% palladium-carbon catalyst for 10 hr. at 3 atm. hydrogen pressure. After removal of the catalyst and concentration the product crystallized as colorless plates, 23 g. (82%), m.p. 98–99°. Recrystallization from methanol raised the m.p. to 104–105°, λ^{KBr} 4.46 (med).

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96. Found: C, 72.06; H, 6.91.

1-Aminomethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VIIIa). A. From VII. A solution of 23 g. of the saturated nitrile VIII in ether was refluxed for 5 hr. with excess lithium aluminum hydride. The excess reagent was decomposed with water and the inorganic solid filtered and washed with ether. The combined ether solutions were concentrated to a syrup which crystallized to give 19 g. of white needles, m.p. 86–87°.

B. From VI. A solution of 215 mg. of the unsaturated nitrile in 25 ml. of ethanol containing 0.16 ml. of concd. hydrochloric acid was stirred with 10% palladium-carbon catalyst for 10 hr. in a hydrogen atmosphere. The catalyst was filtered and the solution evaporated to a syrup which was dissolved in hydrochloric acid, decolorized and then made alkaline. The amine separated in white crystals, m.p. and mixed m.p. 83–85°.

1-Aminomethyl-5,8-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (VIIIb). A solution of 15 g. of the dimethoxyamine in 350 ml. of 48% hydrobromic acid was refluxed for 2 hr. On cooling the salt of VIIIb crystallized as violet plates, which were recrystallized twice from ethanol to give 13 g. of nearly colorless crystals which decomposed above 150° without melting.

Anal. Calcd. for $C_{11}H_{16}O_2NBr$: C, 48.18; H, 5.88, N, 5.11. Found: C 48.53; H, 5.82; N, 5.38.

6-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (IX). A solution of 1.23 g. of hydrobromide VIIIb in 100 ml. of water was shaken for 30 min. with freshly precipitated silver chloride and then filtered. To this solution of the hydrochloride of VIIIb was added in one portion a solution of 3.11 g. of potassium ferricyanide and 5 g. of sodium bicarbonate in 50 ml. of water. The solution immediately became magenta, and carbon dioxide was evolved for 2–3 min. The solution was then extracted with four 50-ml. portions of ether and the combined extracts were dried with magnesium sulfate; the drying agent immediately developed a brilliant azure color. The ether was then evaporated *in vacuo* to give 701 mg. of brown crystalline residue. A solution of this material in benzene was passed over a 1.5 x 20 cm. column of alumina. A band of dark violet material was retained at the top of the column; after elution of a small amount of oily material, increasing concentrations of chloroform eluted the indole, which crystallized as pale tan prisms, 452 mg., m.p. 117–118°. Sublimation furnished 406 mg. of sparkling white material. m.p. 125–126°, $\lambda_{max}^{C_2H_5OH}$ 276 μ (6000), 301 μ (4700). The Ehrlich reaction with *p*-dimethylaminobenzaldehyde gave a violet color.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.25; H, 6.80; N, 8.41.

The *tosylate* was prepared by heating a solution of 100 mg. of IX and 300 mg. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine at 50° for 26 hr. After pouring onto iced hydrochloric acid the product precipitated. It was recrystallized from ethanol-ether to give 121 mg. of colorless prisms, m.p. 164–165° and 25 mg., m.p. 162–163°.

Anal. Calcd. for $C_{18}H_{17}O_3NS$: C, 66.05; H, 5.24. Found: C, 66.15; H, 5.25.

In an attempted reduction, 100 mg. of the tosylate was refluxed with Raney nickel in ethanol with a stream of hydrogen for 6 hr. After removing the catalyst, evaporation of the solution furnished 65 mg. of the tosylate, m.p. 157–161°. None of the reduced indole was obtained by distillation of the mother liquor.

NEWARK, DEL.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, HOFFMANN LAROCHE, INC.]

Quinazolines and 1,4-Benzodiazepines. II.[1] The Rearrangement of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide into 2-Amino Derivatives of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine 4-Oxide

L. H. STERNBACH AND E. REEDER

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On treatment with ammonia or primary amines, 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) rearranges into 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II, IX). Reaction of I with secondary amines proceeds without rearrangement with formation of the expected 6-chloro-2-aminomethyl-4-phenylquinazoline 3-oxides.

The structure determination of quinazoline 3-oxides was described in a preceding communication.[1] This paper is concerned with further reactions of these compounds.

In attempts to prepare secondary amino derivatives of quinazoline 3-oxides we treated 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I)[1] with primary amines. In a few cases the expected products were formed, but in addition we obtained in all reactions compounds of a different character whose infrared and ultraviolet absorption spectra[2a] indicated a structural change. A closer study of the "abnormal" reaction products showed that a ring enlargement[2b] had occurred and that these compounds were 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

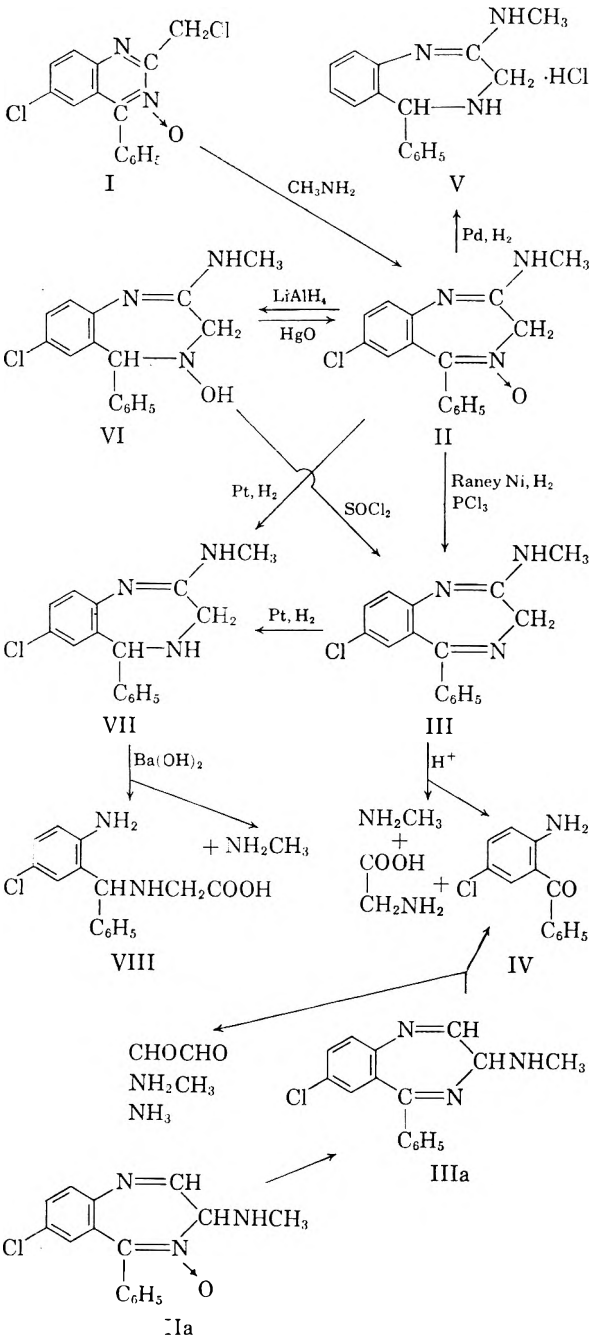
For the structure determination we chose the product formed on treatment of 6-chloro-

(1) Paper I. L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.* 82, 475 (1960).

2-chloromethyl-4-phenylquinazoline 3-oxide with methylamine. This reaction yielded only the rearranged compound II[3] which was obtained in high yield (about 80%).

The product had the empirical formula $C_{16}H_{14}N_3OCl$ and was shown to be a base by its ability to form a stable hydrochloride. It had a hydrogen atom attached to the basic nitrogen as it could be easily acetylated to form a neutral monoacetyl derivative which in turn could be deacetylated and reconverted into the original base by mild alkaline hydrolysis. It proved to be an *N*-oxide, as it could be converted with excellent yield into a desoxy derivative by treatment with phosphorus trichloride or by hydrogenation with Raney nickel.[4] Both the *N*-oxide and the desoxy derivative yielded on hydrolysis 2-amino-5-chlorobenzophenone (IV) in almost quantitative yield which proved that on reaction with methylamine the 2-amino-5-chlorobenzophenone moiety of the molecule had remained unchanged. For the molecular weight determination we chose the dihydrodesoxy derivative $C_{16}H_{16}N_3Cl$, obtained from $C_{16}H_{14}N_3OCl$ by hydrogenation in the presence of a platinum catalyst. This compound was selected because it was soluble in the usual organic solvents whereas both the oxide and the desoxy derivative were not. The product was found to be a monomer by the Rast and the isothermic distillation methods.

Only structures II and IIa consistent with the above data could be proposed for this compound. To establish the correct one we studied the hydrolytic cleavage of the desoxy derivative III or IIIa. As degradation products, we expected in addition to the 2-amino-4-chlorobenzophenone (IV), glycine and methylamine, if structure II were correct. If IIa were the structure of the compound, glyoxal, ammonia, and methylamine would be the decomposition products. Energetic hydrolysis with dilute hydrochloric acid gave an almost quantitative yield of 2-amino-5-chlorobenzophenone (IV), which was extracted from the



acidic reaction mixture.[5] The aqueous solution was concentrated and the residue was treated with benzoyl chloride in the presence of alkali in order to convert the expected smaller basic fragments into their benzoyl derivatives. We obtained a yield of 55% of hippuric acid, formed from the glycine, and a 59% yield of benzoylmethylamine, formed from the methylamine. This proved conclusively structure II for our product and showed that 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) on treatment with methylamine undergoes a ring enlargement resulting in the formation of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - 1,4-

(2)(a) Characteristic for these compounds is a very strong maximum in the infrared spectrum at 1620–1605 cm.$^{-1}$ accompanied by a sharp peak of medium intensity at 1590–1580 cm.$^{-1}$ whereas the starting material and the normal reaction products showed only two sharp weak peaks at 1605 and 1550 cm.$^{-1}$ The ultraviolet spectra also showed characteristic differences. The starting material and the normal reaction products have two maxima at 230–234 mμ (ε, 25 000–30,000) and at 266–270 mμ (ε 27,000–32,000). The abnormal reaction products have two maxima at 243–247 mμ (ε 25,500–30,500) and at 263–267 mμ (ε 22,000–32,000) separated by a flat minimum (ε 25,000–29,000). (b) We have not yet established the mechanism of this rearrangement.

(3) The generic name of this compound is chlordiazepoxide and it is marketed under the trade name Librium.®

(4) The desoxy derivative was not a quinazoline as shown by the absence of the strong band at 1543–1539 cm.$^{-1}$ (see Ref. 1, footnote 15) in its infrared spectrum. The similarity of its infrared spectrum to that of the oxide from which it was obtained indicated that the removal of the oxygen atom had occurred without change in the ring structure.

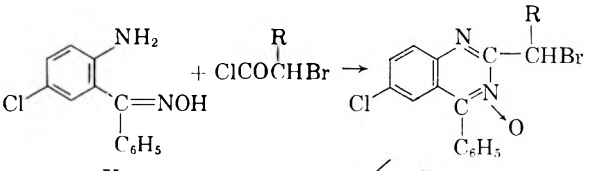
(5) Compound IV is not basic enough to form a salt with 3*N* hydrochloric acid.

benzodiazepine 4-oxide (II), a seven-membered cyclic compound.

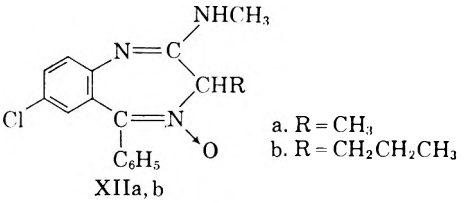
We also studied the hydrolytic degradation of the "dihydrodesoxy" derivative VII which was prepared by catalytic hydrogenation of II or III in the presence of platinum oxide. After acid hydrolysis we isolated methylamine hydrochloride but encountered difficulties in the purification of other degradation products. On hydrolysis with 1*N* barium hydroxide we observed the escape of a volatile base and isolated with excellent yield an insoluble, crystalline barium salt which was converted into a crystalline amino acid. Its composition, amphoteric character, and the presence of a primary aromatic amino group which was demonstrated by a positive diazo reaction pointed to structure VIII for this compound. The hydrolysis of VII to a compound of structure VIII corroborated the structures of II and III from which it was derived and in addition showed that the catalytic hydrogenation of III had resulted in the saturation of the double bond in the 4,5-position.

Further study of II led to the preparation of two additional reduction products. Hydrogenation in the presence of a palladium catalyst resulted in the removal of the oxygen and chlorine atoms, the addition of two hydrogen atoms, with the formation of V. The structure of this product was established by analysis, and by the similarity of the infrared and ultraviolet spectra of its free base with the spectra of VII. Reduction of II with lithium aluminum hydride yielded the hydroxylamine derivative VI.[6] The structure of this compound was proved by its reoxidation to II with mercuric oxide and by its dehydration with thionyl chloride to III.

Compound II showed, as found by L. O. Randall and co-workers,[7] interesting psychosedative properties. Therefore, a series of homologs and analogs of II was prepared by treating 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide (I) with ammonia and various primary amines in dioxane or methanol solutions. In all cases products were formed to which the benzodiazepine oxide structure IX was assigned on account of their characteristic infrared and ultraviolet spectra. The high melting points were also characteristic (in most cases above 200°) as well as the low solubility in acetone and methanol, and the sedative properties, which were observed only in compounds belonging to this group. Two homologs of II were also prepared as shown below (X → XI → XII):



X XIa,b

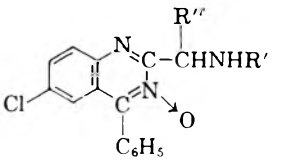


XIIa,b

a. R = CH_3
b. R = $CH_2CH_2CH_3$

The six amines IX a–f and the homolog XIIa showed sedative and muscle relaxant properties.[8] The primary amine IXa was about equally active, the others less active than II. The diamine IXg was pharmacologically inactive.

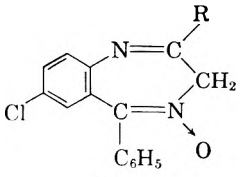
In four cases, the normal reaction products (XIII a–d) were isolated in addition to the rearranged compounds IXd–f and XIIb.[9]



XIII

XIIIa. R′ = $CH_2CH{=}CH_2$; R″ = H
b. R′ = CH_2CH_2OH; R″ = H
c. R′ = $CH_2CH_2OCH_3$; R″ = H
d. R′ = CH_3; R″ = $CH_2CH_2CH_3$

The reaction of I with secondary amines as described for the 2-chloromethyl-6,7-dimethyl-4-phenylquinazoline 3-oxide[1] yielded only the normal reaction products. Two compounds (XIV a and b) belonging to this series were synthesized.



IXa–g

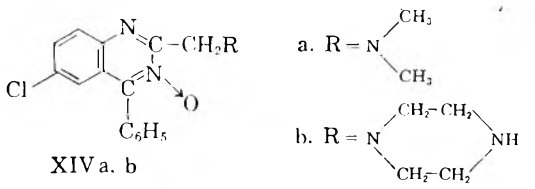
IXa. R = NH_2
b. R = NHC_2H_5
c. R = NHC_4H_9-*n*
d. R = $NHCH_2CH{=}CH_2$
e. R = $NHCH_2CH_2OH$
f. R = $NHCH_2CH_2OCH_3$
g. R = $NHCH_2CH_2NH_2$

(6) O. Exner [*Coll. Czech. Chem. Comm.*, **20**, 202 (1955)] discovered this interesting method for the reduction of nitrones to hydroxylamines.

(7) L. O. Randall, W. B. Schallek, G. A. Heise, E. F. Keith, and R. E. Bagdon, *J. Pharmac. and Experim. Therap.*, **129**, 163 (1960).

(8) Private communication from L. O. Randall.

(9) It is possible that in other reactions, compounds of type XIII were also formed, but no particular attempts were made to isolate them. The preparation of II, however, was thoroughly studied in order to find also the unrearranged reaction product (XIII, R = CH_3; R″ = H). We were, however, unable to demonstrate its presence; variations of the solvents used in this reaction did not result in its formation.



XIV a. b

EXPERIMENTAL

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared wherever necessary in order to establish structural changes. The infrared spectra were determined in 1–5% chloroform solutions using a Perkin Elmer Model 21 spectrophotometer; the ultraviolet absorption spectra, in isopropyl alcohol and in 0.1*N* hydrochloric acid.

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II). Into 600 cc. of a cold 25% solution of methylamine in methanol was introduced with stirring 98 g. of the hydrochloride of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I).[1] The mixture was initially cooled to about 30° and then stirred at room temperature for 15 hr. The precipitated chemically pure reaction product (50 g.) was then filtered off. The mother liquor was concentrated *in vacuo* and the residue dissolved in methylene chloride. The methylene chloride solution was washed with water, dried with sodium sulfate, and concentrated *in vacuo*. The crystalline residue was triturated with a small amount of hot acetone to dissolve the more soluble impurities. The mixture was then cooled to 5° for 10 hr. and filtered, yielding 20.3 g. of almost chemically pure material. The total yield was 70.3 g. (82%). The product could be recrystallized from the fifteen-fold amount of boiling ethanol and formed then light yellow plates melting at 236–236.5°.

Anal. Calcd. for $C_{16}H_{14}N_3OCl$: C, 64.11; H, 4.71. Found: C, 64.38; H, 4.66.

Hydrochloride. A solution of the base in the calculated amount of 2*N* methanolic hydrochloric acid was diluted with ether and petroleum ether and the precipitated hydrochloride was filtered off. It could be recrystallized from methanol or a mixture of methanol and acetone and formed colorless water soluble plates melting at 215–216°. It discolored on exposure to light.

Anal. Calcd. for $C_{16}H_{15}N_3OCl_2$: C, 57.15; H, 4.50. Found: C, 57.20; H, 4.37.

Phosphate. To a stirred suspension of 13.2 g. (44.1 mmoles) of the base in 250 cc. of alcohol were added 44.1 mmoles of 85% phosphoric acid and as much water as necessary to keep the phosphate in solution. The solution was then concentrated to dryness *in vacuo* and the residue triturated with acetone. The crystalline phosphate (13.4 g.) was filtered off. It formed colorless plates melting at 206–207°.

Anal. Calcd. for $C_{16}H_{17}ClO_5P$: C, 48.31; H, 4.31. Found: C, 48.34; H, 4.23.

Bisulfate: To a suspension of 29.4 g. (98 mmoles) of the base in 55 cc. of methanol was added with stirring a solution of 98 mmoles of sulfuric acid in 25 cc. of methanol. The mixture was diluted with 100 cc. of acetone and the crystals formed (39.2 g.) were filtered off. The salt formed colorless plates melting at 214–215°.

Anal. Calcd. for $C_{16}H_{16}N_3O_5ClS$: C, 48.30; H, 4.05. Found: C, 48.81; H, 4.25.

Monoacetyl derivative. To a solution of 100 g. of the base in 1.2 l. of dry pyridine was added 600 cc. of acetic anhydride. The mixture was left at room temperature for 14 hr. and concentrated *in vacuo*. The residue was crystallized from a mixture of ether and petroleum ether (b.p. 30–60°) and yielded 93 g. (82%) of colorless prisms melting at 186–187°.

Anal. Calcd. for $C_{18}H_{16}N_3O_2Cl$: C, 63.25; H, 4.72; N, 12.30. Found: C, 62.96; H, 4.65; N, 12.26.

This compound reformed the base on mild alkaline hydrolysis: To a solution of 2 g. of the acetyl derivative in a mixture of 20 cc. of dioxane and 35 cc. of alcohol was added 25 cc. of 3*N* potassium hydroxide. The solution was left at room temperature for 20 days, diluted with water, and extracted with methylene chloride. The methylene chloride solution was concentrated *in vacuo* and the residue crystallized from a mixture of acetone, ether, and petroleum ether to yield 0.6 g. of the pure base II. It was identified by mixed melting point and infrared spectrum.

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III). A mixture of 20 g. of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 3-oxide (II), 300 cc. of chloroform and 38 cc. of phosphorus trichloride was refluxed for 1 hr. and concentrated *in vacuo* to dryness. To this residue methylene chloride, an excess of 50% potassium hydroxide and ice were added. The mixture was stirred energetically to achieve complete decomposition and the precipitated reaction product was filtered off (12.2 g. m.p. 237–238°). The methylene chloride solution was then separated, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield additional 5.9 g. of the product melting at 227–230°. The total yield was 95%. In other reactions, yields of about 80% were obtained. The product formed after recrystallization from acetone rhombic, yellowish plates melting at 240–241°.

Anal. Calcd. for $C_{16}H_{14}N_3Cl$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.68; H, 4.93; N, 14.78.

The same compound was obtained by catalytic hydrogenation of the *N*-oxide, II. A solution of 15 g. of II in 200 cc. of warm dioxane was cooled to room temperature and then hydrogenated at atmospheric pressure in the presence of about 20 g. of Raney nickel. After 2 hr. 1 mole of hydrogen was absorbed and the uptake came to an almost complete stop. The precipitated hydrogenation product was dissolved by heating and the Raney nickel removed by filtration. The product was isolated by crystallization in almost quantitative yield.

Hydrochloride. A methanol suspension of the base was neutralized with the calculated amount of 1*N* methanolic hydrochloric acid. The product was crystallized by the addition of ether and petroleum ether. It formed rosettes of plates melting at 260–261°.

Anal. Calcd. for $C_{16}H_{15}N_3Cl_2$: C, 60.02; H, 4.72. Found: C, 59.95; H, 4.63.

Acid hydrolysis of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (II). *Isolation of a 2-amino-5-chlorobenzophenone* (IV), *glycine as hippuric acid, and methylamine as N-methylbenzamide.*

A solution of 2.83 g. (10 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (II) in a mixture of 25 cc. of 3*N* hydrochloric acid and 15 cc. of alcohol was refluxed for 19 hr. The mixture was then cooled, diluted with water, and extracted with ether. The ether extract was dried and concentrated *in vacuo* yielding 2.0 g. (87%) of 2-amino-5-chlorobenzophenone,[5] which was identified by melting point and mixed melting point with an original sample.

The aqueous solution was concentrated *in vacuo* and the residue was dissolved in 30 cc. water. To the stirred and cooled solution were added in portions within 0.5 hr. 4.2 g. benzoyl chloride and about 25 cc. of 3*N* potassium hydroxide at such a rate as to maintain a *p*H of 6–7. The mixture was then made alkaline, heated to 60°, to destroy small amounts of unchanged benzoyl chloride, cooled, and extracted with ether. The ether solution containing the *N*-methylbenzamide was dried, concentrated *in vacuo*, and the *N*-methylbenzamide was extracted from the residual oil with boiling water. The aqueous extract was concentrated *in vacuo*, yielding 0.8 g. (59%) of crystalline *N*-methylbenzamide melting at 77–78°. The analysis sample was recrystallized from ether and formed plates melting at 78–79°. It gave no melting point depression with a synthetic sample.[20]

(20) The melting point reported in the literature is 80°.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 71.37; H, 6.79.

The alkaline aqueous solution, remaining after the removal of the *N*-methylbenzamide was acidified and concentrated *in vacuo* to a small volume until the hippuric acid started to crystallize. The mixture was then extracted with ethyl acetate. The extract was dried, concentrated *in vacuo*, and the crystalline residue was treated with hot benzene to dissolve the admixed benzoic acid. The undissolved hippuric acid (0.75 g.) was filtered off. The benzene solution deposited after partial concentration and cooling an additional amount (0.25 g.) of hippuric acid. The total yield was 55%. The hippuric acid was identified by melting point (187°), mixed melting point with an authentic sample, and analysis.

7-Chloro-2-methylamino-5-phenyl-3H-4,5-dihydro-1,4-benzodiazepine (VII). A) *From the desoxy compound* III. The desoxy compound III (2.83 g., 10 mmoles) was hydrogenated in acetic acid solution (20 cc.) at room temperature and atmospheric pressure in the presence of 0.3 g. prehydrogenated platinum oxide. After 1 hr., 10 mmoles of hydrogen was absorbed and the uptake had slowed down considerably. The catalyst was filtered off and the solution concentrated *in vacuo*. The residue was dissolved in ether and washed with ice cold 3*N* sodium hydroxide. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from a mixture of ether and petroleum ether, yielding 1.8 g. (63%) of crystalline material. The product formed colorless plates softening at 176° and melting at 179–180°.

Anal. Calcd. for $C_{16}H_{16}N_3Cl$: C, 67.24; H, 5.64; N, 14.71; Cl, 12.41; mol. wt., 285.77. Found: C, 66.84; H, 5.79; N, 14.79; Cl, 12.41; mol. wt., (Rast in exaltone) 282, 280; (isothermic distillation in acetone) 295, 302.

B) *From the N-oxide* II. *Isolation as dihydrochloride.* To 0.3 g. of prehydrogenated platinum oxide was added a solution of 2.99 g. (10 mmoles) of II in 40 cc. of acetic acid. The product was hydrogenated at room temperature and atmospheric pressure for 1.5 hr., until 20 mmoles of hydrogen were absorbed and the uptake came to a complete stop. The solution was filtered, concentrated *in vacuo*, and the residue dissolved in ether. The ether solution was washed with alkali, dried, and concentrated *in vacuo*. The residue was dissolved in 20 cc. of 1*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and ether. The yield was 2.4 g. 67%. The material can be recrystallized from a mixture of methanol and ether and forms then flat prisms or plates softening at 233° and melting at 236–238°. The analysis sample which was recrystallized from dilute hydrochloric acid, formed fine flat needles.

Anal. Calcd. for $C_{16}H_{18}N_3Cl_3$: C, 53.57; H, 5.06; Cl, 29.65. Found: C, 53.53; H, 5.05; Cl, 29.24.

The material could be converted into the above described base by treatment with alkali.

2-Amino-5-chloro-benzhydrylaminoacetic acid (VIII) *and its barium salt.* A solution of 2 g. (7 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-4,5-dihydro-1,4-benzodiazepine (VII) in a mixture of 30 cc. of methanolic 1*N* barium hydroxide and 10 cc. of water was refluxed for 6 hr. The mixture containing an appreciable amount of crystals was left at room temperature for 2 days and filtered. The precipitated barium salt (1.1 g., 3.07 mmoles) was filtered off, washed with some methanol, and recrystallized from water. It formed white needles melting at 207–208°.

Anal. Calcd. for $C_{30}H_{28}O_4N_4Cl_2Ba$: C, 50.26; H, 3.94; Ba, 19.16. Found: C, 50.54; H, 4.14; Ba, 19.27, 18.91.

The mother liquor containing the excess barium hydroxide and the rest of unchanged starting material was refluxed for 6 more hr., freed from barium ions with about 27 cc. of 1*N* sulfuric acid, filtered, concentrated *in vacuo*, diluted with a small amount of water, and extracted with ether. The free amino acid forming a crystalline precipitate (needles 0.3 g., 1 mmole) was filtered off and recrystallized from methanol or dilute methanol. The product formed needles or prisms softening at 191° and melting at 212–214°. It was soluble in acids and alkali. A strongly acidic solution gave after diazotation a positive color test with β-naphthol.

Anal. Calcd. for $C_{15}H_{15}O_2N_2Cl$: C, 61.96; H, 5.20; N, 9.64; Cl, 12.20. Found: C, 61.81; H, 5.22; N, 9.84; Cl, 12.13. The ether solution was concentrated *in vacuo* and yielded 0.6 g. (2 mmoles) of starting material. Thus 5 mmoles of hydrolyzed starting material yielded 3 mmoles of the barium salt of the amino acid and 1 mmole of the free amino acid.

2-Methylamino-5-phenyl-4,5-dihydro-3H-benzodiazepine hydrochloride (V). Six grams (20 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II) was hydrogenated at room temperature and atmospheric pressure in 200 cc. methanol with 2 g. of 10% palladium on charcoal as catalyst. After the absorption of about 50 mmoles of hydrogen (3.5 hr.) the reaction was stopped. The solution was filtered, concentrated *in vacuo*, and the residue crystallized from a mixture of alcohol, ether, and petroleum ether. The yield was 4.2 g. (*ca.* 70%). The pure material formed colorless plates melting at 240–242°.

Anal. Calcd. for $C_{16}H_{18}N_3Cl$: C, 66.77; H, 6.30. Found: C, 67.00; H, 5.76.

Base. The base was liberated from the hydrochloride with alkali and formed after crystallization from a mixture of ether and petroleum ether long prisms melting at 153–155°. The ultraviolet and infrared spectra of VII and this base showed a similarity which leaves no doubt as to the identity of their ring structures.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.00; H, 6.45.

Dihydrochloride. The free base was dissolved in 2 moles of 1*N* methanolic hydrogen chloride. The solution was concentrated *in vacuo* and the salt crystallized from a mixture of methanol, ether and petroleum ether. It formed crystals melting like the monohydrochloride at 240–242°.

Anal. Calcd. for $C_{16}H_{19}N_3Cl_2$: C, 59.26; H, 5.91. Found: C, 59.37; H, 6.50.

7-Chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI). A solution of 20 g. 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II) in 200 cc. of dry tetrahydrofuran was added at room temperature in portions to a stirred suspension of 3.8 g. of lithium aluminum hydride in 250 cc. of tetrahydrofuran. The mixture was refluxed for 30 min., then the excess of lithium aluminum hydride was destroyed with ethyl acetate. Ice water was added and the reaction product extracted with ether. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from ether. The yield was 17 g. (85%). After recrystallization from acetone, the product formed rosettes of colorless needles melting at 183–184°.

Anal. Calcd. for $C_{16}H_{16}N_3OCl$: C, 63.68; H, 5.35; Cl, 11.75. Found: C, 63.65; H, 5.46; Cl, 11.46.

Dihydrochloride. A solution of the base in an excess of 1*N* methanolic hydrogen chloride was concentrated *in vacuo* to a small volume and diluted with ether. The precipitated dihydrochloride was recrystallized from a mixture of methanol and ether and formed then yellowish needles melting with decomposition at 166–170°.

Anal. Calcd. for $C_{16}H_{18}N_3OCl_3$: C, 51.29; H, 4.84. Found: C, 51.57; H, 5.21.

Diacetyl derivative. A solution of 3 g. of the base in a mixture of 48 cc. of pyridine and 24 cc. of acetic anhydride was left at room temperature for 16 hr. and then concentrated *in vacuo* to dryness. The residue was dissolved in ether; the solution was washed with ice cold dilute hydrochloric acid, dilute sodium carbonate solution and water. The dried ether solution was concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether. It formed rosettes of plates melting at 133–134°.

Anal. Calcd. for $C_{20}H_{20}N_3O_3Cl$: C, 62.52; H, 5.22; acetyl, 22.36. Found: C, 62.54; H, 5.18; acetyl, 21.99.

Dehydration of VI to 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III). To a warm solution of 0.5 g.

of 7-chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI) in 25 cc. of chloroform was added 0.5 cc. of thionyl chloride. The mixture was refluxed for 10 min., poured on ice, and neutralized with 3*N* alkali. The organic layer was separated, dried, and concentrated *in vacuo*. The residue yielded after crystallization from acetone 0.2 g. of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III) which was identified by melting point, mixed melting point, and infrared spectrum.

Oxidation of VI *with mercuric oxide to 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide* (II). A mixture of 1.5 g. of 7-chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI), 2.1 g. of mercuric oxide, 30 cc. of acetone and 3 cc. of water was shaken at room temperature for 1.5 hr. Then methylene chloride was added and the mixture was filtered. The organic layer was separated, washed with water, dried and concentrated *in vacuo*. The residue was recrystallized from ethanol and yielded 0.2 g. of pure 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II), which was identified by melting point, mixed melting point, and infrared spectrum. In addition, 0.6 g. of less pure lower melting material was obtained.

7-Chloro-2-amino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXa). A suspension of 40 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 400 cc. of 15% alcoholic ammonia was stirred for 5 hr. at room temperature. The precipitated reaction product was then filtered off and washed with water and ether. The yield was 24 g. (60%), the melting point 245–246°. The product could be recrystallized from a large amount of methanol and formed then slightly yellowish prisms melting at 255–256°.

Anal. Calcd. for $C_{15}H_{12}N_3OCl$: C, 63.05; H, 4.23. Found: C, 63.22; H, 4.43.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted with ether and petroleum ether. The salt precipitated as colorless, water soluble plates melting at 245–246°.

Anal. Calcd. for $C_{15}H_{13}N_3OCl_2$: C, 55.91; H, 4.07. Found: C, 55.68; H, 3.97.

Monoacetyl derivative. To a solution of 0.45 g. of the base in 12 cc. of pyridine was added 12 cc. of acetic anhydride. The precipitated crystalline product (0.4 g.) was filtered off after 2 hr. and was purified by solution in warm pyridine and reprecipitation with acetic anhydride. The pure acetyl derivative forms fine white needles melting at 243–244°.

Anal. Calcd. for $C_{17}H_{14}N_3O_2Cl$: C, 62.29; H, 4.31; N, 12.82; acetyl, 13.13. Found: C, 61.80; H, 4.54; N, 12.96; acetyl, 12.84.

7-Chloro-2-ethylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXb) was prepared in the same manner as IXa. 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) gave after 14 hr. stirring with the five-fold amount of 33% alcoholic ethylamine a yield of 69%. After recrystallization from acetone the product formed slightly yellowish prisms melting at 231–233°.

Anal. Calcd. for $C_{17}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.33; H, 5.00.

Hydrochloride. A solution of the base in the calculated amount of 1*N* alcoholic hydrochloric acid was diluted with ether and petroleum ether. The salt precipitated as colorless water soluble prisms melting at 208–209°.

Anal. Calcd. for $C_{17}H_{17}N_3OCl_2$: C, 58.29; H, 4.89. Found: C, 57.93; H, 4.72.

7-Chloro-2-butylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXc) was prepared like IXb, using for 15 g. of I a mixture of 60 cc. of methanol and 30 cc. of *n*-butylamine. The yield was 50%. The pure compound crystallized from acetone in yellowish prisms melting at 202–203°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.82; H, 5.82.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted with acetone, ether, and petroleum ether. The precipitated product was recrystallized from isopropyl alcohol with the addition of acetone and ether. It forms thin colorless plates melting at 171–173°. The product dissolved in water only on addition of dilute hydrochloric acid.

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.09; H, 5.83.

7-Chloro-2-allylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXd) *and 6-chloro-2-allylaminomethyl-4-phenylquinazoline 3-oxide* (XIIIa). A solution of 30 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in a cooled mixture of 120 cc. of methanol and 60 cc. of allylamine was left at room temperature for 24 hr. The precipitated 7-chloro-2-allylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXd) was filtered off (7 g. of prisms, m.p. 201–202°). The mother liquors were concentrated *in vacuo* and the residue dissolved in ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with ether; the acid aqueous part was made alkaline with ice cold 3*N* alkali and the basic products were extracted with ether. The ether layer was dried with sodium sulfate, concentrated *in vacuo*, and the residue crystallized by the addition of acetone and petroleum ether yielding an additional 4.2 g. of IXd. The total yield was 35%. The material was recrystallized from methanol and formed then yellowish prisms melting at 202–204°.

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95. Found: C, 66.19; H, 4.93.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrogen chloride and the salt was precipitated by the addition of acetone, ether and petroleum ether. It formed colorless rosettes of plates, darkening at 180° and melting with decomposition at 221–227°. It was soluble in water only after addition of some hydrochloric acid.

Anal. Calcd. for $C_{18}H_{17}N_3OCl_2$: C, 59.68; H, 4.73. Found: C, 59.45; H, 4.96.

In other reactions also the isomeric 6-chloro-2-allylaminomethyl-4-phenylquinazoline 3-oxide (XIIIa) was isolated. It was separated from IXd by crystallization from methanol and acetone. The less soluble compound IXd crystallized and was filtered off. The mother liquors were partially concentrated, filtered again, then concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of acetone and petroleum ether to yield compound XIIIa as yellowish needles melting at 135–136°.

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95. Found: C, 66.85; H, 5.23.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid, and the salt precipitated by the addition of isopropyl alcohol and ether. After crystallization from a mixture of methanol and isopropyl alcohol, it formed needles melting at 168–169°.

Anal. Calcd. for $C_{18}H_{17}N_3OCl_2$: C, 59.67; H, 4.73. Found: C, 60.14; H, 5.04.

7-Chloro-2-ethanolamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXc) *and 6-chloro-2-ethanolaminomethyl-4-phenylquinazoline 3-oxide* (XIIIb). A suspension of 40 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide in a mixture of 200 cc. of methanol and 100 cc. of ethanolamine was first cooled and then stirred at room temperature for 16 hr. The solution formed was concentrated *in vacuo* and the residue dissolved in 2*N* ice cold hydrochloric acid. Neutral impurities were extracted with methylene chloride, the aqueous part was cooled, made alkaline and mixed with a small amount of methylene chloride. The precipitated (17.7 g., 45%) benzodiazepine oxide (IXe)[2] was filtered off and recrystallized from methanol. It formed yellowish prisms melting at 216–218°. The methylene chloride mother liquor contained the isomer XIIIb which was isolated as described below.

Anal. Calcd. for $C_{17}H_{16}N_3O_2Cl$: C, 61.91; H, 4.89. Found: C, 62.18; H, 4.81.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted

with ether and petroleum ether. The precipitated hydrochloride was filtered off. It could be recrystallized from a mixture of methanol and ether and formed rosettes of needles melting at 210–211° dec.

Anal. Calcd. for $C_{17}H_{17}N_3O_2Cl_2$: C, 55.75; H, 4.68. Found: C, 55.84; H, 4.80.

The methylene chloride solution mentioned above was separated from the aqueous layer, dried and concentrated *in vacuo*. The residue yielded after crystallization from a mixture of methanol and ether 6.7 g. (17%) of the 6-chloro-2-ethanolaminomethyl-4-phenylquinazoline 3-oxide (XIIIb). It formed yellow needles melting at 149–150°.

Anal. Calcd. for $C_{17}H_{16}N_3O_2Cl$: C, 61.91, H, 4.89. Found: C, 61.87, H, 4.80.

7-Chloro-2-(2-methoxyethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXf) and *6-chloro-2-(2-methoxyethylaminomethyl)-4-phenylquinazoline 3-oxide* (XIIIc). A solution of 12 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 70 cc. warm dioxane was cooled and combined with 30 cc. of β-methoxyethylamine containing 30% water. After 3 days, the mixture was concentrated *in vacuo* and the residue dissolved in ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with ether; the acidic aqueous part was cooled, made alkaline, and the basic reaction products were extracted with ether. The ether layer was dried over sodium sulfate and quickly filtered, as one of the reaction products started to crystallize out. The filtrate was partially concentrated *in vacuo* and yielded two fractions of crystals, 5.7 g. melting at 160–190° and 1.7 g. melting at 115–116°. The higher melting less soluble product was isolated from these fractions by repeated crystallization from acetone, yielding finally 2.5 g. of pure 7-chloro-2-(2-methoxyethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide[2] (IXf) crystallizing in yellowish prisms melting at 225–226°. The mother liquors yielded the isomer (XIIIc) described below.

Anal. Calcd. for $C_{18}H_{18}N_3O_2Cl$: C, 62.88; H, 5.28. Found: C, 62.75; H, 5.29.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid and the salt was crystallized by the addition of ether. The product forms prisms melting at 207–209°. It dissolved in water only on addition of hydrochloric acid.

Anal. Calcd. for $C_{18}H_{19}N_3O_2Cl_2$: C, 56.93; H, 4.77. Found: C, 57.00; H, 4.84.

The low melting product (m.p. 115–116°) and the mother liquors after the separation of IXf, containing the acetone soluble parts, were concentrated *in vacuo* and the residue was purified by repeated recrystallization from ether. The pure 6-chloro-2-(2-methoxyethylamino)-4-phenylquinazoline 3-oxide (XIIIc) thus obtained (3 g.) formed yellow needles melting at 127–130°.

Anal. Calcd. for $C_{18}H_{18}N_3O_2Cl$: C, 62.88; H, 5.28; N, 12.22. Found: C, 63.10; H, 4.77; N, 11.76.

7-Chloro-2-(2-aminoethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXg) *dihydrochloride.* To a solution of 10 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 100 cc. of dioxane was added 10 cc. of ethylenediamine. The solution was left at room temperature for 2 hr. and then concentrated to dryness *in vacuo*. The residue was dissolved in an excess of ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with methylene chloride; the aqueous part was made alkaline with the addition of ice and the basic reaction product was extracted with methylene chloride. The organic solution was separated, dried, concentrated *in vacuo*, and the residue was crystallized from a mixture of methylene chloride, ether, and petroleum ether. The base (4.7 g., 43%) formed yellowish prisms melting at 170–171°. The infrared spectrum proved the benzodiazepine 4-oxide structure.[2] The compound was dissolved in methanol and treated with 2 moles of 1*N* hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and ether. The salt forms colorless plates melting at 219–220°.

Anal. Calcd. for $C_{17}H_{19}N_4OCl_3$: C, 50.82; H, 4.77. Found: C, 50.35; H, 4.61.

6-Chloro-2-(α-bromoethyl)-4-phenylquinazoline 3-oxide (XIa). A solution of 24.6 g. (0.1 mole) of the α-oxime of 2-amino-5-chlorobenzophenone (X)[1] in 120 cc. of warm glacial acetic acid was cooled, and 34.2 g. (0.2 moles) of α-bromopropionyl chloride was added while the temperature was kept at 30°. The mixture was left for 48 hr. at room temperature and then concentrated *in vacuo*. The residue was dissolved in methylene chloride, the solution was washed neutral with ice cold aqueous sodium carbonate, dried with sodium sulfate, and partly concentrated *in vacuo*. The crystalline reaction product (17.5 g.) was precipitated by the addition of ether and petroleum ether. It formed, after crystallization from a mixture of methylene chloride and petroleum ether, yellow needles or rhombic prisms melting at 183–184°.

Anal. Calcd. for $C_{15}H_{12}ON_2BrCl$: N, 7.70. Found: N, 7.73.

7-Chloro-2-methylamino-3-methyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide (XIIa). A solution of 7 g. of 6-chloro-2-(α-bromoethyl)-4-phenylquinazoline 3-oxide (XIa) in 30 cc. warm dioxane was cooled and added to an ice cold 20% solution of methylamine in dioxane. The mixture was left at room temperature for 48 hr. and then concentrated *in vacuo*. The residue was mixed with ether and extracted with ice cold dilute hydrochloric acid. The acidic solution was made alkaline and the reaction product extracted with ether. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from acetone yielding 1.5 g. of yellowish prisms melting at 246–247°. A fairly large amount of basic material (most probably the normal reaction product) which remained in solution was not further investigated.

Anal. Calcd. for $C_{16}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.56; H, 5.12.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid, and the salt was crystallized by the addition of acetone, ether, and petroleum ether. After recrystallization from methanol with the addition of acetone and ether, it formed flat needles melting at 190–191°.

Anal. Calcd. for $C_{17}H_{17}N_3OCl_2$: N, 12.00. Found: N, 11.67.

2-(α-Bromobutyl)-4-phenyl-6-chloroquinazoline 3-oxide (XIb). To a cool solution of 7.4 g. (30 mmoles) of a mixture of the α- and β-oximes of 2-amino-4-chlorobenzophenone[1] (X) in 40 cc. of glacial acetic acid was added with cooling 6.0 g. (30 mmoles) of α-bromo-*n*-valeryl chloride. The mixture was kept at room temperature for 2 hr., saturated, with cooling, with hydrogen chloride, left at room temperature for 15 hr. and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed neutral with ice cold sodium carbonate solution. The methylene chloride solution was dried and concentrated *in vacuo*. The residue crystallized on addition of ether yielding 5 g. of yellow crystals melting at 155–160°. After recrystallization from a mixture of methylene chloride and petroleum ether, the product formed yellow needles melting at 173–174°.

Anal. Calcd. for $C_{18}H_{16}N_2OClBr$: C, 55.19; H, 4.13. Found: C, 55.31; H, 3.93.

7-Chloro-2-methylamino-3-propyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide (XIIb) *and 2-(α-methylaminobutyl)-4-phenyl-6-chloroquinazoline 3-oxide* (XIIId). A suspension of 14.4 g. of 2-(α-bromobutyl)-4-phenyl-6-chloroquinazoline 3-oxide (XIb) in 500 cc. of a 30% methylamine solution in methanol was stirred at room temperature for 1 hr. The solution formed was concentrated *in vacuo* and the residue dissolved in ice cold dilute hydrochloric acid. Neutral impurities were extracted with ether, the acidic aqueous solution was made alkaline with ice cold sodium hydroxide, and the reaction product extracted with ether. This ether solution was concentrated and treated with petroleum ether yielding the benzodiazepine *N*-oxide (XIIb)[2] in crystalline form. (The mother liquor contains the other isomer.) The crude material (3.6 g. m.p. 214–215°) was filtered off and recrystallized from a mixture of acetone and petroleum

ether. It formed yellowish small plates or large irregular prisms melting at 213–214°, resolidifying and melting again at 221–222°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.28; H, 5.35.

Hydrochloride. A suspension of the base in methanol was neutralized with an equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and separate ether. The hydrochloride formed colorless flat needles melting at 187–189°.

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.28; H, 6.05.

The mother liquor after the separation of the benzodiazepine *N*-oxide (XIIb) described above was concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether yielding 4 g. of yellowish crystals melting at 103–104°. After recrystallization from petroleum ether the quinazoline *N*-oxide (XIIId)[2] formed rosettes of yellowish needles melting at 106–107°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.77; H, 6.11.

Hydrochloride. A suspension of the base in methanol was neutralized with the equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol, acetone, and petroleum ether. The hydrochloride formed fine white needles melting at 187–189°. It gave a melting point depression with the hydrochloride of the isomeric benzodiazepine *N*-oxide (XIIb).

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.23; H, 5.54.

6-Chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (XIVa). A solution of 100 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 250 cc. of dioxane was added to 150 cc. of a 50% solution of dimethylamine in dioxane. The mixture was left at room temperature for 20 hr., cooled with ice, acidified with 3*N* hydrochloric acid, and extracted with ether to remove neutral impurities. The aqueous layer was then made alkaline with 50% potassium hydroxide (ice was added to keep the mixture cold) and extracted with benzene. The benzene layer was dried with sodium sulfate, concentrated *in vacuo* to a small volume, and diluted with petroleum ether. The crystalline precipitate was recrystallized from a mixture of acetone and petroleum ether. It formed fine yellowish needles melting at 133–134°. The yield was 93 g. (90%).

Anal. Calcd. for $C_{17}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.44; H, 4.86.

Hydrochloride monohydrate. A solution of the base in methanol was neutralized with 1*N* hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of isopropyl alcohol and ether. The salt formed yellowish needles melting at 172–173°.

Anal. Calcd. for $C_{17}H_{19}N_3O_2Cl$: C, 55.45; H, 5.20. Found: C, 55.79; H, 5.30.

6-Chloro-2-(1-piperazinylmethyl)-4-phenylquinazoline 3-oxide (XIVb). A suspension of 15 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in a solution of 30 g. of piperazine hydrate in 250 cc. of methanol was stirred for 20 hr. The precipitated reaction product was filtered off, the filtrate was concentrated *in vacuo*, combined with the precipitate, and dissolved in hydrochloric acid. The acidic solution was washed with methylene chloride and insoluble impurities were filtered off. The aqueous solution was cooled, made alkaline, and the reaction product extracted with methylene chloride. The organic solution was dried, partially concentrated *in vacuo*, and diluted with ether. The reaction product precipitated in yellowish prisms (10.2 g.) melting at 174–175°. After recrystallization from hot benzene with the addition of ether and petroleum ether, the product formed long flat prisms or plates melting at 175–176°. The infrared spectrum showed that the compound had the quinazoline 3-oxide structure.

Anal. Calcd. for $C_{19}H_{19}OClN_4$: C, 64.31; H, 5.40. Found: C, 64.60; H, 5.33.

Dihydrochloride. The base was dissolved in the calculated amount of 0.5*N* methanolic hydrochloric acid and the salt was precipitated by the addition of ether and petroleum ether. It can be recrystallized from methanol, containing a small amount of water, and ether. It formed colorless plates melting at 178–180°.

Anal. Calcd. for $C_{19}H_{21}OCl_3N_4$: C, 53.35; H, 4.95. Found: C, 52.88; H, 5.41.

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NUTLEY 10, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE]

New 5-Substituted 6-Azauracils[1]

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The 5-position of 6-azauracil (*asym*-triazine-3,5-dione) may be halogenated to yield the 5-chloro, 5-bromo, and 5-iodo derivatives. By reaction of 5-bromo-6-azauracil with molten ammonium acetate, 5-amino-6-azauracil was obtained. 5-Hydroxy-6-azauracil was prepared from the amino compound by basic hydrolysis or by reaction with nitrous acid. The acid dissociation constants, ultraviolet spectra, and infrared spectra were measured.

Recent work on the antitumor activity of 6-azauracil (*asym*-triazine-3,5-dione,1)[2,3] has suggested that its various derivatives substituted at the 5-position might have biological interest. For

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(2) M. T. Hakala, L. W. Law, and A. D. Welch, *Proc. Amer. Assoc. Cancer Research*, 2, 113 (1956).

(3) J. J. Jaffe, R. E. Handschumacher, and A. D. Welch, *Yale J. Biol. & Med.*, 30, 168 (1957).

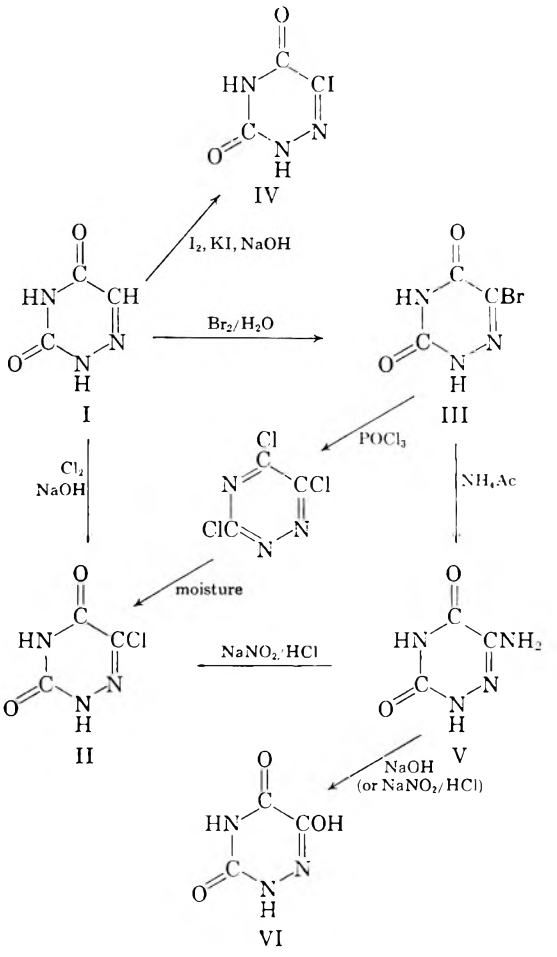
example, the 5-alkyl-6-azauracils,[4] as compared to 6-azauracil, possessed enhanced narcotic activity in mice.[5] The present paper deals with the preparation of several new 5-substituted 6-azauracils (6-substituted *asym*-triazine-3,5-dione).

Bromination of 6-azauracil was found to proceed with ease to give the 5-bromo derivative in excellent yield.[6] However, chlorination and iodination required the presence of base and the yields dropped to 40% and 15%, respectively. 5-Bromo-6-azauracil reacts with phosphorus oxychloride to give an intermediate containing neither hydrogen nor bromine; it is believed to be trichloro-*asym*-triazine,[7] which reacts with moisture instantly to give 5-chloro-6-azauracil.

When 5-bromo-6-azauracil was refluxed with molten ammonium acetate under an atmosphere of ammonia, a 50% yield of crude 5-amino-6-azauracil (V) was obtained. The amino compound underwent basic hydrolysis smoothly to give a 70% yield of 5-hydroxy-6-azauracil (*asym*-triazine-3,5,6-trione, VI). It is of interest to note that this compound is the hitherto unknown asymmetric isomer of cyanuric acid. Rätz and Schroeder report that reaction of oxamic acid hydrazide and phosgene failed to produce the desired VI.[8] A poorer yield of VI, together with an equal amount of II, could also be obtained *via* diazotization of the amino compound in concentrated hydrochloric acid. However, when the diazotization was carried out in 48% fluoboric acid in an attempt to prepare 5-fluoro-6-azauracil by a modified Schieman reaction,[9] only substances which lack absorption in the ultraviolet were isolated, suggesting that the triazene ring had been ruptured. 5-Amino-6-azauracil does not react with ethylene oxide (either in the cold or in a sealed tube at 100°) to give 5-bis(2-hydroxyethyl)-amino-6-azauracil as in the case of 5-aminouracil.[10] When 5-bromo-6-azauracil was refluxed with diethanolamine in a solution of ethylene glycol monomethyl ether, instead of the expected 5-bis(2-hydroxyethyl)-amino-6-azauracil, a one to one complex, which regenerates the starting materials upon acid treatment was obtained.

The acid dissociation constants and ultraviolet absorption spectra are shown in Table I. It can be seen that the acidity of the halogenated 6-azauracils increases from iodine to bromine to chlorine, parallel to their increasing electron-withdrawing

REACTION SCHEME



effect. The very low pk_a value of 5-hydroxy-azauracil may be compared to that of 4-methyl-6-hydroxypyrimidine, which is reported to have a value of 2.15.[11]

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

6-Azauracil	pKa	0.1N HCl max, mμ	0.1N HCl ϵ_{max}	0.1N NaOH max, mμ	0.1N NaOH ϵ_{max}
5-H	6.90[4]	258	5590	286	3770
5-Cl	5.80	270	5500	297	5680
5-Br	6.05	274	5000	299	6240
5-I	6.27	291	5010	306	6110
5-NH_2	7.35	296	4065	289	4050
5-OH	2.95	246	4960	250	2886

The infrared spectra of these *asym*-triazines all show broad peaks in the 3.0–3.6 μ region and very sharp doublets in the 5.75–5.95 μ region because of the —C(=O)—NH— groups. The substituted imine bond, which normally has a weak peak at 6.25 μ, shifts in the 6.25–6.45 μ region depending on the

(4) P. K. Chang, *J. Org. Chem.*, **23**, 1951 (1958).

(5) A. D. Welch, R. E. Handschumacher, and J. J. Jaffe, unpublished data.

(6) This compound was first prepared by Dr. R. E. Handschumacher.

(7) P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).

(8) R. Rätz and H. Schroeder, *J. Org. Chem.*, **23**, 2017 (1958).

(9) J. A. Montgomery and K. Hewson, *J. Am. Chem. Soc.*, **82**, 463 (1960).

(10) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, **80**, 6459 (1958).

(11) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951).

substitution at the 6-position. As in the 6-alkyl-*asym*-triazine-3,5-dione series, the medium peak at 13.42–13.6 μ region may be ascribed to the ring.[4]

EXPERIMENTAL[12]

5-Chloro-6-azauracil (II). This compound may be prepared by either of two methods. The first method, using 6-azauracil as the starting material, is simpler in operation.

A. *Chlorination of 6-azauracil.* A 5.65-g. sample (0.05 mole) of 6-azauracil and 8 g. (0.2 mole) of sodium hydroxide was placed in 500 ml. of water. Chlorine was bubbled through the mixture at a moderate rate at room temperature with stirring until the *p*H of the solution became 1.5. After evaporation of the solution to dryness on a water aspirator at 60°, the residue was extracted with ethyl acetate in a Soxhlet extractor. The crude 5-chloro-6-azauracil, 2.95 g., was obtained after removal of ethyl acetate (40%). After recrystallization from water, it melted at 225–227°.

Anal. Calcd. for $C_3H_2ClN_3O_2$: C, 24.42; H, 1.36; N, 28.48; Cl, 24.03. Found: C, 24.50; H, 1.28; N, 28.34; Cl, 23.85.

B. *Chlorination of 5-bromo-6-azauracil and hydrolysis to 5-chloro-6-azauracil.* A mixture of 5-bromo-6-azauracil (7.8 g., 0.04 mole) in 40 ml. of phosphorus oxychloride was refluxed at 125° until the mixture became homogeneous (48 hr.). Most of the excess phosphorus oxychloride was removed on a water aspirator, and the residue distilled *in vacuo* to give a colorless oil, b.p. 72°/3 mm., yield 2.2 g. (30%). The oil was added dropwise to 6 ml. of methanol. Hydrogen chloride was evolved and the solution was concentrated to give a colorless substance, 1.2 g. (70% conversion). After recrystallization from water, it melted at 225–227°.

5-Bromo-6-azauracil (III). A mixture of 6-azauracil (5 g., 0.026 mole), bromine (5 ml.) and water (75 ml.) was stirred with a magnetic stirrer for 27 hr. The colorless crystalline product was filtered and dried (4.7 g.). Concentration of the filtrate gave an additional 2.94 g. (total yield of 5-bromo-6-azauracil, 90%). After recrystallization from water it had m.p. 232–234°.

Anal. Calcd. for $C_3H_2BrN_3O_2$: C, 18.77; H, 1.05; N, 21.89; Br, 41.62. Found: C, 18.75; H, 1.04; N, 22.02; Br, 41.57.

5-Iodo-6-azauracil (IV). A mixture of 1.13 g. (0.01 mole) of 6-azauracil, 5 g. (0.02 mole) of iodine, 5.3 g. of potassium iodide, and 1.6 g. of sodium hydroxide in 35 ml. of water was refluxed for 40 hr. After acidification to *p*H 2 with concd. hydrochloric acid, the mixture was first extracted with carbon tetrachloride to remove excess iodine then followed by continuous extraction with ether for 24 hr. The residue after removal of the ether was taken up with 100 ml. of water, made alkaline (*p*H 10–11) with concd. ammonium hydroxide and put on a Dowex 1 (chloride) column. After washing with water, the column was eluted with 0.005*N* hydrochloric acid. 6-Azauracil was eluted first, followed by 5-iodo-6-azauracil. The residue after removal of the acid was recrystallized from water to yield 0.37 g. of 5-iodo-6-azauracil (15%), m.p. 218–220°.

Anal. Calcd. for $C_3H_2IN_3O_2$: C, 15.76; H, 0.84; N, 17.58. Found: C, 15.94; H, 0.92; N, 17.90.

5-Amino-6-azauracil (V). In a 35-ml. 3-necked flask was placed 4.8 g. (0.025 mole) of 5-bromo-6-azauracil and 6 g. of ammonium acetate. The mixture was heated in an oil bath to 170°. The solids melted and refluxed for 24 hr. under an atmosphere of ammonia. The solution was allowed to cool and taken up with 5 ml. of water. The remaining solid, crude 5-amino-6-azauracil, was filtered; yield 1.7 g. (53%). After recrystallization from water, it melted at 310–315°.

Anal. Calcd. for $C_3H_4N_4O_2$: C, 28.13; H, 3.14; N, 43.74. Found: C, 28.04; H, 3.19; N, 43.71.

5-Hydroxy-6-azauracil (VI). A solution of 256 mg. (2 mmoles) of 5-amino-6-azauracil in 10 ml. of 1*N* sodium hydroxide was refluxed for 2 hr. To the cooled solution was added 10 g. of damp Dowex 50 to remove the sodium ion. When the filtrate from the Dowex 50 was reduced to dryness on a water aspirator, 253 mg. of impure 5-hydroxy-6-azauracil was obtained. After recrystallization from water, it melted at 228–230° (70%).

Anal. Calcd. for $C_3H_3N_3O_3.1/2H_2O$ (sample dried at 60°/0.1 mm.): C, 26.10; H, 2.92; N, 30.47. Found: C, 26.29; H, 2.86; N, 30.02. Calcd. for $C_3H_3N_3O_3$ (sample dried at 140°/0.1 mm.): C, 27.91; H, 2.34; N, 32.55. Found: C, 28.13; H, 2.45; N, 32.44.

Reaction of nitrous acid and 5-amino-6-azauracil. A mixture of 256 mg. (2 mmoles) of 5-amino-6-azauracil in 5.3 ml. of 28% hydrochloric acid was cooled to −10°. A solution of sodium nitrite (0.33 g./ml.) was added dropwise below 5° until the mixture gave a permanent positive test on the potassium iodide–starch test paper (0.5 ml.). The mixture was stirred for an additional hour at 0–5°. It was then diluted with 3 ml. of water and heated on a steam bath for 0.5 hr., during which all solids dissolved. After the solution was boiled for 5 min., it was cooled to yield 56 mg. of crude 5-hydroxy-6-azauracil as a pale yellow solid. The filtrate was reduced to dryness on a water aspirator. Extraction of the residue with ethyl acetate yielded 50 mg. of 5-chloro-6-azauracil.

Infrared spectra. The spectra were measured in pressed potassium bromide disks on a Perkin-Elmer double-beam instrument, model 21.

Ultraviolet spectra. The spectra were measured on a Beckman spectrophotometer, model DU. Solutions were made up in volumetric flasks from weighed quantities of the compounds.

Dissociation constants. The pK_a's were determined potentiometrically in duplicate using a Photovolt *p*H meter, model 110. A solution of 0.0005 mole of the compound in 100 ml. of carbon dioxide-free water was titrated with 0.066*N* sodium hydroxide.

Acknowledgment. The author wishes to express her thanks to Professor A. D. Welch for his interest in and encouragement of this work.

NEW HAVEN, CONN.

(12) Melting points are uncorrected. Analysis by Huffman Microanalytical Labs., Wheatridge, Col., and by Schwarzkopf Microanalytical Labs., Woodside, N. Y.

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XXIII. The Reaction of *s*-Triazine with Active Methylene Compounds[1,2a]

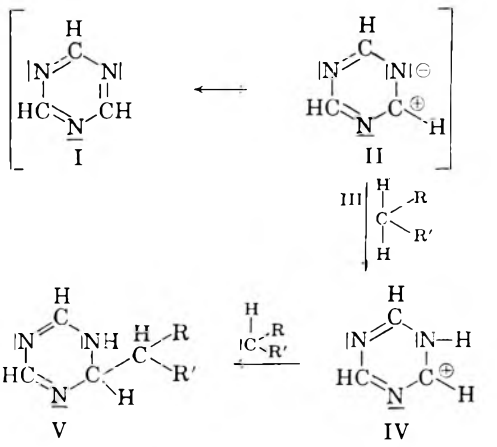
ALFRED KREUTZBERGER[2b] AND CHRISTOPH GRUNDMANN[2c]

Received May 27, 1960

The behavior of *s*-triazine (I) towards active methylene compounds has been investigated. I reacts with ethyl acetoacetate (IIIa) to give 2,6-dimethyl-3,5-dicarbethoxypyridine (IX). The reaction of I with 2,4-pentanedione (IIIb) and ethyl cyanoacetate (IIIc) leads to the formation of 3-aminomethylene-2,4-pentanedione (Xa) and ethyl 2-aminomethyleneeyanoacetate (Xb), respectively. Malononitrile (IIId) cleaves the *s*-triazine ring with formation of a mixture of aminomethylenemalononitrile (Xc) and 4-amino-5-cyanopyrimidine (XIVa). In the reaction of I with diethyl malonate (IIIe), 4-hydroxy-5-carbethoxypyrimidine (XIVb) is formed exclusively, the structure of which has been proved by an independent synthesis starting with formamidine hydrochloride (XV) and diethyl ethoxymethylenemalonate (XVI). 4-Phenyl-5-carbethoxypyrimidine (XIVc) results from the reaction of I with ethyl benzoylacetate (IIIf). I does not react with fluorene, triphenylmethane, acetic and benzoic acid.

Several investigations following the identification of the polymerization product of hydrocyanic acid under acidic conditions as *s*-triazine,[3,4] allow the conclusion that this heterocycle is to be considered a resonance hybrid receiving major contributions from structures I and II. In consequence, all C atoms in *s*-triazine are expected to be amenable to nucleophilic reagents. This expectation is fulfilled in the readily occurring ring cleavage of *s*-triazine under the influence of amines[5] and hydrazines.[6]

The electromeric displacement in II becomes a particularly important factor in the neighborhood of an organic compound from which a hydrogen atom attached to a carbon atom is removable as a proton. This effect creates especially electron-rich nitrogen atoms in II which are expected to attract the proton, thus forming IV. This step, in the case of organic active methylene compounds (III), would result in the occurrence of a carbanion which subsequently could add to an adjacent electron-deficient carbon atom with the formation of V.



RESULTS AND DISCUSSION

As a matter of fact, *s*-triazine does react with a great variety of active methylene compounds (III). Representatives of III selected for investigations are given in Table I.

TABLE I

ACTIVE METHYLENE COMPOUNDS $H_2C(R)(R')$ (III) USED

Name	R	R′	Designation
Ethyl acetoacetate	$CO_2C_2H_5$	Ac	IIIa
2,4-Pentanedione	Ac	Ac	IIIb
Ethyl cyanoacetate	C≡N	$CO_2C_2H_5$	IIIc
Malononitrile	C≡N	C≡N	IIId
Diethyl malonate	$CO_2C_2H_5$	$CO_2C_2H_5$	IIIe
Ethyl benzoylacetate	Bz	$CO_2C_2H_5$	IIIf

The reaction between *s*-triazine and III proceeds smoothly upon heating a mixture of the components either without solvent or dissolved in an inert sufficiently high boiling solvent. Within two to four hours at a bath temperature between 140–160°, in exceptional cases at room temperature, the reaction is usually completed. A significant difference from the reaction of *s*-triazine with amines is that with III no evolution of ammonia takes place, indicating that in this type reaction

(1) This article is based on work performed under project 116-B of the Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2)(a) Preceding communication: E. Kober and Ch. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959). (b) Present Address: Ford Motor Company, Scientific Laboratory, Dearborn, Mich. (c) Present Address: General Cigar Co., Research Laboratory, Lancaster, Pa.

(3) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 632 (1954).

(4) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 5646 (1954).

(5) (a) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955). (b) Ch. Grundmann and A. Kreutzberger, *J. Polymer Sci.*, **38**, 425 (1959).

(6) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.* **79**, 2839 (1957).

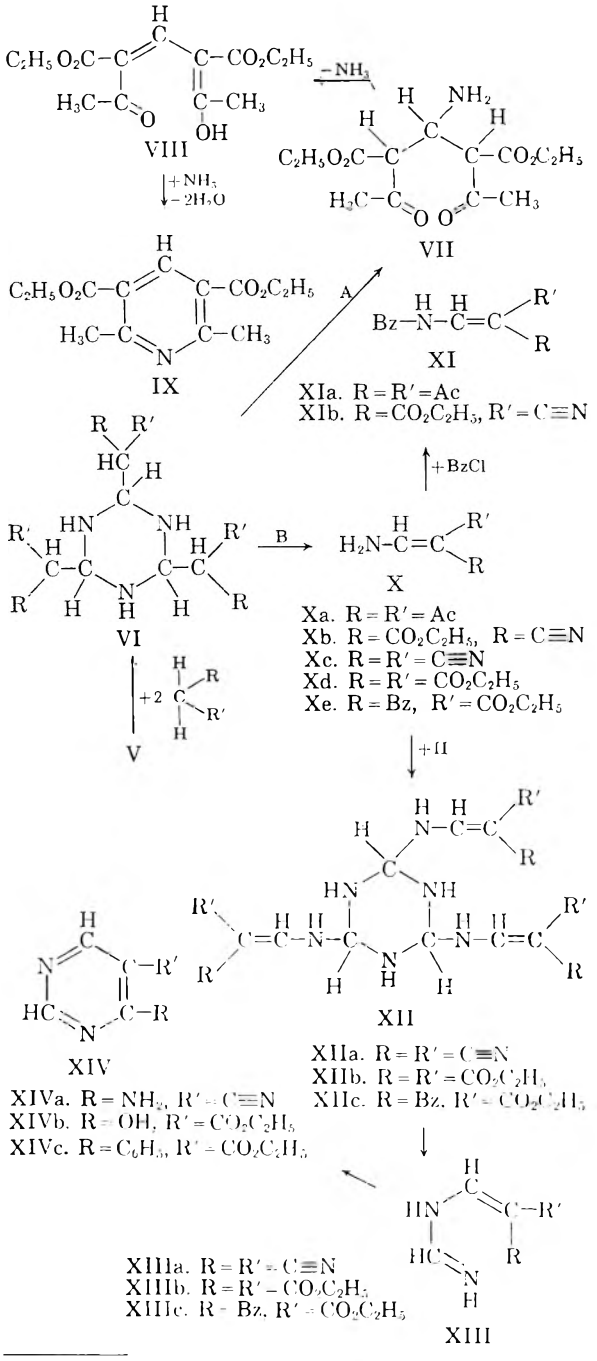
all of the ring atoms of *s*-triazine are used to build a new molecule.

Largely depending on the nature of the substituents R and R′ in III, the reaction of *s*-triazine with III follows one of two different courses ending up with either a pyridine (course A) or pyrimidine derivative (course B). The last joint hypothetical intermediate of these two courses is presented by structure VI which is formed by repetition of the reaction sequence II → IV → V on the remaining four C and N centers in V.

Course A is realized with ethyl acetoacetate (IIIa), three molecules of which add to VI and concomitantly cleave the ring to form three molecules of the aminomethane derivative VII. Ammonia is eliminated in the subsequent step to form the glutaconic derivative VIII, the very species which, as in the glutaconic type pyridine synthesis,[7] gives rise to the formation of 2,6-dimethyl-3,5-dicarbethoxypyridine (IX), the end product in this course.[7b] The preparative advantage of this one-step-synthesis of IX as compared with the known two-step-process starting with IIIa, formaldehyde, and ammonia and proceeding *via* 1,4-dihydro-IX[8a] is obvious, the yield being approximately equal in both cases.

All of the other active methylene compounds listed above (IIIb, IIIc, IIId, IIIe, and IIIf) enter the reaction course B, *i.e.*, the hexahydrotriazine derivative VI breaks down into three molecules of an aminomethylene derivative X.[8b] This in some cases is so stable that it does not undergo any further reaction and thus represents then the end of course B. Examples of this reaction type are IIIb and IIIc in which cases two compounds could be isolated which proved to be identical with 3-aminomethylene-2,4-pentanedione (Xa)[9] and ethyl 2-aminomethylenecyanoacetate (Xb)[10] respectively. The aminomethylene compounds or their tautomeric forms, the aldimines, call to mind Stephen's aldehyde synthesis[11] in which they are used as intermediates and in the simplest case may be prepared according to the sequence III → III-halide → III-nitrile → X. Also, there is a procedure for preparing Xa from IIIb and liquid hydrogen cyanide in the presence of aluminum chloride and hydrochloric acid as catalysts.[12] Upon comparing the previous processes with the new one-step procedure III → X requiring no catalyst, the simplicity of the latter becomes clearly apparent.

Whereas the attempt failed to characterize X through acetylation with acetic anhydride as the corresponding *N*-acetyl-X, successful structure characterization of X could be had by benzoylation with benzoyl chloride in pyridine leading to 3-benzamidomethylene-2,4-pentanedione (XIa) and ethyl 2-benzamidomethylenecyanoacetate (XIb), respectively.



(7)(a) L. Claisen, *Ann.*, **297**, 71 (1897); P. Baumgarten, *Ber.*, **57**, 1622 (1924). (b) The alternative path by which IX may have been formed *via* ethyl aminomethylenacetoacetate (X. R = $CO_2C_2H_5$, R′ = Ac) must tentatively be ruled out, because there is no reaction known to convert this intermediate into IX, whereas the cleavage of VI into VIII *via* VII parallels a known path (see footnote 5) followed by the well established step VIII → IX.

(8)(a) H. Meyer and H. Tropsch, *Monatsh.*, **35**, 208 (1914); A. Singer and S. M. McElvain, *Org. Syntheses*, **Coll. Vol. II**, 214 (1943). (b) In the formula scheme, X is given as the aminomethylene form with the understanding that it may be in a tautomeric equilibrium with its iminomethyl form.

(9) L. Claisen, *Ann.*, **297**, 65 (1897).

(10) E. G. DeBollemont, *Bull. soc. chim. France*, [3] **25**, 41 (1901).

(11) H. Stephen, *J. Chem. Soc.*, 1874 (1925); L. N. Ferguson, *Chem. Revs.*, **38**, 243 (1946).

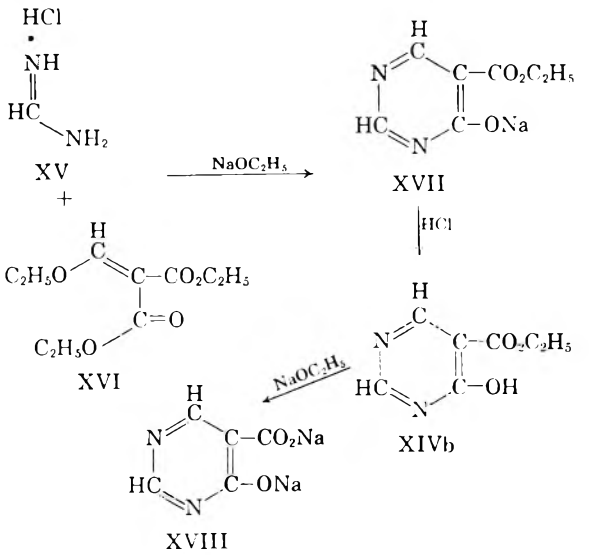
(12) H. Wieland and E. Dorrer, *Ber.*, **58**, 819 (1925).

Also with IIId the corresponding aminomethylene compound X is formed, *i.e.*, aminomethylenemalononitrile (Xc).[13] This, however, is not so stable as to represent the only final product in this reaction, but rather belongs to that category of X which, once formed, undergoes further reaction with *s*-triazine. In the case of IIId at least part of Xc originally formed reacts further with *s*-triazine to end up with 4-amino-5-cyanopyrimidine (XIVa).[14] The mixture of Xc and IVa obtained from IIId is readily separable, Xc being easily soluble and IVa sparingly so in ethanol. Application of an inert solvent like ethanol or xylene was found inevitable for the reaction between IIId and *s*-triazine because these two components without solvent react violently upon heating to give a dark red tarry product from which only trimeric IIId[15] could be isolated.

To explain the formation of XIVa, it may be assumed that first three molecules of Xc add to one still unchanged *s*-triazine ring to give the hexahydro-*s*-triazine intermediate XIIa which subsequently breaks down into three molecules of an *N*-vinylformamidine derivative (XIII). The latter finally stabilizes by cyclization to XIV.

Contrary to Xa and Xb, diethyl aminomethylenemalonate (Xd), which is to be expected of the reaction of *s*-triazine with IIIe, is so prone to further reaction with *s*-triazine that it could not be isolated at all. The only detectable end product in this case was a white substance $C_7H_8N_2O_3$ which, if it had been formed through an analogous reaction sequence—*i.e.*, Xd → XIIb → XIIIb → XIVb—should be 4 - hydroxy - 5 - carbethoxypyrimidine (XIVb).

This compound has been mentioned briefly[16] in connection with desulfurization attempts of 2 - mercapto - 4 - hydroxy - 5 - carbethoxypyrimidine, when 5-carbethoxyuracil was obtained as chief product which "was contaminated with a small quantity" of XIVb. Aside from an elemental analysis, no further structure proof for this compound was given. As XIVb is, however, a critical structure in the formulation of the mechanism of these reactions with *s*-triazine, its preparation by an independent route was most desirable. Such a synthesis was found in the reaction of formamidine hydrochloride (XV) with diethyl ethoxymethylenemalonate (XVI) which, in the presence of sodium ethoxide, led to the sodium compound of 4-hydroxy-5-carbethoxypyrimidine (XVII). Liberation of free XIVb from XVII by means of hydrochloric acid met, however, with considerable difficulties, mainly because of the solubility in water, dilute hydrochloric acid and dilute sodium hydroxide of XIVb as well as of XVII and sodium chloride. The attempt to circumvent this situation by ethylating XVII with ethyl bromide in a pressure vessel failed. Also the attempt to substitute piperidine for sodium ethoxide in the condensation of XV with XVI was unsuccessful. Consequently it was tried to treat XIVb with sodium ethoxide to identify possibly the reaction product with XVII, but this reaction took a different course and yielded the disodium compound of 4-hydroxy-5-carboxypyrimidine (XVIII). Finally the clue for liberating the free XIVb was found in treating XVII with hydrochloric acid and subsequently subjecting the obtained mixture to vacuum-sublimation when only XIVb sublimed, the latter establishing its identity with the reaction product from *s*-triazine and IIIe.



The successful synthesis of XIVb from XV and XVI is particularly noteworthy in view of the fact that urea which may be commonly used for the synthesis of the pyrimidine nucleus has been found not to react with XVI.[17]

The same course as with IIIe is taken if *s*-triazine is caused to react with IIIf. The reaction sequence proceeds through the intermediates Xe → XIIc → XIIIc to yield a compound $C_{13}H_{12}N_2O_2$ to which, in analogy to XIVb, the structure of 4-phenyl-5-carbethoxypyrimidine (XIVc) has been ascribed.

Supporting the postulate that the aminomethylene compounds X are intermediates and not side products in the reaction of *s*-triazine with IIId, IIIe and IIIf leading to pyrimidine derivatives, are the facts that XV reacts with both IIId[14] and Xc[18] to give the same end product, namely XIVa, and that Xd also reacts with certain other agents

(13) T. Passalacqua, *Gazz. chim. ital.*, **43**, II, 566 (1913); O. Diels, H. Gärtner, and R. Kaack, *Ber.*, **55**, 3443 (1922).

(14) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

(15) R. Schenck and H. Finken, *Ann.*, **462**, 274 (1928).

(16) E. Ballard and T. B. Johnson, *J. Am. Chem. Soc.*, **64**, 796 (1942).

(17) H. L. Wheeler, T. B. Johnson, and C. O. Johns, *Am. Chem. J.*, **37**, 394 (1907).

(18) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 388 (1943).

with formation of cyclic α-hydroxycarboxylic esters.[19]

Pyrimidine unsubstituted in position 2 have generally been prepared by reduction of 2-halopyrimidines,[20] desulfurization of 2-mercaptopyrimidines,[21] or decarboxylation of 2-carboxypyrimidines.[22] *s*-Triazine offers now another interesting possibility, aside from XV, for a direct synthesis of 2-unsubstituted pyrimidines.

Theoretically the production of IX and X requires a molar ratio of *s*-triazine: III = 1:6 and 1:3 respectively, while the formation of pyrimidines XIV calls for a molar ratio of *s*-triazine: III = 2:3. However, in several cases, it was found expedient to have one of the components in excess in order to arrive at a better yield of end product.

So far, of active methylene compounds investigated fluorene has been found not to undergo reaction with *s*-triazine. This failure is most probably to be attributed to too small a permanent polarization in fluorene due to the lack of any activating substituents. Likewise, triphenylmethane could not be caused to react with *s*-triazine.

As another class of compounds containing removable hydrogen, organic acids were included in these investigations. The reaction of *s*-triazine with glacial acetic acid yielded a main fraction of the composition $C_{17}H_{31}N_3O_{14}$. By the ring cleavage reaction with aniline,[5] the presence of unchanged *s*-triazine in this fraction was established. The product $C_{17}H_{31}N_3O_{14}$ is thus to be considered an azeotropic mixture $7CH_3COOH.C_3H_3N_3$. A clear-cut answer on the question concerning the behavior of organic acids towards *s*-triazine was obtained from the reaction with benzoic acid, in which case both components could be recovered unchanged.

EXPERIMENTAL[23]

2,6-Dimethyl-3,5-dicarbethoxypyridine (IX). *s*-Triazine (5 g.) was dissolved at room temperature in 24 g. of IIIa and the mixture immersed into an oil bath preheated to 140° and kept there for 2 hr. After cooling, the reaction contents were subjected to vacuum-distillation at 6 mm. As main fraction a yellowish viscous oil of b.p.$_6$ 167–169° was obtained, which crystallized mostly in the receiving flasks. By vacuum-filtration, 11.5 g. of colorless needles was obtained. These were recrystallized from ethanol and showed then a melting point of 72–73°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.58. Found: C, 62.18; H, 6.60; N, 5.49.

The identity of this product with structure IX was established by a mixed melting point with an authentic sample.[8] Based on IIIa, the yield of 11.5 g. of IX corresponds to 49.7%. Furthermore, the compound obtained could be characterized by a picrate. Upon the addition of a saturated ethanolic picric acid solution to a solution of the needles referred to above in ethanol, crystallization of clusters of yellow needles set in. These were filtered and dried, melted at 118–119°, and showed no depression in melting point when mixed with authentic IX-picrate.[24]

3-Aminomethylene-2,4-pentanedione (Xa). A mixture containing 5 g. of *s*-triazine and 37 g. of IIIb was heated to gentle boiling (155° bath temperature) for 0.5 hr., when it turned slightly orange in color. Extending the reaction period does not increase the yield of end product, but causes a reddish-brown discoloration of the reaction contents and merely renders the work-up more difficult. Upon cooling, a beige crystalline mass deposited, which was suction-filtered and amounted to 8.1 g. An additional amount of 6.8 g. of this substance could be obtained by concentrating the mother liquor in vacuum until b.p. 100° (16 mm.) was reached and then allowing the residue to crystallize. The crude crystalline material could be recrystallized best from methanol; beige scales, m.p. 145–146°. The mixed melting point with an authentic sample of Xa[9] was not depressed; total yield: 14.9 g., or 63% based on *s*-triazine.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.62; H, 7.15; N, 10.94.

3-Benzamidomethylene-2,4-pentanedione (XIa). Benzoyl chloride (5.6 g., 0.04 mole) was added dropwise to a suspension of Xa (5.1 g., 0.04 mole), obtained as described in the preceding paragraph, in absolute pyridine (6.4 g., 0.08 mole) with intermittent shaking at a rate not to exceed 50° reaction temperature. The reaction contents became gradually viscous and finally solidified largely. After two successive treatments with 40-ml. portions of water at room temperature, 7.3 g. of a white solid could be collected. Repeated crystallizations from ethanol furnished faintly yellowish fine needles, the melting point of which (101–102°) was not depressed when mixed with an authentic sample[25]; yield: 7.3 g., 78.8%.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.60; N, 6.00.

Ethyl 2-aminomethylenecyanoacetate (Xb). It was found advisable to conduct this experiment in an inert solvent; without this, it was rather difficult to extricate a pure material from the viscous reaction contents.

An absolute ethanolic solution of 4 g. of *s*-triazine and 17 g. of IIIc was kept at gentle boiling (140° bath temperature) for 7 hr., when the originally colorless solution turned gradually bright brown. On cooling, a slightly yellowish material crystallized which was filtered after standing for 3 weeks; weight: 14.2 g. This substance was insoluble in ether, soluble in water, dil. hydrochloric acid, dil. sodium hydroxide, ethanol, methanol and acetone and could best be recrystallized from ethanol, from which solvent it crystallized as fine white needles, m.p. 134–135°. Authentic Xb[10] is reported to melt at 130°, but was found in this laboratory to have a melting point of 134–135°. A mixed melting point showed no depression. The amount of 14.2 g. equals 68.0% based on IIIc.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.43; H, 5.76; N, 20.00. Found: C, 51.50; H, 5.66; N, 20.01.

Ethyl 2-benzamidomethylenecyanoacetate (XIb). To 4.2 g. (0.03 mole) of Xb obtained as described above and dispersed in 4.8 g. (0.06 mole) of dry pyridine was added dropwise 4.2 g. (0.03 mole) of benzoyl chloride with periodic shaking at a rate such as not to exceed 50°. The reaction contents turned orange, assumed first a honey-like consistency and then gradually crystallized upon standing for 3 hr. Pyridine hydrochloride formed during the reaction was removed by trituration with two 100-ml. portions of water. By vacuum-filtration, 6.8 g. (92.6%) of a yellowish product was obtained which was insoluble in water and dilute hydrochloric acid and soluble in methanol, ethanol, butanol, acetone, acetic acid, dioxane, benzene, acetic anhydride,

(19) S. Ruhemann and R. W. Morrell, *Ber.*, **27**, 2742, 2747 (1894).

(20) S. Angerstein, *Ber.*, **34**, 3957 (1901).

(21) H. Andersag and K. Westphahl, *Ber.*, **70**, 2035 (1937).

(22) S. Gabriel and J. Colman, *Ber.*, **32**, 1531 (1899).

(23) All melting points are corrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(24) E. Knoevenagel and J. Fuchs, *Ber.*, **35**, 1793 (1902).

(25) L. Claisen, *Ann.*, **297**, 31, 67 (1897).

and dil. sodium hydroxide. Recrystallization from ethanol furnished white needles, m.p. 121–122°.

As no authentic XIb was known, Xb as prepared according to DeBollemont[10] was treated with benzoyl chloride in pyridine suspension and worked up as described above. Again white needles were obtained which melted at 121–122°. A mixed melting point of the two specimen of XIb was undepressed.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.87; H, 4.74; N, 11.57.

4-Amino-5-cyanopyrimidine (XIVa). When 4 g. of *s*-triazine (0.05 mole) and 9.9 g. of IIId were dissolved in 50 ml. of absolute ethanol, the colorless solution within a few minutes turned yellow, became warm and started precipitating a yellow solid. The reaction mixture was shaken from time to time, allowed to stand overnight, and then vacuum-filtered (filtrate A). The filter-cake consisted of 3.8 g. of a yellow substance which was insoluble in ether, petroleum ether, carbon tetrachloride, acetone, ethyl acetate, benzene, chlorobenzene, toluene, and cyclohexane, scarcely soluble in ethanol, 1-pentanol, and dioxane and soluble in the following boiling solvents: methanol, water, glacial acetic acid, butyl alcohol, nitrobenzene, tetrahydrofuran, acetic anhydride, diethyl malonate, aniline, and dil. sodium hydroxide. By repeated recrystallization from methanol, the substance was obtained as fine beige needles, m.p. and mixed m.p. with authentic XIVa[14] 255–256°. The yield of 3.8 g., 21.3%, remained essentially unaltered if a batch of the same size was refluxed for 6 hr.

Anal. Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 50.15; H, 3.40; N, 46.67.

While the attempt to obtain a picrate of XIVa in ethanolic solution failed, the addition of aqueous picric acid solution saturated at room temperature to a hot aqueous solution of XIVa caused precipitation of yellow needles, m.p. 189°, which were identical in all aspects with authentic XIVa-picrate.[14]

Aminomethylenemalononitrile (Xc). Filtrate A obtained in the isolation of XIVa as described above was stripped of solvent and the remaining bright yellow powder recrystallized from a concentrated aqueous solution. Thereby 11.1 g. (78.7%) of slightly yellowish crystals was obtained, which melted at 145–146° and proved to be identical with authentic Xc.[13]

4-Hydroxy-5-carbethoxypyrimidine (XIVb). A. *From s-triazine and* IIIe. A solution of 6 g. of *s*-triazine in 35.6 g. of IIIe was heated for 4 hr. at a bath temperature of 160°. Any *s*-triazine that sublimed during the reaction period was caught in the reflux condenser and from time to time pushed back into the reaction flask. Upon cooling a yellowish substance precipitated which was vacuum-filtered after standing for several days. An additional amount of the same substance was obtained by stripping the filtrate of any solvent *in vacuo*, thus bringing the total amount of crude material to 16.5 g. This was triturated with ether and then repeatedly recrystallized from ethanol to give fine white needles, m.p. and mixed m.p. with XIVb as obtained by an independent route (see below under B) 194–195°. The total amount of 16.5 g. of XIVb corresponds to a yield of 88.6% based on *s*-triazine. XIVb is insoluble in ether, scarcely soluble in acetone and ethyl acetate, and soluble in methanol, ethanol, dioxane, water, dil. sodium hydroxide, and dil. hydrochloric acid.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.98; H, 4.80; N, 16.66. Found: C, 49.90; H, 4.72; N, 16.67.

This compound could be further characterized by its picrate, which was obtained by adding a cold saturated ethanolic solution of picric acid to a hot ethanolic solution of XIVb. Upon cooling, stout yellow needles crystallized which, after recrystallization from methanol, melted at 164–165°. This melting point was not depressed when mixed with XIVb-picrate as obtained from an independent synthesis (see following chapter).

Anal. Calcd. for $C_7H_8N_2O_3 \cdot C_6H_3N_3O_7$: N, 17.63. Found: N, 17.56.

B. *From* XVII. The sodium compound of 4-hydroxy-5-carbethoxypyrimidine (8.9 g.) (see next paragraph) was dissolved in 100 ml. of warm water and filtered. An amount of 4.6 ml. of 37.5% hydrochloric acid was added and the whole mixture taken to dryness *in vacuo* resulting in 10.6 g. of a beige crystalline substance. Divided into four individual portions, this material was subjected to fractional sublimation at 2 mm. The white crystals condensing at the cold finger were collected and amounted to 2.6 g. (33.0%) of XIVb. The analytical sample was thrice vacuum-sublimed and exhibited then a melting point of 194–195°.

The reported[16] melting point of "185° with sintering" is probably due to an insufficient amount of XIVb isolated, not enabling the previous investigators to further purify this substance.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.98; H, 4.80; N, 16.66. Found: C, 49.84; H, 4.66; N, 16.63.

The *picrate*, prepared in ethanol and recrystallized from the same solvent, melted at 164–165°.

Anal. Calcd. for $C_7H_8N_2O_3 \cdot C_6H_3N_3O_7$: N, 17.63. Found: N, 17.42.

Sodium compound of 4-hydroxy-5-carbethoxypyrimidine (XVII). Sodium (1.5 g.) was dissolved in absolute ethanol (30 ml.) and XV (4.4 g.) added. When XVI (12.0 g.) was added in small portions, the reaction mixture warmed up and turned yellow. After heating for 2 hr. on the steam bath, the suspension was allowed to cool and the white solids suction-filtered, wt. 10.6 g. (100%). Purification could be achieved by digestion with acetone, which rendered the solid as a white powder. On heating, it turned brown at 210–220° and decomposed at 262–264°.

Anal. Calcd. for $C_7H_7N_2NaO_3$: C, 44.21; H, 3.71; N, 14.74. Found: C, 44.31; H, 3.92; N, 15.15.

Disodium compound of 4-hydroxy-5-carboxypyrimidine (XVIII). To a solution of 0.74 g. of sodium in 20 ml. of absolute ethanol was added 2.7 g. of XIVb and the suspension well agitated at room temperature. No heat evolution was noticeable, but within 10 min. the contents assumed a lard-like consistency. An additional amount of 20 ml. of ethanol had to be added to make stirring still possible. After stirring for a total of 2 hr., the reaction contents were allowed to stand overnight and then were vacuum-filtered, washed with ethanol and dried in a vacuum-desiccator. Thereby 2.3 g. of a beige solid was obtained. For analysis, the substance was digested successively with ethanol and acetone and then exhibited a melting point of 414–416°.

Anal. Calcd. for $C_5H_2N_2Na_2O_3 \cdot H_2O$: C, 29.71; H, 2.00; N, 13.87; Na, 22.76. Found: C, 29.97; H, 2.02; N, 14.05; Na, 22.53.

4-Phenyl-5-carbethoxypyrimidine (XIVc). Upon heating a clear solution of 5 g. of *s*-triazine in 30 g. of IIIf for 2 hr. at 140°, a reddish brown viscous oil resulted which was allowed to stand at room temperature overnight. The contents were concentrated under reduced pressure, whereupon a brown somewhat tacky solid remained. Repeated triturations of this material with ether afforded 6.4 g. of a dry brown powder which was insoluble in water, dil. hydrochloric acid, dil. sodium hydroxide, ether, ethyl acetate, toluene, and cyclohexane and soluble in methanol, acetone, dioxane, acetic acid, acetic anhydride, pyridine, and concd. hydrochloric acid. Further purification of the material could best be achieved by digestion with boiling ether. In this manner XIVc was obtained as a yellow powder, m.p. 159–161°. The yield of 6.4 g. equals 30.4% based on *s*-triazine.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.28. Found: C, 68.52; H, 5.49; N, 12.09.

s-Triazine and glacial acetic acid. *s*-Triazine (8 g.) dissolved in glacial acetic acid (60 g.) without any noticeable change in temperature or color. This solution was heated for 3 hr. at 135–140°, allowed to stand overnight, and then vacuum-distilled. The main fraction consisted of 51 g. of a colorless liquid which was three more times fractionated,

whereupon refractive index and boiling point remained constant; b.p.$_{3\mathrm{mm}}$ 43–44°, n_D^{30} 1.3912.

This fraction was shown to react with aniline under evolution of heat. If this reaction were carried out at 60°, a white solid was formed. Next it could be shown that this solid was not acetanilide, despite the literature statement that a mixture of aniline and acetic acid at room temperature within four months had formed acetanilide.[26]

Finally, by recrystallization from benzene, white needles were obtained which, through m.p. and mixed m.p. (143°) with authentic material, were identified as *N,N*-diphenylformamidine.[5] This result, along with the analytical data, suggests the conclusion that the fraction of n_D^{30} 1.3912 is an azeotropic mixture of the composition $7CH_3COOH.C_3H_3N_3$.

Anal. Calcd. for $7CH_3COOH.C_3H_3N_3$: C, 40.73; H, 6.23; N, 8.38. Found: C, 40.68; H, 6.25; N, 8.04.

Acknowledgment. The authors are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

COLUMBUS, OHIO

(26) J. R. Pound and R. S. Russell, *J. Chem. Soc.*, 769 (1924).

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

3-Azaphenothiazine and Dialkylaminoalkyl Derivatives

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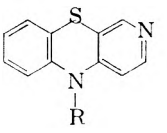
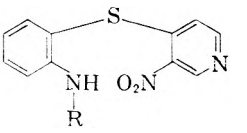
3-Azaphenothiazine has been synthesized and converted to 10-(3-dimethylaminopropyl)-3-azaphenothiazine. When 3-azaphenothiazine is alkylated with methyl iodide, or with the salts of aminoalkyl halides it forms novel quaternary salts which, upon treatment with aqueous alkali, liberate the corresponding anhydronium bases. The structures of these 3-alkyl derivatives of 3-azaphenothiazine are supported by their infrared and ultraviolet spectra as well as by *p*Ka measurements. The dipole moments of 3-azaphenothiazine and of 3-methyl-3-azaphenothiazine anhydronium base have been measured in dioxane solution. The pharmacology of the aminoalkyl derivatives of 3-azaphenothiazine is discussed.

The possibility that 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I) might possess tranquilizing properties similar to those of the corresponding phenothiazine derivatives[1] led us to prepare and alkylate 3-azaphenothiazine (II).[2] Although in recent years many azaphenothiazines[3] and diazaphenothiazines[4] have been synthesized, the unsubstituted 3-azaphenothiazine[5] has not been described. We found that the Smiles rearrangement[6] of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide (III) proceeded smoothly in acetone solution by the addition of powdered potassium hydroxide[7] to give a 62% yield of 3-azaphenothiazine (II). The preparation of the intermediate 2-aminophenyl 3-nitro-4-pyridyl sulfide (IV) in a number of steps starting from pyridine has been described.[3e]



I. R = $CH_2CH_2CH_2N(CH_3)_2$
II. R = H



III. R = $COCH_3$
IV. R = H

3-Azaphenothiazine (II) was alkylated with 3-dimethylaminopropyl chloride using sodium amide in refluxing toluene to give 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I). The dihydrochloride of I was nearly inactive as a tranquilizing agent when injected intraperitoneally in mice and, in marked contrast to the corresponding 10-dialkylaminoalkyl-1-azaphenothiazines[8] had only slight sedative and antihistamine properties.

On the other hand, alkylation of 3-azaphenothiazine (II) with 3-dimethylaminopropyl chloride in the absence of a stronger base gave the novel 3-(3-dimethylaminopropyl)-3-azaphenothiazinium chloride (V chloride) which on treatment with

(1) For a review see D. G. Friend, *Clin. Pharmacol. Therap.*, 1, Adv. p. 5 (1960).

(2) For numbering of the phenothiazine nucleus see v. J. P. Bourguin *et al.*, *Helv. Chim. Acta*, 42, 2541 (1959).

(3) (a) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945); (b) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, 80, 1651 (1958); (c) A. R. Gennaro, *J. Org. Chem.*, 24, 1156 (1959); (d) Y. Maki, *Chem. Abstr.*, 52, 1174 (1958); (e) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, 23, 1906 (1958); (f) T. Takahashi and E. Yoshii, *Pharm. Bull.*, 2, 382 (1954).

(4) (a) J. Druey, *Angew. Chem.*, 70, 5 (1958); (b) T. Takahashi and Y. Maki, *Chem. Abstr.*, 52, 14622 (1958); (c) Y. Maki, *Chem. Abstr.*, 51, 14738 (1957); (d) T. Takahasi and Y. Maki, *Chem. Pharm. Bull.*, 6, 369 (1958).

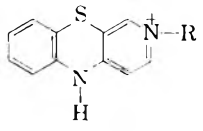
(5) 1-Nitro- and 1-amino-3-azaphenothiazines have been synthesized, and treatment of the latter compound with nitrous acid led to the formation of 3-azaphenothiazine-1,10-diazole.[3a] Attempts to prepare 3-azaphenothiazine by the fusion of 4-anilinopyridine with sulfur[3a] or by the Smiles rearrangement[6] of 2-formamidophenyl 3-nitro-4-pyridyl sulfide[3e] were unsuccessful.

(6) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 151, 1263 (1935).

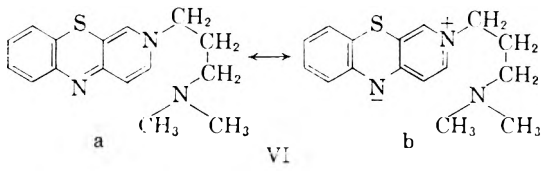
(7) The use of anhydrous potassium hydroxide in acetone as a medium for condensation reactions has been described, see K. A. Latif, M. M. Hossain, and M. A. Salam, *J. Ind. Chem. Soc.*, 35, 619 (1958). We found that when the alkali was added in alcoholic solution by the usual procedure the product was more difficult to isolate and the yield was lower.

(8) (a) Report of the Committee on New and Unused Therapeutics, *Ann. Allergy*, 16, 237 (1958); (b) A. Von Schlichtegroll, *Arz. Forsch.*, 7, 237 (1957); (c) *Arz. Forsch.*, 8, 489 (1958).

aqueous alkali gave reddish-brown crystals of the anhydronium base VI.[9] Although an *excess* of methanolic hydrogen chloride converted the anhydronium base VI to bright yellow crystals of the chloride hydrochloride of V, orange crystals of V chloride were generated with *one equivalent of* methanolic hydrogen chloride. A more convenient method of obtaining V chloride consisted in mixing methanolic solutions of equivalent weights of the anhydronium base VI and the chloride hydrochloride of V. The bromide hydrobromide and the dimaleate of V were also obtained.



V. R = $CH_2CH_2CH_2N(CH_3)_2$
VII. R = $CH_2CH_2CH_2NC_5H_{10}$
VIII. R = $CH_2CH_2NC_5H_{10}$
IX. R = $CH_2CH_2NH_2$
XII. R = CH_3



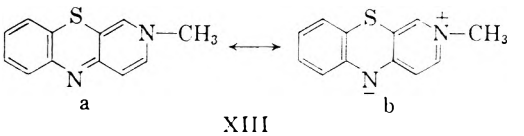
VI

The pharmacological evaluation of 3-(3-dimethylaminopropyl) - 3 - azaphenothiazinium chloride hydrochloride (V chloride hydrochloride) showed it to be a potent hypotensive agent. The intravenous injection of a dose of 2 mg./kg. caused a marked fall in the blood pressure of phenobarbital-anesthetized dogs which lasted for about one hour. In order to study further the hypotensive activity of this class of compounds a number of analogues were prepared. In VII, VIII, and IX the 3-dimethylaminopropyl substituent of V is replaced by 3-(*N*-piperidino)propyl, 2-(*N*-piperidino)ethyl, and 2-aminoethyl groups, respectively.

The chloride hydrochloride of VII was obtained as with V *via* the anhydronium base when 3-(*N*-piperidino)propyl chloride was substituted for 3-dimethylaminopropyl chloride. However, the product was obtained more conveniently by refluxing a solution of 3-azaphenothiazine (II) and 3-(*N*-piperidino)propyl chloride hydrochloride in absolute ethanol. The latter method also gave the halide hydrohalide salts of VIII and IX when 3-azaphenothiazine (II) was refluxed in alcoholic solution with 2-(*N*-piperidino)ethyl chloride hydrochloride and 2-aminoethyl bromide hydrobromide respectively. It is interesting that when 4-(*N*-piperidino)butyl chloride hydrochloride was treated with 3-azaphenothiazine in a similar manner, the 3-azaphenothiazine was recovered unchanged as its hydrochloride, probably because of selfquaternization of the 4-(N-piperidino)butyl chloride.

(9) (a) The anhydronium base VI may be considered to be a resonance hybrid of structures VIa and VIb. For the use of the term "anhydronium base" see B. Witkop, *J. Am. Chem. Soc.*, **75**, 3361 (1953); (b) For a critical discussion of the resonance hybrid structure of β-carboline anhydronium bases see I. D. Spenser, *J. Chem. Soc.*, 3659 (1956).

The halide hydrohalide salts of VII, VIII, and IX caused a fall in the blood pressure of normotensive dogs when given intravenously, but the effect was less marked and more transient than that of V chloride hydrochloride.



XIII

In accord with the structural assignments of the 3-aminoalkyl derivatives of 3-azaphenothiazine is the fact that, when 3-methyl-3-azaphenothiazinium iodide (XII iodide) (from 3-azaphenothiazine and methyl iodide) is converted to the corresponding anhydronium base XIII, the latter may again be alkylated with methyl iodide to form 3,10-dimethyl-3-azaphenothiazinium iodide (XIV iodide). The structure of the anhydronium base XIII may be represented as a resonance hybrid to which XIIIa and XIIIb make the major contributions, while XIVa and XIVb are the most important resonance structures of the quaternary cation XIV.

The infrared spectra of 3-azaphenothiazine (II), the anhydronium base XIII and the quaternary iodide XIV in Nujol mull provide an interesting confirmation of the structural assignments. Thus, while the spectrum of II has an intense band at 12.14 μ which may be attributed to the out of plane vibrations of two adjacent hydrogens on the pyridine ring,[10] this band is absent from the spectrum of XIII and is replaced in the spectrum of XIV by a weak, broad band at 12.02 μ. On the other hand, the spectrum of XIII has the characteristic intense band at 6.08 μ expected for conjugated ethylene and imine double bonds,[11] and, although this band is absent in the spectrum of II, it occurs in the spectrum of XIV as a band of medium intensity at 6.12 μ.

Some measure of the contribution of the dipolar amphion[12] XIIIb to the structure of the anhydronium base XIII was obtained by comparing the dipole moment of XIII with that of 3-azaphenothiazine (II). The dipole moments were measured[13] in dioxane solution and found to be 6.08 D and 4.65 D for XIII and II, respectively. These values indicate a considerable contribution of XIIIb to the structure of the anhydronium base XIII in dioxane solution.[14]

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley, New York, N. Y., 2nd Ed. (1958), p. 280.

(11) This band occurs in the spectrum of the naturally occurring anhydronium base, serpentine.[19b]

(12) See Ref. 9b for the use of this term.

(13) See Experimental.

(14) The dipole moment of the naturally occurring anhydronium base, sempervirine, in dioxane solution has been reported to be 8.5D: K. A. Jensen, *Acta Chem. Scand.*, **3**, 1447 (1949); see also R. Bentley and T. S. Stevens, *Nature*, **164**, 141 (1949); and B. Witkop, Ref. 9a.

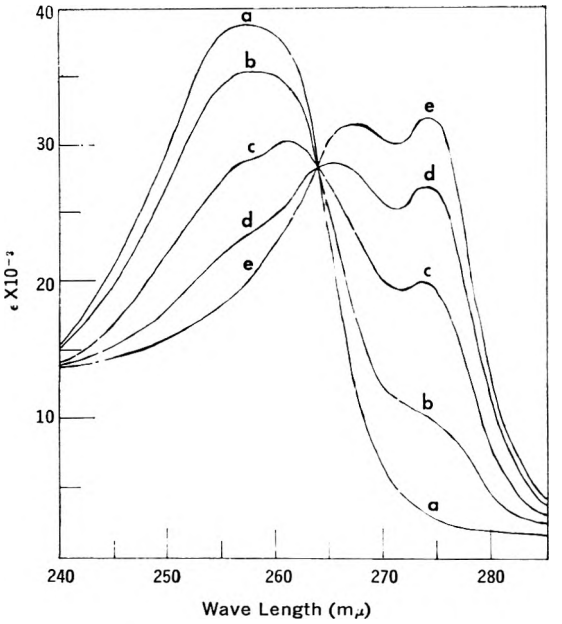
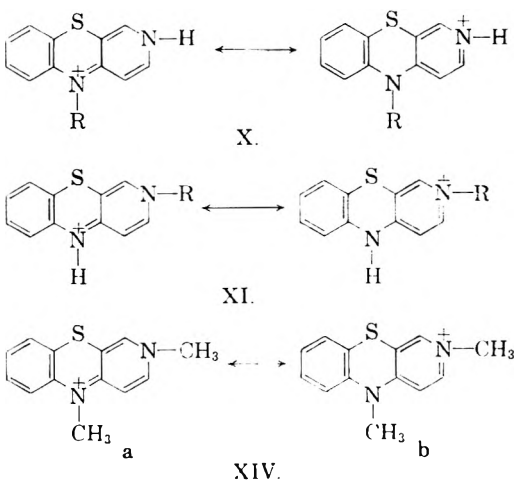


Fig. 1. Ultraviolet spectra of the hydrochloride of II in 50% ethanol: a, 0.1*N* in NaOH; b, at *p*H 6.36 (0.08*M* phosphate buffer); c, at *p*H 5.77 (0.08*M* phosphate buffer); d, at *p*H 4.87 (unbuffered); e, 0.1*N* in HCl

The ultraviolet spectra and base strengths of 3-azaphenothiazine and its 3- and 10-alkylated derivatives (Tables I and II) lend further support to the assigned structures. For instance the ultraviolet spectrum of 3-azaphenothiazine in 50% ethanol (or of its hydrochloride in alkaline solution, Fig. 1, a), has an intense maximum at 258 mμ which is replaced in acid solution by two maxima at 267 mμ and 274 mμ (Fig. 1, e). This bathochromic displacement is a consequence of increased resonance of the cation X (R = H).[15] As 3-azaphenothiazine is a weak base (pK_a = 5.9), its salts are partially dissociated in dilute solution so that the ultraviolet spectrum is a composite of the spectrum of the cation X (R = H) and the free base II. As may be seen in Fig. 1 the ultraviolet spectrum changes as the *p*H of the solution is varied and there is an isobestic point at 264 mμ, (*i.e.*, only one equilibrium is involved[16]). An alternate method for the determination of the pK_a is thus provided[17] (see Experimental) which may be applied in dilute aqueous solutions.[18]

The ultraviolet spectrum of 10-(3-dimethylaminopropyl)-3-azaphenothiazine dihydrochloride (I dihydrochloride) in 50% ethanol is similar to that of 3-azaphenothiazine hydrochloride (II hydrochloride) in 50% ethanol (Table I). As anticipated, the spectrum of I dihydrochloride is similarly altered in acid and alkaline solution to give the spectrum of the cation X [R = $CH_2CH_2CH_2N^+H(CH_3)_2$] and of the free base I respectively. Furthermore the pK_a's of I dihydrochloride (5.2 and 8.2) indicate a weakly basic aromatic nitrogen and a typical tertiary aliphatic amine, respectively.



It should be noted that the structures of 3,10-dimethyl-3-azaphenothiazinium iodide (XIV iodide) and of the 3-alkyl-3-azaphenothiazinium salts (XI) closely resemble those of the cation X of 10-(3-dimethylaminopropyl)-3-azaphenothiazine, [R = $CH_2CH_2CH_2N^+H(CH_3)_2$], and of 3-azaphenothiazine itself (R = H). It is not surprising then that the spectra of X, XI and XIV are very similar in acid solution (Table I). The fact that the spectrum of the quaternary compound XIV remains unchanged in 50% ethanol and in alkaline solution is in accord with its structure.

It may be seen from Table I that the spectrum of 3-(3-dimethylaminopropyl)-3-azaphenothiazinium chloride hydrochloride (V chloride hydrochloride) remains unchanged in 50% ethanol and in acid solution, but gives a new shoulder at 285 mμ in alkaline solution. The spectra of the other 3-alkyl derivatives (VII, VIII, IX and XII) behave similarly. Furthermore the 3-alkyl derivatives all have pK_a values near 11.0 (Table II), as expected for the salts of anhydronium bases.[19] Because of the strongly basic nature of these compounds an alkaline solution is required to alter the spectra of the "quaternary salts" by removing a proton from the onium ions to form the corresponding anhydronium bases.[9b] This interpretation is supported in the present case by the fact that when the crystalline anhydronium bases are dissolved in chloroform the ultraviolet spectra of the solutions have the characteristic

(15) Similar bathochromic displacements have been observed when β-carboline and dihydro-β-carboline bases are converted to the corresponding salts.[9]

(16) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold (Publishers) Ltd., London, 2nd Ed. (1957), p. 289.

(17) For detailed experimental procedure see H. C. Brown and X. R. Milm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(18) The low solubility of the free base in water renders direct titration in aqueous solution impractical, although aqueous alcohol or aqueous dimethylformamide may be used.

(19) (a) A. P. Gray *J. Am. Chem. Soc.*, **77**, 5930 (1955); (b) K. G. Krebs and N. Futscher, *Artz. Forsch.*, **10**, 75 (1960); (c) Ref. 9b.

TABLE I

ULTRAVIOLET SPECTRA OF THE 3-AZAPHENOTHIAZINE SERIES

Compound	Solution[a]	Wave Length Maxima, mμ (ε × 10⁻³)						
I[b]	A[c]	238 (11.4)		269[s] (22.4)	275 (24.6)		300 (2.9)	380 (2.5)
	B	235 (10.2)	258 (29.4)				308 (1.3)	
II[d]	A	237 (14.5)		267 (32.2)	274 (32.9)		308 (2.5)	405 (2.7)
	B	232 (10.4)	258 (38.8)				317 (1.8)	
V[e]	A	240 (14.5)		271 (32.5)	278 (34.0)		310 (3.0)	415 (3.6)
	B		260[s] (15.7)	270[s] (21.8)	276 (26.5)	285[s] (20.1)		444 (6.2)
VI[f]	C		260[s] (18.2)	270[s] (23.3)	277 (26.1)	284[s] (22.8)		425 (4.0)
VII[e]	A	240 (14.6)		271 (34.0)	279 (35.5)		310 (3.0)	415 (3.8)
	B		260[s] (16.1)	270[s] (22.9)	276 (27.8)	283[s] (21.2)		443 (6.5)
VIII[g]	A	240 (15.6)		271 (34.5)	279 (35.6)		310 (3.4)	420 (4.2)
	B		260[s] (16.6)	270[s] (23.5)	276 (29.0)	283[s] (22.5)		444 (6.9)
IX[h]	A	241 (15.6)		272 (34.1)	279 (35.2)		310 (3.4)	418 (4.0)
	B		260[s] (17.0)	270[s] (24.7)	276 (29.3)			443 (6.8)
XII[i]	A	240[s] (16.0)		270 (32.2)	277 (33.7)		305 (2.6)	410 (3.3)
	B		260[s] (15.3)	270[s] (22.1)	276 (26.4)	283[s] (19.7)		443 (5.9)
XIII[f]	C		260[s] (18.3)	270[s] (24.0)	277 (25.6)	285[s] (21.3)		440 (5.9)
XIV[i]	A[j]			270[s] (26.0)	276 (31.1)		300[s] (3.5)	390 (3.4)
	B[k]			270[s] (21.4)	278 (27.7)		300[s] (2.2)	390 (3.3)

[a] Approximately $4 \times 10^{-5} M$ solutions in: A, 0.1N hydrochloric acid in 50% aqueous ethanol; B, 0.1N sodium hydroxide in 50% ethanol; C, chloroform. [b] Dihydrochloride. [c] Also 222 (15.5). [d] Hydrochloride. [e] Chloride hydrochloride. [f] Anhydronium base. [g] Chloride hydrochloride monohydrate. [h] Bromide hydrobromide. [i] Iodide. [j] Also 222 (30.7). [k] Also 222 (27.0). [s] Shoulder.

TABLE II

BASICITIES OF 3-AZAPHENOTHIAZINE SERIES

Compound	pK_a Values[a]	
I	5.2	8.2
II	5.3	
V	10.8	7.5
VII	10.8	7.7
VIII	10.8	5.7
IX	10.8	6.6
XII	11.0	

[a] Determined by titration of the corresponding salts in 66% dimethylformamide.

shoulder at 284–285 mμ (Table I, VI C and XIII C). On the other hand when the anhydronium bases are dissolved in 50% ethanol the spectra of the quaternary salts are obtained.[20]

The effect of N-aminoalkylation on the position of the long wave-length band (at 405 mμ) of 3-azaphenothiazine in acid solution is worth noting. For instance the 3-dimethylaminopropyl group in the 10-position causes a hypsochromic shift to 380 mμ while in the 3-position the same substituent causes a bathochromic displacement to 415 mμ (Table I, V A; note the same effect in VII A). The bathochromic effect of the aliphatic amine cation on the spectrum of the onium ion is even greater when the ions are separated by only two carbon atoms. Thus in VIII A and IX A of Table I the long wave-length bands are at 420 mμ and 418 mμ, respectively.

The pK_a data recorded in Table II indicate the extent to which the aromatic cation lowers the basicity of the alkyl amine. As anticipated, the alkyl amines are less basic when separated from the aromatic cation by only two carbon atoms.

(20) All known anhydronium bases exhibit this behavior.[9b]

EXPERIMENTAL[21]

2-Aminophenyl 3-nitro-4-pyridyl sulfide[22] (IV). To a stirred, ice cooled solution of 80.0 g. (1.42 moles) of potassium hydroxide in 500 ml. of water was added 100.0 g. (0.80 mole) of *o*-aminothiophenol, followed by 650 ml. of dioxane. 4-Chloro-3-nitropyridine hydrochloride[23] (122 g., 0.63 mole) was then added and the solution stirred with ice water cooling for 2 hr. Ice water (2 l.) was then added to the reaction mixture and the solid was collected and washed, first with cold dilute aqueous alkali and then with ice water. The crude product (m.p. 134–137°) was recrystallized from about 2 l. of 95% ethanol to give 105.0 g. (68%) of yellow crystals, m.p. 150–151° (reported[3e] m.p. 146–147°).

2-Acetamidophenyl 3-nitro-4-pyridyl sulfide (III). 2-Aminophenyl 3-nitro-4-pyridyl sulfide (105 g.) was covered with 300 ml. of acetic anhydride and the mixture heated on the steam bath for 15 min. during which time the solid completely dissolved. The hot solution was poured onto ice and 500 ml. of concentrated aqueous ammonia (28%) added. The yellow solid was collected, dried, and recrystallized from 300 ml. of 95% ethanol to give 110 g. (89%) of product, m.p. 123–124°. Further recrystallization from 95% ethanol did not raise the melting point.

Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.96; H, 3.83; N, 14.54. Found: C, 54.26; H, 3.77; N, 14.22.

3-Azaphenothiazine (II). To a stirred, refluxing solution of 32.5 g. (0.089 mole) of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide in 2.5 l. of acetone under nitrogen was added 14.5 g. (0.26 mole) of powdered potassium hydroxide in small portions over a 30-min. period. The stirring and refluxing under nitrogen were continued for 1 hr. and then the acetone was distilled over 1.5 hr., vacuum being used at the end. Ice water (*ca.* 1 l.) was added to the residue, the mixture was stirred, and the solid collected, washed well with water, and dried to give 13.8 g. (62%) of 3-azaphenothiazine as a light yellow solid, m.p. 243–244° dec. Several recrystal-

(21) All melting points are corrected, but boiling points are uncorrected. Percent yields are enclosed in brackets.

(22) The preparation of this compound using the anhydrous sodium salt of *o*-aminothiophenol is described in Ref. 3e.

(23) T. Takahashi and K. Ueda, *Pharm. Bull.* (*Japan*), 2, 34 (1954).

lizations from ethanol or acetone raised the melting point to 246–248° dec.

Anal. Calcd. for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found: C, 65.95; H, 4.40; N, 13.63.

3-Azaphenothiazine hydrochloride was obtained as orange crystals upon addition of ethanolic hydrogen chloride to a solution of the base in acetone, m.p. 279–281° dec. (from ethanol).

Anal. Calcd. for $C_{11}H_8N_2S.HCl$: C, 55.81; H, 3.83; N, 11.84. Found: C, 55.83; H, 3.74; N, 11.52.

3-Azaphenothiazine hydrobromide formed yellow crystals from ethanolic hydrogen bromide and was recrystallized from aqueous ethanol for analysis, m.p. 263–265°, dec.

Anal. Calcd. for $C_{11}H_8N_2S.HBr$: C, 46.96; H, 3.23; N, 9.96. Found: C, 46.94; H, 3.40; N, 9.48.

10-(3-Dimethylaminopropyl)-3-azaphenothiazine (I). 3-Azaphenothiazine (29.2 g., 0.15 mole) and sodium hydride (7.2 g., 0.30 mole) (30 ml. of a 25% suspension in mineral oil) were added to 720 ml. of toluene and 180 ml. of anhydrous dioxane and the mixture refluxed with stirring. After 1 hr., 3-dimethylaminopropyl chloride (18.6 g., 0.15 mole) was added all at once followed by an additional 37.2 g. (0.30 mole) of the halide over a 4-hr. period. The reaction mixture first became green and then turned yellow and finally red as the halide was added. Refluxing and stirring were continued overnight and then the reaction mixture was cooled, excess sodium hydride decomposed with water, and the product extracted into 10% hydrochloric acid. The aqueous solution was made alkaline with ammonia and the product taken up in ether. The ether extract was dried over anhydrous sodium sulfate and distilled, first to remove ether, then under reduced pressure to remove unchanged halide and finally under high vacuum to give 33.5 g. (80.5%) of product as an orange oil, b.p. 200–210°/0.7 mm.; n^{26} 1.6347.

Anal. Calcd. for $C_{16}H_{19}N_3S$: C, 67.34; H, 6.71; S, 11.23. Found: C, 67.67; H, 6.92; S, 11.13.

The *dihydrochloride* formed yellow crystals from absolute ethanol-anhydrous ether, m.p. 262–264° dec.

Anal. Calcd. for $C_{16}H_{29}N_3S.2HCl$: C, 53.64; H, 5.91; N, 12.00. Found: C, 53.90; H, 6.00; N, 11.72.

When ethanol alone was used as a solvent the dihydrochloride separated as a monohydrate, m.p. 120–130° (with gas evolution) which solidified and remelted at 261–263° dec.

Anal. Calcd. for $C_{16}H_{19}N_3S.2HCl.H_2O$: N, 11.17. Found: N, 11.00.

The solvate was readily converted to the anhydrous salt when suspended in refluxing toluene or when recrystallized from absolute ethanol-anhydrous ether.

The *dihydrobromide* was recrystallized from absolute ethanol, m.p. 244–246° (dec.).

Anal. Calcd. for $C_{16}H_{19}N_3S.2HBr$: C, 42.97; H, 4.73; N, 9.40. Found: C, 43.08; H, 4.70; N, 9.62.

The *dimaleate* formed yellow crystals from 95% ethanol, m.p. 149–150° dec.

Anal. Calcd. for $C_{16}H_{19}N_3S.2C_4H_4O_4$: C, 55.70; H, 5.26; N, 8.12. Found: C, 55.35; H, 5.08; N, 8.17.

3-(3-Dimethylaminopropyl)-3-azaphenothiazine anhydronium base (VI). A solution of 15.0 g. of 3-azaphenothiazine and 37 ml. of 3-dimethylaminopropyl chloride in 325 ml. of anhydrous dioxane was refluxed for 24 hr. and then the solvent was distilled. The residue was triturated with water and filtered and the filtrate was made strongly alkaline with 50% sodium hydroxide solution. The precipitate was extracted with methylene chloride, the extract was evaporated, and the residue was crystallized from anhydrous ether to give 6.2 g. (29%) of the anhydronium base as orange crystals, m.p. 84–91°. Several recrystallizations from ether raised the melting point to 95–96°. A small portion of the base was distilled in a collar flask at 0.005 mm. pressure (bath temperature 175–210°).

Anal. Calcd. for $C_{16}H_{19}N_3S$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.21; H, 6.51; N, 14.43.

3-(3-Dimethylaminopropyl)-3-azaphenothiazinium chloride hydrochloride (V *Chloride hydrochloride*). The chloride hydrochloride of V was prepared by treating an alcoholic solution of the anhydronium base VI with an excess of alcoholic hydrogen chloride. The yellow product was recrystallized from methanol-ethanol or methanol-ethyl acetate, m.p. 285–286° dec.

Anal. Calcd. for $C_{16}H_{20}N_3S.Cl.HCl$: C, 53.64; H, 5.91; N, 12.00. Found: C, 53.69; H, 5.99; N, 11.88.

V *Chloride* was obtained as orange crystals when 1 equivalent of anhydrous methanolic hydrogen chloride was added to a methanolic solution of the anhydronium base VI the solution concentrated, and anhydrous ether added. Recrystallization from methanol–anhydrous ether gave an analytical sample, m.p. 170–172°.

Anal. Calcd. for $C_{16}H_{20}N_3S.Cl$: C, 59.71; H, 6.26; N, 13.05. Found: C, 59.90; H, 6.61; N, 13.51.

V Chloride was also obtained by dissolving molar equivalents of the anhydronium base VI and V chloride hydrochloride in methanol, then gradually displacing the methanol from the boiling solution with acetone and cooling.

V *Bromide hydrobromide* was obtained as yellow crystals from ethanol, m.p. 267–269° dec.

Anal. Calcd. for $C_{16}H_{20}N_3S.HBr$: C, 42.97; H, 4.73; N, 9.39. Found: C, 43.03; H, 5.00; N, 9.30.

When a hot solution of V bromide hydrobromide in 70% ethanol was allowed to cool slowly to room temperature the monohydrate was obtained as orange crystals which did not melt but lost water on heating to give the yellow anhydrous salt, m.p. 267–269° dec. The infrared spectrum of the monohydrate showed strong hydroxyl absorption at 2.95 mμ which was absent in the spectrum of the anhydrous salt.

Anal. Calcd. for $C_{16}H_{20}N_3S.Br.HBr.H_2O$: C, 41.30; H, 4.93; N, 9.03. Found: C, 41.51; H, 4.95; N, 9.11.

V *Dimaleate* formed yellow crystals from 95% ethanol, m.p. 186–187° dec.

Anal. Calcd. for $C_{15}H_{19}N_3S.2C_4H_4O_4$: C, 55.70; H, 5.26; N, 8.12. Found: C, 55.86; H, 5.58; N, 8.20.

3-(3-N-Piperidinopropyl)-3-azaphenothiazinium chloride hydrochloride (*VII Chloride hydrochloride*). A solution of 5.0 g. of 3-azaphenothiazine and 10 ml. of 3-(*N*-piperidino)-propyl chloride[24] in 80 ml. of dioxane was refluxed overnight and the solution decanted. The gum which had separated was dissolved in water, the solution made strongly alkaline with 50% aqueous sodium hydroxide and the precipitate taken up in methylene chloride. The extract was dried over anhydrous sodium sulfate and evaporated to give an oil which did not crystallize. Treatment with an excess of methanolic hydrogen chloride and dilution with ether gave 7.8 g. (79%) of VII chloride hydrochloride, m.p. 290–295° dec. Several recrystallizations from methanol–ethyl acetate gave yellow needles, m.p. 298–300° dec.

Anal. Calcd. for $C_{19}H_{24}N_3S.Cl.HCl$: C, 57.28; H, 6.33; N, 10.55. Found: C, 57.31; H, 6.33; N, 10.39.

Alternatively VII chloride hydrochloride was prepared by refluxing a solution of 1.0 g. of 3-azaphenothiazine and 2.0 of 3-(*N*-piperidino)propyl hydrochloride[25] in 50 ml. of absolute ethanol for 2 days, concentrating the solution and cooling to give 1.75 g. (90%) of yellow crystals, m.p. 295–300° dec., undepressed upon admixture with the product prepared as described above.

3-(2-N-Piperidinoethyl)-3-azaphenothiazinium chloride hydrochloride (*VIII Chloride hydrochloride*). 2-(*N*-Piperidino)-ethyl alcohol was obtained by allowing a solution of 11.0 g. of ethylene oxide and 21.2 g. of piperidine in 100 ml. of absolute ethanol to stand overnight and then distilling at atmospheric pressure to give 21.8 g. (67.7%) of an oil,

(24) A. Marxer, *Helv. Chim. Acta*, **24**, E209 (1941).

(25) P. Ofner, *J. Chem. Soc.*, 1800 (1951), reports m.p. 213–214° for the hydrochloride and m.p. 111–112° for the picrate. We found melting points of 225–226° and 116–117° for the hydrochloride and picrate, respectively.

b.p. 204–208° (reported,[26] b.p. 200–202°/742 mm.). Treatment of the alcohol with thionyl chloride in chloroform in the usual manner followed by recrystallization from absolute ethanol gave 2-(*N*-piperidino)ethyl chloride hydrochloride, m.p. 233–236° (reported[27] m.p. 234°).

A solution of 3.8 g. of 3-azaphenothiazine and 5.4 g. of 2-(*N*-piperidino)ethyl chloride hydrochloride in 75 ml. of absolute ethanol was refluxed overnight and then concentrated and cooled to give 5.6 g. (75%) of VIII chloride hydrochloride as yellow crystals, m.p. 284–291° dec. The salt was recrystallized several times from methanol–anhydrous ether for analysis, m.p. 290–293° dec. The analytical results and the presence of an hydroxyl band at 3.0 mμ in the infrared spectrum indicate 1 mole of methanol of crystallization.

Anal. Calcd. for $C_{18}H_{22}N_3S.Cl.HCl.CH_4O$: C, 54.80; H, 6.54; N, 10.09. Found: C, 54.32; H, 6.34; N, 9.76.

3-(2-Aminoethyl)-3-azaphenothiazinium bromide hydrobromide (IX Bromide hydrobromide). A solution of 3.8 g. of 3-azaphenothiazine and 6.2 g. of 2-aminoethyl bromide hydrobromide in 100 ml. of absolute ethanol was refluxed overnight, cooled, and filtered to give 3.5 g. (45%) of IX bromide hydrobromide, m.p. 288–293° dec. The salt was recrystallized several times from aqueous ethanol for analysis, m.p. 296–298° dec.

Anal. Calcd. for $C_{13}H_{14}N_3S.Br.HBr$: C, 38.53; H, 3.73; N, 10.37. Found: C, 38.33; H, 3.63; N, 10.43.

The reaction of 3-azaphenothiazine with 4-(N-piperidino)-butyl chloride hydrochloride. 4-(*N*-Piperidino)butyl alcohol was obtained in low yield when piperidine and 4-chlorobutyl alcohol were refluxed overnight in dioxane solution and the reaction worked up in the usual manner to give a colorless oil, b.p. 131–133°/19 mm. (reported[28] b.p. 133–134°/20 mm.). Treatment of the alcohol with thionyl chloride in chloroform solution followed by distillation of the solvent and excess thionyl chloride gave 4-(*N*-piperidino)butyl chloride hydrochloride, m.p. 162–163° (from 2-propanol-ether) (reported[29] m.p. 162°).

A solution of 2.83 g. of 3-azaphenothiazine and 3.46 g. of *N*-(4-chlorobutyl)piperidine hydrochloride in 50 ml. of absolute ethanol was refluxed overnight, then concentrated, cooled, and filtered to give 3.4 g. of yellow solid, m.p. 265–278°. Two recrystallizations, first from methanol–ethyl acetate, then from methanol-2-propanol raised the melting point to 279–281° (undepressed upon admixture with 3-azaphenothiazine hydrochloride). The infrared and ultraviolet spectra were superimposable upon those of 3-azaphenothiazine hydrochloride.

Anal. Calcd. for $C_{11}H_8N_2S.HCl$: N, 11.84. Found: N, 11.81.

3-Methyl-3-azaphenothiazinium iodide (XII Iodide). A solution of 2.0 g. of 3-azaphenothiazine and 10 g. of methyl iodide in 100 ml. of acetone was refluxed for 1 hr., cooled, and filtered to give 2.7 g. (78%) of XII iodide as a deep yellow solid, m.p. 228–231°. Several recrystallizations from water gave a sample for analysis, m.p. 231–232°.

Anal. Calcd. for $C_{12}H_{11}N_2S.I$: C, 42.12; H, 3.24; N, 8.19. Found: C, 42.55; H, 3.44; N, 7.69.

XII Maleate was obtained by treating the anhydronium base XIII (see below) with maleic acid in methanol solution. Recrystallization from methanol gave yellow crystals, m.p. 233–234°.

Anal. Calcd. for $C_{12}H_{11}N_2S.C_4H_4O_4$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.10; H, 4.47; N, 8.62.

3-Methyl-3-azaphenothiazine anhydronium base (XIII). To a stirred mixture of 50 ml. of benzene and 30 ml. of 20% aqueous sodium hydroxide was added 1.8 g. of XII iodide. After a short time the benzene solution was separated, dried over anhydrous sodium sulfate, concentrated, and diluted with pentane to give 0.8 g. (71%) of the anhydronium base as a vermilion solid, m.p. 162–166°. One recrystallization from benzene-pentane raised the melting point to 166–167°, which was unchanged on further recrystallization.

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.08. Found: C, 67.65; H, 4.47; N, 13.01.

3,10-Dimethyl-3-azaphenothiazinium iodide (XIV Iodide). A solution of 0.5 g. of 3-methyl-3-azaphenothiazine anhydronium base and 5 ml. of methyl iodide in 30 ml. of acetone was concentrated and cooled to give 0.65 g. (78%) of XIV iodide as a bright yellow solid, m.p. 189–192°. The melting point was unchanged after recrystallization from methanol. The sample was dried at 80° in high vacuum for analysis.

Anal. Calcd. for $C_{13}H_{13}N_2S.I$: C, 43.83; H, 3.68; N, 7.87. Found: 43.60; H, 4.07; N, 7.59.

Determination of the pK_a of 3-azaphenothiazine hydrochloride from ultraviolet spectra. Solutions of 3-azaphenothiazine hydrochloride ($4.27 \times 10^{-5}M$) were prepared in 50% ethanol as follows: a, 0.1*N* in hydrochloric acid; b, 0.1*N* in sodium hydroxide; c, d, e, 0.08*M* in phosphate buffer. The *p*H of solutions c, d, and e were measured on a Beckman *p*H Meter and the molar extinction coefficients (ϵ) of all of the solutions were determined at 274 mμ on a Beckman DU Spectrophotometer. pK_a values were calculated using the expression: $pK_a = pH - \log[(\epsilon_a - \epsilon)/(\epsilon - \epsilon_b)]$, in which *p*H is the measured *p*H of the solution, ϵ_a is the molar extinction coefficient in acid, ϵ_b is the value in alkali and ϵ is the value at the measured *p*H.[30] The results recorded in Table III are in good agreement with the mean value of 5.9 determined by titration of the salt in 50% aqueous ethanol.

TABLE III

pK_a VALUES FROM ULTRAVIOLET SPECTRA

No.	*p*H	$\epsilon \times 10^{-3}$	$\log \frac{\epsilon_a - \epsilon}{\epsilon - \epsilon_b}$	pK_a
a	Acid	32.1		
b	Base	1.09		
c	6.36	10.3	+0.48	5.88
d	6.00	15.4	+0.13	5.87
e	5.77	19.9	−0.11	5.88

Measurement of dipole moments. Dipole moments were calculated according to the method of Halverstadt and Kumler.[31] Dielectric constants were determined with a Sargent Chemical Oscillometer, Model V. Specific volume measurements were made with a pycnometer. The molar refractions (R_D) were calculated from bond refractions.[32] The molar orientation polarization P_μ^2 was calculated from the equation: $P_\mu^2 = p_2^2M - R_D$ and the dipole moment μ from the equation $\mu = 0.0127(P_\mu^2 T)^{1/2}$. In Tables IV and V values are given for 3-azaphenothiazine (II) and the anhydronium base XII, respectively, in dioxane solution at 25°. The symbols have the same significance as in the paper by Halverstadt and Kumler.[31]

Acknowledgment. The authors are indebted to S. Irwin and Dr. F. Roth of the Department of Pharmacology, Schering Corporation, for the pharmacological data. We are also grateful to the members of the Department of Physical Chemistry under the direction of Dr. P. Kabasakalian for

(26) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

(27) T. Bany, *Chem. Abstr.*, **50**, 12042*e* (1956).

(28) J. v. Braun, *Ber.*, **49**, 2629 (1916).

(29) A. Albert, *Ber.*, **42**, 545 (1909).

(30) J. C. Gage, *J. Chem. Soc.*, 221 (1949).

(31) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(32) A. I. Vogel, W. T. Cresswell, G. H. Jefferey, and J. Leicester, *J. Chem. Soc.*, 514 (1952).

TABLE IV

w_2	ϵ_{12}	v_{12}			
0.00168	2.238	0.97593	ϵ_1 = 2.212	β = 0.48	R_D = 53.8
0.00331	2.260	0.97520	v_1 = 0.9768	p_2° = 2.5105	P_μ° = 448.9
0.00561	2.292	0.97412	α = 14.33	M = 200.3	μ = 4.65 D

TABLE V

w_2	ϵ_{12}	v_{12}			
0.00150	2.246	0.97636	ϵ_1 = 2.212	β = 0.29	R_D = 54.5
0.00281	2.281	0.97596	v_1 = 0.9768	p_2° = 3.8381	P_μ° = 768.0
0.00488	2.324	0.97537	α = 22.04	M = 214.3	μ = 6.08 D

physical measurements carried out in the course of this work. In particular we wish to thank Mr. E. Townley for the ultraviolet spectra, Mr. J. McGlotten for the *p*Ka and dipole moment data, Mr. R. Wayne for the determination and interpretation of infrared spectra, and Mr. E. Connor for microanalyses. Microanalyses were also performed by Galbraith Laboratories, Knoxville, Tennessee.

BLOOMFIELD, N. J.

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

The Cyclization of *N*-Alkenylthionamides to Thiazolines and Dihydrothiazines

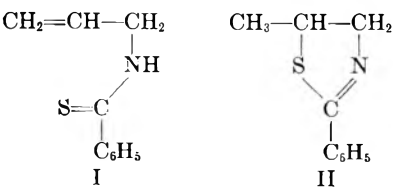
PETER A. S. SMITH AND JOHN M. SULLIVAN[1]

Received June 23, 1960

A group of *N*-alkenylbenzthionamides and acetthionamides have been prepared from the corresponding isothiocyanates and Grignard reagents. Allylic *N*-alkenylthionamides cyclize when treated with acidic catalysts such as aluminum chloride, but not with benzoyl peroxide. The position of cyclization follows the Markovnikov rule with an apparent slight preference for thiazolines over dihydrothiazines when other factors are equal.

In the course of the wartime penicillin project, one of us found that *N*-allyldicarboethoxyacetthionamide could be cyclized to a thiazoline ring.[2] It was the object of the present work to learn something of the nature of the reaction and to determine whether the cyclization of allylthionamides might have any generality. If so, an efficient synthetic route might become available, since allylic isothiocyanates are readily available, and thionamides can be prepared by the addition of Grignard reagents to them.[3]

N-Allylbenzthionamide (I) was chosen as an uncomplicated model. Cyclization to 2-phenyl-5-methyl-2-thiazoline (II) was effected by a variety of acidic catalytic agents, such as zinc chloride, boron fluoride, and sulfuric acid; aluminum chloride in nitrobenzene was the most effective, giving II in 47% yield. In contrast, benzoyl peroxide did not produce detectable cyclization. The assignment of structure II to the cyclization product, instead of the isomeric dihydrothiazine structure, is supported by the agreement of the melting point of its picrate with that reported for 2-phenyl-5-methyl-2-thiazoline picrate prepared in a different way, but more direct proof that cyclization had taken place at the β-rather than the γ-carbon was obtained by hydrolyzing II to 1-aminopropan-2-thiol, isolated and identified as the hydrochloride of the corresponding disulfide.



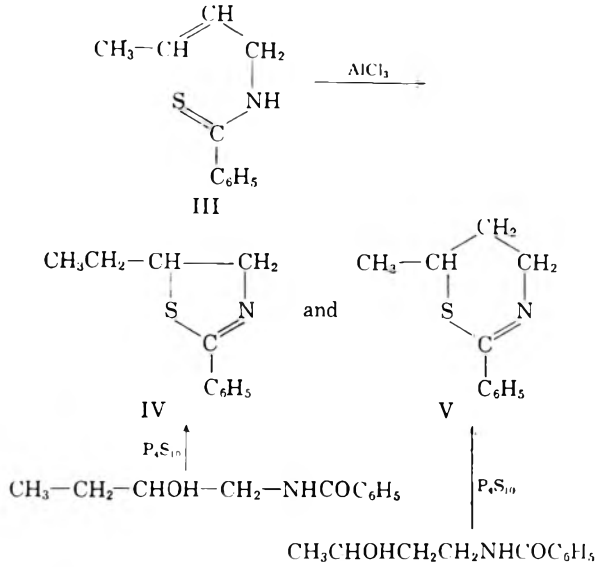
This cyclization is stoichiometrically identical to the intermolecular addition of mercaptans to olefins, and is readily conceived as a reaction of the enethiol tautomer of the thionamide. The

(1) From the doctoral thesis of J. M. S., Union Carbide Summer Fellow, 1957. Presented at the National Meeting, American Chemical Society, New York, September, 1960.

(2) *The Chemistry of Penicillin*, ed. by H. T. Clarke, Princeton University Press, Princeton, 1949, p. 470. [A similar reaction had been postulated previously, but not experimentally established as an intermediate stage in the acid-catalyzed condensation of phenols with allyl isothiocyanate: J. B. Niederl, W. F. Hart, and J. V. Scudi, *J. Am. Chem. Soc.*, **58**, 707 (1936); J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952)].

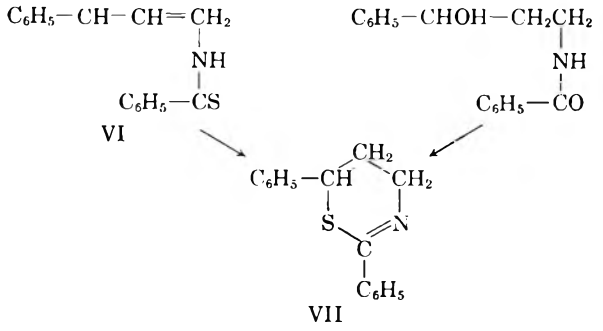
(3) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 1200.

intermolecular reaction does not require acid catalysts, however, and is promoted by light or benzoyl peroxide; addition takes place in the anti-Markovnikov position, as is to be expected of a free-radical reaction.[4,5] Our cyclization reaction therefore seemed, in contrast, to be an ionic addition of sulfur to an olefin. The evidence given by the position of cyclization is in this example ambiguous, however, since it might have been determined as much by a preference for forming a five-membered ring rather than a six-membered one, as by a preference for the formation of a carbonium ion at the more highly substituted β-carbon. Accordingly, we next investigated *N*-crotylbenzthionamide (III), in which the unsaturated carbon atoms are equally substituted. A mixture was produced in poor yield (20%), and separated by fractional distillation. The components were 2-phenyl-5-ethyl-2-thiazoline (IV) and 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine (V) in a ratio of between three and eight to one. This result is consistent with the concept of preferred cyclization to the most highly substituted carbon atom combined with a weak preference for five-membered ring formation; but, of course, certainty cannot be attached to such a conclusion in view of the low yields.



For identification, the thiazoline IV was prepared independently by treatment of *N*-(2-hydroxybutyl)benzamide with phosphorus pentasulfide; the samples were compared as their picrates. In a similar manner, V was prepared from *N*-(3-hydroxybutyl)benzamide.

When the stability of the carbonium ion at the γ-carbon was enhanced by phenyl substitution, as in *N*-cinnamylbenzthionamide (VI), cyclization appeared to occur there exclusively, to give the thiazine VII, although in low yield. This thiazine was identified through independent synthesis from *N*-(3-hydroxy-3-phenylpropyl)benzamide and phosphorus pentasulfide. The required 3-phenyl-3-hydroxypropylamine was obtained by the Curtius degradation applied to γ-phenyl-γ-butyrolactone through the hydrazide, azide, and 6-phenyltetrahydro-1,3-oxazin-2-one.



The cyclization of allylic thionamides was found to proceed as readily with acetthionamides as with benzthionamides. *N*-Allyl- (IX), *N*-(β-methallyl)- (X) and *N*-(α-methallyl)acetthionamide (XI) gave respectively 2,5-dimethyl-2-thiazoline (48%), 2,5,5-trimethyl-2-thiazoline(46%), and 2,4,5-trimethyl-2-trimethyl-2-thiazoline (46%).

A structural situation not permitting formation of the thiazoline ring is presented by *N*-(3-butenyl)-benzthionamide (VIII). Cyclization gave only a small conversion to isolable product, which was identified as 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine by comparison with an authentic sample.

EXPERIMENTAL[6]

Isothiocyanates. Allyl isothiocyanate is commercially available; 3-butenyl,[7] crotyl,[7] and β-methallyl[8] isothiocyanates were prepared according to published methods. α-Methallyl isothiocyanate, b.p. 51–57°/22 mm. (reported[9] b.p. 70–72°/34 mm.) was prepared from crotyl chloride and sodium thiocyanate, through crotyl thiocyanate, according to the procedure used by Bruson and Eastes[8] for β-methallyl isothiocyanate. Cinnamyl isothiocyanate, b.p. 120–127°/1 mm. (reported[10] b.p. 162°/12 mm.) was prepared in 54% yield by the Kaluza reaction according to the general directions of Moore and Crossley,[11] and less satisfactorily by the isomerization of cinnamyl thiocyanate.[12]

N-(Hydroxyalkyl)benzamides. These compounds, with the exception of 3-hydroxy-3-phenylpropylamine, whose prep-

(4) F. G. Bordwell and W. A. Hewett, *J. Am. Chem. Soc.*, **79**, 3493 (1957).

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

(6) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting and boiling points are uncorrected.

(7) M. G. Ettlinger and J. E. Hodgkins, *J. Am. Chem. Soc.*, **77**, 1834 (1955).

(8) H. A. Bruson and J. W. Eastes, *J. Am. Chem. Soc.*, **59**, 2011 (1937).

(9) A. Kjaer, K. Rubinstein, and K. A. Jensen, *Acta Chem. Scand.*, **7**, 518 (1953).

(10) E. Bergmann, *J. Chem. Soc.*, 1361 (1935).

(11) M. L. Moore and F. S. Crossley, *Org. Syntheses*, **Coll. Vol. III**, John Wiley and Sons, New York, 1955, p. 599.

(12) P. A. S. Smith and D. W. Emerson, *J. Am. Chem. Soc.*, **82**, 3076 (1960).

aration follows, were prepared by benzoylating the known amino alcohols, mostly commercially available, in the presence of saturated aqueous potassium carbonate, and showed physical constants in agreement with published values. Two compounds were previously unreported. *N-(2-Hydroxybutyl)benzamide* formed colorless crystals, m.p. 106.5–108° (from benzene).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.34; H, 7.80; N, 7.33.

N-(3-Hydroxybutyl)benzamide was obtained as a viscous oil, b.p. 174–180°/0.5 mm.; it could not be induced to crystallize, but its infrared spectrum showed the absorptions to be expected of a hydroxy amide structure.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.90; N, 7.34.

4-Hydroxy-4-phenylbutyryl hydrazide. γ-Phenyl-γ-butyrolactone[13] (16.2 g., 0.1 mole) prepared by sodium borohydride reduction of β-benzoylpropionic acid, was refluxed for 12 hr. with 3.2 g. (0.1 mole) of hydrazine. Upon cooling, the hydrazide precipitated; the yield of crude material, m.p. 118–128°, was 85%. A small amount was recrystallized three times from a mixture of benzene and ethanol for an analytical sample, m.p. 124.5–126°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.84; H, 7.30; N, 14.59.

6-Phenyltetrahydro-1,3-oxazin-2-one. γ-Hydroxy-γ-phenylbutyryl hydrazide (5.2 g., 0.027 mole) was dissolved in 200 ml. of water which contained 1.4 ml. (0.025 mole) of sulfuric acid. This solution was stirred at −5° with 70 ml. of ether while 1.83 g. (0.027 mole) of sodium nitrite, dissolved in 75 ml. of water, was added over a 0.5-hr. period. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried, an equal amount of benzene was added, and the solution was refluxed for 12 hr. During this time, 6-phenyltetrahydro-1,3-oxazin-2-one separated in a ring of beautiful, white, analytically pure crystals around the surface of the liquid; weight 2.4 g. (50%), m.p. 180–181°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.89; H, 6.30; N, 7.77.

An additional 0.7 g. of crude product, m.p. 170–178°, was obtained by evaporation of the mother liquors.

3-Hydroxy-3-phenylpropylamine oxalate. A solution of 2.4 g. (0.0135 mole) of 6-phenyltetrahydro-1,3-oxazine-2-one and 7 g. of 85% potassium hydroxide in 20 ml. of ethanol was refluxed for 20 hr. The mixture was then poured into water and carefully acidified to *p*H 2; carbon dioxide was evolved. The acidified solution was extracted with ether to remove nonbasic impurities and was then made basic and extracted successively with ether and benzene. The combined extracts were dried and evaporated, leaving 1.2 g. of yellowish oil with an amine-like odor. Davies and Powell[14] report 3-hydroxy-3-phenylpropylamine to be a solid, m.p. 63.5–64.5°. The impure amino alcohol was converted to its oxalate by precipitation from ether with ethereal oxalic acid and recrystallized from aqueous ethanol; weight 0.6 g., m.p. 190–194°. A second recrystallization gave an analytical sample, m.p. 194–195°.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.27; H, 7.22; N, 7.09.

Another form of the oxalate can also be obtained with m.p. 148–150°.

N-Alkenylthionamides. These compounds were prepared by the reaction of Grignard reagents with alkenyl isothiocyanates. The results are summarized in Table I. The following example is typical of the procedure followed.

N-Crotylbenzthionamide. trans-Crotyl isothiocyanate[7] (17 g., 0.15 mole) was added dropwise to a stirred ether solution of 0.2 mole of phenylmagnesium bromide. When the reaction subsided, refluxing was maintained for 0.5 hr. The Grignard complex was hydrolyzed with aqueous ammonium chloride. Removal of solvent from the ether layer and distillation of the residue gave 21 g. (73%) of *N*-crotylbenzthionamide, b.p. 156–157°/0.9 mm. (Analytical data are in Table I.)

TABLE I

THIONAMIDES PREPARED FROM ISOTHIOCYANATES
RNCS + R′MgX → RNHCSR′

No.	R	R′	M.P. °, or B.P. °/mm.	Yield, %
III	$CH_3CH{=}CHCH_2$	C_6H_5	156–157/0.9	73[a]
VI	$C_6H_5CH{=}CHCH_2$	C_6H_5	88–89	62[b]
VII	$CH_2{=}CHCH_2CH_2$	C_6H_5	137–145/0.4	42
IX	$CH_2{=}CHCH_2$	CH_3	87/0.4[c]	52
X	$CH_2{=}CHCHCH_3$	CH_3	90–98/1	46[d]
XI	$CH_2{=}C(CH_3)CH_2$	CH_3	98–103/0.3	67[e]

[a] *Anal.* Calcd. for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.31; H, 7.06; N, 7.19. [b] *Anal.* Calcd. for $C_{15}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53. Found: C, 75.54; H, 6.26; N, 5.38. [c] Sachs and Loevy[14] report b.p. 135–136°/17 mm. [d] *Anal.* Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.78; H, 8.58; N, 10.93. [e] *Anal.* Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.54; H, 8.34; N, 11.02.

Cyclization of N-alkenylthionamides to 2-thiazolines and/or 5,6-dihydro-1,3,4-thiazines. The cyclizations were brought about by heating the thionamides with anhydrous aluminum chloride, with minor variations among the examples. The results are summarized in Table II. The following example is typical of the procedure used.

2-Phenyl-5-methyl-2-thiazoline. Anhydrous aluminum chloride (33 g., 0.25 mole) was added directly to 44.3 g. (0.25 mole) of *N*-allylbenzthionamide[15] and the mixture was stirred. Much heat was evolved and a solid cake soon formed. Nitrobenzene was added to dissolve the cake and the mixture was held at 125° for 2 hr. Excess 25% sodium hydroxide solution was added to the cooled mixture, which was then stirred for 0.5 hr., and extracted with ether. The ether layer was extracted with 10% hydrochloric acid, and the acid layer was neutralized with excess 10% sodium hydroxide solution and extracted with ether. After removal of solvent from the dried ether extracts and distillation of the residue, 21 g. (47%) of 2-phenyl-5-methyl-2-thiazoline, was obtained, b.p. 148–150°/18 mm., or 86–91°/1 mm. A Kuhn-Roth C-methyl determination showed 0.72 equiv. per mole. (Other analytical data are in Table II.)

A similar experiment using zinc chloride in place of aluminum chloride and 12 hr. of heating gave a 31% yield. In another experiment where boron trifluoride etherate was used as the catalyst, with heating at 105° for 12 hr. in a sealed tube, the yield was 35%. In an experiment where benzoyl peroxide was the only catalytic agent, no basic products of any kind could be detected, and the thionamide remained apparently unchanged.

Hydrolysis of 2-phenyl-5-methylthiazoline. A solution of 5.5 g. of 2-phenyl-5-methyl-2-thiazoline in 25 ml. of concentrated hydrochloric acid was heated at 175° for 5 hr. in a sealed tube. The cooled reaction mixture deposited 2.2 g. (58%) of benzoic acid, which was removed by filtration. The filtrate was extracted with ether, and the aqueous layer was made strongly basic with 10% sodium hydroxide and extracted with ether in order to remove unchanged thiazoline. The aqueous layer was then acidified and the amino mercaptan salt was converted to the amino disulfide salt by adding iodine-potassium iodide solution until the iodine color persisted. Then the mixture was made basic

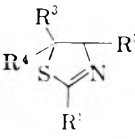
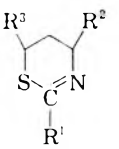
(13) R. R. Russell and C. A. Vander Werf, *J. Am. Chem. Soc.*, 69, 12 (1947).

(14) R. E. Davies and G. Powell, *J. Am. Chem. Soc.*, 67, 1466 (1945).

(15) F. Sachs and H. Loevy, *Ber.*, 37, 874 (1904).

TABLE II

CYCLIZATION OF *N*-ALKENYLTHIONAMIDES TO

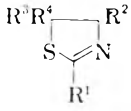
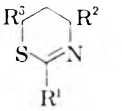
2-Thiazolines,  , and Dihydrothiazines, 

Thionamide No.	R¹	R²	R³	R⁴	M.P. °, or B.P. °/Mm.	Yield, %	Picrate, M.P. °
I	C_6H_5	H	CH_3	H	148–150/18[a]	47	158–160[b]
III	C_6H_5	H	C_2H_5	H	88–90/0.2[c]	12	131–132[c]
	C_6H_5	H	CH_3	[d]	112–119/0.3[c]	1.5	162.5–164.5[c]
VI	C_6H_5	H	C_6H_5	[d]	86.5–87.5[e]	19	160–162[f]
VIII	C_6H_5	H	CH_3	[d]			164–165.5[c]
IX	CH_3	H	CH_3	H	48/22[g]	48	
X	CH_3	CH_3	CH_3	H	55–56/25[h]	46	170–172[i]
XI	CH_3	H	CH_3	CH_3	52/25[j]	46	150–154[k]

[a] *Anal.* Calcd. for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.31; N, 7.94. [b] Reported picrate m.p. 156–157°; chloroplatinate, m.p. 179° [A. Salomon, *Ber.*, 26, 1321 (1893)]; nitro derivative, m.p. 70.5–71.5° (R. Adams and S. H. Babcock, *J. Am. Chem. Soc.*, 59, 2260 (1937)). Found: Chloroplatinate, m.p. 184–186° dec.; nitro derivative, m.p. 67–69°. [c] See Table III for analyses. 2-Phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine was obtained from both thionamide III and VIII. Thionamide (III) also produced 7% of an intermediate fraction, b.p. 90–112°/0.3 mm., presumably a mixture of thiazoline and dihydrothiazine. The ratio of thiazoline to dihydrothiazine is 8:1 if the composition of this fraction is ignored; it is still 3:1 if the intermediate fraction is a 1:1 mixture, the most unfavorable possibility to be expected. [d] Dihydrothiazine, no R⁴. [e] *Anal.* Calcd. for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53. Found: C, 75.67; H, 5.86; N. 5.47. [f] *Anal.* Calcd. for $C_{22}H_{18}N_4O_7S$: C, 54.77; H, 3.76; N, 11.61; S, 6.65. Found: C, 54.67; H, 3.92; N, 11.71; S, 6.54. [g] Reported, b.p. 152°: S. Gabriel and C. F. von Hirsch, *Ber.*, 29, 2609 (1896). [h] *Anal.* Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.95; H, 8.79; N, 10.70. [i] *Anal.* Calcd. for $C_{12}H_{14}N_4O_7S$: C, 40.22; H, 3.94; N, 15.63. Found: C, 40.21; H, 4.09; N, 15.77. [j] B.p. 152°/760 mm. *Anal.* Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.64; H, 8.42; N, 10.86. [k] *Anal.* Calcd. for $C_{12}H_{14}N_4O_7S$: C, 40.22; H, 3.94; N, 15.63. Found: C, 40.28; H, 4.06; N, 15.74.

TABLE III

CYCLIZATION OF β- OR *N*-HYDROXYALKYLBENZAMIDES TO

Thiazolines,  , or Dihydrothiazines, 

R¹	R²	R³	R⁴	M.P. °, or B.P. °/Mm.	Yield, %	Picrate, M.P. °	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	H	CH_3	H	146–149/18[a]	30	153–155[a]						
C_6H_5	H	H	[b]	124/1.5[c]	8.5	181–182.5	47.29	3.47	13.79	47.39	3.65	13.88
C_6H_5	H	C_2H_5	H	106–109/1[d]	60	131–132	48.57	3.84	13.33	48.72	3.89	13.52
C_6H_5	H	C_6H_5	[b]	86–88[a]	40	157.5–159.5[a]						
C_6H_5	H	CH_3	[b]	122–123/1.5[e]	44	162.5–164.5	48.57	3.84	13.33	48.64	3.86	13.46

[a] See Table II. [b] Dihydrothiazine, no R⁴. [c] M.p. 44–46° [reported m.p. 44–45° by G. Pinkus, *Ber.*, 26, 1077 (1893)]. [d] Anal. Calcd. for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.86; H, 6.72; N, 7.40. [e] *Anal.* Calcd. for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.88; H, 6.80; N, 7.52.

and subjected to continuous ether extraction for 2 hr. The ether was dried and saturated with dry hydrogen chloride to precipitate β-aminoisopropyl disulfide [2,2′-dithiobis(propylamine)] dihydrochloride. After two recrystallizations from absolute alcohol it melted at 222–222.5° (reported[16] m.p. 213–214°), undepressed by a sample prepared from 2-mercapto-5-methyl-2-thiazoline (*vide infra*).

Anal. Calcd. for $C_6H_{18}N_2S_2Cl_2$: C, 28.45; H, 7.16; N, 11.06; S, 25.32; Cl, 28.00. Found: C, 28.53; H, 7.25; N, 10.94; S, 25.21; Cl, 27.84.

2-Mercapto-5-methyl-2-thiazoline. This substance was prepared by the reaction of 1-amino-2-bromopropane hydrobromide[17] with carbon disulfide in basic solution according to the procedure of Hirsch.[18] The product melted at 93–95°, although Hirsch reported 82°.

Anal. Calcd. for $C_4H_7NS_2$: C, 36.06; H, 5.30; N, 10.51. Found: C, 36.34, 36.25; H, 5.22, 5.28; N, 10.56, 10.47.

β-Aminoisopropyl disulfide [2,2′-dithiobis(propylamine)] hydrochloride. A 3.4-g. sample of 2-mercapto-5-methyl-2-thiazoline was hydrolyzed by the same procedure as that used in the hydrolysis of 2-phenyl-5-methyl-2-thiazoline except that the removal of benzoic acid was not necessary.

(16) S. Gabriel and E. Leupold, *Ber.*, 31, 2832 (1898).

(17) M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, 59, 2252 (1937).

(18) P. Hirsch, *Ber.*, 23, 964 (1890).

It gave 1.1 g. (33%) of crude β-aminoisopropyl disulfide dihydrochloride, m.p. 202–210°. After recrystallization from ethanol, it melted at 223.5–226°.

Cyclization of N-(hydroxyalkyl)benzamides to 2-thiazolines or 5,6-dihydro-1,3,4-thiazines. These preparations were carried out by heating the amides with phosphorus pentasulfide; the results are summarized in Table III. The following example is typical of the procedure used.

2-Phenyl-5-methyl-2-thiazoline from N-(2-hydroxypropyl)-benzamide. A mixture of 16 g. of *N*-(2-hydroxypropyl)-benzamide,[18] 10 g. of phosphorus pentasulfide, and 250 ml. of toluene was refluxed for 12 hr. The toluene was decanted from a gummy residue which remained in the flask. The residue was warmed on a steam bath with 10% sodium hydroxide solution. The basic solution was extracted with ether and the ether layer was combined with the toluene and extracted with 10% hydrochloric acid. The acid extracts were neutralized and extracted with ether. After drying of the ether solution, removal of solvent, and distillation of the residual oil, 4.8 g. (30%) of 2-phenyl-5-methyl-2-thiazoline was obtained; b.p. 146–149°/18 mm. The picrate prepared from this sample had m.p. 153–155°, undepressed when mixed with the product obtained from *N*-allylbenzthionamide.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Syntheses and Properties of Some *N*-Substituted Sulfamides

ANTONIO VANDI, THERALD MOELLER, AND LUDWIG F. AUDRIETH

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Reactions of dialkylsulfamyl chlorides with ammonia or with aliphatic, aromatic, and heterocyclic amines have been employed to synthesize seventeen new *N*-substituted derivatives of sulfamide of the types $R_2NSO_2NH_2$, R_2NSO_2NHR, and $R_2NSO_2NR_2$. These compounds have been characterized in terms of analysis, melting or boiling point, refractive index, and infrared spectrum. Two intense absorption bands in the 1140–1145 cm.$^{-1}$ and 1320–1350 cm.$^{-1}$ regions are associated with S—O vibrations in the —SO_2— group. The compounds are either low-melting crystalline solids or high-boiling oily liquids. Certain of the solids show promise as derivatives for the characterization of amines.

Of the various known aquo-ammono sulfuric acids, sulfamide is of particular interest because of the many analogies, both formal and actual, between its chemistry and that of urea. Like urea, it is capable of forming derivatives in which alkyl or aryl groups are bonded to one or both of the nitrogen atoms. Such *N*-substituted derivatives may be of the types $RNHSO_2NH_2$, $RNHSO_2NHR$, $R_2NSO_2NH_2$, R_2NSO_2NHR, or $R_2NSO_2NR_2$, where the R-groups may be the same or different. Most of these classes are represented by a few known compounds,[1] but the total information available on them is limited. It has been of interest, therefore, to investigate in detail methods of synthesis and both chemical and physical properties for a number of such compounds.

All of these substances can be regarded as ammonolysis or aminolysis products of sulfuryl chloride. Their direct formation from sulfuryl chloride, however, is often complicated by lack of control or the production of polymeric products.[1] Sulfuryl chloride reacts readily with secondary aliphatic amines or saturated heterocyclic amines to yield disubstituted sulfamyl chlorides, R_2NSO_2Cl. From these by reaction with ammonia, primary, or secondary amines, compounds of the types $R_2NSO_2NH_2$, R_2NSO_2NHR, or $R_2NSO_2NR_2$, respectively, are more conveniently prepared than by any other procedure. Secondary aromatic amines, however, are apparently insufficiently basic to yield comparable sulfamyl chlorides and undergo preferential ring chlorination on treatment with sulfuryl chloride. Primary amines give a variety of products with sulfuryl chloride, but sulfamyl chlorides of the type $RNHSO_2Cl$ are apparently not among them.

The present communication is concerned with the ammonolysis and aminolysis products obtainable from diethyl and cyclopentamethylene sulfamyl chlorides as typical starting materials. These compounds were obtained either by treating the sulfamyl chloride with liquid ammonia or by refluxing in admixture with the appropriate amine in an inert solvent such as chloroform, benzene, or ether. Reactions with aliphatic amines were complete in twelve hours; those with aromatic amines required up to twenty-four hours.

The compounds prepared are listed in Table I, together with important data pertaining to their syntheses and properties. The tri- and tetra-substituted sulfamides are either colorless oils or white crystalline solids. They dissolve readily in the common organic solvents but are insoluble in cold water and only slightly soluble in boiling water. Recrystallization is best effected from *n*-heptane, carbon tetrachloride, or ether. The formation of characteristically and sharply melting compounds with many amines suggests that the sulfamyl chlorides may be useful reagents for the characterization of such amines.

No systematic investigation of the infrared spectra of the *N*-substituted sulfamides has been reported. The spectra of a number of related *N,N*-disubstituted sulfonamides contain strong bands, which have been ascribed,[2,3] respectively, to the

(1) L. F. Audrieth, M. Sveda, H. H. Sisler, and M. J. Butler, *Chem. Revs.*, 26, 49 (1940).

TABLE I

PROPERTIES AND ANALYSES OF TRI- AND TETRA-SUBSTITUTED SULFAMIDES

Compound	Formula	Yield, %	M.P.,[a]	B.P.,[a] Mm.	n_D^t	Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
N,N-Diethylsulfamide	$C_4H_{12}N_2O_2S$	53	44	—	—	31.57	31.49	7.95	7.72	18.41	18.49
N,N-Diethyl-*N'*-butylsulfamide	$C_8H_{20}N_2O_2S$	50	—	87/0.1	1.4510[25]	46.16	45.90	9.68	9.56	13.45	13.59
N,N-Diethyl-*N'*-cyclohexylsulfamide	$C_{10}H_{22}N_2O_2S$	60	49	—	—	51.28	51.00	9.47	9.40	11.95	11.85
N,N-Diethyl-*N'*-phenylsulfamide	$C_{10}H_{16}N_2O_2S$	61	—	171/2.5	1.5260[26.5]	52.64	52.48	7.06	7.11	12.28	11.95
N,N-Diethyl-*N',N'*-dibutylsulfamide	$C_{12}H_{28}N_2O_2S$	65	—	88/0.15	1.4500[25]	54.53	54.35	10.68	10.65	10.60	10.75
N,N-Diethyl-*N'*-cyclohexyl-*N'*-methyl sulfamide	$C_{11}H_{24}N_2O_2S$	52	—	101–102/0.2	1.4726[24]	53.21	53.40	7.74	9.78	11.28	11.16
N,N-Diethyl-*N'*-phenyl-*N'*-methyl sulfamide	$C_{11}H_{18}N_2O_2S$	50	—	98/0.1	1.5160[25]	54.55	54.32	9.49	7.16	11.56	11.35
N-Cyclopentamethylene-*N'*-cyclohexyl sulfamide	$C_{11}H_{22}N_2O_2S$	65	75	—	—	53.64	53.62	9.00	8.90	11.37	11.26
N-Cyclopentamethylene-*N'*-2-naphthyl sulfamide	$C_{15}H_{18}N_2O_2S$	20	115–116	—	—	62.05	61.81	6.25	6.32	9.65	9.63
N-Cyclopentamethylene-*N'*-phenyl sulfamide	$C_{11}H_{16}N_2O_2S$	42	83	—	—	54.98	55.18	6.71	6.69	11.66	11.39
N-Cyclopentamethylene-*N'*-benzyl sulfamide	$C_{12}H_{18}N_2O_2S$	42	100–101	—	—	56.67	56.71	7.13	7.33	11.02	11.00
N-Cyclopentamethylene-*N'*-*p*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	55	97–98	—	—	56.67	56.91	7.13	7.20	11.02	10.94
N-Cyclopentamethylene-*N'*-methyl-*N'*-cyclohexyl sulfamide	$C_{12}H_{24}N_2O_2S$	45	—	134/0.5	1.4970[22]	55.34	55.11	9.29	9.20	10.75	10.46
N-Cyclopentamethylene-*N'*-*m*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	70	123–124	—	—	56.67	56.83	7.13	7.15	11.02	10.74
N-Cyclopentamethylene-*N'*-*o*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	62	94	—	—	56.67	56.87	7.13	7.11	11.02	10.74
N-Cyclopentamethylene-4-morpholine sulfamide	$C_9H_{18}N_2O_3S$	81	71–72	—	—	45.14	46.27	7.74	7.70	11.96	11.93
N-Cyclopentamethylenesulfamide	$C_5H_{12}N_2O_2S$	55	120	—	—	36.57	36.82	7.36	7.31	17.06	16.88

[a] Melting points and boiling points are uncorrected.

symmetric and antisymmetric vibrations of the S—O bonds in the —SO_2— group, near 1160 cm.$^{-1}$ and 1350 cm.$^{-1}$ Absorption in the 1300–1350 cm.$^{-1}$ region is also characteristic of sulfones but not of sulfides.[4] The Raman spectra of sulfamide and trisulfimide show the frequencies 1163 cm.$^{-1}$ and 1350 cm.$^{-1}$, characteristic again of symmetric and antisymmetric vibrations within the —SO_2— group.[5] It has been of interest, therefore, to compare these data with those obtained for the compounds described herein.

Significant data from the infrared spectra of chloroform or carbon tetrachloride solutions of nine *N*-substituted sulfamides of the types described above are given in Table II. Corresponding spectral data for four compounds of the type RNH-SO_2NHR, prepared in another connection,[6] are given also for comparison. Characteristic absorptions in the 1140–1145 cm.$^{-1}$ and 1320–1340 cm.$^{-1}$ regions undoubtedly reflect, respectively, symmetric and antisymmetric vibrations within the —SO_2— group. A third band at 3280 cm.$^{-1}$ is found only for the di- and tri-substituted compounds and is due to the N—H stretching vibration. This band is particularly apparent for the RNHSO$_2$NHR compounds. Assignment of absorptions in the 1070-cm.$^{-1}$ region to the S—N bond is open to some question.[3] Neither of the first two bands is dis-

TABLE II

INFRARED DATA FOR *N*-SUBSTITUTED SULFAMIDES

Compound	Frequency, Cm.$^{-1}$		
	S—O	S—O	N—H
N-Cyclopentamethylene-*N'*-*p*-tolylsulfamide	1140	1332	3280
N-Cyclopentamethylene-*N'*-phenylsulfamide	1142	1320	3280
N-Cyclopentamethylene-*N'*-methyl-*N'*-cyclohexylsulfamide	1142	1320	—
N,N-Diethyl-*N'*-cyclohexylsulfamide	1142	1320	3280
N,N-Diethylsulfamide	1150	1342	3280
N,N-Diethyl-*N'*-butylsulfamide	1142	1320	3280
N,N-Diethyl-*N',N'*-dibutylsulfamide	1142	1320	—
N,N-Diethyl-*N'*-methyl-*N'*-cyclohexylsulfamide	1142	1325	—
N,N-Diethyl-*N'*-methyl-*N'*-phenylsulfamide	1142	1340	—
N,N'-Dipropylsulfamide	1147	1320	3280
N,N'-Dibutylsulfamide	1145	1315	3280
N,N'-Dicyclohexylsulfamide	1142	1320	3280
N,N'-Diamylsulfamide	1145	1320	3280

(2) R. Adams and J. J. Tjepkema, *J. Am. Chem. Soc.*, **70**, 4204 (1948).

(3) J. N. Baxter, J. Cymerman-Craig, and J. B. Willis, *J. Chem. Soc.*, **1955**, 669.

(4) K. C. Schreiber, *Anal. Chem.*, **21**, 1168 (1949).

(5) H. J. Hofmann and K. Andress, *Z. anorg. allgem. Chem.*, **248**, 234 (1956).

(6) T. Moeller and A. Vandi, Contract DA-11-022-ORD-2956, Quarterly Progress Report No. 2, University of Illinois, Nov. 30, 1959.

placed particularly among the compounds examined by change from an aliphatic to an aromatic substituent.

EXPERIMENTAL

Sulfamyl chlorides. Diethylsulfamyl chloride was prepared as described by Binkley and Degering.[7] *N*-Pentamethylene sulfamyl chloride was prepared by Derivelle's procedure[8] as modified by Audrieth and von Brauchitsch.[9] The compounds boiled at 62°/0.02 mm. and 95°/1 mm., respectively.

N-Substituted sulfamides. Ammonolysis could be effected with liquid ammonia but not in the presence of a diluting solvent. As the procedure followed in all aminolysis reactions was essentially the same, only one synthesis of this type is described. With diethylsulfamyl chloride, chloroform is a suitable solvent; with pentamethylenesulfamyl chloride, benzene is better.

N,N-Diethylsulfamide. One hundred milliliters of liquid ammonia was placed in a three necked flask fitted with a mechanical stirrer, an outlet tube, and a small separatory funnel and immersed in a bath of Methyl Cellosolve and Dry Ice to maintain the temperature at −70°. Twenty grams (0.117 mole) of diethylsulfamyl chloride was added dropwise with vigorous agitation over a period of 2 hr. The resulting solution was stirred for 2 hr. and then kept at room temperature in order to permit evaporation of the excess of ammonia. The residue was dissolved in hot ether, the solution filtered, and the ether removed from the filtrate under vacuum. The product was recrystallized twice from ether.

N,N-Diethyl-N'-cyclohexylsulfamide. Seventeen and one-tenth grams (0.1 mole) of diethylsulfamyl chloride, 20.0 g. (0.2 mole) of cyclohexylamine, and 50 ml. of chloroform were placed in a flask equipped with a reflux condenser. The solution was then refluxed at 70° for 12 hr. The solvent was removed by distillation, and the dark residue was shaken with water and ether in a separatory funnel. The ether layer was dried over anhydrous calcium chloride. Removal of the ether by distillation left a dark oily residue which, upon fractional distillation, yielded a colorless, viscous oil. Upon standing, this solidified to a crystalline mass. Final purification was effected by recrystallization from *n*-heptane.

Infrared spectra. These were measured with a Perkin-Elmer Model 21 instrument, using a sodium chloride prism.

Acknowledgment. Support received for this investigation under Contract DA-11-022-ORD-2956 with the Feltman Research and Engineering Laboratory, Ordnance Corps, Picatinny Arsenal, Dover, N. J., is gratefully acknowledged.

URBANA, ILL.

(7) W. W. Binkley and E. F. Degering, *J. Am. Chem. Soc.*, **61**, 3250 (1939).

(8) L. Denivelle, *Bull. soc. chim. France*, [5], **3**, 2143 (1936).

(9) L. F. Audrieth and M. von Brauchitsch, *J. Org. Chem.*, **21**, 426 (1956).

[CONTRIBUTION FROM SMITH KLINE AND FRENCH LABORATORIES AND TEMPLE UNIVERSITY RESEARCH INSTITUTE]

Synthesis of Phenothiazines. VI. Certain 2-Substituted Phenothiazines and Their 10-Aminoalkyl Derivatives

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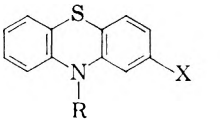
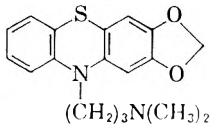
2-Dimethylaminophenothiazine, 2,3-methylenedioxyphenothiazine, 2-cyanophenothiazine and phenothiazine-2-carboxamides were synthesized. Several 10-aminoalkyl derivatives of these compounds and of 2-acetylphenothiazine and its oxime were prepared for pharmacological evaluation.

Various investigators have found that introduction of certain substituents such as chlorine or the trifluoromethyl group in the 2-position of 10-dimethylaminopropylphenothiazine (promazine) (Ia) produces agents having enhanced tranquilizing and antiemetic activities.[2] In the course of our studies on the chemistry and pharmacology of 2-substituted phenothiazines[3] related to Ia, we synthesized derivatives Ib-d, II and several compounds derived from 2-acetylphenothiazine listed in Table I.





II

Ia. X = H, R = $(CH_2)_3N(CH_3)_2$
b. X = $N(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
c. X = $CON(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
d. X = CN, R = $CH_2CH(CH_3)CH_2N(CH_3)_2$

2-Dimethylaminophenothiazine (IV) was prepared by the Ullman route starting with *N,N*-dimethyl-4-bromoaniline (III).[4]

An attempt to obtain IV by thionation of 3-dimethylaminodiphenylamine (Bernthsen method) was unsuccessful.

Alkylation of IV with 3-dimethylaminopropyl chloride was carried out in the usual way to yield

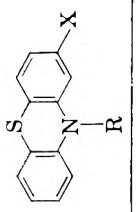
(1) Research Institute of Temple University.

(2) See E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.* **25**, 60 (1960) (Paper III of this series) and references therein.

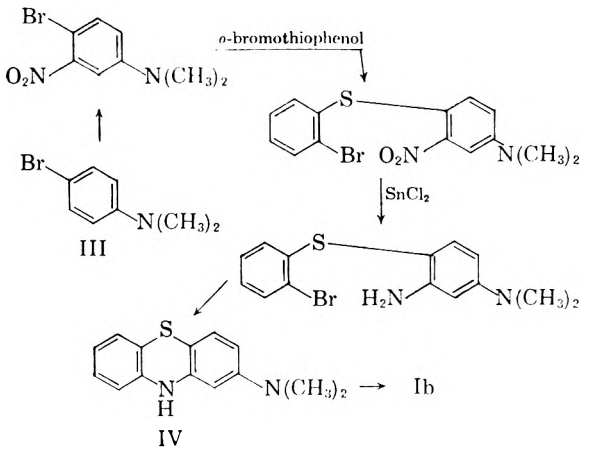
(3) Paper IV of this series: P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **25**, 944 (1960).

(4) G. R. Clemo and J. M. Smith, *J. Chem. Soc.*, 2414 (1928).

TABLE I DERIVATIVES OF 2-ACETYLPHENOTHIAZINE

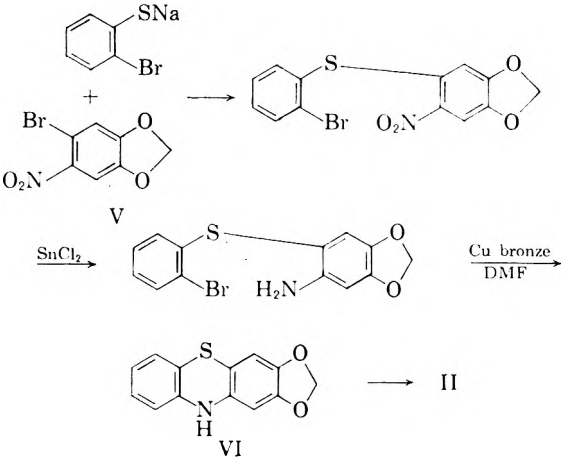


	X	R	Yield, %	B.P. Free base (mm.)	Salt	M.P.	Molecular Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XI	$COCH_3$	$(CH_2)_3N$–N–CH_3	60	255–260° (0.75)	Dimaleate	179–180°	$C_{22}H_{27}N_3OS.2C_4H_4O_4$ $\frac{1}{2}H_2O$	57.95	5.71	—	57.86	5.83	—
XII	$COCH_3$	CH_3–CH(–CH_3)–CH_2–N(–CH_3)–	65	260–265° (0.1)	Dihydrochloride	249–50° (dec.)	$C_{23}H_{32}N_3OS.2HCl$	58.96	6.67	—	58.72	6.92	—
XIII	$COCH_3$	$CH_2CH(CH_3)CH_2N(CH_3)CH_2CH_3$	56	215–220° (0.1)	Hydrochloride	219–221°	$C_{10}H_{34}N_2OS.HCl$ $\frac{1}{4}H_2O$	62.97	6.74	—	62.99	6.99	—
XIV	$C(CH_3)_2OH$	$(CH_2)_3N(CH_3)_2$	—	—	Free base	107.5–109°	$C_{20}H_{26}N_2OS$	70.13	7.65	8.18	69.83	7.58	8.30
XV	$C(CH_3)$=NOH	$(CH_2)_3$–N–CH_3	65	—	Dimaleate	171–172° (dec.)	$C_{22}H_{28}N_4OS_2.C_4H_4O_4$	57.31	5.77	—	57.08	5.75	—

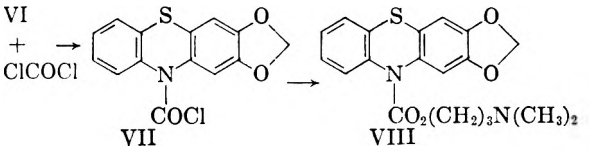


2-dimethylamino-10-(3-dimethylaminopropyl)-phenothiazine (Ib).

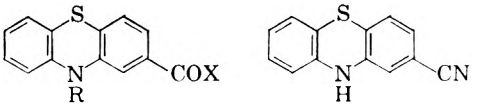
By a similar route 2,3-methylenedioxyphenothiazine (VI) was prepared from 4-nitro-5-bromocatechol methylene ether (V).[5]



From VI were obtained 2,3-methylenedioxy-10-(3-dimethylaminopropyl)-phenothiazine (II) by aminoalkylation and 3-dimethylaminopropyl 2,3-methylenedioxyphenothiazine-10-carboxylate (VIII) *via* the carbamyl chloride VII.



Several derivatives (IX and X) of phenothiazine 2-carboxylic acid (IXa)[6] were prepared as indicated below.



IX. a. X = OH, R = H
b. X = Cl, R = H
c. X = NH_2, R = H
d. X = OH, R = $COCH_3$
e. X = Cl, R = $COCH_3$
f. X = $N(CH_3)_2$, R = $COCH_3$
g. X = $N(CH_3)_2$, R = H

X

The acid IXa was converted to its amide IXc *via* the acid chloride IXb which was obtained by treatment of IXa with phosphorus pentachloride. Dehydration of IXc with phosphorus oxychloride gave the 2-cyano derivative X. By alkylation of the latter compound with 3-dimethylamino-2-methylpropylchloride, 2-cyano-10-(3-dimethylamino-2-methylpropyl)phenothiazine (Id) was obtained.[7]

Starting with 10-acetylphenothiazine-2-carboxylic acid (IXd), the *N,N*-dimethylamide IXg was prepared *via* intermediates IXe and IXf. Alkylation of IXg with 3-dimethylaminopropyl chloride gave 2 - (*N,N* - dimethylcarboxamido) - (3- dimethylaminopropyl)phenothiazine (Ic).

Several 10-aminopropyl derivatives of 2-acetylphenothiazine were prepared by alkylation of its ethylene ketal derivative. This procedure was used after it was found that the ketone is not smoothly alkylated under the usual conditions employing sodamide as a condensing agent. The usual conditions gave large amounts of resinous material, probably resulting from base catalyzed condensation reactions involving the methyl ketone group. While this work was in progress Schmitt *et al.*[8] reported the synthesis of a number of these compounds by the same route. These workers also prepared 10-aminoalkyl derivatives of 2-acetylphenothiazine oxime.[9] In Table I are listed those derivatives (XI–XV) of 2-acetylphenothiazine prepared in this work that have not been previously reported. The oxime derivative XV was obtained by oximation of XI and compound XIV, 2 - (1 - hydroxy - 2 - propyl) - 10 - (3 - dimethylaminopropyl)phenothiazine,[10] was prepared by the action of methyl lithium on 2-acetyl-10-(3-dimethylaminopropyl)phenothiazine.[8,9]

The results of pharmacological studies on these compounds will be reported elsewhere.

EXPERIMENTAL

Analyses were performed by Analytical and Physical Chemistry Section of Smith Kline and French Laboratories.

Synthesis of 2-dimethylaminophenothiazine (IV). (a) *o-Bromothiophenol.* This preparation was successfully conducted from 1.5 moles *o*-bromoaniline according to the procedure described previously.[11] *o*-Bromothiophenol was obtained in 80% yield.

(b) *2'-Bromo-2-nitro-4-(n,N-dimethylamino)diphenylsulfide.* An aqueous ethanolic solution of sodium *o*-bromothiophenolate [57 g. (0.3 mole) *o*-bromothiophenol[11] in 300 ml. ethanol and 12 g. (0.3 mole) sodium hydroxide in 20 ml. water] was added dropwise to a stirred refluxing solution of 4-bromo-3-nitrodimethylaniline[4] (prepared from 4-bromo-*N,N*-dimethylaniline (III)[12] in 600 ml. of ethanol in a 2-l. three-neck flask. The solution was stirred and refluxed for 20 hr. It was then treated with Norit and filtered. The filtrate yielded two crops upon cooling. The first crop was orange crystals, m.p. 117.5–119°; the second yellow, m.p. 120–122°. A mixed melting point gave 118.5–120°. Recrystallization of the combined crops gave the sulfide (82.5 g., 78%) as yellow crystals, m.p. 120–121°. The analytical sample from methanol melted 120.5–121.5°. It is to be noted that the above sulfide was obtained at times as distinct yellow crystals, distinct orange crystals, and as an intimate mixture of both forms.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_2S$: C, 47.60; H, 3.71. Found: C, 47.64; H, 4.00.

2'-Bromo-2-amino-4-(N,N-dimethylamino)diphenylsulfide. The nitro compound above (91.9 g., 0.26 mole) was added in portions to a stirred solution of stannous chloride dihydrate (235 g., 1.04 mole) in concd. hydrochloric acid (690 ml.) in a 2-l., three-neck flask at 50–60°. The white suspension was refluxed for 4 hr. after which time it was diluted with water and made alkaline with sodium hydroxide solution. A solid which formed on cooling was collected, dried *in vacuo* and extracted with hot benzene. Dilution with petroleum ether (b.p. 35–60°) gave the amino sulfide as white crystals, m.p. 125–127.5° in 65% yield. The analytical sample melted 126.5–127.5°.

Anal. Calcd. for $C_{14}H_{15}BrN_2S$: C, 52.01; H, 4.68. Found: C, 52.21; H, 4.94.

2-(N,N-Dimethylamino)phenothiazine (IV). 2'-Bromo-2-amino-4-(*N,N*-dimethylamino)diphenyl sulfide (49.5 g., 0.153 mole), anhydrous granular potassium carbonate (28.8 g., 0.208 mole), cuprous iodide (8 g.) and copper bronze powder (2.88 g.) were stirred and heated in refluxing dimethylformamide (500 ml.) for 21 hr. under a slow stream of prepurified nitrogen. There was no further indication of carbon dioxide evolution after this time. The mixture was filtered and the filtrate diluted with water. A light-purple precipitate was collected and dried *in vacuo* at 100°. Recrystallization from benzene with a Nuchar treatment gave 2-(*N,N*-dimethylamino)phenothiazine (IV) (24.1 g., 65%) as microscopic white needles, m.p. 157.5–158.5°.

Anal. Calcd. for $C_{14}H_{14}N_2S$: C, 69.38; H, 5.82; N, 11.56. Found: C, 69.27; H, 5.86; N, 11.63.

Two previous attempts to produce cyclization in the absence of a solvent were unsuccessful. After 1.5 hr. at 180–190° (the temperature was allowed to rise slowly from 120°), only some starting material was recovered from the black reaction mass. When the reaction tube was placed in a bath at 250° and the temperature raised to 155° vigorous effervescence occurred after 20 min. A low boiling liquid having a fishy odor escaped from the reaction tube. The products from this attempt were not identified.

Attempted synthesis of 2-dimethylaminophenothiazine via the Bernthsen thionation reaction N'Acetyl-N,N-dimethyl-m-phenylenediamine. 3-Nitrodimethylaniline[13] (49.8 g., 0.3 mole) was added in portions to a stirred solution of stannous chloride dihydrate (251 g., 1.2 moles) in concd. hydrochloric acid (300 ml.) at 50–60° in a 2-l., three-neck flask. The solution was refluxed for 4 hr. and diluted with water. It was then made alkaline with sodium hydroxide. The oil that

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(6) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(7) Since completion of this work several patents have appeared describing the synthesis of 2-cyanophenothiazine derivatives by a different route; Aust. Pat. **34,737/58**; July 24, 1958; Belgian Pat. **552,557**; May 15, 1957; South African Pat. Appl., **3595/56** June 19, 1957.

(8) J. Schmitt, A. Hallot, P. Comoy, M. Suquet, R. Fallard, and J. Boitard, *Bull. soc. chim. France*, 1474 (1957).

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(10) We are indebted to W. S. Gump and E. Nikowitz of the Givaudan Corp. for preparing supplies of 2-acetylphenothiazine for us and for the synthesis of compound XIV (Table I).

(11) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).

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(13) H. M. Fitch, *Org. Syntheses*, **Coll. Vol. III**, 658 (1955).

formed was extracted from the cooled mixture with ether. The ether extracts were dried and the solvent distilled at atmospheric pressure. The residue was dissolved in pyridine. To this solution at 5° was added dropwise, with stirring, 27 g. acetic anhydride. After remaining overnight at room temperature the solution was thrown on to water. The precipitated solid was collected, washed and dried. Recrystallization from petroleum ether gave the acetylated product as white crystals (37.8 g., 70%) m.p. 86–87° (lit.[14] m.p. 87°).

3-Dimethylaminodiphenylamine. Bromobenzene (17.2 g., 0.11 mole), *N'*-acetyl-*N*,*N*-dimethyl-m-phenylene diamine (17.8 g., 0.10 mole), anhydrous granular potassium carbonate (8.5 g.) and copper-bronze powder (0.35 g.) were stirred at a bath temperature of 180° for 16 hr. and at 200° for 8 hr. The mixture was then extracted with acetone and filtered. The acetone was evaporated *in vacuo* and the residue refluxed with 250 ml. of 7*N* hydrochloric acid for 2 hr. The solution was made alkaline and then cooled. The oil that formed solidified. Recrystallization from petroleum ether (b.p. 35–60°) gave white crystals of the diphenylamine (8.4 g., 40%), m.p. 64–65° (lit.[15] m.p. 65–66°).

Attempted thionation of 3-dimethylaminodiphenylamine. An intimate mixture of 3-dimethylaminodiphenylamine (2.12 g., 0.01 mole), sulfur (0.61 g., 0.019 mole) and iodine (0.03 g.) was placed in an atmosphere of prepurified nitrogen in a scrupulously predried test tube. The reactor was fitted with a T-tube through which a stream of nitrogen was passed during the course of the reaction. The tube was placed in a bath at 140°. Hydrogen sulfide evolution commenced. After 0.5 hr., *ca.* 30% of the theoretical amount of hydrogen sulfide had been produced. Effervescence, however, had ceased. An additional 0.1 g. sulfur and a few iodine crystals were introduced into the reactor. The bath temperature was maintained at 170–185° until the theoretical amount of hydrogen sulfide was liberated. The reaction mass upon vacuum distillation gave a dark red oil which would not solidify. Attempted recrystallizations with alternate and combined alumina and Norit treatments from benzene-petroleum ether, high-boiling ligroin, carbon tetrachloride, chloroform, ethyl acetate, water, dilute hydrochloric acid, acetone-water and alcohol, were unsuccessful in producing any crystalline material.

10-(3-Dimethylaminopropyl)-2-dimethylaminophenothiazine dihydrochloride monohydrate (Ib). To a solution of 19.5 g. of 2-dimethylaminophenothiazine in 700 ml. of dry xylene was added 4.0 g. of sodamide. The mixture was stirred and refluxed under nitrogen atmosphere for 80 min. A solution of 12.4 g. of 3-chloro-1-dimethylaminopropane in 50 ml. of dry xylene was added. The mixture was refluxed and stirred under a nitrogen atmosphere for 6 hr. After cooling, 200 ml. of water was added. The xylene layer was extracted with four 50-ml. portions of 15% acetic acid. The acid extracts were made alkaline and extracted with benzene. The benzene extracts were combined and the solvent evaporated. The residue was distilled at 215–220°/0.3–0.5 mm., to give 21.1 g. (80%) of free base. The amine was dissolved in dry ether and treated with a solution of isopropyl alcohol containing 2 equivalent amounts of hydrogen chloride. The precipitated dihydrochloride salt was recrystallized from benzene-methanol and melted at 214–215°.

Anal. Calcd. for $C_{19}H_{25}N_3S.2HCl.H_2O$:C, 54.54; H, 6.91. Found: C, 54.41; H, 6.99.

Synthesis of 2,3-methylenedioxyphenothiazine. 6-Bromopiperonal. A stirred solution of piperonal (Eastman) (300 g., 2 moles) in glacial acetic acid (600 ml.) was gradually treated dropwise with a solution of bromine (120 ml., 4.6 moles) in glacial acetic acid (300 ml.). During the addition the reaction was cooled. After standing 48 hr. at room temperature, crystals of 6-bromopiperonal were filtered and water added to the filtrate. The precipitate that formed consisted of a mixture of 6-bromopiperonal and 4,5-dibromocatechol methylene ether. This mixture was stirred rapidly with a warm aqueous solution of sodium bisulfite. The latter dissolved the 6-bromopiperonal which was recovered from the filtrate after the addition of sodium carbonate. Both fractions of 6-bromopiperonal were recrystallized from hot ethanol to give 230 g., 50%, m.p. 127–128.5° (lit.[16] m.p. 129°).

4-Nitro-5-bromocatechol methylene ether (V). To stirred concentrated nitric acid (1400 ml., *d.* 1.42) in a 5-l., three-neck flask immersed in a water bath at 25°, was added gradually in portions over 1.5 hr., 6-bromopiperonal (210 g., 0.92 mole). The addition was conducted at such a rate as to maintain an internal temperature no greater than 25°. After 2 hr. the mixture was poured on to 4-l. ice water. The precipitated light yellow solid was collected and washed well with water. Recrystallization from ethanol gave V (136 g., 60%) as yellow needles, m.p. 88–89° (lit.[17] m.p. 89°).

4,5-Methylenedioxy-2-nitro-2'-bromodiphenylsulfide. To a stirred solution of the 4-nitro-5-bromocatecholmethylene ether (147.6 g., 0.6 mole) in hot ethanol (1250 ml.) in a 3-l., three-neck flask was added dropwise a solution of sodium *o*-bromothiophenolate (113.4 g., 0.6 mole, *o*-bromothiophenol in 500 ml. ethanol; 23.9 g., 0.6 mole, sodium hydroxide in 25 ml. water). During the addition the bright yellow product commenced to precipitate from the reddish-orange reaction solution. The mixture was allowed to reflux for 3 hr. It was then cooled to 0° and the precipitated product filtered. Several washings with cold ethanol afforded the sulfide (186 g., 88%) as bright yellow crystals, m.p. 149–150°.

Anal. Calcd. for $C_{13}H_8BrNO_4S$: C, 44.08; H, 2.28. Found: C, 44.29, 44.25, 44.29; H, 2.65, 2.32, 2.66.

2-Amino-4,5-methylenedioxy-2'-bromodiphenylsulfide. To a stirred solution of stannous chloride dihydrate (426.6 g., 1.89 moles) in concd. HCl (675 ml.) and ethanol (675 ml.) at 70–80° was added, in portions, the nitro compound above. The mixture was then allowed to reflux for 4 hr. The brown solution was subsequently poured on to 4-l. ice water. A gum formed which slowly solidified. The tan solid was collected and washed well with water. It was dried *in vacuo* at 100°. Recrystallization from benzene-petroleum ether with a Norit treatment yielded the amine (126 g., 74%) as white crystals, m.p. 142–143.5°. The analytical sample melted at 143–144°.

Anal. Calcd. for $C_{13}H_{10}BrNO_2S$: C, 48.16, H, 3.11. Found: C, 48.36; H, 2.85.

2,3-Methylenedioxyphenothiazine (VI). A mixture of the above amine (3.6 g., 0.0111 mole, m.p. 143–144°), anhydrous granular potassium carbonate (1.56 g., 0.0113 mole) and copper bronze powder (0.2 g.), was refluxed in 45 ml. dimethylformamide with stirring for 6 hr. The evolution of carbon dioxide had ceased at this time. The purple mixture was filtered and the filtrate diluted with warm water. The purple precipitate was collected and dried *in vacuo*. It was then extracted with benzene and the extracts treated with alumina and charcoal. Cooling the benzene filtrate gave VI as light purple platelets, m.p. 202–203°. The analytical sample was obtained by sublimation as white platelets from benzene, m.p. 202–203.5°. The estimated yield in this reaction on this scale is 50%.

Anal. Calcd. for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.21; H, 3.96; N, 5.72.

3-Dimethylaminopropyl 2,3-methylenedioxyphenothiazine-10-carboxylate hydrochloride VIII. A solution of 7.3 g. of 2,3-methylenedioxyphenothiazine in 50 ml. of chlorobenzene was heated at 115–120° for 90 min. while a brisk stream of phosgene was bubbled through the mixture. On cooling to 100° a vigorous stream of nitrogen was passed through the solution for 30 min. Following the addition of 4.2 g. of 3-dimethylaminopropanol in 10 ml. of chlorobenzene, the solu-

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tion was refluxed for 15 min. On cooling the mixture was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and taken up in ether. The ethereal solution was dried over magnesium sulfate and treated with an isopropanolic hydrogen chloride solution. The precipitated crude salt was removed by filtration and a small sample recrystallized from benzene-methanol which melted at 229–230°. The yield of crude product was 5.7 g. (48%). The salt appears to be light sensitive, darkening slowly to a deep blue.

Anal. Calcd. for $C_{19}H_{20}N_2O_4S.HCl$: C, 55.81; H, 5.18. Found: C, 56.14, 56.17; H, 5.96, 5.48.

10-(3-Dimethylaminopropyl)-2,3-methylenedioxyphenothiazine maleate II. A well stirred suspension of 1.17 g. of sodamide, 6.5 of 2,3-methylenedioxyphenothiazine VI and 110 ml. of dry xylene was refluxed for 70 min. under a nitrogen atmosphere and then treated with 4.3 g. of 3-dimethylaminopropyl chloride. The mixture was stirred and refluxed for 8 hr. On cooling, the mixture was treated cautiously with 60 ml. of water. The xylene layer was extracted with three 20-ml. portions of 10% hydrochloric acid. The acid extracts were made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene solution was dried over magnesium sulfate and evaporated to dryness. The residue was distilled at 230–233°/0.5 mm. to give 4.1 g. (48%) of 10-(3-dimethylaminopropyl)-2,3-methylenedioxyphenothiazine. The base was converted to a maleate salt in ethylacetate and recrystallized from ethyl acetate-methanol solutions. The maleate salt melted at 151–152.5°.

Anal. Calcd. for $C_{18}H_{20}N_2.C_4H_4O_4$: C, 59.44; H, 5.44. Found: C, 59.24; H, 5.59.

2-Carboxamidophenothiazine IXc. A mixture of 67 g. phenothiazine-2-carboxylic acid[6] in 900 cc. of dry benzene was cooled to +5 to 7°. To the stirred mixture was added 62.8 g. of phosphorus pentachloride portionwise over a period of 30 min. The cooling bath was removed and the stirring was continued for 2 hr. The acid chloride mixture was poured onto excess concentrated ammonia and ice with stirring and then was allowed to stand for several hours. The greenish yellow crystals were filtered, washed with water and dried at +40 to 60°. The 46.0 g. of crude amide (69%) was recrystallized from ethanol-isopropyl alcohol and decolorizing carbon to give 24.0 g. of yellow needles, melting at 232.5–233.5°. Another 7.0 g. of amide was obtained from the mother liquor by concentration and cooling.

Preparation of 2-cyanophenothiazine X. Various dehydrating agents were investigated for the conversion of phenothiazine-2-carboxamide to the corresponding nitrile. Although phosphorus pentoxide, phosphorus oxychloride and a mixture of the two were tried, none of these procedures were very satisfactory. In one experiment 1.6 g. of the carboxamide was refluxed for 4 hr. in 10 ml. of phosphorus oxychloride. The mixture was poured onto ice and then the solution was made slightly basic. A product was filtered off (1.6 g.), which softened at 192–194° and melted at 198–205°. This material was characterized by its peak at 4.5 μ in the infrared spectrum, and by its alkylation to Id, which was identical with a sample of Id prepared by an alternate route.[7]

2 Cyano-10[3-dimethylamino-2-methylpropyl]phenothiazine maleate (Id). Alkylation of 1.6 g. of 2-cyanophenothiazine was accomplished as usual using 0.4 g. of sodamide and 1.2 g. of 3-dimethylamino-2-methylpropylchloride in 25 ml. toluene. Distillation of the free base gave 1.4 g. (64%) of a yellow oil; b.p. 205–220° (0.2–0.5 mm.).

This oil was converted to the maleate salt, which, after two recrystallizations from methanol-ethanol, gave 1.4 g. of pale yellow plates melting at 196–197°.

Anal. Calcd. for $C_{23}H_{25}N_3O_4S.{}^1/_4\ H_2O$: C, 62.21; H, 5.79. Found: C, 62.41; H, 5.65.

Infrared spectral data shows the presence of the cyano peak at 4.5 μ.

2-N,N-Dimethylcarboxamido-10-acetylphenothiazine (IXf) *Method A.* 2-Carboxy-10-acetylphenothiazine (10.0 g.) was treated with an equivalent amount of sodium carbonate solution. The water was removed by azeotroping with benzene and the benzene removed by freeze drying. To a stirred suspension of the salt in 100 cc. of dry benzene was added 7.6 g. of oxalyl chloride in 40 cc. of benzene. After warming for several minutes on a water bath the mixture was stirred for 7 hr. at room temperature and then allowed to stand for 2 days. The mixture was filtered and the filtrate was evaporated to an orange residue. The residue was dissolved in benzene and a solution of 19 g. of dimethylamine in benzene was added. After heating for 10 min. on the steam bath the mixture was cooled and filtered. Evaporation of the filtrate gave 12.2 g. of a yellow solid which melted over a wide range. A small sample of this solid (1.5 g.) was vacuum distilled but this did not improve the melting point. The remainder of the yellow solid was dissolved in hot benzene and extracted twice with very dilute sodium bicarbonate. The benzene was dried over magnesium sulfate, and after evaporation of the benzene there remained 8.3 g. of a yellow solid. This was subjected to deacetylation without further purification.

Method B. An intimate mixture of 2-carboxy-10-acetylphenothiazine (7.2 g.) and 10 g. of phosphorus pentachloride was heated for 5 min. After the addition of 25 cc. of benzene the mixture was filtered, and the filtrate was heated for 5 min. The cooled solution was treated with 50 cc. of 25% aqueous dimethylamine, and the mixture was stirred for 15 min. The layers were separated and the water layer was extracted twice with benzene. The combined benzene layers were washed three times with water, dried over magnesium sulfate, and the benzene evaporated. The residue was 7.9 g. (98%) of a thick brown oil. This material was subjected to deacetylation without further purification.

2-N,N-Dimethylcarboxamidophenothiazine (IXg). A mixture of 65.5 g. 31% hydrochloric acid and 20 g. glacial acetic acid was stirred at reflux with 8.3 g. of crude 2-(*N,N*-dimethylcarboxamido)-10-acetylphenothiazine. The mixture was poured into 400 cc. of water and the yellow solid which formed (6.9 g., 97%) was filtered. Upon recrystallization from acetone using decolorizing charcoal, 5.7 g. of yellow crystals melting at 161–163.5° were obtained.

2-N,N-Dimethylcarboxamido-10-(3-dimethylaminopropyl)-phenothiazine citrate (Ic). 2-*N,N*-Dimethylcarboxamido phenothiazine (7.6 g.) in 100 cc. xylene was refluxed and stirred with 1.4 g. sodamide for 1 hr. After the addition of 4.9 g. of 3-dimethylaminopropyl chloride in 25 cc. xylene, refluxing was continued for 4 hr. The cooled mixture was treated with 50 cc. of water and the layers were separated. The organic layer was taken through acid and base to give 6.7 g. of a dark brown oil. Upon distillation there was obtained 4.8 g. (35%) of an oil; b.p. 225–240° (0.06–0.09 mm.). There was also recovered 2.8 g. of neutral material.

The 4.8 g. of oil was converted to the citrate which was dried under a vacuum to give a foamy-looking solid melting at 94.5–96.5°.

Anal. Calcd. for $C_{20}H_{25}N_3OS.C_6H_8O_7.2H_2O$: C, 53.50; H, 6.39. Found: C, 53.73, 53.60; H, 6.23, 6.15.

This material was amorphous, rather than truly crystalline, and was hygroscopic.

10-[3-(4-Methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketoxime dimaleate (XV). To 5 g. of 10-[3-(4-methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketone in 200 ml. of dry pyridine was added 2 g. of hydroxylamine hydrochloride. The solution was refluxed 90 min. and the pyridine removed under vacuum. The residue was washed with 5% sodium carbonate solution and dissolved in ethyl acetate. This solution was added to another solution of ethyl acetate containing 2 equimolar amounts of maleic acid. The precipitated dimaleate salt was recrystallized from methanol; m.p. 171°–172° dec.; 5.2 g. (65%).

10-[3-(4-Methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketone dimaleate (XI). To a solution of 24.2 g. of 2-acetylphenothiazine in 450 ml. of dry toluene were added

6.2 g. of redistilled ethylene glycol and 0.2 g. of *p*-toluenesulfonic acid. The mixture was azeotroped for 3 hr. and washed with 40% sodium hydroxide solution. The toluene solution was azeotroped for 1 hr. over 2 g. of potassium hydroxide, filtered and added to a suspension of 4.5 g. of freshly prepared sodamide in 100 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 20 min. To the mixture was added a solution of 4-methyl-4-(3-chloropropyl) piperazine (20 g.) in 50 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 4 hr. On cooling, 150 ml. of water was added. The toluene layer was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and extracted with benzene. The benzene was evaporated and the residual oil was distilled; b.p. 255°–260°/75 mm.; 23 g. (60%). The free base was dissolved in 100 ml. of ethyl acetate and added to a solution of ethyl acetate containing 2 equimolar amounts of maleic acid. The precipitated dimaleate salt was recrystallized from methanol; m.p. 179–180°.

2-(1-Hydroxyisopropyl)-10-dimethylaminopropylphenothiazine (XIV). To a solution of methyllithium prepared from 2 g. of lithium and 18.2 g. of methyl iodide in ether was added a solution of 41.7 g. of 2-acetyl-10-dimethylaminopropylphenothiazine[8] in 100 ml. of ether. The mixture was stirred and refluxed for 2.5 hr. and then poured into water. The organic layer was washed with water, dried and evaporated to give 43.5 g. of brown viscous oil. By trituration of 24 g. of this material with an ether-petroleum ether mixture 14.4 g. of yellow solid, m.p. 97.5–100.5°, was obtained. Further purification of the product by distillation, b.p. 203–210° (50 microns), followed by recrystallization from hexane gave pure carbinol (XIV), m.p. 107.5–109°.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, THE WELLCOME RESEARCH LABORATORIES]

5-Arylthiopyrimidines. I. 2,4-Diamino Derivatives

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Arylmercaptoacetonitriles are readily acylated with lower aliphatic esters. Their crude enol ethers, obtained by reaction with diazomethane, condense with guanidine to produce 2,4-diamino-5-arylmercaptopyrimidines. In contrast with the closely related 5-phenoxy- and 5-benzylpyrimidines, these compounds are practically devoid of activity *vs.* protozoan and bacterial infections. However, several members of the series are central nervous system depressants.

Derivatives of 2,4-diaminopyrimidine bearing weighty substituents in the 5-position are, in general, antimetabolites with considerable potency as antifolic acids.[2,3] Several subseries, the 5-phenyl-, 5-benzyl-, and 5-phenoxypyrimidines, were found to possess antimicrobial activity, which is most strikingly exemplified by the antimalarial activity of pyrimethamine, 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine.[4–8] It was of considerable interest, therefore, to prepare the isologous 5-phenylmercaptopyrimidines for comparison.

Very few 5-pyrimidyl aryl or alkyl sulfides have been reported in the literature. P. F. Hu[9] reported the synthesis of 2-amino-4-hydroxy-5-(4′-nitrophenylmercapto)-6-methylpyrimidine and the corresponding 4,6-dimethyl derivative. These were obtained by condensations of guanidine with ethyl α-(4′-nitrophenylmercapto)acetoacetate and 3 - (4′ - nitrophenylmercapto) - 2,4 - pentanedione, respectively. Johnson and Guest[10] prepared some 5-benzylmercaptopyrimidines by condensing *S*-ethylisothiourea with ethyl α-formylbenzylmercaptoacetate. Subsequent conversions yielded 5-benzylmercaptouracil and -cytosine. No 2,4-diamino derivatives were described, however.

It was found here that 2,4-diamino-5-arylmercaptopyrimidines could be obtained by the condensation of guanidines with α-arylmercapto-β-methoxyacrylonitriles. This procedure is similar to that reported by Russell and Hitchings[7] for the corresponding 5-phenyl derivatives. The intermediate arylmercaptoacetonitriles were most conveniently prepared by the reaction of arylmercaptans with chloroacetonitrile[11]; however, some of the nitriles employed here were obtained by dehydration of the corresponding amides. The nitriles were readily acylated by treatment of the esters in ethanol with two moles of sodium methylate. The resultant α-acylphenylmercaptoacetonitriles (I) failed to condense with guanidine to form pyrimidines, as was found earlier with the phenyl derivatives.[7] However, their crude enol ether derivatives (presumably of structure II),

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(8) G. H. Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 467 (1952).

(9) P. F. Hu, *Sci. Repts. Natl. Tsing Hua Univ. Ser.* **A5**, 260 (1948); *Chem. Abstr.*, **43**, 6634 (1949).

(10) T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **42**, 271 (1909).

(11) R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 569 (1954).

TABLE I

ARYLMERCAPTOACETAMIDES $ArSCH_2CONH_2$

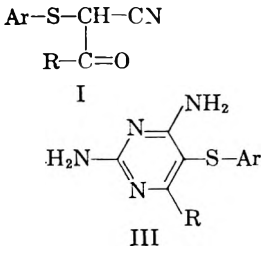
Compound No.	Ar	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	C_6H_5	108–109	C_8H_9NOS	57.5	57.9	5.4	5.3
II	$C_6H_4Cl(2)$	117–118	C_8H_8ClNOS	47.6	47.9	4.0	4.4
III	$C_6H_4Cl(4)$	130–131	C_8H_8ClNOS	47.6	47.6	4.0	4.0
IV	$C_6H_4OCH_3(4)$	111–112	$C_9H_{11}NO_2S$	54.8	54.7	5.6	5.5

TABLE II

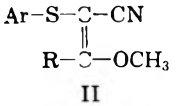
ARYLMERCAPTOACETONITRILES $ArSCH_2CN$

Compound No.	Ar	B.P./3 mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
VI	$C_6H_4Cl(2)$	160–166	C_8H_6ClNS	52.3	52.3	3.3	3.6
VII	$C_6H_4OCH_3(4)$	168–173	C_9H_9NOS	60.3	60.6	5.0	4.9

prepared by reaction with diazomethane readily yielded the desired pyrimidines (III).



I



II

III

R = H, CH_3, C_2H_5

The isomeric 2,4-diamino-6-arylmercaptopyrimidines could be prepared readily by the reaction of 2,4-diamino-6-chloropyrimidine with a thiophenol in ethylene glycol in the presence of potassium carbonate. One such example, described in the experimental section, was prepared for pharmacological comparisons.

The ultraviolet absorption spectrum of 2,4-diamino-5-phenylmercaptopyrimidine (XII) is characterized by maxima at 245 and 289 mμ in alkaline or neutral medium, and in acid by a high maximum in the very low wave-length region at 211 mμ, which very nearly obscures a second peak at 235 mμ, creating a shoulder. A slight suggestion of a third peak is given by an inflection at 270 mμ. The acid shoulder is of higher intensity than the alkaline peak at 245 mμ (Table V).

The effect of substituents either in the 6-position of the pyrimidine ring or in the benzene nucleus produced minor changes in spectrum, which in general are similar to those observed in the 5-phenoxypyrimidine series.[5]

The introduction of a *p*-chlorophenylmercapto group into the 6-position of the 2,4-diaminopyrimidine nucleus produced a quite different spectrum, as was to be expected. The neutral molecule had a single maximum at 288 mμ, which underwent a hyperchromic and slight bathochromic shift in acid.

The 5-phenylmercaptopyrimidines were tested against *Plasmodium gallinaceum* infections in chicks and *vs. P. berghei* in mice, and found to be surprisingly devoid of activity. They were also found to have very low activity as antagonists of pteroylglutamic acid in the *L. casei* screen, and to have little or no antibacterial action against a variety of bacteria. However, it was observed that several derivatives in this series produced hypnotic and hypothermic effects in mice and other animals. The corresponding 6-*p*-chlorophenylmercapto analog had no such activity. The results of pharmacological testing of these compounds will be reported elsewhere.

EXPERIMENTAL[12]

Arylmercaptoacetamides. These compounds were prepared from the corresponding ethyl arylmercaptoacetates by treatment with saturated ethanolic ammonia solutions containing trace amounts of sodium methoxide.[13] These compounds are listed in Table I; all crystallized from ethanol in colorless plates.

Arylmercaptoacetonitriles. (a) *From thiophenols plus chloroacetonitrile.* This procedure, which is essentially that of Dijkstra and Backer[11] is exemplified by the preparation described below.

4-Chlorophenylmercaptoacetonitrile (V). To a solution of 38 g. (0.7 mole) sodium methylate in 1 l. of absolute ethanol was added 100 g. (0.69 mole) of 4-chlorothiophenol, followed by the slow addition of 53 g. (0.7 mole) of chloroacetonitrile. The mixture was then heated under reflux for 1 hr. It was filtered hot to remove sodium chloride, and the filtrate then was refrigerated overnight. The shiny white plates which precipitated were filtered off and air dried; weight, 103 g. (81%); m.p. 88–90°.

Anal. Calcd. for C_8H_6ClNS: C, 52.3; H, 3.3. Found: C, 52.3; H, 3.6.

(b) *From arylmercaptoacetamides.* The arylmercaptoacetamides were treated with a slight excess of thionyl chloride in boiling benzene. Excess thionyl chloride was removed by partial distillation of the reaction mixture. The residual solution was washed with dilute sodium carbonate solution, dried over sodium carbonate, and distilled to remove benzene, followed by vacuum distillation of the product. The compounds of Table II were prepared by this procedure.

(12) Melting points are uncorrected.

(13) P. B. Russell, *J. Am. Chem. Soc.*, 72, 1853 (1950).

TABLE III

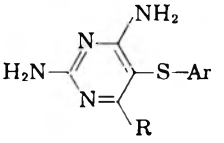
ULTRAVIOLET ABSORPTION SPECTRA OF INTERMEDIATE NITRILES

Compound No.	Solvent	Maximum λ mμ	Maximum Em × 10^{-3}	Minimum λ mμ	Minimum Em × 10^{-3}
V	Ethanol	258	5.7	244	4.6
	Cyclohexane	227, 259	12.6, 4.4	247	3.3
VIII	Ethanol	250	14.3	—[a]	—
IX	Ethanol	255	20.8	222	9.3
	*p*H 11 buffer	257	21.5	—[a]	—
	0.1*N* HCl	248	18.0		
	Cyclohexane	243	16.9		

[a] Spectrum not determined below 230 mμ.

TABLE IV

2,4-DIAMINO-5-ARYLMERCAPTOPYRIMIDINES



Compound No.	Ar	R	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XII	C_6H_5	H	217–220	$C_{10}H_{10}N_4S$	55.0	54.9	4.6	4.6	25.7	25.3
XIII	C_6H_5	CH_3	173	$C_{11}H_{12}N_4S$	56.9	57.1	5.2	4.9	24.1	24.1
X	$C_6H_4Cl(4)$	H	231–233	$C_{10}H_9ClN_4S$	47.5	47.4	3.6	3.5	22.2	22.3
XI	$C_6H_4Cl(4)$	CH_3	223–224	$C_{11}H_{11}ClN_4S$	49.6	49.6	4.2	4.3	21.0	21.1
XIV	$C_6H_4Cl(4)$	C_2H_5	188–190	$C_{12}H_{13}ClN_4S$	51.3	51.2	4.7	4.4	20.0	20.5
XV	$C_6H_4Cl(2)$	CH_3	206–208	$C_{11}H_{11}ClN_4S$	49.6	49.1	4.2	4.3	21.0	21.5
XVI	$C_6H_4OCH_3(4)$	H	196–197	$C_{11}H_{12}N_4OS$	53.2	53.4	4.8	4.7	22.6	22.6
XVII	$C_6H_4CH_3(4)$	CH_3	221–222	$C_{12}H_{14}N_4S$	58.5	58.9	5.7	5.4	22.8	23.1

TABLE V

ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINO-5-ARYLMERCAPTOPYRIMIDINES

Compound No.	*p*H 1 Maximum λ mμ	*p*H 1 Maximum Em × 10^{-3}	*p*H 1 Minimum λ mμ	*p*H 1 Minimum Em × 10^{-3}	*p*H 11 Maximum λ mλ	*p*H 11 Maximum Em × 10^{-3}	*p*H 11 Minimum λ mμ	*p*H 11 Minimum Em × 10^{-3}
XII	211	41.9	—		245	18.3	271	7.3
	235[a]	21.4			289	9.2		
	270[a]	6.3						
XIII	237	23.6	—		246	20.0	270	8.5
	270[a]	7.8			285	9.1		
X	245	21.6	—		251[b]	20.6	277	8.2
					290	9.6		
XI	244	23.4	—		252	22.5	275	10.0
	275[a]	8.0			284	10.4		
XIV	246	23.9	—		250	20.7	277	7.6
	275[a]	8.3			284	7.9		
XV	238	23.6	—		247	20.3	270	8.0
	270[a]	8.0			285	9.8		
XVI	243	22.4	232	20.8	248	20.4	275	7.7
	275[a]	7.1			290	9.1		
XVII	241	23.9	—		247	21.4	270	8.7
	270[a]	8.4			286	9.9		

[a] Inflection. [b] In 95% ethanol.

α-Acylarylmercaptoacetonitriles. These compounds were prepared by the condensation of the above nitriles with the appropriate ester in the presence of 2 moles of sodium ethylate.[14] In some instances the compounds were utilized in the crude form. The preparation of two of these compounds is given below.

α-Formyl-4-chlorophenylmercaptoacetonitrile (VIII). To a solution of 11.14 g. (0.484 g.-atom) of sodium in 450 ml. of absolute ethanol was added 44.4 g. (0.242 mole) of 4-chlorophenylmercaptoacetonitrile and 37 g. (0.5 mole) of ethyl formate. The mixture was heated under reflux for 3.5 hr., followed by distillation of the solvent from the reaction mixture. The residue was slurried in water and filtered from a small amount of insoluble material, followed by one extraction with ether. The resultant aqueous solution yielded an oil on acidification. This was extracted with ether, and dried over Drierite, followed by removal of the ether. The residual oil solidified on chilling. The substance was recrys-

(14) W. Wislicenus, *Ann.*, **291**, 202 (1896).

tallized from a benzene-hexane mixture, giving 29 g. (57%) of white product melting at 97–98°.

Anal. Calcd. for C_9H_6ClNOS: C, 51.06; H, 2.85; N, 6.61. Found: C, 51.18; H, 3.27; N, 6.23.

α-Acetyl-4-chlorophenylmercaptoacetonitrile (IX). From the reaction of 7.5 g. (0.041 mole) of 4-chlorophenylmercaptoacetonitrile with 9 g. (0.1 mole) of ethyl acetate in 100 ml. of absolute ethanol containing 4.5 g. (0.083 mole) of sodium methylate there was obtained by the above procedure 3.9 g. of crude product, which crystallized on acidification of the aqueous extract of the reaction mixture. After two recrystallizations from benzene-hexane, with the aid of decolorizing charcoal (Darco G 60), rosettes of white needles were obtained, melting at 113°.

Anal. Calcd. for $C_{10}H_8ClNOS$: C, 53.21; H, 3.57. Found: C, 53.43; H, 3.40.

2,4-Diamino-5-arylmercaptopyrimidines. The preparation of these compounds followed the method of Russell and Hitchings[7] for 2,4-diamino-5-arylpyrimidines. The α-acylarylmercaptoacetonitriles (crude in most cases) were treated with an excess of diazomethane in ether and the resulting β-methoxyacrylonitriles were condensed with guanidine. This procedure is exemplified below. The pyrimidines prepared by this procedure are listed in Table IV.

2,4-Diamino-5-(4′-chlorophenylmercapto)pyrimidine (X). To 12 g. (0.057 mole) of α-formyl-4-chlorophenylmercaptoacetonitrile in 150 ml. of ether was added an ethereal solution of diazomethane prepared from 12.4 g. (0.12 mole) of nitrosomethylurea. The mixture was allowed to stand in an open wide-mouthed Erlenmeyer flask for 2 days, after which time a sirupy residue remained. This was dissolved in 75 ml. of absolute ethanol and added to a solution of guanidine in ethanol, prepared by dissolving 1.31 g. (0.057 g. atom) sodium in 75 ml. of absolute ethanol, followed by the addition of 5.42 g. (0.057 mole) of guanidine hydrochloride. This mixture was heated to reflux temperature for 5 hr., cooled, and filtered. The precipitate was washed well with water and dried; weight, 8.3 g. (58% crude yield); m.p. 228–231°. Recrystallization from an 85:15 ethanol-toluene mixture with the aid of decolorizing charcoal (Darco G 60) yielded 5.9 g. of off-white product melting at 231–233°.

2,4-Diamino-5-(4′-chlorophenylmercapto)-6-methylpyrimidine (XI). α-Acetyl-4-chlorophenylmercaptoacetonitrile (17 g., 0.075 mole) was treated with diazomethane [from nitrosomethylurea (15 g., 0.15 mole)] as in the previous experiment. The product, after removal of the ether and excess diazomethane, was treated with guanidine [from the hydrochloride (8.0 g., 0.084 mole)] and sodium (1.8 g., 0.078 g.-atom) in 200 ml. of ethanol. After 5 hr. on the steam bath, the product was isolated as in the previous example. It was purified by reprecipitation with sodium hydroxide from solution in acetic acid, followed by recrystallization from 85% ethanol. Colorless needles were obtained (5.0 g., 25%); m.p. 223–224°.

2,4-Diamino-6(4′-chlorophenylmercapto)pyrimidine. A mixture of 5 g. (0.035 mole) of 2,4-diamino-6-chloropyrimidine,[15] 5 g. (0.035 mole) of 4-chlorothiophenol, 4.8 g. (0.035 mole) of anhydrous potassium carbonate, and 50 ml. of ethylene glycol was heated to refluxing for 10 min., and then placed on the steam bath overnight. The mixture was then poured into several volumes of water, made strongly basic with sodium hydroxide, chilled, and filtered. The white precipitate, 6.0 g., was recrystallized three times from ethanol, yielding long white needles (4.1 g.) melting at 219°.

Anal. Calcd. for $C_{10}H_9ClN_4S$: C, 47.52; H, 3.59; N, 22.17. Found: C, 47.75; H, 3.25; N, 22.57.

Ultraviolet absorption peaks were as follows: (a) in 0.1*N* hydrochloric acid: λ_{max}, 292 mμ (Em × 10^{-3} 12.6); λ_{min} 264 mμ (Em × 10^{-3} 7.7). (b) in *p*H 11.0 buffer: λ_{max} 288 mμ (Em × 10^{-3} 9.5); λ_{min} 262 mμ (Em × 10^{-3} 6.1).

Absorption spectra. Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer, with 1 cm. quartz cuvettes. The absorptions were measured at a concentration of 10 mg. per liter in 0.1*N* hydrochloric acid and Sørensen glycine–sodium hydroxide buffer at *p*H 11.0, or in 95% ethanol or other solvents as noted.

Acknowledgments. The authors are indebted to Kurt Ledig for technical assistance in the preparation of some of the compounds reported here, to Samuel W. Blackman, Veronica Purdey, and Charles Marr for the microanalyses, and to Mrs. Linda Wright Sheehan for the determination of the ultraviolet absorption spectra.

TUCKAHOE, N. Y.

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, 72, 1914 (1950).

[CONTRIBUTION FROM THE INDUSTRIAL AND BIOCHEMICALS DEPARTMENT
E. I. DU PONT DE NEMOURS AND CO., INC. EXPERIMENTAL STATION]

The Reaction of Disodium Ethylenebisdithiocarbamate with Trichloromethanesulfenyl Chloride[1]

H. L. KLOPPING

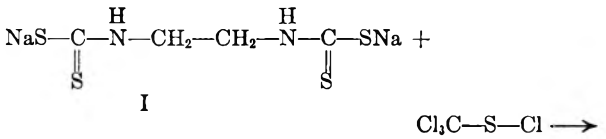
Received August 12, 1960

The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride (II) in aqueous medium gives a complex mixture of solids. The main components of this mixture are a polymer (III), bis(trichloromethyl)-ethylenebistrithiopercarbamate (IV), bis(trichloromethyl)-*N*-(trichloromethylthio)ethylenebistrithiopercarbamate (V), and bis(trichloromethyl)-*N*,*N*′-bis(trichloromethylthio)ethylenebistrithiopercarbamate (VI). The mechanism of formation of these compounds is discussed. A method for the specific synthesis of the most chemically stable component (IV) is described. This method, which involves inactivation of the —NH— groups of I toward II, consists in reaction of an emulsion containing free ethylenebisdithiocarbamic acid (IX), water, and an inert immiscible solvent with II in the presence of a large excess of hydrogen ions.

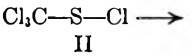
The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride[2] (II) was considered to be of interest because I contains four sites capable of reacting with II (two —NH— groups and two mercaptide groups), and II contains four chlorine atoms all of which

are capable, under the proper conditions, of reacting with mercaptides.[3] A variety of reaction products could therefore be expected to form.

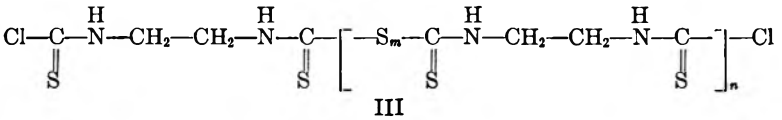
Products formed in aqueous medium. Slow addition of II to a well agitated, cooled, dilute aqueous solution of I gave a solid material which, as expected, consisted of a complex mixture of reaction products (*cf.* Experiment 1). By means of extraction with hot benzene, this mixture could be separated into a benzene insoluble, polymeric material (III) and a benzene soluble mixture of low molecular weight materials. The latter mixture was found to contain, in addition to some unidentified debris, bis(trichloromethyl)ethylenebistrithiopercarbamate (IV), bis(trichloromethyl) - *N* - (trichloromethylthio)ethylenebistrithiopercarbamate (V), and bis(trichloromethyl) - *N,N'* - bis(trichloromethylthio)ethylenebistrithiopercarbamate (VI):



I

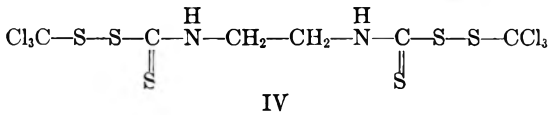


II

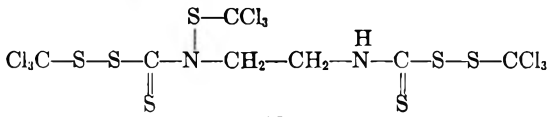


III

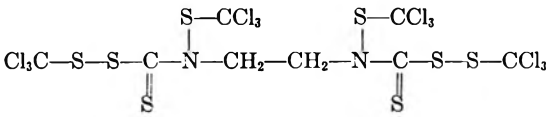
m = 1 or 2 n averages close to 5



IV

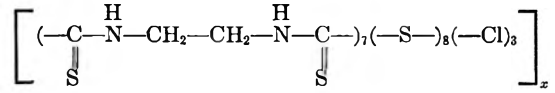


V



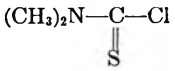
VI

The structure III assigned to the polymeric material shows that it is built up of an average of five ethylenebisthiocarbamyl units joined together by mono- and disulfide linkages, and capped by thiocarbamyl chloride end groups. This structure is in accordance with the mechanism of its formation discussed below and with the experimental evidence of Experiment 1. The compound is very similar in appearance and physical properties to polyethylenethiuram monosulfide[4] (VII) and disulfide[5] (VIII) which are obtained by treatment of aqueous I with, respectively, phosgene or common oxidizing-agents. The elemental formula $C_{28}H_{42}N_{14}S_{22}Cl_3$ can be written as



The proportion of —S— atoms to ethylenebisthiocarbamyl units indicates that there is one disulfide linkage for every two monosulfide linkages. The proportion of these units to chlorine atoms (assuming the latter to be present exclusively in thiocarbamyl chloride end groups) indicates an average chain length of close to five units.

The conclusion that the chlorine atoms must be present in the form of thiocarbamyl chloride end groups is based on the following considerations. First, the formation of these groups is to be expected on the basis of the mechanism of polymer formation discussed below. Second, aqueous suspensions of the polymer gradually turn acidic on standing at room temperature and show an increasingly positive reaction for chloride ions. Third, the infrared spectrum of III contains no evidence for the presence of —CCl_3 groups or any common C—Cl linkage (no bands in the 12.7–15 μ region). Neither is there any indication that the chlorine is present in the form of amine hydrochloride groups (the band at 3.15 μ is very sharp). However, the spectrum is not in disagreement with the presence of thiocarbamyl chloride groups, as the spectrum of the model compound dimethylthiocarbamyl chloride:



contains no peaks in the 12.7–15 μ region either.[6]

The structure of IV is based on the mode of formation of the compound, its elemental analysis and its infrared spectrum. The latter contains bands at 12.65, 13.10, and 13.47 μ, which may be

(1) Presented in part at the Symposium of the Delaware Section of the American Chemical Society, Newark, Del., February 14, 1959, and at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 15, 1959.

(2) The chemistry of this compound has been reviewed by G. Sosnovsky, *Chem. Reviews*, **58**, 509 (1958).

(3) H. J. Backer and E. Westerhuis, *Rec. Trav. Chim.*, **71**, 1065 (1952); *Rec. Trav. Chim.*, **71**, 1071 (1952); *Rec. Trav. Chim.*, **71**, 1082 (1952).

(4) R. A. Ludwig and G. D. Thorn, *Plant Disease Reptr.*, **37**, 127 (1953); British Patent **819,779**.

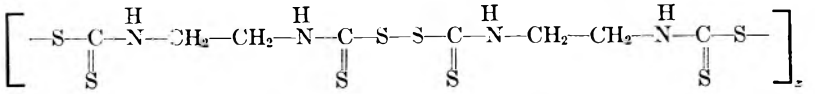
(5) H. L. Klopping and G. J. M. van der Kerk, *Rec. Trav. Chim.*, **70**, 958 (1951); L. Wheschky and O. Flieg, German Patent **919,350**.

(6) The major absorption bands in the infrared spectrum of this compound are at 7.24, 8.09, 8.61, 9.48, 10.40, and 11.65 μ.

assigned to the $-CCl_3$ groups, and a sharp band at 3.12 μ (NH stretching) which indicates that the $-S-CCl_3$ groups are attached to sulfur rather than to nitrogen. Moreover, the spectrum contains no SH bands.

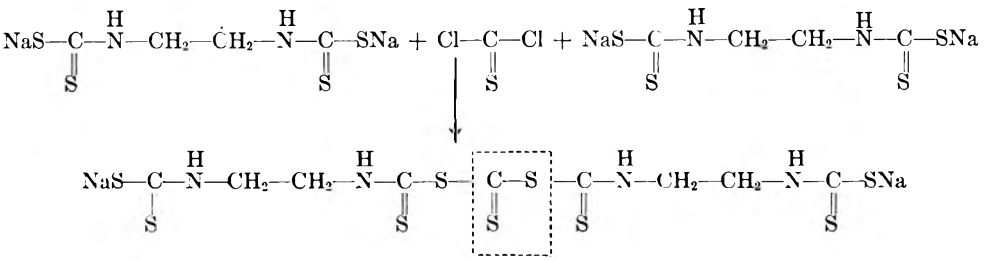
The structures of V and VI are based on the elemental analyses and on the fact that these compounds can be synthesized by reacting IV with II (*cf.* Experiment 3).

Mechanism of the reaction in aqueous medium. On the basis of a combination of published information and the experimental results presented in this paper, the formation of the products III through VI is proposed to take place as follows. Trichloromethanesulfenyl chloride (II) is known to be capable of oxidizing reducing agents such as sulfur dioxide in aqueous solution, whereby II itself is reduced to thiophosgene.[7] In the present reaction, the reducing agent is an aqueous solution of I; oxidation of this compound is known to yield polyethylenethiuram disulfide,[5] VIII, a cyclic or linear polymer in which ethylenebisthiocarbamyl units are joined together by means of disulfide linkages:

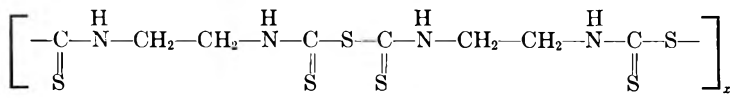


VIII

The thiophosgene produced in this process is also capable of reacting with dithiocarbamates.[8] The initially formed trithiocarbonyl linkages are unstable:



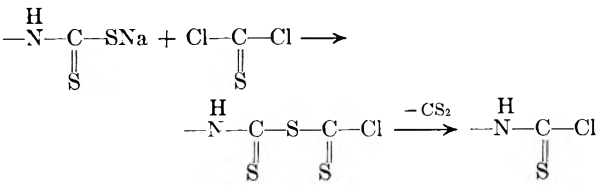
and eliminate carbon disulfide with formation of monosulfide linkages, so that the final product is polyethylenethiuram monosulfide (VII):



VII

As these reactions can take place simultaneously, the polymers actually formed are expected to be of a mixed nature, containing both disulfide and monosulfide linkages.

Instead of reacting with two sodium dithiocarbamate end groups, thiophosgene may react with one such group—which may be part of a molecule of I or of an already formed polymer chain—with formation of a thiocarbamyl chloride end group:



In view of the low temperature of the reaction mixture, a considerable proportion of these end groups escapes hydrolysis.

The experimental evidence indicates that the chlorine in the polymer is largely, if not exclusively, present in the form of these end groups. The absence of infrared absorption bands for $-CCl_3$ groups indicates that these latter groups do not enter the polymer in detectable amounts, so that II does not appear to enter into metathetical reactions with —NH— or dithiocarbamate groups as long as reduction of II by I is possible. Thus, formation of IV, V, and VI should be negligible during this stage of the reaction.[9]

As the reaction proceeds, however, the concentration of I diminishes and as a result more and more molecules of II escape reduction and react, as such, with the polymer present in the reaction mixture. What happens in this reaction between II and the polymeric product is illustrated by a model experiment (No. 4) in which II was treated with pure polyethylenethiuram disulfide, VIII, prepared by oxidation of I. In this experiment, the initially chlorine free polymer broke down with formation of 1) a polymer containing 13% Cl

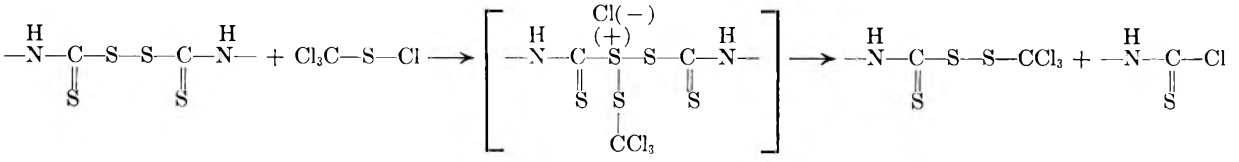
(7) French Patent **1,152,827**. G. Malcolm Dyson, *Org. Syntheses*, **Coll. Vol. I**, 509 (1932).

(8) G. M. Zbirovsky and V. Ettel, *Coll. Czechosl. Chem. Comm.* **10**, 1896 (1958).

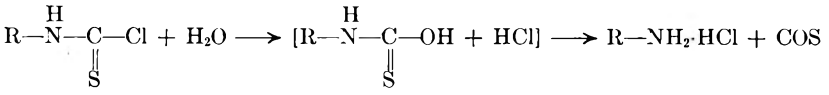
(9) This conclusion is borne out by the observation that samples of the reaction product withdrawn during the early stages of the reaction consist largely of polymeric material. These polymer samples are very low in chlorine content.

(39% of the weight of the starting material), 2) compound IV (30%), and 3) the usual residue containing V and VI. The latter compounds may either form directly from polymer fragments or *via* IV. The latter route is illustrated by Experiment 3, in which IV was treated with II to give V and VI.

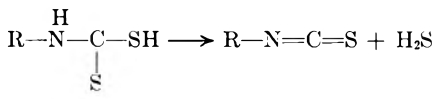
As regards the mechanism of this breakdown reaction between polymer and II, the nature of the products formed is a strong indication that the exchange reaction between sulfenyl chlorides and disulfides discovered by Moore and Porter[10] plays an important part. Application of this exchange reaction to the present case, II attacking the disulfide bonds in the polymer, shows how the end groups discussed above may enter the picture:



Other reactions likely to occur in aqueous medium are 1) hydrolysis of thiocarbamyl chloride groups:



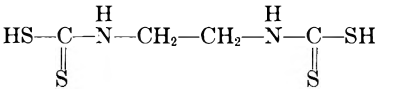
and 2) hydrolysis of dithiocarbamate groups with loss of hydrogen sulfide[5,11]:



followed by polymerization of the isothiocyanates. These reactions most likely contribute to the formation of the debris normally found in the crude reaction product.

Specific synthesis of IV. As the *S,S'*-disubstitution product (IV) turned out to be the most chemically stable among the reaction products described, the development of a specific method of synthesis for this compound became an important goal of this investigation. The approach to this goal was to modify the original reaction of Experiment 1 in such a fashion that all reactions other than *S*-substitution would be suppressed. These reactions were 1) polymer formation, and 2) *N*-substitution (formation of products V and VI). In attempting to suppress polymer formation, a helpful clue was, of course, the mechanism of polymer formation discussed above: Polymer formation should not occur if oxidation-reduction reactions between I and II were avoided.

The latter reactions can only occur where I can act as a reducing agent—*i.e.*, in aqueous solution. Thus, avoiding polymer formation required avoiding the combination of I with water in the reaction mixture. This left a choice between two alternatives: 1) carry out the reaction under anhydrous conditions, or 2) use an aqueous system but render I insoluble in water by modifying its structure in some way. The first alternative is studied using dry I in hexane as described in Experiment 5. The result of this experiment was encouraging in that it was in accordance with the mechanism of polymer formation described above, the percentage of polymer in the crude product being very low. However, excessive *N*-substitution had occurred under these conditions. The second alternative was studied using, instead of I, free ethylenebisdithiocarbamic acid IX, which is insoluble in water and easily prepared in aqueous suspension by acidifying an aqueous solution of I.



IX

Addition of II to this aqueous suspension (Experiment 6) gave a product which again was very low in polymer content. However, it also contained a high percentage of *N*-substituted compounds V and VI. In this three phase reaction, the two hydrophobic phases (ethylenebisdithiocarbamic acid and II) lumped together, and in the next experiment (No. 10), hexane was added to eliminate this difficulty. It was found that under these conditions an emulsion formed which remained intact during the addition of II. In spite of these improved mixing conditions, a high percentage of *N*-substituted materials was again present in the reaction product.

In the course of further studies with the emulsion system, conditions were found under which both polymer formation and *N*-substitution were strongly suppressed. In experiments discussed up to this point, the emulsion had been prepared by adding to the stirred mixture of aqueous I and hexane (or some other inert immiscible solvent such as carbon tetrachloride or chloroform) an amount of hydrochloric acid just sufficient to convert I to free ethylenebisdithiocarbamic acid. However, when a large excess of hydrochloric acid was added

(10) C. G. Moore and M. Porter, *J. Chem. Soc.*, 2890 (1958).

(11) R. A. Ludwig, G. D. Thorn, and C. H. Unwin, *Can. J. Botany*, **33**, 42 (1955).

TABLE I

SUMMARY OF EXPERIMENTAL RESULTS

Exp. No.	Starting Materials: I or derivative	H_2O, ml.	II	Acid	Org. solvent	Product: Weight, g.	Composition, %: III	IV	V + VI
1	I, 25.6 g. (0.1 mole)	300	12.5 ml. (0.115 mole)	—	—	24.3	58	32	10
2	I, 36 g.	200	44 ml. (0.4 mole)	—	Hexane, 500 ml.	15.0	Predominantly V + VI		
3	IV, 10.2 g. (0.02 mole)	—	22 ml. (0.2 mole)	—	—	14.4	"		"
4	VIII, 11 g. (0.052 mole)	300	7.5 ml. (0.068 mole)	—	—	17.6	39	30	30
5	I, 25.6 g. (0.1 mole)	—	22 ml. (0.2 mole)	—	Hexane, 250 ml.	46.0	6	37	57
6	IX, 42.4 g. (0.2 mole)	1050	44 ml. (0.4 mole)	—	—	76.7	5	45	50
7	I, 25.6 g. (0.1 mole)	100	22 ml. (0.2 mole)	Concd. HCl, 100 ml.	Hexane, 100 ml.	47.5[a]	2	91	7
8	I, 25.6 g. (0.1 mole)	150	22 ml. (0.2 mole)	Concd. HCl, 50 ml.	Hexane, 100 ml.	32.1[a]	"	"	"
9	I, 25.6 g. (0.1 mole)	175	22 ml. (0.2 mole)	Concd. HCl, 25 ml.	Hexane, 100 ml.	19.0[a]	"	"	"
10	I, 25.6 g. (0.1 mole)	183	22 ml. (0.2 mole)	Concd. HCl, 16.6 ml.	Hexane, 100 ml.	17.0[a]	"	"	"

[a] Solid obtained by filtering the reaction mixture. Products dissolved in hexane filtrate (mostly V + VI) not included.

(Experiment 7), the emulsion upon reaction with II yielded a product which consisted of over 90% of IV.

Subsequent experiments (No. 8 and 9, see also 10) showed that reducing this excess of hydrochloric acid in the reaction mixture proportionally reduced the yield of IV. It was also found that other suitable mineral acids (*e.g.*, sulfuric acid) had the same effect as hydrochloric acid. Thus, it appeared that a high concentration of hydrogen ions in the reaction mixture was capable of inactivating the —NH— groups of ethylenebisdithiocarbamic acid toward II. This effect is reminiscent of the observation made by Argyle and Dyson[12] that compounds of the general formula $R_1—\overset{\displaystyle SCCl_3}{\underset{|}{N}}—R_2$, when treated with dry hydrogen chloride in ligroin, quantitatively regenerate the hydrochloride of the original amine and trichloromethanesulfenyl chloride. In view of the basic character of these thiolamine derivatives, the regenerative reaction probably involves the approach of a proton toward the lone pair of electrons on the nitrogen, with formation of an unstable quaternary intermediate:

$$[R_1—\overset{\displaystyle \delta^-CCl_3}{\underset{\displaystyle H}{\overset{|}{\underset{|}{N}}}}—\overset{\displaystyle \delta^+S}{\overset{|}{R_2}}]^{(+)}Cl^{(-)} \longrightarrow R_1—\underset{\displaystyle H}{\overset{|}{N}}—R_2 + Cl—S—CCl_3$$

In the case of the present reaction, the degree of S—N bond formation was found to be inversely proportional to the hydrogen ion concentration in the medium. It would appear, therefore, that the trichloromethanesulfenyl cation (or the strongly polarized trichloromethanesulfenyl chloride molecule) approaching the lone pair of electrons on the —NH— groups of the ethylenebisdithiocarbamic acid has to compete with hydrogen ions, the mass activity of the latter ions determining the degree of S—N bond formation.

(12) C. S. Argyle and G. M. Dyson, *J. Chem. Soc.*, 1629 (1937).

EXPERIMENTAL

A summary of the experimental results is given in Table I. A detailed description of the experiments is given below.

Experiment 1. Reaction of I with II in aqueous medium. Isolation of III and IV. A solution of 25.6 g. (0.1 mole) of I in 300 ml. of water was cooled in an ice bath. While stirring vigorously, II was added dropwise at a rate of 4 ml. per hr. Gradually, a light yellow solid precipitated. Addition was continued until a filtered sample of the reaction mixture no longer gave a precipitate when mixed with ferrous sulfate solution. At that moment, 12.5 ml. (0.115 mole) of II had been added.

The reaction mixture was stirred for two additional hours. The precipitate was then filtered, washed with water, and dried. The dried product, a light cream colored powder, weighed 24.3 g. It melted at 122–130° with decomposition and then resolidified to give a product melting at 175–185°.

This crude product was separated into its components as follows: a) *Isolation of the polymeric product* (III). Five grams of the above reaction product was extracted twice with 200 ml. of boiling benzene. The residue was washed with hot benzene and dried. It weighed 2.9 g. (58% of original crude product) and melted at 131–135°, with decomposition and resolidification. (The resolidified material melted at 165–170°.)

Anal. Calcd. for $(C_{28}H_{42}N_{14}S_{22}Cl_3)_x$: C, 24.2; H, 3.0; N, 14.1; S, 50.9; Cl, 7.7. Found: C, 24.0; H, 3.0; N, 14.1; S, 50.3; Cl, 7.7.

The major absorption bands in the infrared (potassium bromide disc) spectrum of product III are at 3.15 (sharp),

6.63, 7.24, 7.42, 7.58, 8.00, 8.92, 9.30, 10.53, 10.80, and 11.65 μ.

An aqueous slurry of product III on agitation at room temperature gradually turned acidic and showed an increasingly positive reaction for chloride ions.

Attempts to determine the average molecular weight of product III were unsuccessful, because of either insufficient solubility or insufficient stability under the conditions of the method of determination. The product slowly decomposed on standing at room temperature.

b) *Isolation of* IV. The hot benzene extracts from above were combined and vacuum concentrated until crystallization occurred.

The mixture was cooled to 8° and scratched until no further separation of crystalline material occurred.

Filtration, washing with a little benzene, and drying gave 1.6 g. (32% of the original crude product) of white crystals, melting at 141–142° with decomposition. The orange melt resolidifies.

Anal. Calcd. for $C_6H_6N_2S_6Cl_6$ (IV): C, 14.1; H, 1.2; N, 5.5; S, 37.6; Cl, 41.6. Found: C, 14.3; H, 1.4; N, 5.8; S, 37.6; Cl, 41.6.

The major absorption bands in the infrared spectrum of IV are at 3.12, 6.85, 7.29, 7.73, 8.05, 9.43, 10.86, 12.65, 13.10, and 13.47 μ.

The benzene filtrate from IV was treated with an excess of hexane and cooled in ice. The solid obtained by filtration weighed 0.4 g. (8% of the original crude product) and melted at 75–80°. It consisted of a mixture of compounds V and VI. A larger quantity of this solid was prepared and separated into its components by methods described in Experiment 2.

Experiment 2. Reaction of I *with an excess of* II *in water-hexane mixture. Isolation of* V *and* VI. A solution of 36 g. (0.14 mole) of I in 200 ml. of water was added dropwise, over a period of 15 min., to a stirred solution of 44 ml. (0.4 mole) of II in 500 ml. of hexane. At first, the temperature of the reaction mixture dropped from 25° to 15° and then slowly increased to room temperature while a light yellow solid separated. Gradually, the reaction mixture turned into a thick suspension. Stirring was continued. The temperature rose gradually to about 35° and then, rather suddenly, to 40°, while the solid dissolved almost completely.

Stirring was continued for 3 hr. After standing overnight, the hexane layer was separated and dried over anhydrous sodium sulfate. The hexane was removed by evaporation *in vacuo* until the volume was reduced to about half. At this point a cloudiness occurred in the liquid.

After standing overnight in the refrigerator, the mixture was filtered. The solid product, after drying, weighed 15 g. and melted at 75–80°. It consisted mainly of a mixture of V and VI.

This mixture was dissolved in boiling hexane and the solution was allowed to cool slowly. The first fraction to crystallize consisted predominantly of V. After several recrystallizations from hexane this product was obtained in the form of white needles melting at 98–99° (4.1 g.).

Anal. Calcd. for $C_7H_5N_2S_7Cl_9$ (V): C, 12.7; H, 0.8; N, 4.2; S, 34.0; Cl, 48.3. Found: C, 12.9; H, 0.8; N, 4.6; S, 34.8; Cl, 48.4.

On cooling the filtrate from V in ice, a second fraction was obtained which consisted mainly of VI. After several recrystallizations from hexane, this compound was recovered as a white microcrystalline powder, m.p. 80–84° (4.6 g.).

This compound is very unstable and decomposes rapidly in boiling hexane.

Anal. Calcd. for $C_8H_4N_2S_8Cl_{12}$ (VI): C, 11.8; H, 0.5; N, 3.5; S, 31.7; Cl, 52.5. Found: C, 12.2; H, 0.7; N, 3.9; S, 32.8; Cl, 51.3.

Both compounds V and VI decompose rather rapidly on standing at room temperature.

Experiment 3. Synthesis of V *and* VI *starting from* IV *and* II. To 10.2 g. (0.02 mole) of IV was added sufficient II to make a stirrable suspension (22 ml.). The mixture was stirred until the evolution of heat and hydrogen chloride had ceased. The mixture was then spread out on a watch glass and allowed to dry in a stream of air.

The solid, which weighed 14.4 g. and melted at 75–80°, was separated into its main components V and VI as described above (Experiment 2).

Experiment 4. Reaction of VIII *with* II. A solution of 14 g. of I in 200 ml. of water was stirred and kept at 0–3°. Dilute aqueous hydrochloric was added until the *p*H was 5. This solution was oxidized by slowly introducing chlorine gas until it no longer contained free I. The suspension was filtered and the white solid, consisting of VIII, was washed with water. The wet cake, corresponding to a dry weight of 11 g., was resuspended in 300 ml. of water. The suspension was kept at 3 to 5° and stirred, while 7.5 ml. of II was added over a period of 2 hr. The suspension was filtered, washed with water, and dried. The solid, which weighed 17.6 g., was subjected to the hot benzene extraction procedure of Experiment 1 and yielded 6.8 g. (39%) of polymer containing 13.0% chlorine, 5.2 g. (30%) of IV, m.p. 139–141° dec., and 5.2 g. (30%) of a residue consisting mostly of a mixture of V and VI, m.p. 75–80°, which was separated as described in Experiment 2.

Experiment 5. Reaction of I *with* II *in hexane.* One hundred grams of I hexahydrate (theor. 29.5% H_2O) was refluxed with benzene using a Dean-Starke trap. After 7 hr., no additional water collected in the trap; the volume of the water was 29.5 ml., and the solid weighed 71 g.

A 25.6-g. sample (0.1 mole) of anhydrous I was slurried in 250 ml. of hexane. While stirring at room temperature, 22 ml. (0.2 mole) of II was added over a period of 3 hr. There was no heat evolution. Stirring was continued until an aqueous extract of a sample of the reaction mixture gave a negative test (no precipitate with ferrous sulfate solution) for I. The mixture was filtered, washed with hexane, and dried. The solid weighed 40 g. The filtrate on evaporation left a mixture of V and VI, 16 g. The solid contained 10 g. of sodium chloride, 3 g. of polymer, 17 g. of IV and 10 g. of the mixture of V and VI, so that the composition of the organic portion of the reaction product was polymer III, 6%; IV, 37%; and V + VI, 57%.

Experiment 6. Reaction of IX *with II in aqueous suspension.* A solution of 73 g. (0.2 mole) of I hexahydrate in 1000 ml. of water was stirred and cooled in ice. Hydrochloric acid, 6*N*, was added dropwise until precipitation was complete.

Then, 44 ml. (0.4 mole) of II was added over a period of 30 min. The cooling bath was then removed and stirring was continued at room temperature until the lumps of product formed initially had broken up (16 hr.). The solid was collected on a filter, washed with water, and dried. It weighed 76.7 g. (theor. yield if product consisted entirely of IV, 102 g.). The composition of this product, as determined by the hot benzene extraction method described in Experiment 1, was: polymer III, 5%; IV, 45%; residue containing mixture of V and VI, 50%.

Experiments 7 through 10. Reaction of IX *with* II *in water-hexane emulsion in the presence of decreasing excesses of hydrochloric acid. Experiment 7.* To a solution of 25.6 g. (0.1 mole) of I in 100 ml. of water was added 100 ml. of hexane. The mixture was kept at 10°, and 100 ml. of 37% hydrochloric acid was added over a period of 20 min. with vigorous stirring. The emulsion of IX thus prepared[13] was allowed to warm up to 18°. Then, with vigorous stirring, 22 ml. (0.2 mole) of II was added over a period of 4 min., without external cooling. The temperature rose rapidly to 40°, then gradually dropped back to room temperature. After stirring for 2 more hr., the product was collected on a filter, washed with hexane and water, and dried. It weighed 47.5 g. (theor. yield if product consisted entirely of IV, 51.1 g.). The com-

(13) Since 0.1 mole of I requires 16.6 ml. of 37% hydrochloric acid for its neutralization, the concentration of hydrochloric acid in the aqueous phase of the reaction mixture was 15.4%.

position of this product, as determined by the hot benzene extraction method of Experiment 7, was: polymer, 2%; IV, 91%; residue containing V + VI, 7%.

Experiment 8. Experiment 7 was repeated using a mixture of 50 ml. of water and 50 ml. of concd. hydrochloric acid instead of 100 ml. of concd. hydrochloric acid.[14] The yield of solid product was 32.1 g. (62%), and its composition was the same as in the preceding experiment. The hexane layer of the reaction mixture contained most of the mixture of V + VI formed in this reaction.

Experiment 9. Experiment 7 was repeated using a mixture of 25 ml. of concd. hydrochloric acid and 75 ml. of water instead of 100 ml. of concd. hydrochloric acid.[15] The yield of solid product was 19.0 g. (37%), and its composition was the same as that of the product of Experiment 7. Most of the mixture of V and VI formed in this reaction was dissolved in the hexane layer of the filtrate.

Experiment 10. Experiment 7 was repeated using a mixture of the amount of concd. hydrochloric acid theoretically required to neutralize 0.1 mole of I (16.6 ml.) and 83.4 ml. of water, instead of 100 ml. of concd. hydrochloric acid. The yield of solid product was 17.0 g. (33%), and its composition was the same as in the case of Experiment 7. The hexane layer of the filtrate contained most of the mixture of V and VI formed in this reaction.

WILMINGTON, DEL.

(14) Concentration of hydrochloric acid in the aqueous phase: 7.7%.

(15) Concentration of hydrochloric acid in the aqueous phase: 1.5%.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA]

A Synthesis of Unsymmetrical Aliphatic Disulfides[1]

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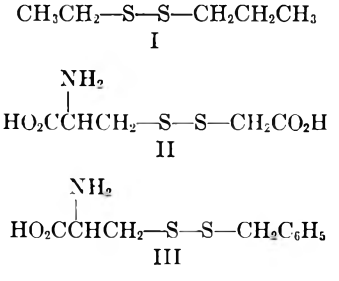
Received September 21, 1960

A general method for the synthesis of unsymmetrical aliphatic disulfides has been developed from a procedure previously described in the literature. The route involves the formation of an alkylsulfenyl thiocyanate, prepared from the desired mercaptan and thiocyanogen. Treatment of the sulfenyl thiocyanate with a second mercaptan results in displacement of thiocyanic acid and the formation of an unsymmetrical disulfide. Several examples of aliphatic disulfides containing the methoxyl, nitro, carbomethoxy and carboxy groups have been prepared in 50–70% yield.

The increased interest in the chemical behavior of the disulfide bond in natural macromolecules has prompted an investigation of the synthesis and general reactivity of unsymmetrically substituted aliphatic disulfides. The unsymmetrical disulfides are desirable for study, as a disulfide bond cross-linking two peptide chains, composed of different arrangements of amino acids, may be considered an unsymmetrical aliphatic disulfide containing reactive functional groups as side chains. The present report concerns our preliminary studies on the synthesis of such molecules.

Although several methods of preparation of *mixed* disulfides have been reported, the scope of these syntheses remain unexplored. The published examples of molecules of this type, with the exception of a few cyclic aliphatic disulfides, are limited to: (a) purely aliphatic molecules with no functional groups[4,5] represented by 3,4-dithiaheptane (I)[5]; (b) disulfides composed of cysteine and another mercaptocarboxylic acid such as penicillamine,[6b] β-mercaptopropionic acid,[6a] or thioglycolic acid (II)[6a,7]; and (c) disulfides containing cysteine or another mercaptocarboxylic acid and cysteamine,[6a] β-mercaptoethanol,[3a] or, in one case,[8] benzyl mercaptan (III). Thus virtually all known unsymmetrical aliphatic disulfides contain only the carboxyl and/or amino residues as functional groups. Evaluation of the available synthetic routes in terms of



I

II

III

neutral molecules containing functional groups led to the conclusion that, in general, the published methods would not be applicable since either oxidation[4–6] or the formation of the disulfide in aqueous solution[8] was involved. Initially however several attempts were made to utilize the published procedures[4,6] for the synthesis of methyl 5-phenyl-2,3-dithiapentanoate (V) by treatment of IV with

(1) Supported in part by a Frederick Gardner Cottrell Grant from the Research Corporation.

(2) Tennessee Eastman Corporation Fellow, 1959–1960.

(3)(a) Undergraduate research student. (b) Supported by the National Science Foundation Undergraduate Research Program, Summer 1960. (c) 1959–1960.

(4) L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **69**, 1710 (1947).

(5) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

(6)(a) A. Schoberl and H. Grafje, *Ann.* **617**, 71 (1958). (b) A. Schoberl, H. Tausent, and H. Grafje, *Angew. Chem.*, **68**, 213 (1956).

(7) H. Lamfrom and S. O. Nielsen, *Compt. rend. Lab. Carlsberg, Ser. Chim.*, **30**, 360 (1958).

(8) J. M. Swan, *Nature*, **180**, 643 (1957).

TABLE I

ALIPHATIC DISULFIDES PREPARED *Via* ALKYLSULFENYL THIOCYANATES

VIII					B.P.°/Mm. or M.P.°	M_R		Calcd.			Found		
R	R′	Yield, %	n_D^{25}	d^{25}		Calcd.	Obs.	C	H	S	C	H	S
$C_6H_5CH_2$[a]	$CH_2CO_2CH_3$	58	1.5774	1.2044	120/0.3	62.66	62.86	52.60	5.30	28.09	52.27	5.36	28.22
$C_6H_5CH_2$[b]	$CH_2CO_2CH_3$	45.4	1.5770	1.2045	120/0.3								
$C_6H_5CHCH_3$	$CH_2CO_2CH_3$	62.5	1.5689	1.1795	120/0.2	67.28	67.31	54.51	5.82	26.46	54.21	5.80	26.36
p-$NO_2C_6H_4CH_2$	$CH_2CO_2CH_3$	54.7			52.5–53[c]			43.94	4.06	23.46	43.73	4.26	23.32
p-$CH_3OC_6H_4CH_2$	$CH_2CO_2CH_3$	48.0	1.5762	1.2406	142/0.15	68.92	68.94	51.14	5.46	24.82	50.66	5.66	24.69
$C_6H_5CH_2$	$CHCO_2H$	51.5			147–148			48.51	4.44	23.55	48.53	4.79	23.33
	CH_2CO_2H												
$C_6H_5CH_2$	$(CH_2)_5CH_3$	59.5	1.5487	1.0143	117/0.3	74.87	75.36	64.93	8.39	26.67	64.67	8.50	27.06
$C_6H_5CH_2$	$C(CH_3)_3$	62.0	1.5636	1.0537	87/0.3	65.63	65.45	62.25	7.59	30.16	62.24	7.74	30.23
$CH_3(CH_2)_5$	$CH_2CO_2CH_3$	73.0	1.4939	1.0566	86/0.2	61.73	61.26	48.61	8.16	28.84	48.82	7.97	28.78
$(CH_3)_3C$[d]	$CH_2CO_2CH_3$	60.8	1.4991	1.0963	56/0.15	52.21	52.00	43.33	7.21	32.97	43.17	7.37	32.95
$(CH_3)_3C$[e]	$CH_2CO_2CH_3$	22.9	1.4995	1.0966	56/0.15								

[a] *Via* $NCSSCH_2CO_2CH_3$. [b] *Via* $C_6H_5CH_2SSCN$. [c] Recrystallized from ether–petroleum ether (b.p. 30–60°). [d] *Via* $NCSSCH_2CO_2CH_3$. [e] *Via* $(CH_3)_3CSSCN$.

benzyl mercaptan. In our hands the method was unsuccessful.

$$[CH_3O_2CCH_2\text{—}S]_2 \longrightarrow$$

$$CH_3O_2CCH_2\text{—}\overset{\overset{O}{|}}{S}\text{—}S\text{—}CH_2CO_2CH_3 \longrightarrow$$

IV

$$CH_3O_2CCH_2\text{—}S\text{—}S\text{—}CH_2C_6H_5$$

V

The Bunte salt method[8] was similarly attempted in the synthesis of VI and although several experiments were preformed at various *p*H values none of the desired disulfide was obtained.

$$C_6H_5COCH_2\text{—}S\text{—}SO_3Na + HSCH_2CO_2CH_3 \longrightarrow$$

$$C_6H_5COCH_2\text{—}S\text{—}S\text{—}CH_2CO_2CH_3$$

VI

The procedure which seemed most versatile for the synthesis of neutral disulfides involved the production of an alkylsulfenyl thiocyanate (VII) followed by displacement of thiocyanic acid from VII with a second mercaptan. Lecher[9] prepared several alkylaryl disulfides by this method but the only aliphatic thiol to be investigated was ethyl mercaptan.

$$RSH + (SCN)_2 \longrightarrow \underset{VII}{R\text{—}S\text{—}SCN} \xrightarrow{R'SH}$$

$$R\text{—}S\text{—}S\text{—}R' + HSCN$$

VIII

Ethylsulfenyl thiocyanate (VII. R = C_2H_5) was found[9] to be a volatile unstable substance which decomposed within fifteen to thirty minutes at 0°. In contrast, the arylsulfenyl thiocyanates were reasonably stable compounds and could be prepared with little difficulty. Ethylsulfenyl thiocyanate was found to decompose readily when treated with warm water or alcohols but afforded a 71% yield of 1-phenyl-1,2-dithiabutane (VIII. R = CH_2CH_3, R′ = C_6H_5) when allowed to react with thiophenol at 0°. The only recent application of this method involved the preparation of II in 32% yield.[7] The experimental conditions employed for this synthesis however were unsuitable for large amounts of neutral molecules and thus reaction conditions similar to those reported by Lecher have been employed. The method has been found to be quite versatile and to produce reasonable yields (50–70%) of pure unsymmetrical aliphatic disulfides (Table I). In general the sulfenyl thiocyanates have not been isolated and the yields reported are based on the amount of initial mercaptan used.

The disulfide V was initially synthesized in 58% yield by treatment of VII (R = $CH_2CO_2CH_3$) with benzyl mercaptan. The substance could be readily isolated by distillation and was characterized as a single pure substance, rather than an

(9) H. Lecher and M. Wittwer, *Ber.*, 55B, 1474 (1922).

equimolar mixture of two symmetrical disulfides, by the elemental analysis and physical properties. The infrared spectrum was of little aid on this point, other than to identify the functional groups present, since in the cases studied, the spectra of the unsymmetrical disulfides were the sum of their symmetrical counterparts. To establish further the identity of V, the mercaptans were allowed to react in reverse order. Thus treatment of VII ($R = C_6H_5CH_2$) with methyl mercaptoacetate afforded a 45.5% yield of V, identical in all respects to the previous preparation. In addition to providing increased confidence in the purity of V, the synthetic value of the sulfenyl thiocyanate method is considerably enhanced by the fact that either mode of combination of the two mercaptans is successful. Some discretion as to the choice of alkylsulfenyl thiocyanate is necessary, however, as the displacement of thiocyanic acid by the second mercaptan appears to be subject to some steric requirements. Thus the 60.8% yield of VIII [$R = CH_2CO_2CH_3$, $R' = C(CH_3)_3$]*via* VII ($R = CH_2CO_2CH_3$) was lowered to 22.9% when *t*-butylsulfenyl thiocyanate [VII $R = (CH_3)_3C$] was employed.

Preliminary experiments[10] involving the effect of solvent on the course of the reaction between benzylsulfenyl thiocyanate and methyl mercaptoacetate indicate dioxane, rather than ether, may also be employed for the displacement of thiocyanic acid from VII. For example VII($R = C_6H_5CH_2$), isolated by removal of the ether but not purified, was redissolved in dry dioxane. Addition of the theoretical amount, based on the amount of benzyl mercaptan employed, of methyl mercaptoacetate in dry dioxane, afforded a 42.9% yield of V. A similar experiment using methanol as the solvent resulted in the formation of benzyl disulfide and unchanged thiol. In all cases in which benzylsulfenyl thiocyanate was isolated the crude yield was 85–95%. An indication of the yield in the second step was obtained when a weighed portion of VII ($R = C_6H_5CH_2$), isolated without purification, was redissolved in ether and treated with an equivalent amount of methyl mercaptoacetate. A 71% yield of V, based on sulfenyl thiocyanate, resulted.

Another modification leading to more versatile reaction conditions was employed in the synthesis of VIII ($R = C_6H_5CH_2$, $R' = CHCO_2H$ / CH_2CO_2H). As thiols capable of zwitterion formation or possessing several polar functional groups are generally quite insoluble in relatively nonpolar solvents, it was of some interest to determine whether an ether insoluble mercaptan could be used in a two phase reaction with VII. Accordingly, solid α-mercaptosuccinic acid was added to an ether solution of VII ($R = C_6H_5CH_2$). The displacement reaction progressed in the usual fashion and afforded VIII ($R = C_6H_5CH_2$, $R' = CHCO_2H$ / CH_2CO_2H) in 51.5% yield. The application of this method to the synthesis of unsymmetrical peptides containing cystine will be reported separately.

The effect of temperature on the course of the overall reaction was also studied in several cases. The intermediate, benzylsulfenyl thiocyanate, decomposed rapidly above 0° and thus the preparation of VIII ($R = C_6H_5CH_2$, $R' = (CH_3)_3C$) was conducted at −80°. The yield of disulfide was increased from 62% to 69%. The yield of V was also increased (49% to 58%) by conducting the reaction at −15° rather than 0°; however, several experiments involving the preparation of V at −80° gave indications of incomplete reaction and resulted in somewhat lower yields (35–45%).

The physical properties of the disulfides prepared in this study are listed in Table I. With the exception of the two disulfides containing highly polar functional groups which were solids, the substances were readily distillable liquids. Unless subjected to temperatures above 170–200° the unsymmetrical disulfides showed no tendency to disproportionate and were unchanged after several months storage at room temperature. The single exception encountered thus far seems to be VIII ($R = C_6H_5CH_2$, $R' = CH_2CH_2OH$) which could be readily prepared and distilled but disproportionated after standing several hours at room temperature. As the purity of this material has not been verified by elemental analysis, the physical properties are not included in Table I.

Further extensions of this method of synthesis as well as the results of cleavage experiments of these and other disulfides will be reported in a separate communication.

EXPERIMENTAL[11]

α-Phenethyl mercaptan was prepared in 51.5% overall yield from α-phenethylbromide by the method of Siegel,[12] b.p. 75–77° at 5 mm.; reported,[12] 71–72° at 4 mm.

p-Nitrobenzyl mercaptan was prepared in 52.5% overall yield from *p*-nitrobenzyl chloride[13]; m.p. 51–52°; reported,[14] m.p. 52°.

All other mercaptans were obtained from Eastman Organic Chemicals and were recrystallized or distilled prior to use.

(10) The reactions of several alkylsulfenyl thiocyanates with various substrates will be reported in a separate communication.

(11) Boiling points and melting points are uncorrected. Elemental analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Micro-Tech Laboratories, Skokie, Ill.

(12) S. Siegel and A. F. Graefe, *J. Am. Chem. Soc.*, **75**, 4521 (1953).

(13) G. M. Bennett and W. A. Berry, *J. Chem. Soc.*, 1666 (1927).

(14) W. S. Hoffman and E. E. Reids, *J. Am. Chem. Soc.*, **45**, 1833 (1923).

Preparation of thiocyanogen in diethyl ether. The thiocyanogen solution was prepared as described by Wood[15] using a somewhat modified technique. To an ice cold solution of 70.0 g. (0.214 mole) of lead nitrate in 160 ml. of water was added a cold solution of 32.4 g. (0.4 mole) of sodium thiocyanate in 160 ml. of water. The fine precipitate of lead thiocyanate was washed with large volumes of ice water and thoroughly dried, in the dark, *in vacuo* over phosphorus pentoxide. The lead thiocyanate was powdered and, if necessary, redried over phosphorus pentoxide. A 45.0-g. (0.139 mole) sample of the lead thiocyanate was suspended in 150 ml. of anhydrous ether in a 1-l. three neck flask, equipped with a mechanical stirrer, drying tube, and stopper. The suspension was cooled to 5–10° and treated with a cold solution of 18.6 g. (0.116 mole) of bromine in 400 ml. of anhydrous ether. The bromine solution was added in small portions with rapid stirring. After each addition the bromine color was allowed to disappear before the next portion was added. After the bromine addition was complete, the suspended solids were allowed to settle and the completely colorless thiocyanogen solution was decanted. The cold thiocyanogen solution was used immediately, following the general procedure of Lecher[9] described below.

Preparation of the unsymmetrical disulfides. The ether solution of thiocyanogen was decanted directly into a 1-l. three neck flask fitted with a mechanical stirrer, dropping funnel, and drying tube. The solution was cooled to 5–10° or in some cases to lower temperatures, and 0.1 mole of mercaptan, in 200 ml. of dry ether, was added dropwise with stirring. The addition required about 2 hr. after which no odor of mercaptan remained. The second mercaptan, 0.1 mole in 100 ml. of anhydrous ether, was added rapidly to the cold solution containing the alkylsulfenyl thiocyanate. The addition required about 0.5 hr. after which the reaction mixture was stirred for another 0.5 hr. at 5–10° and 1 hr. at room temperature.

The ether solution was washed six to eight times or until colorless with water to remove the thiocyanic acid and dried over magnesium sulfate. The ether was removed *in vacuo* and the residual liquid, usually clear, was distilled using a 6-inch Vigreux column at 0.1 to 0.3 mm. Usually two distillations afforded analytically pure disulfide. The yields reported in Table I represent the amount of disulfide obtained having physical constants identical to the sample on which the analytical results were obtained. No attempt was made to redistill the foreruns which contained mainly unsymmetrical disulfide and whatever symmetrical disulfide was present. The yields, therefore, represent minimum values of pure disulfide obtainable by this method.

Preparation of 5-phenyl-3,4-dithiapentane-1,2-dicarboxylic acid (VIII. R = $C_6H_5CH_2$, R′ = $\begin{matrix}CHCO_2H\\|\\CH_2CO_2H\end{matrix}$). The desired disulfide was prepared by the method described above with the following modifications. To a cold etheral solution of benzylsulfenyl thiocyanate was added 15.0 g. (0.1 mole) of solid α-mercaptosuccinic acid. The acid was added in small portions over a period of 1 hr. with vigorous stirring. The clear solution was stirred an additional hour, washed with water and dried. Removal of the ether afforded 20.0 g. of a yellow solid which was recrystallized twice from an ethyl acetate–benzene mixture (1:4) to yield 14.0 g. (51.5%) of white crystals, m.p. 147–148°. A mixture melting point of the disulfide with a sample of α-mercaptosuccinic acid m.p. 147–148°, melted at 125–138°.

Preparation of methyl-5-phenyl-3,4-dithiapentanoate (V). A. *Using dioxane.* Thiocyanogen in ether was prepared in the usual manner from 18.7 g. (0.117 mole) of bromine and 45.0 g. (0.17 mole) of lead thiocyanate. The thiocyanogen solution was cooled to −80° and 9.92 g. (0.08 mole) of benzyl mercaptan in 100 ml. of dry ether was added in 1 hr. The solution was stirred 0.5 hr., washed ten times with 100-ml. portions of ice water and dried at 0°, over magnesium sulfate, for 1.5 hr. The ether was removed *in vacuo*, under nitrogen, at −8°. The crude liquid benzylsulfenyl thiocyanate which weighed 12.37 g. (85.5%, 0.068 mole) was redissolved in 100 ml. of dry dioxane at 0° and treated with 7.23 g. (0.068 mole) of methyl mercaptoacetate in 100 ml. of dry dioxane. The reaction mixture was stirred and allowed to warm to room temperature over a 2.5-hr. period. The dioxane was removed *in vacuo* and the residue dissolved in ether, washed with water and dried. Removal of the ether followed by distillation of the residue yielded 7.85 g. (52.0% based on benzylsulfenyl thiocyanate) of product, b.p. 120° at 0.2 mm., n_D^{25} 1.5783. The infrared spectra of the products obtained with and without isolation of benzylsulfenyl thiocyanate were identical.

B. *Using diethyl ether.* Following the procedure described in A, 9.3 g. (0.075 mole) of benzyl mercaptan afforded 12.8 g. (94.1%) of crude benzylsulfenyl thiocyanate when treated with thiocyanogen in ether at −80°. A 5.0-g. (0.028 mole) sample of the liquid sulfenyl thiocyanate was redissolved in ether and immediately added to 2.92 g. (0.028 mole) of methyl mercaptoacetate in 100 ml. of dry ether at −10°. After stirring 2.5 hr. the ether solution was worked up in the usual manner and distilled. The yield of II was 4.4 g. (70.05%), b.p. 115–116° at 0.15 mm, n_D^{25} 1.5785.

C. *Using methanol.* Using the method described in A, 9.92 g. (0.08 mole) of benzyl mercaptan in ether was converted to 12.8 g. (88.4%, 0.071 mole) of crude benzylsulfenyl thiocyanate. The intermediate was dissolved in dry methanol at 0° and treated with 7.49 g. (0.071 mole) of methyl mercaptoacetate in 100 ml. of cold dry methanol. After stirring 2.5 hr. the methanol was removed *in vacuo* and replaced with ether. The ether solution was washed with water, dried, and concentrated under vacuum. A 1.0-g. aliquot of the remaining residue was treated with 5 ml. of methanol and 0.01 mole of sodium methoxide. The solution was warmed 15 min. and treated with 2.18 g. (0.009 mole) of diphenylcarbamyl chloride. Upon cooling 0.65 g. of the *N,N*-diphenylthiocarbamate derivative of methyl mercaptoacetate was obtained, m.p. 116–117°.[16]

Anal. Calcd. for $C_{16}H_{15}O_3NS$: C, 63.76; H, 5.02. Found: C, 64.14; H, 5.23.

A mixture melting point with a sample of the derivative prepared from authentic methyl mercaptoacetate melted at 117°.

The remaining residue was crystallized from methanol and afforded 5.0 g. (28.5%) of benzyl disulfide m.p. 69–70°; reported[17] 71.5°. Although some of V may have been present the reaction mixture was not characterized further.

CHAPEL HILL, N. C.

(15) J. L. Wood, *Org. Reactions*, **3**, 240 (1946).

(16) We are indebted to Mr. Kenneth Shepard for the elemental analysis of this substance.

(17) D. F. Twiss, *J. Chem. Soc.*, 105, 36 (1914).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLII. Tetrahydroquinazoline Analogs of Tetrahydrofolic Acid. III. An Improved Synthesis of 5,8-Dideaza-5,6,7,8-tetrahydrofolic Acid

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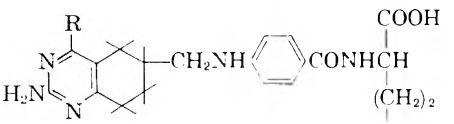
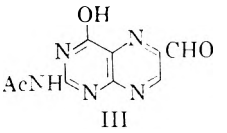
The conversion of 4-oxocyclohexanecarboxaldehyde dimethyl acetal (VIII) to 2-acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxaldehyde (XIV) provided the key intermediate for an improved synthesis of 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (I). The transformation of XIV to I was accomplished either by the direct reductive alkylation of *p*-aminobenzoyl-L-glutamic acid with XIV, followed by hydrolysis, or by the preparation of *p*-[(2-acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methylamino]benzoic acid (XVIII) from XIV, followed by the condensation of the appropriately blocked XVIII with diethyl L-glutamate and a final hydrolysis to give the crystalline and chromatographically homogeneous I.

An earlier paper in this series[2] described the synthesis of 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (I) and a later paper was concerned with approaches to the synthesis of 5,8-dideaza-5,6,7,8-tetrahydroaminopterin (II).[3] These approaches to the preparation of II were unsuccessful and a new synthetic scheme was devised for its preparation which, from a common intermediate, permitted an improved synthesis of I. The present manuscript describes this new preparation of I; it is anticipated that a later paper will describe the application of the synthetic scheme to the synthesis of II.



I. R = OH
II. R = NH_2

The key compound in the original synthesis of I was 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxylic acid (XI)[2]; the corresponding 2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid,[3] however, could not be converted to II. Sletzinger and co-workers[4] have reported an efficient synthesis of folic acid via the reductive alkylation of *p*-aminobenzoyl-L-glutamic acid (PABGA) with the pteridine aldehyde (III).



III

It seemed possible that analogous intermediates in the 5,8-dideaza-5,6,7,8-tetrahydroquinazoline series might lead to useful syntheses of both I and II. The preparation of the intermediates XIV and XV was accomplished; that of XIV and its conversion to I are described in this manuscript.

The reaction of a methanolic solution of butadiene (IV) with *N*,*N*-dibromobenzenesulfonamide was carried out as described by Petrov[5] and gave a 65% yield of 1-(bromomethyl)allyl methyl ether (V). The dehydrobromination of V with potassium hydroxide in diethylene glycol gave a 64% yield of 2-methoxybutadiene (VI), which was distilled from the reaction mixture as it formed. The Diels-Alder condensation of VI with acrolein was carried out in benzene solution at 160° for thirty minutes in a steel bomb[6] and gave a 75% yield of 4-methoxy-3-cyclohexene-1-carboxaldehyde (IX). This Diels-Alder reaction between an unsymmetrical diene and an unsymmetrical dienophile is known to give IX as the single isomer.[7] When relatively small amounts of the aldehyde IX were heated with dry methanol in the presence of a catalytic amount of ammonium chloride, an excellent yield of 4-oxocyclohexanecarboxaldehyde dimethyl acetal (VIII) resulted. The water produced in the formation of the acetal moiety was efficiently utilized in the hydrolysis of the enol ether of IX. In a larger scale preparation of VIII, the water formed in the initial reaction was insufficient to cleave the enol ether and it was necessary to add water deliberately after the acetal formation had proceeded.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* L. Goodman, L. O. Ross, M. O. Greene, J. Greenberg, and B. R. Baker, *J. Med. Pharm. Chem.*, in press.

(2) R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5779 (1958).

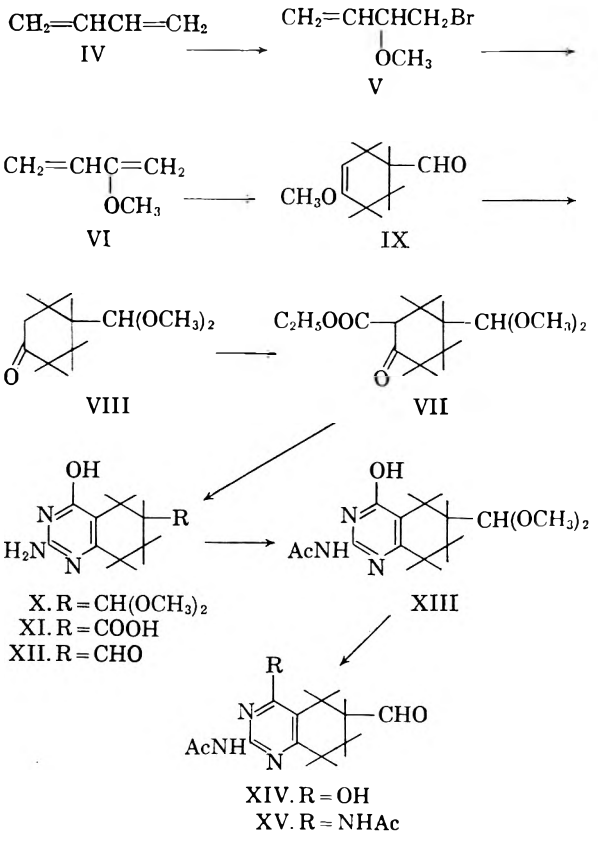
(3) J. DeGraw, L. Goodman, R. Koehler, and B. R. Baker, *J. Org. Chem.*, **24**, 1632 (1959).

(4) M. Sletzinger, D. Rheinhold, J. Grier, M. Beachem, and M. Tischler, *J. Am. Chem. Soc.*, **77**, 6365 (1955).

(5) A. Petrov, *J. Gen. Chem.* (*USSR*), **8**, 208 (1938); *Chem. Abstr.*, **32**, 5370 (1938).

(6) H. Fiesselmann, *Ber.*, **75B**, 881 (1942).

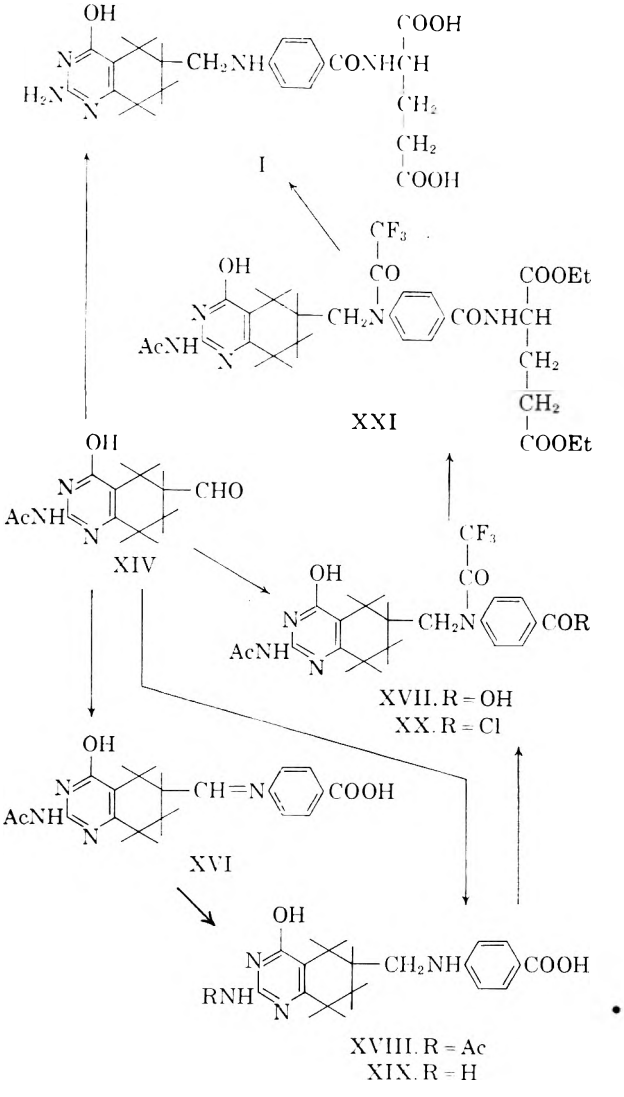
(7) H. L. Holmes, *Org. Reactions*, **4**, 63 (1948).



Carbethoxylation of the keto acetal VIII to give the β-keto ester VII was best accomplished with diethyl carbonate in ether solution using sodium hydride to form the anion of VIII. The yield was only 25%; low yields were noted by Hauser and Swamer[8] in their studies of the carbethoxylation of cyclohexanone. Efforts to improve the yield of VII by the use of ethyl chloroformate rather than ethyl carbonate or through the enamine of VIII were unsuccessful. The infrared spectrum of VII showed the presence of both the keto form and the chelated enol form of the β-keto ester.

Reaction of the crude keto ester VII with quanidine in methanolic sodium methoxide afforded the tetrahydroquinazoline acetal X as an easily purified solid. Treatment of X with acetic anhydride at 100° gave 2-acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxaldehyde dimethyl acetal (XIII) in good yield. The further reaction of XIII with 90% formic acid at room temperature[4] selectively hydrolyzed the acetal to generate the aldehyde function of XIV. A crystalline phenylhydrazone was prepared from XIV. The direct hydrolysis of the acetal X with dilute aqueous hydrochloric acid to the crystalline aldehyde XII was also carried out. A small-scale oxidation of XIV with aqueous hydrogen peroxide gave a mixture of the carboxylic acid XI and its N^2-acetyl derivative, as was shown by infrared spectra and paper chromatographic comparison with authentic materials. This experiment confirmed the orientation of the product IX of the Diels-Alder reaction,[7] as compound XI had been prepared unambiguously by another route.[2]

Attempts were made to alkylate reductively *p*-aminobenzoyl-L-glutamic acid (PABGA) with the acetylated aldehyde XIV using anhydrous formic acid or thiocresol as the reducing agent according to the procedures described by Sletzinger, *et al.*[4] Neither procedure was successful, which suggests that the aldehydes that can be employed as alkylating agents using these reagents must have carbonyl groups approximating the activity of aromatic aldehydes. The catalytic reductive alkylation of *p*-aminobenzoyl-L-glutamic acid with XIV using platinum oxide proceeded readily, however, and the product was hydrolyzed with dilute alkali to give the 5,8-dideazatetrahydrofolic acid I in 20% yield (from XIV) as a crystalline hydrate. Different samples of I recrystallized in different ways contained varying amounts of water of crystallization but all samples gave the same single spot when chromatographed on paper and



(8) F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).

materials of a given degree of hydration had unique and reproducible infrared spectra.

When the aldehyde XIV was heated in ethanol with *p*-aminobenzoic acid (PABA), a good yield of the anil XVI was formed. The anil XVI was catalytically reduced over palladium-on-charcoal at 60–65° and gave a 55% yield of the recrystallized 5,8-dideazapteroic acid XVIII. The direct reductive alkylation of *p*-aminobenzoic acid with XIV in 2-methoxyethanol over platinum oxide gave a 40% yield of XVIII. The hydrolysis of XVIII to the free 5,8-dideazatetrahydropteroic acid XIX was readily accomplished by heating with dilute aqueous base.

Treatment of XVIII with trifluoroacetic anhydride gave good yields of a solid which had an infrared spectrum in agreement with that of XVII but which was not further purified. Gentle treatment of XVII with thionyl chloride gave the acid chloride XX which, without purification, was allowed to react with diethyl glutamate to give the diester XXI. Saponification of the diester XVI was accompanied by loss of the *N*-acetyl and *N*-trifluoroacetyl groups and gave a 39% yield of I (based on XVII) collected in two crops as the hemihydrate and as the hydrate with 2.5 moles of water. These samples agreed well in physical properties with the material isolated from the direct reductive alkylation of *p*-aminobenzoyl-L-glutamic acid. An effort to condense XVIII with diethyl glutamate by means of the dicyclohexyl carbodiimide procedure was unsuccessful.

As 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (I), prepared from XIV, gave only one spot on paper chromatography[9]—in contrast to I prepared from 2-amino-6-chloromethyl-5,6,7,8-tetrahydro-4-hydroxyquinazoline,[2] which was not uniform on paper chromatography—the suspicion that the earlier preparation of I may not have been pure was confirmed. The pure I at 50 mγ/ml. gave 50% inhibition of growth of *S. faecalis* on a Flynn folic acid medium containing 3 mγ of folic acid; thus, the earlier preparation, which had resisted attempted purification, had a purity of 15–25%. It follows that the physical constants for I recorded in this paper should supersede the old values.

EXPERIMENTAL[9]

1-(Bromomethyl)allyl methyl ether (V). To a flask equipped with a stirrer, a Dry Ice condenser and a drying tube, was added 680 ml. of reagent methanol. The flask was cooled to −10° and 720 ml. (8.7 moles) of butadiene (dried by passing over Drierite) was condensed. Then 2800 ml. of methanol was added and, with good stirring, 640 g. (2.03 moles) of *N,N*-dibromobenzenesulfonamide (Arapahoe Chemical, Inc.) was added over a 2.5-hr. period while maintaining the temperature at −8 to −12°. The solution was allowed to warm to room temperature. After being stirred for an additional 3.5 hr., the mixture was poured into 8 l. of water. The aqueous mixture was extracted with four 1-l. portions of pentane, the extract dried over magnesium sulfate, filtered, and distilled, to give 434 g. (65%) of product, b.p. 71–88° (62 mm.); λ_{max}^{film} (μ) 3.27 7.05, 10.10, and 10.70 (CH of vinyl group), 6.05 (C=C), 9.02 (C—O—C). In an earlier run the product was distilled at atmospheric pressure, b.p. 140–142° (Petrov[5] gave b.p. 141–142° and yield of 54%).

2-Methoxybutadiene-1,4 (VI). To a hot (95–100°) solution of 42.0 g. (0.75 mole) of potassium hydroxide in 500 ml. of diethylene glycol in a flask equipped for distillation was added 79.0 g. (0.48 mole) of the bromo ether V over a period of 75 min. The temperature was slowly raised to 130° over a 2-hr. period and about 30 ml. of distillate was collected. Water (25 ml.) was added to the glycol solution and about 5 ml. of a steam distillate was collected. The combined distillate, which contained two layers, was separated and the aqueous phase discarded. The organic layer was dried over magnesium sulfate, leaving 30.5 g. of liquid which was distilled using a Vigreux column to give 25.5 g. (64%) of product, b.p. 74–76° (Petrov[6] used a different dehydrohalogenation technique and gave b.p. 74–74.5°); λ_{max}^{film} (μ) 3.30, 7.06, 10.13 and 10.75 (CH of vinyl group), 6.13 (C=C), 9.05 and 9.25 (C—O—C).

4-Methoxy-3-cyclohexene-1-carboxaldehyde (IX). A mixture of 9.5 g. (0.17 mole) of acrolein, 9.5 g. (0.11 mole) of 2-methoxybutadiene (VI), 29 ml. of benzene and 0.50 g. of hydroquinone was heated at 160° for 30 min. in a stainless steel bomb. After cooling to room temperature, the solution was transferred and distilled using a short Vigreux column to give 23.8 g. (75%) of IX, b.p. 80–85° (5 mm.) (Fiesselmann[6] reported a 75% yield, b.p. 94–95° (13 mm.)); λ_{max}^{film} (μ) 3.71 (aldehyde CH), 5.80 (C=O), 6.00 (C=C), 8.53 (C—O—C).

4-Oxocyclohexanecarboxaldehyde dimethyl acetal (VIII). To a solution of 9.90 g. (70.7 mmoles) of the aldehyde IX in 15 ml. of reagent methanol was added 0.20 g. of ammonium chloride. A vigorous, exothermic reaction resulted, after which the solution was heated at reflux for 1.5 hr. The solution was distilled from a short Vigreux column, yielding 10.25 g. (85%) of product, b.p. 92–96° (5 mm.). A portion of this disillate was redistilled for analysis, b.p. 79.5–80.0° (3 mm.); λ_{max}^{film} (μ) 5.80 (C=O), 8.85, 9.05, 9.30, 9.50 (C—O—C).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.36. Found: C, 62.9; H, 9.19.

When the preparation of VIII was carried out on a preparative scale, it was necessary to add water deliberately to complete the hydrolysis of the enol ether. To a mixture of 446 g. (3.18 moles) of IX and 13.0 g. of ammonium chloride was added 900 ml. of reagent methanol. After the exothermic reaction subsided, the solution was heated on the steam bath for 2.5 hr., then was cooled to 40–50° and 39 ml. (2.2 moles) of water was added. The solution was stirred for 1.5 hr. without application of heat and was evaporated at 55° (2 mm.), leaving a residue that was filtered to remove ammonium chloride. Distillation of the residue from a Claisen flask gave 360 g. (65.5%) of VIII, b.p. 96–108° (1 mm.), n_D^{21} 1.4653, whose infrared spectrum agreed well with the above analytical sample. A run using 249 g. of IX gave 228 g. (74%) of VIII, b.p. 90–108° (1 mm.), n_D^{25} 1.4610.

Ethyl 5-formyl-2-oxocyclohexanecarboxylate dimethyl acetal (VII). A mixture of sodium hydride (12 mmoles) (0.52 g.

(9) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus. Paper chromatography was done by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light. Generally, adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. These solvent systems were used: A,[10] *n*-butyl alcohol–acetic acid–water (5:2:3); B, *N,N*-dimethylformamide–water (6:4); C,[11] *n*-butyl alcohol–ethanol–12*N* ammonium hydroxide–water (4:1:1:4); D,[12] *n*-butyl alcohol–acetic acid–water (4:1:5); E,[13] benzene–methanol–water (2:6:1); F,[14] 5% aqueous disodium hydrogen phosphate (no organic phase).

of a 54% suspension in mineral oil), 1.75 ml. (15 mmoles) of diethyl carbonate and 5 ml. of ether was prepared and to it was added 1.0 g. (6 mmoles) of the keto acetal VIII. The mixture was heated at reflux for 6.5 hr. and poured into 15 ml. of ice water. The organic layer was separated and extracted with 5 ml. of chilled (0°) 5% aqueous sodium hydroxide. The extract was combined with the original aqueous layer, the *p*H of the resulting solution adjusted to 7 to 8 with glacial acetic acid, the solution saturated with sodium chloride, and extracted with three 10-ml. portions of ether. The ether was dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*, leaving 0.40 g. (28%) of VII which was suitable for use in the next step; $\lambda_{max\ (\mu)}^{hlm}$ 5.72 (ester C=O), 5.80 (ketone C=O), 6.03 (chelated carbonyl), 6.17 (C=C), 8.15 and 8.25 (ester C—O—C), 8.80, 9.15 and 9.45 (acetal C—O—C).

2-Amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxaldehyde dimethyl acetal (X). To a solution of 1.57 g. (29 mmoles) of sodium methoxide in 26 ml. of reagent methanol was added 1.35 g. (14 mmoles) of guanidine hydrochloride and 2.10 g. (8.6 mmoles on a pure basis, but actually of unknown purity) of keto ester VII. The solution was heated at reflux for 4 hr. and was evaporated to dryness *in vacuo*. Water (10 ml.) was added to dissolve the residue, the solution was extracted with 5 ml. of ether and the ether extract discarded. The aqueous layer was adjusted to *p*H 7–8 with glacial acetic acid, giving a gummy precipitate which was separated by decantation. Water (5 ml.) was added to the precipitate and the suspension was stirred until the precipitate solidified. The solid was separated by filtration, washed with water and air dried to give 0.90 g. (44%) of product, m.p. >290°. This was recrystallized from 30 ml. of methanol to give the analytical sample, m.p. >300°; $\lambda_{max\ (\mu)}^{Nujol}$ 2.98, 3.20 (OH, NH), 6.02 (NH_2, pyrimidine ring), 6.20 (pyrimidine ring), 8.80, 9.20, and 9.43 (C—O—C); $\lambda_{max\ (m\mu)}^{pH\ 1}$ 226 (ϵ 9060), 262 (ϵ 7080); $\lambda_{max\ (m\mu)}^{pH\ 7}$ 270 (ϵ 4850), 284 (shoulder, ϵ 4050); $\lambda_{max\ (m\mu)}^{pH\ 13}$ 230 (ϵ 8270), 276 (ϵ 6360). On paper chromatography[9] in solvents A and F, the compound moved as a single spot with R_{Ad} 1.29 and 1.68, respectively.

Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.2; H, 7.16; N, 17.6. Found: C, 55.0; H, 7.39; N, 17.4.

2-Amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxaldehyde (XII). The acetal X (0.300 g., 1.26 mmoles) was stirred for 1 hr. with 3 ml. of 0.5*M* hydrochloric acid on the steam bath. The solution was filtered and the filtrate was brought to *p*H 8 with saturated aqueous sodium bicarbonate. The solid was collected, washed, and dried, giving a material with m.p. >300°; $\lambda_{max\ (\mu)}^{KBr}$ 2.97 and 3.05 (NH, OH), 3.65 (aldehyde CH), 5.85 (C=O), 6.03–6.13 (NH_2, pyrimidine ring), 6.55 (pyrimidine ring, NH); $\lambda_{max\ (m\mu)}^{pH\ 1}$ 262 (ϵ 6950); $\lambda_{max\ (m\mu)}^{pH\ 7}$ 269 (ϵ 6850); $\lambda_{max\ (m\mu)}^{pH\ 13}$ 276 (ϵ 6050). On paper chromatography in solvent A, the compound moved as a single spot with R_{Ad} 1.14 and was easily distinguishable from X (R_{Ad} 1.29).

Anal. Calcd. for $C_9H_{11}N_3O_2 \cdot {}^3/_4H_2O$: C, 52.5; H, 6.18; N, 20.3. Found: C, 52.3, 52.5; H, 6.56, 6.35; N, 20.2, 20.4.

2-Acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxaldehyde dimethyl acetal (XIII). To 0.30 g. (1.26 mmoles) of the quinazoline acetal X was added 2 ml. of acetic anhydride and the mixture was heated on the steam bath for 10 min., complete solution resulting. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in 8 ml. of chloroform. The chloroform solution was washed with 5 ml. of saturated aqueous sodium bicarbonate and 5 ml. of water and was dried over magnesium sulfate. After filtration, the solution was evaporated *in vacuo*, leaving 0.29 g. (83%) of product which was recrystallized from benzene to give 0.17 g. (49%) of crystalline material collected in two crops, m.p. 187–191° and 191–193°. The analytical sample was obtained by a second recrystallization from benzene, m.p. 188.0–189.5°; $\lambda_{max\ (m\mu)}^{KBr}$ 2.95 and 3.15 (NH, OH), 6.05 (amide C=O and pyrimidine ring), 6.37 (pyrimidine ring and NH), 8.05 (NAc), 8.85, 9.25, 9.50 (C—O—C); $\lambda_{max\ (m\mu)}^{C_2H_5OH}$ 243 (ϵ 11,700), 286 (ϵ 8750). On paper chromatography in solvent E the compund gave a single spot with R_{Ad} 1.83.

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.5; H, 6.81; N, 14.9. Found: C, 56.1; H, 6.74; N, 14.7.

2-Acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxyaldehyde (XIV). To 20 ml. of 90% formic acid was added 11.3 g. (40.2 mmoles) of the acetamido acetal XIII and the solution was allowed to stand at room temperature for 2 hr. Ether (400 ml.) was added, the solution was chilled, and the crystals filtered to give 7.5 g. of solid. The filtrate was evaporated to dryness *in vacuo* and the residue was extracted with 15 ml. of hot toluene. Evaporation of the toluene extract *in vacuo* yielded 0.80 g. more of product. The combined solids (8.3 g.) were recrystallized from 40 ml. of acetone to give three crops of XIV, totaling 6.45 g. (68%), m.p. 203–204°, 202–208° and 203–205°. From another run an analytical sample was obtained, m.p. 208.5–211.0°; $\lambda_{max\ (\mu)}^{KBr}$ 2.95 and 3.16 (NH, OH), 3.57 and 3.72 (aldehyde CH), 5.81 (C=O), 6.03–6.10 (amide C=O and pyrimidine ring), 6.22 and 6.40 (NH and pyrimidine ring), 8.05 (NAc). On paper chromatography in solvents D and E the compound moved as a single spot with R_{Ad} 1.46 and 1.32, respectively.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.2; H, 5.57; N, 17.9. Found: C, 56.1; H, 5.95; N, 17.9.

By gentle heating, a solution of 0.200 g. (0.85 mmole) of the aldehyde XIV was dissolved in 5 ml. of 95% ethanol and to the solution was added 0.15 ml. (1.53 mmoles) of phenylhydrazine and 1 drop of glacial acetic acid. The solution was warmed for 15 min. at 50–60°, centrifuged warm to isolate the precipitate, the crystals washed with 5 ml. of 95% ethanol, and dried to give 0.17 g. (64%) of the phenylhydrazone of XIV. This was recrystallized with large losses from aqueous 2-methoxyethanol to give yellow crystals, m.p. 207–212° (the melting point was strongly dependent on the rate of heating); $\lambda_{max\ (\mu)}^{KBr}$ 2.87 and 3.05 (NH, OH), 6.02 (amide C=O and pyrimidine ring), 6.25 (pyrimidine ring), 6.35 (NH), 7.96–8.04 (NAc), 13.32 and 14.40 (monosubstituted phenyl); $\lambda_{max\ (m\mu)}^{Methyl\ cellosolve}$ 243 (ϵ 15,000), 253 (ϵ 13,600), 281 (ϵ 24,400). On paper chromatography in solvents A and E, the product moved as a single spot with R_{Ad} 1.60 and 1.66, respectively.

Anal. Calcd. for $C_{17}H_{19}N_6O_2$: C, 62.8; H, 5.89. Found: C, 62.2; H, 5.92.

p-[(2-Acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methyleneamino]benzoic acid (XVI). A solution of 0.40 g. (1.7 mmoles) of the *N*-acetyl aldehyde XIV, 0.24 g. (1.7 mmoles) of *p*-aminobenzoic acid, and 25 ml. of absolute ethanol was heated to boiling under a nitrogen atmosphere and the solvent slowly distilled until 18 ml. of distillate had been collected. The remaining solution was chilled and the solid filtered and washed with ethanol; yield, 0.43 g. (72%) of yellow solid. A portion (0.33 g.) of this was extracted with 20 ml. of hot 2-methoxyethanol, the insoluble portion separated by centrifugation, dissolved in 10 ml. of hot *N,N*-dimethylformamide, and the solution diluted with 1.5 ml. of water and chilled. The crystalline solid was filtered, washed with 2 ml. of *N,N*-dimethylformamide and with 10 ml. of ethanol, and dried to yield 0.10 g. (22%), decomposing in the range 200–240°; $\lambda_{max\ (\mu)}^{KBr}$ 2.95–3.20 (OH, NH), 2.90–4.05 (OH of COOH), 5.95–6.10 (C=O of carboxyl; amide C=O; and C=N), 6.25 (pyrimidine ring and NH), 7.85–8.15 (NAc and COOH), 11.90 (disubstituted phenyl), 12.85 (pyrimidine ring); there was no absorption at 10.5 μ characteristic of *p*-aminobenzoic acid; $\lambda_{max\ (m\mu)}^{Methyl\ cellosolve}$ 243 (ϵ 13,800), 318 (ϵ 22,900).

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: C, 61.0; H, 5.12; N, 15.8. Found: C, 60.6; H, 5.37; N, 15.0.

p-[(2-Acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methylamino]benzoic acid (XVIII). *A. From the anil* XV. A solution of 4.0 g. (17.2 mmoles) of the *N*-acetyl aldehyde XIV, 2.36 g. (17.2 mmoles) of *p*-aminobenzoic acid and 40 ml. of absolute ethanol under nitrogen was heated at reflux for 3 hr. and was cooled to room tempera-

ture. After standing 30 min., the solid was filtered, washed with absolute ethanol and ether, and dried to give 5.8 g. (97%) of the crude anil XVI.

A vigorously stirred mixture of this crude anil, 0.58 g. of 5% palladium-on-charcoal, and 60 ml. of 2-methoxyethanol was shaken with hydrogen at 60–65° and atmospheric pressure. After 8 hr., 0.85 molar equivalent of hydrogen was absorbed and the warm mixture was filtered. The mixture of product and catalyst was suspended in 50 ml. of water and 6*M* ammonium hydroxide was added to adjust the *p*H to 9–10. The suspension was filtered twice through Celite and the vigorously stirred filtrate was adjusted to *p*H 4–5 with 6*M* hydrochloric acid. The precipitated solid was collected, washed with water, absolute ethanol and ether, and dried, leaving 4.2 g. (72%) of product. The crude solid was dissolved in 20 ml. of boiling *N*,*N*-dimethylformamide, the solution filtered, and 5 ml. of water added to the filtrate. After chilling, 2.95 g. (46%) of material was collected, m.p. 279–281°, and the mother liquors yielded a second crop of 0.15 g., giving a total yield from XIV of 49.6%. From a previous run an analytical sample was obtained, m.p. 276–277°; $\lambda_{max\ (\mu)}^{KBr}$ 2.95 and 3.12 (NH, OH), 3.78–4.05 (OH of COOH), 5.93–6.05 (C=O of carboxyl and acetyl), 6.20 (phenyl ring, pyrimidine ring and NH), 7.97–8.05 (NAc), 11.90 (disubstituted benzene), 12.90 (pyrimidine ring); $\lambda_{max\ (m\mu)}^{Methyl\ cellosolve}$ 226 (ε 15,200), 242 (ε 12,500), 252 (ε 10,500), 302 (ε 32,100). The product moved as a single spot in solvents B and C with R_{Ad} 1.25 and 0.43, respectively.

Anal. Calcd. for $C_{18}H_{20}N_4O_4.{}^1/_2H_2O$: C, 59.1; H, 5.71; N, 15.4. Found: C, 58.7, 59.0; H, 5.51, 5.39; N, 15.4.

B. From the aldehyde (XIV). A stirred mixture of 0.50 g. (2.1 mmoles) of aldehyde XIV, 0.30 g. (2.1 mmoles) of *p*-aminobenzoic acid, 0.05 g. of platinum oxide, and 10 ml. of 2-methoxyethanol was stirred with hydrogen at 30° and atmospheric pressure for 4 hr., 1 mole-equivalent of hydrogen being absorbed. The suspension was filtered and the product separated from the catalyst by extraction with 5 ml. of boiling *N*,*N*-dimethylformamide. Water (1 ml.) was added to the solution and, on chilling, 0.23 g. of product separated, with an infrared spectrum identical with that of the analytical sample of XVIII, described above. From the mother liquors was recovered a second crop of product, 0.07 g., giving a total yield of 40%.

p-[(5,6,7,8-Tetrahydro-4-hydroxy-6-quinazolinyl)methylamino]benzoic acid (XIX). A solution of 0.50 g. (1.40 mmoles) of the *N*-acetyl acid XVIII in 5.0 ml. of 1*M* aqueous sodium hydroxide was heated on the steam bath for 30 min. The solution was adjusted to *p*H 5 with 6*M* hydrochloric acid, filtered, and the precipitate washed with water and dried to give 0.39 g. (89%) of solid which did not melt at 300°. A portion of this (0.25 g.) was stirred with warm (40°) concentrated hydrochloric acid; the insoluble solid was collected and washed with water. The solid was dissolved in 5 ml. of 1*M* aqueous sodium hydroxide and precipitated by adjusting the *p*H to 4–5 with 6*M* hydrochloric acid. The purified solid was collected, washed with water and dried to give 0.15 g. (50%) of product, m.p. >300°; $\lambda_{max\ (\mu)}^{Nujol}$ 3.01 and 3.17 (NH), 3.66–3.90 (OH of COOH), 5.92 (C=O), 6.19 (pyrimidine and phenyl rings), 6.50 (pyrimidine ring), 11.96 (disubstituted phenyl), 12.91 (pyrimidine ring); lack of absorption near 8.0 μ indicated the loss of the N-acetyl; $\lambda_{max\ (m\mu)}^{pH\ 1}$ 226 (ε 21,200), 268 (ε 9800), 307 (ε 8640); $\lambda_{max\ (m\mu)}^{pH\ 13}$ 281 (ε 24,000). On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 0.22.

Anal. Calcd. for $C_{16}H_{18}N_4O_3.H_2O$: C, 57.8; H, 6.02; N, 16.9. Found: C, 57.6; H, 5.88; N, 16.6, 16.7.

p-{N-[(2-Acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methyl]-2,2,2-trifluoroacetamido}benzoic acid (XVII). A mixture of 2.0 g. (5.6 mmoles) of *N*-acetyl acid XVIII and 20 ml. of trifluoroacetic anhydride was heated under reflux for 35 min. The solution was evaporated to dryness *in vacuo*, the residue was stirred vigorously with 25 ml. of ether, filtered, and washed with ether. The solid was suspended in 20 ml. of water, stirred vigorously for 2 hr., filtered, washed with water, and dried to give 2.07 g. (82%) of solid which was not purified further and was not analytically pure, although it moved as a single spot in solvent E with R_{Ad} 1.67 and was free of XVIII. In the infrared it had $\lambda_{max\ (\mu)}^{Nujol}$ 3.12 (NH), 3.75–3.90 (OH of COOH), 5.81–5.88 (carboxyl C=O and CF_3CO), 6.0 (CH_3CO), 6.20 (phenyl and pyrimidine rings), 8.05 (NAc), 8.29 and 8.61 (CF_3), 11.96 (disubstituted benzene).

Anal. Calcd. for $C_{20}H_{16}N_4O_5F_3$: F, 12.6. Found: F, 13.4.

Diethyl N-{p-[N-[(2-acetamido-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methyl]-2,2,2-trifluoroacetamido}benzoyl}glutamate (XXI). A mixture of 0.45 g. (1 mmole) of the *N*-trifluoroacetyl acid XVII and 4.5 ml. of thionyl chloride was heated under reflux for 20 min., giving a light yellow solution which was evaporated *in vacuo*. To the residue was added 5 ml. of dry 1,2-dichloroethane and the solution was again evaporated *in vacuo*. The solution in 1,2-dichloroethane and the evaporation were repeated twice more, giving a residue of the acid chloride XX.

A solution of 1.0 g. (4.2 mmoles) of diethyl L-glutamate hydrochloride[15] (m.p. 107.5–108.5°) in 10 ml. of chloroform was washed with 4.0 ml. of 10% aqueous potassium carbonate. The carbonate extract was washed with 5 ml. of chloroform which was combined with the original chloroform solution and the combined solutions dried over potassium carbonate. After filtration, the solution was evaporated *in vacuo*, leaving a residue of 0.67 g. (3.3 mmoles) of diethyl glutamate.

The diethyl glutamate, dissolved in 3 ml. of dry methylene chloride, was added to a solution of the acid chloride XX in 5 ml. of methylene chloride; the resulting solution was heated under reflux for 2 hr. protected from moisture, then allowed to stand overnight. The solution was washed with 5 ml. of 1% aqueous potassium carbonate and dried over potassium carbonate. After filtration, the solution was evaporated *in vacuo* to give a gum which solidified when it was stirred with water. The solid was filtered, washed with water, and dried to give 0.58 g. (91%) of crude product; $\lambda_{max(\mu)}^{Nujol}$ 3.15 (NH), 5.74 (ester C=O), 5.85 (C=O of CF_3CON), 5.98–6.01 (amide C=O and pyrimidine ring), 6.21 (phenyl and pyrimidine rings), 8.00 (NAc), 8.28 (ester C—O—C and CF_3), 8.64 (CF_3), 11.60 (disubstituted phenyl).

N-{p-[(2-Amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinyl)methylamino]benzoyl}glutamic acid (5,8-dideaza-5,6,7,8-tetrahydrofolic acid) (I). A. *From the diester* XXI. A stirred mixture of 0.57 g. (0.9 mmole) of the diester XXI (*cf.* above) and 40 ml. of 0.25*M* aqueous sodium hydroxide was heated on the steam-bath for 30 min., then adjusted to *p*H 3–4 with 1*M* hydrochloric acid. The precipitate was collected, washed with water and dried to give 0.29 g. (74%) of product. A portion of this (0.28 g.) was dissolved in 3 ml. of hot *N*,*N*-dimethylformamide and the solution, on chilling, gave 0.080 g. (20.4% calculated as the hemihydrate) of white crystals which darkened near 220°, softened near 240°, and vigorously decomposed above 260°; $\lambda_{max\ (\mu)}^{Nujol}$ 2.98 and 3.19 (NH), 3.80–3.92 (OH of COOH), 5.81 (carboxyl C=O), 5.95 (amide C=O), 6.19 (pyrimidine and phenyl rings), 6.56 (amide NH), 11.89 (disubstituted phenyl), 13.03 (pyrimidine ring); $\lambda_{max\ (m\mu)}^{pH}$ 224 (ε 20,100), 265 (ε 10,300); $\lambda_{max\ (m\mu)}^{pH\ 7}$ 290 (ε 20,100); $\lambda_{max\ (m\mu)}^{pH\ 13}$ 284 (ε 21,000). The product moved as a single spot in solvent A with R_{Ad} 1.17.

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Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot {}^1/_2H_2O$: C, 55.8; H, 5.79. Found: C, 55.9; H, 5.90.

The mother liquors from the separation of the above material (0.080 g.) were diluted with 2.5 ml. of water and chilled, giving 0.100 g. (21.3% calculated as the hydrate with 2.5 moles of water), of crystalline solid which showed the same melting behavior as the hemihydrate (*cf.* above); λ_{max}^{Nujol} (μ) 2.98 (NH), 5.84–5.92 (carboxyl and amide C=O), 6.21 (pyrimidine and phenyl rings), 6.60 (amide NH), 11.95 (disubstituted phenyl), 13.10 (pyrimidine ring). The paper chromatographic behavior of the sample was identical with that of the hemihydrate.

Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot 2{}^1/_2H_2O$: C, 51.6; H, 6.19; N, 14.3. Found: C, 51.7, 51.7; H, 5.89, 6.11; N, 14.2.

B. From the N-acetyl aldehyde XIV. A suspension of 0.47 g. (2.00 mmoles) of aldehyde XIV, 0.53 g. (2.00 mmoles) of *p*-aminobenzoyl-L-glutamic acid, 0.050 g. of platinum oxide, and 10 ml. of 2-methoxyethanol was vigorously stirred with hydrogen at 35° and atmospheric pressure for 3.5 hr., when 1 molar equivalent of hydrogen had been absorbed. The mixture was filtered, the filtrate was concentrated *in vacuo* to 3 ml., water (2 ml.) was added, and the solution was chilled. A black gum deposited and was removed by decantation of the supernatent liquid which was evaporated *in vacuo*, leaving 0.90 g. (93%) of residue. The residue was dissolved in 40 ml. of 0.1*M* aqueous sodium hydroxide, the solution heated on the steam bath for 30 min., filtered and the filtrate adjusted to *p*H 3–4 with 1*M* hydrochloric acid. The precipitate (0.60 g.) was stirred with 4.0 ml. of hot (100°) *N,N*-dimethylformamide and the insoluble, white crystalline material removed by filtration to give 0.033 g. (3.65% calculated as the hemihydrate) of solid which had the same melting behavior, infrared spectrum and paper chromatographic behavior as the hemihydrate isolated from procedure A (*cf.* above).

Anal. Calcd. for $C_{21}H_{25}N_5O_5 \cdot {}^1/_2H_2O$: C, 55.8; H, 5.79; N, 15.5. Found: C, 56.0, 55.9; H, 5.80, 5.83; N, 15.0, 15.2.

The *N,N*-dimethylformamide solution, after removal of the hemihydrate, was diluted with 4 ml. of water and chilled. The crystalline precipitate was washed with *N,N*-dimethylformamide, then water; yield 0.156 g. (16.5% calculated as the sesquihydrate) of solid whose melting and chromatographic behaviors were identical with those of the hemihydrate and whose infrared spectrum was almost identical with that of the compound containing 2.5 moles of water isolated from procedure A (*cf.* above).

Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot 1{}^1/_2H_2O$: C, 53.6; H, 5.99; N, 14.9. Found: C, 53.8, 53.8; H, 6.21, 6.29; N, 14.7, 14.8.

Acid hydrolysis of I. A solution of 5 mg. of the hemihydrate of I (prepared by procedure A) in 5 ml. of 6*M* hydrochloric acid was heated at 100° for 1 hr. and was evaporated to dryness *in vacuo*. Water (1 ml.) and 2 drops of 10% aqueous sodium hydroxide were added to the residue and the *p*H was adjusted to 5 with 1*M* hydrochloric acid. The precipitate was separated by centrifugation and the supernatent liquid was removed. Both the solid (3.5 mg.) and the supernatent liquid were subjected to paper chromatography in solvent A. The solution showed the presence of glutamic acid (R_f 0.30) and the solid showed two spots at R_f 0.65 and 0.80 which lined up exactly with the spots from the product of a similar acid hydrolysis of the *N*-acetylpteroic acid XVIII.

Acknowledgment. The authors are indebted to Dr. Peter Lim for interpretation of the infrared spectra and to his staff for the paper chromatography. They also wish to thank Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates and Dr. J. Greenberg for the microbiological assays.

MENLO PARK, CALIF.

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

Condensation of Isocyanates with Reissert Compounds; Synthesis of an Analog of Lidocaine

LEE R. WALTERS, EUGENE G. PODREBARAC, AND WILLIAM E. McEWEN

Received July 8, 1960

O-Benzoyl-*N*-phenylisoquinaldamide and *O*-benzoyl-*N*-(α-naphthyl)isoquinaldamide were prepared by the reaction of phenyl and 1-naphthyl isocyanate, respectively, with the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile. Hydrolysis of the *O*-benzoyl derivatives gave *N*-phenylisoquinaldamide and *N*-(α-naphthyl)isoquinaldamide, respectively, plus benzoic acid. There was no analogous reaction between the isocyanates and the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile.

Catalytic hydrogenation of *N*-phenylisoquinaldamide gave the tetrahydro derivative, and treatment of the latter compound with ethyl iodide afforded *N*-phenyl-2-ethyl-1,2,3,4-tetrahydroisoquinaldamide, an analog of the local anesthetic Lidocaine.

Although Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II), are mainly noted for their ability to form aldehydes on acid-catalyzed hydrolysis, increased attention in recent years has been directed toward the use of such compounds in the synthesis of diverse quinoline and isoquinoline derivatives.[1-11] The present communication describes an extension of the latter area of work, one leading to the production of the *O*-acyl derivatives

(1) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(2) R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(3) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

(4) F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 3773 (1957).

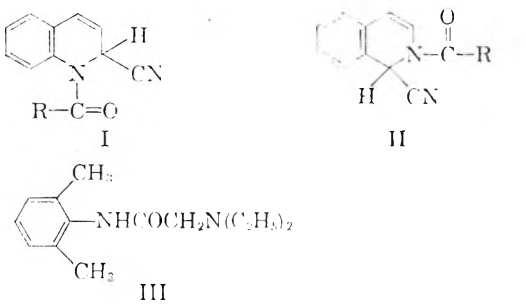
(5) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

(6) F. D. Popp and W. E. McEwen. *J. Am. Chem. Soc.*, **80**, 1181 (1958).

(7) N. C. Rose and W. E. McEwen, *J. Org. Chem.*, **23**, 337 (1958).

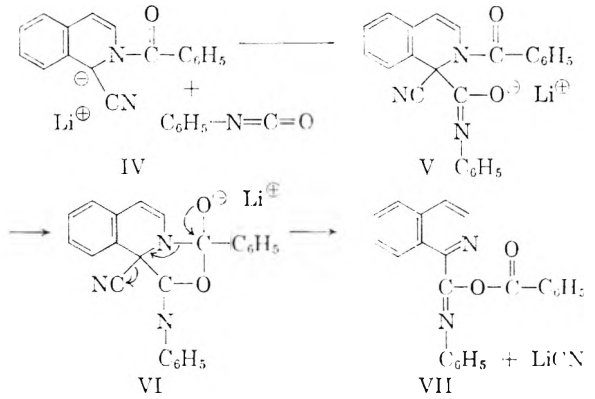
(8) N. C. Rose, L. R. Walters, and W. E. McEwen, *J. Org. Chem.*, **23**, 341 (1958).

of *N*-substituted isoquinaldamides. One such condensation product has been converted by a series of three reactions into an analog of Lidocaine (III), a prominent local anesthetic.



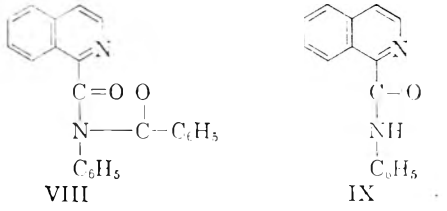
I II III

The reaction of the lithium salt (IV) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) with phenyl isocyanate to give *O*-benzoyl-*N*-phenylisoquinaldamide (VII) plus lithium cyanide will be taken as the basis for a discussion of the condensation reactions. There can be little doubt that the mechanism of the reaction involves an initial nucleophilic addition of the anion of the Reissert compound to the carbonyl carbon atom of phenyl isocyanate to form V, which then gives the cyclic intermediate VI. Elimination of lithium cyanide (see curved arrows) affords VII, and, in common with other similar reactions of Reissert compounds, the gain in resonance energy accompanying the elimination-rearrangement step provides an important driving force for the reaction.



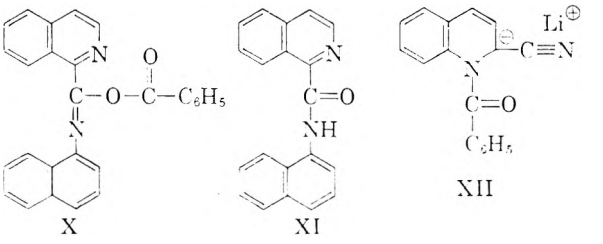
IV V VI VII

The structure *O*-benzoyl-*N*-phenylisoquinaldamide (VII) rather than *N*-benzoyl-*N*-phenylisoquinaldamide (VIII) was assigned to the final condensation-rearrangement product on the basis of the infrared spectrum of the product, which had absorption peaks at 1690 and 1600 cm.$^{-1}$ If VIII had been formed, the infrared absorption spectrum should have contained peaks in the regions 1790–1720 and 1710–1670 cm.$^{-1}$ [12] It should also be noted that hydrolysis of the condensation product gave *N*-phenylisoquinaldamide (IX) and benzoic acid as the sole products. That the hydrolysis product was IX was established beyond question by its unequivocal synthesis; an authentic sample of the compound was prepared by the reaction of isoquinaldoyl chloride with aniline.



VIII IX

O-Benzoyl-*N*-(α-naphthyl)isoquinaldamide (X) was obtained by the condensation of IV with α-naphthyl isocyanate. Hydrolysis of X afforded *N*-(α-naphthyl)isoquinaldamide (XI) and benzoic acid. However, no condensation product was obtained when IV was treated with *p*-tolyl isocyanate, and, furthermore, the lithium salt, XII, of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) did not give condensation products in attempted reactions with phenyl isocyanate and α-naphthyl isocyanate.



X XI XII

As yet, the electronic and steric influences on the course of the condensation-rearrangement reactions have not been clarified completely. However, it appears that in the case of the anion of the lithium salt, XII, the diffusion of the negative charge by resonance decreases the nucleophilic character of the 2-position of the quinoline ring to such an extent that condensation with the isocyanates does not take place.[13] Even in the case of the anion of the lithium salt, IV, the nucleophilicity of the carbon atom at the 1-position of the isoquinoline ring appears to be very nearly the minimum value possible for a successful condensation reaction, inasmuch as even a relatively small

(9) R. F. Collins and T. Henshall, *J. Am. Chem. Soc.*, 80, 159 (1958).

(10) J. W. Davis, Jr., *J. Org. Chem.*, 24, 1691 (1959).

(11) J. W. Davis, Jr., *J. Org. Chem.*, 25, 376 (1960).

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, p. 190.

(13) In the anion of XII the negative charge is shared mainly by the nitrogen atom of the cyano group and by the carbon atoms in the 2 and 4 positions of the quinoline ring. These structures having a formal negative charge on carbon carry double the weight of the structures in which the negative charge appears on carbons 5, 7, and 8a of the quinoline ring because of the presence of an intact benzene ring in the former, but not the latter structures. In the anion of IV, on the other hand, the negative charge is shared mainly by the nitrogen atom of the cyano group and the carbon atom in the 1-position of the isoquinoline ring. Thus, the negative charge density is greater at the 1-carbon of the anion of IV than at the 2-carbon of the anion of XII.

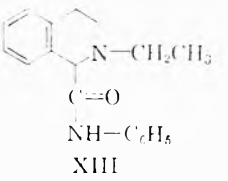
decrease in the electrophilicity of the carbonyl carbon atom of phenyl isocyanate, caused by the presence of a mildly electron-repelling methyl group in the para position of the benzene ring, causes the reaction to be inhibited.

All of the condensation reactions were carried out in ether-dioxane solution at a temperature not exceeding 30°, with but one exception to be mentioned later. The lithium salt of the Reissert compound was first prepared by a metalation reaction with phenyllithium. Following this, the isocyanate was added to the organometallic reagent. The lithium salt of each Reissert compound possesses a deep red color in ether-dioxane solution, and this color disappears as the condensation reaction with the isocyanate progresses. It is noteworthy that in those cases in which both the nucleophilicity of the Reissert anion and the electrophilicity of the isocyanate are relatively great, as evidenced by theoretical considerations, rapid discharge of the red color of the anion of the Reissert compound, and isolation of a high yield of the *O*-benzoylamide, the final reaction mixture, before the hydrolysis step, was nearly colorless. In the case of the attempted condensation of IV with *p*-tolyl isocyanate, the bright red color remained unchanged throughout the entire reaction period and, after the hydrolysis step, II (R = C_6H_5) was recovered in 81% yield. The attempts to effect condensation of XII with phenyl and α-naphthyl isocyanate gave orange reaction mixtures which, upon hydrolysis, afforded only intractable materials.

The above mentioned exception to the usual reaction conditions was in one of the attempted condensation reactions between XII and phenyl isocyanate. In this case, an attempt was made to carry out the reaction in refluxing dioxane subsequent to the initial formation of the lithium salt and addition of the isocyanate at 0°, but the increased reaction temperature proved to have no beneficial effect.

The introduction of Lidocaine (III) into the field of medicinal chemistry as a local anesthetic agent by Löfgren[14] in 1948 marked a departure from the benzoate ester type of structure commonly associated with such agents. Lidocaine (III), which has an aminoacyl amide structure, was found to be about two and one-half times as active as procaine.

On the basis of the success of Lidocaine as a local anesthetic, an attempt was made to determine the effect of the incorporation of the basic side chain into a ring system. The compound considered for synthesis was *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII), wherein the nitrogen and one ethyl radical of the tertiary amino group form a part of the isoquinoline ring system. The analogy between the two compounds is readily apparent in a comparison of the structural formulas.



XIII

N-Phenylisoquinaldamide (IX), after conversion to the hydrochloride, was successfully reduced to *N*-phenyltetrahydroisoquinaldamide in 84% yield in a Parr low pressure hydrogenator at 52 p.s.i. gauge.

An initial attempt to convert *N*-phenyltetrahydroisoquinaldamide into *N*-phenyltetrahydroisoquinaldamide ethiodide by refluxing with ethyl iodide failed. However, when a solution of N-phenyltetrahydroisoquinaldamide and ethyl iodide was heated in a Parr bomb for five hours at 135°, there was obtained, after treatment with base, *N* - phenyl - 2 - ethyltetrahydroisoquinaldamide (XIII). Use of benzene as solvent resulted in a 55% yield; use of the polar solvent ethanol gave an 88% yield based on unrecovered starting material.

N-Phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride was formed in quantitative yield by passing a stream of anhydrous hydrogen chloride gas through a solution of *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII) in anhydrous ethanol.

Pharmacological testing. The pattern of activity suggests that *N*-phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride may be a weak central nervous system depressant. This compound produced clonic convulsions in the mice at 150 mg./kg. The compound, while not exhibiting significantly strong effect in the mouse behavior test (i.p. dosing), was somewhat unusual in that the toxicity was much less than that commonly associated with isoquinoline compounds.[15]

EXPERIMENTAL[16]

1-Benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5). This compound was prepared by the method of Rupe, Paltzer, and Engel.[17] Recrystallization from ethanol yielded light yellow crystals, melting point 151–153° (reported,[17] m.p. 154–155°).

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5). This compound was prepared by the method of Padbury and Lindwall.[18] Recrystallization from ethanol yielded colorless crystals, melting point 124–127° (reported,[18] m.p. 125–126°).

(14) N. Löfgren, *Studies on Local Anesthetics. Xylocaine, A New Synthetic Drug*, Ivar Haeggströms, Stockholm, 1948.

(15) We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the testing of this compound.

(16) All melting points are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(17) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

(18) J. J. Padbury and J. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

Phenyllithium. Freshly prepared phenyllithium, made by the method of Gilman,[19] was used for each experiment. The lithium bromide formed during the reaction was not removed.

O-Benzoyl-N-phenylisoquinaldamide (VII). To a solution of 10.4 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) in 150 ml. of anhydrous ether and 75 ml. of anhydrous dioxane maintained at −10° in an atmosphere of pure nitrogen was added with mechanical stirring an ether solution of 0.04 mole of freshly prepared phenyllithium. To the resultant red solution was added dropwise with stirring a solution of 4.7 g. (0.04 mole) of phenyl isocyanate in 25 ml. of anhydrous ether. The mixture was stirred for an hour at −10°, then warmed to room temperature and stirred for an additional 8 hr., at the end of which time it was cream colored.[20] Sufficient ether was added to increase the total volume of the mixture to 500 ml., and 12 ml. of water was added. This caused a solid to precipitate. The solid material was collected by filtration, and, when dried, it amounted to 8.82 g. (63.4%) of crude VII, m.p. 170–190°. Several recrystallizations from acetone-water gave colorless, crystalline material of m.p. 203.2–205.5°.

Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.40; H, 4.56; N, 7.95. Found: C, 78.12; H, 4.84; N, 7.84.

The yield of VII could be raised to 96% by the use of a twofold excess of the lithium salt, IV, of 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Hydrolysis of O-benzoyl-N-phenylisoquinaldamide (VII). A solution of 3.0 g. of VII in 45 ml. of ethanol was added to a solution of 3.0 g. of potassium hydroxide, and the resulting mixture was refluxed for 7 hr. Some of the ethanol was removed by distillation *in vacuo*, and a solid precipitated from the cooled residue. This was collected by filtration, washed with water, and dried to give 1.77 g. (51%) of crude *N*-phenylisoquinaldamide (IX), m.p. 105–118°. An additional 0.89 g. (26%) of the same compound could be obtained by further concentration of the mother liquor. Several recrystallizations from ethanol gave colorless, crystalline material of m.p. 119–121°.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.43; H, 4.87; N, 11.23. Found: C, 77.66; H, 4.94; N, 11.30.

Benzoic acid was obtained by acidification of the alkaline filtrate, from which the last traces of organic solvents and solids had been removed.

N-Phenylisoquinaldamide (IX). To a solution of 0.5 g. of isoquinaldic acid in 30 ml. of anhydrous benzene was added a solution of 1.5 ml. of thionyl chloride in 10 ml. of benzene. The mixture was refluxed until evolution of hydrogen chloride ceased. The bright red solution was cooled to room temperature, and to it was added a solution of 1 ml. of aniline in 10 ml. of benzene. A colorless solid which precipitated was collected by filtration, washed with water, dried, and recrystallized from ethanol. There was obtained colorless crystals of *N*-phenylisoquinaldamide (IX), m.p. 119–121°, also in admixture with the sample obtained by hydrolysis of VII. The infrared spectra of the two samples, taken in chloroform solution, were identical.

O-Benzoyl-N-(α-naphthyl)isoquinaldamide (X). The condensation reaction between IV and α-naphthyl isocyanate was carried out in exactly the same manner as described for the preparation of VII. There was obtained a 90% yield of crude X. After several recrystallizations from acetone-water, its m.p. was 214.5–215.5° dec.

Anal. Calcd. for $C_{27}H_{18}N_2O_2$: C, 80.56; H, 4.50; N, 6.96. Found: C, 80.44; H, 4.52; N, 7.17.

N-(α-Naphthyl)isoquinaldamide (XI). The hydrolysis of X was carried out in the same manner as the hydrolysis of VII. There was obtained a 49% yield of crude XI, m.p. 160–170°. After several recrystallizations from ethanol (Norite), XI was obtained as a yellow, crystalline solid, m.p. 168–170°.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.48; H, 4.87; N, 9.67.

N-Phenyltetrahydroisoquinaldamide. *N*-Phenylisoquinaldamide (IX), 1.2 g. (0.0048 mole), was dissolved in 150 ml. of absolute ethanol. Addition of an equivalent amount of concentrated hydrochloric acid solution, 0.46 g. of 37% hydrochloric acid (0.0048 mole), resulted in the formation of a flocculent yellow precipitate. After addition of 50 mg. of platinum oxide, the mixture was reduced in a Parr low pressure hydrogenator at a pressure of approximately 52 p.s.i. gauge. After the solid had completely dissolved the reduction was stopped, and the catalyst was removed by filtration. The filtrate was evaporated to dryness under an air-jet and the residue suspended in an aqueous solution of sodium bicarbonate. The mixture was extracted several times with ether. After having been dried over Drierite, the combined ether extracts, on evaporation, yielded 1.00 g. (84%) of crude *N*-phenyltetrahydroisoquinaldamide, m.p. 125–129°. After three recrystallizations from ethanol-water the compound melted at 138.5–139.4°.

Anal. Calcd. for $C_{16}H_{15}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.30; H, 6.55; N, 11.13.

Treatment of N-phenylisoquinaldamide with ethyl iodide. In an attempt to form a quaternary ammonium salt, *N*-phenylisoquinaldamide was refluxed for a short time with excess ethyl iodide in benzene solution. After evaporation of the volatile components, a mixed melting point test of the residue with an authentic sample of *N*-phenylisoquinaldamide showed no depression. Use of a large excess of ethyl iodide as solvent in the above reaction also yielded only starting material.

N-Phenyl-2-ethyltetrahydroisoquinaldamide (XIII). A Parr bomb was charged with 1.0 g. (0.0039 mole) of *N*-phenyltetrahydroisoquinaldamide, 0.70 g. (0.0049 mole) of ethyl iodide and 10 ml. of anhydrous ethanol. The bomb was then heated for 5 hr. in an oil bath maintained at 135°. After the bomb and its contents had been cooled, the bulk of the ethanol was evaporated and the residue stirred with a solution of sodium carbonate. The resulting mixture was extracted several times with ether, and, after drying and evaporation of the combined ether washes, there was obtained 0.76 g. of a tan solid. Recrystallization from an ethanol-water mixture yielded 0.56 g. (52% yield; 88% yield based on unrecovered starting material) of white, hair-like crystals, m.p. 99–101°. Several additional recrystallizations yielded a sample of m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.02; H, 7.06; N, 10.11.

N-Phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride. Anhydrous hydrogen chloride gas, in excess, was passed into a solution of *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII) in anhydrous ethanol. Evaporation of the solvent and recrystallization of the residue from anhydrous ethanol-acetone provided a quantitative yield of a fine white solid, m.p. 231–234°. Several additional recrystallizations gave a sample of m.p. 244–246° dec.

Anal. Calcd. for $C_{18}H_{21}N_2OCl$: C, 68.23; H, 6.68; N, 8.84; Cl, 11.19. Found: C, 68.32; H, 6.77; N, 8.84; Cl, 10.90.

Acknowledgment. This investigation was supported by a research grant, E-1961, from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

LAWRENCE, KAN.

(19) H. Gilman, *J. Am. Chem. Soc.*, **55**, 1262 (1933).

(20) This procedure parallels that used by V. Boekelheide and J. C. Godfrey [*J. Am. Chem. Soc.*, **75**, 3679 (1953)] for the condensation of II with acrylonitrile and related compounds.

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

Condensation of Dialdehydes with Reissert Compounds. Synthesis of a Compound Having Curariform Activity

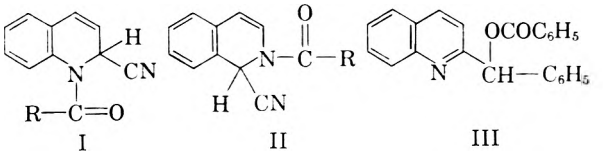
EUGENE G. PODREBARAC AND WILLIAM E. McEWEN

Received July 19, 1960

Reaction of two equivalents of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile with one equivalent of terephthalaldehyde gave both the *meso* form and racemate of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol. The respective diols were obtained by saponification of the esters, and each diol gave the same ketone, α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione, on chromic acid oxidation. The dione was converted to α,α'-bis(2-quinolyl)-*p*-xylylene by a Wolff-Kishner reduction. Treatment of the latter compound with methyl iodide gave α,α'-bis(2-quinolyl)-*p*-xylylene dimethiodide, which was found to be a moderately potent peripheral blocking agent that affects both neuromuscular and ganglionic transmission.

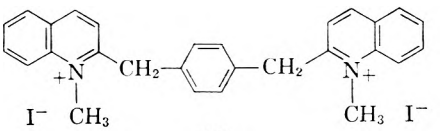
Reaction of two equivalents of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with one equivalent of terephthalaldehyde gave both the *meso* form and racemate of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol. One of the diastereoisomers of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*o*-xylylene-α,α'-diol was obtained by treatment of phthalaldehyde with the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile.

Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) are easily converted to the respective lithium salts in exchange reactions with phenyllithium, and the salts, in turn, readily undergo condensation reactions with a variety of electrophilic reagents. The reactions of the lithium salts with aldehydes, in particular, take place rapidly and give high yields of condensation-rearrangement products.[1] For example, the reaction of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (R = C_6H_5) with benzaldehyde gives phenyl-2-quinolylcarbinyl benzoate (III) in 89% yield.

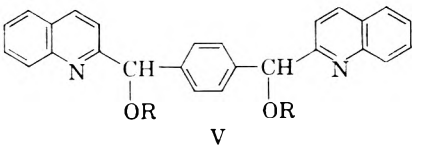


I II III

With the ultimate objective in mind of preparing α,α'-bis(2-quinolyl)-*p*-xylylene dimethiodide (IV) as a possible curariform agent, we decided to investigate the reaction of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) with terephthaladehyde. Condensation of two equivalents of the salt with one of the aldehyde gave two products of the molecular formula $C_{40}H_{28}N_2O_4$, the one of m.p. 258.5–259.5° in 80% yield and the other of m.p. 209–210° in 8% yield. These products, the infrared spectra of which were found to be identical, are undoubtedly the racemic and *meso* forms of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5), but no attempt was made to distinguish one from the other inasmuch as the centers of asymmetry were eventually eliminated in the conversion of these esters to IV.

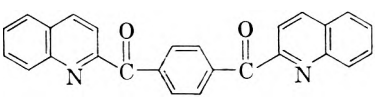


IV



V

Saponification of the diester V (R = COC_6H_5) of m.p. 258.5–259.5° gave α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H) of m.p. 193–196°. In a similar saponification reaction of the diester of m.p. 209–210°, a diol of m.p. 179–184° was obtained. The somewhat large melting point ranges of the two diols suggest that partial interconversion of the *meso* and racemic forms occurred under the alkaline conditions of hydrolysis. This was not unexpected inasmuch as the side chain hydrogen atoms of quanaldine and its derivaties are known to be acidic. Oxidation of each of the two samples of the diol V (R = H) with chromic acid gave the same diketone, α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione (VI), thus confirming the supposition that the two diesters (V. R = COC_6H_5) and the two diols diols (V R = H) were diastereoisomeric pairs. The saponification reactions and oxidation reactions gave the products cited above in yields of 98% and 93%, respectively.



VI

α,α'-Bis(2-quinolyl)-*p*-xylylene was obtained from VI in quantitative yield by application of the Huang-Minlon modification of the Wolff-Kishner reduction. Treatment of α,α'-bis(2-quinolyl)-*p*-xylylene with methyl iodide in a Parr bomb at an

(1) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

elevated temperature gave the dimethiodide IV in 98% yield.

As an extension of the scope of the condensation-rearrangement reaction of Reissert compounds with aldehydes, two equivalents of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile were caused to react with one equivalent of terephthalaldehyde, and both the racemic and *meso* forms of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol were isolated. One isomer of m.p. 208–209° was obtained in 83% yield and the other of m.p. 228–230° in 8% yield. One of the diastereoisomers of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*o*-xylylene-α,α'-diol, m.p. 226.5–227.5°, was obtained in low yield following the condensation of two equivalents of the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile with one equivalent of phthalaldehyde.

Pharmacological testing. α,α'-Bis(2-quinolyl)-*p*-xylylene dimethiodide (IV) was found to be a moderately potent peripheral blocking agent that affects both neuromuscular and ganglionic transmission. It probably should be classed as competitive rather than depolarizing in its action. By usual definitions the median curarizing and ganglionic blocking dose might be estimated at 4 or 5 mg/kg. i.v.[2]

EXPERIMENTAL[3]

1-Benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5). This compound was prepared by the method of Rupe, Paltzer, and Engel.[4]

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5). The method of Padbury and Lindwall[5] was used for the preparation of this compound.

Phenyllithium. Freshly prepared phenyllithium, made by the method of Gilman,[6] was used for each experiment. The lithium bromide formed in the reaction was not removed.

O,O-Dibenzoyl-α,α'-bis(2-quinolyl)-p-xylylene-α,α'-diol (V. R = COC_6H_5). To a solution of 10.4 g. (0.04 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) in 150 cc. of anhydrous ether and 75 cc. of anhydrous dioxane maintained at −10° in an atmosphere of pure nitrogen was added with mechanical stirring an ether solution of 0.04 mole of freshly prepared phenyllithium. To the resulting red solution there was added dropwise with stirring a solution of 2.68 g. (0.02 mole) of terephthalaldehyde in 20 cc. of anhydrous dioxane. As the addition of aldehyde progressed the color faded slowly, and, on completion of the addition, the color was light pink. The mixture was stirred for 2 hr. at −10°, warmed to room temperature and stirred for an additional 4 hr. The reaction mixture was filtered and the solid washed well with water until the washings were no longer basic to litmus. After the solid had been dried for an extended period, it amounted to 9.6 g. (80% yield) of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5), m.p. 228–235°. Recrystallization from anhydrous benzene-petroleum ether (b.p. 60–110°) yielded a white solid melting at 258.5–259.5°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.90; H, 4.97; N, 4.86.

The organic phase, after collection of the above mentioned solid, was evaporated to dryness, yielding a yellow solid. After having been washed well with hot 95% ethanol and dried, the remaining white solid, 0.80 g., melted at 203–216°. From the ethanol wash an additional 0.16 g. of material melting at 199–204° was obtained. The total yield (0.96 g.) of this material, presumed to be the diastereoisomer of the compound cited above, was 8%. Two recrystallizations from acetone yielded a solid melting at 209–210°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 80.21; H, 4.62; N, 4.64.

The infrared spectra of the compounds melting at 258.5–259.5° and 209–210°, respectively, taken in potassium bromide pellets, were found to be identical.

O,O-Dibenzoyl-α,α'-bis(1-isoquinolyl)-p-xylylene-α,α'-diol. These compounds, derived from 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) and terephthalaldehyde as starting materials, were synthesized in the same manner as that described above for the preparation of the corresponding quinoline compounds. Filtration of the colorless reaction mixture followed by a thorough washing and drying of the precipitate yielded 10.0 g. (83% yield) of *O,O*-dibenzoyl-α,α'-bis(1-isoquinolyl)-*p*-xylylene-α,α'-diol, m.p. 160–195°. Several recrystallizations from acetone yielded a white solid melting at 208–209°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.86; H, 4.80; N, 4.95.

As in the preceeding experiment, there was obtained from the organic phase 0.98 g. (8% yield) of a white solid, melting point 215–224°, believed to be the diastereoisomer of the compound of m.p. 208–209°. Two recrystallizations from ethanol-water yielded a sample of m.p. 228–230°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.87; H, 4.63; N, 4.78.

The infrared spectra of the compounds melting at 208–209° and 228–230°, respectively, taken in potassium bromide pellets, were found to be identical.

α,α'-Bis(2-quinolyl)-p-xylylene-α,α'-diol (V. R = H). The first sample of this compound was prepared by saponification of *O,O*-dibenzoyl-α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = COC_6H_5) of m.p. 258.5–259.5°. A suspension of 5.0 g. of the dibenzoate ester in 130 cc. of ethanol was mixed with a solution of 5.0 g. of potassium hydroxide in 30 cc. of water, and the resulting mixture was refluxed for 9 hr. The bulk of the ethanol was removed under an air-jet, and the residue was mixed with 100 cc. of water. The solid was collected by filtration and washed with water until the washings were free of base. There was obtained 3.23 g. (98% yield) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H), m.p. 190–200°. After several recrystallizations from acetone the m.p. was 193–196°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.62; H, 5.24; N, 7.08.

Saponification of the diastereoisomeric ester, m.p. 209–210°, in the same manner yielded a solid, which, after several recrystallizations from an ethanol-water mixture, melted at 179–184°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.56; H, 5.14; N, 7.14. Found: C, 79.40; H, 5.36; N, 7.25.

The infrared spectra of the two diols, taken in potassium bromide pellets, were found to be identical.

α,α'-Bis(2-quinolyl)-p-xylylene-α,α'-dione (VI). A solution of 3.30 g. (0.0111 mole) of sodium dichromate in 15 cc. of glacial acetic acid maintained at 16° was slowly added to a suspension of 6.00 g. (0.0153 mole) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-diol (V. R = H), m.p. 193–196°, in acetic acid. The yellow solid which formed initially gradually underwent a change to a gray-blue color as the reaction mixture was slowly heated to 60°. At this point the mixture was allowed to come to room temperature, then it was filtered

(2) We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the testing of this compound.

(3) All melting points are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, 20, 209 (1937).

(5) J. J. Padbury and J. G. Lindwall, *J. Am. Chem. Soc.*, 67, 1268 (1945).

(6) H. Gilman, *J. Am. Chem. Soc.*, 55, 1262 (1933).

and the precipitate washed well with water. There was obtained 5.50 g. (93% yield) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione (VI) m.p. 282–284°. After several recrystallizations from acetone the compound melted at 283.5–284.5°.

Anal. Calcd. for $C_{26}H_{16}N_2O_2$: C, 80.39; H, 4.15; N, 7.21. Found: C, 80.16; H, 4.37; N, 7.07.

In a similar fashion, oxidation of the diastereoisomeric diol of m.p. 179–184° yielded a white solid of m.p. 282–284°. A mixed melting point test with the analyzed sample of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione (VI) obtained by the oxidation of the diol of m.p. 193–196° showed no depression. The infrared spectra, taken in potassium bromide pellets, of the two samples of the oxidation product were found to be identical.

α,α'-Bis(2-quinolyl)-p-xylylene. A mixture of 5.78 g. (0.0149 mole) of α,α'-bis(2-quinolyl)-*p*-xylylene-α,α'-dione (VI), 40 cc. of 85% hydrazine and 150 cc. of triethyleneglycol was refluxed for 2 hr. The initially white solid gradually changed to yellow. Excess hydrazine and water were evaporated by heating the mixture under an air-jet, and the temperature was raised to about 220°. Addition of about 5.0 g. of potassium hydroxide caused a vigorous reaction to ensue, one terminating in the formation of a golden brown solution. The solution was heated at 220° for 1 hr., then allowed to cool slowly to room temperature. Approximately 100 cc. of water was added to the solution causing formation of a crystalline solid. The solid, α,α'-bis(2-quinolyl)-*p*-xylylene, after filtration and drying, weighed 5.31 g. (quantitative yield) and melted at 132–135°. Recrystallization from an ethanol-water mixture yielded needle-like crystals of m.p. 135–136°.

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59; N, 7.77. Found: C, 86.70; H, 5.50; N, 7.85.

α,α'-Bis(2-quinolyl)-p-xylylene dimethiodide (IV). A Parr bomb was charged with 1.0 g. (0.0028 mole) of α,α'-bis(2-quinolyl)-*p*-xylylene and 12 g. of methyl iodide and heated for 9 hr. at 75°. After evaporation of the excess methyl iodide under vacuum there was obtained 2.30 g. of a yellow-green solid decomposing at 273°. The solid was dissolved in boiling water and hydrogen iodide solution was added until the solution was acidic. After filtration of the hot solution, the filtrate, on cooling, yielded 1.71 g. (98% yield) of a yellow solid, α,α'-bis(2-quinolyl)-*p*-xylylene dimethiodide (IV), melting with decomposition at 289–292°.

Anal. Calcd. for $C_{28}H_{26}N_2I_2$: C, 52.19; H, 4.07; N, 4.35; I, 39.39. Found: C, 52.23; H, 4.45; N, 4.50; I, 39.22.

O,O-Dibenzoyl-α,α'-bis(2-quinolyl)-o-xylylene-α,α'-diol. The lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile was treated with phthalaldehyde in the same manner as that described for the preparation of the *p*-xylylene compounds. Addition of 20 cc. of water to the reaction mixture resulted in complete solution of the solid. The organic layer was separated, washed with three 10-cc. portions of water, dried over anhydrous magnesium sulfate, and evaporated to yield a reddish oil. Subjection of the oil to vacuum treatment for several days failed to induce complete solidification. In an attempt to recrystallize the gum (weight 10.77 g.) from 95% ethanol, a slight amount of a light yellow solid was found to be insoluble. After it had been collected by filtration, the solid weighed 1.50 g. and melted at 217–221°. Recrystallization from a benzene-petroleum ether mixture (b.p. 60–110°) yielded a solid which melted at 226.5–227.5°.

Anal. Calcd. for $C_{40}H_{28}N_2O_4$: C, 79.98; H, 4.70; N, 4.67. Found: C, 79.76; H, 4.84; N, 4.97.

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LAWRENCE, KAN.

CONTRIBUTION FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis and Biological Properties of 4-Amino-5-isopropyl-3-isoxazolidone, a Substituted Cycloserine

KYOZO HAYASHI,[1] CHARLES G. SKINNER, AND WILLIAM SHIVE

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α-Bromo-β-hydroxy-γ-methylpentanoic acid was treated with ammonium hydroxide to yield the desired α-amino acid which was then esterified in the presence of anhydrous hydrogen chloride with ethanol. The β-hydroxy grouping was subsequently replaced by chlorine and the resulting ethyl α-amino-β-chloro-γ-methylpentanoate was finally treated with hydroxylamine and cyclized to yield 4-amino-5-isopropyl-3-isoxazolidone (I). I is inhibitory to the growth of *Leuconostoc dextranicum* when this organism is grown in a medium containing D-leucine as the exogenous source of this required metabolite; however, I is essentially not toxic for *L. dextranicum* when it is grown on media containing DL-leucine. It appears that appropriately substituted cycloserine derivatives may specifically inhibit D-amino acid functions.

Cycloserine (D-4-amino-3-isoxazolidone)[2a] was originally isolated from culture filtrates of streptomycetes[2b] and its chemical structure was subsequently established.[3,4] It is an antibiotic which has been found effective in a number of microbial systems.[5] Metabolic studies with this compound have demonstrated it to be a competitive antagonist of D-alanine in preventing the incorporation of D-alanine into a uridine nucleotide intermediate

(1) Rosalie B. Hite postdoctoral fellow, 1959–1960.

(2)(a) Oxamycin, Merck and Co., Inc.

(2)(b) For references see *Antibiotics, Their Chemistry and Non-Medical Uses*, ed. H. S. Goldberg, Van Nostrand, New York, 1959, p. 71.

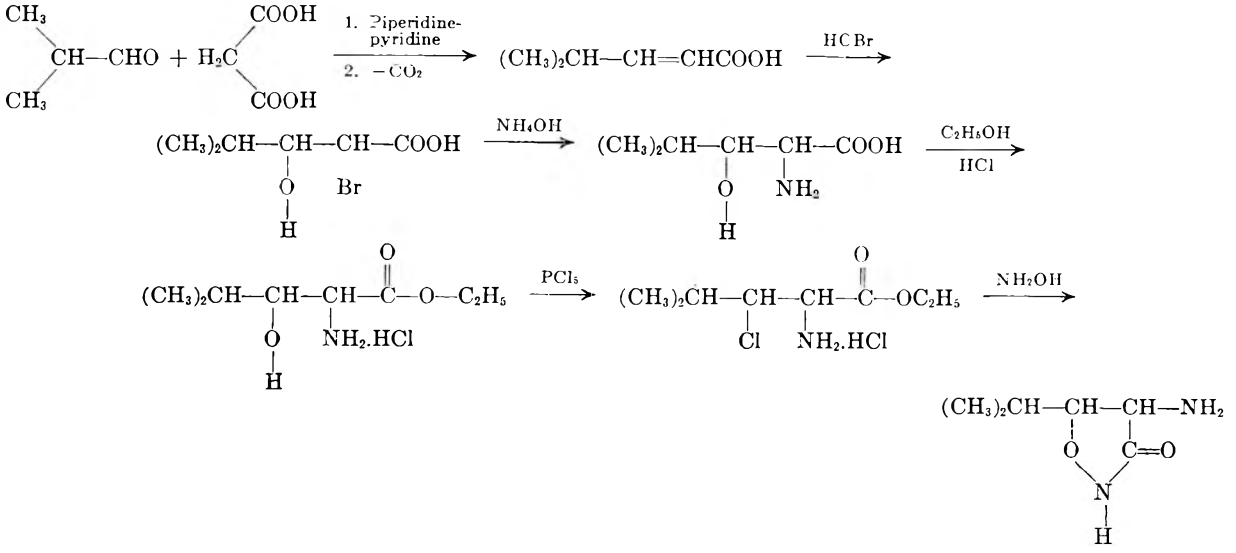
(3) F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Dowing, E. Newstead, R. P. Buhs, I. Putter, R. Ormond, J. E. Lyons, L. Chaiet, and K. Folkers, *J. Am. Chem. Soc.*, **77**, 2344 (1955).

(4) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz, and H. R. Sullivan, *J. Am. Chem. Soc.*, **77**, 2345 (1955).

(5) E. B. Chain, *Ann. Rev. Biochem.*, **27**, 167 (1958).

essential for cell wall synthesis in *Staphylococcus aureus*.[6] Recently, the antibiotic has been reported to inhibit alanine racemase and an enzyme which catalyzes the synthesis of D-alanyl-D-alanine.[7] Cell wall synthesis in *Streptococcus faecalis* is also inhibited by cycloserine, and the toxicity is competitively reversed by D-alanine, but not by L-alanine.[8] The L-form of this antagonist is also less inhibitory than either D- or DL-cycloserine to the growth of *E. coli*.[9] Several 2-phenyl-5-aryl-cycloserine analogs have recently been synthesized, and found to be inhibitory to both gram-positive and gram-negative bacteria[10]; and more recently, the synthesis of the threonine analog, 4-amino-5-methyl-3-isoxazolidone, was reported, but without any microbiological data on its inhibitory activity.[11] In view of the fact that the biological activities of cycloserine indicate that it is an antagonist of D-alanine,[6] the synthesis of comparable analogs structurally related to other natural amino acids would seem to be desirable. Accordingly, the structural analog corresponding to leucine, 4-amino-5-isopropyl-3-oxazolidone, was prepared, and its inhibitory properties were examined in several microbial systems.

The series of reactions leading to the formation of 4-amino-5-isopropyl-3-isoxazolidone are summarized in the accompanying equations.



The synthesis of the desired intermediate, α-bromo-β-hydroxy-γ-methylpentanoic acid, was adapted from the procedure for the preparation of a corresponding α-bromo-β-hydroxy intermediate used in the synthesis of threonine.[12] During the course of this reaction, which involved bromine-water as the source of hypobromous acid, some α,β-dibromo-γ-methylpentanoic acid was also formed. The α-bromo group of the former derivative was then replaced by an amino grouping using concentrated ammonium hydroxide, and the desired hydroxyamino acid was isolated and purified using an Amberlite IR-120 column. α-Amino-β-hydroxy-γ-methylpentanoic acid was converted to the ethyl ester hydrochloride using ethanol and anhydrous hydrogen chloride, after which the hydroxyl grouping was replaced by chlorine using phosphorus pentachloride. Finally, the α-amino-β-chloro ester was treated with hydroxylamine to form the desired cycloserine analog, 4-amino-5-isopropyl-3-isoxazolidone. The latter derivative was isolated and purified on an Amberlite IR-120 column.

An alternate route to prepare the cycloserine analog through a hydantoin intermediate was also considered. α-Amino-β-hydroxy-γ-methylpentanoic acid was treated with potassium cyanate and the desired intermediate, 5-(1-hydroxy-2-methylpropyl)hydantoin, was isolated. Initial attempts to convert this hydroxy grouping to a bromo substituent failed to yield the desired product; instead, the corresponding alkylidene derivative, 5-(2-methylpropylidene)hydantoin, was isolated. The structure of this product was confirmed by reduction to the saturated analog and comparing the resulting derivative with an authentic sample of 5-(2-methylpropyl)hydantoin prepared directly from leucine by the usual procedures. In addition, the hydrogenated alkylidene product was hydrolyzed under alkaline conditions, and leucine was

(6) J. L. Strominger, R. H. Threnn, S. S. Scott, *J. Am. Chem. Soc.*, **81**, 3803 (1959).

(7) J. L. Strominger, *Physiol. Rev.*, **40**, 87 (1960).

(8) G. D. Shockman, *Proc. Soc. Exptl. Biol. Med.*, **101**, 693 (1959).

(9) L. Rawsa and S. Patania, *Giovn. Microbiol.*, **4**, 219 (1957); through *Chem. Abstr.*, **54**, 4768 (1960).

(10) N. K. Kochetkov, E. I. Budovskii, R. M. Khomutov, and M. M. Karpeiskii, *Zhur. Obshchei Khim.*, **29**, 635 (1959); through *Chem. Abstr.*, **54**, 507 (1960).

(11) R. M. Khomutov, M. M. Karpeiskii, E. I. Budovskii, E. S. Severin, and N. K. Kochetkov, *J. Gen. Chem., U.S.S.R.*, **29**, 1302 (1959).

(12) H. E. Carter and C. L. Zirkle, *J. Biol. Chem.*, **178**, 709 (1949).

identified as the amino acid formed by paper chromatographic techniques and by elemental analysis.

5-(1-Chloro-2-methylpropyl)hydantoin was finally prepared from the corresponding 5-(1-hydroxy-2-methylpropyl)hydantoin derivative using phosphorus pentachloride with acetyl chloride as a solvent. However, subsequent attempts to introduce the aminoxy grouping failed to yield analytically homogenous derivatives, and this potential route of synthesis was rejected in favor of the procedure initially presented in this article.

The growth inhibitory properties of 4-amino-5-isopropyl-3-isoxazolidone were examined in a variety of microörganisms including *Streptococcus lactis* 8039, *Lactobacillus arabinosus* 17-5, *Streptococcus faecalis* 8043, *Leuconostoc dextranicum* 8086, *Pediococcus cerevisiae* 8081, and *Escherichia coli* 9723, but no general toxicity was observed up to a level of 200 γ/ml. The media used contained a minimal amount of valine, isoleucine and leucine, all of which were in the DL-configuration. Under comparable assay conditions, cycloserine was inhibitory to the growth of these organisms at levels of 60, 200, 20, 60, >200, and <6 γ/ml., respectively. Since D-leucine may not be required by these organisms for essential metabolic roles, it was of interest to determine whether the isopropyl-cycloserine analog would inhibit utilization of D-leucine as a substitute for L-leucine in the usual assay media. For *L. dextranicum*, D-leucine is utilized about one-tenth as effectively as the L-isomer; a supplement of 10 γ/ml. of the D-form gives near maximal growth. Under these latter testing conditions with *L. dextranicum*, using an amino acid medium containing L- or DL-amino acids in every case except that D-leucine was the sole exogenous source of this amino acid, the isopropylcycloserine derivative was inhibitory to growth, and was reversed in a competitive manner over a four-fold range of increasing concentrations of D-leucine (Table I). The inhibition index (ratio of inhibitor to substrate necessary for maximal inhibition) is about 20.

TABLE I

INHIBITION OF D-LEUCINE UTILIZATION BY 4-AMINO-5-ISOPROPYL-3-ISOXAZOLIDONE IN *Leuconostoc dextranicum*[a]

4-Amino-5-isopropyl-3-isoxazolidone, γ/ml.	Supplement, D-leucine, γ/ml. 5	10	20
	Galvanometer readings		
0	50	55	51
10	49		
20	49	51	
50	36	48	48
100	13	34	50
200		7	21
500			8

[a] Media described in ref. 14; except that the DL-isoleucine and DL-valine were decreased to 10 γ/ml.; the DL-glutamic acid was increased to 100 γ/ml.; the DL-leucine was omitted, and D-leucine was added as indicated.

Since it is probable that D-leucine does not perform an essential role in the metabolic processes of *L. dextranicum*, the inhibition of the racemization and/or utilization of D-leucine by isopropyl-cycloserine is of no consequence to the organism grown on L-leucine. In contrast, D-alanine performs an essential role in several metabolic functions and thus an inhibitor of this amino acid, cycloserine, is an effective antimetabolite. Since there are other D-amino acids which have been demonstrated to have essential roles in microörganisms, the corresponding substituted-cycloserine analogs of these metabolites may be expected to have growth inhibitory activities similar to cycloserine.

EXPERIMENTAL[13]

Biological assays. For the survey of microbial toxicity with lactic acid bacteria a previously described amino acid medium[14] was modified by the addition of calcium pantothenate (0.2 γ/ml.) and by decreasing the concentrations of DL-leucine, DL-isoleucine and DL-valine to 10 γ/ml.; by increasing the concentration of DL-glutamic acid to 100 γ/ml.; and with the additional modifications noted for each organism. The media was used without further modifications for *Streptococcus lactis* 8039, *Lactobacillus arabinosus* 17-5 and *Streptococcus faecalis* 8043. For *Leuconostoc dextranicum* 8086 pantethine was added (0.02 γ/ml.) and the phosphate concentration was increased four-fold. For *Pediococcus cerevisiae* 8081 the phosphate concentration also increased four-fold. All of the assays were incubated at 30° with the exception of *P. cerevisiae* which was incubated at 37°. The *S. faecalis* assay was allowed to grow for about 40 hr., while the other assays were completed in about 20 hr.

For *Escherichia coli* 9723 a previously described inorganic salts-glucose medium[15] was used, and the assays were incubated at 37° for about 16 hr.

For the assays reported in Table I utilizing D-leucine as the source of this amino acid in the medium, the basal media previously described for *L. dextranicum* was used except that DL-leucine was omitted, and D-leucine was added as indicated in the Table. In all assays, the amount of growth was determined turbidimetrically in terms of galvanometer readings so adjusted that in the particular instrument distilled water read 0 and an opaque object 100.

α-Bromo-β-hydroxy-γ-methylpentanoic acid[16]. 4-Methyl-2-pentenoic acid was prepared by the condensation of 72 g. of isobutyraldehyde and 104 g. of malonic acid followed by decarboxylation to yield 101 g. of product, b.p. 115–118° (24 mm.).[17] A well stirred solution of 300 g. of 4-methyl-2-pentenoic acid in 5 l. of water was cooled to 0–5° in an ice bath, and 270 g. of bromine mixed with air was bubbled through the reaction mixture at such a rate that only a slight yellowish bromine color was evident during the addition reaction. The bromine-air mixture was obtained by bubbling dry air through the liquid bromine in a suitable vessel, and about 5 hr. was required to utilize all of the

(13) All melting points are uncorrected. The authors are indebted to Dr. J. M. Ravel and Mrs. Jean Humphries for assistance with the microbial testing. The analyses were carried out by Dr. Alfred Bernhardt, Mülheim, Germany.

(14) J. M. Ravel, L. Woods, B. Felsing, and W. Shive, *J. Biol. Chem.*, **206**, 391 (1954).

(15) E. H. Anderson, *Proc. Natl. Acad. Sci.*, **32**, 120 (1946).

(16) This preparative procedure was patterned after that of H. E. Carter and C. L. Zirkle (10) for the synthesis of α-bromo-β-hydroxybutyric acid.

(17) R. P. Linstead, *J. Chem. Soc.*, 2498 (1929).

halogen. After all of the bromine was added, air was bubbled through the solution to expel any excess bromine gas. During the bromine addition, a crystalline precipitate formed which was recovered and is characterized below as α,β-dibromo-γ-methylpentanoic acid. The resulting reaction mixture was extracted with 500 ml. of petroleum ether (b.p. 60–68°); the aqueous phase was then saturated with sodium chloride and finally extracted three times with 200-ml. portions of ether. The combined organic phase was dried over sodium sulfate, and the solvents were then removed *in vacuo*. There was recovered 300 g. of product which was recrystallized from petroleum ether, m.p. 126–127°.

Anal. Calcd. for $C_6H_{11}BrO_3$: C, 34.14; H, 5.25. Found: C, 34.11; H, 5.57.

α,β-Dibromo-γ-methylpentanoic acid. The crystalline precipitate formed during the course of the reaction above for the synthesis of α-bromo-β-methylpentanoic acid was filtered to yield 27 g. of product. The material was recrystallized from petroleum ether, m.p. 124–125°.

Anal. Calcd. for $C_6H_{10}Br_2O_2$: C, 26.30; H, 3.65. Found: C, 26.66; H, 3.84.

α-Amino-β-hydroxy-γ-methylpentanoic acid. A sample of 40 g. of α-bromo-β-hydroxy-γ-methylpentanoic acid was dissolved in 400 ml. of concd. ammonium hydroxide and allowed to stand at room temperature for 4 days. The reaction mixture was then reduced in volume *in vacuo* to yield a residue containing the desired amino acid derivative and ammonium bromide. The residue was taken up in 200 ml. of water and charged to an Amberlite IR-120 column (35 mm. × 300 mm.). The column was washed with distilled water until the effluent gave a negative test for bromide ion. The amino acid was then eluted with 1000 ml. of 0.5*N* ammonium hydroxide, and after the combined ninhydrin-positive eluates were concentrated to a small volume *in vacuo*, ethyl alcohol was added to induce crystallization. The resulting product was then recrystallized from alcohol-water to yield 16 g. of material, m.p. 237–238°.

Anal. Calcd. for $C_6H_{13}NO_3$: C, 49.10; H, 8.85; N, 9.52. Found: C, 49.01; H, 9.13; N, 9.43.

5-(1-Hydroxy-2-methylpropyl)hydantoin. A solution containing 12 g. of α-amino-β-hydroxy-γ-methylpropanoic acid and 6.5 g. of potassium cyanate in 75 ml. of water was heated at 65° for 2 hr. with stirring. The resulting reaction mixture was then treated with 50 ml. of 48% hydrobromic acid and heated an additional 2 hr. at 90°. Finally, the solution was reduced to dryness *in vacuo* and the residue was crystallized from ethanol-water to yield 7 g. of product, m.p. 223–225°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 6.98; N, 16.30. Found: C, 48.86; H, 6.99; N, 16.20.

5-(2-Methylpropyledene)hydantoin. Several attempts were made to convert the hydroxyl group of 5-(1-hydroxy-2-methylpropyl)hydantoin (I) to the corresponding bromo derivative; however, in each instance the product isolated was an unsaturated compound which gave a negative test for halogen. (1) A solution of 5 g. of I in 50 ml. of 48% hydrobromic acid was heated at 90–95° for 2 hr., the reaction mixture was reduced to dryness *in vacuo* to yield 6.5 g. of white needles. The product was recrystallized from ethanol-water, m.p. 194–195° (II). (2) A mixture of 1.2 g. of I suspended in 10 ml. of carbon tetrachloride was treated with 5 g. of phosphorus tribromide and heated at 60–70° for 2 hr. After reduction in volume *in vacuo* the residue was crystallized from ethanol-water to yield the same product as indicated above, 5-(2-methylpropyledene) hydantoin, II.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.10. Found: C, 54.64; H, 6.71; N, 17.62.

A 0.3-g. sample of II was dissolved in 30 ml. of ethanol and hydrogenated in the presence of 0.1 g. of platinum oxide at atmospheric pressure for 2 hr. The catalyst was filtered, the filtrate was reduced to dryness *in vacuo*, and the residue was crystallized from ethanol-water to yield 250 mg. of compound, m.p. 209–211°. The saturated product isolated did not depress the melting point of an authentic sample of 5-(2-methylpropyl)hydantoin prepared from DL-leucine by the usual procedure with potassium cyanate under acidic conditions.

The hydrogenated hydantoin isolated above from II was finally hydrolyzed in the presence of barium hydroxide to yield the amino acid DL-leucine which was identified by elemental analyses, and by paper chromatography in several solvent systems.

5-(1-Chloro-2-methylpropyl)hydantoin. A sample of 1.5 g. of 5-(1-hydroxy-2-methylpropyl)hydantoin was suspended in 30 ml. of acetyl chloride and cooled to 0–5°, after which, 2.5 g. of phosphorus pentachloride was added and the reaction was allowed to continue for about 2 hr. The resulting precipitate was filtered, and the filter was washed with carbon tetrachloride and finally water. The solid was crystallized from ethanol-water to yield 0.85 g. of product, m.p. 175–177°.

Anal. Calcd. for $C_7H_{11}N_2O_2Cl$: C, 44.10; H, 5.81; N, 14.70. Found: C, 44.58; H, 5.82; N, 14.75.

Ethyl α-amino-β-hyuroxy-γ-methylpentanoate hydrochloride. Dry hydrogen chloride gas was bubbled through a suspension of 8.3 g. of α-amino-β-hydroxy-γ-methylpentanoic acid in 50 ml. of ethanol while the reaction mixture was maintained at reflux temperature. After about 5 hr., the resulting solution was cooled and concentrated to a small volume *in vacuo*. The residue was finally crystallized from ethanol-ethyl acetate to yield 9 g. of product, m.p. 124–125°.

Anal. Calcd. for $C_6H_{18}NO_3Cl$: C, 45.38; H, 8.54; N, 6.62. Found: C, 44.77; H, 8.55; N, 6.57.

Ethyl α-amino-β-chloro-γ-methylpentanoate hydrochloride. To a suspension of 2 g. of ethyl α-amino-β-hydroxy-γ-methylpentanoate hydrochloride in 20 ml. of acetyl chloride was added 3 g. of phosphorus pentachloride with continuous stirring and external cooling. The solid reactant dissolved after about 30 min., and stirring was continued for an additional 2 hr. The reaction mixture was then concentrated to a small volume *in vacuo*, and ether was then added plus a small amount of petroleum ether to induce turbidity. After the solution was kept in the refrigerator overnight, there was recovered 2 g. of white needles, m.p. 132–133°.

Anal. Calcd. for $C_8H_{17}NO_2Cl_2$: C, 41.75; H, 7.44; N, 6.09. Found: C, 42.14; H, 7.61; N, 6.16.

DL-*4-Amino-5-isopropyl-3-isoxazolidone.* A solution of 5.8 g. of sodium hydroxide in 12 ml. of water was cooled to −5° and 3.4 g. of hydroxylamine hydrochloride was added with stirring. To this cold solution was then added 6 g. of ethyl α-amino-β-chloro-γ-methylpentanoate hydrochloride, and the temperature was maintained at −5° with stirring for about 1 hr. The temperature was then allowed to rise to 25° and stirring was continued an additional 2 hr. The reaction mixture was then cooled to −10° and the *p*H of the solution was adjusted to 6 with concentrated hydrochloric acid, after which it was concentrated *in vacuo* to a viscous residue. The residue was extracted with ethanol, the alcohol was removed, and the resulting residue was finally taken up in 200 ml. of water. This aqueous solution was then charged to an Amberlite IR-120 column (15 mm. × 150 mm.), the column was washed with 250 ml. of water, and then eluted with a total of 250 ml. of 0.2*N* ammonium hydroxide. The ammonia eluate was concentrated *in vacuo* to give a precipitate which was subsequently recrystallized from water to yield 0.7 g. of product, m.p. 183–184° dec.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.93; H, 8.27; N, 19.61.

AUSTIN, TEX.

[CONTRIBUTION FROM THE TECHNICAL DEVELOPMENT DEPARTMENT OF HOFFMANN-LA ROCHE, INC.]

A New Synthesis of *trans*-β-Carotene and Decapreno-β-carotene[1]

JOSEPH D. SURMATIS AND ALFRED OFNER

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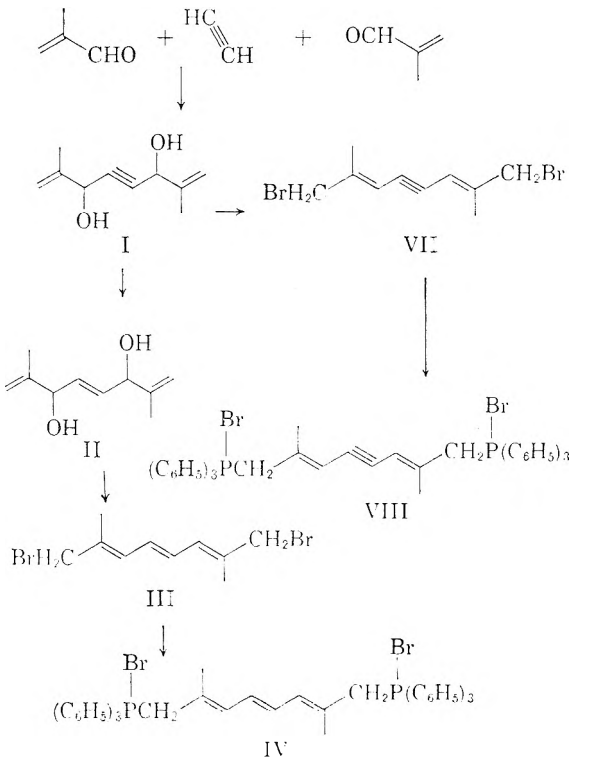
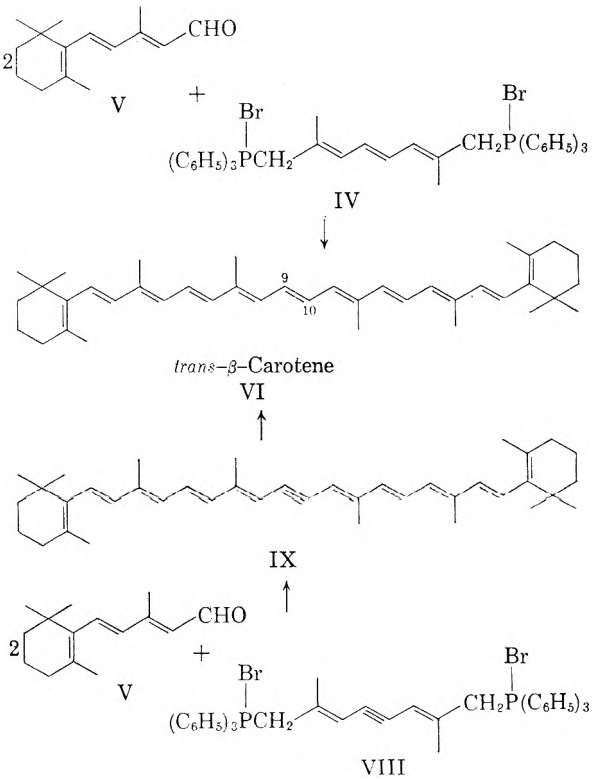
trans-β-Carotene was synthesized in good yield by following a $C_{15} + C_{10} + C_{15}$ building scheme using β-ionylideneacetaldehyde as the C_{15} component. When vitamin A aldehyde was substituted for β-ionylideneacetaldehyde, decapreno-β-carotene, a C_{50} carotenoid with LO vitamin A activity, was obtained.

In 1907, Willstätter[2] proved that carotene found in green leaves is identical with that in carrots. Zechmeister[3] in 1928 established the presence of eleven conjugated double bonds and two ring systems in carotene. Karrer[4] by oxidative degradation determined the ring structure and four additional C-methyl groups. Application of the isoprene rule enabled him to establish the now accepted formula, which is made up of eight isoprene units. In 1950, Karrer,[5] Inhoffen,[6] and Milas[7] synthesized *trans*-β-carotene independently. The industrial manufacturing procedure developed by Isler and his group[8] followed the building principle of $C_{19} + C_2 + C_{19}$ of Inhoffen, whereas a later synthesis devised by Isler[13] used the intermediates $C_{14} + C_{12} + C_{14}$.

The synthesis presented here follows a $C_{15} + C_{10} + C_{15}$ building scheme. *trans*-β-Ionylideneacetaldehyde was condensed with a Wittig[9] compound prepared from a C_{10} diol.

To prepare the C_{10} Wittig compound (IV), methacrolein was treated with acetylenedimagnesium bromide according to the procedure of Strong[10] to give the acetylenic diol (I) in 70% yield. Reduction of I with Lindlar catalyst[11] afforded the ethylenic diol (II) in 80% yield. To form the dibromide (III), 48% hydrobromic acid was dropped into an alcoholic solution of II at −10°, whereby III was obtained in 90% yield. The Wittig compound (IV)





(1) Presented at the 137th National Meeting of the American Chemical Society, April 12, 1960, Cleveland, Ohio.

(2) R. Willstätter and W. Mieg, *Ann.*, **355**, 1 (1907).

(3) L. Zechmeister *et al.*, *Ber.*, **61**, 566 (1928); *Ber.*, **66**, 123 (1933).

(4) P. Karrer *et al.*, *Helv. Chim. Acta*, **12**, 1142 (1929); **13**, 1084 (1930); **14**, 1033 (1931).

(5) P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **33**, 1172 (1950).

(6) H. H. Inhoffen *et al.*, *Ann.*, **570**, 54–69 (1950).

(7) N. A. Milas *et al.*, *J. Am. Chem. Soc.*, **72**, 4844 (1950).

(8) O. Isler *et al.*, *Helv. Chim. Acta*, **39**, 294 (1956).

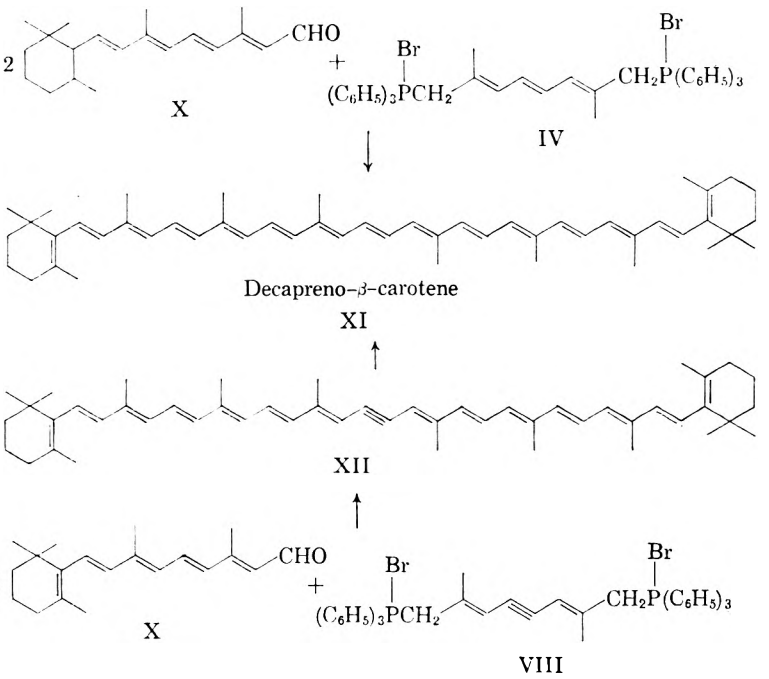
(9) G. Wittig, *Ber.*, **87**, 1318 (1954); G. Wittig and Geissler, *Ann.*, **580**, 44 (1953).

(10) F. M. Strong, *J. Am. Chem. Soc.*, **70**, 154 (1948).

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 442 (1952).

was made by dropping a benzene solution of the dibromide (III) into a stirred solution of triphenylphosphene also in benzene. The condensation proceeded smoothly at 40–45° in the presence of iodine catalyst. The crude Wittig compound (IV) crystallized from the reaction mixture in 90% yield.

To effect the condensation to *trans*-β-carotene, the Wittig compound (IV) was added to a stirred solution of phenyllithium in ethyl ether. Reaction with *trans*-β-ionylideneacetaldehyde (V) resulted in a 50.8% yield of pure *trans*-β-carotene (VI). The ultraviolet and visible absorption spectrum and the infrared spectrum for *trans*-β-carotene prepared by the new synthesis were identical with the spectra from an authentic sample of natural *trans*-β-carotene. There was no lowering of mixed melting points. When the Wittig compound of the acetylenic C_{10} diene (VIII) was used for the condensation with *trans*-β-ionylideneacetaldehyde (V), 9,10-dehydrocarotene[8] (IX) resulted in 55% yield. Hydrogenation in the presence of a poisoned palladium catalyst[11] afforded the corresponding ethylenic compound in which the double bond at carbon atom 9 was *cis*. This was readily converted to *trans*-β-carotene (VI) by heating at reflux temperature in normal hexane.



When vitamin A aldehyde (X) was substituted for the C_{15} aldehyde, a C_{50} carotenoid (XI) resulted which was identified as decapreno-β-carotene.[12,13] It was obtained in 38% yield as a dark violet crystalline solid. The absorption spectrum showed maxima at 475, 501, and 537 mμ (petroleum ether) with the curve closely resembling that of *trans*-β-carotene except that it is shifted to the right, as can be expected for the longer chain of conjugated double bonds. The decapreno-β-carotene showed a marked difference from carotene in the color of the pigment. Instead of the typical yellow, a dilute benzene solution showed a brilliant violet red.

Condensation of vitamin A aldehyde (X) with the acetylenic C_{10} compound (VIII) resulted in a dehydro C_{50} carotenoid (XII)[13] having absorption maxima at 481 and 512 mμ (petroleum ether). Selective reduction of XII followed by isomerization afforded decapreno-β-carotene (XI) which was identical in all respects with the sample obtained above. The decapreno β-carotene differs from *trans*-β-carotene by two isoprene units in the chain structure. It showed no vitamin A activity as determined by the rat liver storage test[14,15] and curative growth assay.

EXPERIMENTAL[16]

2,7-Dimethyl-1,7-octadien-4-yne-3,6-diol (I). Ethynylene magnesium bromide was prepared by bubbling dry acetylene for 24 hr. into ethylmagnesium bromide obtained from magnesium turnings (97.2 g.), ethyl bromide (436 g.), dry ethyl ether (1600 cc.), and toluene (800 cc.). Methacrolein (140 g.) was rapidly added to the stirred reaction, which was then refluxed for 1 hr. The resultant Grignard complex was poured onto crushed ice (500 g.), and dilute (5%) sulfuric acid was added until the mixture was faintly acid. The ether solution containing the product was washed to neutrality with sodium bicarbonate and then water, and dried over anhydrous calcium sulfate.

Removal of the solvent *in vacuo* afforded the crude diol.

(12) P. Karrer, *Helv. Chim. Acta*, **34**, 28–35 (1951).
(13) O. Isler *et al.*, *Ann.*, **603**, 129 (1957).
(14) J. R. Foy and K. Morgareidge, *Anal. Chem.*, **20**, 304 (1948).
(15) K. Guggenheim and W. Koch, *Biochem. J.*, **38**, 256 (1944).
(16) The melting points were determined in vacuum capillaries. Uncorrected.

After recrystallization from toluene, there resulted I, in a yield 116 g. (70%) m.p. 88–91°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.10; H, 8.45.

2,7-Dimethyl-1,4,7-octatriene-3,6-diol (II). A solution of I (83 g.) in toluene (500 cc.) was hydrogenated in the presence of poisoned palladium catalyst[11] until 1 molar equivalent of hydrogen was consumed. The catalyst was filtered off and washed thoroughly with additional portions of hot toluene. Finally the filtrate was concentrated *in vacuo*. The crystalline product remaining in the flask was redissolved in hot petroleum ether (b.p. 60–80°) and allowed to crystallize in a refrigerator. Filtration and drying afforded 67 g. (80%) of II, m.p. 69–70°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.69; H, 9.65.

1,8-Dibromo-2,7-dimethyl-2,4,6-octatriene (III). A solution of II (36.6 g.) in 95% ethyl alcohol (100 cc.) was placed in a 1-l., round bottom flask fitted with a thermometer, mechanical stirrer, and a dropping funnel. The solution was cooled to −10°, then 48% hydrobromic acid (250 cc.) was added from the dropping funnel with vigorous stirring, in 30 min. The reaction was stirred cold (0° to −10°) for an additional 15 min., then the crystalline dibromide was filtered by suction under a blanket of nitrogen. The product was washed on the filter with sodium bicarbonate (5%) and dried *in vacuo* at 35°. There was obtained 53 g. (90%) of III, m.p. 80–82°.

Anal. Calcd. for $C_{10}H_{14}Br_2$: C, 40.84; H, 4.79. Found: C, 40.91; H, 4.65.

2,7-Dimethyl-2,4,6-octatrienylenebis(triphenylphosphonium bromide) (IV). A solution of triphenylphosphene (131 g.) in benzene (400 cc.) was placed in a 1-l., round bottom flask. A solution of III (53 g.) and iodine (0.1 g.) in benzene (400 cc.) was placed in the dropping funnel and added to the stirred reaction at 40–45° in 2 hr. The reaction was stirred while warm for 4 hr., then allowed to stand at room temperature overnight. The product was filtered by suction, washed with petroleum ether (200 cc.), and dried *in vacuo* at 50°. The product (IV) was obtained in yield of 133 g. (90%). An analytical sample after repeated recrystallization from methyl alcohol-ethyl acetate, melted at 280°.

Anal. Calcd for $C_{46}H_{44}Br_2P_2$: C, 67.49; H, 5.42. Found: C, 66.98; H, 5.93.

trans β-Carotene (VI). To a solution of phenyllithium (0.22 mole) in ethyl ether (300 cc.), there was added 92 g. of IV during 30 min. with vigorous stirring. This caused the color of the reaction mixture to become a deep violet-red, while the temperature rose from 22° to 34°. The reaction was tested for completeness by means of the Gilman test.[17] A solution of β-ionylideneacetaldehyde (48 g.) in ethyl ether (200 cc.) was added from a dropping funnel in 1 hr. The reaction was stirred while heating at reflux for 8 hr. It was then cooled to −10° and methyl alcohol (400 cc.) was added. After cooling for an additional 4 hr. at −5° to −10°, the violet crystals of VI were filtered off by suction, washed with 95% ethyl alcohol (200 cc.), and petroleum ether (200 cc.). Recrystallization from benzene and drying *in vacuo*, yielded 29.6 g. (50.8%) of *trans*-β-carotene melting at 181°. The infrared and ultraviolet absorptions of VI and from an authentic sample of *trans*-β-carotene were identical. There was no lowering of mixed melting point.

Anal. Calcd. for $C_{40}H_{56}$: C, 89.48; H, 10.52. Found: C, 89.45; H, 10.40.

(17) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

1,8-Dibromo-2,7-dimethyl-2,6-octadien-4-yne (VII). This was prepared in the same manner as III from 2,7-dimethyl-1,7-octadien-4-yne-3,6-diol (I) (200 g.) and 48% hydrobromic acid (1000 cc.) in yield of 279 g. (79%); m.p. 40°. This compound was not reliably stable, so it was used for the next step without further purification.

2,7-Dimethyl-2,6-octadien-4-ynylenebis(triphenylphosphoniumbromide) (VIII). In a similar fashion to the preparation of IV, there was obtained by the action of triphenylphosphene (400 g.) in benzene (1200 cc.) on VII (175 g.) and iodine (0.2 g.) in benzene (1200 cc.) 472 g. (90%) of VIII melting at 223–227°. An analytical sample, after repeated recrystallizations from methyl alcohol–ethyl acetate, melted at 256–258°.

Anal. Calcd. for $C_{46}H_{42}Br_2P_2$: C, 67.65; H, 5.18. Found: C, 67.58; H, 5.31.

9,10-Dehydrocarotene (IX). By the same procedure described for the preparation of VI, there was obtained from VIII (100 g.) and β-ionylideneacetaldehyde (48 g.), 31.5 g. (55%) of IX, m.p. 154° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{40}H_{54}$: C, 89.82; H, 10.18. Found: C, 89.80; H, 10.10.

trans-β-Carotene by reduction of IX. A suspension of IX (20 g.) in hexane (200 cc.) was hydrogenated in the presence of poisoned palladium catalyst[11] until 1 molar equivalent of hydrogen was consumed. The suspension was heated to boiling before filtration of the catalyst, and the latter was washed with additional hot hexane. The filtrate was concentrated until a pasty mass remained. This was heated at 90° for 16 hr. in an inert atmosphere to effect the transformation to the *trans*-compound. Filtration and recrystallization from benzene afforded 15 g. (75%) of VI, m.p. 181°. The identity of VI was confirmed by ultraviolet and infrared absorption spectra.

3,7,11,16,20,24-Hexamethyl-1,26-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17,19,21,23,25-hexacosatridecaene (XI). By a procedure similar to that for the preparation of VI, IV (42.6 g.) and vitamin A aldehyde (28.4 g.) were allowed to react to yield 14.8 g. (38%) of XI as a black colored crystalline solid, after recrystallization from methylene chloride and methyl alcohol. The melting point was 191°. The absorption spectrum had maxima at 327 mμ, $E^{1\%}_{1cm}$ = 692, 399 mμ, $E^{1\%}_{1cm}$ = 497, 475 mμ, $E^{1\%}_{1cm}$ = 2100, 501 mμ, $E^{1\%}_{1cm}$ = 2737, and 537 mμ, $E^{1\%}_{1cm}$ = 2243 (in heptane.)

Anal. Calcd. for $C_{60}H_{68}$: C, 89.76; H, 10.24. Found: C, 89.70; H, 10.15.

3,7,11,16,20,24-Hexamethyl-1,26-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,15,17,19,21,23,25-hexacosadecaen-13-yne (XII). XII was obtained in the same manner as XI from VIII (85 g.) and vitamin A aldehyde (56.8 g.) in yield of 32.8 g. (42%); m.p. 189°; absorption maxima at 328 mμ, $E^{1\%}_{1cm}$ = 623, 481 mμ, $E^{1\%}_{1cm}$ = 2467, and 512 mμ, $E^{1\%}_{1cm}$ = 1879.

Anal. Calcd. for $C_{50}H_{66}$: C, 90.03; H, 9.97. Found: C, 89.88; H, 10.02.

Decapreno-β-carotene XI *by partial reduction of* XII. A suspension of XII (5.0 g.) in hexane (50 cc.) was hydrogenated by a procedure similar to that described for the reduction of IX. After recrystallization from methylene chloride–methyl alcohol, there was obtained 3.5 g. of XI, m.p. 191°. The ultraviolet and infrared absorption spectra were identical with those obtained from X. There was no lowering of mixed melting point.

NUTLEY 10, N. J.

[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

Derivatives of Podocarpic Acid. IV. Reduction of the Aromatic Ring[1]

ROY H. BIBLE, JR., AND ROBERT R. BURTNER

Received August 16, 1960

Hydrogenation of the aromatic ring of podocarpic acid (Ia) gave the *trans-anti-cis*-perhydro derivative (IIa). This reduction product was converted by a series of reactions, in which the rearrangement of a bromo ketone (VII) during dehydrobromination was observed, to a compound having the *trans-anti-trans* skeleton (IVb). This same compound was prepared from the Birch reduction product of *O*-methylpodocarpinol (XI). The complete stereochemistry of the products has been elucidated by interconversions and by a study of the spectra and optical rotations.

In a search for compounds having biological activities, the availability and interesting structure of podocarpic acid[2] (Ia) led us to prepare a number of its derivatives. One area of our investigation was the reduction of the aromatic ring.

Sherwood and Short[2c] found in their early structural work that podocarpic acid in acetic acid did not absorb hydrogen over a platinum catalyst which was capable of promoting a rapid reduction of benzaldehyde. These workers considered this resistance to hydrogenation as evidence that podocarpic acid contained an aromatic ring but reported no further attempts to reduce the aromatic ring under more drastic conditions.

We have found that hydrogenation of podocarpic acid (Ia) proceeds over platinum in acetic acid at 60–70°, to give an easily-isolated perhydro derivative melting at 234–236°.[3] The formation of this perhydro podocarpic acid was accompanied by the formation of a mixture of isomeric C_{12} desoxy acids (m.p. 136–171°). Oxidation of the resulting hydroxy acid IIa gave the corresponding keto acid IIIa which in turn was easily converted to the keto ester IIIb. It was felt that much could be learned about the sterochemistry of the keto ester IIIb by the preparation of a compound having this same structure by an alternate method of reduction of the aromatic ring.

O-methylpodocarpinol[2a,4] (XI) was reduced with lithium and *t*-butyl alcohol in a mixture of tetrahydrofuran and ammonia.[5] Hydrolysis of the crude enol ether X followed by the separation of the ketonic and nonketonic fractions gave the conjugated ketone IXa along with the ring-C desoxy dodecahydropodocarpinol. It was reasonable to assume that the conjugated ketone obtained was the thermodynamically more stable (C-8$_{8\beta}$) form.

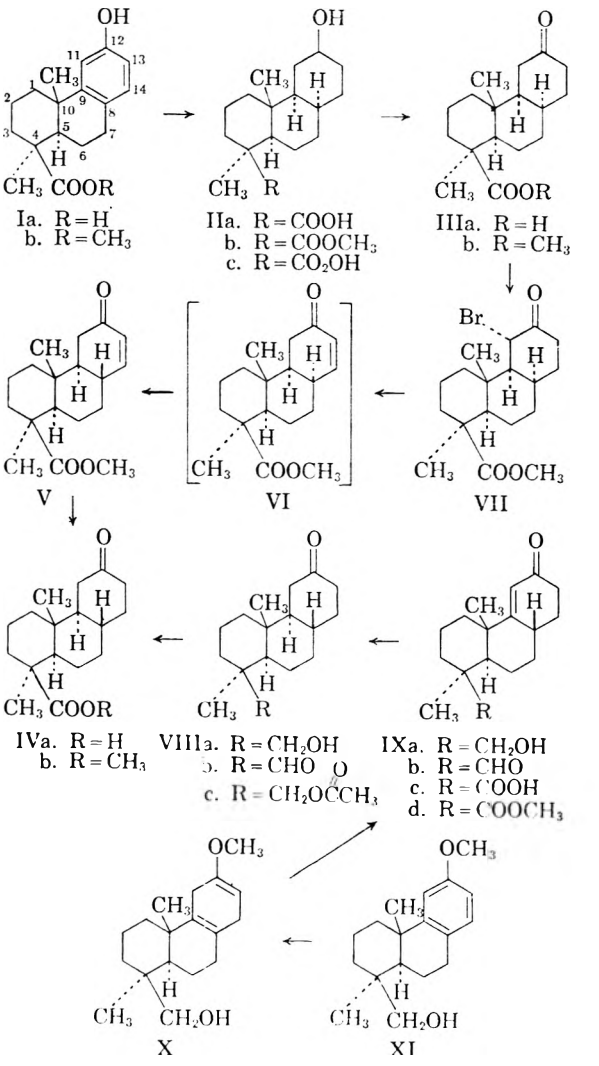


Figure 1

The position of the carbon-carbon double bond in the conjugated ketone IXa was clearly established by the position of the ultraviolet absorption maximum[6] (λ_{max} 240 mμ). Reduction of

(1) This work was presented in part at the 138th Meeting of the American Chemical Society, September 11–16, 1960, New York, N. Y. For previous papers in this series see (a) III, R. H. Bible, Jr., *Tetrahedron*, **11**, 22 (1960); (b) II, R. H. Bible, Jr., *Tetrahedron Letters*, No. 9, 20 (1960); (c) I, R. H. Bible, Jr., *J. Am. Chem. Soc.*, **79**, 3924 (1957).

(2)(a) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **64**, 928 (1942); (b) L. F. Fieser and W. P. Campbell, *J. Am. Chem. Soc.*, **61**, 2528 (1939); (c) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938).

(3) Hydrogenation over ruthenium oxide in ethanol at 100° follows a different steric course; this will be dealt with in a future communication.

(4) See H. H. Zeiss, C. E. Slimowicz, and V. Z. Pasternak, *J. Am. Chem. Soc.*, **70**, 1981 (1948).

(5) This technique was described by H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, before the 126th meeting of the AAAS, Chicago, Ill. (1959).

(6) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

this conjugated ketone (IXa) with lithium and *t*-butyl alcohol in a mixture of tetrahydrofuran and ammonia[5] gave the saturated ketone VIIIa. Here again, the method of formation strongly indicated that the isomer obtained was the more stable form.[7] It is of interest that the keto group in VIIIa was not reduced even though alcohol was present.[8] Oxidation of the primary alcohol group in VIIIa with chromic acid–sulfuric acid in acetone[9] gave the aldehyde VIIIb. Oxidation of either VIIIa or crude VIIIb with chromic acid and acetic acid gave the keto acid IVa. This keto acid (IVa) was easily converted to a keto ester (IVb) which was shown to be different from IIIb by direct comparison of the two substances. That IVb had the *trans-anti-trans* arrangement expected by its method of formation was clearly demonstrated by its strongly positive Cotton effect (amplitude +70).[10] Of the four possible isomers of different configurations at C_8 and C_9 (Fig. 2), IVb alone would be expected by the octant rule[11] to give a positive Cotton effect.

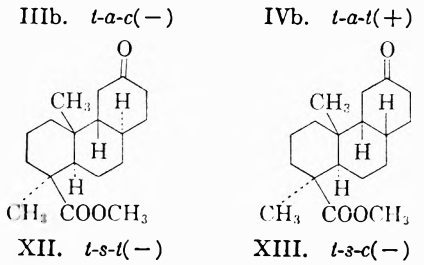


Fig. 2. Predicted Cotton Effects

It seemed reasonable that the hydrogenation of podocarpic acid had proceeded to give the $C_{8\alpha}$, $C_{9\alpha}$ ring junction, an assumption consistent with the observed[10] negative Cotton effect of the keto ester IIIb. If this were indeed the case, then the keto ester IIIb should be convertible to the keto ester IVb by epimerization at C_8. Introduction of a double bond either at $C_{9(11)}$ or at $C_{13(14)}$ in the keto ester IIIb should permit a test of this hypothesis. Bromination of the keto ester IIIb with *N*-bromosuccinimide in carbon tetrachloride at room temperature gave an axial bromo ketone VII (λ_{max} 310 mμ).[12] This bromo ketone, which will be discussed in the sequel, on dehydrobromination either with lithium chloride–lithium carbonate[13] or with collidine followed by equilibration over basic alumina gave the unsaturated keto ester V. The position of the ultraviolet absorption maximum[6] (230 mμ) was conclusive evidence that the double bond was in the indicated position. Hydrogenation of V gave a saturated keto ester (IVb) which was identical with the saturated keto ester prepared by way of the Birch reduction.

The conversion of IIIb to IVb clearly demonstrated that the difference in these two compounds resided in a difference in sterochemistry at C_8. This interconversion together with the observed Cotton effects proved that the skeletal sterochemistry of the keto ester IIIb and IVb were those predicted on chemical grounds.

The establishment of the skeletal stereochemistry of the reduction products of podocarpic acid permitted a further examination of the orientation of the substituents on ring C. The introduction of the axial bromine atom in IIIb to give VII was accompanied by a large *dextro* contribution to the molecular rotation[14] and a positive Cotton effect (amplitude +210).[10,11] As the nature of the B/C ring junction had been established and thus the complete absolute configurations were known,[15] the newly introduced bromine atom had to be assigned the C-11α position. The rearrangement observed in the dehydrobromination of VII to V is consistent with similar observations in other series.[16]

Equilibration of the bromo ketone VII gave (Fig. 3) an equatorial bromo ketone (λ_{max} 280

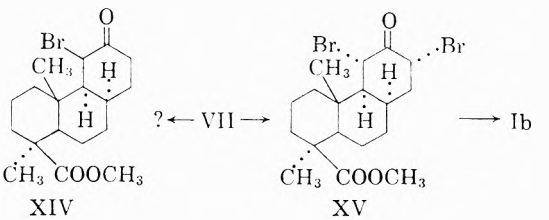


Fig. 3. Equilibration of the bromo ketone VII

(7) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(8) A number of examples of the reduction of a conjugated ketone to the saturated ketone by lithium in ammonia *in the absence of alcohol* have been reported [see F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952); and A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957)].

(9) This reagent was prepared by dissolving chromic acid (136.2 g.) and concd. sulfuric acid (110 ml.) in water (total volume = 500 ml.) see K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(10) We are indebted to Dr. William Klyne of the Postgraduate Medical School, University of London, London, England, for the determination and interpretations of the rotary dispersion curves.

(11) W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, unpublished observation; see C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill Book Co., New York, 1960, Chapter 13, and W. Klyne, *Advances in Organic Chemistry* (1960), **1**, 333.

(12) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(13)(a) R. Joly and J. Warnant, *Bull. Soc. Chim. France*, 367 (1958); (b) R. P. Holysz, *J. Am. Chem. Soc.*, 75, 4432 (1953).

(14) See E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **77**, 3667 (1955).

(15) See W. Klyne in *Determination of Organic Structures by Physical Methods*, E. A. Braude and F. C. Nachod, ed., Academic Press, New York, 1955, p. 122.

(16) See, for example, B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959); M. Gates and G. M. K. Hughes, *Chem. & Ind.*, 1506 (1956); and J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

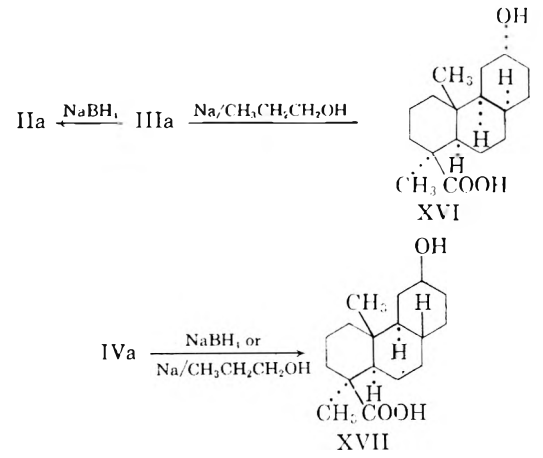


Fig. 4. Reduction of the keto acid IIIa

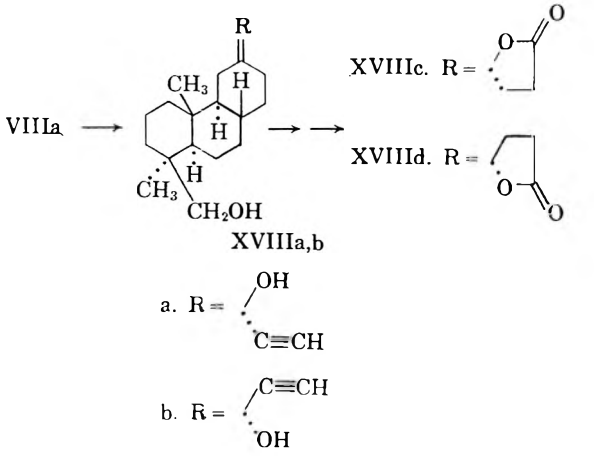


Fig. 5. Addition of acetylene to the keto alcohol VIIIa

mμ)[12] which must be either XIV or the isomeric $C_{13\beta}$ bromo compound. Unfortunately, the molecular rotatory dispersion cannot be employed in this case to establish the location of the bromine atom. Further bromination of VII yielded an α,α'-diaxial bromo derivative (XV; λ_{max} 342 mμ)[12] for which only one formulation is possible. Dehydrobromination of XV gave the known methyl podocarpate (Ib)[2c] in high yield.

Reduction of the keto acid IIIa (Fig. 4) with sodium in *n*-propyl alcohol gave a new hydroxy acid XVI in 65% yield while reduction with sodium borohydride gave a mixture of the hydroxy acid IIa and XVI in a ratio of 70:30. Since reduction with sodium in *n*-propyl alcohol is known to give a mixture of alcohols corresponding to the ratio of their thermodynamic stabilities,[17a] the new hydroxy acid XVI must have the hydroxy group in the equatorial ($C_{12\alpha}$) position. The hydroxy group in IIa must then be assigned the axial ($C_{12\beta}$) position which is consistent with its formation from the ketone IIIa by the approach of the reducing agent from the less hindered side. In contrast, the isomeric keto acid IVa yielded the same hydroxy acid by either reduction with sodium in *n*-propyl alcohol or by sodium borohydride. Accordingly, the hydroxyl in XVII was assigned the equatorial (β) position.

The addition of acetylene to the keto alcohol VIIIa congruously with the *trans-anti-trans* skeleton of VIIIa and the relatively low steric requirements of the reagent, (Fig. 5) gave a mixture of isomeric acetylenic hydroxy compounds (XVIIIa and XVIIIb). These substances were converted by a series of reactions to the saturated spirolactones[18] (XVIIIc and XVIIId).

The hydroxy acid IIa and its acetate displayed interesting anti-inflammatory properties in animals.[19] The details of the investigation of these properties will be reported elsewhere.

EXPERIMENTAL[20]

Except where noted, rotations were determined using 1% ethanol solutions and ultraviolet absorption spectra were run on methanol solutions. All melting points were taken on a Fisher-Johns block and were corrected using standard compounds.

trans-anti-cis-Perhydropodocarpic acid (IIa). A solution of podocarpic acid[2c] (50.0 g.) in acetic acid (250 ml.) was agitated under an atmosphere of hydrogen (965–875 lb./sq. in.) with platinum oxide (1.5 g.) at 60–76°. The uptake of hydrogen ceased after 2 hr. After 4.75 hr., the reaction mixture was filtered. Fresh catalyst (1.0 g.) was added. The mixture was stirred in an atmosphere of hydrogen (875–820 lb./sq. in.; 55–78°) for 5.5 hr. Removal of the catalyst and solvent gave a residual tan glass. This residue was refluxed for 2 hr. with a solution of potassium hydroxide (50 g.) in water (50 ml.) and methanol (200 ml.). Dilution of the reaction mixture with water followed by acidification with 5% hydrochloric acid gave a tan solid. Two recrystallizations from aqueous isopropyl alcohol (charcoal) gave *trans-anti-cis*-perhydropodocarpic acid (IIa); m.p. 230–233°; 14.2 g. A sample for analysis was obtained by two further recrystallizations; m.p. 234.5–236°; $[\alpha]_D$ +23°; λ_{max} 2.98 and 5.94 μ (KBr); no detectable band in the region 220–300 mμ at a concentration of 10 mg./100 ml.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.80; H, 9.98.

The material remaining in the mother liquor (23 g.) after removal of a second crop (7.0 g.; m.p. beginning at 155°) was chromatographed over silica (350 g.). Elution with 2% ethyl acetate in benzene gave desoxyperhydropodocarpic acid; 3.3 g.; m.p. 136–171°. The melting point of this material was not changed rapidly by recrystallization from aqueous methanol. A sample for analysis was obtained by one recrystallization from aqueous methanol; $[\alpha]_D$ +52°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.44; H, 10.56.

The *acetate* of *trans-anti-cis-perhydropodocarpic acid* was prepared by heating the hydroxy acid (25.0 g.; IIa) in acetic

(17)(a) For references see D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (b) E. P. Oliveto, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 1505 (1953).

(18) See J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(19) The determinations of the biological properties of these substances have been made by the staff of the Division of Biological Research of G. D. Searle and Company.

(20) All ultraviolet and infrared spectra and rotations were performed by the Analytical Department of G. D. Searle and Company under the direction of Dr. R. T. Dillon. Elementary analyses were determined by the Analytical Department and by Micro-Tech, Skokie, Ill.

anhydride (50 ml.) containing hydrochloric acid (0.1 ml.) at 80° for 30 min. The solid which formed on standing after dilution of the reaction mixture with water was collected and washed with water. Recrystallization from aqueous methanol gave the acetate of *trans-anti-cis*-perhydropodocarpic acid; m.p. 134.5–136°; $[\alpha]_D$ −11°; λ_{max} 5.78 and 5.91 μ (KBr); no detectable band in the region 220–370 mμ at 40 mg./100 ml.; ϵ 198 at 220 mμ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.97; H, 9.60.

Esterification of IIa with dimethylsulfate and sodium hydroxide in aqueous methanol[23] gave *methyl trans-anti-cis-perhydropodocarpate* (IIb). The product, which did not crystallize, was distilled at about 154° (0.15 mm.) to give the methyl ester as a colorless glass; $[\alpha]_D$ +31°; λ_{max} 2.77 and 5.83 μ ($CHCl_3$).

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.07.

Methylation of the acetate of perhydropodocarpic acid with dimethyl sulfate and sodium hydroxide in aqueous methanol[2c] followed by recrystallization of the product from aqueous methanol gave the acetate of *methyl trans-anti-cis-perhydropodocarpate;* m.p. 82–84°; $[\alpha]_D$ −1°; λ_{max} 5.78; ϵ 198 at 220 mμ.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59; OCH_3, 9.22. Found: C, 71.35; H, 9.33; OCH_3, 8.95.

4β-Carboxy-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrone (IIIa). The hydroxy acid IIa (100 g.) in acetone (40 ml.) was oxidized by the slow addition of an 8N chromic acid solution[9] (150 ml.). The solid which separated on dilution of the reaction mixture with water was collected, washed with water, and then recrystallized three times from aqueous methanol; m.p. 167.5–174°; 93.5 g.; $[\alpha]_D$ +35°; λ_{max} 3.18, 5.82, and 5.95 μ (broad) (KBr) and 281 mμ (ϵ 21.2).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.03; H, 9.27.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrone (IIIb). Methylation of the keto acid IIIa with dimethyl sulfate and sodium hydroxide in aqueous methanol[2c] gave the corresponding keto ester IIIb. Recrystallization from aqueous methanol gave either a lower melting point (110–113°) crystalline modification or a higher (120–121.5°) form. The lower melting form could be obtained by sublimation at reduced pressure; $[\alpha]_D$ +41°; λ_{max} 5.83 μ ($CHCl_3$) and 281 mμ (ϵ 24).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.07; H, 9.51.

4β-Methoxycarbonyl-4α,10β-dimethyl-11α-bromo-trans-anti-cis-perhydro-12-phenanthrone (VII). *N*-Bromosuccinimide (8.81 g.) was added to a solution of IIIb (14.5 g.) in carbon tetrachloride (70 ml.). Exposure of the reaction mixture to diffused sunlight initiated a reaction which was moderated by occasional cooling in an ice bath. The reaction was complete in about 30 min. After removal of the solid by filtration, the solvent was distilled using a rotating flask evaporator under reduced pressure over a warm (35°) water bath. Addition of hexane to the residual glass gave a crystalline solid which on three recrystallizations from hexane gave the pure bromo ketone; m.p. 152–153°; 6.7 g.; $[\alpha]_D$ +167°; λ_{max} 5.82 μ (KBr) and 310 mμ (ϵ 130).

Anal. Calcd. for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52. Found: C, 58.63; H, 7.37; Br, 20.94.

Hydrogenation of the material in the mother liquor over 5% palladium on calcium carbonate (10 g.) in ethanol (200 ml.) at 25° gave the starting keto ester IIIb which, after two recrystallizations from aqueous methanol amounted to 4.9 g.; m.p. 116.5–121.5°.

Isomerization of the axial bromo ketone VII. A solution of the bromo ketone VII (1.79 g.) and 48% hydrobromic acid (6 ml.) in acetic acid (60 ml.) was allowed to stand at room temperature for 48 hr. The reaction mixture, after dilution with water, was extracted with ether. The ether solution was washed with water. Distillation of the ether followed by azeotropic drying of the residue with benzene gave a residual glass. Recrystallization of this residue from hexane (charcoal) gave the equatorial bromo ketone XIV; 0.210 g.; m.p. 143.5–147°; $[\alpha]_D$ +59 ± 4°; λ_{max} 5.83 μ ($CHCl_3$) and 280 mμ (ϵ 45).

Anal. Calcd. for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52. Found: C, 58.08; H, 7.23; Br, 21.89.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-1,2,-3,4,5α,6,7,8β,9α,10,11,12-dodecahydro-12-phenanthrone (V). (A) The bromo ketone VII (4.31 g.) was added under nitrogen with stirring to redistilled collidine (50 ml.) which had been preheated to reflux temperature. The reaction mixture was stirred and heated at reflux temperature for an additional 30 min. The product was extracted into ether after dilution of the reaction mixture with 2% hydrochloric acid. The ether solution was washed with water and then dried over anhydrous sodium sulfate. Removal of the drying agent and solvent gave the crude material as a light yellow glass.

The residue was stirred in benzene (200 ml.) with basic aluminum oxide (Woelm; activity grade I; 20 g.) at reflux temperature for 35 min. The aluminum oxide was filtered off and washed with benzene. Removal of the solvent from the combined filtrates gave a light yellow crystalline solid which was recrystallized from aqueous methanol (charcoal); 0.52 g.; m.p. 117–123°. Two further recrystallizations from aqueous methanol gave the pure conjugated ketone V as flat blades; m.p. 126.5–129°; $[\alpha]_D$ +72°; λ_{max} 5.79, 5.95 (broad), 6.24, and 11.36 (broad) μ and 230 mμ (ϵ 8,710).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.29; H, 9.03.

(B) A mixture of the bromo ketone VII (6.7 g.), lithium chloride (1.34 g.), and lithium carbonate (1.0 g.) was heated at reflux temperature in dimethylformamide (142 ml.) for 6 hr.[13] The reaction mixture was diluted with water (total volume 1.5 l.). Three recrystallizations of the resulting solid from aqueous methanol (charcoal) gave the conjugated ketone V (1.13 g. m.p. 122.5–126.5°) which was identical with the material obtained by Method A. Further work-up of the mother liquors gave an additional amount of V; 0.32 g.; m.p. 121–126.5°.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (IVa). The conjugated ketone V (0.30 g.) was hydrogenated in ethanol (30 ml.) in the presence of 5% palladium-charcoal (0.030 g.) at room temperature. The absorption of hydrogen amounted to 92% of the required theoretical amount. The crystalline residue, which was obtained after removal of the catalyst and solvent, was recrystallized twice from aqueous methanol followed by one recrystallization from aqueous acetone (charcoal) to give the saturated ketone IVa; m.p. 116.5–121.5°; 0.16 g.; $[\alpha]_D$ +48° (0.5% ethanol). This compound was identical (no depression of melting point on admixture; identical infrared absorption spectra) with the saturated ketone prepared below by means of the Birch reduction.

4β-Hydroxymethylene-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrol (IIc). Reduction of the hydroxy acid IIa (5.0 g.) in ether (200 ml.) with lithium aluminum hydride (3.0 g.) at room temperature for 4 days[4] gave both starting material (1.8 g.) and *trans-anti-cis*-perhydropodocarpinol (1.2 g.). Recrystallization of the perhydropodocarpinol from aqueous methanol followed by drying of the product at 100° (0.1 mm.) gave the pure material; m.p. 120–123°; $[\alpha]_D$ −52°; λ_{max} 3.96 μ (KBr).

Anal. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.79; H, 11.36.

4β-Methoxycarbonyl-4α,10β-dimethyl-11α,13α-dibromo-trans-anti-cis-perhydro-12-phenanthrone (XV). The keto ester VII (10.0 g.) in carbon tetrachloride (100 ml.) was brominated with *N*-bromosuccinimide (12.2 g.) at room temperature in diffused sunlight. The product, worked up by the procedure given above for the monobromo ketone, and recrystallized three times from aqueous methanol, melted at 162–164.5°; 1.44 g.; $[\alpha]_D$ +5°; λ_{max} 5.82 μ and 342 mμ (ϵ 180).

Anal. Calcd. for $C_{18}H_{26}Br_2O_3$: C, 43.02; H, 5.82; Br, 35.50. Found: C, 47.97; H 6.20; Br, 34.82.

Dehydrobromination of the dibromoketone XV. A solution of XV (0.50 g.) in dimethyl formamide (6 ml.) was refluxed with lithium chloride (0.282 g.) for 1.5 hr.[13b] Recrystallization of the product from aqueous methanol gave methyl podocarpate; 0.27 g.; m.p. 204.5–208°. This compound was identical with an authentic sample of methyl podocarpate[2c] (no depression of the melting point on admixture; identical infrared spectra; identical ultraviolet spectra).

4β-Carboxy-4α,10β-dimethyl-trans-anti-cis-perhydro-12α-phenanthrol (XVI). A solution of the keto acid IIIa (0.50 g.) in *n*-propyl alcohol (25 ml.) was maintained at the reflux temperature during the addition of 2.5 g. of sodium.[17b] The reaction mixture was maintained at the reflux temperature for 1 hr. after the addition of the sodium was completed and was then treated successively with methanol, water, and 5% hydrochloric acid. The residue remaining after removal of the solvents was stirred with water and then collected. Two recrystallizations from aqueous methanol gave the hydroxy acid XVI; 0.33 g.; m.p. 253–256°. A sample for analysis was obtained by sublimation under reduced pressure; $[\alpha]_D$ +52°; λ_{max} 2.97 and 5.93 μ (KBr); no detectable band in the region 220–370 mμ at 11 mg./100 ml.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.64; H, 10.21.

An admixture of the two isomeric hydroxy acids IIa and XVI melted in between the melting points of the two pure substances.

Reduction of the keto acid IIIa *with sodium borohydride.* A solution of sodium borohydride (2.80 g.) in water (10 ml.) was added slowly to a warm solution of the ketone IIIa (5.10 g.) and sodium hydroxide (0.74 g.) in ethanol (53 ml.). The reaction mixture was allowed to stand at room temperature for 40 hr. The mixture was diluted with water (total volume = 2 l.). Acetic acid and then 10% hydrochloric acid were added. The resulting solid was collected, washed with water, and then dried overnight in the steam-oven; 4.98 g.; m.p. 235–240°; $[\alpha]_D$ +23°. The infrared absorption spectrum of this material resembled very closely the spectrum of a mechanical mixture of IIa (70%) and XVI (30%) which exhibited a melting point of 234–244° and $[\alpha]_D$ +30°.

4β-Hydroxymethylene-4α,10β-dimethyl-12-methoxy-1,2,3,4,-5α,6,7,10,11,14-decahydrophenanthrene (X). Ten grams of lithium wire was added during a 12 min. period to stirred solution of 20 g. of *O*-methylpodocarpinol (XI)[2a,4] in 250 ml. of *t*-butyl alcohol, 250 ml. of tetrahydrofuran and 600 ml. of ammonia[5] contained in a 3-l. three-necked flask fitted with a sealed stirrer and a Dry Ice cooled condenser. The deep blue solution topped by a bronze liquid amalgam phase decolorized spontaneously after about 1 hr. After the addition of 50 ml. of methanol, the ammonia was evaporated and 500 ml. of water was added. Vacuum distillation of about 500 ml. of the mixed solvent caused the separation of a waxy solid which was then collected on a filter, rinsed free of alkali and dried at room temperature. The crude mixture weighed 19.3 g. The ultraviolet spectrum at 100 mg./100 ml. showed the absence of aromatic compounds. Crystallization of a sample from hexane gave small needles, m.p. 100–103°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.80; H, 10.49.

4β-Hydroxymethylene-4α,10β-dimethyl-1,2,3,4,5α,6,7,8β,-10,12,13,14-dodecahydro-12-phenanthrone (IXa). The crude enol ether X was dissolved in 153 ml. of methanol containing 10.2 ml. of 12*M* hydrochloric acid and 6.8 ml. of water and stored at room temperature for 2 hr. Dilution with 600 ml. of water precipitated a viscous oil which failed to crystallize and was therefore recovered by chloroform extraction to yield 18 g. of a clear yellow glass. A solution of the latter in 180 ml. of anhydrous alcohol containing 18 g. of Girard's T reagent and 18 ml. of acetic acid was refluxed for 0.5 hr. The cooled mixture was then poured into a solution of 25.2 g. of sodium bicarbonate in 720 ml. of water. The curdy precipitate was recovered by extraction with three 200-ml. portions of ether and removal of the solvent to give 6.0 g. of a non-ketonic fraction as a colorless glass. The aqueous alkaline solution from the above extraction was acidified to a *p*H of about 2.0 with 6*M* hydrochloric acid. After 2.0 hr. the mixture was extracted with three 200-ml. portions of ether and the extract was washed with water, dried and evaporated to yield 10.6 g. of a viscous yellow oil which crystallized on standing. Recrystallization from 30 ml. of ethyl acetate and 30 ml. of isopropyl ether gave 7.4 g. of IXa melting at 105–107°. An analytical sample, crystallized from ethyl acetate, melted at 111–112°; λ_{max} 240 mμ (ϵ 16,250).

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.53; H, 9.78.

The *semicarbazone* melted at 255° with decomposition after crystallization from alcohol.

Anal. Calcd. for $C_{18}H_{29}N_3O_2$: N, 13.15. Found: N, 13.26.

The crude non-ketonic fraction was dissolved in benzene and chromatographed over 420 g. of silica gel. Elution with benzene afforded 4.5 g. of *4β-hydroxymethylene-4α,10β-dimethyldodecahydrophenanthrene,* which upon crystallization from 80% methanol (charcoal), melted at 108–109° and weighed 3.2 g.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 81.98; H, 11.50.

4β-Methoxycarbonyl-4α,10β-dimethyl-1,2,3,4,5α,6,7,8β,-10,12,13,14-dodecahydro-12-phenanthrone (IXd). The alcohol IXa (10.6 g.) was oxidized in acetone (500 ml.) with a standard solution of chromic acid-sulfuric acid (23 ml.).[9] After the excess oxidant was decomposed by the addition of isopropyl alcohol, about two-thirds of the solvent was distilled under reduced pressure. The residue was diluted with water and the product was then extracted into chloroform. Removal of the solvent gave the crude aldehyde IXb; 10 g.; λ_{max} 3.61, 5.79, 5.97, and 6.22 μ ($CHCl_3$).

A solution of the crude aldehyde IXb (10 g.) in acetic acid (100 ml.) was treated at 15–20° with a solution of chromic acid (3.2 g.) in 66% acetic acid (12 ml.). The reaction mixture, after standing overnight, was diluted with water (2 l.). The resulting mixture was heated to 80° and then cooled. The solid was collected, washed with water, and then dried to give the crude acid IXc; 7.5 g.; λ_{max} 2.81, 5.86, 5.97, and 6.22 μ ($CHCl_3$).

The crude acid IXc (7.0 g.) was methylated with dimethyl sulfate and sodium hydroxide in 50% methanol.[2c] The ester was extracted into ether from an alkaline aqueous mixture. The ether extract was washed with water and then evaporated to give the crystalline ester IXd (5.5 g.) which, after two recrystallizations from methanol amounted to 1.42 g.; m.p. 116–118°; $[\alpha]_D$ −8°; λ_{max} 5.78, 5.98, 6.25, and 11.36 μ ($CHCl_3$) and 238.5 mμ (ϵ 15,800).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.64; H, 9.13.

4β-Hydroxymethylene-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (VIIIa). A solution of 2 g. of the unsaturated ketone IXa in 25 ml. of *t*-butyl alcohol, 25 ml. of tetrahydrofuran and 60 ml. of ammonia was reduced with 1.0 g. of lithium as described above. Spontaneous decoloration occurred after 3.0 hr., whereupon 20 ml. of methanol was added and the ammonia was permitted to evaporate. Addition of 50 ml. of water, followed by vacuum distillation of solvent and extraction with ether gave 2.0 g. of crude VIIIa as a pale yellow glass. The infrared spectrum showed a strong band at 5.83 μ indicating that the carbonyl group had not been reduced.

Acetylation with acetic anhydride and pyridine at room temperature provided the acetate VIIIc which melted at 114.5–116° after crystallization from hexane; $[\alpha]_D$ +13.5°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.61; H, 10.02.

Saponification of this acetate gave the carbinol VIIIa which, after crystallization from ethyl acetate, melted at 105°; $[\alpha]_D$ +18.8°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.37; H, 10.64.

4β-Carboxyl-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (IVa). A solution of 3.0 g. of chromic anhydride in 2.0 ml. of water and 8.0 ml. of acetic acid was added during a 20-min. period at 15–20° to a stirred solution of 5.3 g. of the crude keto alcohol (VIIIa) in 50 ml. of acetic acid. The dark mixture was stirred for 20 min. longer, stored overnight, and then diluted with 1 l. of hot water. After several hours the finely divided precipitate was collected on a filter, rinsed well with water, and dried to yield 3.0 g. of crude acid (IVa). This crude acid was used without further purification.

Oxidation of the keto alcohol VIIIa in acetone with chromic acid–sulfuric acid gave the crude keto aldehyde VIIIb (λ_{max} 3.63 μ in $CHCl_3$).[21] Further oxidation of this aldehyde with chromic anhydride in acetic acid gave the keto acid IVa.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-12-phenanthrone (IVb). The crude acid IVa (2.22 g.) was methylated with dimethyl sulfate and sodium hydroxide in 50% methanol.[20] After extraction with chloroform, the extract was washed well with water and the solvent was vacuum distilled to give 2.0 g. of a dark oil which crystallized on standing. Vacuum sublimation (120°/0.3 mm.) followed by two crystallizations from methanol produced 0.65 g. of the methyl ester IVb melting at 119–120°; $[\alpha]_D$ +51° (ethanol); λ_{max} 5.83 μ.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.99; H, 9.58. Found: C, 73.88; H, 9.68.

The melting point of this material was depressed on admixture with IIIb.

4β-Carboxy-4α,10β-dimethyl-trans-anti-trans-perhydro-12β-phenanthrol (XVII). Method A. A solution of 3 g. of the crude acid (IVa) in 100 ml. of ethanol containing 0.8 g. of sodium hydroxide was heated to reflux and treated with a solution of 1.8 g. of sodium borohydride in 25 ml. of 80% ethanol. The stirred mixture was refluxed for 2 hr., cooled and cautiously acidified with 20 ml. of 6*M* hydrochloric acid. Dilution with 500 ml. of water gave a granular white precipitate which was collected on a filter, rinsed and dried. The crude acid XVII was recrystallized twice from ethyl acetate, yielding 1.0 g. of colorless spikes; m.p. 248–250°; $[\alpha]_D$ +41.4° λ_{max} 2.97 and 5.89 μ (KBr).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.75; H, 10.13. Found: C, 72.53; H, 9.88.

Method B. Reduction of the crude keto acid IVa with sodium in *n*-propyl alcohol gave XVII which was identical (no depression of the melting point on admixture identical infrared absorption spectra) with the material prepared by Method A.

Acetylation of 530 mg. of the carbinol XVII with acetic anhydride in pyridine at room temperature gave 436 mg. of the acetate of *4β-carboxy-4α,10β-dimethyl-trans-anti-trans-perhydro-12β-phenanthrol* melting at 152–154° after crystallization from hexane; $[\alpha]_D$ +5.5°; λ_{max} 2.83 (weak), 5.78, 5.89, and 7.92 μ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 71.03; H, 9.40.

4β-Hydroxymethylene-4α,10β-dimethyl-12ξ-ethynyl-trans-anti-trans-perhydro-12ξ-phenanthrol (XVIIIa *and* XVIIIb).[22] A solution of 35 g. of potassium in 800 ml. of dry *t*-butyl alcohol (prepared under nitrogen atmosphere) was diluted with 200 ml. of dry toluene, chilled to 5°, and saturated with acetylene. A solution of 25 g. of the ketone VIIIa in 200 ml. of dry toluene was added all at once to the stirred mixture, after which the treatment with acetylene under a slight positive pressure was continued at 0–5° for 5 hr. After dilution with 2 l. of water, the toluene layer was separated and the aqueous layer was extracted with 2 × 600 ml. of ether. The combined extracts were washed with water, dried, and evaporated to yield 28.5 g. of a brittle yellow glass (no carbonyl band in infrared). Crystallization from 300 ml. of ethyl acetate (charcoal) and concentration of the mother liquor to a volume of 100 ml. gave two crops of crystals (total of 7.1 g.) each of which melted at 180–220°. These were combined and recrystallized twice from ethanol to give 3.03 g. of XVIIIa (or b); colorless needles; m.p. 217–219°; $[\alpha]_D$ +3.5°; λ_{max} 2.79, 2.90–2.95 (doublet), 3.1 and 4.76 μ ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.51; H, 10.46. Found: C, 77.99; H, 10.21.

All mother liquors were combined and evaporated, yielding 22 g. of viscous oil which was dissolved in benzene and chromatographed over 1.5 kg. of silica gel. The 85% benzene–15% ethyl acetate eluate produced 5.07 g. of crystalline XVIIIb (or a) which, after crystallization from 40 ml. of acetonitrile (charcoal), weighed 4.33 g., and melted at 165°; $[\alpha]_D$ +39.5°; λ_{max} 2.72 and 3.0 μ ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.51; H, 10.46. Found: C, 78.08; H, 10.40.

The 80% benzene–20% ethyl acetate yielded 3.64 g. of XVIIIa (or b) melting at 216–218°.

4β-Hydroxymethylene-4α,10β-dimethyl-12ξ-carboxyethyl-trans-anti-trans-perhydro-12ξ-phenanthrol α-lactone (XVIIIc *and XVIIId*).[22] A solution of 2.95 g. (0.01 mole) of the ethynyl derivative XVIIIa in 40 ml. of tetrahydrofuran was added during a 5-min. period to a stirred solution of 0.15 mole of methylmagnesium bromide in tetrahydrofuran. The mixture was refluxed and stirred for 24 hr. (positive color test for RMgX) and then treated with carbon dioxide just above the stirred liquid surface at room temperature for 24 hr. A trap with a 1-in. head of mercury was used to prevent undue loss of solvent during carbonation. The gray suspension was poured onto 500 ml. of 5% sulfuric acid and then about 200 ml. of solvent was removed by vacuum distillation. After decanting the supernatant liquor, the resinous crude acid was taken up in 140 ml. of water containing 3 ml. of diethanolamine at 65°. The nearly clear hot solution was filtered through Celite and the hot filtrate was acidified. The solid white acid was collected on a filter, rinsed with water, and dried to yield 1.52 g. of crude *4β-hydroxymethylene-4α,-10β-dimethyl-12ξ-carboxyethynyl-trans-anti-trans-perhydro-12ξ-phenanthrol* which was used without further treatment.

A solution of 1.50 g. of the crude acetylenic acid in 100 ml. of alcohol was hydrogenated at atmospheric pressure. The filtered solution was treated with 4 ml. of 10% sodium hydroxide, boiled down to a volume of about 25 ml., and cooled to *ca.* 25°. Four milliliters of 6*N* hydrochloric acid was added and the solution was allowed to stand for 5 min. (to insure complete lactone formation). Dilution with 500 ml. of water gave a viscous product which soon granulated. The crude lactone (1.32 g.) was crystallized from 7 ml. of ethyl acetate (charcoal) to obtain 0.8 g. of pure XVIIIc (or d); m.p. 179–180°; $[\alpha]_D$ +17°; λ_{max} 2.72 and 5.64 μ ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.91; H, 10.07. Found: C, 74.54; H, 9.98.

Carboxylation of 4.3 g. of the acetylenic alcohol XVIIIb (or a) was conducted in the above manner to furnish 1.4 g. of crude acid which upon hydrogenation yielded 1.23 g. of crude lactone XVIIId (or c). Crystallization from 100 ml. of ethyl acetate (charcoal) gave 1.17 g. of lusterous white plates, m.p. 235–240°; $[\alpha]_D$ +23.6°; λ_{max} 2.72 and 5.65 μ ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.91; H, 10.07. Found: C, 74.94; H, 9.95.

(21) This observation led to the employment of this procedure in the preparation of *O*-methyl-7-methylpodocarpinal Ref. 1a and 1b.

(22) This sequence of reactions was patterned after that described in Ref. 18.

Acknowledgment. The authors express their thanks to Dr. William Klyne for his determination and interpretation of the rotatory dispersion curves, and to Messrs. W. J. Heidtke, R. L. Johnson C. J. Jung, M. G. Scaros, and W. M. Selby for their valuable technical assistance.

CHICAGO 80, ILL.

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

Naturally Occurring Oxygen Heterocyclics. X.[1] 4-Phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin[2,3]

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The yellow toxic principle isolated from the peelings of the fruits of *Mammea americana L.* is shown to be 4-phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin(III).

In a recent report[6] from this laboratory, mammein, the insecticidal constituent isolated[7] from the seeds of *Mammea americana L.* (family *Guttiferae*) was shown to possess structure I. Through the generous cooperation of Dr. Murrell P. Morris of the U. S. Department of Agriculture Experiment Station of Mayaguez, Puerto Rico, we have obtained a supply of a yellow toxic[8] principle isolated from the peelings of the fruits of the same plant, and the present article is concerned with its structure elucidation.

Repeated chromatography and recrystallization of the yellow substance led to homogeneous samples with wide melting point ranges, apparently due to solvation. The analytical specimen had m.p. 98–109°, was optically inactive, gave a dark brown color with ferric chloride and was soluble in aqueous sodium hydroxide but insoluble in dilute hydrochloric acid.

The analytical results were consistent with the empirical formula $C_{25}H_{26}O_5$ which was confirmed by the preparation of a beautifully crystalline diacetate, m.p. 122–124° ($C_{29}H_{30}O_7$) and dimethyl ether, m.p. 86–89° ($C_{27}H_{30}O_5$). The ultraviolet and infrared spectral data (see Experimental) were reminiscent of a coumarin structure similar to that of mammein,[6] while the analytical data suggested the replacement of the *n*-propyl substituent in the latter by a phenyl substituent. Indeed, the presence of a mono-substituted phenyl group was indicated by infrared absorbtion bands at 776 and 698 cm.$^{-1}$ (carbon disulfide). Along with the spectral and analytical data, the recovery of the unchanged yellow compound after treatment with alkali under conditions previously[9] used to effect isomerization[10] of mammein (I) to isomammein (II) led us to consider structure III for this substance. All details of this structure (III) were verified by the experiments discussed below.

The presence of a double bond in the side chain was indicated by the facile uptake of one mole of hydrogen to yield a yellow dihydride, m.p. 99–103°, which was characterized as its diacetate derivative, m.p. 98–102°. The ultraviolet and infrared spectra of the dihydride IV were very similar to those of III, thus showing that the reactive olefinic link is not conjugated with the main chromophoric system. Ozonization of III, followed by reductive work up of the ozonide, led to the isolation of acetone (69% yield as the 2,4-dinitrophenylhydrazone) unaccompanied by formaldehyde, as well as the aldehydic moiety V, whose empirical formula substantiated its formation by simple fission of the double bond.

A more drastic, as well as more infomative, breach of the molecule was accomplished by prolonged refluxing of III with aqueous potassium hydroxide. Under these conditions, III was degraded to a mixture from which acetophenone (79% yield), isovaleric acid (57% yield), and two

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(1) Paper IX, C. Djerassi, J. D. Gray, and F. A. Kincl, *J. Org. Chem.*, **25**, 2174 (1960).

(2) For preliminary communication, see R. A. Finnegan and C. Djerassi, *Tetrahedron Letters*, No. 13, 11 (1959).

(3) Financial support of this work by The National Heart Institute (grant No. H-2574) of the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

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(6) C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *J. Org. Chem.*, **25**, 2164 (1960).

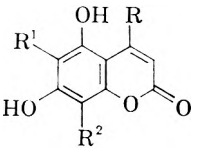
(7) M. P. Morris and C. Pagan, *J. Am. Chem. Soc.*, **75**, 1489 (1953).

(8) For a discussion of the toxicity of this fruit see M. P. Morris, C. Pagan, and J. Garcia, *Revista de Agricultura de Puerto Rico, Suplemento-Seccion Alimentos Nutricion*, Vol. XLIII, No. 1, 288a (1952).

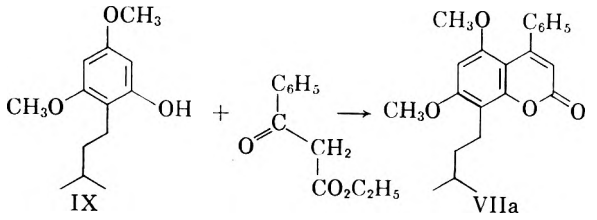
(9) C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey, and M. P. Morris, *J. Am. Chem. Soc.*, **80**, 3686 (1958).

(10) For discussion of the nature of this isomerization, see Ref. 6.

crystalline phenols: $C_{11}H_{14}O_3$, m.p. 102° (44% yield), and $C_{20}H_{18}O_4$, m.p. 214° (6% yield) could be isolated. The C_{11} phenol was shown to be isopentenylphloroglucinol (VIII) by its ultraviolet spectrum which is typical of monoalkyl phloroglucinols,[11] and by the formation of the known[6,12] isopentylphloroglucinol (VIIIa) upon hydrogenation. The structure of the C_{20} phenol VI followed from the conversion of its dimethyl ether VIa by hydrogenation to 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin (VIIa), identical with an authentic specimen synthesized by the Pechmann condensation[13] of 2-isopentyl-3,5-dimethoxyphenol[14] (IX) with benzoylacetic ester.



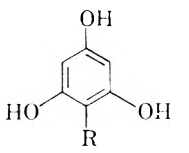
I.	R = $CH_3CH_2CH_2$—,	R^1 = $(CH_3)_2C$=$CHCH_2$—,	R^2 = $(CH_3)_2CHCH_2CO$—
II.	R = $CH_3CH_2CH_2$—,	R^1 = $(CH_3)_2CHCH_2CO$—,	R^2 = $(CH_3)_2C$=$CHCH_2$—
III.	R = C_6H_5—,	R^1 = $(CH_3)_2CHCH_2CO$—,	R^2 = $(CH_3)_2C$=$CHCH_2$—
IV.	R = C_6H_5—,	R^1 = $(CH_3)_2CHCH_2CO$—,	R^2 = $(CH_3)_2CHCH_2CH_2$—
V.	R = C_6H_5—,	R^1 = $(CH_3)_2CHCH_2CO$—,	R^2 = $OCHCH_2$—
VI.	R = C_6H_5—,	R^1 = H,	R^2 = $(CH_3)_2C$=$CHCH_2$—
VIa.	= VI with OH = OCH_3		
VII.	R = C_6H_5—,	R^1 = H,	R^2 = $(CH_3)_2CHCH_2CH_2$—
VIIa.	= VII with OH = OCH_3		
X.	R = C_6H_5—,	R^1 = $(CH_3)_2C$=$CHCH_2$—,	R^2 = $(CH_3)_2CHCH_2CO$—



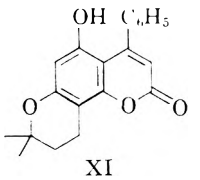
The results of the experiments described above are consistent only with structures III or its isomer X for the parent.[15]

In order to locate unambiguously the position of the isopentenyl substituent in III, use was made of the deacylation reaction conveniently brought about by 75% sulfuric acid. Discovered during synthetic studies,[14] this reaction found important application in the structure determination of mammein.[6] Accordingly, the dihydride IV was treated at room temperature with 75% aqueous sulfuric acid and the resultant phenolic coumarin VII converted to its dimethyl ether, VIIa. The product VIIa obtained in this sequence of reactions proved to be identical with the authentic sample of 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin described above. The combination, then, of the alkaline and acidic degradations along with the hydrogenation and ozonolysis experiments, provides the necessary evidence for the assignment of structure III to the toxic principle.[16]

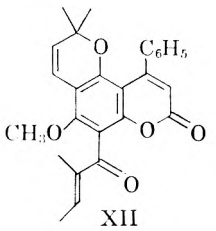
Although it does not bear directly on the structure proof, we wish to report one additional transformation of III. When the sulfuric acid–catalyzed deacylation reaction was applied to the parent III, there was readily obtained as the sole product (in addition to isovaleric acid), a phenol, m.p. 273–276°. Structure XI was assigned to this product on the basis of its microanalysis, infrared,



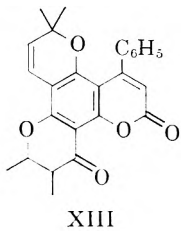
VIII. R = $(CH_3)_2C$=$CHCH_2$-
VIIIa. R = $(CH_3)_2CHCH_2CH_2$-



XI



XII



XIII

(11) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 2708 (1951).

(12) T. S. Kenny, A. Robertson, and S. W. George, *J. Chem. Soc.*, 1601 (1939).

(13) S. Sethna and R. Phadke, *Org. Reactions*, **7**, 1 (1953).

(14) R. A. Finnegan, B. Gilbert, E. J. Eisenbraun, and Carl Djerassi, *J. Org. Chem.*, **25**, 2169 (1960).

(15) The inference that the isopentenyl substituent which appears at position 8 in VI also occupies position 8 in III cannot be drawn from the alkaline degradation results, since the intermediate coumarinate salt may be cyclized in two directions upon acidification. For a discussion of the analogous situation with respect to mammein (I) and isomammein (II) see Ref. 6. Structure X may be ruled out, however, on the basis of its failure to isomerize to III on treatment with mild alkali. Ref. 6 contains a discussion of the mechanism and driving force operating during this isomerization.

(16) While it may be argued that the evidence cited does not rigorously place the isovaleryl substituent at position 6, we believe that its alternate location at position 3 is ruled out by the failure of the compound to isomerize during mild alkaline treatment (carbonyl group H-bonded with the C-5 hydroxyl group), by the failure to isolate either benzoic acid or methyl isopentyl ketone upon vigorous alkaline hydrolysis; and finally by the compelling biogenetic relationship to mammein.

and ultraviolet spectra, and the fact that it formed only a *monoacetate* and a *monomethyl* ether. It is apparent that cyclization of the 8-isopentenyl group with the 7-hydroxyl group has accompanied deacylation.

In conclusion, it may be noted that naturally occurring 4-substituted coumarins are very rare and that the isolation of mammein (I) and III from the same plant is of some biogenetic interest. Other 4-phenyl coumarins found in nature include dalbergin,[17] dalbergin methyl ether (4-phenyl-6,7-dimethoxycoumarin),[17] calophyllolide (XII)[18] and inophyllolide (XIII).[18,19] The close structural resemblance of the latter two to the presently described coumarin III is emphasized by the fact that both plant sources (*Calophyllum inophyllum L.* and *Mammea americana L.*) belong to closely related genera of the same family (*Guttiferae*).[20]

The authors are pleased to acknowledge many helpful conversations with Dr. E. J. Eisenbraun regarding this work.

EXPERIMENTS[21]

Isolation of III. The cylinder of a large Soxhlet extractor was filled with 900 g. of the dried peelings of the mamey fruit. The 3-l. receiver was filled with petroleum ether (b.p. 30–40°) and the extraction started and continued for 4 hr. The solvent in the receiver was then replaced by fresh solvent and the extraction continued for another 4 hr. The solvent was again changed and the extraction continued for 72 hr., the solvent being replaced every 24 hr. Each batch of solvent was evaporated to a small volume and allowed to stand at room temperature. The crystalline fractions which appeared at this point were combined into one main fraction. The yield of crude yellow solid was 5.2% based on the weight of dried peelings, or 1.5% if based on the weight of dried fruit minus seeds. (The latter figure is calculated from the fact that the dried unpeeled fruits minus seed contain 29% peel.) Seventy-five marketable fruit will yield 1 kg. of dried peel.[22]

The material thus obtained was a yellow powdery solid, m.p. 70–107°. It gave a dark brown ferric chloride test. It dissolved in 3*N* sodium hydroxide producing an orange solution, but did not dissolve in dilute hydrochloric acid. Its rotation in chloroform solution (21.3 mg./2 ml.) at 589 and 430 mμ was zero. Chromatography of the yellow solid (10 g.) on Merck acid-washed alumina (650 g.) did not effect resolution into more than one substance. Twenty-two fractions eluted in benzene-ether mixtures and in pure ether were separately crystallized from chloroform-hexane. Although the crystals were well formed needles, all fractions melted over the range 65–100°. Their infrared spectra were identical. After several recrystallizations from aqueous ethanol there was obtained material with m.p. 95–108° which was dried 48 hr. *in vacuo* to furnish the analytical sample, m.p. 98–109°; $\nu_{max}^{CHCl_3}$ 3436, 3289, 1730, 1621, 1587 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 1745, 1620, 1597, 766, 698 cm.$^{-1}$; ν_{max}^{KBr} 1715 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol-HCl}$ 281, 338 mμ, log ε 4.41, 4.00; $\lambda_{min}^{95\%\ ethanol-HCl}$ 249, 317 mμ, log ε 3.96, 3.94; $\lambda_{max}^{95\%\ ethanol-NaOH}$ 243, 301, 427 mμ, log ε 4.10, 4.15, 4.10; $\lambda_{max}^{95\%\ ethanol-NaOH}$ 256, 343 mμ, log ε 4.04, 3.43.

Anal. Calcd. for $C_{25}H_{26}O_5$: C, 73.86; H, 6.45; O, 19.68, mol. wt., 406. Found: C, 74.42; H, 6.47; O, 19.26; mol. wt., 350 (Rast). Material used in subsequent reactions was purified by passing it in ether solution through a column of Merck acid-washed alumina. (A grey-green band remained at the top of the column.). The residue remaining after evaporation of the eluate was crystallized from ether-hexane, m.p. 65–105°, then from aqueous ethanol, m.p. 97–109°.

Diacetate of III. When a solution of III (0.50 g.) in pyridine (12 ml.) was treated with acetic anhydride (3 ml.), the yellow color was almost immediately discharged. After a few minutes, the reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with hydrochloric acid, then with water. These aqueous washings were extracted with ether and the combined ether extracts were washed with aqueous sodium bicarbonate, then with water. These washings were extracted with ether and the combined organic extracts dried and evaporated to give a pale yellow oil which was crystallized from ether-hexane, m.p. 76–87°, 0.48 g. Recrystallization from chloroform-hexane afforded material with m.p. 83–91°. One additional recrystallization caused the m.p. to rise abruptly to 122–124°, unchanged by further recrystallization. The product gave a negative ferric chloride test.

Anal. Calcd. for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16; O, 22.83. Found: C, 71.00; H, 6.20; O, 22.99. $\nu_{max}^{CHCl_3}$ 1773, 1733, 1705 (shoulder), 1592, 1183 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 1783, 1748, 1709, 1592, 1179 cm.$^{-1}$; ν_{max}^{KBr} 1815, 1795, 1742, 1704, 1179 (broad) cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 286 mμ, log ε 4.06; $\lambda_{min}^{95\%\ ethanol}$ 272 mμ, log ε 4.03.

Dimethyl ether of III. To a solution of III (0.30 g.) in 15 ml. acetone, 2 g. of potassium carbonate and 0.25 ml. of dimethyl sulfate were added. The mixture was allowed to reflux 4 hr. before it was cooled and filtered. The residue remaining after evaporation of the solvent was recrystallized three times from hexane to give the product, m.p. 86–89°, 79 mg., negative ferric chloride test.

Anal. Calcd. for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96; O, 18.41; 2 OCH_3, 14.3; mol. wt., 434.5. Found: C, 74.61; H, 6.71; O, 18.26; OCH_3, 14.47; mol. wt., 401 (Rast). $\nu_{max}^{CHCl_3}$ 1727, 1582 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 1742, 1705, 1592, 766, 699 cm.$^{-1}$; ν_{max}^{KBr} 1739, 1706, 1580, 766, 703 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 299 mμ, log ε 4.08; $\lambda_{min}^{95\%\ ethanol}$ 272 mμ, log ε 3.94.

Treatment of III in ether with diazomethane afforded a substance identical with that described above.

The dihydride IV. An ethanol solution (100 ml.) of the parent substance III (3 g.) was hydrogenated at 28° in the presence of 300 mg. 10% palladium on charcoal. After three hours, 1.1 moles of hydrogen were absorbed. The mixture was filtered and concentrated to yield 1.41 g. of product IV, yellow needles, m.p. 96–101° from aqueous ethanol. A portion was recrystallized twice from 95% ethanol, m.p. 99–103°; $\nu_{max}^{CHCl_3}$ 1730, 1623, 1595 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 1745, 1626, 1605 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol-HCl}$ 282, 340 mμ, log ε 4.39, 3.98; $\lambda_{min}^{95\%\ ethanol-HCl}$ 248, 319 mμ, log ε 3.82, 3.91; $\lambda_{max}^{95\%\ ethanol-NaOH}$ 230 (very broad), 301, 429 mμ, log ε 4.18, 4.22, 4.05; $\lambda_{min}^{95\%\ ethanol-NaOH}$ 255, 346 mμ, log ε 4.13, 3.69.

Anal. Calcd. for $C_{25}H_{28}O_5$: C, 73.50; H, 6.91; O, 19.58. Found: C, 73.44; H, 6.94; O, 19.35.

Diacetate of IV. The dihydride IV (100 mg.) was dissolved in pyridine (5 ml.) with acetic anhydride (2 ml.). Within 1 min. the yellow color had disappeared and the reaction was worked up in the usual manner. The product was recrystallized four times from hexane, m.p. 98–102°, 34 mg.; $\nu_{max}^{CHCl_3}$ 1776, 1736, 1592, 1186 cm.$^{-1}$; $\nu_{max}^{CS_2}$ 1779, 1745, 1706, 1174 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 247, 286, 325 mμ (shoulder), log ε 4.25, 4.11, 3.65; $\lambda_{min}^{95\%\ ethanol}$ 271.5 mμ, log ε 4.07.

Anal. Calcd. for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55; O, 22.74. Found: C, 70.75; H, 6.36; O, 22.42.

(17) V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.*, 970 (1957).

(18) J. Polonsky, *Bull. Soc. chim. France*, 929 (1958).

(19) *Cf.* also calophyllic acid,[18] the *o*-hydroxycinnamic acid corresponding to XIII.

(20) The biogenetic relationship of 4-phenylcoumarins with flavonoids and benzophenones is briefly discussed by T. R. Seshadri, *Tetrahedron*, **6**, 172–173 (1959); also Ref. 17.

(21) All melting points were determined on a Kofler block. Microanalyses are by Dr. A. Bernhardt, Mulheim, Germany.

(22) The isolation procedure described is that of Dr. M. P. Morris, private communication.

Ozonolysis of III. (a) *Acetone.* A stream of ozonized oxygen was passed through a solution of III (1 g.) in glacial acetic acid (20 ml.) maintained at 15°. The exit gas gave a positive test for ozone with moist starch-iodide paper in less than 5 min. The reaction mixture was poured into a cooled (ice bath) aqueous solution of ferrous sulfate and the resulting mixture was stirred 45 min. Nitrogen was then passed through the gently warmed mixture for 20 hr. The exit gases were led in series through two bottles containing 2,4-dinitrophenylhydrazine in aqueous sulfuric acid. The precipitate was collected by extraction with benzene. The extract was dried, concentrated, and filtered through a column of Merck acid-washed alumina. The benzene eluate was evaporated to give 405 mg. (69% yield) acetone 2,4-dinitrophenylhydrazone m.p. 95–122°. The absence of the corresponding formaldehyde derivative was shown by chromatography of this product on Whatman number 7 filter paper, using a phenylcellosolve-heptane solvent system.[23]

Two recrystallizations of the product from chloroform-hexane raised the melting point to 123–124°, alone or admixed with an authentic sample of acetone 2,4-dinitrophenylhydrazone. The infrared spectra (chloroform) of the two samples were identical.

(*b*) *The aldehyde V.* The residue remaining after removal of the acetone (above) was extracted with ether. After the ether extracts were dried and concentrated, 0.60 g. of tan crystals were obtained, m.p. 156–174° from ether-hexane. These were recrystallized six times from chloroform-hexane to give pure V as pale yellow needles, m.p. 175–183°. The melting point did not change after two additional recrystallizations. ν_{max}^{KBr} 1721, 1621 (both broad), 768, 703, cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1733 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\text{-}HCl}$ 279, 343 mμ, log ε 4.43, 4.04; $\lambda_{min}^{95\%\ ethanol\text{-}HCl}$ 247.5, 314 mμ, log ε 3.73, 3.38; $\lambda_{max}^{95\%\ ethanol\text{-}NaOH}$ 298, 415 mμ, log ε 4.32, 4.16; $\lambda_{min}^{95\%\ ethanol\text{-}NaOH}$ 343 mμ, log ε 3.92.

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30; O, 25.24; Found: C, 69.28; H, 5.28; O, 25.14.

Attempted isomerization of III. A solution of III (300 mg.) in 50 ml. methanol containing 3 g. of potassium hydroxide was allowed to stand in a refrigerator for 8 hr. The reaction mixture was then diluted with water and extracted with ether (discarded). The aqueous layer was acidified and extracted with ether. These ether extracts, after being dried and evaporated, afforded 140 mg. yellow semisolid which was recrystallized from chloroform-hexane, m.p. 64–109°. The infrared spectrum of this substance was identical with that of the starting material III.

Alkaline degradation of III. (a) *Acetophenone.* The parent compound III (2.6 g.) was dissolved in 120 ml. of water with 18 g. of potassium hydroxide and the resulting orange solution was allowed to reflux for 67 hr. under a nitrogen atmosphere. The reaction mixture was then steam distilled. The distillate was collected in a solution of 2,4-dinitrophenylhydrazine (made up in the proportion: 1 g. of reagent, 20 ml. of sulfuric acid, 80 ml. of water) until no further precipitation was observed. The precipitate was collected on a filter, air dried, and passed in benzene solution through a column of Fisher (A-540) alumina. From the eluate was obtained, after evaporation of the solvent, 1.53 g. (79% yield) of acetophenone 2,4-dinitrophenylhydrazone, m.p. 243–245°. Recrystallization from chloroform-hexane afforded 1.1 g. of product, m.p. 245–246° alone or admixed with an authentic sample of acetophenone 2,4-dinitrophenylhydrazone. The infrared spectrum of the naturally derived material was identical to that of the authentic sample.

(b) *Isovaleric acid.* The aqueous residue remaining after removal of the acetophenone was acidified with 85% phosphoric acid and then steam distilled until the distillate no longer gave an acid reaction to litmus paper. The distillate was made basic, concentrated, reacidified, and extracted with ether. The ether extracts were dried and the solvent was removed through a Vigreux column. Upon distillation of the residue there was obtained 372 mg. (57%) of a colorless liquid whose infrared spectrum (carbon disulfide) was identical with that of an authentic sample of isovaleric acid. Confirmation of the identity of the naturally derived acid was obtained by vapor phase chromatography of its methyl ester and comparison of the elution curve with that of mixtures of authentic methyl esters. This study also indicated the presence in trace amount of methyl isobutyrate in the naturally derived ester.

(c) *4-Phenyl-5,7-dihydroxy-8-isopentenylcoumarin* (VI). The aqueous residue remaining after removal of the volatile acids (see above) was extracted with ethyl acetate. The extracts, after being dried and evaporated, afforded a brown resin which was chromatographed on 100 g. Merck acid-washed alumina. Elution was begun with 4:1 benzene-hexane and continued with benzene, benzene-ether mixtures, ether, ether–ethyl acetate mixtures, and ethyl acetate. From the 4:1 ether-benzene eluate through the 1:1 ether–ethyl acetate eluate was obtained a brown semisolid which crystallized from benzene, m.p. 182–213° subl., 130 mg. Two sublimations of a portion of this material afforded pale yellow crystals of 4-phenyl-5,7-dihydroxy-8-isopentenylcoumarin (VI), m.p. 208–214°; ν_{max}^{KBr} 3311, 1712, 1610, 1563, 747, 703 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 266.5, 337 mμ, log ε 4.22, 4.06; $\lambda_{min}^{95\%\ ethanol}$ 244.5, 294 mμ, log ε 3.90, 3.66; $\lambda_{max}^{95\%\ ethanol\text{-}NaOH}$ 282, 405 mμ, log 4.15, 3.95; $\lambda_{min}^{95\%\ ethanol\text{-}NaOH}$ 275, 320 mμ, log ε 4.13, 3.35.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63; O, 19.85. Found: C, 74.45; H, 5.90; O, 18.68.

(d) *Isopentenylphloroglucinol* (VIII). After elution of coumarin VI from the column (see above), the main band was obtained by continued elution with 1:1 ether-ethyl acetate and pure ethyl acetate. Evaporation of the solvent afforded a solid which was recrystallized from hexane-chloroform, m.p. 96–100°, 0.55 g. (44% yield). Two additional recrystallizations from the same solvent furnished the analytical sample of isopentenylphloroglucinol (VIII), m.p. 101–102°; ν_{max}^{KBr} 3205, 1618 cm.$^{-1}$ (both broad); $\lambda_{max}^{methanol}$ 271, 274, 279 mμ, log ε 2.84, 2.82, 2.76; $\lambda_{min}^{methanol}$ 253 mμ log ε 2.49; $\lambda_{max}^{methanol\text{-}NaOH}$ 257, 279, 355 mμ, log ε 3.84, 3.76, 3.42; $\lambda_{min}^{methanol\text{-}NaOH}$ 245, 270, 315 mμ, log ε 3.79, 3.71, 2.94.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; O, 24.71; 1 C—CH_3, 7.73. Found: C, 67.97; H, 7.26; O, 25.06; C—CH_3, 5.60.

Hydrogenation of isopentenylphloroglucinol (VIII). *Formation of isopentylphloroglucinol* (VIIIa). Isopentenylphloroglucinol (VIII) (37 mg.) was stirred in ethanol solution with 10% palladium on carbon (10 mg.) in a hydrogen atmosphere for 2 hr. at 30°. The reaction mixture was filtered and evaporation of the filtrate afforded 33 mg. of tan crystals, m.p. 121–125° subl. Sublimation (110° at 0.1 mm.) raised the m.p. to 125–126.5°, undepressed upon admixture with an authentic sample[14] of isopentylphloroglucinol. The infrared spectra (potassium bromide) of the two samples were identical.

4-Phenyl-5,7-dimethoxy-8-isopentenylcoumarin (VIa). *Methylation of* VI. 4-Phenyl-5,7-dihydroxy-8-isopentenylcoumarin (VI) (100 mg. crude) obtained by alkaline degradation of the parent III (see above) was dissolved in 5 ml. of acetone with 0.3 ml. of dimethyl sulfate and the solution was allowed to reflux for 24 hr. over 1 g. of anhydrous potassium carbonate. After the mixture was cooled and filtered, the residue obtained by evaporation of the filtrate was chromatographed on 10 g. of Merck acid-washed alumina. The product dimethyl ether VIa was obtained in the benzene eluate and recrystallized twice from chloroform-hexane, m.p. 157–159°, 19 mg.; ν_{max}^{KBr} 1730, 1610, 1580, 763, 749, 707 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 74.82; H, 6.38.

4-Phenyl-5,7-dihydroxy-8-isopentylcoumarin (VII). *Acid-*

(23) W. S. Lynn, L. A. Steele, E. Staple, *Anal. Chem.*, **28**, 132 (1956).

catalyzed deacylation of the dihydride IV. The dihydride IV (0.5 g.) was allowed to stand with occasional shaking at room temperature for 44 hr. with 10 ml. of 75% of sulfuric acid. The mixture (strong fatty acid odor) was poured onto ice, diluted with water and filtered. The yellow solid collected was recrystallized twice from chloroform-hexane to give VII as pale yellow crystals, m.p. 183–185.5°, 151 mg. A portion was recrystallized for analysis, m.p. 184–186°: ν_{max}^{KBr} 1695, 1608 cm.$^{-1}$ (both broad); $\lambda_{max}^{95\%\ ethanol}$ 266, 338 mμ, log ε 4.08, 4.04; $\lambda_{min}^{95\%\ ethanol}$ 242, 286 mμ, log ε 3.06; 3.32; $\lambda_{max}^{95\%\ ethanol\text{-}NaOH}$ 286, 415 mμ, log ε 4.22, 4.07; $\lambda_{min}^{95\%\ ethanol\text{-}NaOH}$ 277, 322 mμ, log ε 4.21, 3.70.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22; O, 19.73. Found: C, 74.15; H, 6.43; O, 19.69.

4-Phenyl-5,7-dimethoxy-8-isopentylcoumarin (VIIa). (a) *Hydrogenation of* VIa. 4-Phenyl-5,7-dimethoxy-8-isopentenylcoumarin (VIa) (11.4 mg.) was dissolved in absolute alcohol (1 ml.) and stirred with 10% palladium on charcoal (1.5 mg.) in an atmosphere of hydrogen at 29°. In 2 hr., 0.91 molar equivalents of hydrogen were absorbed. The mixture was stirred an additional 12 hr. before it was filtered and evaporated to give 9 mg. of crystalline product, m.p. 94–128°. Four recrystallizations from chloroform-hexane furnished pure 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin, m.p. 131–132° alone or admixed with authentic VIIa. The infrared spectra (potassium bromide) of the two specimens were identical.

(b) *Methylation of* VII. 4-Phenyl-5,7-dihydroxy-8-isopentylcoumarin (VII) (127.) was treated in refluxing acetone with dimethyl sulfate (0.4 mL) and anhydrous potassium carbonate (1 g.). The mixture was allowed to reflux 12 hr. before it was filtered and evaporated to give an oil which was chromatographed on 15 g. Merck acid-washed alumina. Crystalline fractions eluted in 3:1 benzene-hexane and in pure benzene were combined and recrystallized from chloroform-hexane, 62 mg., m.p. 131–132.5° alone or admixed with an authentic sample of 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin (VIIa). The infrared spectra were identical.

Synthesis of 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin (VIIa). 2-Isopentyl-3,5-dimethoxyphenol[14] (275 mg.) was dissolved in 5 ml. glacial acetic acid along with 0.5 ml. of benzoylacetic ester and 0.3 ml. of concd. sulfuric acid. The dark red solution was allowed to stand at room temperature for 72 hr. before it was poured onto ice, diluted with water, and filtered. The solid thus obtained was dissolved in chloroform-hexane, treated with Norite, and recrystallized twice to give 109 mg. 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin (VIIa), m.p. 130–132°; ν_{max}^{KBr} 1730, 1613, 1587, 762, 705 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1715, 1610, 1590 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 262, 330 mμ, log ε 4.19, 4.08; $\lambda_{min}^{95\%\ ethanol}$ 242, 276.5 mμ, log ε 3.99, 3.66.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86; O, 18.16; 2 OCH_3, 17.7. Found: C, 74.95; H, 6.63; O, 18.36; OCH_3, 17.24.

Acid-catalyzed deacylation of III. *The formation of* XI. The parent compound III (0.50 g.) was stirred with 5 ml. of 75% sulfuric acid at room temperature for 27 hr. The mixture was then poured onto ice, diluted with water, and filtered. The air dried solid, 370 mg., had m.p. 265–275° subl. A portion was twice sublimed to give XI as pale yellow crystals, m.p. 273–276°; ν_{max}^{KBr} 3279, 1695, 1629, 1592, 755, 697 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol}$ 265, 336 mμ, log ε 4.26, 4.16; $\lambda_{min}^{95\%\ ethanol}$ 247, 294 mμ, log ε 4.01, 3.80; $\lambda_{max}^{95\%\ ethanol\text{-}NaOH}$ 287, 342, 418 mμ, log ε 4.19, 4.02; 3.79; $\lambda_{min}^{95\%\ ethanol\text{-}NaOH}$ 267, 308, 374 mμ, log ε 4.01, 3.73, 3.46.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63; O, 19.85. Found: C, 74.26; H, 5.58; O, 19.75.

From the colorless aqueous filtrate (above), after saturation with sodium sulfate, extraction with ether, evaporation of the solvent, and distillation of the residue, there was obtained 81 mg. colorless liquid identified as isovaleric acid by its infrared spectrum and by vapor phase chromatography of its methyl ester.

Methyl ether of XI. The compound XI (100 mg.) was treated for 3 hr. in refluxing acetone with 0.2 ml. of dimethyl sulfate and 1 g. of anhydrous potassium carbonate. The methyl ether obtained after filtration and evaporation of the mixture was recrystallized twice from chloroform-hexane, 35 mg., m.p. 130–132°; $\nu_{max}^{CS_2}$ 1745, 1626, 1597, 760, 698 cm.$^{-1}$ (no hydroxyl); $\lambda_{max}^{methanol}$ 261, 287, 333 mμ, log ε 4.13, 3.77, 4.11; $\lambda_{min}^{methanol}$ 245, 277, 292 mμ log ε 4.01, 3.72, 3.77.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99; O, 19.03; 1 OCH_3, 9.22. Found: C, 75.44; H, 6.08; O, 18.35; OCH_3, 9.14.

Acetate of XI. The phenol XI (100 mg.) was dissolved in 10 ml. of pyridine with 2 ml. of acetic anhydride and the resulting solution was warmed on a steam bath for 8 hr. Work-up in the usual manner afforded 75 mg. of the product acetate, m.p. 161–163° after three recrystallizations from chloroform-hexane. $\nu_{max}^{CS_2}$ 1776, 1745, 1626, 1603, 1200, 760, 699 cm.$^{-1}$; $\lambda_{max}^{methanol}$ 250–251 (doublet), 261, 330 mμ, log ε 4.02, 4.00, 4.13; $\lambda_{min}^{methanol}$ 247, 257, 272 mμ, log ε 4.00, 3.99, 3.67.

Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.51, H, 5.53, O, 21.96. Found: C, 73.01; H, 5.65; O, 21.54.

DETROIT 2, MICH.

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND THE FACULTAD DE QUIMICA Y FARMACIA, UNIVERSIDAD NACIONAL DE LA PLATA]

Structure of Julocrotine[1,2]

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Degradative and synthetic experiments are reported which show that julocrotine is the β-phenylethyl imide of *N*-α-methylbutyrylglutamic acid (I). Some observations on the alkaline cleavage of an *N*-acyl-2-keto-pyrrolidine-5-carboxamide (XIVb) and the isomeric glutarimide (I) are recorded.

A number of years ago, Anastasi[5] reported the isolation of a crystalline alkaloid "julocrotine" from *Julocroton montevidensis* Klotzsch (fam. *Euphorbiaceae*)[6] and proposed for it the empirical formula $C_{19}H_{26}N_2O_3$. The substance gave precipitates with the usual alkaloid reagents, but it dissolved only in concentrated acids, dilution resulting in "dissociation" of the salt and regeneration of the parent substance. When heated with dilute sulfuric acid, fatty acids were liberated which according to their odor were assumed to be predominantly butyric and valeric acids. Finally,

treatment with alcoholic potassium hydroxide followed by acidification furnished a substance, in which it was believed that a lactone ring had been opened, while boiling with alkali provided a steam-volatile base together with a nitrogen-containing acid. Precise experimental details for these reactions were not recorded nor were any physical constants listed with the exception of the melting point (m.p. 105°) of the alkaloid itself. As no further publications on this subject have appeared since 1925, we have repeated the isolation of this substance and have established its structure.[7]

In our hands, julocrotine showed m.p. 108–109°, $[\alpha]_D$ −9° (chloroform), −50° (methanol), and the analytical results were more in concordance with the empirical formula $C_{18}H_{24}N_2O_3$ rather than Anastasi's[5] $C_{19}H_{26}N_2O_3$. In the strict sense of the word, julocrotine is not really an alkaloid since it does not possess any titratable basic nitrogen atom and we were unable to prepare any salts of it. The ultraviolet absorption spectrum was typical of an isolated benzene ring, while the infrared spectrum contained characteristic bands at 2.93 μ (sharp), 5.76 μ (weak to medium), 5.93 μ (strong), and 6.65 μ (strong). The absorption in the carbonyl region did not appear to be due to a ketonic function, since the substance exhibited only a plain negative optical rotatory dispersion curve.[8] Functional group analysis indicated the absence of a methoxyl function and the presence of two C-methyl groups. Paper chromatographic analysis[9] of the volatile acids from the Kuhn-Roth oxidation revealed the formation of both acetic and propionic acids, whereupon it may be concluded that julocrotine contains both a C-methyl and a C-ethyl group.

The presence of a benzene ring, already suggested by the ultraviolet absorption of julocrotine, was confirmed by catalytic hydrogenation with platinum oxide in acetic acid. This resulted in the uptake of three molar equivalents of hydrogen and the formation of hexahydrojulocrotine (II), which was now transparent in the ultraviolet.

Of considerable diagnostic value was the lithium aluminum hydride reduction of julocrotine ($C_{18}H_{24}N_2O_3$), leading to an oxygen-free base, $C_{18}H_{30}N_2$ (subsequently shown to be III), which now lacked the four characteristic infrared bands of julocrotine at 2.93, 5.76, 5.93, and 6.65 μ. In contrast to the nonbasic julocrotine, the lithium aluminum hydride reduction product contained two basic nitrogen functions as demonstrated by the formation of a dipicrate and a dimethiodide. The loss of the three oxygen atoms with the simultaneous generation of two basic nitrogens can be rationalized[10] most readily by the presence in julocrotine of an amide as well as of an imide moiety, the infrared bands at 5.76 and 5.93 μ being assigned to them. The presence of at least one secondary amide is indicated by the sharp band at 2.93 μ in julocrotine as well as the absorption at 6.65 μ attributable[11] to the N—H deformation of secondary amides.

Catalytic hydrogenation of the base $C_{18}H_{30}N_2$ (III) again caused the uptake of three equivalents of hydrogen with production of a hexahydro base $C_{18}H_{36}N_2$ (IV), which could also be obtained from hexahydrojulocrotine (II) by treatment with lithium aluminum hydride. The empirical formula of the saturated base $C_{18}H_{36}N_2$ (IV) requires that in addition to the benzene nucleus, there be present in julocrotine a second ring. For the sake of simplicity, we shall present the further discussion of the degradative evidence in terms of the eventually established formulation I for julocrotine, its lithium aluminum hydride reduction product being III, while their respective hexahydro derivatives can be represented by expressions II and IV.

The ready availability of the basic transformation product $C_{18}H_{30}N_2$ (III) suggested application of the classic Hofmann degradation and for this purpose the base was transformed into its "dimethiodide" V[12] and then boiled with 40% potassium hydroxide. The neutral product of this reaction was presumably styrene (VI), since upon oxidation with permanganate at room tempera-

(1) Paper XXIV in the series "Alkaloid Studies" (preceding paper, B. Gilbert, L. D. Antonaccio, A. A. P. G. Archer, and C. Djerassi, *Experientia*, **16**, 61 (1960)), and paper V in the series "Estudios sobre Plantas" (preceding paper, O. O. Orazi and R. A. Corral, *Anales Asoc. Quim. Argentina*, **44**, 193 (1956)).

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(4) Recipient of a Fulbright travel grant while on leave from the University of Kyoto.

(5) C. Anastasi, *Anales Asoc. Quim. Argentina*, **13**, 348 (1925).

(6) Subsequently, this alkaloid was also encountered in other *Julocroton* species such as J. *subpannosus* and J. *camporum* (unpublished results of A. Novelli cited by A. Novelli and O. O. Orazi, *Rev. Farmacéutica (Buenos Aires)* **92**, 109 (1950)).

(7) For preliminary communication see T. Nakano, C. Djerassi, R. A. Corral, and O. O. Orazi, *Tetrahedron Letters*, No. **14**, 8 (1959).

(8) See C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1960, especially chapter 16.

(9) C. F. Garbers, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **37**, 1336 (1954); H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955).

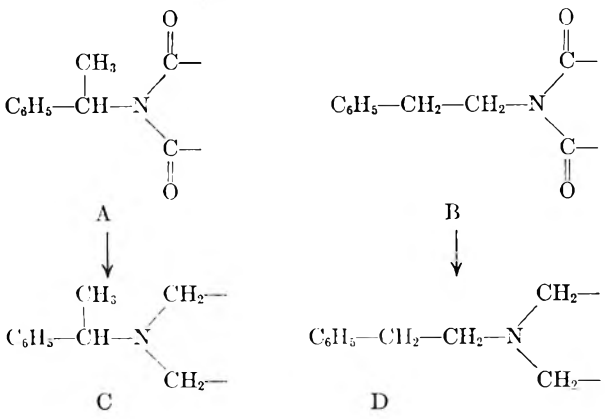
(10) For pertinent references see J. Rudinger and M. Ferles, *Hydrid Lithno-Hlinity*, Czechoslovak Academy, Prague, 1956, pp. 411–450; N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, Chap. 10.

(11) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, 2nd ed., Chap. 12.

(12) The substance is actually formulated (see V) as the monomethiodide of the hydroiodide of the *N*-methylated base.

ture it furnished benzoic acid. The basic companion product was represented by an optically active amine $C_{12}H_{23}N_2$, which was further characterized as its dipicrate. The amine was saturated (no hydrogen uptake upon attempted hydrogenation with platinum oxide in acetic acid solution) and by analysis was shown to contain two *N*-methyl functions. On the basis of structure I (*vide infra*) for julocrotine, we formulate it, therefore, as 1-methyl-3-(*N'*-methyl-*N'*-β-methylbutyl)aminopiperidine (VII).

At this stage of our knowledge of julocrotine, the results of the Hofmann degradation can only be interpreted as implying the presence of partial structure A or B in the parent substance, lithium aluminum hydride treatment converting it into C or D, which upon quaternization and Hofmann elimination would yield styrene (VI) and a basic fragment corresponding in terms of empirical formula to VII.



A secure differentiation between partial structures A and B should be possible by hydrolytic cleavage of the imide linkage, which would then yield[13] either α- or β-phenylethylamine. Indeed, when julocrotine was heated under reflux with methanolic potassium hydroxide, β-phenylethylamine (VIII) could be isolated, whereupon it can be concluded that partial structure B must be represented in the complete expression for julocrotine.

The next question, namely whether the imide moiety in B was cyclic or open chain, could be answered by the results of the same alkali cleavage experiment. The principal product of this alkaline hydrolysis was acidic and upon methylation, followed by crystallization and resaponification could be separated into two isomeric acids, which we have named julocrotic acid-A and acid-B. Their structures will be discussed below in connection with synthetic studies, but at this point it need only be emphasized that the empirical formula ($C_{18}H_{26}N_2O_4$) of these two acids, which contained no basic nitrogen atom, when contrasted with that ($C_{18}H_{24}N_2O_3$) of julocrotine itself, clearly showed that they must have arisen by *alternate hydrolytic opening of an unsymmetrical cyclic imide.*

In order to determine the size of the imide ring, *N*-β-phenylethylsuccinimide and *N*-β-phenylethylglutarimide were synthesized and their infrared spectra determined. The former exhibited a weak band at 5.63 μ and a strong one at 5.85 μ, while the corresponding bands of *N*-β-phenylethylglutarimide occurred at 5.78 μ (weak) and 5.96 μ (strong).[14] As noted in the beginning of the present article, the infrared spectrum of julocrotine (I) is characterized by a weak band at 5.76 μ and a very strong one at 5.93 μ. It follows, therefore, that julocrotine must be a substituted glutarimide derivative. The *N*-β-phenylethylglutarimide portion of the molecule accounts for thirteen of the eighteen carbon atoms of julocrotine; at least four carbon atoms are represented by the secondary amide function, whose presence has already been demonstrated (infrared spectrum and course of lithium aluminum hydride reduction), and the C-methyl and C-ethyl groupings (from the paper chromatographic results of the Kuhn-Roth oxidation). Hence only one carbon atom remains to be defined.

Anastasi[5] has already remarked on the liberation of volatile acids from the dilute sulfuric acid treatment of julocrotine. While his assumption of the presence of butyric and valeric acids is not tenable on the basis of the structural information already accumulated, the isolation and definite characterization of a volatile acid would appear to afford the remaining clue to the complete structure elucidation of julocrotine. In our hands, the optimum conditions for the complete acid hydrolysis of julocrotine involved heating for twenty-four hours with a mixture of dioxane and concentrated hydrochloric acid. Aside from β-phenylethylamine (VIII), there was obtained a volatile acid as well as an amino acid. The volatile acid was identified as (+)-α-methylbutyric acid (IX) by direct comparison with authentic specimens of the anilide and *p*-bromoanilide of (+)-α-methylbutyric acid. The amino acid proved to be identical with L-(+)-glutamic acid (X), thus establishing unambiguously structure I for julocrotine.

In an attempt to synthesize julocrotine, L-(+)-glutamic acid (X) was transformed into its diethyl ester and treated with (+)-α-methylbutyryl chloride. The resulting *N*-α-methylbutyryl glutamic acid diethyl ester (XIIa) was heated[15] with β-phenyl-

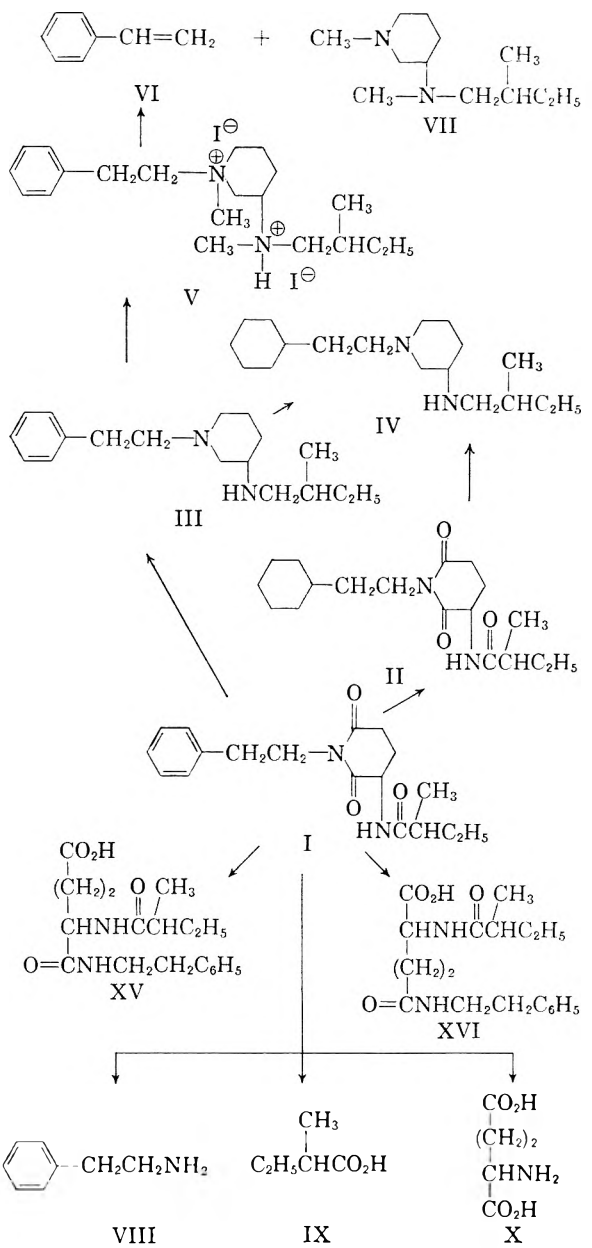
(13) It should be recalled that already Anastasi (Ref. 5) had noted the liberation of an unidentified volatile base upon heating julocrotine with alkali.

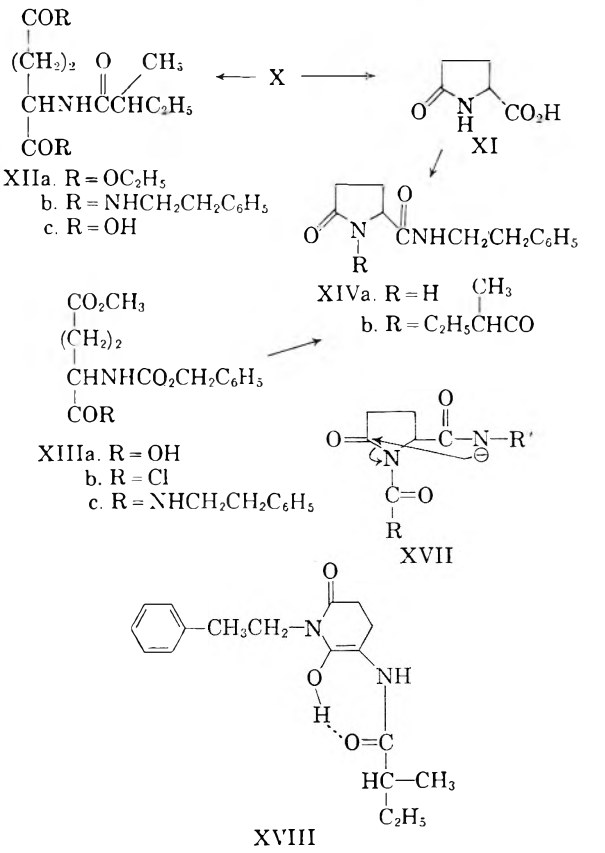
(14) Subsequent to these measurements, there appeared two articles in which the positions of the infrared bands of a number of other substituted succinimides and glutarimides were reported: H. K. Hall and R. Zbinden, *J. Am. Chem. Soc.*, 80, 6428 (1958); V. M. Clark, A. W. Johnson, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 3283 (1958).

(15) See R. Child and F. L. Pyman, *J. Chem. Soc.*, 2010 (1929).

ethylamine, but the only product was the corresponding β-phenylethylamide XIIb. As an alternate procedure, the diethyl ester XIIa was hydrolyzed to *N*-α-methylbutyryl glutamic acid (XIIc), which was then transformed to the anhydride by heating with acetic anhydride. The crude anhydride was immediately heated without a solvent with β-phenylethylamine to yield predominantly the diamide XIIb in partially racemized form. From the mother liquors, there was isolated in poor yield a substance, whose analysis coincided with that of julocrotine and whose infrared spectrum was very similar to that of natural julocrotine (I). However, it melted over a wide range (m.p. 96–105°) and its rotation ($[\alpha]_D$ +2.7° *vs.* −50° for julocrotine) indicated extensive racemization of at least one asymmetric center. It would appear, therefore, that the synthetic compound was structurally but not stereochemically identical with julocrotine.

The relative ease of racemization (under alkaline conditions) of amides of glutamic acid has already been commented upon in the literature.[16] This appears to be true at times under acidic conditions as well since in the dioxane–hydrochloric acid cleavage of julocrotine (I), the resulting L-(+)-glutamic acid (X) was usually partially racemized. On the other hand, natural L-(+)-glutamic acid (X) or the diethyl ester of *N*-α-methylbutyryl glutamic acid (XIIa) yielded optically pure L-(+)-glutamic acid under the same conditions. It is conceivable that partial racemization is facilitated in cyclic imides of glutamic acid by hydrogen bonding in an intermediate such as XVIII.





As an alternate synthetic approach leading to julocrotic acid, γ-methyl *N*-carbobenzyloxy-L-glutamate (XIIIa)[17] was converted into its acid chloride XIIIb and thence, by addition of β-phenylethylamine, into its β-phenylethylamide XIIIc. In an attempt to remove the carbobenzyloxy blocking group, the amide XIIIc was subjected to hydrogenolysis with palladium black in methanol

(16) (a) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954); *J. Am. Chem. Soc.*, **79**, 3767 (1957); (b) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).

(17) W. E. Hanby, S. G. Waley, and J. Watson, *J. Chem. Soc.*, 3239 (1958); R. A. Boissonnas, S. Guttmann, P. A. Jaquenoud, and J. P. Waller, *Helv. Chim. Acta*, **38**, 1491 (1955).

containing a small amount of acetic acid. Evaporation of the solution to dryness and recrystallization afforded in 54% yield a very weakly basic product. The analysis indicated that cyclization had occurred, possibly during the evaporation of the hydrogenolysis solution, and the structure of 2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVa) was proved by direct comparison with an authentic specimen prepared by successive treatment of 2-ketopyrrolidine-5-carboxylic acid[18] (XI) with thionyl chloride and then with β-phenylethylamine.

The above pyrrolidone XIVa was now acylated with (+)-α-methylbutyryl chloride to *N*-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVb). Alkaline hydrolysis of this pyrrolidone afforded in 32% yield an acid, m.p. 120–122°, $[\alpha]_D$ +10.7°, methyl ester, m.p. 148–149°, $[\alpha]_D$ −3.4°, which proved to be identical with julocrotic acid-A (and its methyl ester), the prodiminant product of the alkaline cleavage of julocrotine (I). Julocrotic acid-A can be either the α-glutamyl (XV) or γ-glutamyl (XVI) amide and a probable differentiation seems possible with the following information. Thus, it has been shown[19] that 1-acyl-2-ketopyrrolidine-5-carboxylic acid amides of type XIVb may give rise to a mixture of the direct cleavage product, the α-glutamyl derivative, and the rearranged γ-isomer. The latter is usually[20] the predominant hydrolysis product of glutarimides of the type exemplified by julocrotine (I) and Battersby and Robinson[19] have pointed out that rearrangement of acylpyrrolidones to glutarimides is clearly feasible through the path indicated in XVII.

While julocrotic acid-A was obtained only in 32% yield by alkaline hydrolysis of the pyrrolidone XIVb, countercurrent distribution of the mother liquors provided only a trace of a second isomer which was insufficient for further work. In the alkaline cleavage of julocrotine (I), in addition to julocrotic acid-A, a second isomer, julocrotic acid-B could be isolated. It has been pointed out[19,20] that the γ-isomers (*e.g.* XVI) are considerably stronger acids than the α-isomers (*e.g.* XV). Using this criterion, julocrotic acid-A (pK_a 6.3) should be assigned structure XVI and julocrotic acid-B (pK_a 6.95) should be represented by XV. It appears, therefore, that alkaline hydrolysis of *N*-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVb) proceeds to a considerable extent by rearrangement (*via* XVII) to afford julocrotic acid-A (XVI).[21] It is pertinent to mention that saponification of the methyl ester of julocrotic acid-A (XVI) is not accompanied by rearrangement.

Finally, it is worth noting that while the occasional occurrence of glutamine and two related amides of glutamic acid has been mentioned in the phytochemical literature,[22] julocrotine (I) represents a rather unique structure among plant products.

EXPERIMENTAL[23]

Isolation of julocrotine (I). The dried and powdered roots (1 kg.) of *Julocroton montevidensis* Klotzsch[24] were heated under reflux for 6 hr. with 4 l. of alcohol, the mixture was filtered and the process was repeated three times. The combined extracts were evaporated to dryness and the residue (75 g.) was extracted continuously in a soxhlet extractor with petroleum ether (b.p. 60–70°). Upon cooling, a precipitate separated which was combined with a second crop obtained upon concentration of the mother liquors, thus totalling 13 g. Two recrystallizations from ether–petroleum ether afforded 6.2 g. of faintly colored julocrotine, m.p. 103–105°. The analytical sample, obtained after sublimation at 160–165°/0.25 mm. and repeated recrystallization, exhibited m.p. 108–109°, $[\alpha]_D$ −9° (*c*, 1.24 in chloroform), −50.1° (c, 1.19 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.76 (w), 5.93 (s), 6.65 μ (s), $\lambda_{max}^{C_2H_5OH}$ 252, 258, 264, and 268 mμ, log ε 2.43, 2.44, 2.30, and 2.18, $\lambda_{min}^{C_2H_5OH}$ 250, 256, 263, and 267 mμ, log ε 2.41, 2.37, 2.27, and 2.16; R.D.[8] in methanol (c, 0.691): $[\alpha]_{589}$ −49°, $[\alpha]_{500}$ −74°, $[\alpha]_{400}$ −150°, $[\alpha]_{350}$ −205°, $[\alpha]_{300}$ −362°. Electrometric titration[25] did not show any titratable basic nitrogen nor did titration with perchloric acid in acetic acid solution.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85; O, 15.17; C—CH_3, 4.75; mol. wt., 316. Found: C, 68.09; H, 7.72; N, 9.03; O, 15.41; OCH_3, 0.0; C—CH_3, 6.11;[26] Rast mol. wt., 309.

Hexahydrojulocrotine (II). Julocrotine did not consume any hydrogen at 30° in methanol solution in the presence of 5% palladized charcoal, but when 17.2 mg. of I was hydrogenated in 5 cc. of acetic acid with platinum oxide catalyst at 30° and atmospheric pressure, 3 equivalents of hydrogen were taken up within 20 min. The catalyst was filtered, the filtrate was made basic with ammonia solution and the product was extracted with ether. After washing, drying, and evaporation, the residue was recrystallized from ether-hexane to afford 13 mg. of colorless crystals, m.p. 94–95°, $[\alpha]_D$ −5.2° (*c*, 0.98 in chloroform), which did not exhibit any selective absorption in the ultraviolet; $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.76 (w), 5.93 (s) and 6.65 μ (s).

Anal. Calcd. for $C_{18}H_{30}N_2O_3$: C, 67.04; H, 9.37; N, 8.68; O, 14.88. Found: C, 66.79; H, 9.33; N, 8.40; O, 14.93.

(18) E. Abderhalden and K. Kautzsch, *Z. Physiol. Chem.*, **68**, 487 (1910).

(19) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 2076 (1955). See also G. Amiard, R. Heymes and L. Velluz, *Bull. Soc. Chim. France*, 97 (1953).

(20) D. W. Clayton, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc.*, 371 (1956).

(21) In our preliminary communication (Ref. 7), julocrotic acid-A had been assigned tentatively structure XV since *p*K measurements had not been performed at that time.

(22) W. Karrer, *Konstitution und Vorkommen der organischen Pflanzenstoffe*, Birkhäuser, Basel, 1958, pp. 404 and 967.

(23) Melting points were determined on the Kofler block. We are indebted to Miss B. Bach for the infrared spectra and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses.

(24) We are indebted to Prof. José F. Molfino and Prof. Manuel G. Escalante for botanical identification of material collected by Mr. Carlos A. Sieyra in Entre Rios, Argentina, and by Mr. A. G. Schulz in Chaco, Argentina.

(25) Grateful acknowledgment is made to Dr. H. Boaz of Eli Lilly & Co. for the electrometric titrations.

(26) Paper chromatographic determination (Ref. 9) showed the presence of acetic and propionic acids.

1-β-Phenylethyl-3-(β-methylbutyl)aminopiperidine (III). A solution of 0.5 g. of julocrotine in 200 cc. of ether was added to 1.1 g. of lithium aluminum hydride dissolved in 150 cc. of ether and the mixture was heated under reflux for 22 hr. The excess reagent was decomposed with ethyl acetate, a concentrated aqueous solution of sodium sulfate was added to precipitate inorganic salts followed by the addition of anhydrous sodium sulfate. The solution was filtered, extracted with 5% hydrochloric acid, the latter was made basic with dilute ammonia and again extracted with ether. After drying, the ether was evaporated and the resulting 0.44 g. of oil was distilled at a bath temperature of 110–120°/0.005 mm., $[\alpha]_D$ −12.6° (*c*, 1.47 in chloroform), −4.4° (*c*, 1.27 in methanol). The characteristic infrared bands listed above for julocrotine had disappeared.

Anal. Calcd. for $C_{19}H_{30}N_2$: C, 78.77; H, 11.01; N, 10.28; C—CH_3, 5.48. Found: C, 78.10; H, 10.92; N, 9.84; C—CH_3, 8.10.

The *dipicrate* was obtained by treatment of a portion of III with picric acid in ethanol-ether followed by recrystallization from methanol; m.p. 186–187°.

Anal. Calcd. for $C_{18}H_{30}N_2 \cdot 2C_6H_3N_3O_7$: C, 49.17; H, 4.95; N, 15.29. Found: C, 49.39; H, 5.29; N, 15.14.

1-β-Cyclohexylethyl-3-(β-methylbutyl)aminopiperidine (IV). (a) *By catalytic hydrogenation of 1-β-phenylethyl-3-(β-methylbutyl)aminopiperidine* (III). The catalytic hydrogenation of III (17.2 mg.) was performed exactly as described above for julocrotine and the total crude product was dissolved in methanol and a few drops of concd. hydrochloric acid were added. After evaporation to dryness and two recrystallizations from methanol-acetone, the *dihydrochloride* melted at 285–286° dec. in sealed capillary.

Anal. Calcd. for $C_{18}H_{36}N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 59.64; H, 10.84; N, 7.73; Cl, 19.56. Found: C, 59.31; H, 10.37; N, 8.38; Cl, 19.30.

The above hydrochloride was dissolved in a few drops of water, a saturated aqueous solution of sodium picrate was added and the resulting precipitate of the *dipicrate* was recrystallized from methanol whereupon it exhibited m.p. 178–180°.

Anal. Calcd. for $C_{18}H_{36}N_2 \cdot 2C_6H_3N_3O_7$: C, 48.77; H, 5.73; N, 15.17. Found: C, 48.57; H, 5.67; N, 14.85.

(b) *By lithium aluminum hydride reduction of hexahydrojulocrotine* (II). Hexahydrojulocrotine (140 mg.) was reduced with lithium aluminum hydride as described above for julocrotine and the resulting basic oil was distilled at 100–110°/0.008 mm. The oil yielded a hydrochloride, m.p. 285–286° dec. and a dipicrate, m.p. 178–180°, which proved to be identical by mixture melting point determination with the specimen described under (a).

Hofmann degradation of 1-β-phenylethyl-3-(β-methylbutyl)-aminopiperidine (III). A solution of 0.3 g. of the amine III and 0.9 g. of methyl iodide in 10 cc. of methanol was heated under reflux for 1 hr. After standing overnight at room temperature, addition of acetone and ether caused the separation of 0.17 g. of crystals. The filtrate was treated again with 0.3 g. of methyl iodide yielding a further 0.26 g. of crystals. Recrystallization from methanol afforded the analytical sample of the methiodide *N*-methyl hydroiodide V[12] of m.p. 226–227°.

Anal. Calcd. for $C_{20}H_{36}I_2N_2$: C, 43.02; H, 6.48; N, 5.06; I, 45.46. Found: C, 42.59; H, 6.82; N, 4.82; I, 45.75.

The above salt (1.59 g.) was boiled for 2 hr. with 80 cc. of 40% aqueous potassium hydroxide solution and after cooling, the mixture was extracted with ether. The organic layer was extracted with 5% aqueous hydrochloric acid which was made alkaline with dilute ammonia and extracted with ether. The ether solution was washed with water until neutral, dried, and evaporated to afford 0.54 g. of *1-methyl-3-(N'-methyl-N'-β-methylbutyl)aminopiperidine* (VII), which was distilled at a bath temperature of 70–80°/1.5 mm., $[\alpha]_D$ +7° (c, 0.76 in methanol). Microhydrogenation with platinum oxide in acetic acid confirmed the absence of any double bond.

Anal. Calcd. for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12; 2N—CH_3, 15.19. Found: C, 72.09; H, 13.12; N, 14.68; N—CH_3, 16.31.

A small amount of the amine was dissolved in ether and treated with a solution of picric acid in ethanol-ether. Recrystallization of the resulting precipitate from ethanol-acetone afforded the *dipicrate*, m.p. 227–228°.

Anal. Calcd. for $C_{12}H_{26}N_2 \cdot 2C_6H_3N_3O_7$: C, 43.90; H, 4.91; N, 17.06; O, 34.11; 2 N—CH_3, 4.57. Found: C, 43.63; H, 5.00; N, 17.15; O, 34.17; N—CH_3, 4.99.

The original ether solution (after extraction with 5% hydrochloric acid) was dried and to it was added at room temperature over a period of 6 hr. a 4% solution of potassium permanganate in acetone until the purple color persisted (*ca.* 50 cc.). After acidification with 5% hydrochloric acid, the excess reagent was decomposed by the addition of sodium sulfite, the resulting clear solution was washed with water, and the organic layer was extracted with 10% aqueous sodium bicarbonate. Acidification of this extract followed by ether extraction afforded 0.15 g. of *benzoic acid*, m.p. 121–122°. Identity was established in the usual manner.

Alkali cleavage of julocrotine. Isolation of β-phenylethylamine (VIII) *and julocrotic acids* (XV, XVI). Julocrotine (1.76 g.) was heated under reflux for 3 hr. with 100 cc. of 10% methanolic potassium hydroxide in a current of nitrogen. The mixture was diluted with water, most of the methanol was removed *in vacuo* and the solution was extracted thoroughly with ether. The latter was washed with 5% hydrochloric acid, the washings were made alkaline and re-extracted with ether. Evaporation yielded 0.11 g. of a basic oil which was transformed into its picrate (m.p. 168–169°) undepressed upon admixture with β-phenylethylamine picrate. Furthermore, an oxalate was obtained (m.p. 197–198° after recrystallization from aqueous ethanol), whose melting point was undepressed when mixed with authentic β-phenylethylamine oxalate.

Anal. Calcd. for $2C_8H_{11}N \cdot C_2H_2O_4$: C, 65.03; H, 7.27; N 8.42. Found: C, 65.02; H, 7.58; N, 8.37.

The original aqueous alkaline solution was acidified with hydrochloric acid and extracted with ethyl acetate. The acidic material obtained upon evaporation of the washed and dried ethyl acetate solution was directly methylated with ethereal diazomethane to afford 1.61 g. of a crystalline mass of methyl ester. Two recrystallizations from benzene-ether gave 0.45 g. of *julocrotic acid-A* (XVI) *methyl ester*, m.p. 148–149°, $[\alpha]_D$ −4.0° (c, 0.97 in methanol), $\lambda_{max}^{CHCl_3}$ 2.99, 3.10, 5.75, 6.00, and 6.62 μ, the ultraviolet absorption spectrum being very similar to that of julocrotine.

Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04; O, 18.36; OCH_3, 8.90. Found: C, 65.63; H, 7.85; N, 8.20; O, 18.20; OCH_3, 8.48.

A portion of the methyl ester was saponified by heating under reflux for 1 hr. with 25 cc. of 5% methanolic sodium hydroxide solution. After acidification and extraction with ethyl acetate, there was obtained *julocrotic acid-A* (XVI), which exhibited after recrystallization from ether–ethyl acetate m.p. 119–122°, $[\alpha]_D$ +14.4° (*c*, 0.973 in methanol), $\lambda_{max}^{CHCl_3}$ 2.82, 3.03, 5.75, 5.98, and 6.55 μ; R.D.[8] in methanol (c, 0.627): $[\alpha]_{589}$ +12.1°, $[\alpha]_{500}$ +17.5°, $[\alpha]_{400}$ +32.5°, $[\alpha]_{350}$ +52.3°, $[\alpha]_{300}$ +96.3°. Methylation with diazomethane regenerated the original methyl ester, m.p. 148–149°, thus showing that saponification of the methyl ester to the acid had not involved any rearrangement.

Anal. Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.64; H, 7.83; N, 8.37; O, 19.13; mol. wt., 334. Found: C, 64.20; H, 7.78; N, 8.60; O, 19.21; OCH_3, 0.0; pK_a 6.3[25] (initial *p*H in 66% dimethylformamide solution 4.6; mol. wt. 325 by electrometric titration).

The mother liquors from the crystallization of julocrotic acid-A methyl ester deposited 50 mg. of crystals, which after recrystallization from benzene-ether had m.p. 133–134°. The infrared spectrum was identical with that of julocrotic acid-A methyl ester, but a mixture melting point

was depressed to 116–124° and it is conceivable (see also Discussion) that this may represent partially racemized material. Lack of substance precluded further work.

Anal. Found for $C_{19}H_{28}N_2O_4$: C, 65.52; H, 8.16; N, 8.02; O, 18.32; OCH_3, 8.46.

Further concentration of the filtrate produced 100 mg. of gel-like crystals, which were hydrolyzed directly with 5% methanolic sodium hydroxide to yield after recrystallization from ether–ethyl acetate 70 mg. of *julocrotic acid-B* (XV), m.p. 133.5–135°, $[\alpha]_D$ +10.0° (*c*, 0.275 in methanol), λ_{max}^{Nujol} 3.05, 5.85, 5.98, 6.10 μ (insolubility in chloroform precluded measurements in that solvent); R.D. in methanol (*c*, 0.474): $[\alpha]_{589}$ +10.5°, $[\alpha]_{500}$ +15.6°, $[\alpha]_{400}$ +28.6°, $[\alpha]_{300}$ +69.6°.

Anal. Found for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.90; N, 8.51; O, 19.21; OCH_3, 0.0; pK_a 6.95[25] (initial *p*H in 66% dimethylformamide solution 5.1; mol. wt. by electrometric titration 321).

Acid hydrolysis of julocrotine. A solution of 1.3 g. of julocrotine was heated under reflux with a mixture of 70 cc. of dioxane and 21 cc. of concd. hydrochloric acid for 24 hr., diluted with water and extracted with chloroform (*extract A*). The aqueous layer was evaporated to dryness *in vacuo*, taken up in water, made alkaline (*p*H 9–11) with aqueous sodium hydroxide and extracted with ether (*extract B*). The aqueous solution was now acidified to Congo Red with hydrochloric acid and again evaporated to dryness under reduced pressure. The residue was dissolved in 200 cc. of water and transferred to a 29 × 2.7 cm. column of Amberlite IRA-400 (80 g.) in the chloride form, which had been transformed to the acetate by treating with 3*M* sodium acetate solution until no further turbidity developed in the filtrate on addition of an acidic solution of silver nitrate; prior to use, the resin was washed thoroughly with water. Elution from the resin column was performed with 0.5*N* aqueous acetic acid. Evaporation to dryness under diminished pressure and recrystallization of the residue from aqueous ethanol afforded 0.41 g. of *glutamic acid* (X), m.p. 184–185°, $[\alpha]_D$ +17.2° (*c*, 0.888 in 1*N* aqueous hydrochloric acid).[27]

Anal. Calcd. for $C_5H_9NO_4$: C, 40.81; H, 6.16; N, 9.52; O, 43.59. Found: C, 40.79; H, 6.24; N, 9.45; O, 43.27.

A mixture melting point determination with authentic L-(+)-glutamic acid (m.p. 195–196°, $[\alpha]_D$ +32.1° (*c*, 0.89 in 1*N* aqueous hydrochloric acid) showed no depression. The two specimens gave identical infrared spectra (Nujol) as well as identical R_f values by paper chromatography (descending technique) on Whatman No. 1 paper using the solvent system *n*-butyl alcohol-acetic acid–water (4:1:2).

The chloroform *extract A* was washed with 2% sodium hydroxide, the alkaline washes were acidified and extracted with chloroform to afford after distillation 0.40 g. of an acid. This was heated under reflux for 30 min. with 0.6 g. of thionyl chloride, cooled, a solution of 2.5 g. of *p*-bromoaniline in 30 cc. of benzene was added, and the mixture warmed on the steam bath for a few minutes. The benzene solution was then washed with dilute acid, sodium hydroxide, water, dried, evaporated, and recrystallized from ether-hexane to give 0.46 g. of *(+)-α-methylbutyric acid* (IX) *p*-bromoanilide, m.p. 133–134°, $[\alpha]_D$ +31.3° (*c*, 0.78 in acetone). An authentic sample, prepared in identical fashion from (+)-α-methylbutyric acid derived from optically active amyl alcohol, exhibited m.p. 135–136°, $[\alpha]_D$ +31.4° (*c*, 0.735 in acetone); no depression in melting point was encountered upon mixing the two samples.

Anal. Calcd. for $C_{11}H_{14}BrNO$: C, 51.57; H, 5.50; Br, 31.19; N, 5.46; O, 6.25. Found: C, 51.31; H, 5.25; Br, 31.01; N, 5.30; O, 6.05.

In a second experiment, the volatile acid was transformed into its *anilide*, m.p. 98–99° (after sublimation and recrystallization from ether–petroleum ether (b.p. 40–60°)), $[\alpha]_D$ +39.5° (*c*, 0.87 in acetone), which was shown to be identical by direct comparison with an authentic specimen.[28]

The *ether extract B* was dried and evaporated to afford 0.39 g. of a basic oil which was transformed directly in its picrate (0.62 g.), m.p. 168–169°, undepressed when mixed with a sample of *β-phenylethylamine* picrate.

Attempted synthesis of julocrotine. (+)-α-Methylbutyryl chloride (1.3 g.)[29] was added to 5.0 g. of L-(+)-glutamic acid diethyl ester[30] in 20 cc. of benzene and the solution was kept at room temperature overnight before washing with 5% hydrochloric acid and then with 2% sodium hydroxide. The dried benzene solution was evaporated and the residue was recrystallized from ether-hexane, giving 2.6 g. of *N-α-methylbutyryl glutamic acid diethyl ester* (XIIa), m.p. 48–49°, $[\alpha]_D$ −17.1° (*c*, 1.07 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93, 5.77 (s) and 5.95 (s) μ, λ_{max}^{Nujol} 3.05, 5.76, and 6.07 μ; R.D. in methanol (*c*, 0.088): $[\alpha]_{589}$ −23°, $[\alpha]_{400}$ −50°, $[\alpha]_{300}$ −86°, $[\alpha]_{265}$ −118°.

Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.51; H, 8.77; N, 4.87; O, 27.84. Found: C, 58.80; H, 8.72; N, 5.34; O, 27.51.

The above diethyl ester XIIa (5.0 g.) was saponified by heating under reflux for 2 hr. with 250 cc. of 5% methanolic potassium hydroxide, diluted with water, acidified with 22 cc. of concd. hydrochloric acid, and evaporated to dryness *in vacuo*. The residue was extracted with hot acetone, filtered from sodium chloride, the acetone was evaporated, and the *N-α-methylbutyryl glutamic acid* (XIIc) was recrystallized from ether-hexane; yield, 3.98 g., m.p. 110–112°, $[\alpha]_D$ −3.4° (*c*, 0.52 in methanol).

Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06; O, 34.60; neut. equiv., 115. Found: C, 51.65; H, 7.34; N, 6.26; O, 34.78; neut. equiv., 114.

The diethyl ester XIIa (2.0 g.) was heated[15] at 190° for 7 hr. under an air condenser with 2.4 g. of β-phenylethylamine (VIII). The crystalline mass possessed m.p. 192–194° after recrystallization from methanol and its infrared spectrum indicated the formation of the bisamide XIIb. Since further heating of such amides in the succinic acid series[15] had been shown to lead to cyclization with elimination of 1 equivalent of β-phenylethylamine, the entire product was heated for a further 6 hr. at 220°. Recrystallization of the total material from acetone-methanol furnished 0.8 g. of the *bisamide* XIIb, m.p. 193–194°, $[\alpha]_D$ +9.7° (*c*, 1.013 in methanol), $\lambda_{max}^{CHCl_3}$ 2.94, 3.04, and 6.00 μ. The mother liquor remained as a brown oil and no pure product could be isolated from it.

Anal. Calcd. for $C_{26}H_{34}N_2O_3$: C, 71.36; H, 8.06; N, 9.60; O, 10.97. Found: C, 71.77; H, 7.96; N, 9.83; O, 10.85.

As an alternate approach to the production of the desired glutarimide I, 1.75 g. of the *N-α*-methylbutyryl glutamic acid (XIIc) was boiled for 5 min. with 3 cc. of acetic anhydride and then evaporated to dryness *in vacuo* leaving the corresponding anhydride ($\lambda_{max}^{CHCl_3}$ 2.94, 5.50, 5.65, and 5.93 μ) as a viscous oil. This was heated at 170° for 1 hr. with 0.9 g. of β-phenylethylamine, cooled, taken up in benzene, and then washed successively with 5% hydrochloric acid, 2% sodium hydroxide and water, dried, and evaporated. Recrystallization from methanol-ether afforded 0.22 g. of the *bisamide* XIIb, m.p. 187–192°, $[\alpha]_D$ +1.5° (*c*, 1.102 in methanol), $\lambda_{max}^{CHCl_3}$ 2.94, 3.04, and 6.00 μ. The melting point range could not be sharpened on further recrystallization and judging from the rotation partial racemization seemed to have occurred.

(27) In one experiment a rotation of +31.8° was obtained, but in two successive ones the rotations were considerably lower and indicated partial racemization (see Discussion section). Identical acid treatment of XIIa or of L-(+)-glutamic acid followed by purification through Amberlite afforded optically pure glutamic acid.

(28) R. H. Baker and L. E. Linn, *J. Am. Chem. Soc.*, **70**, 3721 (1948).

(29) J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.*, 1080 (1935).

(30) E. Fischer, *Ber.*, **34**, 453 (1901).

Anal. Calcd. for $C_{20}H_{35}N_3O_3$: C, 71.36; H, 8.06; N, 9.60. Found: C, 71.15; H, 7.73; N, 9.60.

The combined mother liquors were evaporated to dryness and the residue (1.0 g.) was chromatographed on 36 g. of Merck acid-washed alumina. From the 1:1 benzene–ether eluates there was obtained 87 mg. of colorless crystals, m.p. 95–105°, $[\alpha]_D$ +2.7° (*c*, 1.01 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.73 (w), 5.93 (s) and 6.51 (s) μ: R.D.[8] in methanol (*c*, 0.113): $[\alpha]_{589}$ +11°, $[\alpha]_{400}$ +14°, $[\alpha]_{300}$ +25°, $[\alpha]_{275}$ +32°. The infrared spectrum of this product was very similar but not identical with that of natural julocrotine (I) and a mixture melting point showed m.p. 95–103°. It appears that the synthetic material represents partially racemized julocrotine and repeated recrystallization did not afford sharper melting crystals.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.61; H, 7.51; N, 8.97.

Synthesis of julocrotic acid-A (XVI). To an ice-cold solution of 1.0 g. of γ-methyl *N*-carbobenzyloxy-L-glutamate (XIIIa)[17] in 5 cc. of anhydrous ether was added in portions with stirring 0.71 g. of powdered phosphorus pentachloride. After 20 min., a solution of 5.0 g. of β-phenylethylamine in 20 cc. of benzene was added dropwise with stirring and while cooling in ice water. The mixture was left overnight at room temperature, diluted with benzene, and washed first with 5% hydrochloric acid and then with 2% sodium hydroxide. The organic layer was washed with water, dried, evaporated (*in vacuo*), and the residue was recrystallized from ether-hexane to yield 1.02 g. of *γ-methyl N-carbobenzyloxy-L-glutamate α-(β-phenylethyl)amide* (XIIIc), m.p. 124–125°, $[\alpha]_D$ −8.6° (*c*, 1.106 in chloroform), $\lambda_{max}^{CHCl_3}$ 2.92, 5.75 (s) and 5.93 (s) μ.

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03; O, 20.08. Found: C, 66.15; H, 6.36; N, 7.29; O, 20.11.

The above carbobenzyloxy derivative XIIIc (3.0 g.) was submitted to hydrogenolysis by dissolving in 140 cc. of 90% aqueous methanol containing a few drops of acetic acid and shaking the solution in a current of hydrogen at atmospheric pressure and room temperature in the presence of 0.9 g. of palladium black. After 8 hr., the solution was filtered and evaporated to dryness *in vacuo*. The residue was taken up in chloroform, dried over anhydrous potassium carbonate, again evaporated to dryness and crystallized from ether, leading to 0.563 g. of *2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide* (XIVa), m.p. 140–142°. The mother liquor was evaporated to dryness, taken up in 5% aqueous hydrochloric acid, washed with ether, the aqueous phase was made alkaline with ammonia and extracted with chloroform. The latter was dried, evaporated to dryness[31] and the residue was crystallized from ether to afford an additional 0.521 g. of crystals, m.p. 140–142°. The analytical sample showed the same melting point, $[\alpha]_D$ −47° (*c*, 1.115 in chloroform), $\lambda_{max}^{CHCl_3}$ 2.93, 3.01, 5.83 (s), 5.95 (s), and 6.50 (s) μ.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.73. Found: C, 66.84; H, 6.86; N, 11.98; O, 14.03; OCH_3, 0.0.

As an alternate approach to this substance, 0.4 g. of 2-ketopyrrolidine-5-carboxylic acid (XI) (prepared[18] from L-(+)-glutamic acid and possessing the following constants: m.p. 153–154°, $[\alpha]_D$ −11.2° (*c*, 1.06 in water), +3.9° (*c*, 1.02 in methanol)) was heated for 30 min. at 55° with 0.54 g. of thionyl chloride, the mixture was cooled and treated with a solution of 2.2 g. of β-phenylethylamine in 20 cc. of benzene. After standing for 20 min. at room temperature, the mixture was worked up in the usual manner and furnished 0.49 g. of XIVa, m.p. 138–139°, $[\alpha]_D$ −44.4° (*c*, 1.06 in chloroform). Identity with the above described specimen was demonstrated by mixture melting point determination and infrared comparison.

A solution of 1.972 g. of 2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVa) and 3.0 g. of (±)-α-methylbutyryl chloride in 50 cc. of dry pyridine was kept at room temperature overnight and then diluted with benzene. After washing with dilute acid and base, water, drying, evaporating, and crystallizing from ether-hexane, there was obtained 2.2 g. of *N-(α-methylbutryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide* (XIVb) with m.p. 102–104°. Repeated recrystallization provided the analytical sample, m.p. 105–107°, $[\alpha]_D$ −24.1° (*c*, 1.02 in methanol), $\lambda_{max}^{CHCl_3}$ 2.97, 3.04, 5.72 (s), 5.93 (s), and 6.55 (s) μ. Although the compound is isomeric with julocrotine (I) and possesses the same melting point, a mixture melting point showed a marked depression (m.p. 50–70°) and the infrared spectra were quite different.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.12; H, 7.45; N, 8.92.

Hydrolysis of XIVb (0.983 g.) was effected by heating under reflux for 1 hr. with 50 cc. of 5% methanolic potassium hydroxide. The reaction mixture was concentrated *in vacuo* to remove most of the methanol and the residue was taken up in water, washed with ether, acidified with hydrochloric acid to Congo Red, and then extracted with ethyl acetate. The extract was dried, evaporated, and the residue was crystallized from ether–ethyl acetate to furnish crystals with m.p. 100–115°. Further recrystallization from ethyl acetate provided 0.332 g. of *julocrotic acid-A* (XVI), m.p. 120–122°, $[\alpha]_D$ +10.7° (*c*, 0.746 in methanol), $\lambda_{max}^{CHCl_3}$ 2.82, 3.03, 5.75, 5.98, and 6.55 μ. Identity with julocrotic acid-A derived from natural julocrotine (I) was established by infrared comparison and mixture melting point determination.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.64; H, 7.83; N, 8.37. Found: C, 64.12; H, 7.41; N, 8.60.

Methylation with diazomethane in ether containing a small amount of methanol followed by recrystallization from ether-chloroform-hexane led to the *methyl ester*, m.p. 148–149°, undepressed when mixed with the methyl ester of julocrotic acid-A, $[\alpha]_D$ −3.4° (*c*, 0.902 in methanol). The infrared spectra were also identical.

Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.14; H, 7.91; N, 8.35.

N-β-Phenylethylglutarimide. To 1.09 g. of glutarimide in 20 cc. of absolute ethanol was added a solution of 0.4 g. of potassium metal in 20 cc. of ethanol. The solution was evaporated to dryness under reduced pressure and the residue was heated with 2.2 g. of β-phenylethyl bromide for 3 hr. at 180–200°. The reaction mixture was poured into water, extracted with ether, washed, dried, and evaporated. Crystallization from ether-hexane produced 0.907 g. of the desired glutarimide, m.p. 84–85°, $\lambda_{max}^{CHCl_3}$ 5.78 (w) and 5.96 (s) μ.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45; O, 14.73. Found: C, 71.78; H, 6.98; N, 6.47; O, 14.90.

N-β-Phenylethylsuccinimide. Succinimide (1.0 g.) was treated exactly as described above for glutarimide and led to 0.953 g. of product, m.p. 130–131°, $\lambda_{max}^{CHCl_3}$ 5.63 (w) and 5.85 (s) μ. The same substance (m.p. 133–134°) had already been obtained earlier[15] by heating diethyl succinate with β-phenylethylamine.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.82; H, 6.45; N, 6.89; O, 15.75. Found: C, 70.82; H, 6.51; N, 6.99; O, 15.76.

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(31) We believe that the material extracted with acid was the primary amine corresponding to XIIIc, which cyclized during the evaporation step.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY, AND VARIAN ASSOCIATES]

Terpenoids. XLVII.[1] The Structure of Genipin[2]

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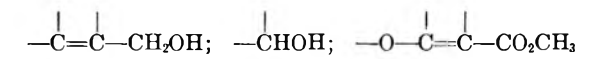
Extensive degradation experiments and NMR measurements are reported which lead to expression I for genipin. Its absolute configuration has been established by degradation to the dibasic acid XIIIa, which was shown to be the antipode of one of the nepetic acids derivable from nepetalactone (XI). The close biogenetic relationship of genipin to aucubin, plumieride, and other monoterpenoids is emphasized. Attention is also called to the behavior of some genipin degradation products towards lithium aluminum hydride resulting in cleavage of the dihydropyran ring.

In an earlier article,[3] there was reported the isolation of the active principle of *Genipa americana* L. as well as the characterization of its functional groups. The substance, named genipin, corresponded in terms of empirical formula to $C_{11}H_{14}O_5$ and its five oxygen functions could be defined as follows:



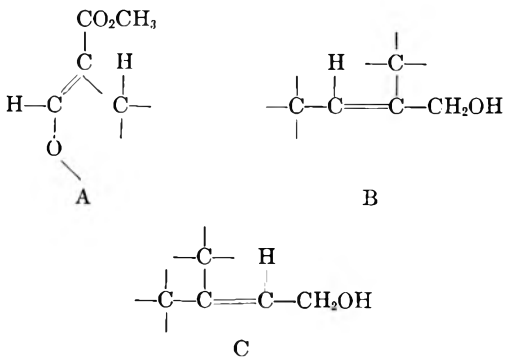
Furthermore, it was noted that genipin had to be bicyclic and that the ether oxygen atom was involved in one of these rings. We should now like to present degradative and spectroscopic evidence which establishes unambiguously the structure and absolute configuration of this substance.

The rather small total number of hydrogen atoms coupled with the relative abundance of oxygen atoms or double bonds indicated that NMR measurements[4] might be very instructive and this has indeed proved to be the case. We shall, therefore, present NMR spectroscopic data concurrently with the most important chemical degradation experiments.

In order to simplify comparison with data obtained at other field strengths, it is proposed that the positions of single peaks and centers of multiplets (see for instance $\delta = 4.81$ in Fig. 1) be expressed in dimensionless "chemical shift" units, $\delta^{int}_{SiMe_4}$, defined as follows:

$\delta^{int}_{Si(CH_3)_4} = 10^6\ (\nu - \nu Si(CH_3)_4)/\nu Si(CH_3)_4$ p.p.m., which for the presently used 60 megacycle instrument reduces to $\delta^{int}_{Si(CH_3)_4} = \frac{\text{c.p.s.}}{60} \times 10^6$ p.p.m. Although this definition leads to a chemical shift scale which differs from the one proposed by Tiers[4c, 5] both in direction and in the position of the zero, the present authors feel that it offers an advantage in that the directly measured "working units" of peak position, *i.e.*, c.p.s., can be readily converted by simple division to the field-independent "reporting units," *i.e.*, p.p.m. Furthermore, the assignment of the position of the internal reference compound, tetramethylsilane ($Si(CH_3)_4$), as zero both on the frequency and p.p.m. scales for all instruments regardless of frequency appears to be the least arbitrary choice possible. In consequence of this choice, increasing δ corresponds to decreased shielding.

For the sake of simplicity, the entire discussion will be presented in terms of the eventually established structure I for genipin.[6] Its NMR spectrum, reproduced in Fig. 1, confirms as well as amplifies the characterization of the functional groups made earlier.[3] Diagnostically, the most significant peaks proved to be the ones at $\delta = 7.52$, 5.86, 4.81 (doublet at 293 and 284 c.p.s.), 4.29 and 3.73. The 7.52 peak is assigned to the conjugated olefinic proton (attached to C-3) and the unusually large shift of this peak confirms the location of the oxygen atom as adjacent to it. A very slight doubling of this peak, observable in some spectra of genipin and its transformation products, is characteristic of spin coupling through four bonds, one of which is the double bond, and suggests that the partial structure A is present, the hydrogen atoms of the carbomethoxy group being responsible for the peak at $\delta = 3.73$.



A B C

(1) Paper XLVI, T. Nakano, and C. Djerassi, *J. Org. Chem.*, **26**, 167 (1961).

(2) The investigations at Stanford University and Wayne State University were supported by the National Heart Institute (grants No. H-5048 and H-2574) of the National Institutes of Health, U. S. Public Health Service.

(3) C. Djerassi, J. D. Gray, and F. Kincl, *J. Org. Chem.*, **25**, 2174 (1960).

(4) See (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959; (b) J. D. Roberts, *Nuclear Magnetic Resonance. Applications to Organic Chemistry*, McGraw-Hill, New York, 1959; (c) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959.

(5) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958). The Tiers τ scale can be readily interconverted into the presently proposed scale by the relationship $\tau = 10 - \delta^{int}_{Si(CH_3)_4}$.

(6) We are employing a numbering system which coincides with that selected for plumieride (O. Halpern and H. Schmid, *Helv. Chim. Acta*, **41**, 1109 (1959)).

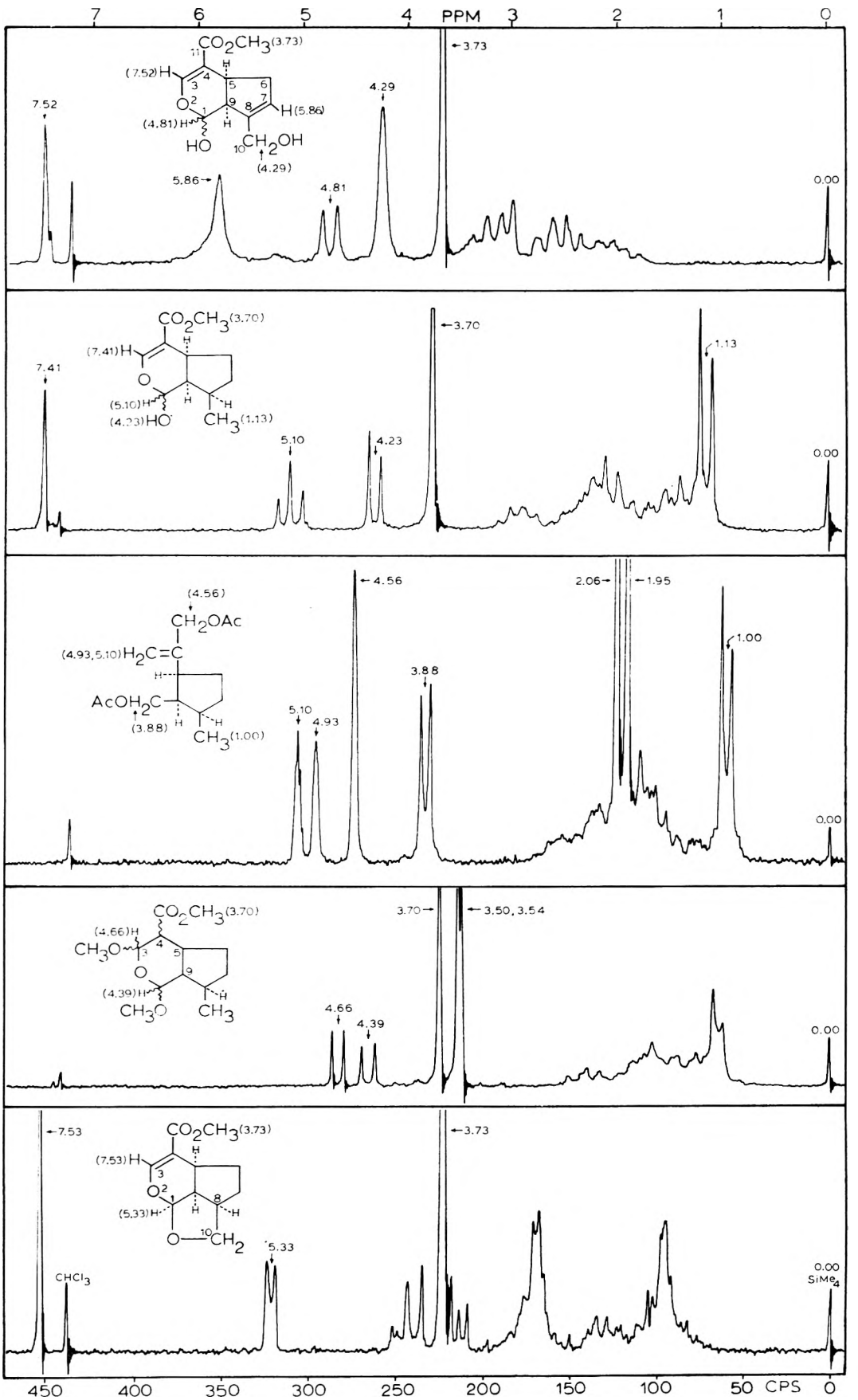

7
6
5
4
PPM
3
2
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Fig. 1
7.52
5.86
4.81
4.29
3.73
0.00
Fig. 2
7.41
5.10
4.23
3.70
1.13
0.00
Fig. 3
4.56
5.10
4.93
3.88
2.06
1.95
1.00
0.00
Fig. 4
4.66
4.39
3.70
3.50, 3.54
0.00
Fig. 5
7.53
CHCl3
5.33
3.73
0.00
SiMe4
450
400
350
300
250
200
150
100
50
CPS
0

The presence of an enol ether grouping conjugated with the carbomethoxy function was already indicated earlier[3] by the chemical and especially ultraviolet spectroscopic evidence. The ultraviolet absorption maximum at 240 mμ is much more compatible with partial structure A than one, in which the carbon atom β to the carbomethoxy group is substituted, since the maximum should then be displaced to approximately 248 mμ.[6,7] The NMR peak at $\delta = 5.86$ can be attributed to a single proton on a double bond, thus enabling us to place the allylic primary hydroxyl group, known[3] to be present on the basis of hydrogenation experiments and trityl ether formation, into partial structures B or C. The peak at $\delta = 4.29$ is due to the hydrogen atoms of the methylene group (C-10 to which the primary hydroxyl group is attached. Structure C is less likely because there exists no spin coupling of the anticipated magnitude between the olefinic proton and the two adjacent ones.

The doublet (293 and 284 c.p.s.) at $\delta = 4.81$ is caused by the proton adjacent to the secondary hydroxyl group (C-1) and is shifted to 5.88 when genipin is transformed into its diacetate;[3] similarly, the peak at $\delta = 4.29$ is moved to 4.65. Such shifts are typical of protons adjacent to hydroxyl groups and thus confirm the assignments. Of particular consequence is the 9 c.p.s. spacing of the doublet, since this is characteristic[8] of spin-coupling between two axial protons on adjacent carbon atoms of a six-membered ring. As will be noted below, this represents the most important evidence for the equatorial orientation of the secondary hydroxyl function of genipin.

The remaining peaks in the NMR spectrum (Fig. 1) of genipin (I) are complex due to spin-spin coupling between protons which have small differences in their chemical shifts. All signals have sufficiently large δ values to permit the conclusion that *no protons are attached to carbon atoms which are not adjacent to either an oxygen atom or a doubly bonded carbon atom.*

In our first paper[3] it was pointed out that catalytic hydrogenation of genipin can lead to a fairly complex mixture due to hydrogenation of one or both double bonds as well as hydrogenolysis. Since one of the complicating aspects of the chemistry of genipin is its great lability to acid or base, it was desirable to remove some of the oxygen functions in the hope that a transformation product would be obtained which would lend itself to more convenient chemical manipulations. Therefore, we returned to a careful examination of the catalytic hydrogenation of genipin and as noted in the Experimental section, depending upon the conditions, five pure products (IIa, XXIVa, XXVI, XXVII, XXXIII) could be isolated and their constitutions determined. The single most important hydrogenation product was 10-deoxy-7,8-dihydrogenipin (IIa)[6] and its structure proof will be presented first since it led directly to the structure of genipin itself.

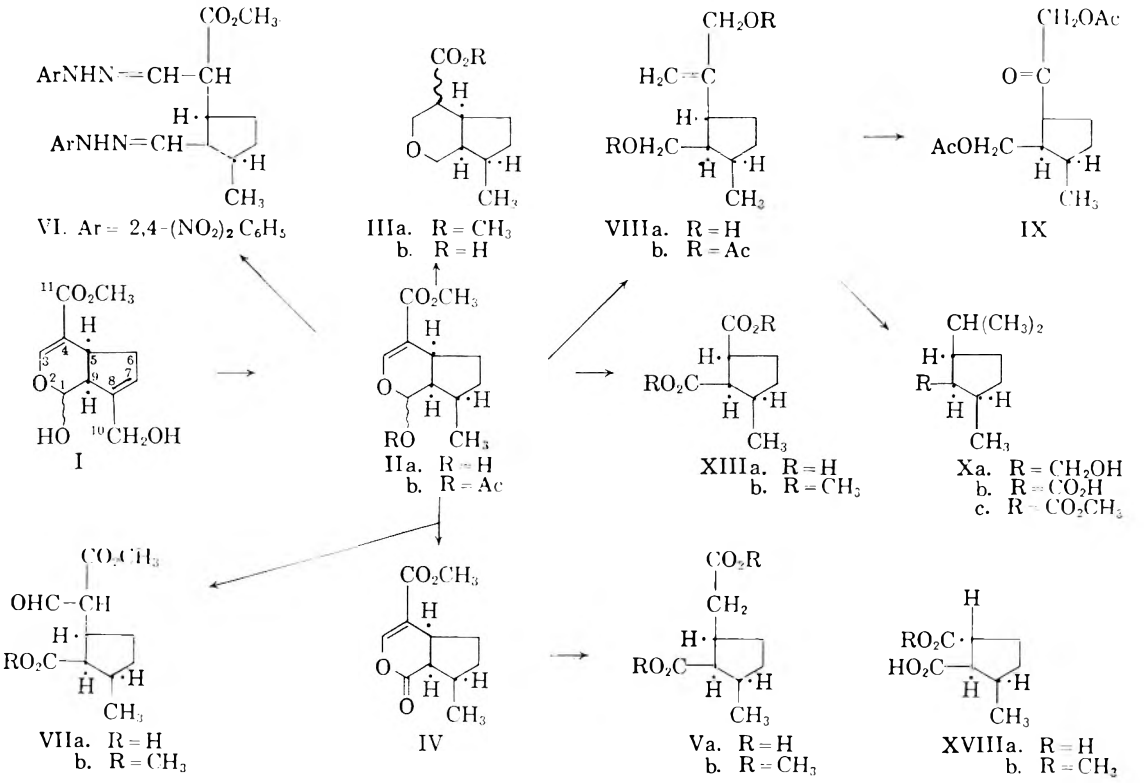
10-Deoxy-7,8-dihydrogenipin (IIa). Of the five hydrogenation products of genipin (I), only one, 10-deoxy-7,8-dihydrogenipin (IIa) is produced both with palladium charcoal in methanol solution or with platinum oxide in acetic acid. From a preparative standpoint (see Experimental), the latter method was preferable and a pure product could be isolated in over 30% yield. The empirical formula $C_{11}H_{16}O_4$ of the crystalline substance (IIa) m.p. 81.5–83°, $[\alpha]_D$ −2.4°, when contrasted with that of genipin (I) ($C_{11}H_{14}O_5$), showed that reduction of one double bond and hydrogenolytic loss of one hydroxyl group had occurred. Accordingly, only a monoacetate (IIb) was formed upon acetylation. Genipin (I) does not possess a C-methyl function, while the presence of one such grouping could be demonstrated in IIa by Kuhn-Roth oxidation. It follows, therefore, that the allylic primary hydroxyl group had been lost and since the ultraviolet absorption spectrum (λ_{max} 240 mμ, log ε 4.06) was essentially identical with that of genipin, the enol ether double bond was intact and the isolated double bond had been reduced. This conclusion was confirmed by the infrared and especially the NMR spectrum (Fig. 2). The latter had lost the peak at 5.86, due to the proton on the isolated double bond of genipin (Fig. 1), but still retained the peaks at $\delta = 7.41$ (single proton on enol ether double bond) and 3.70 (carbomethoxy group) showing that partial structure A is present in unaltered form in IIa.

A doublet (64 and 71 c.p.s.) at $\delta = 1.13$ is characteristic of a methyl resonance split by spin coupling to *one* proton on the adjacent carbon atom. It can be concluded, therefore, that partial structure B rather than C has given rise to this structural fragment by hydrogenation with hydrogenolysis.

A triplet is found at $\delta = 5.10$, which changes to a doublet upon addition of a trace of hydrogen chloride gas to the sample. A doublet at $\delta = 4.23$ undergoes a similar collapse to a singlet and shifts slightly to 4.31 upon addition of hydrogen chloride, showing that it arises from a hydroxyl group which couples its spin to the adjacent CH group. The *downfield* shift of 0.29 p.p.m. of the CH group (C-1) adjacent to this hydroxyl function in going from genipin (I) to its reduction product IIa is a strong indication that the secondary hydroxyl group is not adjacent to the unconjugated double bond (partial structure B) of genipin (I), since it would have been expected to shift *upfield* upon removal of the unshielding effect of an adjacent unsaturated carbon atom. The 7 c.p.s. spin coupling of the C-1 proton at $\delta = 5.10$ suggests that this proton is

(7) F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).

(8) See for instance Chap. 14 in Ref. 4a and p. 86 in Ref. 4c.



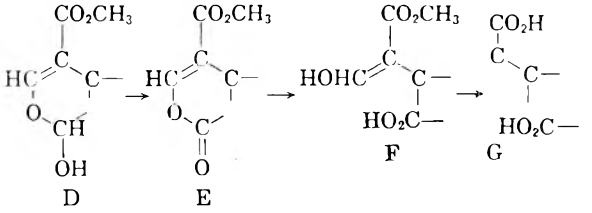
slightly less axial in 10-deoxy-7,8-dihydrogenipin (IIa) than it was in genipin (I). This would also account for the downfield shift of 0.29 p.p.m. After addition of hydrogen chloride gas to promote hydroxyl exchange, it was observed that the 5.10 peak slowly (over a period of a few minutes) acquired a neighbor doublet at $\delta = 5.51$ with a 3 c.p.s. spin coupling. After removal of the solvent and the hydrogen chloride by vacuum distillation, re-examination in fresh, acid-free deuterochloroform disclosed two hydroxyl resonances as well as the two CH resonances at 5.10 and 5.51. These results clearly show that a trace of strong acid catalyses the isomerization of some of the secondary hydroxyl group from the equatorial to the axial orientation, resulting in an equilibrium mixture which contains about 75% equatorial and 25% axial hydroxyl components.

When 10-deoxy-7,8-dihydrogenipin (IIa) was hydrogenated further with Raney nickel catalyst at elevated temperature and pressure, reduction of the conjugated double bond was accompanied by loss of the secondary hydroxyl group. The formation of 1,10-bisdeoxy-3,4,7,8-tetrahydrogenipin (IIIa) implies that the secondary hydroxyl group is also potentially labile and its behavior towards oxidizing reagents was, therefore, examined. The best results were encountered with chromium trioxide–sulfuric acid in acetone solution[9] which led to a neutral and an acidic product of which the former proved to be of great diagnostic value. While its analytical composition indicated that only oxidation of the secondary hydroxyl group to a carbonyl function had occurred, the optical rotatory dispersion curve[10] was plain and the absence of a Cotton effect made it very unlikely that the substance possessed a cyclic ketone grouping. The ultraviolet absorption spectum ($\lambda_{max}^{C_2H_5OH}$ 237 mμ) indicated the presence of the intact enol ether–carbomethoxy chromophore of genipin (I), but its infrared spectrum now exhibited a new, strong band at 5.64 μ. Its position is consistent with that of a γ-lactone grouping or a vinyl ester,[11] which would imply that partial structure A of genipin can be expanded to D, oxidation leading to a lactone (cyclic vinyl ester) E. Indeed, when this lactone E was exposed to alkali, it dissolved readily and upon acidification furnished a *dibasic* acid, lacking the methoxyl function of the starting material. Aside from saponification of the ester grouping, the elementary analysis indicated the loss of an additional carbon and oxygen atom which can readily be rationalized by opening of the lactone ring of E to the intermediate F. Reverse Claisen condensation with loss of formate and saponification of the ester function are unexceptional and would lead from F to the dibasic acid G, completely consistent with the observed analytical results.

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(10) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill, New York, 1960.

(11) See L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, London, 1958, 2nd ed., Chap. 11.



D E F G

In terms of the eventually deduced structure of genipin (I), the lactone possesses structure IV, while its alkali degradation product, the dibasic acid and its derived dimethyl ester can be assigned structures Va and Vb. The partial structure D in genipin (I) and in 10-deoxy-7,8-dihydrogenipin (IIa) also explains the course of the reaction of IIa with 2,4-dinitrophenylhydrazine, which affords a bis-2,4-dinitrophenylhydrazone (VI), whose ultraviolet spectroscopic properties[12] are only compatible with two isolated, non-conjugated 2,4-dinitrophenylhydrazone groupings of aliphatic aldehydes.

The acidic product from the chromium trioxide oxidation could not be purified readily and proved to be quite labile. Nevertheless, there seems to be little doubt that it can be assigned structure VIIa, since methylation afforded a dimethyl ester, whose analytical composition was consistent with formulation VIIb. Vacuum distillation of the acid VIIa led in part to the lactone IV, while treatment with alkali furnished the crystalline dibasic acid Va.

Partial structure D can be closed into the required[3] heterocyclic ring in two fashions, leading to the six-membered (H) or five-membered (J) alternatives. The former is more likely, because the NMR spectrum of genipin (*vide supra*) suggests the attachment of a CH function in the α position of the conjugated double bond, while the infrared spectral data of the oxidation product E could not be used[11] safely for purposes of differentiation.

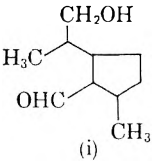
H J

In order to settle this point, it was intended to reduce the carbomethoxy function in 10-deoxy-7,8-dihydrogenipin (IIa) with lithium aluminum hydride and to remove the resulting primary hydroxyl group by hydrogenolysis to an intermediate suitable for further degradation. In actual fact, the lithium aluminum hydride reduction took a completely unexpected course, which will now be described. The principal product was an optically active, low-melting solid (m.p. 37–39°) of the composition $C_{10}H_{18}O_2$. Since the starting material IIa possesses the empirical formula $C_{11}H_{16}O_4$, the anticipated reduction of the carbomethoxy function was accompanied by additional loss of oxygen elsewhere in the molecule. The infrared spectrum exhibited no carbonyl absorption,[13] but two bands at 6.08 and 11.03μ, typical of a terminal double bond, were noted. The NMR spectrum confirmed the presence of a terminal methylene grouping by a pair of lines at δ = 5.20 and 4.99, while a peak at δ = 4.10 with intensity corresponding to two protons is assignable to the allylic protons on the carbon atom (C-11 of genipin) bearing the primary hydroxyl group. The two hydroxyl groups of this substance (subsequently shown to be VIIIa) appear to be exchanging and their resonance partially obscures some signals in the region near δ = 3.5. Consequently, the NMR spectrum (Fig. 3) of its diacetate VIIIb was studied and it will be noted that the peak attributable to the two allylic protons has shifted from δ = 4.10 to 4.56. This downfield shift of 0.46 p.p.m. is quite comparable to the change in δ of 0.36 p.p.m. (upon acetylation) for the two allylic protons attached to C_{10} of genipin (I). A doublet (spacing 6 c.p.s.) at δ = 3.88 is now observed, free of hydroxyl interference, which has shifted 0.38 p.p.m. downfield. Electronic integration of this doublet showed unequivocally that it corresponds to *two* protons. This information, together with the size of the downfield shift and the fact that the doublet lies 0.68 p.p.m. toward higher field than the allylic methylene group requires that the acetate VIIIb (and hence the parent alcohol (VIIIa) possesses two primary hydroxyl groupings, one allylic and the other nonallylic. Aside from the peaks at δ = 5.10 and 4.93 corresponding to the terminal methylene group and the doublet at δ = 1.00 attributable to the methyl group, the NMR spectrum (Fig. 3) also possesses sharp peaks at δ = 2.06 and 1.95 showing that the two acetate groups are nonequivalent. In the chronological sequence of events, the NMR analysis of the alcohol VIIIa and its diacetate VIIIb preceded the structure elucidation of the lactone IV described above and thus represented crucial evidence for the mode of attachment of the C-1 hydroxyl group in genipin (I).

Chemical support for the spectroscopic conclu-

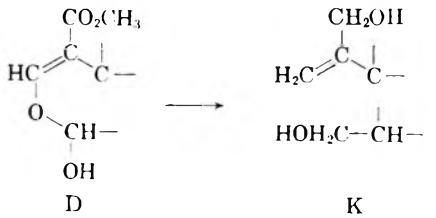
(12) E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945); J. D. Roberts and C. Green, *J. Am. Chem. Soc.*, **68**, 214 (1946); C. J. Timmons, *J. Chem. Soc.*, 2613 (1957).

(13) A minor product of the lithium aluminum hydride reduction was represented by a liquid, isomeric substance, which possessed a strong infrared carbonyl absorption, no exocyclic methylene group and two C-methyl functions. No further work was done but the most likely structure (i) is excluded by the NMR spectrum which showed the absence of an aldehydic proton.



(i)

sion of the presence of a terminal methylene function was adduced by ozonolysis of the diacetate VIIIb to a crystalline nor-ketone IX. The infrared absorption of the new keto group in IX was masked by the strong acetate band, but its presence was demonstrated by the analytical composition of the substance and most importantly, by the strong positive Cotton effect typical[10] of carbonyl groups. The NMR spectrum of the ketone IX proved to be very instructive, because it offered a means of distinguishing partial structure H from J. The conversion of the terminal methylene group to a carbonyl function results in a "magnetic" nonequivalence of the two protons in the nonallylic CH_2 group [corresponding to C-1 in genipin (I)]. A pattern of lines was observed over the range 224 to 262 c.p.s. from the internal tetramethylsilane reference, which was readily recognized as the AB part of an ABX spin-coupling pattern.[4a] The X proton is located on the ring (not possible in partial structure J) and its resonance is complex and is also obscured by the other ring protons. Thus observation of the ABX pattern in the NMR spectrum of IX removes all doubt from the assignment of two protons in the nonallylic alcoholic group of the precursor VIIIa and provides proof of the presence of a proton on the neighboring carbon atom (C-9). It is also pertinent to note that the allylic CH_2 group (now adjacent to carbonyl) shifted to $\delta = 4.78$, an additional shift of 0.22 p.p.m. arising from the greater unshielding ability of carbonyl compared to a carbon-carbon double bond. The principle course of the lithium aluminum hydride reduction therefore can be expressed in terms of the transformation D → K and at least two precedents for this type of enol ether cleavage have been recorded in the literature.[14]

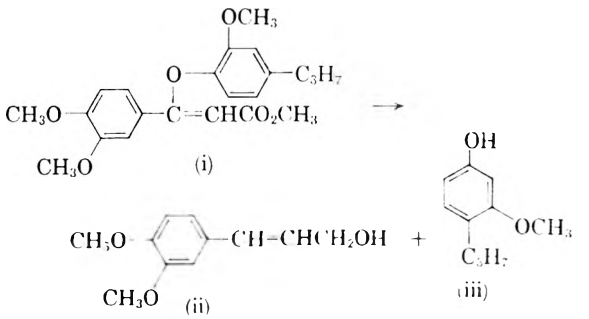


D K

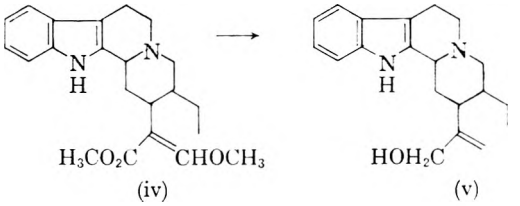
According to partial structure K, which is required by the NMR spectral evidence, it should be possible to remove the primary allylic alcohol of VIIIa by hydrogenolysis. Indeed, when the alcohol VIIIa was exposed to hydrogenation in methanol solution in the presence of a palladized charcoal catalyst, two equivalents of hydrogen were consumed with formation of an alcohol (Xa), $C_{10}H_{20}O$, which possessed only a single hydroxyl function. Oxidation of this alcohol with chromium trioxide provided a liquid acid (Xb), $C_{10}H_{18}O_2$, which was further characterized as the methyl ester Xc and especially as the crystalline *S*-benzylthiouronium salt m.p. 121–122°, $[\alpha]_D$ −5.5°.

Turning now to partial structure H for 10-deoxy-7,8-dihydrogenipin (IIa) only four saturated carbon atoms remain, one of them a methyl group, which must be attached to H in order to construct the second ring known[3] to be present. The only manner in which this can be done is represented by partial structure L, with the methyl group occupying one methyl group occupying one of three positions in the cyclopentane ring Successive exposure of a substance such as L to lithium aluminum hydride, catalytic hydrogenation, and finally oxidation, as mentioned in the preceding paragraph, then leads to structure M for the monobasic acid $C_{10}H_{18}O_2$. The methyl group in M can only be attached to one of the starred carbon atoms and of these three representations, only one (XII) follows the isoprene rule. In fact, structure XII (for absolute configuration see Ref. 15) corresponds to the hydrogenation-with-hydrogenolysis product[16] of nepetalactone (XI),[15,16] a naturally occurring monoterpene. The reduction of nepetalactone (XI) was, therefore, repeated according to the literature directions[16] and the resulting liquid acid XII transformed into its crystalline *S*-benzylthiouronium salt, m.p. 118–119°. The infrared spectrum of this salt was virtually identical with that of the corresponding salt, m.p. 121–122° derived from genipin, but their respective rotations differed somewhat (*S*-benzylthiouronium salt of Xb, $[\alpha]_D$ −5.5°; of XII,

(14) K. Freudenberg and G. Wilke, *Ber.*, **85**, 78 (1952) reported that in the lithium aluminum hydride reduction of (i), in addition to the anticipated primary alcohol, there were also isolated the two fission products (ii) and (iii).



According to P. Karrer, R. Schwyzer, and A. Flam, *Helv. Chim. Acta*, **35**, 851 (1952) dihydrocorynanthein (iv) is converted in part by lithium aluminum hydride into (v).

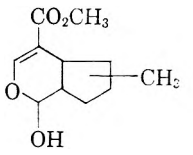


(iv) (v)

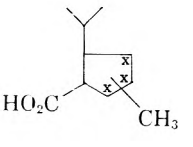
(15) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Am. Chem. Soc.*, **80**, 3420 (1958); E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955); S. M. McElvain and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **77**, 1599 (1955).

(16) J. Meinwald, *J. Am. Chem. Soc.*, **76**, 4571 (1954).

$[\alpha]_D$ +2.8°). The significance of this difference was confirmed by rotatory dispersion measurements,[10] the two salts exhibiting plain disperion curves of opposite sign.

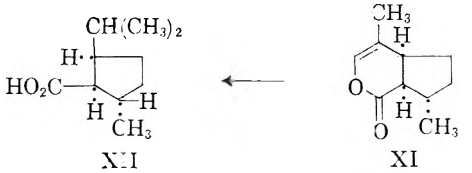


L

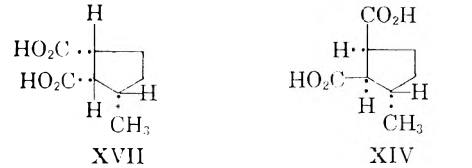


M

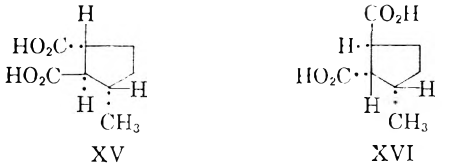
The above results strongly suggest that the acid Xb derived from genipin possesses the same structure as the acid XII obtained from nepetalactone, but that they differ in terms of their stereochemistry. Two approaches were open to settle this crucial point. The first would be to convert the carboxyl group of Xb into a ketone function, since the resulting cyclopentanone can be racemized[16] and compared with synthetic[17] 2-methyl-5-isopropylcyclopentanone. This route suffers from the disadvantage that it would not offer any information on the absolute configuration of the acid Xb and hence of genipin (I). The second approach involved possible correlation through the nepetic acids[15,18] where several stereoisomers are known, and it was selected for actual examination.



XII XI



XVII XIV



XV XVI

For this purpose, 10-deoxy-7,8-dihydrogenipin (IIa) was ozonized in methylene chloride solution at −70° and the ozonide decomposed with alkaline hydrogen peroxide. The resulting crystalline acid was purified through its barium salt and then regenerated, whereupon it exhibited m.p. 136–137°, $[\alpha]_D$ −0.9° (chloroform[19]). In terms of elementary analysis, this acid (XIIIa) corresponded to the nepetic acids (XIV–XVII) but its physical constants and notably the negligible rotation in chloroform solution precluded identity with any of the three known[15] optically active nepetic acids ($[\alpha]_D$ in chloroform: XIV, +69.1°; XV, −35.4°; XVI, +85.8°). The remaining all *cis* isomer XVII is only reported[18] as the racemate, but it is pertinent to mention that Brewster,[20] on the basis of his rotation rules, has predicted a negligible rotation[19] for isomer XVII. This suggested that the dibasic acid from the ozonolysis of 10-deoxy-7,8-dihydrogenipin (IIa) may be the remaining unknown nepetic acid (XVII) or its antipode (XIIIa). Structurally, this conclusion was verified by infrared comparison of the dibasic acid XIIIa and its dimethyl ester XIIIb with the corresponding racemates of the *cis, cis*-nepetic acid.[18,21] Since the infrared spectra of all four racemic nepetic acids (racemates corresponding to XIV–XVII) have been found to show characteristic differences,[18] there remains no doubt that the dibasic acid from the genepin series must be either XIIIa or its antipode XVII.

In order to settle this remaining question, the dibasic acid XIIIa was converted into its anhydride, treated with methanol to afford the half ester, and then heated under reflux with methanolic sodium methoxide in order to epimerize the carbomethoxy function. The crude, epimerized half-ester (XVIIIb) was then saponified to give a new nepetic acid, which should correspond either to the known nepetic acid XVI or its antipode XVIIIa. Bates, Eisenbraun, and McElvain[18] have shown that such a sequence can be employed to convert the racemate of the *cis,cis*-nepetic acid (XVII) into racemic *trans,cis*-nepetic acid (XVI). The isomerized acid exhibited m.p. 95–100°, $[\alpha]_D$ −66.2° as compared to m.p. 114–115°, $[\alpha]_D$ +85.8° for XVI.[15] We can conclude,[22] therefore, that the isomerized dibasic acid in the genipin series should be represented by stereoformula XVIIIa, its precursor, the

(17) J. Golé, *Bull. Soc. Chim. France*, 894 (1949).

(18) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Am. Chem. Soc.*, 80, 3413 (1958).

(19) A considerable solvent dependence was noted, the rotation being considerably higher (+37°) in methanol and this weakens somewhat the validity of applying rotation rules (Ref. 20) to acids of this series.

(20) J. H. Brewster, *J. Am. Chem. Soc.*, 81, 5483 (1959).

(21) We are indebted to Prof. S. M. McElvain and Dr. C. B. Abrahams of the University of Wisconsin for this valuable gift.

(22) The fact that the isomerized acid could not be obtained with a narrower melting point range and that the magnitude of its rotation did not correspond exactly to that of the antipodal acid XVI is probably due to the fact that methanolysis of the anhydride did not give exclusively one monomethyl ester. The final product would, therefore, be contaminated by some of the antipode of the *trans, trans*-nepetic acid (XV), thus resulting in a less negative rotation of XVIIIa. It should be noted that the optically active nepetic acid (XVI), whose constants are used for comparison with the antipode XVIIIa, was not prepared by such an isomerization sequence but rather by oxidation of the corresponding nepetonic acid (see Ref. 15). In any event, the change in rotation accompanying the epimerization of the *cis,cis*-acid XIIIa is of such an order of magnitude as to preclude any structure other than XVIIIa as the principal product.

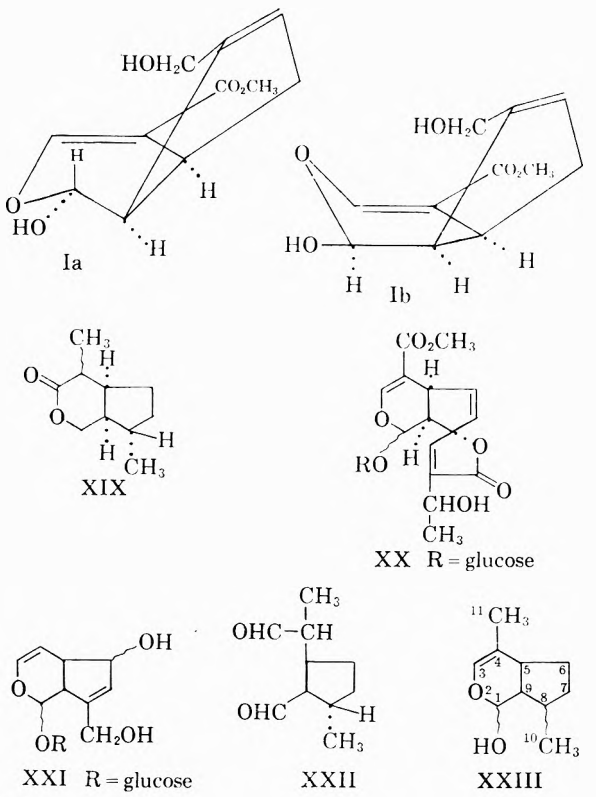
cis,cis-dibasic acid by XIIIa, and hence 10-deoxy-7,8-dihydrogenipin by IIa.

Complete structure of genipin (I) *and biogenetic considerations.* With the establishment of the structure and absolute configuration of 10-deoxy-7,8-dihydrogenipin, the constitution of genipin follows automatically from the information already available. The conversion of genipin into 10-deoxy-7,8-dihydrogenipin (IIa) involves the removal of a primary hydroxyl group with the generation of a methyl substituent as well as reduction of a double bond allylic to that hydroxyl function. Since 10-deoxy-7,8-dihydrogenipin (IIa) possesses only one C-methyl group, the primary hydroxyl function must be attached to it (C-10 in structure I). This leaves only two locations for the double bond, which suffered saturation in the conversion of genipin to IIa, namely between carbon atoms 7 and 8 or between positions 8 and 9. A differentiation can be made readily on the basis of the NMR spectrum (Fig. 1) of genipin, since this shows clearly the presence of one proton on that double bond and this is only possible in the 7-8 location of the double bond. This completes the assignment of the structure and absolute configuration of genipin in terms of the expression I,[23] with the exception of the secondary hydroxyl group attached to C-1. The NMR spectrum (Fig. 1) demonstrated the equatorial orientation of this hydroxyl group, but it can nevertheless be assigned to α- or β-notation,[23] depending upon whether genipin possesses conformation IA or IB.

Biogenetically, genipin belongs to a very interesting group of monoterpenoids. This includes nepetalactone (XI),[15,16] the ant lactones[24] (e.g. iridomyrmecin (XIX)), plumieride (XX),[6] and aucubin (XXI).[25] In all cases where the absolute configuration of the ring juncture has been established (I, XI, XIX, XX) this has proved to be identical and it is very likely that this will also apply to aucubin (XXI).

It has been suggested[26] that the naturally occurring [27] iridodial (XXII) is the biological precursor of iridomyrmecin (XIX) involving disproportionation of the dialdehyde. Such dialdehydes may also represent the precursors of the other monoterpenoids of this series, direct cyclization rather than disproportionation leading to the enol–half acetal XXIII. Oxidation at C-1 would then furnish nepetalactone (XI), while allylic oxidation at C-1 would result in production of the carboxyl group of genipin (I) and plumieride (XX). In aucubin, C-11 has been lost, most likely by decarboxylation. Hydroxylation at C-6 and/or C-10 (I, XX, XXI) as well as introduction of unsaturation in the cyclopentane ring are probably secondary processes, which may happen either before or after generation of the dihydropyran ring. This probably also applies to the attachment of the additional four carbon atoms of plumieride (XX) involved in the third ring; Halpern and Schmid[6] have already noted that these arise probably from acetoacetate and a precursor, which can now be seen to have a very close structural resemblance to genipin (I).

Structure of some hydrogenation products. In the introductory section, it was pointed out that the catalytic hydrogenation of genipin (I) yielded a mixture, from which five pure constituents could be separated. While the structure of one of them, 10-deoxy,7,8-dihydrogenipin (IIa), sufficed for the establishment of the constitution of genipin (I),



(23) Throughout this paper we are using absolute configurational representations following the steroid notation.

(24) For leading references see R. Fusco, R. Trave, and A. Vercellone, *Chim. e Ind.* (*Milano*), **37**, 251, 958 (1955); G. W. K. Cavill and H. D. Locksley, *Austral. J. Chem.*, **10**, 352 (1957); R. H. Jaeger and R. Robinson, *Tetrahedron Letters*, No. 15, 14 (1959); T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Butsugan, *Bull. Chem. Soc. Japan*, **32**, 1154 (1959).

(25) S. Fujise, H. Obara, and H. Uda, *Chem. & Ind.* (*London*), 289 (1960); see also P. Karrer and H. Schmid, *Helv. Chim. Acta*, **29**, 525 (1946); J. Grimshaw and H. R. Juneja, *Chemistry & Ind.* (*London*), 656 (1960). M. W. Wendt, W. Haegele, E. Simonitsch and H. Schmid, *Helv. Chim. Acta*, **43**, 1440 (1960) have pointed out that in addition to structure XXI for aucubin an alternate expression is possible in which the C-6 hydroxyl group is placed at C-7 and the double bond is located between C-8 and C-9.

(26) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(27) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Chem. & Ind.* (*London*), 465 (1956).

parallel work was also conducted with the other products as discussed below.

Hydrogenation of genipin (I) in methanol solution in the presence of palladized charcoal catalyst led to three substances which could be separated by a combination of distillation and chromatography. The most polar product was 10-deoxy-7,8-dihydrogenipin (IIa), which has already been covered in the preceding section. The least polar one, now named 1,10-bisdeoxy-7,8-dihydrogenipin (XXIVa) initially presented considerable difficulties, since no satisfactory analytical results could be obtained. Apparently this is due to the hygroscopic nature of the substance, whose structure XXIVa was demonstrated as follows. The presence of the intact chromophore involving the carbomethoxy moiety and the enol ether grouping was confirmed by the characteristic infrared and ultraviolet spectroscopic properties. Saponification of XXIVa led to the free acid XXIVb, which formed a crystalline *S*-benzylthiouronium salt and which upon regeneration provided a specimen of the oily acid XXIVb with analytical figures consistent with the empirical formula $C_{10}H_{14}O_3$. Remethylation with diazomethane again provided 1,10-bisdeoxy-7,8-dihydrogenipin (XXIVa). Heating of the free acid resulted in decarboxylation, while treatment with 2,4-dinitrophenylhydrazine yielded a bis-2,4-dinitrophenylhydrazone corresponding in terms of analytical composition and ultraviolet spectroscopic properties with structure XXV. Apparently, opening of the dihydropyran ring was accompanied by oxidation of the intermediate hydroxyaldehyde to the dialdehyde.

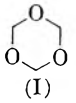
Further hydrogenation of XXIVa could be effected with platinum oxide in acetic acid solution which resulted in the uptake of one equivalent of hydrogen and the saturation of the double bond. The oily product, 1,10-bisdeoxy-3,4,7,8-tetrahydrogenipin (IIIa), upon saponification afforded the free acid IIIb, which formed a crystalline *S*-benzylthiouronium salt. The same salt had already been obtained earlier[3] from genipin (I) without isolation of intermediates by successive hydrogenation with palladium-charcoal and then platinum oxide in acetic acid. These reactions, notably the conversion to 1,10-bisdeoxy-3,4,7,8-tetrahydrogenipin (IIIa), settle the constitution of 1,10-bisdeoxy-7,8-dihydrogenipin (XXIVa).

A third substance, of intermediate polarity between XXIVa and IIa, could be separated in crystalline form from the palladium–methanol hydrogenation of genipin. Its empirical formula corresponded to $C_{13}H_{22}O_5$ and no free hydroxyl or enol ether absorption was noted in the infrared. Treatment with hydroxylamine or semicarbazide under alkaline conditions did not afford any carbonyl derivative, but exposure to 2,4-dinitrophenylhydrazine in acid solution yielded the bis-2,4-dinitrophenylhydrazone VI, which had already been obtained by a similar reaction from 10-deoxy-7,8-dihydrogenipin (IIa). The isolation of the bis-2,4-dinitrophenylhydrazone VI demonstrates the unsubstituted nature of the cyclopentane ring and requires that the additional two carbon atoms must have entered into the pyran ring. The NMR spectrum (Fig. 4) immediately settled the structure of the product as 3-methoxy-10-deoxy-3,4,7,8-tetrahydrogenipin 1-methyl ether (XXVI) since its three peaks at δ = 3.50, 3.54, and 3.70 can all be assigned to methoxy group resonances and this was confirmed by Zeisel methoxyl analysis. The formation in an acid medium of the bis-2,4-dinitrophenylhydrazone VI from such a structure is, of course, unexceptional. The NMR peak at δ = 3.70, which is distinctly different from the other two, lies close to the value (3.73) observed for the carbomethoxy group in genipin (Fig. 1). A pair of lines is found at 259 and 267 c.p.s. (δ = 4.39) and a similar pair at 276 and 284 c.p.s. (δ = 4.66) with intensities corresponding to one proton for each pair. The size of the spin coupling, 8 c.p.s., shows that each proton is axial and possesses one axial neighbor in a six-membered saturated ring. The equality of intensities of the lines in each pair indicates that the two protons in question are not coupled to one another and hence are not on adjacent carbon atoms. Furthermore, the doublets are found in a region of the spectrum which is characteristic of CH groups adjacent to two oxygen atoms.

Catalytic hydrogenation of genipin (I) in glacial acetic acid in the presence of platinum oxide catalyst furnished three crystalline substances. The most abundant one (32% yield) was 10-deoxy-7,8-dihydrogenipin (IIa), a second one was isolated in 8% yield, while the third one was only encountered in trace quantities.

This second product from the platinum oxide–acetic acid hydrogenation was less polar than 10-deoxy-7,8-dihydrogenipin (IIa). Its empirical formula ($C_{11}H_{14}O_4$) differed by only two hydrogen atoms from that of IIa ($C_{11}H_{16}O_4$) and the new product was characterized by its unusually high positive rotation ($[\alpha]_D$ +161°). Its infrared spectrum still exhibited the bands at 5.89 and 6.09 μ associated with the carbomethoxy and enol ether functions, respectively, but it did not show any absorption due to a hydroxyl group. The fourth oxygen must, therefore, be etheral in nature. The ultraviolet absorption maximum at 234 mμ was somewhat displaced to shorter wave length, as compared to genipin (I). The simplest structure consistent with the above data is the tricyclic one, 1,10 - anhydro - 7,8 - dihydrogenipin (XXVII), in which a new oxide ring had been produced between C-1 and C-10, since the substance did not possess a C-methyl function (in contrast to the other hydrogenation products IIa, XXIVa, and

XXVI) by Kuhn-Roth oxidation. Stereochemically, such ring closure appears perfectly feasible by inspection of models and the NMR spectrum (Fig. 5) confirms such a formulation. The characteristic peak of the proton attached to C-3 (δ = 7.53 and I and 7.41 in IIa) can be found in the expected region at δ = 7.53. The doublet at δ = 5.33 with a spacing of 5 c.p.s. can be assigned to the proton at C-1, since it is adjacent to two oxygen atoms.[28]



(I)

The carbomethoxy peak is found at δ = 3.73 falling among a group of lines which can be recognized as the AB part of an ABX multiplet, thus confirming the presence of a CH_2 group (C-10) in a ring adjacent to oxygen and possessing only one adjacent proton neighbor (attached to C-8).

In view of the unusual behavior of 10-deoxy-7,8-dihydrogenipin (IIa) towards lithium aluminum hydride, it appeared of interest to examine the corresponding cyclic ether XXVII under identical conditions. The minor product of this reaction proved to be the unsaturated triol XXIXa, formally generated by cleavage of the enol ether grouping and complete reduction of the carbomethoxy and masked aldehyde functions. The triol XXIXa was not analyzed as such, but transformed into its triacetate XXIXb, which gave satisfactory analytical figures. The infrared spectrum showed the presence of acetate groups as well as the terminal olefin, while its NMR spectrum was quite unambiguous, the triacetate XXIXb simply representing the analog of the diacetate VIIb with an additional acetoxy group attached to the methyl substituent. Consequently, the only significant differences in the NMR spectra of the diacetate VIIIb (Fig. 3) and the triacetate XXIXb are the appearance of a third (methyl) acetate group at δ = 2.05 and the disappearance of the methyl doublet of VIIIb, which is now replaced by a complex CH_2 multiplet centered at about δ = 3.84.

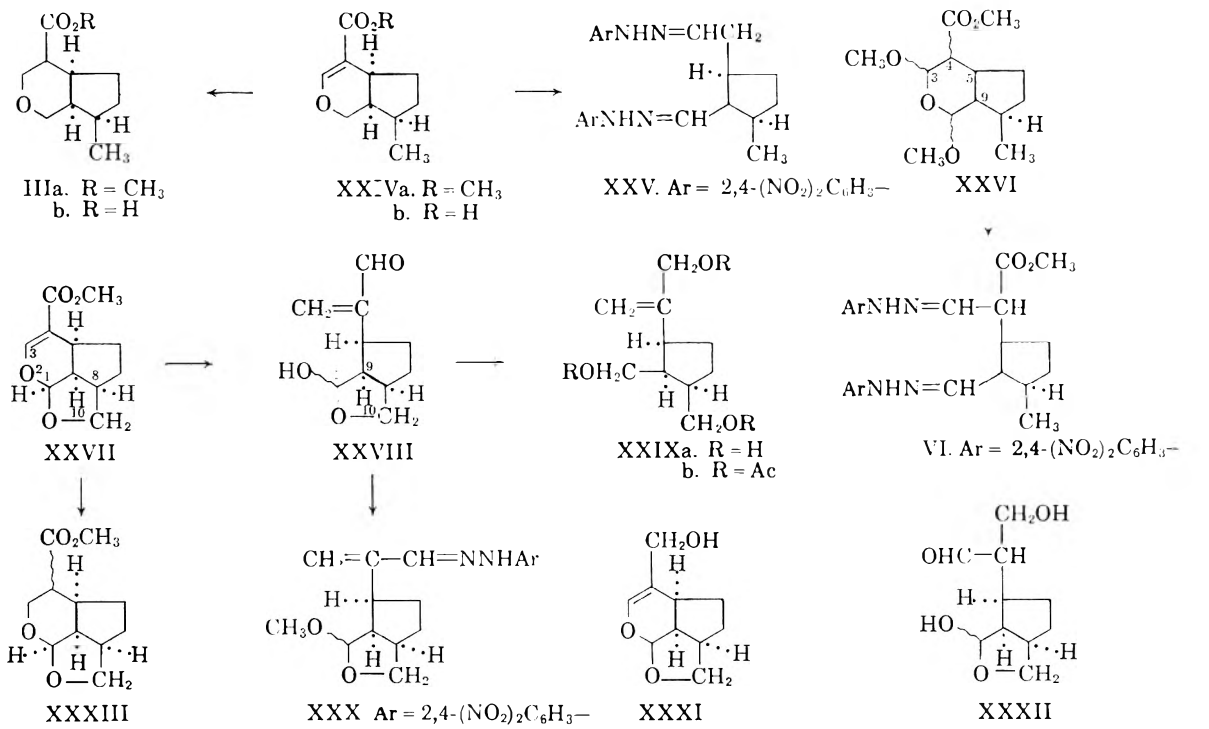
The principal product in the lithium aluminum hydride reduction turned out to be the α,β-unsaturated aldehyde XXVIII. The analytical composition of the oil was consistent with this formulation and the presence of the α,β-unsaturated aldehyde was indicated by the ultraviolet and infrared spectral properties of the substance. The existence of the cyclic hemiacetal grouping was demonstrated by treatment with 2,4-dinitrophenylhydrazine in *methanolic* hydrochloric acid, whereupon the 2,4-dinitrophenylhydrazone XXX of the methyl ether of XXVIII was obtained, the introduction of a methoxyl group being established by Zeisel determination. The interpretation of the NMR spectrum, though somewhat complicated, lends support to structure XXVIII. An aldehyde peak is observed at δ = 9.58 and a pair of lines at δ = 6.11 and 6.30 represent the protons on the terminal methylene group.[29] A rather poorly resolved multiplet is found, centered at about δ = 3.83, which seems to be characteristic of the two protons of the methylene group (C-10) in the five-membered ring adjacent to oxygen. The peak at δ = 4.86 was first suspected of arising from the proton on the hydroxyl group, but its temperature and concentration independence require that it be assigned instead to the hydrogen atom attached to C-1. The proton on this same carbon atom in XXVII (Fig. 5) is found at δ = 5.33 and the reduced shielding in XXVII relative to its reduction product XXVIII or trioxan[28] may be due to the six-membered unsaturated ring, which may result in some long range effects. A small sample of XXVIII was acetylated and the NMR spectrum of the total crude product examined. The major change in the spectrum was a shift of this peak (due to proton at C-1) from δ = 4.86 to 5.71, thus confirming its assignment.[30]

It would be attractive to assume that the α,β-unsaturated aldehyde XXVIII is an intermediate in the formation of the triol XXIXa by lithium aluminum hydride reduction of 1,10-anhydro-7,8-dihydrogenipin (XXVII). In fact, further reduction of the aldehyde XXVIII led directly to the triol XXIXa. Nevertheless, no reasonable mechanism for the sequential production of XXVIII and XXIX seems available. The simplest rationalization would be assumption of initial reduction of the carbomethoxy group to XXXI followed by cleavage of the acetal grouping to XXXII when the reaction mixture is decomposed. Dehydration of the β-hydroxyaldehyde in XXXII would then lead to XXVIII. Two difficulties immediately arise if one visualizes such a picture. First, the decomposition was conducted with aqueous sodium sulfate and no acid was employed, thus implying that the acetal linkage in XXXI is unusually labile. Secondly,

(28) Trioxan (i) exhibits a peak at δ = 5.00 (observation by G. V. D. Tiers).

(29) The fact that they are 1.2 p.p.m. less magnetically shielded as compared to VIIIb (Fig. 3) indicates that the terminal methylene group is conjugated, presumably with the aldehyde.

(30) The lack of doubling of the resonance of the proton attached to C1 through spin-spin coupling to the adjacent proton at C9 can be rationalized as follows. Recent theoretical work (M. Karplns, *J. Chem. Phys.*, **30**, 11 (1959)) has shown that there is quite a range (70–100°) for the dihedral angle between the H—C—C planes for two protons on adjacent carbon atoms which leads to the expectation of a near-zero spin coupling. In fact, the coupling for the proton attached to C-1 in XXVII (Fig. 5) is slightly less than 5 c.p.s. which would correspond to a dihedral angle near 120°. Reduction of the angle from 120° to 100° upon opening of the six-membered ring (XXVII → XXVIII) would reduce the spin coupling to an unresolvable value. Therefore, the absence of observable doubling of the resonance in question need not be regarded as an obstacle to the explanation of the NMR spectrum in terms of structure XXVIII.



such a mechanism does not explain the formation of the triol XXIXa since generation of the intermediate XXXII *after* decomposition of the lithium aluminum hydride does not permit further reduction of the aldehyde and hemicacetal groupings. We believe, therefore, that the unsaturated aldehyde XXVIII is not an intermediate in the formation of the triol XXIXa. The latter apparently arises from cleavage of the 2–3 bond[14] followed by further reduction of the carbomethoxy and hemiacetal functions. As far as the production of the aldehyde XXVIII is concerned, we are reduced to assume that an intermediate of type XXXI is unusually labile to hydrolytic opening yielding XXXII.

In some platinum oxide–acetic acid hydrogenations of genipin (I), in addition to IIa and XXVII there was also encountered in trace amounts a third crystalline product. Its empirical formula ($C_{11}H_{16}O_4$) differed by only two hydrogen atoms from that of the cyclic acetal XXVII and like it, the substance possessed a high positive rotation and showed no hydroxyl absorption in the infrared. The most significant difference resided in the position of the carbomethoxy peak, which now occurred at 5.79 μ and the absence of any selective ultraviolet absorption maximum. The most likely structure satisfying all these requirements is that expressed by 1,10-anhydro-3,4,7,8-tetrahydrogenipin (XXXIII) and this was confirmed by hydrogenation of the unsaturated precursor XXVII with platinum oxide in acetic acid.

EXPERIMENTAL[31]

Nuclear magnetic resonance measurements. All compounds were studied as dilute solutions in deuterochloroform unless otherwise specified. A trace of tetramethylsilane was added to the solvent to serve as an internal reference. Peak positions were measured in c.p.s. relative to the reference by the usual audio side-band technique, using a Hewlett-Packard 200 CD audio oscillator. Frequencies were checked with an HP 521C electronic counter.

The NMR instrument was a Varian Associates HR-60 High Resolution Spectrometer. Thin-walled sample coils (0.195″ o.d., 0.165″ i.d.) were employed for maximum signal-to-noise with dilute solutions. The magnetic field strength was 14,092 oersteds, corresponding to a proton resonance frequency of 60 mc. Spectra were swept from low to high field. We are indebted to Mr. LeRoy Johnson for all of the NMR measurements.

Hydrogenation of genipin (I) *with platinum oxide in acetic acid solution.* A solution of 30 g. of genipin (I)[3] in 250 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 6.0 g. of prereduced platinum oxide catalyst. Hydrogen uptake corresponding to 2 equivalents occurred within 9 hr., whereupon the catalyst was filtered and most of the acetic acid was removed *in vacuo*. The residue was taken up in ether, washed with aqueous sodium carbonate solution, water, dried, and evaporated to yield 27 g. of a slight yellowish oil. Crystallization from ether–petroleum ether afforded 6.55 g. of *10-deoxy-7,8-dihydrogenipin* (IIa), m.p. 81–82.5°, which together with an additional 2.60 g. obtained from chromatography of the mother liquors raised the yield to 32%. The analytical sample crystallized from the same solvent pair as leafy plates, m.p. 81.5–83°, $[\alpha]D$ −2.4° (*c*, 1.22 in methanol), $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.06, $\lambda_{max}^{CHCl_3}$ 2.76, 2.93, 5.90, 6.11, and 11.09 μ, plain negative rotatory dispersion curve[16] ($[\alpha]_{500}$ −50°, $[\alpha]_{400}$ −126°, $[\alpha]_{300}$ −475°, $[\alpha]_{285}$ −690°) in methanol solution (*c*, 0.12).

(31) All melting points were determined on the Kofler block. We are indebted to Miss B. Bach for most of the ultraviolet and infrared spectral measurements, to Mrs. A. James and Mrs. T. Nakano for the optical rotatory dispersion curves, to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses and to Dr. D. K. Cox (Syntex, S.A., Mexico City) for collecting the plant material.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; O, 30.15; OCH_3, 14.61; C—CH_3, 7.15. Found: C, 62.16; H, 7.37; O, 30.45; OCH_3, 14.31; C—CH_3, 6.45.

A sample was acetylated with pyridine and acetic anhydride at room temperature (16 hr.) and since *10-deoxy-7,8-dihydrogenipin acetate* (IIb) could not be crystallized, it was distilled for analysis; $\lambda_{max}^{CHCl_3}$ 5.72, 5.87, 6.11, and 8.10 μ.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14; O, 31.46; C—CH_3, 11.78. Found: C, 61.64; H, 7.30; O, 31.86; C—CH_3, 11.76.

A 54-mg. portion of 10-deoxy-7,8-dihydrogenipin was treated with 2.0 cc. of 2,4-dinitrophenylhydrazine solution (1.0 g. of 2,4-dinitrophenylhydrazine, 7.5 cc. of concd. sulfuric acid, 75 cc. of ethanol diluted with water to a volume of 250 cc.) and the resulting precipitate chromatographed on 2.0 g. of acid-washed alumina. Elution with benzene and recrystallization from the same solvent afforded leafy orange plates, m.p. 176.5–177.5°, $[\alpha]_D$ +68° (c, 0.58 in chloroform), $\lambda_{max}^{CHCl_3}$ 348 mμ, log ϵ 4.63, which corresponded to the *bis-2,4-dinitrophenylhydrazone* VI of 1-methylcyclopentane-2-carboxaldehyde-3-(α-methoxycarbonyl) acetaldehyde.

Anal. Calcd. for $C_{23}H_{24}N_8O_{10}$: C, 48.25; H, 4.22; N, 19.57; O, 27.95. Found: C, 48.20; H, 4.22; N, 19.58; O, 27.91.

The mother liquor from the crystallization of 10-deoxy-7,8-dihydrogenipin (IIa) was chromatographed on 270 g. of Merck acid-washed alumina. The first benzene-ether (9:1) eluates afforded after crystallization from petroleum ether (b.p. 30–60°) at −70° approximately 40 mg. of *1,10-anhydro-3,4,7,8-tetrahydrogenipin* (XXXIII), which exhibited m.p. 42–42.5°, $[\alpha]_D$ +113° (methanol), $\lambda_{max}^{CHCl_3}$ 5.79 μ, no selective ultraviolet absorption.

Anal. Calcd. for $C_{11}H_{16}O_4$: C. 62.25; H, 7.60; OCH_3, 14.61. Found: C, 62.28; H, 7.55; OCH_3, 14.72.

The other benzene-ether (9:1 and 3:1) fractions were combined and crystallized from ether–petroleum ether leading to 2.24 g. (8%) of *1,10-anhydro-7,8-dihydrogenipin* (XXVII), m.p. 60–61.5°, $[\alpha]_D$ +161° (c, 1.12 in methanol), $\lambda_{max}^{C_2H_5OH}$ 234 mμ, log ϵ 4.10, $\lambda_{max}^{CHCl_3}$ 5.89, and 6.09 μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H. 6.71; O, 30.44; OCH_3, 14.76. Found: C, 62.97; H, 6.79; O, 30.11; OCH_3, 14.80; C—CH_3, 0.0.

Final elution with ether and 9:1 ether-methanol provided an additional 2.60 g. of 10-deoxy-7,8-dihydrogenipin (IIa) of m.p. 81–82.5°.

Hydrogenation of 1,10-anhydro-7,8-dihydrogenipin (XXVII). 1,10-Anhydro-7,8-dihydrogenipin (XXVII) (0.367 g.) was hydrogenated in 40 cc. of glacial acetic acid with 70 mg. of prereduced platinum oxide at atmospheric pressure and 30°. Hydrogen uptake did not cease until 6 hr., whereupon 1.9 molar equivalents had been consumed indicating reduction beyond simple saturation of the double bond. The catalyst was filtered, the filtrate was diluted with a large amount of water and extracted with ether. The ether solution was washed with water, 5% aqueous sodium bicarbonate, then water, dried, and evaporated. The resulting colorless oil (0.23 g.) was crystallized from ether–petroleum ether (while cooling in Dry Ice) to afford 68 mg. of 1,10-anhydro-3,4,7,8-tetrahydrogenipin (XXXIII), m.p. 41–43°. Its infrared spectrum (chloroform) was identical with that of the sample isolated in the direct hydrogenation of genipin.

Hydrogenation of genipin (I) *with palladium-charcoal in methanol solution.* A solution of 8.32 g. of genipin (I) in 170 cc. of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladized charcoal catalyst, approximately 2 molar equivalents of hydrogen being consumed over a period of 20 hr. The "non-polar" constituents were separated by chromatography on basic alumina (Alcoa, grade F-20) and elution with benzene, thus affording 2.14 g. of oil. This material was fractionated at 1.0 mm. pressure into two major portions, (a) b.p. 91–97°/1.0 mm. and (b) b.p. 113–116°/1.0 mm.

Fraction (a) was redistilled twice and material boiling constantly at 85°/0.4 mm., corresponded to *1,10-bisdeoxy-7,8-dihydrogenipin* (XXIVa), n_D^{24} 1.4853, $\lambda_{max}^{CHCl_3}$ 5.87 and 6.10 μ, $\lambda_{max}^{C_2H_5OH}$ 238 mμ, log ϵ 3.91, $[\alpha]_D$ +46.7° (methanol), plain positive rotatory dispersion curve ($[\alpha]_{400}$ +71°, $[\alpha]_{300}$ +150°, $[\alpha]_{285}$ +230°) in methanol (*c*, 0.13).

Anal. Calcd. for $C_{11}H_{16}O_3 \cdot 1/3\ H_2O$: C, 65.32; H, 8.30; O, 26.35; C—CH_3, 7.43. Found: sample (1): C, 65.86; H, 8.28; O, 26.36; sample (2): C, 66.15; H, 8.35; O, 25.56; C—CH_3, 6.03.

The poor analytical results appeared to be due to the hygroscopic nature of the oil XXIVa as demonstrated as follows. Saponification of a portion of the oily methyl ester XXIVa by heating under reflux for 3 hr. with 0.5*N* ethanolic potassium hydroxide solution afforded in 92% yield an oily acid (XXIVb), which was converted into its *S*-benzylthiouronium salt by dissolving in 10% aqueous sodium hydroxide, adjusting the *p*H to 6.5 and adding the filtered solution to a saturated aqueous solution of *S*-benzylthiourea hydrochloride. Recrystallization from hot water provided an analytical specimen of the salt, m.p. 143–144°.

Anal. Calcd. for $C_{18}H_{24}N_2O_3S$: C, 62.05; H, 6.94; N, 8.04; O, 13.77; S, 9.20. Found: C, 61.62; H, 7.29; N, 7.91; O, 14.00; S, 8.99.

The above *S*-benzylthiouronium salt (94 mg.) was dissolved in 50% aqueous methanol and passed through a column of Dowex 50 ion exchange resin. The eluate was evaporated on the water pump to remove methanol and the aqueous solution was extracted with ether. Washing with sodium bicarbonate solution, acidification and re-extraction with ether provided 46 mg. of the *acid XXIVb*, which was distilled at 0.005 mm. for analysis; $\lambda_{max}^{CHCl_3}$ 5.94, 6.14 μ and typical "acid" absorption in 3–4 μ region.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74; O, 26.34. Found: C, 65.74; H, 7.83; O, 26.66.

The acid XXIVb (22 mg.)[32] was now methylated with diazomethane and the resulting ester (pure XXIVa) redistilled; $\lambda_{max}^{CHCl_3}$ 5.87 and 6.12 μ. The analytical results were essentially identical to those of 1,10-bisdeoxy-7,8-dihydrogenipin (XXIVa) isolated directly from the hydrogenation.

Anal. Found: C, 65.45; H, 8.16; O, 26.21.

Treatment of an ethanolic solution of the acid XXIVb with 2,4-dinitrophenylhydrazine in sulfuric acid–ethanol–water afforded after chromatographic purification and recrystallization from benzene orange needles of the *bis-2,4-dinitrophenylhydrazone* XXV of 1-methylcyclopentane-2,3-dicarboxaldehyde, m.p. 219.5–220.5°, $[\alpha]_D$ −21.8° (*c*, 0.22 in chloroform), $\lambda_{max}^{CHCl_3}$ 352 mμ, log ϵ 4.74.

Anal. Calcd. for $C_{21}H_{22}N_8O_8$: C, 49.03; H, 4.31; N, 21.78; O, 24.99. Found: C, 49.29; H, 4.24; N, 21.63; O, 24.62.

The higher boiling fraction (b) from the distillation of the original "non-polar" hydrogenation products after two redistillations afforded *3-methoxy-10-deoxy-3,4,7,8-tetrahydrogenipin 1-methyl ether* (XXVI), b.p. 111–112.5°/1.2 mm., n_D^{25} 1.4682. The same substance was also obtained (eventually in crystalline form) by washing the original basic alumina chromatogram column with ether-methanol mixtures and re-chromatographing the "polar" fraction on Brockmann neutral alumina (activity VI). The hexane-benzene eluates gave the dimethoxy compound XXVI, while development of the column with ether-benzene (1:1), ether and chloroform produced *10-deoxy-7,8-dihydrogenipin* (IIa). Further purification of the latter was best effected by chromatography on silica gel and elution with chloroform. The resulting product was identical in all respects with the specimen obtained by the preferred platinum oxide–acetic acid procedure.

Crystallization of *3-methoxy-10-deoxy-3,4,7,8-tetrahydro-*

(32) Heating of the acid above 145° causes partial decarboxylation as was shown in a larger scale experiment: heating of 388 mg. of XXIVb at 145–150° and sweeping with dry nitrogen (free of oxygen and carbon dioxide) liberated 50 mg. of carbon dioxide, which was weighed by absorption on ascarite.

genipin 1-methyl ether (XXVI) could be effected from hexane to afford an analytical sample, m.p. 61–62°, $\lambda_{max}^{CHCl_3}$ 5.79 μ, which lacked selective ultraviolet absorption.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59; O, 30.97; OCH_3, 36.05; C—CH_3, 5.82. Found: C, 30.78; H, 8.49; O, 30.66; OCH_3, 39.25; C—CH_3, 4.64.

Treatment of a sample of XXVI with 2,4-dinitrophenylhydrazine as reported above for 10-deoxy-7,8-dihydrogenipin (IIa) produced the same bis-2,4-dinitrophenylhydrazone VI, m.p. 176–178°, undepressed upon admixture with a sample prepared from IIa. The infrared spectra of the two 2,4-dinitrophenylhydrazones were undistinguishable.

1,10-Bisdeoxy-3,4,7,8-tetrahydrogenipin (IIIa). (a) *By Raney nickel hydrogenation of 10-deoxy-7,8-dihydrogenipin* (IIa). A mixture of 218 mg. of 10-deoxy-7,8-dihydrogenipin (IIa) and 0.6 g. of W-2 Raney nickel catalyst (7 months old) in 25 cc. of ethanol was shaken for 24 hr. in the presence of hydrogen at 1500 p.s.i. and 200°. The resulting colorless liquid did not exhibit any more an infrared band near 6.10 μ corresponding to the enol ether and after chromatography on 7.5 g. of neutral Brockmann alumina (activity VI) there was eluted with benzene-chloroform (1:1) a liquid, which was distilled at 0.1 mm. for analysis; $\lambda_{max}^{CHCl_3}$ 5.79 μ with a very small band at 2.82 μ, indicating the presence of a small amount of hydroxyl-containing impurity, which is also indicated by the analytical results. The substance did not exhibit any selective ultraviolet absorption.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 65.97; H, 9.04; O, 25.06.

(b) *By platinum oxide-acetic acid hydrogenation of 1,10-bisdeoxy-7,8-dihydrogenipin* (XXIVa). A solution of 109 mg. of 1,10-bisdeoxy-7,8-dihydrogenipin in 5 cc. of acetic acid consumed 1 equivalent of hydrogen after hydrogenation (room temperature, atmospheric pressure) for 20 hr. in the presence of 21 mg. of platinum oxide catalyst. The infrared spectrum of the resulting oil (IIIa) did not contain any more the 6.1 μ enol ether band. The ester was saponified by heating under reflux for 3 hr. with 0.5*N* ethanolic sodium hydroxide solution and the acid IIIb was converted directly at *p*H 6.5 (for details see above described reaction of XXIVb) into its *S*-benzylthiouronium salt. After recrystallization from hot water, the colorless needles possessed m.p. 138–141°, $[\alpha]_D$ +40° (*c*, 0.445 in methanol) and proved to be identical in all respects with the earlier reported[3] *S*-benzylthiouronium salt of the acid IIIb obtained (without isolation of intermediates) by successive hydrogenation of genipin (I) with palladium-charcoal in methanol and then platinum oxide in acetic acid solution.

Chromium trioxide oxidation of 10-deoxy-7,8-dihydrogenipin (IIa). To a solution of 1.90 g. of 10-deoxy-7,8-dihydrogenipin (IIa) in 5 cc. of acetone cooled to 10° was added dropwise 3.4 cc. of 8*N* chromium trioxide–sulfuric acid solution,[9] rapid reaction occurring only with the first 1.2 cc. of reagent. Water was added, the mixture was extracted with ether, and the product was then separated into a neutral (0.96 g., not extracted by bicarbonate) and an acidic (0.544 g., bicarbonate-soluble) fraction.

The neutral product was chromatographed on 100 g. of silica gel, fifty-nine 25-cc. fractions being collected. Fractions 13–20 were removed from the column with benzene and after distillation at 80°/0.01 mm. there was obtained 133 mg. of a colorless mobile oil corresponding to the lactone *1-dehydro-10-deoxy-7,8-dihydrogenipin* (IV), $\lambda_{max}^{CHCl_3}$ 5.64, 5.83, and 6.05 μ, $\lambda_{max}^{C_2H_5OH}$ 237 mμ, log ϵ 4.02, plain positive rotatory dispersion curve[10] ($[\alpha]_{589}$ +82°, $[\alpha]_{500}$ +130°, $[\alpha]_{400}$ +205°, $[\alpha]_{300}$ +530°, $[\alpha]_{280}$ +780°) in methanol solution (*c*, 0.16).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71; OCH_3, 14.72; C—CH_3, 7.14. Found: C, 62.83; H, 6.74; OCH_3, 14.91; C—CH_3, 7.41.

From the more polar fractions of the chromatogram there was obtained a viscous yellowish oil, whose infrared spectrum was practically indistinguishable from that of 10-deoxy-7,8-dihydrogenipin (IIa).

The acid fraction (VIIa) was methylated with diazomethane and the methyl ester chromatographed carefully on neutral alumina (activity II). The portion eluted with benzene-chloroform was distilled in high vacuum to afford an oil, $\lambda_{max}^{CHCl_3}$ 5.75 μ, whose analysis was consistent with formulation VIIb.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; O, 35.05. Found: C, 57.68; H, 7.13; O, 35.22.

1-Methyl-2-carboxycyclopentane-3-acetic acid (Va). 1-Dehydro-10-deoxy-7,8-dihydrogenipin (IV) (122 mg.) was left at room temperature for 20 hr. with 5 cc. of 10% sodium hydroxide solution and 1 cc. of ethanol. Dilution with water, acidification, extraction with ether, washing with bicarbonate solution, and acidification of the washes afforded 84 mg. of the dibasic acid Va, m.p. 99.5–104° after distillation at 150°/0.005 mm. Two recrystallizations from hexane ether yielded an analytical specimen, m.p. 99.5–105° (104.5–107.5° after drying for 3 days at 0.5 mm. over phosphorus pentoxide), $[\alpha]_D$ +20° (*c*, 0.21 in methanol), $\lambda_{max}^{CHCl_3}$ 5.83 μ and typical "acid" absorption in 3–4 μ region.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58; O, 34.37; C—CH_3, 8.08; mol. wt., 186.2. Found: C, 58.14; H, 7.38; O, 34.60; C—CH_3, 6.97; neut. equiv., 90.

The same acid Va was also obtained when the crude aldehydo acid VIIa was stirred overnight with aqueous 10% sodium hydroxide.

A 28-mg. sample of the dicarboxylic acid Va was methylated with diazomethane and the resulting dimethyl ester Vb distilled at 0.1 mm; $\lambda_{max}^{CHCl_3}$ 5.78 μ.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.11; H, 8.20.

Lithium aluminum hydride reduction of 10-deoxy-7,8-dihydrogenipin (IIa). A solution of 7.01 g. of 10-deoxy-7,8-dihydrogenipin (IIa) in 100 cc. of anhydrous ether was added dropwise to a stirred suspension of 13 g. of lithium aluminum hydride in 300 cc. of dry ether. The mixture was stirred at room temperature for 17 hr., the excess reagent was destroyed with ethyl acetate, saturated aqueous sodium sulfate was added to precipitate inorganic salts, and the solution was then dried by addition of anhydrous sodium sulfate. The solution was decanted from the residue which was triturated with ether. The combined ether solutions were evaporated and the resulting 5.46 g. of colorless oil was chromatographed in ether-benzene (1:1) on 200 g. of Merck acid-washed alumina. The amount of ether was gradually increased up to 100% and then methanol was added to the ether in proportions of 2–5% collecting a total of 13 fractions. Fractions 3–4 (ether-benzene 7:3) yielded 0.32 g. of a colorless oil[13] which was distilled at a bath temperature of 60–70°/0.15 mm., $\lambda_{max}^{CHCl_3}$ 2.95 and 5.77 μ, $[\alpha]_D$ +22° (*c*, 1.09 in chloroform). It was not investigated further.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; O, 18.79; C—CH_3, 8.83. Found: C, 70.01; H, 10.14; O, 19.21; C—CH_3, 14.16; OCH_3, 0.0.

Fractions 9–10 (ether-methanol 98:2 and 95:5) gave 3.72 g. of colorless oil which could be crystallized at Dry Ice–acetone temperature from ether–petroleum ether[33]; yield, 1.30 g., m.p. 37–39°, $[\alpha]_D$ −9.7° (*c*, 1.34 in chloroform), $\lambda_{max}^{CHCl_3}$ 2.81, 3.00, 6.08, and 11.03 μ. The substance possesses structure VIIIa.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; O, 18.79; C—CH_3, 8.83. Found: C, 70.57; H, 10.58; O, 19.00; C—CH_3, 8.45.

The *acetate* VIIIb was prepared by leaving 823 mg. of VIIIa overnight with 15 cc. of pyridine and 2.9 g. of acetic anhydride. The product was isolated by ether extraction and was purified by chromatography on 46 g. of Merck

(33) Care had to be taken in the crystallization of this material in that it had to be filtered at Dry Ice temperature and then placed immediately into a vacuum desiccator until all traces of solvent had been removed. Failure to remove all solvent led to crystals which melted at room temperature.

acid-washed alumina, elution with benzene-ether (9:1 and 6:1) and distillation at a bath temperature of 130°/0.47 mm., $[\alpha]_D$ −4.6° (*c*, 1.52 in chloroform), $\lambda_{max}^{capill.}$ 5.71, 6.05, 11.02 μ.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.13; H, 8.72; O, 25.17; acetyl, 16.90. Found: C, 65.93; H, 8.69; O, 25.52; acetyl, 32.82.

Ozone was passed at −70° through a 1.003-g. sample of the acetate VIIIb dissolved in 25 cc. of methylene chloride until the solution turned blue. It was then poured into a suspension of 4.0 g. of zinc dust in 15 cc. of acetic acid and the mixture was stirred at room temperature for 3 hr. The zinc was filtered and the filtrate was neutralized with 2% sodium hydroxide solution and extracted with ether. Washing, drying and evaporation of the ether left 0.947 g. of liquid which was chromatographed in benzene solution on 35 g. of Merck's acid-washed alumina. Elution with benzene-ether (95:5) and crystallization from ether–petroleum ether at −70° afforded 0.53 g. of the *keto diacetate* IX, m.p. 35–36°, $\lambda_{max}^{CHCl_3}$ 5.77 μ, positive rotatory dispersion Cotton effect[10] in methanol solution (*c*, 0.095): $[\alpha]_{589}$ +88°, $[\alpha]_{302.4}$ +1078°, $[\alpha]_{260}$ −676°, $[\alpha]_{252.5}$ −613°. This was changed only slightly upon the addition of 0.1*N* sodium hydroxide: $[\alpha]_{302.5}$ +986°, $[\alpha]_{260}$ −756°.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87; O, 31.24; C—CH_3, 5.86; acetyl, 16.79. Found: C, 60.92; H, 7.90; O, 31.52; C—CH_3, 17.20; acetyl, 35.68.

1-Methyl-3-isopropylcyclopentane-2-carboxylic acid (Xb). The diol VIIIa (350 mg.) was hydrogenated in methanol solution at room temperature and atmospheric pressure in the presence of 0.3 g. of prehydrogenated 10% palladized charcoal catalyst, hydrogen uptake corresponding to 2 equivalents having ceased within 2 hr. Filtration of the catalyst and distillation at 3 mm. yielded *1-methyl-2-hydroxymethyl-3-isopropylcyclopentane* (Xa) as a sweet-smelling colorless liquid, which appeared to be homogeneous by vapor phase chromatography at 175° using a 10 ft. column of silicone–fire brick (1:3). The infrared bands at 6.05 and 11.02 μ corresponding to the terminal olefin grouping had disappeared, but peaks at 7.22 and 7.31 μ ascribable to the *gem*-dimethyl grouping could be noted.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.34; H, 12.59.

A solution of the above alcohol Xa (250 mg.) in 5 cc. of acetic acid was oxidized (room temperature, 20 hr.) with 0.2 g. of chromium trioxide in 5 cc. of 90% acetic acid. Dilution with water, extraction with ether, washing with 5% sodium carbonate solution, acidification, and re-extraction with ether led to 0.162 g. of the acid Xb, which was transformed into its *S-benzylthiouronium* salt by the procedure described earlier for the acid XXIVb. Recrystallization from aqueous methanol provided 0.215 g. of the pure salt, m.p. 121–122°, $[\alpha]_D$ −5.5° (*c*, 1.09 in methanol), which exhibited a plain, negative dispersion curve[10] in methanol dropping to $[\alpha]_{272.5}$ −100°.

Anal. Calcd. for $C_{18}H_{28}N_2O_2S$: C, 64.25; H, 8.39; N, 8.33; O, 9.51; S, 9.53. Found: C, 64.17; H, 7.97; N, 8.31; O, 9.78; S, 9.49.

The salt (212 mg.) was dissolved in 30 cc. of 70% aqueous methanol and passed through a column (25 × 1 cm.) of Dowex-50 (pretreated with 2% aqueous sodium hydroxide, 5% aqueous hydrochloric acid, water, and finally 70% aqueous methanol). The eluate was made slightly alkaline by the addition of a few drops of 2% sodium hydroxide solution and most of the methanol was then removed *in vacuo*. The solution was then acidified, extracted with ether, washed, dried, and evaporated to afford 102 mg. of the *acid* Xb, which was distilled at a bath temperature of 80°/0.12 mm., $\lambda_{max}^{capill.}$ 5.88, 7.23, and 7.33 μ. The acid exhibited a plain positive rotatory dispersion curve in methanol solution (*c*, 0.205) which however commenced on the negative side in the visible: $[\alpha]_{700}$ −3°, $[\alpha]_{589}$ −7°, $[\alpha]_{300}$ 0°, $[\alpha]_{257.5}$ +126°.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; O, 18.80; C—CH_3, 8.83; mol. wt., 170. Found: C, 70.75; H, 10.21; O, 18.84; C—CH_3, 12.23; neut. equiv., 176.

Methylation with diazomethane and distillation at a bath temperature of 50°/0.55 mm. led to the *methyl ester* Xc, whose rotatory dispersion curve in methanol (*c*, 0.26) was similar to that of the acid Xb: $[\alpha]_{700}$ −1°, $[\alpha]_{589}$ −6°, $[\alpha]_{275}$ +87°.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; O, 17.37; OCH_3, 16.84. Found: C, 71.06; H, 10.76; O, 17.38; OCH_3, 16.61.

Hydrogenation of nepetalactone (XI). Freshly distilled nepetalactone (XI) (3.196 g.) was hydrogenated in 50 cc. of acetic acid with 0.5 g. of prereduced platinum oxide catalyst as described by Meinwald.[16] Hydrogen uptake ceased after 20 hr. (1.8 equivalents of hydrogen) and the usual work-up gave 2.435 g. of the oily acid XII,[16] which was directly transformed into its *S*-benzylthiouronium salt (4.52 g.), m.p. 118–119° (after recrystallization from aqueous methanol). The infrared spectrum of this salt was practically identical with that of the corresponding salt of the isomeric acid Xb, but a definite difference was noted in their rotations, the *S*-benzylthiouronium salt of XII exhibiting $[\alpha]_D$ +2.8° (*c*, 1.07 in methanol) and its rotatory dispersion curve being of the plain positive type[10] (rising to $[\alpha]_{260}$ +49°).

Anal. Calcd. for $C_{18}H_{28}N_2O_2S$: C, 64.25; H, 8.39; N, 8.33; S, 9.53. Found: C, 64.23; H, 8.22; N, 8.34; S, 9.30.

A portion of this salt was decomposed on Dowex-50 resin and the liberated acid XII was distilled at a bath temperature of 80°/0.44 mm. Its optical rotatory dispersion in methanol (*c*, 0.20) was characterized by a plain negative curve: $[\alpha]_{700}$ −10°, $[\alpha]_{589}$ −12°, $[\alpha]_{260}$ −178° and its infrared spectrum (chloroform or liquid film) was quite distinct from that of the acid Xb.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; O, 18.80; mol. wt., 170. Found: C, 70.30; H, 10.59; O, 18.94; neut. equiv., 175.

Ozonolysis of 10-deoxy-7,8-dihydrogenipin (IIa) *to cis,cis-nepetic acid* (XIIIa). 10-Deoxy-7,8-dihydrogenipin (IIa) (1.638 g.) was ozonized in 10 cc. of methylene chloride at −70° until the solution turned blue (approximately 30 min.). The solution was then added dropwise to 15 cc. of 5% aqueous sodium hydroxide containing 6 cc. of 30% hydrogen peroxide, stirred for 30 min. and the methylene chloride was then removed *in vacuo* at room temperature. An additional 10 cc. of 30% hydrogen peroxide was added and the mixture was stirred overnight. Acidification with hydrochloric acid, addition of solid sodium sulfite, salting out with sodium chloride, and extraction with ether, followed by washing with sodium chloride solution, drying, and evaporation afforded 0.868 g. of crystals, m.p. 90–110°. These were suspended in water, made alkaline to phenolphthalein with aqueous barium hydroxide and the *barium salt* of *cis, cis*-nepetic acid (XIIIa) was filtered. The salt was decomposed with 5% hydrochloric acid, the acid was extracted with ether and recrystallized once from ether–petroleum ether, whereupon 0.518 g. of pure *cis, cis*-nepetic acid (XIIIa) was isolated, m.p. 136–137°, $[\alpha]_D$ −0.9° (*c*, 1.05 in chloroform), plain positive rotatory dispersion curve in methanol solution (*c*, 0.56): $[\alpha]_{700}$ +31°, $[\alpha]_{589}$ +37°, $[\alpha]_{500}$ +51°, $[\alpha]_{400}$ +107°, $[\alpha]_{300}$ +299°, $[\alpha]_{255}$ +774°. The infrared spectrum of this acid in chloroform solution was completely identical with that of racemic *cis, cis*-nepetic acid.[18, 21]

Anal. Calcd. for $C_9H_{12}O_4$: C, 55.80; H, 7.03; O, 37.17; C—CH_3, 8.73; mol. wt., 172. Found: C, 55.93; H, 6.96; O, 37.39; C—CH_3, 7.87; neut. equiv., 92.

Small samples of the optically active and racemic acids were methylated with diazomethane and the methyl esters (XIIIb) distilled at a bath temperature of 70°/0.2 mm. Their respective infrared spectra (liquid film) were completely identical.

(−)-*trans, cis-Nepetic acid* (XVIIIa). The *cis, cis*-nepetic acid XIIIa (0.976 g.) was heated under reflux for 6 hr. with

5.5 cc. of acetic anhydride, the excess acetic acid and acetic anhydride were then removed *in vacuo*, and the residual nepetic acid anhydride was evaporatively distilled at 0.05 mm. The crystalline distillate was immediately heated under reflux for 2 hr. with 6 cc. of anhydrous methanol, a solution of 0.5 g. of sodium metal in 10 cc. of anhydrous methanol was added and heating was continued for 30 min. Water (5 cc.) was now added and the reaction mixture was heated under reflux for a further 1 hr. in order to saponify the half-ester XVIIIb. The methanol was distilled off under reduced pressure and the solution was evaporated repeatedly with water. The residue was dissolved in water, acidified, and the crude acid obtained after ether extraction was converted into its barium salt. This proved to be water-soluble, thus indicating the absence of any *cis, cis* isomer XIIIa (insoluble barium salt) and after acidification and repeated ether extraction, there was obtained (after several recrystallizations from ether–petroleum ether) 0.546 g. of (−)-*trans, cis*-nepetic acid (XVIIIa), m.p. 95–100° (Kofler block), 98–100° (capillary), $[\alpha]_D$ −65.2° (*c*, 1.08 in chloroform). The melting point remained unchanged after countercurrent distribution (ether *vs.* phosphate-citrate buffer of *p*H 6.05) or silica gel chromatography.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03; O, 37.17. Found: C, 55.71; H, 7.16; O, 37.01.

Lithium aluminum hydride reduction of 1,10-anhydro-7,8-dihydrogenipin (XXVII). A solution of 5.203 g. of 1,10-anhydro-7,8-dihydrogenipin (XXVII) in 70 cc. of anhydrous ether was reduced with 9.6 g. of lithium aluminum hydride exactly as described above for the analogous reduction of IIa. The crude product (4.623 g.) was chromatographed in benzene solution on 150 g. of Merck acid-washed alumina to afford in the ether-methanol (9:1) eluates 2.09 g. of the *unsaturated aldehyde* XXVIII. The analytical samples was distilled at 120°/0.05 mm. and exhibited $[\alpha]_D$ +40.3° (*c*, 1.34 in chloroform), $\lambda_{max}^{C_2H_5OH}$ 216 mμ, log ε 3.73, $\lambda_{max}^{CHCl_3}$ 2.77, 2.92, 3.69 (w), 5.92 (s), and 6.03 (w) μ.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.36; H, 7.35.

Treatment of a sample of the aldehyde XXVIII with 2,4-dinitrophenylhydrazine in methanolic hydrochloric acid for 30 min. at room temperature led to the *2,4-dinitrophenylhydrazone* XXX, which was recrystallized from methanol-chloroform; m.p. 182–184°, $\lambda_{max}^{CHCl_3}$ 366 mμ, log ε 4.42.

Anal. Calcd. for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81; O, 25.37; OCH_3, 8.20. Found: C, 54.16; H, 5.59; N, 14.72; O, 25.59; OCH_3, 8.04.

The ether-methanol (7:3) eluates of the original chromatogram furnished 0.303 g. of the *triol* XXIXa as a sticky oil, which was distilled at 150°/0.03 mm, $\lambda_{max}^{CHCl_3}$ 2.90, 6.13 (w) μ. For purposes of characterization, the triol was acetylated by heating under reflux for 6 hr. with acetic anhydride–pyridine, evaporating to dryness and extraction with ether. The crude *triacetate* XXIXb was purified by chromatography on 12 g. of Merck acid-washed alumina, elution with benzene-ether (9:1 and 6:1) and finally distillation at 120°/0.05 mm.; $[\alpha]_D$ +25° (*c*, 1.00 in chloroform), $\lambda_{max}^{CHCl_3}$ 5.79 (s), 6.06 (w), 8–8.4 μ and 11.06 μ.

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 61.52; H, 7.75; O, 30.73. Found: C, 61.89; H, 7.84; O, 30.32.

Reduction of 0.547 g. of the unsaturated aldehyde XXVIII with 1.4 g. of lithium aluminum hydride followed by acetylation of the resulting triol produced 0.44 g. of the triacetate XXIXb.

STANFORD, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Reduction and Oxidation Products of Cucurbitacin B[1]

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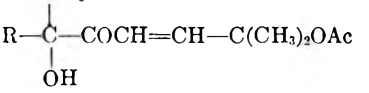
Catalytic hydrogenation of cucurbitacin B yields two products, a dihydro derivative and a dihydrodeacetoxy derivative. Reaction with zinc dust gives a deacetoxy derivative with migration of the double bond out of conjugation with a carbonyl group. Oxidation of acetylated cucurbitacin B with chromic acid gives β,β-dimethylacrylic acid and two methyl ketones. These results can be accommodated by a side chain having the structure



Cucurbitacin B, present in numerous members of the *Cucurbitaceae*,[2] is one of the bitter principles isolated from *Echinocystis fabacea*.[3] A second product, called fabacein, also was isolated, separation being accomplished by fractional crystallization. Since then it has been found that the separations can be made readily by the use of a chromatographic column in which the immobile phase is formamide on Celite (4:5 by weight) and the elutant is benzene or benzene–ethyl actate, thus providing a means of obtaining these substances in relatively large amounts with little difficulty. The present paper reports the details of a number of experiments on cucurbitacin B.

Cucurbitacin B (I) contains an acetoxy group, an α,β-unsaturated carbonyl group, two additional unconjugated carbonyl groups and three hydroxyl groups.[3,4] A determination of the molecular weight

(1) The results of some of these investigations were published in a preliminary report, *J. Org. Chem.*, **24**, 291 (1959).

(2) P. R. Enslin, *J. Sci. Food Agri.*, **5**, 411 (1954); S. Rehm, P. R. Enslin, A. D. J. Meeuse, and J. H. Wessels, *J. Sci. Food. Agr.*, **8**, 679 (1957).

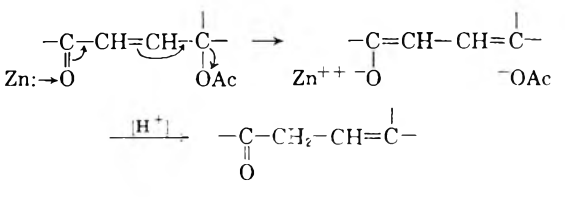
(3) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

(4) P. R. Enslin, S. Rehm, and D. E. A. Rivett, *J. Sci. Food Agri.*, **8**, 674 (1957).

from the density of crystals and the size of the unit cell,[5] indicated the molecular formula $C_{32}H_{48}O_8$. Numerous analyses of our product checked better with the formula $C_{30}H_{44}O_8$.[3] However, it was later noted[1] that our analyses checked equally well with the formula $C_{32}H_{46-48}O_8 \cdot 0.5\ H_2O$ and that the analyses of derived products agree better with a C_{32} formula. Subsequent work indicates that the correct formula of the anhydrous product must be $C_{32}H_{46}O_8$.

It was reported[3] that catalytic hydrogenation of cucurbatacin B in ethyl acetate, using palladium on carbon as catalyst, involves partial hydrogenolysis of the acetoxy group, along with hydrogenation of the double bond. From this mixture, two pure products have been isolated by chromatography on a column of Celite impregnated with formamide. One product is dihydrocucurbitacin B (II), $C_{32}H_{48}O_8$, and the other is dihydrodeacetoxycucurbitacin B (III), $C_{30}H_{46}O_6$. For both products, ultraviolet and infrared spectra show that the α,β-unsaturated carbonyl system has disappeared, and hence the double bond conjugated with the carbonyl group has been reduced. Both reduction products give a yellow color with tetranitromethane, indicating the presence of an additional unconjugated and unreactive bond. The NMR spectra to be reported later indicate that this double bond is trisubstituted, a conclusion that is supported by absorption in the infrared at 12.1 μ (825 cm.$^{-1}$).

Removal of the acetoxy group by hydrogenolysis suggests that it occupies an allylic position with respect to a double bond. If this is true, one would expect the possibility of removal of the acetoxy group by zinc dust and acetic acid by a mechanism analogous to that proposed for the easy removal of an acetoxy group that is *alpha* to a carbonyl group.[6] In fact, treatment of cucurbitacin B with zinc dust in acetic acid at room temperature gave a deacetoxycucurbitacin B. This product gave a deep yellow color with tetranitromethane, and the ultraviolet and infrared spectra show that it lacks α,β-unsaturation. Evidently the double bond moved out of conjugation with the carbonyl group. When



hydrogenated over palladium on charcoal, one mole of hydrogen was absorbed, and the resulting product was identical with dihydrodeacetoxycucurbitacin B (III).

It has been reported[3] that attempts to convert cucurbitacin B into a crystalline acetate were unsuccessful. The same difficulty has been experienced with the reduction products. However, paper chromatograms indicate that the acetates are homogeneous. Because they have been used in oxidative investigations, their properties are reported. It should be noted that the results of carbon-hydrogen analyses of our acetylated products from cucurbitacin B and its reduction products may be interpreted as indicating the presence of three acetylateable hydroxyl groups, or that two hydroxyl groups have been acetylated and the products contain one-half mole of water (despite the fact that they were dried at 120° under 0.1 mm. of mercury pressure). We have not been able to distinguish between these formulations by acetyl determinations because the results have been extremely erratic. Analyses by three different commercial laboratories using several methods of hydrolysis gave wholly inconsistent and frequently impossible results. The infrared spectra of all of the acetylated products still showed the presence of a hydroxyl group, and subsequent work agrees best with the assumption of the presence of two acetylateable secondary hydroxyl groups and one nonacetylateable tertiary hydroxyl group.

Another difficulty in handling these acetates is that an acetyl group may be removed easily by hydrolysis. Thus when the acetylated dihydrodeacetoxycucurbitacin B, $C_{34}H_{50}O_8 \cdot 0.5H_2O$, was chromatographed on acidic alumina, partial hydrolysis took place and a monoacetate, $C_{32}H_{48}O_7$, was isolated.

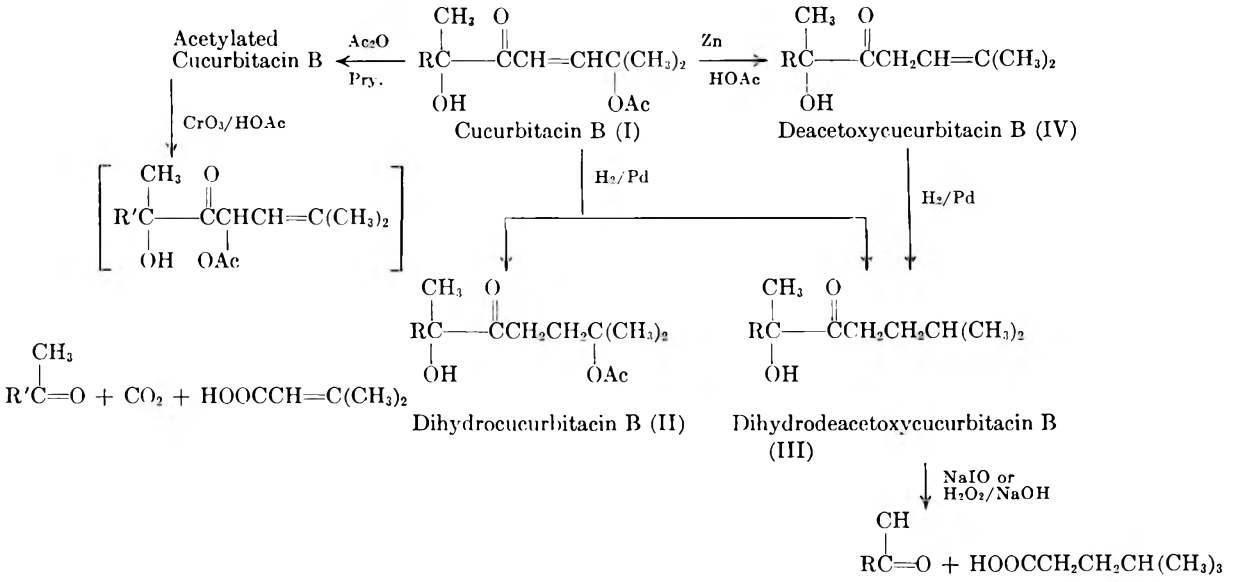
One other point should be noted. The product obtained by hydrogenating acetylated cucurbitacin B is different from but isomeric with that obtained by acetylating dihydrocucurbitacin B. Inasmuch as the difference in molecular rotation between dihydrocucurbitacin B and its acetylation product, $\Delta[M]_D$ −412, is the same as the difference between dihydrodeacetoxycucurbitacin B and its acetylation product, $\Delta[M]_D$ −424, the same change in structure or configuration is involved. On the other hand, the molecular rotation difference between cucurbitacin B and its acetylation product, $\Delta[M]_D$ −288, is considerably different. Hence, a different change in structure or configuration is involved during the acetylation of cucurbitacin B from that involved during the acetylation of its reduction products.

When dihydrodeacetoxycucurbitacin B was oxidized in aqueous dioxane either with sodium periodate or with alkaline hydrogen peroxide, the chief volatile product was isocaproic acid. Thus the carbon skeleton of isocaproic acid is present in the side chain and an α-diketo or α-hydroxy keto group at the sixth and seventh carbon atoms of the side chain is indicated.

Oxidation of acetylated dihydrodeacetoxycucurbitacin B with chromium trioxide likewise gave iso-

(5) D. E. A. Rivett and F. H. Herbstein, *Chem. and Ind.*, (*London*), 393 (1957).

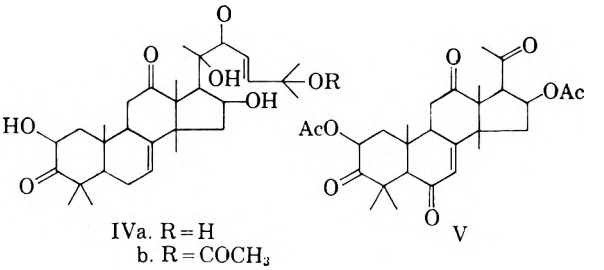
(6) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4225 (1952); R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 10 (1958).



caproic acid as the chief volatile acid. Acetylated cucurbitacin B, however, gave chiefly β,β-dimethylacrylic acid. Both materials gave the same neutral products, which appear to be methyl ketones (positive iodiform reactions). These facts, together with the observations concerning the reduction products, can be explained by partial formula I for cucurbitacin B. The formation of β,β-dimethylacrylic acid would involve an allylic shift of the acetoxyl group. After this work was completed, the presence of this side chain in cucurbitacin B was proved by Enslin and Norton[7] by the isolation of *trans*-4-acetoxy-4-methyl-2-pentenoic acid from the periodic acid oxidation products of acetylated cucurbitacin B. Previously the same side chain had been shown by Lavie and co-workers[8] to be present in elatericin A and B (cucurbitacins D and I) and in α-elaterin (cucurbitacin E).

The neutral fractions from the chromic acid oxidation of acetylated cucurbitacin B, dihydrocucurbitacin B, dihydrodeacetoxycucurbitacin B, or fabacein[3] appear from the paper chromatogram to be identical and to consist of a mixture of at least six substances. When passed through a column of Celite impregnated with formamide, two main fractions were obtained. Both appear to be methyl ketones (positive iodoform reaction). The larger of the two fractions was designated as ketone A and has the formula $C_{28}H_{36}O_8$. It contains an α,β-unsaturated carbonyl group and is formed by the scission of the side chain between the carbonyl group and the adjacent carbon bearing the tertiary hydroxyl group and by introduction of a new carbonyl group into the remainder of the molecule by oxidation of an allylic methylene group. A joint communication by Lavie and Enslin and their co-workers[9] reported the isolation of a product of higher melting point and rotation which was considered to be identical or isomeric with ketone A. Dr. Enslin has kindly compared a sample of ketone A with his product and in a private communication has informed us that the two products are indeed identical. The smaller fraction designated ketone B appears to have the molecular formula $C_{28}H_{38}O_8$. No α,β-unsaturated carbonyl group is present. The additional oxygen probably is a new carbonyl group resulting from rearrangement of an oxide formed by addition of an oxygen atom to the nuclear double bond.

Structure IVa recently has been proposed[10] for elatericin A from which it follows that cucurbitacin B should have structure IVb and ketone A structure V.



IVa. R = H
b. R = $COCH_3$ V

A serious objection to these formulas is the fact that under the conditions under which ketone A is produced, one would expect further oxidation to a conjugated dienedione.

EXPERIMENTAL

Separation of cucurbitacin B and fabacein. The portion of Celite No. 545 which passed a 100-mesh screen and did not

(7) P. R. Enslin and K. B. Norton, *Chem. and Ind. (London)*, 162 (1959).

(8) D. Lavie and Y. Shvo. *Proc. Chem. Soc.*, 220 (1958); D. Lavie, Y. Shvo, and D. Willner, *Chem. and Ind. (London)*, 1361 (1958); *J. Am. Chem. Soc.*, **81**, 3062 (1959).

(9) D. Lavie, Y. Shvo, D. Willner, P. R. Enslin, J. M. Hugo, and K. B. Norton, *Chem. and Ind. (London)*, 951 (1959).

(10) D. Lavie and Y. Shvo, *Chem. and Ind. (London)*, 403 (1960).

pass a 200-mesh screen was washed with 6 *N* hydrochloric acid, then with water until the washings were neutral, and dried at 100° for 50 hr. Five parts by weight of the treated Celite was thoroughly mixed with four parts of formamide and a slurry in benzene saturated with formamide[11] was poured into a column 100 cm. high and 50 cm. in diameter. Packing was accomplished by forcing the liquid phase through the column several times by air pressure. At the end of the procedure, the adsorbent occupied about two-thirds of the height of the column.

In a typical run, a benzene solution of 12.8 g. of the crystalline mixture of cucurbitacin B and fabacein, which was obtained from the syrupy concentrate of extracts of *Echinocystis fabacea*,[3] was placed on the column and eluted with benzene. Each 100-cc. portion of eluate was evaporated to dryness and the residue weighed. Fractions 1–7, amounting to 5.45 g., were crystallized from ethanol and gave 4.61 g. of fabacein, m.p. 203–208°.[12] After recrystallization it melted at 207–210°, and a paper chromatogram indicated that it was homogeneous.[13] Fractions 8–10 (0.18 g.) were mixtures of cucurbitacin B and fabacein together with some third substance. Fractions 11–25 (5.71 g.) were eluted with benzene and with benzene–ethyl acetate (9v.:1v.). Crystallization from acetone-hexane gave 4.16 g. of cucurbitacin B, m.p. 170–175°, which after recrystallization melted at 177–179°. A paper chromatogram showed that it was homogeneous. Fractions 27–30 (0.55 g.), eluted with benzene–ethyl acetate (4v.:1v. and 3v.:2v.), did not crystallize.

Reduction products of cucurbitacin B. To a solution of 3.15 g. of cucurbitacin B in 25 cc. of ethanol and 20 cc. of ethyl acetate was added 0.5 g. of hydrogen-saturated catalyst (Baker and Co., 10% palladium on charcoal), and the suspension was shaken in a hydrogen atmosphere until no more hydrogen was absorbed (155 cc. = 1.28 moles per mole of compound). After filtration and evaporation of the solvent, the residue was separated on a Celite-formamide column. Fractions 1–8 (0.23 g.), eluted with benzene-hexane (1v.:1v. and 3v.:1v.), could not be obtained crystalline. Fractions 9–26 (1.04 g.) were crystallized from acetone-hexane and gave 0.85 g. m.p. 200–205°. After recrystallization from ether it melted at 208–210°; $[\alpha]_D^{25}$ +57° (c 0.93);[14] ultraviolet λ_{max} 279 mμ, log ε 2.46[14]; infrared 2.92 (OH) 5.85 sh (C=O), 5.90 (C=O).[14] It gave a negative test with ferric chloride and a positive test with Tollens reagent. Analysis showed that this product was a *dihydrodeactoxycucurbitacin B.*

Anal.[15] Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.59; H, 9.37.

Fraction 27 (0.02 g.) eluted with benzene was a mixture. Fractions 28–37 (1.26 g.) were eluted with benzene and when crystallized from acetone-hexane gave 0.95 g., m.p. 158–164°. After recrystallization, it melted at 160–163°; $[\alpha]_D^{25}$ +57 (c 0.91); ultraviolet λ_{max} 282 mμ, log ε 2.32; infrared 2.92 (OH), 5.79 (AcO); 5.85 sh (C=O), 5.89 (C=O), 8.10 (AcO). It gave a negative test with ferric chloride and a positive test with Tollens reagent. Analysis of a sample dried in air at room temperature indicated that the product was *dihydrocucurbitacin B.*

Anal. Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.80.

When dried at elevated temperature and reduced pressure, the analytical values for carbon were high.

To a solution of 1.0 g. of cucurbitacin B in 50 cc. of glacial acetic acid was added 2 g. of zinc dust, and the mixture was stirred at room temperature for 1 hr. At this time a paper chromatogram (formamide-benzene) showed the complete absence of cucurbitacin B (R_f 0.51) and the presence of a new compound (R_f 0.81). The mixture was filtered, the filtrate evaporated to dryness at reduced pressure, and the residue dissolved in ether. Evaporation of the ether gave 0.85 g. which could not be crystallized from ethanol. The mixture was chromatographed on a 2.5 × 50-cm. Celite-formamide column and eluted with benzene-hexane (1:1) taking 50-cc. fractions. Fractions 4–11 amounted to 0.08 g. A paper chromatogram showed five spots having R_f values of 0.68–0.89. A second maximum in the chromatogram appeared in fractions 15–23 which amounted to 0.45 g. Crystallization from ethanol followed by recrystallization from acetone-hexane gave 0.31 g., m.p. 178–179°; $[\alpha]_D^{25}$ +78° (c 0.76 in ethanol); ultraviolet λ_{max} 292 mμ, log ε 2.66; infrared 2.91 (OH), 5.87 (C=O), 5.90 (C=O). Tetranitromethane gave an orange color, in contrast to the pale yellow color obtained with cucurbitacin B. The product is *deacetoxycurbitacin B.*

Anal. Calcd. for $C_{30}H_{44}O_6$: C, 71.97, H, 8.86. Found: C, 71.72; H, 9.05.

When deacetoxycucurbitacin B in ethyl acetate was hydrogenated in the presence of palladium on carbon, the product was indistinguishable from dihydrodeacetoxycucurbitacin B by melting point and mixture melting point, by rotation, and by infrared absorption spectra.

Anal. Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.39; H, 9.14.

This two-step procedure was preferable to direct hydrogenation of cucurbitacin B for the preparation of dihydrodeacetoxycucurbitacin B in quantity, because no dihydrocucurbitacin B is obtained. The crude deacetoxycucurbitacin B was dissolved in ethanol and hydrogenated over 10% palladium on carbon and the product chromatographed on a Celite-formamide column using benzene-hexane (2:3) for elution. Crystallization of the main fraction gave 75–80% of the calculated amount based on cucurbitacin B. From the early fractions, a faster running component was isolated in small amounts (0–5%). This product is identical with *isodihydrodeacetoxycucurbitacin B* obtained by the action of 0.05*N* aqueous methanolic sodium hydroxide on dihydrodeacetoxycucurbitacin B.[16]

Acetylations. A solution of 3.0 g. of cucurbitacin B in a mixture of 10 cc. of pyridine and 7.5 cc. of acetic anhydride was allowed to stand for 20 hr. at 25°. The solution was diluted with water and extracted with three portions of ether. The combined extract was washed with water, 2*N* sulfuric acid, water, saturated sodium bicarbonate solution, and water, and dried over sodium sulfate. Because it was not possible to crystallize the product, it was chromatographed on a Celite-formamide column. The main fraction was concentrated and evaporated to dryness at reduced pressure. The resulting foam gave a homogeneous paper chromatogram; $[\alpha]_D^{25}$ +4.4 (*c* 0.95); ultraviolet λ_{max} 228 mμ and 288 mμ, log ε 4.02[17] and 2.41; infrared 2.90 (OH), 5.80 (AcO), 5.92 (C=O), 6.13 (C=C), 8.10 (AcO). It gave a negative test with ferric chloride and a positive test with Tollens reagent.

Anal. Calcd. for $C_{38}H_{52}O_{11}$: C, 66.65; H, 7.65; O, 25.70; for $C_{36}H_{50}O_{10}\cdot 1/2\ H_2O$: C, 66.34; H, 7.89; O, 25.78. Found: C, 66.25, 66.65, 66.37; H, 7.78, 7.88, 7.84; O, 25.38.

Dihydrocucurbitacin B when acetylated and worked up in the same way likewise gave an amorphous tetraacetate,

(11) In all column or paper chromatography, the mobile phase was equilibrated with the immobile phase before use.

(12) All melting points were determined on a Monoscope IV hot-stage.

(13) Unless otherwise noted all paper chromatograms were made on Whatman No. 1 paper impregnated with formamide, using benzene as the elutant and aqueous permanganate as the developer. *Cf.* P. R. Enslin, T. G. Joubert, and S. Rehm, *J. S. African Chem. Inst.*, **7**, 131 (1954).

(14) Unless otherwise noted, all rotations and infrared spectra are in chloroform and all ultraviolet spectra in ethanol.

(15) Unless otherwise noted all analytical samples were dried at 60–100° and 0.2 mm. for 24 hr. Microanalyses were made by commercial laboratories.

(16) A. Melera and C. R. Noller, *J. Org. Chem.*, **26**, 1213 (1961).

(17) The value 4.33 reported in Ref. 1 is a misprint.

or a triacetate with 0.5 mole of water; $[\alpha]_D^{25}$ −16.3° (*c* 0.92); ultraviolet λ_{max} 286 mμ, log ε 2.28; infrared 2.90 (OH), 5.80 (AcO), 5.90 sh (C=O), 8.10 (AcO).

Anal. Calcd. for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; for $C_{36}H_{52}O_{10}$. $^1/_2$ H_2O: C, 66.13; H, 8.17. Found: C, 66.36, 66.14; H, 8.28, 8.24.

Catalytic hydrogenation of acetylated cucurbitacin B gave a product which was different from but isomeric with that from the acetylation of dihydrocucurbitacin B; $[\alpha]_D^{25}$ +3.5° (c 1.49); ultraviolet λ_{max} 286 mμ, log ε 2.43; infrared 2.90 (OH), 5.80 (AcO), 5.90 sh (C=O), 8.10 (AcO).

Anal. Calcd. for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; for $C_{36}H_{52}O_{10}$. $^1/_2$ H_2O: C, 66.13; H, 8.17. Found: C, 66.55, 66.65, 66.71, 66.56, 66.77; H, 8.19, 7.98, 8.21, 8.13, 8.08.

Analysis of the amorphous acetylated dihydrodeacetoxycucurbitacin B indicated that it was either a triacetate, or a diacetate having one-half molecule of water of hydration; $[\alpha]_D^{25}$ −20.4 (*c* 1.37, $CHCl_3$), +5.7° (*c* 0.88, ethanol); ultraviolet 282 mμ, log ε 2.44; infrared 2.90 (OH), 5.80 (AcO), 5.90 (C=O), 8.10 (AcO).

Anal. Calcd. for $C_{36}H_{52}O_9$: C, 68.76; H, 8.34; for $C_{34}H_{50}O_8$. $^1/_2H_2O$: 68.54, 8.63. Found: C, 68.55; H, 8.46.

When 1.15 g. of the amorphous diacetate was placed on a column of 25 g. of Woelm alumina, activity II, and eluted with hexane-benzene (1v.:1v.) 400 mg. of the diacetate was recovered in ten 50-cc. fractions. Elution of the residue with benzene gave a second amorphous product, analysis of which indicated a partial hydrolysis to give a monoacetate; $[\alpha]_D^{25}$ −4° (*c* 0.99, ethanol); infrared 2.90 (OH), 5.80 (AcO), 8.10 (AcO).

Anal. Calcd. for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88; O, 20.56. Found: C, 70.38; H, 8.76; O, 20.58.

Oxidations. To a solution of 1.08 g. of dihydrodeacetoxycucurbitacin B in 40 cc. of dioxane was added a solution of 1 g. of sodium periodate in 40 cc. of water. After standing at 25° for 35 hr. the solution was diluted with water, extracted with ether, and the ether solution washed with water, saturated sodium bicarbonate solution, and water, and dried over sodium sulfate. Evaporation of the ether gave 0.47 g. of neutral products. The bicarbonate extract was immediately acidified and extracted with ether to give 0.60 g. of acidic products which were converted to the methyl esters with an ether solution of diazomethane. The methyl esters were steam distilled, the distillate extracted with ether, the combined extracts dried, and the ether evaporated through a column. The residue was subjected to gas chromatography on a 1.5-m. Carbowax column. Three peaks were observed after 15, 22, and 28 min., which were identified by comparison with known mixtures as methyl isovalerate, dioxane, and methyl isocaproate. The ratio of methyl isocaproate to methyl isovalerate varied from 4:1 to 9:1 in different experiments. The same results were obtained when 1.02 g. of dihydrodeacetoxycucurbitacin B in 30 cc. of dioxane was treated with 15 cc. of 30% hydrogen peroxide in 15 cc. of 2*N* sodium hydroxide for 2 hr. at 25° and 0.5 hr. at 90°.

In a three-necked flask fitted with gas inlet and outlet tubes and a dropping funnel was placed a solution of 2.3 g. of acetylated cucurbitacin B in 25 cc. of acetic acid. Dry nitrogen was passed through the solution and the exit gases were passed through a solution of 2,4-dinitrophenylhydrazine, a drying tower, and a tared U-tube containing Ascarite. A total of 110 cc. of a 2% solution of chromium trioxide in acetic acid was added dropwise and the mixture allowed to stand for 50 hr. During this time a yellow precipitate formed in the dinitrophenylhydrazine solution, which was identified as acetone dinitrophenylhydrazone. The Ascarite tube increased in weight by 151 mg. (calcd. for 1 equiv. of carbon dioxide: 148 mg.). The excess of chromium trioxide was destroyed by adding methanol, and the bulk of the acetic acid was removed at reduced pressure. The residue was diluted with water, extracted with ether, and the ether solution washed with water, bicarbonate solution, and water and dried over sodium sulfate. Acidification of the bicarbonate extract gave only small amounts of acidic products. It was possible, however, to show by paper chromatography the absence of isocaproic acid and the presence of β,β-dimethylacrylic acid by comparison with synthetic samples.

The neutral fraction weighed 1.9 g. and the paper chromatogram showed the presence of at least six substances, although two compounds predominate. The combined neutral fractions from three oxidations, weighing 9.7 g., were chromatographed on a Celite-formamide column using benzene-hexane (1:1) as elutant. Fractions 26–34 gave 1.07 g. and fractions 42–57 gave 2.86 g. of two relatively pure substances. The larger, slower running fraction has been designated as *ketone A*. After several recrystallizations from acetone-hexane, it melted at 219–221°; $[\alpha]_D^{25}$ 86.6 (*c* 0.96); ultraviolet λ_{max} 243 mμ, log ε 4.1; 335 mμ, log ε 2.0; infrared 5.77 (AcO), 5.85 (C=O), 6.00, 6.15 (C=C—C=O), 8.10 (AcO); positive iodoform reaction.

Anal. Calcd. for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C, 67.13, 67.07; H, 7.44, 7.51. The next largest, faster-running fraction has been designated *ketone B*. After repeated crystallization from acetone-hexane, it melted at 154–157°; $[\alpha]_D^{25}$ −84.9° (*c* 1.14); ultraviolet λ_{max} 295 mμ, log ε 2.37; infrared 5.78 (AcO), 5.91 (C=O), 8.10 (AcO); positive iodoform reaction.

Anal. Calcd. for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 67.04, 67.13; H, 7.09, 7.21.

The same ketones were obtained by similar oxidations of acetylated fabacein, of acetylated dihydrocucurbitacin B and dihydrodeacetoxycucurbitacin B, and of the hydrogenation product of acetylated cucurbitacin B. However, acetylated dihydrodeacetoxycucurbitacin B gave isocaproic acid and a small amount of isovaleric acid rather than β,β-dimethylacrylic acid. Peaks in the chromatogram of the neutral products of oxidation were obtained also from fractions 4–5 (0.26 g.), 6–7 (0.25 g.), 11–15 (0.45 g.), and 16–18 (0.23 g.) but these materials have not yet been investigated.

When sodium dichromate in acetic acid was used as an oxidizing agent, ketone A was the chief product and could be obtained in a purer form by direct crystallization of the neutral fraction without requiring a chromatographic separation. A solution of 10.5 g. of acetylated cucurbitacin B in 50 cc. of acetic acid was heated on the steam bath to 95° and a solution of 22 g. of sodium dichromate in 100 cc. of acetic acid was added dropwise with continued heating for 3 hr. Then a solution of 6 g. of sodium bisulfite in 30 cc. of water was added and the solvent evaporated at reduced pressure. The residue was dissolved in 500 cc. of water and the mixture extracted with ether-chloroform (3v.:1v.). The ether-chloroform layer was washed twice with water, once with sodium bicarbonate solution, and then with water until the washings were neutral. After drying over sodium sulfate and evaporation of the solvents, the residue weighed 7.5 g. On solution in 10 cc. of acetone and addition of 100 cc. of ether, crystallization took place. After standing overnight the crystals were removed and repeatedly crystallized from acetone-hexane to give a product, m.p. 230–231°, $[\alpha]_D^{25}$ +92.8 (c 0.98). It was indistinguishable by paper chromatography and infrared spectrum from the previously obtained ketone A.

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STANFORD, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Relation of Fabacein to Cucurbitacin B[1]

W. SCHLEGEL AND C. R. NOLLER

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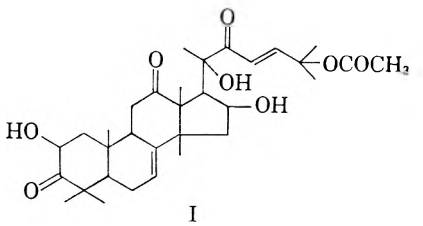
Fabacein is a diacetate of the composition $C_{34}H_{48}O_9$. The products of catalytic hydrogenation of fabacein and the oxidation products of acetylated fabacein indicate that fabacein has the same structure as cucurbitacin B, $C_{32}H_{46}O_8$, except that one additional hydroxyl group is acetylated. However, acetylation of cucurbitacin B gives a product different from that obtained by the acetylation of fabacein. Accordingly a further difference between fabacein and cucurbitacin B must exist, possibly a difference in the configuration of a portion of the molecule.

Two crystalline compounds have been isolated from *Echinocystis fabacea*,[2] cucurbitacin B and fabacein. Our analyses indicated the molecular formula $C_{30}H_{44}O_8$ for both compounds. Cucurbitacin B, however, appears to have the molecular formula $C_{32}H_{46}O_8$,[3] and a complete structural formula (I) has been proposed for it.[4] Our analyses of cucurbitacin B and of several acetylated derivatives can be reconciled with this formula if it is assumed that our products contain one-half mole of water.[5]



I

Further work on fabacein has shown that it has the same structure as cucurbitacin B except that one additional hydroxyl group is acetylated. Hence it has the molecular formula $C_{34}H_{48}O_9$. The original analyses[2] agree almost as well with this formula. (Calcd. for $C_{30}H_{44}O_8$: C, 67.64; H, 8.33; for $C_{34}H_{48}O_9$: C, 67.98; H, 8.05. Found: C, 67.56; H, 8.23; average of ten analyses.) Comparison of the NMR spectra of cucurbitacin B and fabacein to be reported later, shows that the second acetoxy group in fabacein occurs at C-16.

Like cucurbitacin B, fabacein contains an α,β-unsaturated carbonyl group, a hindered carbonyl group, and an allylic acetoxyl group.[2] Small absorption peaks in the infrared spectra of fabacein and certain derivatives at 12.15–12.35 μ (823–810 cm.$^{-1}$) indicate the presence of a trisubstituted double bond,[6] a conclusion that has been confirmed by the NMR spectra.

Fabacein in ethanol in the presence of palladium-on-carbon catalyst absorbs 1.4 moles of hydrogen to give two products which can be separated readily on a Celite-formamide column.[5] One product is dihydrofabacein in which the conjugated double bond of fabacein has been reduced. The other product could not be crystallized, but its paper chromatogram indicated that it was homogeneous. Analysis showed that it is a dihydromonodeacetoxyfabacein in which the acetoxy group in the side chain has been removed by hydrogenolysis and the conjugated double bond has been reduced. These products are analogous to those obtained by the hydrogenation of cucurbitacin B.[5]

The presence of the second acetoxy group in fabacein is shown by the fact that dihydromonodeacetoxyfabacein still absorbs in the infrared at 8.05 μ (1242 cm.$^{-1}$), whereas this peak is absent in dihydrodeacetoxycucurbitacin B. Moreover, a quantitative comparison showed that the infrared absorption at 8.05 μ of dihydrofabacein is twice that of dihydrocucurbitacin B.

Acetylation of fabacein and its hydrogenation products gave only amorphous products which were purified by chromatography on a Celite-formamide column. Analyses indicated that acetylated fabacein and dihydrofabacein contained either four acetyl groups, or three acetyl groups and one half mole of water. Analyses of acetylated dihydromonodeacetoxyfabacein indicated three acetyl groups, or two acetyl groups and one half mole of water. As was true for the acetylated products from curcurbitacin B and its derivatives[5], the inconsistency of acetyl determinations did not permit a differentiation of these two possibilities. However, the analyses of other derivatives forces the conclusion that these acetylated products contain one half mole of water. The presence of an absorption band at 2.95 μ in their infrared spectra probably is due to an unacetylated tertiary hydroxyl group.

Catalytic hydrogenation of acetylated fabacein gives two products which are identical with acetylated dihydrofabacein and acetylated dihydromonodeacetoxyfabacein. This behavior is in contrast to that of acetylated cucurbitacin B which is

(1) A preliminary report of this work was published in *Tetrahedron Letters*, No. 13, p. 16 (1959).

(2) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

(3) D. Lavie, Y. Shvo, D. Willner, P. R. Enslin, J. M. Hugo, and K. B. Norton, *Chem. and Ind. (London)*, 951 (1959).

(4) D. Lavie and Y. Shvo, *Chem. and Ind. (London)*, 403 (1960).

(5) W. Schlegel, A. Melera, and C. R. Noller, *J. Org. Chem.*, **26**, 1206 (1961).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley, 2nd ed., New York, 1958, p. 51

hydrogenated to a product isomeric with that obtained by the acetylation of dihydrocucurbitacin B.[5] Moreover, comparative paper chromatograms show that none of acetylation products of fabacein or its hydrogenated derivatives is identical with the corresponding products derived from cucurbitacin B. It thus appears that acetylation of cucurbitacin B and its hydrogenated derivatives leads to rearrangement, but acetylation of fabacein and its derivatives does not.

Oxidation of acetylated fabacein with chromium trioxide in acetic acid gives the same mixture of neutral products obtained from acetylated cucurbitacin B, namely, chiefly the ketones A and B.[5] Thus it appears that fabacein and cucurbitacin B differ also in the side chain, possibly in the configuration at C_{20}.

EXPERIMENTAL

Hydrogenation of fabacein. A solution of 1.025 g. of fabacein[5] dissolved in 15 cc. of ethanol and 50 cc. of ethyl acetate was hydrogenated over 10% palladium on carbon (Baker and Company). The absorption of hydrogen was 55 cc. (1.44 moles), and titration of the solution after removal of the catalyst indicated the production of 50 mg. (0.49 mole) of acetic acid. After evaporation of the ethanol, the residue was combined with a previous 550-mg. run and separated on a Celite-formamide column,[5] using hexane-benzene (3v.: 1v.) as elutant and collecting 50-cc. fractions. Fractions 1–3 gave small amounts of oil which were discarded. Fractions 4–13 weighed 617 mg. All attempts to crystallize this material were unsuccessful but its paper chromatogram indicated that it was homogeneous; $[\alpha]_D^{25}$ +17.6° (c .42)[7]; ultraviolet λ_{max} 286 mμ, log ε 2.32[7]; infrared 2.90 (OH) 5.78 (OAc), 5.85 and 5.89 (C=O), 8.05 (OAc), 12.30 w (R_2C=CHR).[7] Analysis indicated this product to be a *dihydromonodeacetoxyfabacein.*

Anal. Calcd. for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88. Found: C, 70.26, 8.83.

Fractions 14–16 gave 29 mg. of a mixture. Fractions 17–25 (687 mg.) were eluted with hexane-benzene (1v.: 1v.). Crystallization from acetone-hexane gave 538 mg. of prisms, m.p. 170–175°. Further recrystallization raised the melting point to 177–179°; $[\alpha]_D^{25}$ +24.0° (*c* 1.35); ultraviolet λ_{max} 285 mμ, log ε 2.39; infrared 2.90 (OH), 5.75 and 5.79 (OAc), 5.85 (C=C), 8.05 (OAc), 12.30 w (R_2C=CHR). Analysis indicated this product to be *dihydrofabacein.*

Anal. Calcd. for $C_{34}H_{50}O_9$: C, 67.75; H, 8.36. Found: C, 67.70; H, 8.33.

Acetylations. Acetylations were carried out with acetic anhydride in pyridine at room temperature and worked up in the usual way. All of the products were amorphous, but paper chromatograms showed only a single spot for each. Fabacein gave a product with $[\alpha]_D^{25}$ −2.0° (*c* 1.76); ultraviolet λ_{max} 229 mμ, log ε 4.10 and 289 mμ, log ε 2.31;[8] infrared 2.95 (OH), 5.80 (OAc), 5.92, 6.15 (C=C—C=O), 8.15 (OAc), 12.35 w (R_2C=CHR).

Anal. Calcd. for $C_{38}H_{52}O_{11}$ (4 OAc): C, 66.65; H, 7.66; for $C_{36}H_{50}O_{10}\cdot{}^1/_2\ H_2O$ (3 OAc): C, 66.34; H, 7.89. Found: C, 66.52, 8.05.

Dihydrofabacein gave a product with $[\alpha]_D^{25}$ −8.0° (*c* 1.35); ultraviolet λ_{max} 282 mμ, log ε 2.49; infrared 2.95 (OH), 5.80 (OAc), 5.90 (C=O), 8.10 (OAc).

Anal. Calcd. for $C_{38}H_{54}O_{11}$ (4 OAc): C, 66.45; H, 7.92; for $C_{36}H_{52}O_{10}\cdot{}^1/_2\ H_2O$ (3 OAc): C, 66.13; H, 8.17. Found: C, 66.08; H, 8.19.

Dihydromonodeacetoxyfabacein gave a product with $[\alpha]_D^{25}$ +13° (c 1.15); ultraviolet λ_{max} 287 mμ, log ε 2.37; infrared 2.95 (OH), 5.80 (OAc), 5.90 (C=O), 8.10 (OAc).

Anal. Calcd. for $C_{36}H_{52}O_9$ (3 OAc): C, 68.76; H, 8.34; for $C_{34}H_{50}O_8\cdot 0.5\ H_2O$ (2 OAc): C, 68.54; H, 8.63. Found: C, 68.72; H, 8.70.

Oxidations. Oxidations of acetylated fabacein, dihydrofabacein, and dihydrodeacetoxyfabacein were carried out by the same procedure described for the oxidation of acetylated cucurbitacin B and its hydrogenation products.[5] The neutral products were identical in all cases and consisted chiefly of the ketones A and B. The acidic products of the oxidation of acetylated fabacein and dihydrofabacein could not be positively identified. Isocaproic acid was isolated and identified by gas chromatography as a product of oxidation of acetylated dihydrodeacetoxyfabacein just as was true in the oxidation of dihydrodeacetoxycucurbitacin B. One difference was noted, however. During the oxidation of the latter, carbon dioxide was evolved, but no carbon dioxide could be detected as a product of the oxidation of acetylated dihydrodeacetoxyfabacein.

Acknowledgment. This investigation was supported in part by a research grant, RG-5076, from the National Institutes of Health of the U. S. Public Health Service.

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(7) All rotations and infrared spectra are in chloroform and all ultraviolet spectra in ethanol.

(8) The previously reported values for log ε of 4.24 and 2.49 (Ref. 1) are in error.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Action of Alkali on Alcoholic Solutions of Dihydro Derivatives of Cucurbitacin B

A. MELERA AND C. R. NOLLER

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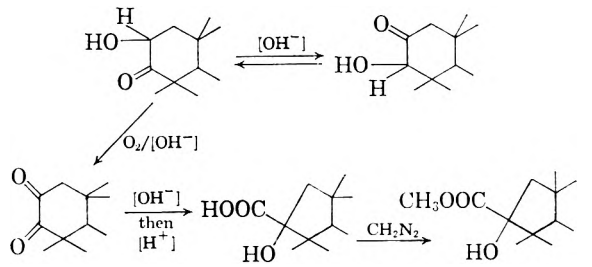
Dilute methanolic sodium hydroxide catalyzes an isomerization of dihydrocucurbitacin B and of dihydrodeacetoxycucurbitacin B involving the α ketol group in ring A. In ethanolic sodium hydroxide solution the α-ketol group of both compounds is converted by air oxidation to the corresponding diosphenol. The diosphenol from dihydrocucurbitacin B undergoes a further change which appears to involve an internal Claisen ester condensation involving the side chain.

During an investigation of dihydrocucurbitacin B and of dihydrodeacetoxycucurbitacin B,[1] it was observed that they undergo a series of changes in the presence of aqueous methanolic and aqueous ethanolic sodium hydroxide. When dihydrodeacetoxycucurbitacin B, m.p. 204–205°, was dissolved in approximately 0.1*N* aqueous methanolic sodium hydroxide and allowed to stand for four hours, a mixture crystallized from which an isomeric ferric chloride–negative product, m.p. 211–213° was obtained. It was called *isodihydrodeacetoxycucurbitacin B*. If either this product or dihydrodeacetoxycucurbitacin B were dissolved in approximately 0.1*N* aqueous ethanolic sodium hydroxide and the solution were allowed to stand at room temperature for two hours, a ferric chloride–positive product could be isolated, m.p. 173–175°. The ultraviolet absorption spectrum of a solution of this compound in ethanol showed a maximum at 268 mμ, ϵ 8700. When dissolved in 0.02*N* ethanolic sodium hydroxide, the compound absorbed only at 315 mμ, ϵ 6300. This behavior, together with absorption in the infrared at 6.02 μ (1660 cm.$^{-1}$) is characteristic of a diosphenol system.[2] The compound was called *diosphenol-I*. Conversion to the diosphenol could be followed by observing the change in absorption in the ultraviolet which took place rapidly in ethanolic solution and only very slowly in methanolic solution. Acetylation of diosphenol I gave an amorphous enol acetate with λ_{max} 231, ϵ 10,000, thus showing the characteristic hyposchromic shift of 32–36 mμ in going from a 1,2-diketone to an enol acetate.[3] Lavie and Shvo[4] have reported the isolation of diosphenols formed by the autoxidation of alkaline solutions of elatericin A (cucurbitacin D) and of dihydroelatericin A, but no reference is made to the isolation of isomerization products analogous to those reported here from dihydrocucurbitacin B or from dihydrodeacetoxycucurbitacin B.

When dihydrodeacetoxycucurbitacin B was refluxed with 1*N* aqueous ethanolic sodium hydroxide for three hours, about two-thirds was converted to an acidic product which was ferric chloride–negative and gave a crystalline ester on treatment with diazomethane. Analysis indicated that this product is the analog of the methyl ester of ecballic acid.[5] These reactions are explainable by the various formulas proposed for cucurbitacin B[6] all of which have an α ketol grouping in the A ring of a tetracyclic triterpene skeleton. In methanolic solution, hydroxide ion catalyzes the establishment of equilibrium between the two possible α ketol structures, whereas in ethanolic solution the α ketol is oxidized by air to the diosphenol, which undergoes a benzilic acid-type rearrangement when refluxed with aqueous ethanolic sodium hydroxide. These reactions are illustrated by the following partial formulas. It



should be noted that the product obtained by the catalytic hydrogenation of diosphenol-I acetate was not identical with the product of acetylation of dihydrodeacetoxycucurbitacin B[1], and it is assumed that they are diastereoisomers.

Dihydrocucurbitacin B likewise gives an isomeric compound, *isodihydrocucurbitacin B*, with methanolic sodium hydroxide andanot her diosphenol, called *diosphenol-II*, with ethanolic sodium hydroxide. The latter compound in ethanol absorbs at 269 mμ, ϵ 8900, and in 0.02*N* alkali at 315 mμ, ϵ 6200. This diosphenol, however, undergoes a further reaction

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on standing in 0.1*N* ethanolic sodium hydroxide. After three days a product was isolated which in ethanolic solution absorbed at 270 mμ, ε 18600 and in 0.02*N* ethanolic sodium hydroxide at 272 mμ, ε 10500 and at 315 mμ, ε 6600. Evidently a new chromophore is present which absorbs at 272 mμ and coalesces with the diosphenol absorption at 268 mμ. In the presence of alkali the absorption at 268 mμ is replaced by the absorption of the diosphenol ion at 315 mμ, whereas the absorption at 272 mμ is not affected. The formation of the new product, which was called *disophenol-III*, can be followed by noting the appearance of the new band at 272 mμ. Analyses of *diosphenol-III* indicate only the loss of one mole of water from diosphenol-II, although the acetoxy band of diosphenol-II at 5.82 μ (1720 cm.$^{-1}$) has disappeared completely. The formation of isodihydrocucurbitacin B and of diosphenol II can be explained in the same way as the formation of isodihydrodeacetoxycucurbitacin B and diosphenol-I. The formation of diosphenol-III may be explained by assuming an internal Claisen ester condensation of the acetate grouping with hydrogen α to a carbonyl group. However, it is difficult to explain the loss of water in the presence of alkali, or even under the neutral or faintly acid condition that may have existed during the isolation.

EXPERIMENTAL

Isodihydrodeacetoxycucurbitacin B. A solution of 250 mg. of dihydrodeacetoxycucurbitacin B[1] in 12.5 cc. of methanol was cooled to 10° and 5 cc. of 0.2*N* aqueous sodium hydroxide added. After standing for 2 hr., 10 cc. of water was added and the mixture warmed to dissolve some amorphous precipitate. After standing 2 hr. longer, 155 mg. of crystals, m.p. 186–194° was obtained. Dilution of the mother liquor with water and extraction with ether gave 90 mg. of amorphous material. A solution of the crystals in the eluant (hexane-benzene, 3 v.: 1 v.) was chromatographed on a Celite-formamide column, collecting 100-cc. fractions. Fractions 9–14 gave a sharp maximum in the chromatogram (97 mg.) and after four crystallizations from acetone-hexane gave 70 mg. of prisms, m.p. 211–213°; $[\alpha]_D^{25}$ 78° (*c* 0.54),[7] infrared 2.92 (OH), 5.87 and 5.91 (C=O). A ferric chloride test was negative.

Anal. Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.24, 71.74; H, 8.95, 9.02.

Diosphenol-I. A solution of 1.1 g. of dihydrodeacetoxycucurbitacin B in 1.9 l. of 75% ethanol and 100 cc. of 2*N* aqueous sodium hydroxide was allowed to stand at room temperature for 2 hr. After this time the ultraviolet absorption at 268 mμ had reached a maximum, and the reaction was stopped by neutralizing with acetic acid. The ethanol was removed under reduced pressure at 60° and the residue diluted with water and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and the ether evaporated to give 1.1 g. of residue which was chromatographed on a 1.5 × 50-cm. Celite-formamide column using hexane-benzene (3 v.: 1 v.) as eluant, and collecting 200-cc. fractions. Fractions 1–4 gave only traces of material. After changing to hexane-benzene (1 v.: 1 v.) fractions 6–9 gave 933 mg. of crystalline product which on recrystallization from acetone-hexane weighed 700 mg., m.p. 173–175°. It gave a deep color with ferric chloride. After three more crystallizations, the analytical sample melted at 174–175°; $[\alpha]_D^{25}$ −62.5° (*c* 1.0); ultraviolet λ_{max} 268 mμ, log ε 3.93; in 0.02 *N* sodium hydroxide, λ_{max} 315 mμ, log ε 3.80; infrared 2.92 (OH), 5.85 and 5.91 (C=O); 6.02 (C=C—C=O).

Anal. Calcd. for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.88; H, 8.76; O, 19.03.

Further treatment with 0.1*N* ethanolic sodium hydroxide produced no further change as indicated by the ultraviolet absorption spectrum and by the paper chromatogram (compare with the behavior of diosphenol-II).

Acetylation of diosphenol-I with acetic anhydride in pyridine at room temperature gave an amorphous acetate; ultraviolet λ_{max} 231 mμ, log ε 4.0; infrared 2.91 (OH), 5.68 and 8.3 (C=C—OAc), 5.77 and 8.05 (OAc), 5.88 and 5.91 (C=O). When hydrogenated in ethanol using 10% palladium on charcoal as catalyst (Baker and Co.) 1 mole of hydrogen was absorbed to give an amorphous diacetate; $[\alpha]_D^{25}$ −9.8° (*c* 0.97); ultraviolet λ_{max} 282 mμ, log ε 2.41; infrared 2.92 (OH), 5.76 and 8.1 (OAc), 5.80 (OAc), 5.88, and 5.91 (C=O).

Anal. Calcd. for $C_{34}H_{50}O_8$: C, 69.59; H, 8.59; O, 21.82. Found: C, 69.33; H, 8.66; O, 22.20.

This product is not identical with dihydrodeacetoxycucurbitacin B acetate[1] and has been named *dihydrodiosphenol-I acetate.*

Alkaline rearrangement of dihydrodeacetoxycucurbitacin B. A solution of 300 mg. of dihydrodeacetoxycucurbitacin B in 30 cc. of 1*N* aqueous ethanolic (1 v.: 4 v.) sodium hydroxide was refluxed for 3 hr. Dilution with water, extraction with ether, drying, and evaporation of the ether gave 95 mg. of material which reacted strongly with ferric chloride. The aqueous alkaline layer when acidified and extracted with ether gave 200 mg. of acidic material which gave a negative test with ferric chloride. The acid fraction was esterified with ethereal diazomethane and the esters chromatographed on 6 g. of Woelm alumina, activity II, and eluted with benzene-ether (4 v: 1 v.) to give 73 mg. of crystalline material, which after several crystallizations from acetone-hexane melted at 221–222°; $[\alpha]_D^{25}$ −34.0° (*c* 0.646); infrared 2.91 (OH), 5.81 ($COOCH_3$), 5.85 and 5.90 (C=O).

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08; OCH_3, 5.82. Found: C, 69.71; H, 9.00; OCH_3, 6.54.

Isodihydrocucurbitacin B. A solution of 500 mg. of dihydrocucurbitacin B[1] in 15 cc. of methanol was cooled to 10° and 10 cc. of 0.2*N* aqueous sodium hydroxide added. After the solution stood for 3 hr. at room temperature, 200 mg. of crystals, m.p. 225–230°, had precipitated. Dilution of the filtrate with water and extraction with ether gave 210 mg. of amorphous material. The chromatograms of both fractions on formamide-impregnated paper, using benzene as the mobile phase, showed them to be a mixture of at least eight compounds with the main spot at R_f 0.879. The combined product was dissolved in benzene with the aid of some ethanol and chromatographed on a 2.6 × 54-cm. Celite-formamide column using benzene as eluant and taking 60-cc. fractions. Fractions 5–7 gave 155 mg. of crystals, m.p. 228–230° dec. After three crystallizations from acetone-hexane it melted at 234–236° and gave a negative ferric chloride test; $[\alpha]_D^{25}$ +54.8° (*c* 0.75); ultraviolet λ_{max} 290 mμ, log ε 2.87; infrared 2.92 (OH), 5.82 and 7.94 (OAc), 5.91 (C=O).

Anal. Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63. Found: C, 68.64, 68.75; H, 8.70, 8.51.

Diosphenol-II. To a solution of 600 mg. of dihydrocucurbitacin B in 950 cc. of 95% ethanol was added 50 cc. of 2*N* aqueous sodium hydroxide and the mixture allowed to stand at room temperature. An absorption band at 315 mμ developed very rapidly and reached maximum intensity after 3 hr. The solution was neutralized with acetic acid and the ethanol removed at 60° under reduced pressure until a precipitate began to form. Dilution with water and

(7) Unless otherwise noted all rotations and ultraviolet spectra are in ethanol and infrared spectra in chloroform. All melting points were determined on a Monoscope IV hot stage.

extraction with ether gave 582 mg. of strongly ferric chloride-positive material. The chromatogram on formamide-impregnated paper, using hexane-benzene (1 v.: 1 v.) as mobile phase, showed four spots with those at R_f 0.055 and 0.620 as the main components. The mixture was separated on a Celite-formamide column using hexane-benzene (1 v:1 v.) as elutant and collecting 100-cc. fractions. Fractions 17–20 gave 204 mg. of crystalline material, m.p. 169–170°, which was unchanged on crystallization from ether-hexane; $[\alpha]_D^{25}$ −41.2° (*c* 0.8); ultraviolet λ_{max} 269 mμ, log ε 3.95; in alkaline solution λ_{max} 315 mμ, log ε 3.79; infrared 2.92 (OH), 5.82 (OAc), 5.86 and 5.91 (C=O), 6.00, 6.14 (C=C–C=O); ferric chloride test strongly positive.

Anal. Calcd. for $C_{32}H_{46}O_8$: C, 68.79, H, 8.30; O, 22.91. Found: C, 68.37; H, 8.65; O, 22.72.

Fractions 22–26 eluted with benzene gave 43 mg. of material, m.p. 273–275°. This product was identical with diosphenol-III.

Diosphenol-III. To a solution of 1.1 g. of dihydrocucurbitacin B in 1.9 l. of 95% ethanol was added 100 cc. of 2*N* aqueous sodium hydroxide, and the mixture was allowed to stand for 22 hr. The ultraviolet absorption spectrum showed two strong bands at 272 mμ and 315 mμ. The solution was neutralized with acetic acid, concentrated at 60° under reduced pressure until a precipitate began to form, diluted with water, and extracted with ether. The combined product of three runs weighed 3.1 g. and gave a strong positive test with ferric chloride. It was chromatographed on a 1.5 × 60-cm. Celite-formamide column using hexane-benzene (1 v.:1 v.) as elutant and collecting 200-cc. fractions. Fractions 1–16 gave 370 mg. of amorphous products. Fractions 17–22 were eluted with benzene and gave 1.2 g. which, after crystallization from chloroform-hexane, weighed 700 mg., m.p. 271–273°. The analytical sample was recrystallized from methylene chloride-ether; m.p. 274–275°; $[\alpha]_D^{25}$ +35° (*c* 0.8); ultraviolet λ_{max} 270 mμ, log ε 4.27; in 0.02 *N* ethanolic sodium hydroxide λ_{max} 272 mμ, log ε 4.02 and λ_{max} 315 mμ, log ε 3.82; infrared 2.90 (OH), 5.87 and 5.89, (C=O), 5.99 and 6.13 (C=C–C=O).

Anal. Calcd. for $C_{32}H_{44}O_7$: C, 71.08; H, 8.20; O, 20.72. Found: C, 71.24; H, 8.09; O, 20.81.

A solution of diosphenol-III on further standing in 0.1*N* aqueous ethanolic solution showed no change in absorption in the ultraviolet. On the other hand diosphenol-II under the same conditions soon showed the appearance of a second maximum in the ultraviolet absorption spectrum at 272 mμ, the original diosphenol maximum at 315 mμ remaining unchanged. Isodihydrocucurbitacin B under these conditions after 3 hr. absorbed strongly at 315 mμ and after 22 hr. at both 272 mμ and 315 mμ.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

Improved Synthesis of Scopoletin

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Scopoletin has been prepared in 30% yield from commercial isovanillin. Reaction of isovanillin with peracetic acid provided a good yield of 3-hydroxy-4-methoxyphenyl formate which could be hydrolyzed to 2,4-dihydroxyanisole. Treatment of either the phenol or its formate with ethyl acetoacetate yielded 4-methylscopoletin, while use of the sodium derivative of diethyl oxalacetate gave ethyl scopoletin-4-carboxylate. Hydrolysis, and decarboxylation of the resulting acid, provided the desired coumarin.

Scopoletin (6-methoxy-7-hydroxycoumarin) has been implicated widely in plant processes such as seed germination,[1] growth,[2] differentiation,[3] and disease.[4] The numerous methods reported for its synthesis involve extended series of reactions based on either a preformed coumarin[5] or 2,4-dihydroxyanisole (VI).[6,7] The phenol (VI) has been obtained from various substituted guaiacols through multistep sequences in which maximum yields have remained below 25%.[6–8] Repeated unsuccessful attempts in our laboratory to improve these procedures necessitated development of a more satisfactory route. Reaction of commercial isovanillin (3-hydroxy-4-methoxybenzaldehyde) (I) with a solution of peracetic acid in ethyl acetate provided 3-hydroxy-4-methoxyphenyl formate (II) in 74% yield (Chart I). Saponification of II gave a 72% yield of the desired phenol, while saponification without isolation of the intermediate formate provided a 66% yield of VI based on isovanillin.

Attempts to prepare scopoletin from VI by standard methods such as reaction with sodium ethyl formylacetate or malic acid and sulfuric acid were unsuccessful, although many variations in the reaction conditions were employed. Previous experience in this laboratory had indicated the utility of 85% phosphoric acid as a condensing agent in the Pechmann reaction, and, in this way, a quantitative yield of 4-methylscopoletin (VII) could be obtained easily from II and ethyl aceto-

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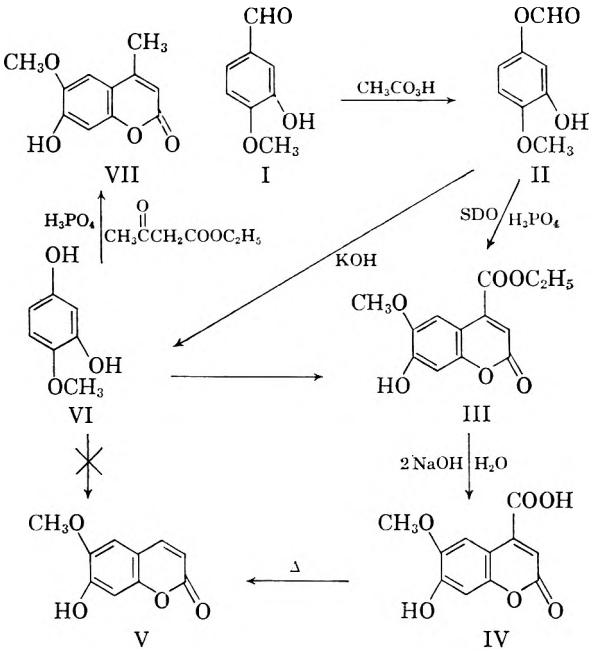
acetate. Condensation of VI with the sodium derivative of diethyl oxalacetate (SDO) similarly produced a 76% yield of ethyl scopoletin-4-carboxylate (III). Replacement of the phenol by its formate ester resulted in a less pure product and a lower yield.

Chart I



The ester III was resistant to hydrolysis with hydrochloric acid. However, hydrolysis at room temperature in the presence of exactly two equivalents of sodium hydroxide provided a 74% yield of scopoletin-4-carboxylic acid (IV) after twenty-four hours. Use of less than two equivalents of base did not permit complete hydrolysis, while three to six equivalents resulted only in the formation of dark tar. The odor of VI in the strongly alkaline hydrolyzate suggested that III undergoes alkaline degradation even more readily than does scopoletin itself.

The decarboxylation of IV to V could be carried out by pyrolysis in the presence of copper powder. However, a higher yield and purer product resulted when the reaction temperature was controlled by the use of a high boiling solvent such as quinoline. In either case, the course of the reaction could be followed by a change in the color of fluorescence under ultraviolet light from bright yellow to vivid blue.

Although no extensive search was made for optimum conditions and yields, the procedure described above permits the preparation of scopoletin in an overall yield of 30% based on isovanillin.

EXPERIMENTAL[9]

3-Hydroxy-4-methoxyphenyl formate (II). Commercial isovanillin[10] (194 g., 1.28 moles) was dissolved in 1 l. of 99% ethyl acetate and the solution was warmed to 40°. This temperature was maintained while 392 g. of peracetic acid (1.40 moles) (27.1% in ethyl acetate) was added over a period of 1 hr. Toward the end of addition, the reaction became exothermic and cooling was required. The mixture was maintained at 40° for an additional hour by continued cooling and then allowed to stand overnight. Ethyl acetate was removed by distillation, 500 ml. of ethylbenzene was added to the residue, and solvent again was removed by distillation. After another treatment with ethylbenzene, the residue was distilled. The colorless product, b.p. 111–115° (1 mm.), weighed 159 g. (74% yield). After 2 weeks at room temperature, the product solidified, and recrystallization from isopropyl ether gave colorless needles, m.p. 57–58°.

Anal. Calcd. for $C_8H_8O_4$: C, 57.1; H, 4.8. Found: C, 57.3; H, 4.7.

In a number of preparations, a semisolid crude product was obtained before distillation. Recrystallization of this material from ethanol afforded 3-hydroxy-4-methoxybenzoic acid, m.p. 255° (lit.[11] m.p. 251°).

2,4-Dihydroxyanisole (VI). The formate II (25 g., 0.15 mole) was mixed with 210 g. of a 10% solution of potassium hydroxide in 80% ethanol and boiled under reflux for 1 hr. The alcohol was removed by distillation, and the residue was acidified, extracted with ether, and the extracts dried. Distillation provided 15 g. (72% yield) of 2,4-dihydroxyanisole, b.p. 123–125° (1.5 mm.); the condenser was heated during distillation in order to prevent solidification of the product. Recrystallization from benzene-hexane provided white crystals, m.p. 70° (lit.[6] m.p. 72°).

In another experiment, 146 g. of isovanillin in 1 l. of 99% ethyl acetate was oxidized with 325 g. of a 24.7% solution of peracetic acid in ethyl acetate as described. After removal of ethyl acetate and treatment with three portions of ethylbenzene, the residue was saponified in 1340 g. of 10% potassium hydroxide in 80% aqueous ethanol to give 86 g. (66% yield) of colorless product, b.p. 115–116° (1 mm.).

4-Methylscopoletin (VII). The formate II (5.0 g., 0.03 mole) was mixed with ethyl acetoacetate (7.0 g., 0.05 mole), and 85% phosphoric acid (15 ml.) was added. After standing at room temperature overnight, the yellow semisolid was stirred with water, filtered, and the crystalline residue washed with water and air-dried. The crude yield of VII was 7.0 g. (100%), m.p. 212–214°, and recrystallization from ethanol gave pale yellow needles, m.p. 213–215° (lit.[8] m.p. 213–215°).

Ethyl scopoletin-4-carboxylate (III). (A) *From 3-hydroxy-4-methoxyphenyl formate.* The phenyl ester II (8.5 g., 0.05 mole), 15 g. (0.06 mole) of 92% sodium ethyl oxalacetate, and 20 ml. of 85% phosphoric acid were mixed and warmed on a steam bath for 30 min. with frequent stirring. The mixture was poured over several hundred grams of ice, and the precipitate was removed by filtration, washed with cold water, and sucked free of excess moisture. Recrystallization from a minimum amount of hot ethanol provided a 46% yield of yellow solid (6.0 g.) m.p. 169–171°. Infrared spectra and mixed m.p. indicated that the product was identical with that formed from 2,4-dihydroxyanisole in (B).

(B) *From 2,4-dihydroxyanisole.* The phenol VI (10 g., 0.07 mole) was melted with 20 g. (0.09 mole) of 92% sodium ethyl oxalacetate, and 85% phosphoric acid (40 ml.) was added. The mixture was heated on a steam bath for 1.5 hr. with frequent stirring, poured into 300 g. of ice, and stirred until a precipitate formed. The solid was isolated by filtration, washed with water, and air-dried to give 22 g. of orange-brown powder. This material was suspended in 100 ml. of ethyl ether, the suspension filtered, and the product washed with several additional portions of ether and air-dried. The yield of crude ester was 14 g. (76%), m.p. 162–165°; recrystallized from ethanol, its m.p. was 173–175°.

(9) All melting points were measured in a Vanderkamp block and are corrected.

(10) L. Light and Co., Ltd., Colnbrook, Bucks, England.

(11) E. Späth and G. Burger, *Ber.*, 59, 1486 (1926).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.1; H, 4.6. Found: C, 58.8; H, 4.7.

Scopoletin-4-carboxylic acid (IV). Crude ester III (3.77 g., 14.3 moles) was slurried in 50 ml. of water and 2.5*M* sodium hydroxide solution (11.5 ml.) was added. After 24 hr. at room temperature, the deep red solution was acidified, the precipitate was removed by filtration, washed with cold water, and air-dried to give 2.50 g. (74% crude yield) of red powder, m.p. 292–293° dec. Trituration with a small amount of cold ethanol provided a yellow-orange powder, m.p. 297–299° dec., while recrystallization from ethanol gave bright yellow needles, m.p. 300–301° dec.

Anal. Calcd. for $C_{11}H_8O_6$: C, 55.9; H, 3.4. Found: C, 55.9; H, 3.5.

Scopoletin (V). The crude acid IV (300 mg.) was mixed with 12 g. of quinoline and 500 mg. of copper powder and boiled under reflux until carbon dioxide evolution ceased (about 30 min.). The cooled mixture was diluted with 100 ml. of chloroform, filtered, and extracted with 10% sulfuric acid. After washing further with water, the chloroform solution was dried, decolorized, and the solvent evaporated under nitrogen. The solid residue was triturated with a few drops of ethanol and filtered. The yield of crystalline scopoletin, m.p. 201–202°, was 200 mg. (82%). The melting point of a mixture with authentic scopoletin (m.p. 203–204°) was undepressed, and infrared spectra and chromatographic properties of the two were identical.

Another portion of IV (300 mg.) was thoroughly mixed with 500 mg. of copper powder and warmed over a small flame. As decomposition proceeded, a yellow solid sublimed onto the walls of the tube. When gas evolution had ceased, the tube was cooled and the contents extracted repeatedly with hot ethanol until extracts no longer were appreciably fluorescent. The combined extracts were filtered, ethanol removed under nitrogen, and the residue recrystallized from glacial acetic acid. The yield of scopoletin, m.p. 198–200°, was 150 mg. (60%).

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SOUTH CHARLESTON, W. VA.

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

Bitter Principles of the Simaroubaceae. I. Chaparrin from *Castela Nicholsoni*

T. A. GEISSMAN AND K. R. CHANDORKAR[1]

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A bitter lactone, chaparrin, has been isolated from *Castela Nicholsoni*, and converted into a bis-dehydration product, chaparrol, also a lactone. The uncharacterized crystalline material accompanying chaparrin yielded glaucanol on treatment with acid, suggesting the presence in *Castela Nicholsoni* of glaucarubol.

Castela Nicholsoni Hook ("Chaparro amargosa") is a bitter shrub of the family Simaroubaceae, native of Mexico. Like a number of species of other genera of this family (*Simarouba, Brucea, Ailanthus, Quassia*), *Castela Nicholsoni* has found extensive use in folk medicine:[2] most of these drugs are used as amoebicides in the treatment of dysentery,[3–12] and several of them have yielded crystalline principles that have been found to be highly effective amoebicidal agents.

C. Nicholsoni has been examined chemically and pharmacologically by numerous investigators. Bosman[13] reported the isolation of three crystalline compounds: castelin, a glycoside; castelagenin, its aglycon; and castelamarin. To the latter, a bitter lactone giving a blue color with concentrated sulfuric acid (characteristic of many of the compounds of this group), was assigned the unlikely structure of the lactone of 2-hydroxy-3-methoxycyclohexaneacetic acid. The synthesis of a compound with this structure was reported by Paranjape *et al.*,[14] and found not to be identical with the natural lactone.

In 1944, Alles and Saunders[15] re-examined "chaparro amargosa" and succeeded in isolating two substances. One of these, m.p. 286–288°, gave a blue coloration with concentrated sulfuric acid; the other, m.p. 280–287°, gave no color with sulfuric acid. Their study was terminated before adequate purification of these materials could be carried out.

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Studies in this laboratory have now led to certain definite results. A bitter lactone, called chaparrin, has been isolated as a pure compound, and its composition and functional groups have been established. Among other, incompletely characterized fractions of the crystalline materials isolated from the plant, the presence of glaucarubol has been inferred by the formation of glaucanol, identified as described below, from a poorly characterized fraction. Glaucarubin, from which glaucarubol is derived, is a constituent of *Simarouba glauca*.[16,17] Like chaparrin, it is a bitter lactone that gives a deep blue coloration with concentrated sulfuric acid.

Chaparrin is a colorless crystalline compound with m.p. 309–310°. It is dextrorotatory (in pyridine), and dissolves with surprising ease in dilute aqueous sodium hydroxide. On acidification chaparrin is regenerated. The presence of a δ-lactone is indicated by a strong, symmetrical infrared absorption band at about 1720 cm.$^{-1}$ Other features of the complex infrared absorption spectra afford little useful structural information: strong hydroxyl group absorption in the 3400 cm.$^{-1}$ region, indications of absorption due to carbon-linked methyl groups at about 1400 cm.$^{-1}$ and carbon-oxygen stretching in the 1250 cm.$^{-1}$ region (most of the infrared spectra were determined in potassium bromide disks because of low solubility of many of the compounds in chloroform) confirm the presence of structural features disclosed by chemical studies. The infrared absorption of the sodium salt of the acid derived by opening of the lactone ring showed the characteristic absorption for hydroxyl groups and the carboxylate ion. A carbon-carbon double bond is suggested by a weak but sharp peak at 1600 cm.$^{-1}$, but no carbonyl absorption of other kinds was observed.

Chaparrin was difficult to purify and reproducible analytical values were not easy to obtain. An indication of a possible reason for this was found in the observation that at least one sample of chaparrin, of proper melting point, showed a small absorption peak in the infrared that could be ascribed to the carboxyl group. This suggests that incomplete lactonization (which would probably not affect the melting point of about 300° or higher) may introduce small and variable amounts of the elements of water. It was always observed that very careful drying of analytical samples was necessary. The results of numerous concordant carbon-hydrogen analyses led to the conclusion that chaparrin has the composition $C_{20}H_{28}O_7$.

Several comments on this formula are pertinent: quassin, the bitter lactone of *Quassia amara*,[18,19] is a dimethyl ether of a (hypothetical) substance of the composition $C_{20}H_{24}O_6$; glaucarubol, of which glaucarubin is the α-methyl-α-hydroxybutyric ester,[16] has the composition $C_{20}H_{28}O_8$; and simarolide, a bitter lactone recently isolated from *Simarouba amara*,[20] is the monacetate of a substance of the composition $C_{20}H_{30}O_6$. It is apparent that there are present in various plants of the Simaroubaceae a group of compounds that appear to be closely allied in structure: They possess or are derived from a C_{20} structure, are lactones, and many of them show a striking red or blue coloration with concentrated sulfuric acid. Moreover, numerous studies on *Brucea* spp.[7–12] have resulted in the isolation of a number of crystalline compounds, many of uncertain homogeneity, most of which show the same kind of color reaction and possess compositions approximating those given above.

Chaparrin is readily acetylated to yield two isomeric pentaacetyl derivatives, m.p. 226–228° and m.p. 135–137°. Both of these show the complete absence of hydroxyl groups by their infrared spectra, and both of them yield chaparrin upon alkaline hydrolysis. Their composition shows that chaparrin contains five hydroxyl groups and thus the seven oxygen atoms are completely accounted for. Benzoylation of chaparrin yields the expected pentabenzoate.

When chaparrin is treated with hot, dilute aqueous hydrochloric acid, two crystalline compounds are formed. One of these, formed in largest amount and called chaparrol, is a bitter lactone, readily soluble in aqueous alkali but insoluble in sodium bicarbonate solution; it gives no coloration with concentrated sulfuric acid, and its infrared absorption spectrum shows the presence of hydroxyl groups and the lactone ring. Chaparrol has the composition $C_{20}H_{24}O_5$, and forms a triacetate which shows no hydroxyl absorption in the infrared. The formation of chaparrol from chaparrin clearly involves the loss of two molecules of water. The ultraviolet absorption spectrum of chaparrol shows two maxima at 271 and 278 mμ (log ε 2.54 and 2.50). The spectrum is strikingly similar to that of 6-methyl-1,2,3,4-tetrahydronaphthalene and is evidence for the presence of an aromatic ring, perhaps in a tetralin-like structure, in chaparrol.

It is of interest to note that glaucanol, formed from glaucarubol by treatment of the latter with aqueous acid, has the composition $C_{20}H_{24}O_6$, and thus differs from glaucarubol by the elements of two molecules of water.

The product formed in small amount along with chaparrol has not been satisfactorily characterized, but its elementary composition appears to be $C_{20}H_{26}O_6$. It is thus a mono-dehydration product of

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chaparrin, but is unusual in that its absorption in the infrared is that of an α,β-unsaturated δ-lactone. Further comment on this compound must be reserved until it can be obtained in sufficient amount for closer study.

Among the lower-melting fractions of crystalline material that accumulate in the purification of chaparrin was a material that could be further recrystallized to a melting point of 290–291°. A mixed melting point with authentic glaucarubol (m.p. 292–293°) showed no depression, but its elementary analysis was intermediate between those of glaucarubol and chaparrin. That this material is impure glaucarubol is probable, since it could be converted by acid hydrolysis into glaucanol, identified by the identity of its infrared spectrum with that of an authentic sample, a mixed melting point, analysis, and the preparation of glaucanol acetate (identical with authentic material by mixed melting point and infrared spectra).

Besides chaparrin (and perhaps glaucarubol), at least one other constituent is present in *C. Nicholsoni*. It was isolated in small yield from plant extracts from which the bulk of the readily crystallizable material had been removed, and had m.p. 263–265°. It was a bitter substance, soluble in alkali but not in aqueous sodium bicarbonate. It was clearly distinguished from chaparrin and glaucarubol by the fact that it gave no coloration with concentrated sulfuric acid. Its elementary analysis gave figures in good agreement with the formula $C_{22}H_{30}O_7$ (a monoacetate of $C_{20}H_{28}O_6$).

Since chaparrin is best regarded as a pentahydroxy lactone, the formation of two isomeric pentaacetates is remarkable. The most reasonable interpretation of this result at the present time is that the lactone ring of chaparrin is sufficiently labile to permit the formation of pentaacetates in which the lactonic oxygen atom of one is found in an acetyloxy group of the other. The regeneration of chaparrin from both acetates shows that no deep-seated change occurs in the acetylation.

EXPERIMENTAL

Isolation of chaparrin: The milled whole aerial part of *Castela Nicholsoni* was extracted with methanol in 9-kg. batches in a stainless steel extractor (percolator) for 48 hr. The concentrated extract was treated with water, reconcentrated, and made up to 3 l. with water and allowed to stand overnight. After separation of a tarry deposit the filtrate was treated with about 25 ml. of 1*M* lead acetate solution, filtered through Celite, and treated again with lead acetate until precipitation was completed. Excess lead was removed with sulfuric acid (to a *p*H of 3.5 to 4.0) and the filtrate was concentrated to a volume of about 300 ml. The concentrated solution was shaken with about one-quarter its volume of chloroform, when a white semicrystalline solid separated. After centrifugation, the solid was shaken with a 1:5 mixture of chloroform and water and then with acetone. The final crude product was a solid with a m.p. of about 200–265°, and amounted to about 6.5 g.

The crude product was dissolved in hot methanol and the filtered solution concentrated by distillation to about 2 l. After 24 hr. a crop of crystalline material was collected, washed with methanol, and dried. Further concentration of the filtrates yielded successive crops of crystalline materials.

Those fractions having melting points of 290° or above were combined and recrystallized several times from methanol, to yield chaparrin as tiny white needles, m.p. 309–10°, $[\alpha]_D^{25.5}$ 45.2° (*c*, 0.2 in pyridine).

Anal. Calcd. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42; mol. wt. 380. Found: C, 62.95; 63.18, 62.98, 62.97; 63.26, 63.13. H, 7.49, 7.32, 7.53, 7.63, 7.02.

The equivalent weight was determined by treatment with 0.0494*N* sodium hydroxide for 6 hr. at 60°, and back titrating with standard acid: 383. C-methyl number, found: 1.73, 1.71, 1.80.

Acetylation of chaparrin. (A) *With acetic anhydride–pyridine.* A solution of 500 mg. of chaparrin in 2 ml. of pyridine and 4 ml. of acetic anhydride was heated on the steam bath for 90 min. Removal of the solvents left a gummy residue which was taken up in 3 ml. of chloroform and passed through a column of 15 g. of acid-washed alumina with 100 ml. of chloroform. The 650 mg. of white solid recovered from the eluate was recrystallized from petroleum ether (b.p. 30–60°) to yield 350 mg. of white needles, m.p. 226–8°, $[\alpha]_D^{25.6}$ 40.0 (*c*, 0.9 in pyridine). Its infrared absorption (in chloroform) showed the complete absence of hydroxyl groups.

Anal. Calcd. for $C_{20}H_{23}O_7(COCH_3)_5$: C, 61.02; H, 6.44, OAc, 36.43. Found: C, 60.86, 61.48, 61.29, 61.70; H, 6.64, 6.89, 6.65, 6.62; OAc, 36.27; C-Methyl, 6.25, 6.24.

After the separation of the 226–228° acetate, the mother liquors were concentrated to yield a second crop, m.p. (after recrystallization from petroleum ether (b.p. 30–60°) 135–137°, $[\alpha]_D^{25.5}$ 41.2 (*c*, 0.75 in pyridine). The infrared absorption spectrum of this acetate was very similar to, but not completely identical with that of the 226–228° acetate; no hydroxyl absorption was present.

Anal. Calcd. for $C_{20}H_{23}O_7(COCH_3)_5$: C, 61.02; H, 6.44; OAc, 36.43. Found: C, 60.66, 60.12; H, 6.60, 6.50; OAc, 35.83, 35.91; C-Methyl, 6.44.

(B) *With acetic anhydride–sodium acetate.* A solution of 500 mg. of chaparrin in 4 ml. of acetic anhydride and 25 mg. of sodium acetate was refluxed for 90 min. The reaction mixture was decomposed with water to yield 300 mg. of white solid, and saturation of the filtrate with sodium chloride gave an additional 225 mg. The crude material was worked up as described above (A) to yield 70 mg. of acetate, m.p. 226–228° and 400 mg. of acetate, m.p. 135–137°.

Hydrolysis of chaparrin acetates. (A) A solution of 60 mg. of the acetate m.p. 226–228° in 3 ml. of 1*N* alcoholic potassium hydroxide was heated for an hour. The ethanol was removed and the residue dissolved in 5 ml. of water. Acidification gave 25 mg. of crystalline material, m.p. 303–304°, undepressed in a mixture (m.p. 304–305°) with pure chaparrin. The infrared absorption spectra of the product and of pure chaparrin were identical in every detail.

(B) Alkaline hydrolysis of 135–137° acetate was carried out as described in (A). The product melted at 299–300° and a mixture with chaparrin also melted at 299–300°. The infrared absorption curves of the product of this hydrolysis and of chaparrin were nearly identical, with the exception that the regenerated material showed a small shoulder at about 1700 $cm.^{-1}$ absent from most chaparrin samples (but observed in one or two).

Anal. Calcd. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C,63.06; H, 7.65.

In another experiment, the regenerated chaparrin (m.p. 295–296°) gave the following analytical figures: C, 61.84; H, 7.17.

Chaparrin benzoate. Benzoylation of chaparrin (200 mg.) with benzoyl chloride–pyridine in the usual way yielded 260 mg. of crude product which was crystallized three times from ethanol to give 110 mg. of white crystals, m.p. 159–160°. Its infrared spectrum showed no hydroxyl group absorption.

Anal. Calcd. for $C_{20}H_{23}O_7(COC_6H_5)$: C, 71.90; H, 5.45. Found: C, 71.28; H, 5.60.

Acid treatment of chaparrin: Chaparrol. A slurry of 500 mg. of chaparrin in 50 ml. of 0.1*N* hydrochloric acid was heated to boiling; in about 20 min. a clear solution was formed. After an additional 1.5 hr. of refluxing the solution was cooled and extracted with chloroform. The dried chloroform solution was chromatographed on 15 g. of acid-washed alumina and eluted with 150 ml. of chloroform. Removal of the solvent left 385 mg. of yellowish solid. This was dissolved in 3 ml. of ethyl acetate and cooled, when 250 mg. of crystalline material was obtained. Recrystallization from petroleum ether (b.p. 60–80°) afforded chaparrol, colorless crystals, m.p. 221–222°, $[\alpha]_D^{25.5}$ 119.0° (*c*, 0.94 in pyridine).

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.92; H, 6.99; mol. wt., 344. Found: C, 69.74, 69.95; H, 7.18; mol. wt. (Rast), 341, 337; C-Methyl, 1.51, 1.52.

The ethyl acetate filtrates were evaporated to dryness and the residue crystallized twice from toluene to yield a *product*, m.p. 159–60°.

Anal. Found: C, 66.40; H, 6.68.

Chaparrol acetate. Acetylation of 200 mg. of chaparrol with acetic anhydride–pyridine, followed by chromatography of the product over alumina (chloroform) yielded 240 mg. of product which after two recrystallizations from petroleum ether (b.p. 30–60°) gave 150 mg. of white needles, m.p. 170–171°, $[\alpha]_D^{25.5}$ 167.0° (*c*, 0.94 in pyridine).

Anal. Calcd. for $C_{20}H_{21}O_5(COCH_3)_3$: C, 66.39; H, 6.38; OAc, 27.45. Found: C, 66.46, 65.85; H, 6.56, 6.52; OAc, 27.35; C-Methyl, 4.78.

Formation of glaucanol from lower-melting fractions. A crystalline fraction, m.p. 280–283°, from the purification of chaparrin, was recrystallized from methanol to give white platelets, m.p. 290–291°. Its mixed melting point with a sample of glaucarubol (m.p. 292–293°) showed no depression.

Anal. Calcd. for $C_{20}H_{28}O_8$, C, 60.60; 7.12. Calcd. for $C_{20}H_{28}O_7$, C, 63.14; 7.42. Found: (m.p. 290–291°) C, 61.93; 61.87; H, 7.23, 7.92.

Acid hydrolysis of material m.p. 280–283°. Hydrolysis of 200 mg. of a crystalline fraction, m.p. 280–283°, from the purification of chaparrin, by the use of 0.1*N* hydrochloric acid as described for chaparrol, yielded 150 mg. of crystalline material after chromatography on alumina. This melted at 230–233° before further purification but after two recrystallizations from ethanol it formed white platelets with m.p. 259–60°. A mixed m.p. of a sample of glaucanol,[21] m.p. 229–233°, and the m.p. 230–233° material was unchanged.

The m.p. 259–260° material also showed no depression in melting point on mixing with a specimen of glaucanol,[22] m.p. 252–253°. Comparison of the infrared spectra of our sample and the authentic specimen showed their complete identity.

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.60; H, 6.66. Found (m.p. 259–260°): C, 66.49; H, 6.59.

Glaucanol acetate. Acetylation of the sample of glaucanol m.p. 259–60°, with acetic anhydride–pyridine yielded (after purification over alumina) 35 mg. of crystalline solid. After two recrystallizations from petroleum ether (b.p. 30–60°) this yielded 20 mg. of white crystals, m.p. 209–210°. A mixed melting point with authentic glaucanol acetate[22] (m.p. 210–211°) showed no depression, and the infrared spectra of the two specimens were identical in every detail.

Anal. Calcd. for $C_{20}H_{20}O_6(COOCH_3)_4$: C, 63.63; H, 6.06. Found: C, 63.58; H, 5.65.

Compound m.p. 263–265°. After recovery of the crude chaparrin that separated upon the addition of chloroform to the first concentrated extract, the aqueous solution was extracted continuously with chloroform for 72 hr. The dried chloroform extract was evaporated and the nearly solid residue triturated with a little ethanol. A white crystalline material separated, and was collected and recrystallized twice from ethanol, when it formed white platelets, m.p. 263–265°. This material was markedly different from chaparrin (both the pure material and the lower-melting fractions), which gave an intense blue-violet color with concentrated sulfuric acid. This new compound gave no color under the same conditions. It was bitter and had the solubility behavior expected of a lactone (soluble in dilute alkali but not in aqueous bicarbonate). Its infrared absorption was markedly different from that of chaparrin and indeed was not that to be expected of a simple δ-lactone; two peaks were present in the carbonyl region, one at 1695 cm.$^{-1}$, the other at about 1715 cm.$^{-1}$ The presence of prominent peaks in the curve at 1236, 1245, and 1265 cm.$^{-1}$ is suggestive of an acetyloxy grouping, and the analytical figures are in good agreement for a monoacetate of a C_{20}-compound.

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.00; H, 7.45. Found: C, 65.06; H, 7.38.

Since only 30 mg. of this compound has been in hand, further study must await the isolation of more material.

Acknowledgment. The authors are grateful for gifts of specimens of the compounds from *Simarouba glauca* from Dr. E. A. Ham and Prof. Peter Yates.

Los Angeles, Calif.

(21) This specimen was kindly provided by Dr. E. A. Ham, Merck Sharpe and Dohme Research Laboratories.

(22) This was provided by Prof. P. Yates, who has recently undertaken further study of *Simarouba glauca*. This difference in melting point of the two "authentic" samples is consistent with our experience that the purification of crude glaucanol raises its melting point some 30°.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Allokhellin[1]

W. J. HORTON AND MASON G. STOUT[2]

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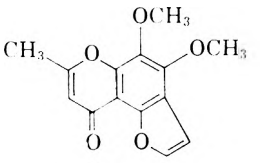
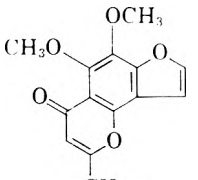
The synthesis of allokhellin from antiarol is reported. It was found that boric acid fails to give a hypsochromic shift of the spectra of a 2,3-dihydroxyacetophenone in alcoholic sodium ethoxide, contrary to dihydroxy compounds which do not permit hydrogen bonding.

The hydrogen iodide demethylation of khellin followed by remethylation[3,4] gave an isomer by rearrangement, for which structure I or II was proposed[3,5] and the latter, isokhellin, was then synthesized.[5]

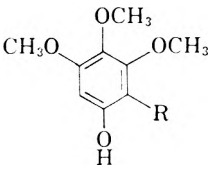


I

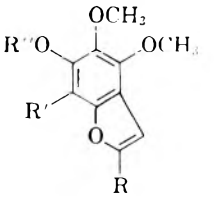


II

We have now prepared I from antiarol, III, and propose the name, *allokhellin*, by analogy to allobergapten.



III. R, H
IV. R, CH (=O)



V. R, CO_2CH_3; R′, H; R″, CH_3
VI. R, CO_2CH_3; R′, CCH_3 (=O); R″, CH_3
VII. R, CO_2CH_3; R′, CCH_3 (=O); R″, H
VIII. R, R″, H; R′, CCH_3 (=O)

Antiarol was converted to the aldehyde IV using *N*-methylformanilide and the aldehyde gave V by reaction with methyl bromoacetate and sodium methoxide.[6] The coumarilic ester V formed the acetyl compound VI by acetylation in polyphosphoric acid (PPA). Selective cleavage of VI in hydrogen bromide–acetic acid at room temperature[7] gave the desired hydroxyketone, VII. The direct production of VII from V was also possible by acetylation using boron trifluoride and acetic acid analogous to an acetylation with cleavage on a dihydrobenzofuran.[8] After saponification of the ester VII, the acid was decarboxylated *via* quinoline and copper powder. The product unexpectedly gave analytical values supporting a dihydroxy compound. Further, no chromone could be obtained from this material. Ethereal diazomethane converted the dihydroxy compound to VIII and this gave an acetoacetyl compound when condensed with sodium hydride and ethyl acetate.[9] The chromone was then formed using alcoholic sulfuric acid.[10]

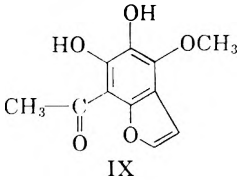
TABLE I

SUMMARY OF DATA ON KHELLINS

	M.P.	λ_{max}^{alc} (log ϵ)
Khellin	153[a]	247 (4.57)[b]
	152–153[c]	281 (3.67)
		331 (3.67)
Isokhellin	176[a]	243 (4.47)[b]
	180[b,d]	319 (3.66)
Allokhellin	152.2–153.2	255.5 (4.37)
		294.5 (3.93)
		~244 (4.29)[e]
		~261 (4.33)

[a] Ref. 3. [b] Ref. 5. [c] Ref. 9. [d] Undepressed when mixed with a sample prepared as in Ref. 3. [e] Inflection.

In order to test the possibility that IX represents the above dihydroxy compound, we investigated the hypsochromic shift of the long wave length band caused by the addition of boric acid to IX in ethanolic sodium ethoxide as proposed by Swain[11]



IX

(1) This investigation was supported by a Public Health Service Grant CY-4817 from the National Cancer Institute, Public Health Service.

(2) A part of the Doctoral dissertation of M. G. Stout.

(3) J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949).

(4) S. K. Mukerjee and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 13B, 400 (1954). *Chem. Abstr.*, 49, 12454 (1955).

(5) H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Assoc.*, 41, 403 (1952).

(6) T. Reichstein, *et al.*, *Helv. Chim. Acta*, 18, 816 (1935).

(7) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, 77, 2894 (1955).

(8) W. J. Horton and E. G. Paul, *J. Org. Chem.*, 24, 2000 (1959).

(9) T. A. Geissman, *J. Am. Chem. Soc.*, 71, 1498 (1949).

(10) R. A. Baker, G. R. Ramage, and J. A. Timson, *J. Chem. Soc.*, S30 (1949).

(11) T. Swain, *Chem. & Ind. (London)*, 1480 (1954).

for 1,2-dihydroxy compounds. No hypsochromic shift was found (Table II). Further, known 2,3-dihydroxy-4-methoxyacetophenone[12] gave no such shift. As a check on our handling of Swain's method, protocatechuic aldehyde gave results essentially as reported[11] (Table II). It is therefore concluded that this test fails in cases capable of hydrogen bonding. Such cases are not reported in the original work.[11]

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA[a]

	$\lambda_{max}^{abs.\ alc.}$	mμ (ε)	$\lambda_{max}^{0.200M\ NaOC_2H_5}$	mμ (ε)
Dihydroxy compound	239	(15700)	223	(16400)
above (IX or isomer)	303.5	(13800)	~245	(7680)[b,c]
	347	(8620)	262	(8350)[c]
			350	(29800)[c]
2,3-$(OH)_2$-4-CH_3O-	236.5	(13100)	243	(4930)[c]
acetophenone	298	(15400)	~320	—[c,d]
			357	(5940)[c]
Protocatechuic	233	(12900)	251.5	(8870)
aldehyde[e]	278.5	(9190)	~295	—[d]
	314	(8520)	350	(23000)

[a] The solvent was absolute ethanol throughout. [b] Indicates an inflection. [c] Identical in position and intensity in 0.002*M* sodium ethoxide-0.002*M* boric acid. [d] Unstable solution. [e] In 0.002*M* sodium ethoxide-0.002*M* boric acid, 245 mμ (14,200), 292 mμ (6690) and 338 mμ (14,300).

EXPERIMENTAL[13]

Antiarolaldehyde (IV). A solution containing 15.2 g. of phosphorus oxychloride and 13.4 g. of *N*-methylformanilide, after mixing and standing for 35 min. was treated at 25° with 18.2 g. of antiarol[14] over a period of 40 min. The solution was stirred for 3.25 hr. and allowed to stand for 18 hr. The dark red complex was poured into 500 ml. of water, allowed to stand for 1 hr., and filtered. The collected solid, dissolved in hot benzene, gave 7.34 g. of antiarol on cooling. The filtrate was evaporated and the residue, crystallized from aqueous methanol, gave 10.2 g. (81%) of pale yellow solid m.p. 60–62°; reported[14] m.p. 65°.

Methyl 4,5,6-trimethoxycoumarone-2-carboxylate (V). A solution of 12.3 g. of antiarolaldehyde and 12.2 ml. of methyl bromoacetate in 153 ml. of absolute methanol was refluxed (1.3 hr.) during the addition of a solution of 3.1 g. of sodium in 40 ml. of methanol. After 7 hr. at the boiling point the solution was allowed to stand overnight. When poured into 800 ml. of water and acidified, 9.12 g. (60%) of the ester was obtained, m.p. 98–99°. Crystallization from aqueous methanol gave material m.p. 98.8–99.1°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.63; H, 5.36.

After saponification, the *acid* was obtained as light tan needles m.p. 156.9–157.5° from cyclohexane-benzene or cyclohexane-acetone.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.60; H, 5.10.

Methyl 4,5,6-trimethoxy-7-acetylcoumarone-2-carboxylate (VI). A mixture containing 3.9 g. of the above ester and 1.33 ml. of acetic acid in 104 ml. of polyphosphoric acid became dark red after 30 min. at 70–75°. The solution after cooling and dilution with water gave a solid which was crystallized from cyclohexane. The yellow material (3.97 g.; 93.5%) melted at 90–110° and after further crystallization from cyclohexane at 111.1–111.6°.

Anal. Calcd. for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.60; H, 5.34.

The *2,4-dinitrophenylhydrazone*, from ethyl acetate, melted at 215.5–216.1°.

Anal. Calcd. for $C_{21}H_{20}O_{10}N_4$: C, 51.64; H, 4.13. Found: C, 51.72; H, 4.26.

Methyl 4,5-dimethoxy-6-hydroxy-7-acetylcoumarone-2-carboxylate (VII). (a) The hydrogen bromide-acetic acid cleavage[7] on VI produced a large amount of precipitate within 10 min. After 4.5 hr. standing, the product, crystallized from benzene, weighed 3.27 g. (86%) m.p. 174–180°. Further recrystallization from methanol gave pearly needles m.p. 182.6–182.9°. These gave a dark rose color with alcoholic ferric chloride.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 57.21; H, 4.85.

The *acetate* after repeated crystallization from aqueous methanol and from cyclohexane formed colorless fleecy needles m.p. 123.4–124.9°.

Anal. Calcd. for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 56.53; H, 4.74.

(b) Boron trifluoride was added at a temperature below 35° to a solution of 3.46 g. of methyl 4,5,6-trimethoxycoumarone-2-carboxylate V in 70 ml. of acetic acid. After addition of 75.3 g. of the gas, the dark green solution was allowed to stand at room temperature for 20.5 hr. By addition of 600 ml. of water, the solid boron complex was obtained and after boiling in 100 ml. of methanol and cooling, 3.57 g. (93%) of colorless needles m.p. 181–183° was obtained, identical by mixed melting point to VII above.

4,5-Dimethoxy-6-hydroxy-7-acetylcoumarilic acid. Saponification of the ester gave the *acid* (94.5%) m.p. 264–267° which produced a dark wine-colored ferric chloride test. From ethanol, light yellow needles m.p. 271–271.5° (uncor.—Fisher-Johns block) were obtained.

Anal. Calcd. for $C_{13}H_{12}O_7$: C, 55.72; H, 4.32. Found: C, 56.02; H, 4.41.

The *oxime* from ethanol formed colorless needles, m.p. 265–267.5°, dec. (uncor.—Fisher-Johns block) with an emerald green ferric chloride reaction.

Anal. Calcd. for $C_{13}H_{13}O_7N$: C, 52.88; H, 4.44. Found: C, 53.10; H, 4.60.

4,5-Dimethoxy-6-hydroxy-7-acetylbenzofuran (VIII). A mixture of 2.28 g. of the hydroxycoumarilic acid with 1.14 g. of copper powder in 65 ml. of quinoline was heated for 30 min. in a metal bath at 230–240°. The cooled and filtered solution in 1 l. of ether was washed three times with 5% hydrochloric acid and eight times with 8% sodium hydroxide. Acidification of the alkaline extract gave a red precipitate which was extracted repeatedly with boiling cyclohexane. The concentrated cyclohexane gave 1.23 g. (68%) of *4-methoxy-5,6-dihydroxy-7-acetylbenzofuran* (IX) *or the isomer* as a yellow solid, m.p. 175–177°, giving an emerald green ferric chloride test. The sample from further cyclohexane crystallization melted at 176.2–176.6°. The ultraviolet absorption spectral data are given in Table II.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.57; H, 4.71.

The compound (2.22 g.) gave *4,5-dimethoxy-6-hydroxy-7-acetylbenzofuran* when allowed to stand with ethereal diazomethane for 1 hr. The residue after evaporation of the solvent was crystallized from methanol to give a light brown solid (2.02 g. 86%), m.p. 109–110°. Purification from methanol gave VIII, m.p. 109.4–110.0°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 61.01; H, 5.12. Found: C, 61.23; H, 5.15.

Allokhellin (I). To 500 mg. of VIII in 5 ml. of dry ethyl acetate was added 500 mg. of sodium hydride in five portions. After standing overnight, ice was added followed by

(12) P. D. Gardner, W. J. Horton, and R. E. Pincock, *J. Am. Chem. Soc.*, 78, 2541 (1956).

(13) Melting points of analytical samples, except as noted, are corrected.

(14) E. Chapman, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 130, 3015 (1927).

25 ml. of dilute hydrochloric acid. The ethyl acetate was removed at room temperature in an air stream and the resultant solid collected, m.p. 95–103°, depressing the melting point of VIII. The crude solid, dissolved in a solution containing 16 ml. of alcohol and 4 ml. of concd. sulfuric acid, was heated on the steam bath for 1 hr. The solution was poured into 50 ml. of ice water, held for 16 hr. at 5°, and extracted with ether. The product obtained after washing the ether with 5% sodium hydroxide, saturated salt, and evaporation of the ether weighed 160 mg. Crystallization from cyclohexane gave 130 mg., m.p. 149.5–153°. Further crystallization brought the melting point to 152.2–153.2°. λ_{max}^{alc} 255.5, 294.5 mμ (ε 23,400, 8470); $\lambda_{inflect.}^{alc}$ 244, 261 mμ (ε 19,500, 21,500).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 65.00 H, 4.99.

2,3-Dihydroxy-4-methoxyacetophenone. A solution of 3.08 g. of 2,6-dimethoxyphenol in 107 ml. of glacial acetic acid with 15.8 ml. of acetic anhydride was treated with anhydrous boron trifluoride, holding the temperature below 30° until 96.5 g. of the gas had been added. The solution was then allowed to stand at room temperature for 48 hr. The reaction mixture was poured into 1 l. of ice and water and the filtered and washed boron complex was decomposed by boiling with 30 ml. of alcohol until it dissolved. On addition of 30 ml. of water and cooling, 2.98 g. (67%) of *2-hydroxy-3-acetoxy-4-methoxyacetophenone*, m.p. 121.5–126°, was obtained. From ethanol-water (3:2) colorless long thin prisms were obtained m.p. 123.4–125.0°.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 58.92; H, 5.40. Found: C, 58.96; H, 5.42.

When 1.0 g. of the above was refluxed for 1 hr. with 10 ml. of water, 10 ml. of concd. hydrochloric acid, and 20 ml. of alcohol, 0.68 g. of 2,3-dihydroxy-4-methoxyacetophenone, was obtained m.p. 130–134.5°, undepressed when mixed with a known sample (m.p. 130–132°).[12]

Acknowledgment. The assistance of the University Research Fund is gratefully acknowledged.

SALT LAKE CITY 12, UTAH

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIV., AMERICAN CYANAMID CO.]

The Synthesis of Certain C-21-Substituted Derivatives of 21-Deoxyhydrocortisone, 21-Deoxy-9α-fluorohydrocortisone, and Progesterone[1]

ROBERT E. SCHAUB AND MARTIN J. WEISS

Received June 15, 1960

The synthesis of certain modified steroidal hormones wherein the primary 21-hydroxy group or a 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties are reported.

At the time of this investigation it had already been shown that modification of the 21-hydroxymethylene grouping in the corticoid series could give structures retaining biological activity, although no case had been reported [2–11] by that time, or since, wherein such a modification has resulted in a dramatic increase in adrenocorticoid activity. C_{21}-Substituted derivatives of 4-pregnene-3,30-dione have also been described.[11–15] These compounds may be considered analogs of the mineralocorticoid deoxycorticosterone wherein the 21-hydroxy group is replaced, and also of progesterone wherein a 21-hydrogen is replaced.

In this paper we wish to report the synthesis of certain modified steroidal hormones wherein the primary 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties.

In our investigation, we have prepared C-21-substituted derivatives of 21-deoxyhydrocortisone,

(1) This investigation is part of a broad exploratory research program in the steroid field. For the previous publication from this laboratory on this program see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, in press.

(2) H. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956) (21-fluoro-21-deoxycortisone).

(3) W. J. Leanza, J. P. Conbere, E. F. Rogers, and K. Pfister 3rd, *J. Am. Chem. Soc.*, **76**, 1691 (1954) (21-aldehydo derivatives).

(4)(a) J. Fried *et al.*, *J. Am. Chem. Soc.*, **77**, 4181 (1955) (21-deoxy-9α-fluoroprednisolone); *J. Am. Chem. Soc.*, **77**, 1068 (1955) (21-deoxy-9α-fluorohydrocortisone). (b) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959) (21-deoxytriamcinolone).

(5) L. H. Sarett, H. D. Brown, and A. R. Matzuk, U. S. Patent **2,853,486** (Sept. 23, 1958) (21-azido derivatives).

(6) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955). (21-halo, cyano, thiocyano and acetylthio derivatives).

(7) C. Djerassi and A. L. Nussbaum, *J. Am. Chem. Soc.*, **75**, 3700 (1953) (21-acetylthio derivatives).

(8) A. L. Nussbaum, U. S. Patent **2,814,632** (Nov. 26, 1957) (21-acetylthio derivatives).

(9) B. G. Christensen, N. G. Steinberg, and R. Hirschmann, *Chem. & Ind.*, 1259 (1958) (21-diazo derivatives).

(10) 21-Amino-21-deoxy-9α-fluorohydrocortisone has recently been prepared by L. L. Smith and M. Marx of the Chemical Process Improvement Dept. of these laboratories; to be published.

(11) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3710 (1959) (21-nitro derivatives).

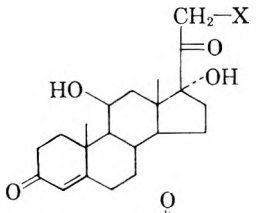
(12) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956) (21-fluoroprogesterone).

(13)(a) S. Nakanishi, K. Morita, and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959) (21,21-difluoroprogesterone). (b) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959). (c) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960). (d) 21,21,21-Trifluoroprogesterone has also been reported,[12a] however, without testing results.

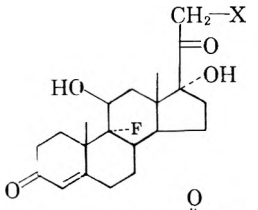
(14) R. A. Micheli and C. K. Bradsher, *J. Am. Chem. Soc.*, **77**, 4788 (1955) (21-morpholinoprogesterone).

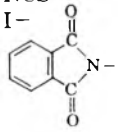
(15) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939) (21-aldehydo derivative).

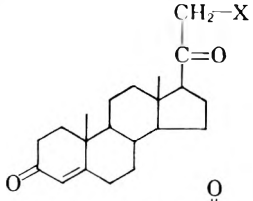
21-deoxy-9α-fluorohydrocortisone and progesterone. These compounds were conveniently synthesized by reaction of a 21-*O*-tosylate with an appropriate nucleophile, a procedure which has been described previously by several investigators.[5,6,16] The required 21-*O*-tosylates of hydrocortisone, 9α-fluorohydrocortisone, and deoxycorticosterone were prepared by tosylation at low temperature of the corresponding 21-ols, according to the method of Borrevang.[6] Reaction of all or certain of these three tosylates with piperidine, morpholine,[14] potassium phthalimide,[14] potassium thioacetate, sodium methylmercaptide, potassium thiocyanate, and potassium iodide then afforded the corresponding C-21-substituted analogs, usually in high yields. Although the reaction of certain 21-mesyloxy(or iodo)-17α-hydroxy steroids with nucelophiles such as potassium fluoride and silver dihydrogen phosphate results not only in the desired displacement but also in an accompanying 17α,21-oxide formation,[2,17] in our work we have observed no oxide formation. The free 21-mercapto derivatives were obtained in excellent yield on methanolic-methoxide treatment for fifteen minutes at room temperature of the 21-acetylthio derivatives. The various analogs are shown above (I–XVII).

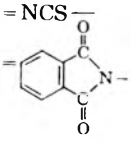


I. X = $CH_3-\overset{O}{\overset{\|}{C}}-S-$
II. X = HS—
III. X = CH_3S-
IV. X = 
V. X = 
VI. X =



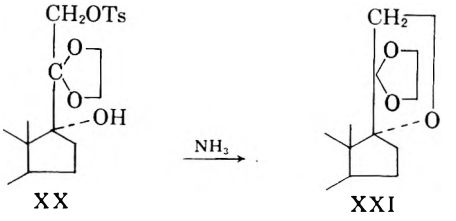
VII. X = $CH_3-\overset{O}{\overset{\|}{C}}-S-$
VIII. X = H—S—
IX. X = CH_3-S-
X. X = NCS—
XI. X = I—
XII. X = 



XIII. X = $CH_3-\overset{O}{\overset{\|}{C}}-S-$
XIV. X = H—S—
XV. X = CH_3-S-
XVI. X = NCS—
XVII. X = 

That these products were in fact 2-aminothiazolyl derivatives (XIX) was substantiated by examination of the infrared spectra which showed disappearance of the 20-carbonyl band (5.8 μ) and the presence of very heavy absorption between 6.0 μ and 6.35 μ (C=N). Further support was obtained from the ultraviolet spectra where the extinction coefficient for the maximum at 241–244 mμ was approximately 20,000, a value which is substantially higher than that usually afforded by a Δ^4-3-keto steroid (ϵ 16,000). The enhancement of the extinction value is consistent with the presence of a 2-aminothiazolyl chromophore (2-aminothiazole has λ_{max} 252 mμ, ϵ 7800).

Several attempts to prepare 21-unsubstituted amino derivatives *via* the reaction of 21-tosylates with ammonia or *via* the dephthaloylation of a 21-phthalimido derivative were unsuccessful.[10] Treatment of the 21-tosylate (XX) of hydrocortisone-3,20-bisethyleneketal with ammonia gave the 17α,21-oxide (XXI).[19]



XX XXI

Most of the compounds prepared in this study were submitted for broad biological evaluation. However, no activity of significant interest was discovered.

EXPERIMENTAL[20]

21-Acetylthio-11β,17α-dihydroxy-4-pregnene-3,20-dione (I). Treatment of a solution containing 1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of reagent acetone with 600 mg. of potassium thiolacetate as described below for the preparation of 21-acetylthio-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (VII) gave

(16) J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956).

(17) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **78**, 4814 (1956).

(18) The formation of thiazolyl derivatives *via* the reaction of a 21-bromo-20-keto steroid with thiourea has been reported [J. Korman, U. S. Patent **2,813,859** (Nov. 19, 1957); *Chem. Abstr.*, **52**, 5492 (1958)].

(19) W. S. Allen, S. Bernstein, M. D. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955).

733 mg. (96%) of product (I), m.p. 219–221° (gas). Two recrystallizations from acetone–petroleum ether afforded white crystals, m.p. 223–225°; $[\alpha]_D^{25}$ +151° (*c*, 1.15% in pyridine); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 19,500); λ_{max} 2.92, 3.00, 5.80, 5.90, 6.13 μ.

Anal. Calcd. for $C_{23}H_{32}O_5S$: C, 65.67; H, 7.67; S, 7.63; SAc, 10.20. Found: C, 65.47; H, 7.95; S, 7.72; SAc, 10.22.

11β,17α-Dihydroxy-21-mercapto-4-pregnene-3,20-dione (II). Treatment of a suspension of 500 mg. of 21-acetylthio-11β,17α-dihydroxy-4-pregnene-3,20-dione (I) in 15 cc. of reagent methanol with 1.3 cc. of 1*N* methanolic sodium methoxide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione (VIII) afforded 296 mg. (66%) of product (II), m.p. 230° dec. Two recrystallizations from dioxane–water gave white crystals, m.p. 254° dec.; $[\alpha]_D^{25}$ +147° (*c*, 0.87% in dioxane); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 18,900); λ_{max} 2.90, 5.85, 6.03, 6.12 μ.

Anal. Calcd. for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99; S, 8.46. Found: C, 66.37; H, 8.23; S, 7.97.

11β,17α-Dihydroxy-21-methylthio-4-pregnene-3,20-dione (III). A solution of 1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of acetone was treated with 190 mg. of sodium methylmercaptide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione (IX) to give 464 mg. (65%) of product (III), m.p. 217–220° (gas). Two recrystallizations from acetone–petroleum ether raised the m.p. to 223–225° (gas) $[\alpha]_D^{25}$ +141° (*c*, 1.02% in $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 17,500); λ_{max} 2.90, 5.85, 6.15 μ.

Anal. Calcd. for $C_{22}H_{32}O_4S$: C, 67.30; H, 7.96; S, 8.17. Found: C, 67.45; H, 8.19; S, 7.79.

11β,17α-Dihydroxy-21-morpholino-4-pregnene-3,20-dione·HCl (IV). To a suspension of 5 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of reagent pyridine was added 15 cc. of morpholine, under an atmosphere of carbon dioxide, solution being complete in approximately 5 min. The stoppered solution was allowed to stand at room temperature for 18 hr. Methylene chloride (200 cc.) was added and the solution was successively washed with saturated aqueous sodium bicarbonate solution, saline, and water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residual solid was dissolved in a solution of methylene chloride-absolute alcohol. The solution was saturated with hydrogen chloride at 0° and then allowed to stand at 5–7° for 24 hr. The resulting mixture was filtered to furnish 1.29 g. (30%) of product (IV), m.p. 241–242° dec.; $[\alpha]_D^{25}$ +89° (*c*, 1.17% in pyridine); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 16,400); λ_{max} 2.93, 3.10, 3.79, 3.91, 5.80, 5.95, 6.17 μ.

Anal. Calcd. for $C_{25}H_{37}NO_5$·HCl: C, 64.16; H, 8.18; Cl, 7.58; N, 2.99. Found: C, 63.84; H, 8.30; Cl, 7.75; N, 3.22.

11β,17α-Dihydroxy-21-piperidyl-4-pregnene-3,20-dione (V). To a suspension of 4 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 60 cc. of reagent benzene was added 20 cc. of piperidine under an atmosphere of nitrogen. The resulting solution was allowed to stand in a stoppered flask at room temperature for 65 hr. The solution was diluted with 200 cc. of methylene chloride, washed with saturated aqueous sodium bicarbonate, then with water, dried with anhydrous magnesium sulfate, and evaporated to dryness to furnish 3.5 g. of a semisolid. Recrystallization from acetone–petroleum ether gave 2.82 g. (90%) of product (V), m.p. 150–155° (gas). Two recrystallizations from the same solvent pair afforded white crystals, m.p. 154–156° dec.; $[\alpha]_D^{25}$ +109° (*c*, 1% in methanol); $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 14,000); λ_{max} 2.93, 5.86, 6.03, 6.19 μ.

Anal. Calcd. for $C_{26}H_{39}NO_4$: C, 72.69; H, 9.15; N, 3.26. Found: C, 72.64; H, 9.53; N, 3.44.

11β,17α-Dihydroxy-21-phthalimido-4-pregnene-3,20-dione (VI). Treatment of a suspension of 1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in *N,N*-dimethylformamide with potassium phthalimide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione (XII) afforded 646 mg. (72%) of product (VI), m.p. 294–297° dec. Two recrystallizations from acetone–petroleum ether gave white crystals, m.p. 303–305° dec.; $[\alpha]_D^{25}$ +206° (*c*, 0.99% in chloroform); $\lambda_{max}^{CH_3OH}$ 220, 238 (shoulder), 293 mμ (ε 49,500; 27,000; 2,460); λ_{max} 2.86, 5.64, 5.84, 5.98, 6.18, 7.06, 13.9 μ.

Anal. Calcd. for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found: C, 70.89; H, 6.93; N, 3.01.

9α-Fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione. To a suspension of 20 g. of 9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (9α-fluorohydrocortisone) in 200 cc. of reagent pyridine, cooled in an acetone-Dry Ice bath, was added a solution (cooled to turbidity) of 12.2 g. of *p*-toluenesulfonyl chloride in 120 cc. of methylene chloride. The suspension was stirred in the bath for 2 hr. during which period solution was completed. The solution was then allowed to stand at −20° for 17 hr. The solution was diluted with 500 cc. of ether, washed successively with water, 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, dried with anhydrous magnesium sulfate, and concentrated to a small volume. The precipitated crystalline material was collected by filtration; yield 20.65 g. (74%), m.p. 110–112° (bubbling) with resolidification and remelting at 175–177°. Recrystallization from acetone-petroleum ether afforded white crystals, m.p. 181–182°; $[\alpha]_D^{25}$ +100° (*c*, 1.0% in chloroform); $\lambda_{max}^{CH_3OH}$ 228 mμ (ε 26,700); λ_{max} 2.92, 5.75, 6.00, 8.50 μ.

Anal. Calcd. for $C_{28}H_{35}FO_7S$: C, 62.90; H, 6.60; F, 3.55; S, 5.99. Found: C, 62.59; H, 6.77; F, 3.26; S, 6.08.

21-Acetylthio-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (VII). To a solution of 1.5 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 75 cc. of acetone was added 925 mg. of potassium thiolacetate. The suspension was refluxed for 2.5 hr. and then concentrated to about one-half the volume. Addition of a small amount of water caused dissolution of the solids; further addition of an equal volume of water induced crystallization. Filtration furnished 1.07 g. (87%) of product (VII), m.p. 216–218° (gas). Two recrystallizations of a sample afforded white crystals, m.p. 220–221°; $[\alpha]_D^{25}$ +150° (*c*, 1.08% in chloroform); $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 20,300); λ_{max} 2.90, 5.90, 6.03 μ.

Anal. Calcd. for $C_{23}H_{31}FO_5S$: C, 63.00; H, 7.13; F, 4.33; S, 7.31. Found: C, 62.81; H, 7.48; F, 4.56; S, 7.00.

9α-Fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione (VIII). To a suspension of 633 mg. of 21-acetylthio-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (VII) in 20 cc. of reagent methanol under an atmosphere of nitrogen was added, with stirring, 1.58 cc. of 1*N* methanolic sodium methoxide, solution being complete in 30 seconds. After stirring for 10 min. the solution was acidified with 0.2 cc. of glacial acetic acid. The crystalline material that separated was collected and washed several times with water and then with ice cold methanol to furnish 411 mg. (72%) of product, m.p. 238–241° (gas). Two recrystallizations from acetone-petroleum ether gave white crystals, m.p. 251–253° (gas); $[\alpha]_D^{25}$ +85.1° (*c*, 1.01% in dioxane); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 17,000); λ_{max} 2.90, 3.02, 5.90, 6.06 μ.

Anal. Calcd. for $C_{21}H_{29}FO_4S$: C, 63.61; H, 7.37; F, 4.80; S, 8.09. Found: C, 63.41; H, 7.73; F, 4.60; S, 7.75.

9α-Fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione (IX). To a solution of 1 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 50 cc. of acetone was added 200 mg. of sodium methylmercaptide. The mixture was stirred under an atmosphere of nitrogen

(20) Melting points were determined in a capillary tube and are uncorrected. All infrared spectra were determined in potassium bromide discs on a Perkin-Elmer spectrophotometer (model 21). Ultraviolet spectra were determined on a Cary recording spectrophotometer. The petroleum ether used was that fraction boiling at 60–70° unless otherwise specified. All concentrations were carried out under reduced pressure on the steam bath.

at room temperature for 4 hr. After acidification with acetic acid, a small amount of water was added and the resulting solution was concentrated to a small volume and chilled. The resulting mixture was filtered to give 656 mg. (85%) of buff-colored solid in two crops, m.p. 215–218°. A sample was recrystallized several times from acetone–petroleum ether to give white crystals, m.p. 217–219°; $[\alpha]_D^{25}$ +127° (*c*, 1% in chloroform); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,600); λ_{max} 2.86, 5.90, 6.04 μ.

Anal. Calcd. for $C_{22}H_{31}FO_4S$: C, 64.36; H, 7.61; F, 4.63; S, 7.81. Found: C, 64.30; H, 7.68; F, 4.97; S, 7.68.

9α-Fluoro-11β,17α-dihydroxy-21-thiocyano-4-pregnene-3,20-dione (X). A solution of 2 g. of 9α-fluoro-11β,17α-dihydroxy-21-toxyloxy-4-pregnene-3,20-dione and 2 g. of potassium thiocyanate (dried by evaporation with 50 cc. of benzene) in 160 cc. of acetone was refluxed for 3.5 hr. The resulting mixture was concentrated to near dryness, water was added to induce crystallization, and the solid was collected by filtration to give 1.45 g. (92%) of product (X), m.p. 229–230°. Recrystallization of a sample from acetone–petroleum ether afforded white crystals, m.p. 233–235°; $[\alpha]_D^{25}$ +129° (c, 1.07% in methanol); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 18,100); λ_{max} 2.95, 4.64, 5.84, 6.05, 9.63 μ.

Anal. Calcd. for $C_{22}H_{28}FNO_4S$: C, 62.69; H, 6.70; F, 4.51; N, 3.33; S, 7.61. Found: C, 63.57; H, 6.88; F, 4.86; N, 3.00; S, 7.59.

9α-Fluoro-11β,17α-dihydroxy-21-iodo-4-pregnene-3,20-dione (XI). To a solution of 3 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 25 cc. of acetone was added a solution of 2.88 g. of sodium iodide in 25 cc. of acetone. After a few minutes sodium tosylate began to separate. The mixture was refluxed for 15 min., most of the acetone was distilled off, and the mixture was cooled to room temperature. On the addition of 10 cc. of 0.1*N* sodium thiosulfate and a small amount of water, a solid began to separate. The cooled solution was filtered to give 1.92 g. (70%) of product (XI), m.p. 156–158° dec. Recrystallization of a sample from acetone–petroleum ether afforded white crystals, m.p. 158° dec.; $[\alpha]_D^{25}$ −138° (*c*, 1.09% in methanol); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 18,400); λ_{max} 2.98, 5.85, 6.05, 6.12 μ.

Anal. Calcd. for $C_{21}H_{28}FIO_4$: C, 51.44; H, 5.76; F, 3.88; I, 25.88. Found: C, 51.39; H, 6.10; F, 3.54; I, 25.52.

9α-Fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione (XII). A suspension of 2.82 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione and 1.08 g. of potassium phthalimide in 70 cc. of *N,N*-dimethylformamide was kept in a water bath at 85–88° for 50 min., solution being complete in 5 min. The cooled solution was diluted with 200 cc. of methylene chloride and washed twice with saturated sodium bicarbonate solution and twice with water, after which a solid began to separate. The cooled mixture was filtered to furnish 1.2 g. (45%) of white crystals, m.p. 311° dec. A sample was recrystallized from acetone to give white crystals, m.p. 315° dec.; $[\alpha]_D^{25}$ +225° (c, 1.04% in chloroform); $\lambda_{max}^{CH_3OH}$ 220, 238 (shoulder), 293 mμ (ε 49,900; 29,000; 2,040); λ_{max} 2.87, 5.65, 5.84, 5.97, 7.06, 13.9 μ.

Anal. Calcd. for $C_{29}H_{32}FNO_6$: C, 68.35; H, 6.33; F, 3.33; N, 2.75. Found: C, 68.21; H, 6.54; F, 3.66; N, 2.92.

21-Tosyloxy-4-pregnene-3,20-dione. Treatment of 25 g. of 21-hydroxy-4-pregnene-3,20-dione (deoxycorticosterone) in 250 cc. of reagent pyridine with a solution of 15.9 g. of *p*-toluenesulfonyl chloride in 150 cc. of methylene chloride as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione gave 21.2 g. of crude product, m.p. 157–160° dec., which by analysis was a mixture of 21-chloride and 21-tosylate.[7, 21] Relatively pure tosylate, prepared by the reaction of 21-diazoprogesterone with *p*-toluenesulfonic acid, is reported to melt at 170–171°.[22]

(21) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(22) T. Reichstein and W. Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).

21-Mercapto-4-pregnene-3,20-dione (XIV). A suspension of 312 mg. of 21-acetylthio-4-pregnene-3,20-dione[7] (XIII) in 10 cc. of methanol was treated with 0.84 cc. of 1*N* methanolic sodium methoxide, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione (VIII), to furnish 224 mg. (81%) of product (XIV), m.p. 185–188°. Three recrystallizations from acetone–petroleum ether gave white crystals, m.p. 188–190°; $[\alpha]_D^{25}$ +206° (*c*, 2.11% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,600); λ_{max} 3.0, 5.85, 6.00, 6.16 μ.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.72; S, 9.25. Found: C, 72.54; H, 8.85; S, 8.97.

21-Methylthio-4-pregnene-3,20-dione (XV). Treatment of a suspension of 1 g. of 21-tosyloxy-4-pregnene-3,20-dione in 100 cc. of acetone with 220 mg. of sodium methylmercaptide, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione (IX), furnished 470 mg. (63%) of product (XV), m.p. 129–135°. Four recrystallizations from acetone–petroleum ether gave white crystals, m.p. 136–138°; $[\alpha]_D^{25}$ +204° (*c*, 2.1% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,000); λ_{max} 5.87, 5.97, 6.13 μ.

Anal. Calcd. for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.89. Found: C, 73.43; H, 9.12; S, 8.39.

21-Thiocyano-4-pregnene-3,20-dione (XVI). Treatment of 2 g. of 21-tosyloxy-4-pregnene-3,20-dione in 160 cc. of acetone with 2 g. of potassium thiocyanate, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-thiocyano-4-pregnene-3,20-dione (X), gave 1.1 g. (72%) of product (XVI), m.p. 156–159°. Three recrystallizations from acetone-petroleum ether furnished white crystals, m.p. 168–170°; $[\alpha]_D^{25}$ +182° (*c*, 1% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,500); λ_{max} 4.65, 5.82, 5.97, 6.18 μ.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: C, 71.13; H, 7.87; N, 3.77; S, 8.63. Found: C, 70.72; H, 7.96; N, 3.95; S, 8.38.

21-Phthalimido-4-pregnene-3,20-dione (XVII). A suspension of 2.74 g. of 21-tosyloxy-4-pregnene-3,20-dione and 1.51 g. of potassium phthalimide in 75 cc. of *N,N*-dimethylformamide was treated as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione (XII) to furnish 1.64 g. (63%) of product (XVII) in two crops, m.p. 215–220°. Three recrystallizations from acetone-petroleum ether afforded white crystals, m.p. 227–230°; $[\alpha]_D^{25}$ +225° (*c*, 1.59% in chloroform); $\lambda_{max}^{CH_3OH}$ 219, 236 (shoulder), 293 mμ (ε 54,500; 28,500; 2,230); λ_{max} 5.60, 5.77, 5.95, 6.15, 13.35 μ.

Anal. Calcd. for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: 75.40; H, 7.41; N, 3.29.

17β-(2-Amino-4-thiazolyl)-4-androsten-3-one p-toluenesulfonate (*see* XIX). A solution of 3 g. of 21-tosyloxy-4-pregnene-3,20-dione and 565 mg. of thiourea in 60 cc. of absolute alcohol was refluxed on the steam bath for 2.5 hr. After concentration to a small volume, the resulting mixture was cooled and filtered to furnish 1.94 g. (58%) of product, m.p. 265–267° dec. Recrystallization of a sample from absolute alcohol gave white crystals, m.p. 268–270° dec.; $[\alpha]_D^{25}$ +42° (*c*, 1% in methanol); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ (ε 22,800; 21,600; 20,900); λ_{max} 5.96, 6.20, 6.34, 8.35, 8.90, 9.65, 9.88, 14.65 μ.

Anal. Calcd. for $C_{25}H_{38}N_2O_4S_2$: C, 64.17; H, 7.06; N, 5.16; S, 11.83. Found: C, 64.47; H, 7.28; N, 5.38; S, 11.37.

17β-(2-Amino-4-thiazolyl)-11β,17α-dihydroxy-4-androsten-3-one p-toluenesulfonate (*see* XIX). A solution of 4.1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione and 625 mg. of thiourea in 80 cc. of absolute alcohol was treated as described directly above for the preparation of 17β-(2-amino-4-thiazolyl)-4-androsten-3-one *p*-toluenesulfonate to give 1.48 g. (35%) of product, m.p. 207–208° dec. Recrystallization of a sample from absolute alcohol afforded white crystals, m.p. 212–213°; $[\alpha]_D^{25}$ +50.3° (*c*, 0.219% in dimethylformamide); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ (ε 19,000; 18,100; 18,700); λ_{max} 2.95, 3.21, 6.01, 6.24, 6.32, 8.5, 8.9, 9.65, 9.88, 12.25, 14.65 μ.

Anal. Calcd. for $C_{29}H_{38}N_2O_6S_2$: C, 60.60; H, 6.66; N, 4.87; S, 11.15. Found: C, 60.92; H, 7.19; N, 4.40; S, 11.19.

17β-(2-Amino-4-thiazolyl)-9α-fluoro-11β,17α-dihydroxy-4-androsten-3-one p-toluenesulfonate (*see* XIX). A solution of 3 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one and 468 mg. of thiourea in 60 cc. of absolute alcohol was treated as described above for the preparation of 17β-(2-amino-4-thiazolyl)-4-androsten-3-one *p*-toluenesulfonate to give 1.14 g. (34%) of product, m.p. 214–216° dec.

In another experiment using crude 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one there was obtained 2.7 g. (15%) of product, m.p. 218° dec.; $[\alpha]_D^{25}$ +38.2° (*c*, 1.05%, dimethylformamide); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ; (ε 21,000; 20,700; 19,800); λ_{max} 2.95, 3.16, 5.99, 6.20, 6.28, 8.50, 8.90, 9.64, 9.87, 12.25, 14.70 μ.

Anal. Calcd. for $C_{29}H_{37}FN_2O_6S_2$: C, 58.76; H, 6.29; F, 3.21; N, 4.73; S, 10.82. Found: C, 59.44; H, 6.66; F, 3.21; N, 5.10; S, 10.56.

17α,21-Epoxy-3,20-bisethylenedioxy-11β-hydroxy-5-pregnene (XXI). A suspension of 500 mg. of 11β,17α-dihydroxy-3,20-bisethylenedioxy-21-tosyloxy-5-pregnene (XX)[19] in 50 cc. of methanol saturated with ammonia was kept in a steel bomb at 90–95° for 18 hr. Evaporation of the solution afforded a semi-solid. Recrystallization from acetone–petroleum ether afforded 284 mg. (79%) of crystalline material, m.p. 236–238°. Several recrystallizations from acetone gave white crystals, m.p. 253–255°; $[\alpha]_D^{25}$ 0° (chloroform), ν_{max} 3450, 1102, and 1055 cm.$^{-1}$ Reported[19] values are m.p. 252–255°; $[\alpha]_D^{25}$ 0°; ν_{max} 3500, 1102, and 1055 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.18; H, 8.52.

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, KYÔTO UNIVERSITY AND FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

The Preparation of Synthetic Estrogens. IX. 3,3′-Disubstituted Derivatives of Hexestrol[1]

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3,3′-Dihalohexestryl dimethyl ethers were prepared from the corresponding *m*-halo-*p*-methoxypropiophenones through reduction to the carbinol, bromination and the subsequent condensation of the Wurtz type. 3,3′-Difluoro- and 3,3′-dichlorohexestryl dimethyl ethers were demethylated smoothly by hydriodic acid, but similar treatment of 3,3′-dibromohexestryl dimethyl ether resulted in dehalogenation to give hexestrol. 3,3′-Dihalogenated butestrols were synthesized similarly. The Friedel-Crafts reaction of hexestryl dimethyl ether with various acids chlorides furnished the corresponding 3,3′-diacylhexestryl dimethyl ethers which were reduced to the respective 3,3′-dialkylhexestrols. Certain other derivatives of nuclear substituted hexestrols are described.

This paper comprises the preparation of heretofore unknown 3,3′-dihalohexestrols and -butestrols, which are of interest in their relation to 16α-chloro- and 16α-iodoestrone methyl ether, compounds reported[2] to be potent blood lipid-shifting agents of low estrogenic potency and thus of potential value in the treatment of atherosclerosis.

These halohexestrols and butestrols were synthesized according to the procedure of Bernstein and Wallis[3] as modified by Sisido and Nozaki,[4] which was summarized in the accompanying flow sheet. Treatment of 3,3′-dibromohexestryl dimethyl ether (IVc) with hydriodic acid gave a bromine-free diphenol which was identified as hexestrol. Apparently, the bromine atoms in the positions *ortho* to the methoxy groups are eliminated by the reducing action of hydriodic acid. Attempted demethylation of the dibromo ether (IVc) with hydrobromic acid yielded a reaction product from which no analytically pure compound could be isolated.[5] The action of a Grignard reagent or of pyridine hydrochloride also failed to afford any demethylation product. The 3,3′-dihalohexestrols and -butestrols are listed in Table I.

Other classes of hexestrol derivatives herein reported are 3,3′-dialkylhexestrols and related compounds. Though Buu-Hoï, Hoán, and Xuong[8] have reported the monoacylation of hexestryl dimethyl ether, the diacylated products have not

(1) For the previous paper in this series see K. Sisido, K. Okano, M. Sindô, and H. Nozaki, *J. Am. Chem. Soc.*, **79**, 3591 (1957).

(2) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958). For the preparation of 3-fluoro-3′-hydroxyhexestrol see R. J. Pratt and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 4430 (1956).

(3) S. Bernstein and E. S. Wallis, *J. Am. Chem. Soc.*, **62**, 2871 (1940).

(4)(a) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 778 (1948). (b) K. Sisido, H. Nozaki, and H. Kuyama, *J. Org. Chem.*, **14**, 1124 (1949). (c) Ng. Ph. Buu-Hoï and Ng. Hoán, *J. Org. Chem.*, **14**, 1023 (1949). (d) For the mechanism of the dehalogenation condensation in the presence of iron powder in water-suspension see K. Sisido, Y. Udô, and H. Nozaki, *J. Am. Chem. Soc.*, **82**, 434 (1960).

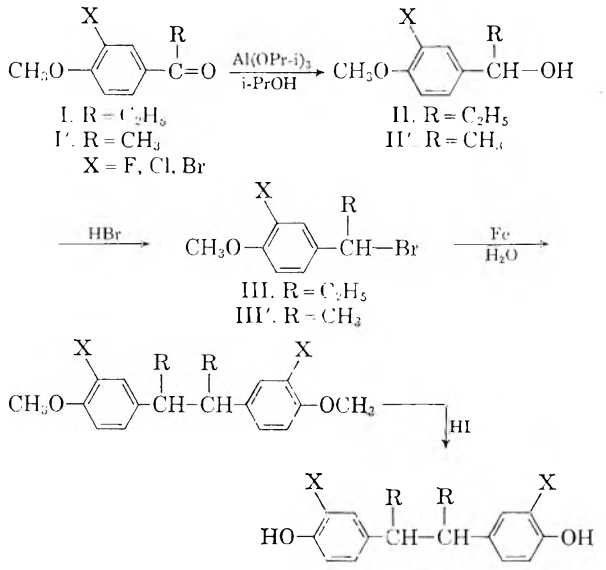
(5) For examples of shift and partial elimination of bromine atoms in the demethylation of bromo ethers with hydrobromic acid see T. Tomita and T. Kugô, *J. Pharm. Soc. Japan*, **75**, 1354 (1955); T. Tomita, Y. Kondo, and S. Tanaka, *J. Pharm. Soc. Japan*, **76**, 1119 (1956).

TABLE I

3,3′-DIHALOHEXESTROLS AND 3,3′-DIHALOBUTESTROLS

Compound	Formula	M.p.	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
IVa[a]	$C_{20}H_{24}F_2O_2$	162	71.83 (F% 11.36)	7.24	71.60 (F% 11.74)	6.75
IVa[a,b]	$C_{20}H_{24}F_2O_2$	92.5–93	71.83 (F% 11.36)	7.24	71.51 (F% 11.69)	7.30
Va[a]	$C_{18}H_{20}F_2O_2$	198	70.57 (F% 12.40)	6.58	70.41 (F% 12.61)	6.57
IVb[c]	$C_{20}H_{24}Cl_2O_2$	159	65.40	6.59	65.33	6.55
Vb[d]	$C_{18}H_{20}Cl_2O_2$	146–147	63.72	5.94	63.43	6.11
IVc[e]	$C_{20}H_{24}Br_2O_2$	184.5	52.65	5.30	52.91	5.38
IV′a[f]	$C_{18}H_{20}F_2O_2$	114	70.57 (F% 12.40)	6.58	70.68 (F% 12.19)	6.54
V′a[g]	$C_{16}H_{16}F_2O_2$	202	69.05 (F% 13.65)	5.80	69.18 (F% 13.52)	5.57
IV′b[h]	$C_{18}H_{20}Cl_2O_2$	160	63.72	5.94	63.24	5.91
V′b[i]	$C_{16}H_{16}Cl_2O_2$	116–117	61.75	5.18	62.08	5.56
VI′b[j]	$C_{20}H_{20}Cl_2O_4$	169	60.77	5.10	60.87	5.24
IV′c[k]	$C_{18}H_{20}Br_2O_2$	155	50.49	4.71	50.72	4.85

[a] Details are given in the Experimental. [b] The lower melting isomer of presumably racemic form has been isolated in this case. Other compounds herein described are considered to be the *meso*-form. [c] IVb was prepared in the same way as IVa from *m*-chloro-*p*-methoxypropiophenone[6] in an overall yield of 13%. Recrystallized from benzene. [d] Demethylation was carried out with hydriodic acid, yield 86%. Recrystallized from ligroin. [e] IVc was prepared in the same way as IVa using *m*-bromo-*p*-methoxypropiophenone[6] in an overall yield of 14%. Recrystallized from benzene. [f] IV′a was prepared from *m*-fluoro-*p*-methoxyacetophenone,[7] in an overall yield of 12%. Recrystallized from ligroin. [g] Demethylation with hydriodic acid gave a quantitative yield of V′a. Recrystallized from a mixture of benzene and alcohol. [h] IV′b was prepared from *m*-chloro-*p*-methoxyacetophenone[6] in an overall yield of 8.5%. [i] The product of demethylation with hydriodic acid formed a dark colored oil, which did not crystallize. The crude oil was treated with acetic anhydride in the presence of a small amount of pyridine to give the diacetate, VI′b, which was then heated under reflux with 2*N* methanolic potassium hydroxide for a half hour. The solid which separated upon acidification with hydrochloric acid was recrystallized from ligroin to give V′b. [j] This is the diacetate of V′b (see footnote[i]). Recrystallized from ethanol. [k] IV′c was prepared from *m*-bromo-*p*-methoxyacetophenone[6] in an overall yield of 7.7%. Recrystallized from benzene.



IVa. R = C_2H_5, X = F
IVb. R = C_2H_5, X = Cl
IVc. R = C_2H_5, X = Br
IV′a. R = CH_3, X = F
IV′b. R = CH_3, X = Cl
IV′c. R = CH_3, X = Br

Va. R = C_2H_5, X = F
Vb. R = C_2H_5, X = Cl
V′a. R = CH_3, X = F
V′b. R = CH_3, X = Cl

been described. The reaction of the hexestryl dimethyl ether with two moles each of the acyl chloride and aluminum chloride proceeded smoothly to give the 3,3′-diacylhexestryl dimethyl ethers. Treatment with hydroxylamine furnished the corresponding dioximes, and Wolff-Kishner reduction and subsequent demethylation with hydriodic acid produced the 3,3′-dialkylhexestrols. These compounds are listed in Table II. Attempted formylation of the 3,3′-positions of hexestryl dimethyl ether by means of the Gattermann-Koch synthesis or of hexestrol itself by the Reimer-Tiemann reaction was unsuccessful.

The dioxime of 3,3′-diacetylhexestryl dimethyl ether was subjected to the Beckmann rearrangement by the action of phosphorus pentachloride to give 3,3′-diacetamidohexestryl dimethyl ether. Treatment of the amide with boiling hydrochloric acid gave the hydrochloride of 3,3′-diaminohexestryl dimethyl ether as a hygroscopic solid, m.p. 201°, but the free base was too unstable to be isolated.

On attempted oxidation of 3,3′-diacetylhexestryl dimethyl ether with sodium hypobromite to yield the 3,3′-dicarboxy compound, the starting ketone was recovered unchanged.

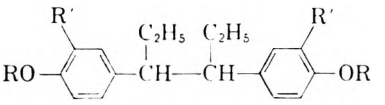
(6) Ng. Hoán and Ng. Ph. Buu-Hoï, *Compt. rend.*, 224 1363 (1947).

(7) Ng. Ph. Buu-Hoï, Ng. D. Xuong, and D. Lavit, *J. Org. Chem.*, 18, 910 (1953).

(8) Ng. Ph. Buu-Hoï, Ng. Hoan, and Ng. D. Xuong, *J. Am. Chem. Soc.*, 72, 3992 (1950).

TABLE II

3,3′-DIACYLHEXESTRYL DIMETHYL ETHERS, AND DIOXIMES, 3,3′-DIALKYLHEXESTRYL DIMETHYL ETHERS, AND 3,3′-DIALKYLHEXESTROLS



R	R′	M.P.	Formula	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
CH_3	$COCH_3$[a]	172	$C_{24}H_{30}O_4$	75.36	7.91	75.21	8.08
CH_3	$C(CH_3)NOH$[a]	228	$C_{24}H_{32}N_2O_4$	69.88	7.82	69.70	7.81
CH_3	C_2H_5[a]	108	$C_{24}H_{34}O_2$	81.31	9.67	81.04	9.54
H	C_2H_5[a]	127.5–128.5	$C_{22}H_{30}O_2$	80.93	9.26	81.10	9.41
CH_3	COC_2H_5[b]	157	$C_{26}H_{34}O_4$	76.06	8.34	75.75	8.47
CH_3	$C(C_2H_5)NOH$[c]	231–232	$C_{26}H_{36}N_2O_4$	70.88	8.24	70.82	8.27
CH_3	n-C_3H_7[d]	71	$C_{26}H_{38}O_2$	81.62	10.01	81.88	10.17
CH_3	n-COC_3H_7[e]	130–131	$C_{28}H_{38}O_4$	76.67	8.73	76.39	8.73
CH_3	$C(n$-$C_3H_7)NOH$[f]	213	$C_{28}H_{40}N_2O_4$	71.76	8.60	71.34	8.84
CH_3	n-C_4H_9[g]	145	$C_{28}H_{42}O_2$	81.90	10.31	81.58	10.33
H	n-C_4H_9[h]	138–139	$C_{26}H_{38}O_2$	81.62	10.01	81.13	10.39
CH_3	$COCH(CH_3)_2$[i]	153	$C_{28}H_{38}O_4$	76.67	8.73	76.80	9.02
CH_3	$C(i$-$C_3H_7)NOH$[j]	195–196	$C_{28}H_{40}N_2O_4$	71.76	8.60	71.76	8.90
CH_3	$CH_2CH(CH_3)_2$[k]	89	$C_{28}H_{42}O_2$	81.90	10.31	81.85	10.32
H	$CH_2CH(CH_3)_2$[l]	161.5–162	$C_{26}H_{38}O_2$	81.62	10.01	81.40	10.18

[a] Details are given in the Experimental. [b] Prepared from hexestryl dimethyl ether and propionyl chloride in the same way as 3,3′-diacetylhexestryl dimethyl ether. Recrystallized from a mixture of methanol and benzene; yield 91%. [c] Recrystallized from benzene. Quantitative yield. [d] Recrystallized from methanol; yield 89%. Demethylation with hydriodic acid gave 3,3′-dipropylhexestrol, m.p. 124–124.5°, after recrystallizations from petroleum ether containing a small amount of benzene. This diphenol has been prepared by Kaiser and Svarz[9] from hexestryl diallyl ether. The recorded m.p. is 123.5–124.5°. [e] Friedel-Crafts reaction with *n*-butyryl chloride. Recrystallized from ethanol containing a small amount of benzene; yield 48%. [f] Recrystallized from benzene; quantitative yield. [g] Recrystallized from ligroin; yield 32%. [h] Recrystallized from ligroin. [i] Friedel-Crafts reaction with isobutyryl chloride. Recrystallized from ethanol; yield 67%. [j] Recrystallized from benzene. [k] Recrystallized from ethanol; yield 64%. [l] Recrystallized from a mixture of benzene and petroleum ether.

EXPERIMENTAL[10]

3,3′-Difluorohexestryl dimethyl ether (IVa). A solution of 14.5 g. (0.08 mole) of *m*-fluoro-*p*-methoxypropiophenone (m.p. 84°, reported[7] 86°) in 60 ml. of anhydrous isopropyl alcohol was added to a solution of aluminum isopropoxide prepared from 2.7 g. (0.1 g.-atom) of aluminum foil, 54 ml. of anhydrous isopropyl alcohol containing 0.2 g. of mercuric chloride and 0.5 ml. of carbon tetrachloride. The mixture was heated under reflux for 2.5 hr., while the acetone was removed by fractional distillation as it was formed. After 50 ml. of distillate had been collected, the residue was treated with ice and hydrochloric acid and extracted with benzene; the benzene solution was washed, dried, and concentrated to afford 14 g. of crude 1-(*m*-fluoro-*p*-methoxyphenyl)-1-propanol as an orange, viscous oil.

Dry hydrogen bromide was passed into 14 g. of this crude carbinol for 3 hr., the reaction temperature being kept at 0–2° by an ice bath. A mixture of 100 ml. of ligroin and 100 g. of crushed ice was added, and the organic layer was separated and washed thoroughly with ice water.

This ligroin solution of crude 1-bromo-1-(*m*-fluoro-*p*-methoxyphenyl)propane was added immediately to a suspension of 12 g. of reduced iron in 120 ml. of ice water. The resulting mixture was heated slowly with stirring, while the ligroin was removed by distillation. When most of the ligroin had been removed, the reaction mixture was heated under reflux with vigorous stirring for an additional 3 hr. After cooling, the reaction mixture was extracted with benzene and the benzene solution was washed with water, dried, and evaporated. Recrystallization of the residue from petroleum ether gave 2.2 g. of 3,3′-difluorohexestryl dimethyl ether of presumably *meso*-form as colorless prisms, m.p. 157–160°. A single recrystallization from ligroin furnished a pure product, m.p. 162° unchanged by further recrystallization.

The combined mother liquors were concentrated and the residue distilled under reduced pressure to give a fraction (3.1 g.) boiling at 189–210 (6 mm.). Fractional crystallization of this distillate from a mixture of ligroin and petroleum ether gave 1.0 g. of the lower melting, presumably racemic, isomer of 3,3′-difluorohexestryl dimethyl ether, m.p. 92.5–93°, along with 0.3 g. of crystals melting at 162°, not depressed by admixture with the specimen mentioned above. The total yield of the higher melting 3,3′-difluorohexestryl dimethyl ether amounts to 18.7% based on *m*-fluoro-*p*-methoxypropiophenone.

Other 3,3′-dihalohexestryl and -butestryl dimethyl ethers listed in Table I were prepared in essentially the same way, starting from appropriately substituted propiophenones or acetophenones.

3,3′-Difluorohexestrol (Va). A mixture of 2.0 g. of the higher melting 3,3′-difluorohexestryl dimethyl ether (m.p. 162°), 30 ml. of glacial acetic acid and 7 ml. of hydriodic acid (d. 1.7) was heated under reflux for 1 hr.; during this time the crystals dissolved gradually to give a dark brown solution. Removal of the solvent followed by single recrystallization of the residue from benzene containing a small amount of alcohol gave 3,3′-difluorohexestrol, m.p. 198°.

The demethylation of other 3,3′-dihalohexestryl and -butestryl dimethyl ethers was carried out similarly. Attempted demethylation of 3,3′-dibromohexestryl dimethyl ether failed to give the desired diphenol. A mixture of 1.8 g. (0.004 mole) of 3,3′-dibromohexestryl dimethyl ether (m.p. 184°), 20 ml. of acetic acid and 7 ml. of hydriodic acid (d. 1.7) was refluxed for 1.5 hr. Recrystallizations of

(9) E. Kaiser and J. J. Svarz, *J. Am. Chem. Soc.*, 68, 636 (1946).

(10) All temperatures are uncorrected.

the reaction product from a mixture of benzene and alcohol afforded 0.8 g. of hexestrol, m.p. and mixed m.p. 186°, which gave correct analyses for carbon and hydrogen.

3,3'-Diacetylhexestryl dimethyl ether. A solution of 4.5 g. (0.015 mole) of hexestryl dimethyl ether, m.p. 144°,[11] 5.9 g. (0.075 mole) of acetyl chloride and 60 ml. of nitrobenzene was cooled in an ice bath, and 10.5 g. (0.079 mole) of finely powdered aluminum chloride was added in small portions with stirring. After 4 hr. stirring at room temperature, the reaction mixture was poured onto crushed ice, acidified with hydrochloric acid, and the nitrobenzene was removed by steam distillation. The remaining solid was collected, dried, and recrystallized from a mixture of methanol and benzene to yield colorless prisms of 3,3'-diacetylhexestryl dimethyl ether, 5.4 g. (93%), m.p. 172°.

Other 3,3'-diacylhexestryl dimethyl ethers listed in Table II were prepared analogously by use of appropriate acyl chloride.

Dioxime of 3,3'-diacetylhexestryl dimethyl ether. A solution of 3.0 g. (0.008 mole) of 3,3'-diacetylhexestryl dimethyl ether, 1.5 g. (0.022 mole) of hydroxylamine hydrochloride and 2.0 g. of anhydrous sodium acetate in 15 ml. of ethanol was heated under reflux for 2 hr. on a water bath. After cooling, the mixture was diluted with cold water, whereupon 3.3 g. (100%) of crystals separated. Three recrystallizations from a mixture of ethanol and benzene gave colorless prisms melting at 228°.

3,3'-Diethylhexestryl dimethyl ether. The reduction was carried out according to the Wolff-Kishner method as modified by Huang-Minlon.[12] A mixture of 3.1 g. (0.008 mole) of 3,3'-diacetylhexestryl dimethyl ether, 7.0 g. (0.125 mole) of potassium hydroxide, 7 ml. of 85% hydrazine hydrate, and 70 ml. of diethyleneglycol was heated under reflux for 1.5 hr. After removal of the water formed, the mixture was heated at 195° for an additional 4 hr. The solution was diluted with cold water and poured into hydrochloric acid. After a few hours the resulting dark oil solidified, and the solid, 2.8 g., (98%), was recrystallized from a mixture of methanol and benzene to give colorless prisms melting at 108°.

3 3'-Diethylhexestrol. A mixture of 1.5 g. of 3,3'-diethylhexestryl dimethyl ether, 20 ml. of glacial acetic acid, and 7 ml. of 48% hydriodic acid was heated under reflux for 1.5 hr. The solution was poured into an aqueous solution of sodium bisulfite. The resulting crystals were collected by filtration and washed with water and then with a small amount of cold ethanol. Several recrystallizations from ligroin gave colorless prisms melting at 127.5–128.5°.

Other 3,3'-dialkylhexestrols listed in Table II were prepared by the similar reduction and demethylation processes.

3,3'-Diacetamidohexestryl dimethyl ether. To a suspension of 2.7 g. (0.007 mole) of the dioxime of 3,3'-diacetylhexestryl dimethyl ether in 50 ml. of absolute ether, 4.5 g. (0.022 mole) of phosphorus pentachloride was added gradually with stirring and cooling in an ice bath. After 10 min., the ice bath was removed, and the stirring was continued for an additional 20 min. at room temperature. The mixture was poured onto crushed ice and the ether layer separated and washed with water. After removal of the solvent, the crystalline residue was recrystallized from ethanol to yield 2.6 g. (96%) of product, m.p. 252°.

Anal. Calcd. for $C_{24}H_{32}N_2O_4$: C, 69.87; H, 7.82. Found: C, 69.53; H, 7.91.

A mixture of this product with the dioxime of 3,3'-diacetylhexestryl dimethyl ether showed a marked depression.

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(11) Hexestryl dimethyl ether was supplied by the Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

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

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

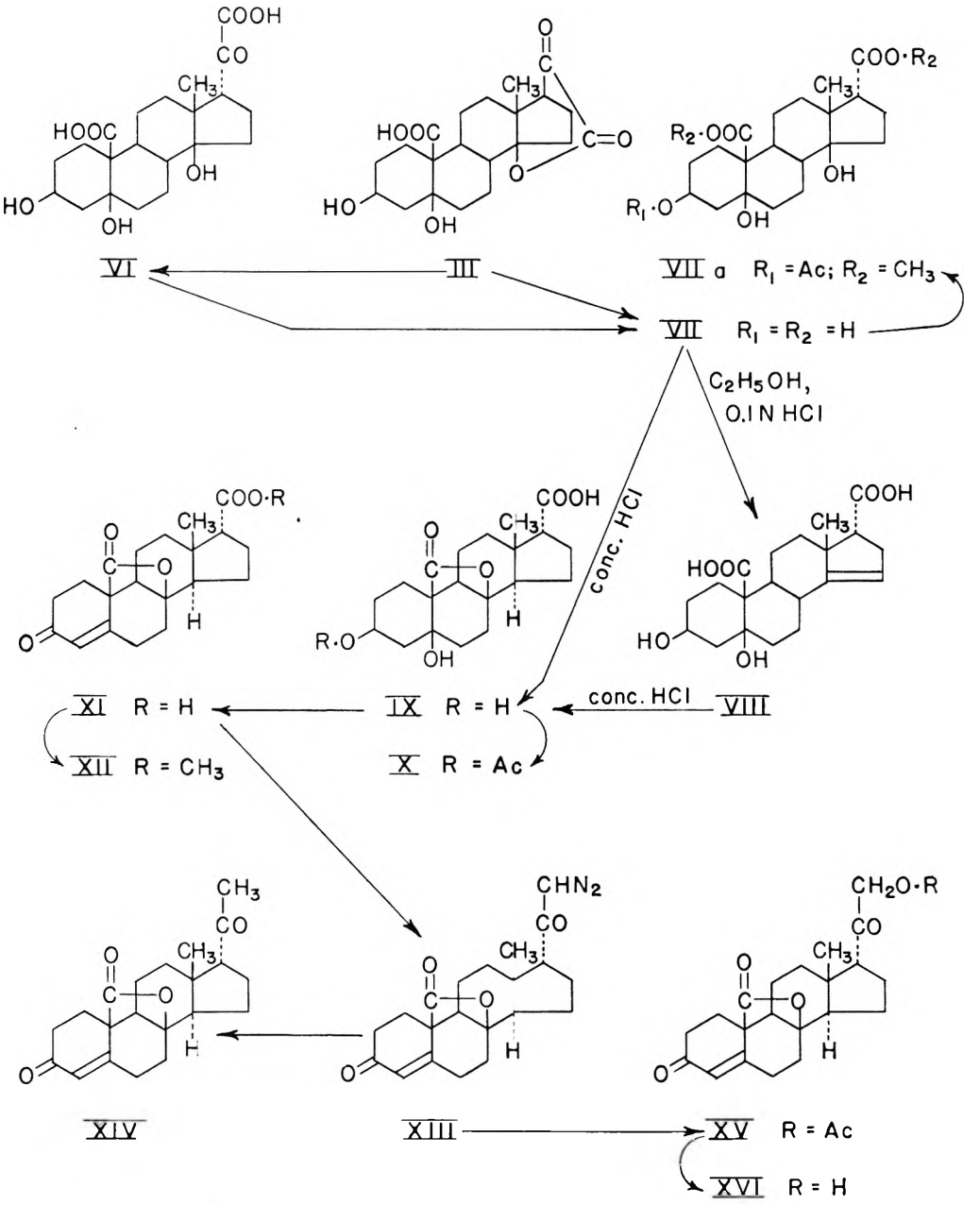
Investigations on Steroids. XXXIII. Conversion of Strophanthidin into 19:8-Lactone Analogs of Progesterone and Cortexone[1,2]

G. WINSTON BARBER AND MAXIMILIAN EHRENSTEIN

Received July 7, 1960

By oxidative procedures, strophanthidin (I) may be converted into 3β,5,14-trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid (VII) or 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid (IV), which differ only regarding their configurations at carbon atom 17. Treatment of VII with concentrated hydrochloric acid gave 3β,5,8-trihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone (IX), whereas with IV the same reaction yielded 3β,5,8-trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XVIII). The latter compound was also obtained by a different pathway, utilizing strophanthidinic acid (II) which on treatment with concentrated hydrochloric acid gave strophanthidinic acid 19:8-lactone (XX). The latter by ozonization yielded 3β,5,8,21-tetrahydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XXI), which by degradation with periodic acid furnished XVIII. Oxidation with chromium trioxide of IX and XVIII, and subsequent treatment of the reaction products with Girard's reagent T gave 8-hydroxy-3-oxo-21-nor-Δ⁴-17α-pregnene-19,20-dioic acid 19:8-lactone (XI) and 8-hydroxy-3-oxo-21-nor-Δ⁴-pregnene-19,20-dioic acid 19:8-lactone (XXII) respectively. The reaction of the acid chloride of XI with diazomethane gave 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone (XIII). By treatment with concentrated hydriodic acid, XIII was converted into 19:8-lacto-17α-progesterone (XIV), whereas with acetic acid 19:8-lacto-17α-cortexone acetate (XV) (amorphous) resulted which by saponification yielded 19:8-lacto-17α-cortexone (XVI). In identical fashion, XXII was converted into 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone (XXIII) which was transformed into 19:8-lactoprogesterone (XXIV) and 19:8-lactocortexone acetate (XXV). By saponification, the latter was converted into 19:8-lactocortexone (XXVI). The infrared absorption spectra of the terminal products XIV and XXIV, as well as XVI and XXVI have been compared. The results of the bioassays on these four compounds are also presented. XIV and XXIV produce only little, if any, progestational action. Both XVI and XXVI are devoid of mineralocorticoid activity.

In studies dealing with the degradation of strophanthidin, we encountered some time ago an etio acid which was first considered to possess a $\Delta^{8,14}$-double bond,[3] but was later[4,5] interpreted to contain a 19:8-lactone bridge (IX). In subsequent publications it was shown that 3β,5,8-trihydroxy-



21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone (IX) can be prepared in good yield by the action of concentrated hydrochloric acid either on 3β,5-dihydroxy-21-nor-Δ^{14}-5β,17α-pregnene-19,20-dioic acid (VIII)[5] or, more conveniently, on 3β,5,14-trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid (VII).[6,7] VII is readily prepared from strophanthidin (I) by way of 3β,5,14-trihydroxy-20-oxo-5β,14β-pregnane-19,21-dioic acid 21:14-lactone (III), which is subjected in one operation to oxidation with hydrogen peroxide after treatment with alkali. The reaction proceeds through the intermediate 3β,5,14-trihydroxy-20-oxo-5β,14β,17α-pregnane-19,21-dioic acid (VI) which, because of the

(1) This investigation was supported by research grants (C757-C4, CY757-C5, CY757-C6 and CY757-C7) from the National Cancer Institute of the National Institutes of Health, Public Health Service. A part of the K-Strophanthin used in this investigation was kindly donated by S. B. Penick & Company, New York.

(2) The findings of this paper were presented on September 5, 1958, at the 4th International Congress of Biochemistry in Vienna (*cf.* Maximilian Ehrenstein: *Biochemistry of the Corticoids,* Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 [Symposium: Biochemistry of Steroids], Pergamon Press, p. 259 (1959)).

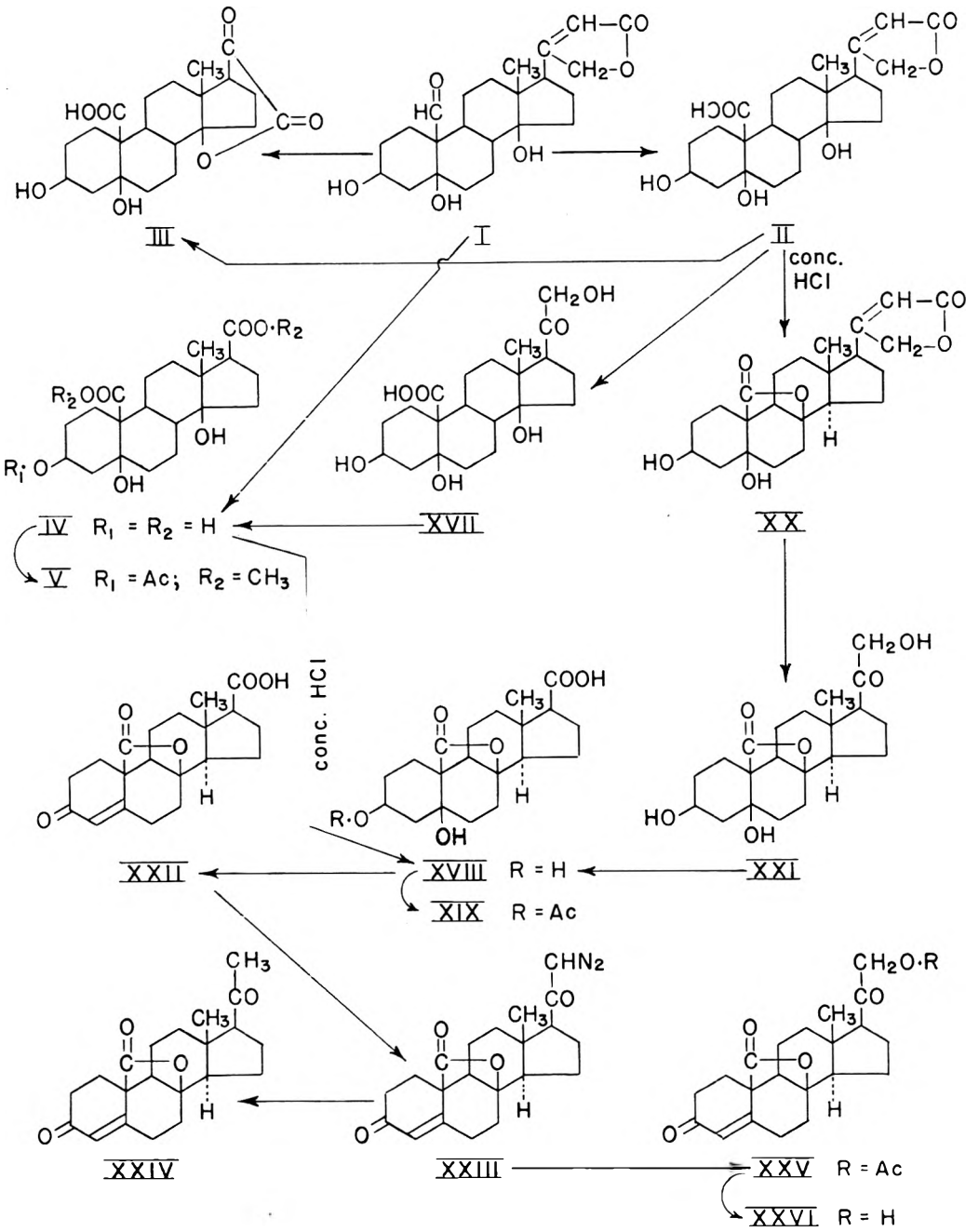
(3) M. Ehrenstein, *J. Org. Chem.*, 9, 435 (1944); *cf.* footnote on p. 446.

(4) M. Ehrenstein, G. W. Barber, and M. W. Gordon, *J. Org. Chem.* 16, 349 (1951); *cf.* p. 357.

(5) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, 16, 1615 (1951).

(6) G. W. Barber and M. Ehrenstein, *Liebigs Ann. Chem.*, 603, 89 (1957).

(7) In a previous publication (*cf.* Ref. 6, formula VII on p. 92) the hydrogen atom at C-14 had been assigned the β-configuration.



inversion at carbon atom 17, does not relactonize. It is to be noted that in VII, the carboxyl group at C-17 possesses the α-configuration. The conversion by concentrated hydrochloric acid of either VII or VIII into IX probably proceeds by way of a $\Delta^{8,14}$-unsaturated intermediate. Because of the presence of the free carboxyl group at C 10, it is unstable and immediately forms the γ-lactone IX. One may assume that this involves the *trans*-addition of the carboxyl group to the double bond and, consequently, the hydrogen atom at carbon atom 14 is denoted as having the α-configuration.

In consideration of the ready availability of the etio acid IX and in view of the recent interest in steroid lactones as potential aldosterone-blocking agents,[8] we decided to convert IX into the corresponding analogs of progesterone (XIV) and cortexone[9] (XVI). Previously, IX had been characterized by the ethyl[10] and methyl[10,5] esters. As an additional derivative, the 3-acetate, *i.e.* 3β-acetoxy-5,8-dihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8 lactone (X) was prepared. Interestingly, IX proved quite resistant to oxidation with *N*-bromoacetamide in *t*-butyl alcohol. By oxidation

(8) *Cf.* paper quoted in Ref. 2.

(9) In agreement with the proposals of Fieser, the trivial name cortexone is preferred to 11-desoxycorticosterone. *Cf. Steroids* by Louis F. Fieser and Mary Fieser, Reinhold Publishing Corporation, New York, 1959; v. pp. 602, 706.

(10) *Cf.* paper quoted in Ref. 4.

with chromium trioxide and subsequent treatment with Girard's reagent T, IX was converted into 8-hydroxy-3-oxo-21-nor-Δ^4-17α-pregnene-19,20-dioic acid 19:8-lactone (XI), which was characterized as the methyl ester (XII). The ethyl ester has been described earlier.[5] Treatment of the acid chloride of XI with diazomethane yielded the corresponding diazoketone, *viz.* 21-diazo-8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone (XIII). By treating XIII with concentrated hydriodic acid,[11–14,6] 8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone ["19:8-Lacto-17α-progesterone"] (XIV) resulted. On the other hand, heating of XIII with acetic acid gave 21-acetoxy-8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone ["19:8-Lacto-17α-cortexone acetate"] (XV) which did not crystallize. By saponification, XV was converted into 8,21-dihydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone ["19:8-Lacto-17α-cortexone"] (XVI).

With the synthesis of 19:8-lacto-17α-progesterone (XIV) and 19:8-lacto-17α-cortexone (XVI) accomplished, it became desirable to prepare the corresponding epimers possessing at carbon atom 17 the normal, *i.e.*, the β-configurations. The logical starting material for such a project was 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid (IV) which has not been described before. We first obtained IV in amorphous form by a somewhat obscure approach. It was mentioned earlier that strophanthidin (I) may be converted into the 21:14-ketolactone III. This reaction is performed in a slightly alkaline medium by the action of potassium permanganate (*cf.* Experimental). It must be assumed that part of the material suffers further degradation leading to IV. In a first attempt to prepare IV, we subjected III to oxidation with hydrogen peroxide in a solution of acetic acid. Unfortunately, the starting material used in this experiment was not pure. Hence, it is difficult to judge whether substantial amounts of IV were present at the beginning of the experiment or whether the major part of IV resulted from the action of hydrogen peroxide on III. The identity of the amorphous IV follows from its chemical behavior as will be presented below.

Crystalline IV was obtained by a sequence of reactions using strophanthidinic acid (II) as starting material. II has been accessible from strophanthidin (I) by oxidation with potassium permanganate in a solution of acetone.[15] It can be more conveniently prepared by oxidizing I with hydrogen peroxide (*cf.* Experimental). II was subjected to ozonolysis[16] in a solution of ethyl acetate followed by reductive cleavage of the ozonide. The crude reaction product, representing the 21-glycolate of 3β,5,14,21-tetrahydroxy-20-oxo-5β,14β-pregnan-19-oic acid (XVII), was subjected to hydrolysis with potassium carbonate which furnished the crystalline ketol XVII. Oxidation of XVII with periodic acid gave crystalline IV in good yield. IV was characterized as the dimethyl ester acetate, viz. 3β-acetoxy-5,14-dihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid dimethyl ester (V), which showed the same melting point and optical rotation as a product of this structure described previously.[17] As expected, treatment of IV with concentrated hydrochloric acid gave a 19:8-lactone. It differs from IX in that the carboxyl group at C-17 possesses the β-configuration. In this instance, we also assume the formation of a $\Delta^{8,14}$-unsaturated compound as an intermediate which is followed by the *trans*-addition of the angular carboxyl group to the double bond. Hence the crystalline reaction product has to be assigned the structure of 3β,5,8-trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XVIII). The same product XVIII was obtained on using either amorphous (see above) or crystalline IV as starting material.

For the preparation of XVIII from strophanthidinic acid (II) a second pathway has been worked out. By the action of concentrated hydrochloric acid on II, Jacobs[18] obtained a compound whose correct structure was recognized by Fieser.[19] The product, namely strophanthidinic acid 19:8-lactone (XX), was subjected to ozonolysis in a solution of methylene chloride. After reductive cleavage of the ozonide, the 21-glycolate of 3β,-5,8,21-tetrahydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XXI) was subjected to hydrolysis which yielded the free crystalline ketol XXI. On oxidizing XXI with periodic acid, a product resulted which was identical with XVIII previously obtained from either amorphous or crystalline IV by treatment with concentrated hydrochloric acid. XVIII was characterized as the 3-acetate, *i.e.* 3β-acetoxy-5,8-dihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XIX).

Oxidation of XVIII with chromium trioxide and

(11) R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, **72**, 4328 (1950).

(12) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954).

(13) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 774 (1956).

(14) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 783 (1956).

(15) W. A. Jacobs, *J. Biol. Chem.*, **57**, 553 (1923).

(16) For method and literature, *cf.* Ch. Tamm, *Neuere Ergebnisse auf dem Gebiete der glykosidischen Herzgifte: Grundlagen und die Aglykone* (Progress in the Chemistry of Organic Natural Products). **13**, 137 (1956). Springer Verlag, Wien. See p. 155. *Cf.* also the more recent pertinent publication by M. Zingg and K. Meyer, *Helv. Chim. Acta*, **43**, 145 (1960).

(17) A. Buzas and T. Reichstein, *Helv. Chim. Acta*, **31**, 84 (1948).

(18) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **65**, 491 (1925); *cf.* p. 499.

(19) Louis F. Fieser and Mary Fieser, *Natural Products Related to Phenanthrene*, 3rd Edition, Reinhold, New York, 1949; v. pp. 523–524; *cf.* also book cited in Ref. 9; v. pp. 742–743.

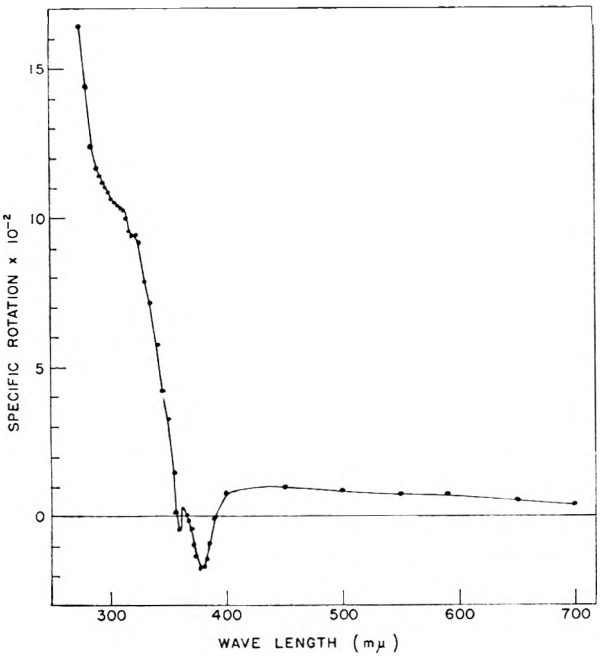


Fig. 1. Rotatory dispersion curve of 8-hydroxy-3-oxo-21-nor-Δ^1-17α-pregnene-19,20-dioic acid 19:8-lactone methyl ester (XII) (m.p. 165–166°) in dioxane (c = 0.084, 700 ~ 275 mμ)

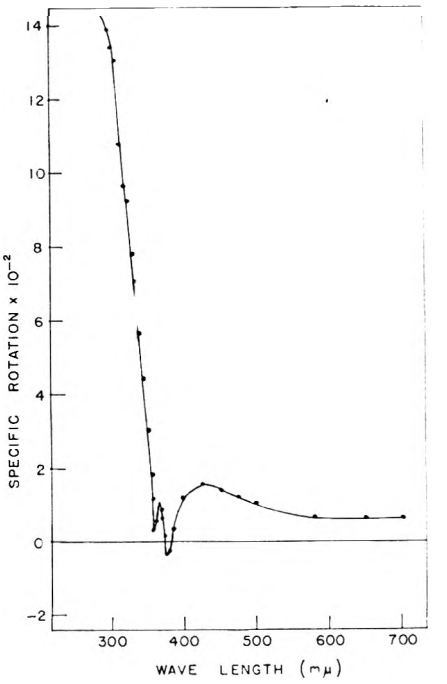


Fig. 2. Rotatory dispersion curve of 8-hydroxy-3-oxo-21-nor-Δ^4-pregnene-19,20-dioic acid 19:8 lactone (XXII) (m.p. 237–239°) in dioxane (c = 0.031, 700 ~ 300 mμ)

subsequent treatment of the reaction product with Girard's reagent T gave 8-hydroxy-3-oxo-21-nor-Δ^4-pregnene-19,20-dioic acid 19:8-lactone (XXII). On treating the acid chloride of XXII with diazomethane, 21-diazo-8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone (XXIII) was obtained. By treatment of XXIII with concentrated hydriodic acid,[11–14,6] 8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone ["19:8-Lactoprogesterone"] (XXIV) resulted in good yield. On heating XXIII with acetic acid, it was readily converted into 21-acetoxy-8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone ["19:8-Lactocortexone acetate"] (XXV) which was obtained in crystalline form.[20] Saponification of XXV with potassium carbonate gave a satisfactory yield of 8,21-dihydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone ["19:8-Lactocortexone"] (XXVI). It should be stated that, although we believe that the reported 19:8-lactones possess the 14α-configurations, this cannot be considered proven. The correlation of the molecular rotations of the corresponding compounds of the 17α- and 17β-series does not permit any definite conclusions and is therefore omitted. Further experimental work will be undertaken to prove the configurations at C-14.

In a forthcoming publication from this laboratory, dealing with 8,19-epoxy compounds, it will be necessary, for purposes of comparison to refer to the rotatory dispersion curves[21] of compounds XII (Fig. 1) and XXII (Fig. 2) which were determined through the courtesy of Professor Carl Djerassi at Wayne State University (now at Stanford University). Both curves show a *negative* multiple Cotton effect and correspond closely to that of a standard Δ^4-3-ketone[22] which does not show any major conformational distortion. As expected, the difference of the configuration at C-17 has no influence.[23]

Of particular interest are the infrared absorption curves which were obtained with the terminal products of this investigation, namely: (a) XIV and XXIV; (b) XVI and XXVI. They were determined through the courtesy of Dr. R. Norman Jones in the Division of Pure Chemistry of the National Research Council of Canada in Ottawa, Ontario, and have previously been discussed to some extent.[24] Noteworthy are the slight displacements of both the C=O and C=C stretching

(20) In an experiment performed for the purpose of orientation, treatment of XXV with selenium dioxide in a solution of *t*-butyl alcohol containing acetic acid gave a crystalline product which possibly represents 21-acetoxy-8-hydroxy-3,20-dioxo-$\Delta^{1,4}$-pregnadien-19-oic acid 19:8-lactone ["19:8-lacto-1-dehydrocortexone acetate"]; m.p. 175–176°. $[\alpha]_D^{20}$ +189° ± 9°; M_D^{20} +753° ± 36° (3.33 mg.; α + 0.63°). λ_{max}^{alc} 250 mμ, ϵ 17,000. *Anal.* Calcd. for $C_{23}H_{26}O_6$ (398.44): C, 69.33; H, 6.58. Found: C, 68.95; H, 7.50. Residue, 0.58. Corrected: C, 68.7; H 7.1.,

(21) For general literature *cf.* Carl Djerassi, *Optical Rotatory Dispersion. Applications to Organic Chemistry*, McGraw-Hill, New York, 1960.

(22) *Cf. e.g.*, Ref. 20, pp. 17, 61, 65.

(23) The authors had the privilege of discussing these aspects with Dr. W. Klyne (Postgraduate Medical School of London) on his visit to their laboratory on January 15, 1960.

(24) R. N. Jones and B. S. Gallagher, *J. Am. Chem. Soc.*, 81, 5242 (1959).

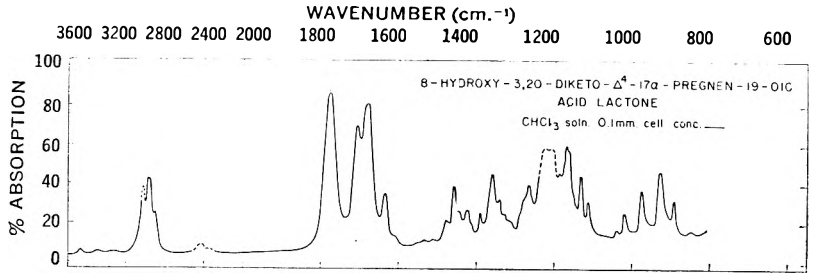


Fig. 3. Infrared spectrum of 19:8-lacto-17α-progesterone (XIV)

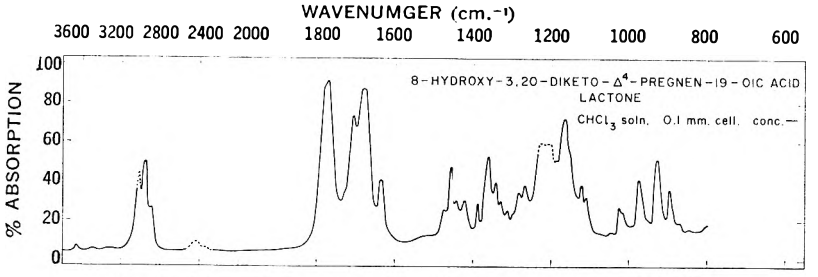


Fig. 4. Infrared spectrum of 19:8-lactoprogesterone (XXIV)

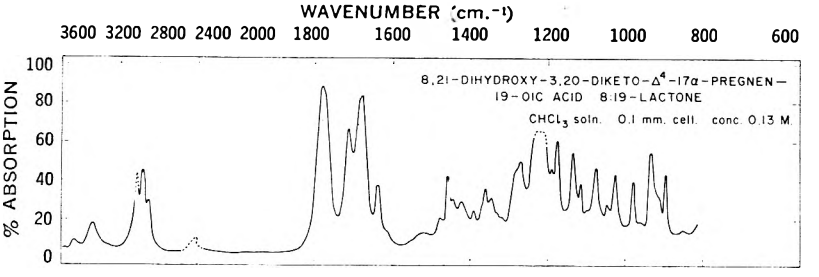


Fig. 5. Infrared spectrum of 19:8-lacto-17α-cortexone (XVI)

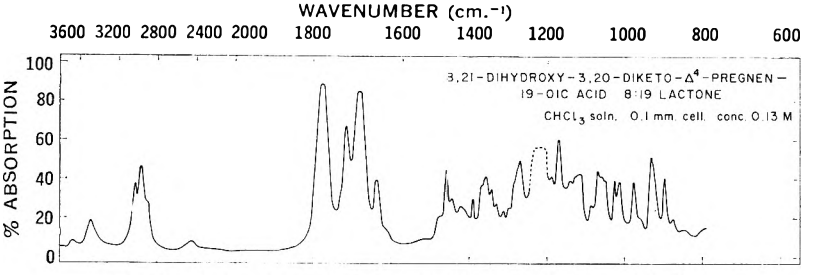


Fig. 6. Infrared spectrum of 19:8-lactocortexone (XXVI)

frequencies from their normal positions. In XIV and XXIV the carbonyl band of the Δ^4-3-ketone occurs at 1686 cm.$^{-1}$ in carbon tetrachloride solution. This is higher than the normal position at 1681–1677 cm.$^{-1}$ In chloroform solution XIV, XXIV, XVI, and XXVI absorb at 1675, 1677, 1678, and 1680 cm.$^{-1}$ respectively, while the normal range is 1668–1660 cm.$^{-1}$ The Δ^4 C=C stretching vibration is also displaced in these compounds from 1619–1613 to 1635 cm.$^{-1}$ (chloroform solution). It would appear therefore that the bridging of ring B by the lactone group increases the rigidity of the A/B ring system and so induces steric strains in the conjugated ketone structure. Dipole-dipole interactions between the two carbonyl groups could also raise the ketone and C=C stretching frequencies, but if this were so, the γ-lactone carbonyl frequency (observed for XIV, XXIV, XVI, and XXVI, in chloroform: 1772, 1772, 1777, and 1775 cm.$^{-1}$, respectively) would also be affected.

The infrared spectra of compounds XIV, XXIV, XVI, and XXVI, measured in chloroform on the Perkin Elmer Model 21 spectrophotometer, are presented in Figs. 3, 4, 5, and 6, respectively.[25] "It is interesting that there are small but still significant changes in the fingerprint regions of the spectra associated with isomerism at C 17. The main differences are:

(25) *Cf.* also: C. L. Angell, B. S. Gallagher, T. Ito, R. J. D. Smith, and R. N. Jones: *The Infrared Spectra of Lactones*, National Research Council Bulletin No. 7, Ottawa 1960; v. charts 51, 50, 53, 52.

(a) Compound XIV (Fig. 3)	Compound XXIV (Fig. 4)
1134 cm.$^{-1}$	1124 cm.$^{-1}$
1114	1110
1018	1022
890	894

(b) Compound XVI (Fig. 5)	Compound XXVI (Fig. 6)
1135 cm.$^{-1}$ singlet	1150–1110 cm.$^{-1}$ complex band group
1075 singlet	1070, 1058, 1050 triplet
—	1012 extra band

At the present state of our knowledge it is not possible to interpret these differences. They are interesting, however, in that they emphasize the importance of paying attention to small spectral differences when using the "fingerprint" spectra for identification purposes."[26]

Physiological activity. Bioassays for progestational activity were carried out by Dr. Roy Hertz, Chief of the Endocrinology Branch of the National Cancer Institute. With 19:8-lacto-17α-progesterone (XIV) the Clauberg test was negative in each of two rabbits with a total dose of 2.5 mg. With 19:8-lactoprogesterone (XXIV) a dosage level of 1.0 mg. per rabbit (two animals) was totally inactive. Since in this assay a maximal effect is obtained with 0.25 mg. of progesterone, the activities of XIV and XXIV, if any, are probably less than one-tenth that of progesterone.

19:8-Lacto-17α-cortexone (XVI) was tested for mineralocorticoid activity by two different groups. (1) In bioassays performed by Dr. Amos H. Lieberman in the laboratory of Dr. John A. Luetscher, Jr., at Stanford University School of Medicine, no sodium retaining or potassium excreting activity was noted in a dose of 30 μg. As rats are usually sensitive to as little as one microgram of cortexone or cortexone acetate,[27] these bioassays show that the mineralocorticoid activity of XVI, if any, is less than one-thirtieth that of cortexone acetate. (2) In assays conducted at the Worcester Foundation for Experimental Biology by Dr. Ralph I. Dorfman, XVI, in doses of 25 and 50 μg., had no significant effect on the excretion of sodium or potassium in salt (sodium chloride) loaded adrenalectomized rats.[28] 19:8-Lactocortexone (XXVI) was bioassayed through the courtesy of Dr. Ralph I. Dorfman in the same fashion. In doses of 6 and 50 μg., XXVI had no effect on the excretion of sodium or potassium. On the basis of these findings it appears that both XVI and XXVI are devoid of mineralocorticoid activity.

(26) The sentences in quotation marks are comments supplied by Dr. R. Norman Jones.

(27) *Cf.* e.g. John A. Luetscher, Jr., and Quentin B. Deming: "Bioassay of sodium-retaining corticoids and some changes in excretion of these substances in disease" in *Renal Function*, Transactions of the Second Conference, 155–178, Josiah Macy, Jr., Foundation, New York, 1951, v. p. 159.

(28) The 6 μg. dose level seemed to have caused minimum sodium excretion, an observation which has to be studied further.

EXPERIMENTAL

Melting points. The melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected.

Absorption spectra. Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU Spectrophotometer.

Analyses. Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide; 80°) according to Milner and Sherman.[29] The percentage loss of weight on drying is recorded; there was in no instance a gain of weight on exposure of the dried sample to the atmosphere.

Optical rotation. No correction for crystal solvent has been made. The sample was dissolved in chloroform to make 2 cc. of solution and the rotation was determined in a 2-dm. semimicro tube.

Chromatography. The alumina,[12] silica gel,[12] and Florisil[30] used as adsorbents for chromatography have been described.

3β,5,14-Trihydroxy-20-oxo-5β,14β-pregnane-19,21-dioic acid 21:14-lactone (III) *from strophanthidin* (I).[31] Crystalline strophanthidin (I) was converted, in 10-g. batches, into brittle foam by dissolving in acetone and evaporating to dryness *in vacuo*. The foam was suspended in 1000 cc. of 0.1*N* aqueous sodium hydroxide and 250 cc. of 5% potassium permanganate solution was added dropwise while vigorous stirring was maintained. The addition required 1 hr., after which 20 cc. of 6*N* hydrochloric acid was added, and the manganese dioxide was filtered by suction and washed with hot water. The filtrate was concentrated *in vacuo* to a volume of approximately 75 cc. and 25 cc. of 6*N* hydrochloric acid was added. After 2 days in the icebox, the resulting precipitate was filtered, washed with water, and dried. The tan powder, thus isolated, was suspended in a mixture of 10 cc. of acetone and 20 cc. of ether. After standing in the icebox overnight, filtration yielded from 3.56 g. to 3.92 g. of crude III as a white powder. The material obtained in this way from 38.376 g. of strophanthidin (I) was repeatedly recrystallized from methanol to give a total of 12.739 g. (yield, 34.2%) of crystalline III with melting points above 270°.

3β,5,14-Trihydroxy-20-oxo-5β,14β,17α-pregnane-19,21-dioic acid (VI) *from 3β,5,14-trihydroxy-20-oxo-5β,14β-pregnane-19,21-dioic acid 21:14-lactone* (III). A total of 100 mg. of III, m.p. 270–272°, dissolved in 5 cc. of 2% aqueous sodium hydroxide, was heated on a steam bath for 45 min. After standing at room temperature overnight, the solution was acidified to Congo Red with 6*N* hydrochloric acid (no precipitate) and was then extracted with five 25-cc. portions of ethyl acetate. After drying over sodium sulfate and evaporating the solvent, 110.5 mg. of a solid white residue resulted. Crystallization from acetone-ether gave 78.4 mg. of minute needles, m.p. 180–182° (foaming), representing 3β,5,14-trihydroxy-20-oxo-5β,14β,17α-pregnane-19,21-dioic acid (VI). By recrystallization from methanol-ether the m.p. was raised to 184° (foaming).

3β,5,14-Trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid (VII) *from 3β,5,14-trihydroxy-20-oxo-5β,14β-pregnane-19,21-dioic acid 21:14-lactone* (III).[32] The purity of the

(29) R. T. Milner and M. S. Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).

(30) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **20**, 1253 (1955).

(31) For alternate method, using strophanthidin acetate as starting material, *cf.* Ref. 6, p. 101.

(32) *Cf.* also Ref. 6, p. 101.

starting material (III) is of crucial importance in that the yield of VII is drastically reduced when samples of III melting below 270° are employed. A solution of 6.021 g. of III, m.p. 273–275°, in 120 cc. of 2% aqueous sodium hydroxide was left at room temperature overnight, and 60 cc. of 30% hydrogen peroxide was then added. After 2 more days, 100 cc. of *N* sulfuric acid was added, whereupon VII began to crystallize slowly. After 2 more days at room temperature and a night in the icebox, the product (prisms) was filtered and washed with water. The yield was 4.348 g. (76%) of VII, m.p. 275–278°.

3β-Acetoxy-5,14-dihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid dimethyl ester (VIIa) *from 3β,5,14-trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid* (VII). To a suspension of 20 mg. of VII, m.p. 275–276°, in 2 cc. of acetone was added an excess of ethereal diazomethane. On evaporating to dryness, a crystalline residue was obtained which was dissolved in 1 cc. of pyridine and then 0.5 cc. of acetic anhydride was added. After standing overnight, 10 cc. of 3*N* hydrochloric acid was added and the reaction product was isolated in the usual fashion. Yield of crude crystalline material: 24.7 mg. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 18.5 mg. of colorless prisms, m.p. 182–184°. Renewed crystallization from acetone-water raised the m.p. to 186° (sharp). $[\alpha]_D^{21}$ +18° ± 2°; M_D^{21} +82° ± 9° (10.45 mg., α + 0.19°). Lit.[17]: m.p. 183–185°. $[\alpha]_D^{20}$ +20.4° ± 2° (chloroform).

3β,5,8-Trihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone (IX) *from 3β,5,14-trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid* (VII).[32] To 548.6 mg. of VII, m.p. 270–272°, was added 25 cc. of concd. hydrochloric acid. After standing overnight, the resulting solution was diluted with 100 cc. of water and extracted with four 100-cc. portions of ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*, leaving 548.6 mg. of a yellow crystalline residue. Repeated recrystallization from methanol-ether gave 252.1 mg. of IX; sparkling colorless prisms, m.p. 307–308°. The product was identical with material prepared by treatment of 3β,5-dihydroxy-21-nor-Δ^{14}-5β,17α-pregnene-19,20-dioic acid (VIII) with hydrochloric acid.[5]

3β-Acetoxy-5,8-dihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone (X) *from 3β,5,8-trihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone* (IX). A solution of 50 mg. of IX, m.p. 308–309°, in 2 cc. of pyridine and 1 cc. of acetic anhydride was left at room temperature. After 18 hr., 20 cc. of 3*N* hydrochloric acid was added, and after 15 min., the mixture was extracted with ethyl acetate. The extract was washed with 3*N* hydrochloric acid and with water and was then dried over sodium sulfate and evaporated *in vacuo*, yielding a crystalline residue; wt. 59.0 mg. Recrystallization from acetone-hexane and twice from acetone-water gave 48.1 mg. of X as colorless needles, m.p. 258–259°. $[\alpha]_D^{21}$ +47° ± 4°; M_D^{21} +191° ± 16° (11.04 mg., α + 0.52°).

Anal. Calcd. for $C_{22}H_{30}O_7$ (406.46): C, 65.00; H, 7.44. Found: C, 64.96; H, 7.54. Weight loss, 3.98.

8-Hydroxy-3-oxo-21-nor-Δ^4-17α-pregnene-19,20-dioic acid 19:8-lactone (XI) *from 3β,5,8-trihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone* (IX). To 487.7 mg. of IX, m.p. 305–307°, in 25 cc. of glacial acetic acid, a solution of 98 mg. of chromic anhydride (10% excess) in 50 cc. of 90% acetic acid was added in five 10-cc. portions at half-hour intervals. After standing at room temperature overnight, the reaction mixture was evaporated *in vacuo*, and the residue was taken up in ethyl acetate. After washing the solution with *N* sulfuric acid and water, it was dried over sodium sulfate and evaporated to dryness, leaving 427.1 mg. of a colorless crystalline residue. This was dissolved in 10 cc. of absolute ethanol, 1 g. of Girard's reagent T, and 1 cc. of glacial acetic acid were added, and the mixture was refluxed for 1 hr. Dilution to 100 cc. with water and extraction with ethyl acetate yielded 61.4 mg. of amorphous nonketonic material. The aqueous phase was acidified to approximately 1*N* by the addition of hydrochloric acid and was left overnight. Extraction with ethyl acetate produced 333.0 mg. of slightly brown crystalline ketonic material. The ketonic fraction was combined with 58.9 mg. of ketonic material obtained from another run, and the total of 391.9 mg. was chromatographed over 20 g. of silica gel (18 × 105 mm.). Pure chloroform first eluted small amounts of two resinous colored impurities, which were followed by 364 mg. of colorless crystalline XI. Recrystallization from acetone-ether and acetone-water gave the analytical sample as long slender needles, m.p. 232–236° when heated from room temperature. When placed on the melting point block at 210°, the crystals melted at once with bubbling, promptly resolidified, and then melted at 236–238°. $[\alpha]_D^{22}$ +83.5° ± 2°; M_D^{22} +289° ± 7° (10.06 mg. in 2.0 cc. of chloroform containing 5 drops of ethanol, α + 0.84°). λ_{max}^{alc} 244 mμ, ε 13,300.

Anal. Calcd. for $C_{20}H_{24}O_5$ (344.39): C, 69.75; H, 7.02. Found: C, 69.80; H, 7.16. Weight loss, 6.67.

8-Hydroxy-3-oxo-21-nor-Δ^4-17α-pregnene-19,20-dioic acid 19:8-lactone methyl ester (XII). To 52.7 mg. of XI, m.p. 230–235°, in 2 cc. of acetone was added an exce ss of ethereal diazomethane. After standing 10 min., the solution was evaporated to dryness. Recrystallization of the residue from acetone-hexane gave 36.8 mg. of clusters of yellow needles, m.p. 160–162°. This product was recrystallized several times alternately from acetone-water and acetone-hexane to give 24.1 mg. of colorless, long, slender needles, m.p. 165–166°. $[\alpha]_D^{21}$ +77° ± 3°; M_D^{21} +276° ± 11° (11.67 mg., α + 0.90°). λ_{max}^{alc} 244 mμ, ε 13,600.

Anal. Calcd. for $C_{21}H_{26}O_5$ (358.42): C, 70.37; H, 7.31. Found: C, 70.13; H, 7.35.

21-Diazo-8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone (XIII) *from 8-hydroxy-3-oxo-21-nor-Δ^4-17α-pregnene-19,20-dioic acid 19:8-lactone* (XI). To a solution of 198.8 mg. of XI, m.p. 229–231°, in 10 cc. of ethanol was added 48.5 mg. of sodium bicarbonate in 1 cc. of water. The mixture was frozen and evaporated *in vacuo*, and the residue was thoroughly dried and suspended in a mixture of 10 cc. of dry benzene and 5 drops of pyridine. This was cooled in ice until partly frozen, and 1 cc. of oxalyl chloride was added. After standing for 15 min., the mixture was frozen and evaporated to dryness *in vacuo*. The residue was dissolved in 10 cc. of dry benzene and the solution was brought to dryness from the frozen state. Finally, the odorless residue was taken up in 10 cc. of dry benzene, and the suspension was filtered through sintered glass under nitrogen pressure into ethereal diazomethane which had been freshly prepared from 8 g. of methylnitrosourea[33] and dried over sodium. The residue of salts was washed with two 5-cc. portions of dry benzene, and the reaction mixture was left at room temperature for 1 hr. and was then evaporated to dryness *in vacuo*. The yellow solid residue was taken up in 100 cc. of ethyl acetate, and the solution was washed with *N* sodium carbonate, dried over sodium sulfate and evaporated, yielding 217.3 mg. of yellow foam. This was chromatographed on 20 g. of alumina (activity I–II, 18 × 80 mm.). Benzene-ether, range 19:1 to 2:3, eluted a total of 127.6 mg. of crystalline fractions of XIII. Successive recrystallization from acetone-ether and acetone-water gave the analytical sample as long, slender, pale-yellow needles with no clearly defined melting point. The crystals decrepitated at 145–150° to give a powder which sintered at 195–200° but never really liquefied. $[\alpha]_D^{25}$ +38° ± 2°; M_D^{25} +141° ± 8° (10.21 mg., α + 0.39°). λ_{max}^{alc} 247 mμ, ε 23,400.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C,[34] 67.94; H,[34] 6.69; N,[35] 7.67. Residue, 0.14. Weight loss, 0.41.

In repeated runs of this experiment, the chromatographic purification occasionally yielded a second, more polar

(33) A. H. Blatt, *Org. Syntheses*, **Coll. Vol. II**, 165, 461 (1943).

(34) Dried at 70°.

(35) Not dried.

product; recrystallization from acetone-hexane and acetone-water; colorless elongated prisms, m.p. 288–289°. Possibly this represents the amide of the starting material XI.[36]

Anal. Calcd. for $C_{20}H_{25}NO_4$ (343.41): C, 69.94; H, 7.34; N, 4.08. Found: C, 70.10; H, 7.56; N, 4.54.

8-Hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone [*"19:8-Lacto-17α-progesterone"*] (XIV) *from 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone* (XIII). A solution of 50 mg. of the analytical sample of the diazo ketone XIII in 20 cc. of chloroform was shaken for 2 min. with 2 cc. of 48% hydriodic acid (Baker's Analyzed Reagent). The chloroform layer was then shaken successively with three 5-cc. portions of saturated aqueous sodium iodide and with 5 cc. of *N* sodium thiosulfate. After drying over sodium sulfate, the chloroform was evaporated *in vacuo*, leaving 50.1 mg. of colorless needles. Recrystallization from acetone-hexane gave 45.1 mg. of needles of m.p. 204–205°. Renewed recrystallization from acetone-water yielded 40 mg. of XIV as fan-shaped clusters of flat needles, m.p. 204–205°. $[\alpha]_D^{25}$ +49° ± 2°; M_D^{25} +168° ± 6° (10.83 mg., α + 0.53°). λ_{max}^{alc} 243 mμ, ϵ 15,900.

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.65. Found: C, 73.33; H, 7.58.

8,21-Dihydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone [*"19:8-Lacto-17α-cortexone"*] (XVI) *from 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone* (XIII). A solution of 110.4 mg. of the diazoketone XIII, m.p. 205–210°, in 10 cc. of glacial acetic acid was heated on the steam bath for 1 hr. Evaporation to dryness *in vacuo* gave a brownish amorphous residue, representing crude 21-acetoxy-8-hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic acid 19:8-lactone ["19:8-lacto-17α-cortexone acetate"] (XV).[37] This was dissolved in 3 cc. of methylene chloride, and 7.5 cc. of 0.05*M* potassium carbonate in 75% aqueous methanol was added.[38] After standing for 15 min., the reaction mixture was diluted with 40 cc. of water and extracted with four 50-cc. portions of ethyl acetate. After drying the extract over sodium sulfate, evaporation left 89.8 mg. of yellow crystalline residue. This was chromatographed over 10 g. of Florisil (18 × 90 mm.). Chloroform containing from 3% to 16% of acetone, eluted a total of 71.8 mg. of crystalline XVI with melting points in the range 188–208°. Recrystallization from acetone-hexane and then from acetone-water gave colorless needles, m.p. 206–207°. $[\alpha]_D^{21}$ +60° ± 6°; M_D^{21} +215° ± 20° (11.21 mg., α + 0.67°). λ_{max}^{alc} 244 mμ, ϵ 13,300.

Anal. Calcd. for $C_{21}H_{26}O_5$ (358.42): C, 70.37; H, 7.31. Found: C, 70.06,[39] 69.93[40]; H, 7.40,[39] 7.43.[40] Residue: 0.23.[40]

3β,5,14,21-Tetrahydroxy-20-oxo-5β,14β-pregnan-19-oic acid (XVII) *from strophanthidinic acid* (II). A solution of 975 mg. of crystalline II[15] (colorless prisms; m.p. 160–175°) in 200 cc. of ethyl acetate was cooled in Dry Ice–acetone and oxygen containing approx. 2.5% of ozone was passed in until a permanent deep blue color was obtained. After standing at Dry Ice–acetone temperature for 30 min., the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 10 cc. of glacial acetic acid, zinc dust was added, and the mixture was heated gently and swirled until a starch-iodide test was negative. The mixture was filtered, the residue was washed with acetic acid, and the filtrate was evaporated *in vacuo*, leaving 1.150 g. of colorless brittle foam. This was taken up in 100 cc. of 0.1*N* potassium carbonate in 75% methanol. After 15 min., this solution was barely acidified to Congo Red with hydrochloric acid, and sodium chloride was added to saturation. Extraction with twenty 100-cc. portions of ethyl acetate yielded 782 mg. of colorless foam which was leached with several portions (total: 10 cc.) of hot water, leaving a small amount of yellow resin. Evaporation of the aqueous extract left 728 mg. of crude XVII. Crystallization from acetone-ether and recrystallization from methanol-ether gave 201 mg. of colorless granules, m.p. 235–237° with effervescence. Chromatography of the mother liquor material on 100 g. of silica gel gave only 84 mg. more of crystalline material. The analytical sample (colorless prisms) melted at 235–237° with effervescence when heated from room temperature and at 238–239° when placed on the block at 230°. $[\alpha]_D^{24}$ +41° ± 3°; M_D^{24} +163° ± 12° (10.44 mg. in 2.0 cc. of chloroform containing 10% of ethanol, α + 0.43°).

Anal. Calcd. for $C_{21}H_{32}O_7$ (396.47): C, 63.62; H, 8.14. Found: C, 63.50; H, 8.12.

3β,5,14-Trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid (IV). A. *From a mixture of products containing 3β,5,14-trihydroxy-20-oxo-5β,14β-pregnane-19,20-dioic acid 21:14-lactone* (III). To a solution of 6.833 g. of impure III, m.p.'s below 200°, in 100 cc. of glacial acetic acid was added 50 cc. of 30% hydrogen peroxide. After standing for 2 weeks, the reaction mixture was concentrated *in vacuo* to about 25 cc., diluted to 200 cc. with water, and extracted with five 200-cc. portions of ethyl acetate. The ethyl acetate extract was washed with water and with saturated aqueous sodium chloride and was then dried and evaporated *in vacuo*, leaving 5.663 g. of yellow foam. This was combined with 3.824 g. of material obtained in exactly the same way from 4.544 g. of pure III, m.p.'s 269–271° and 266–269°, and the total (9.487 g.) was chromatographed on 200 g. of silica gel (38 × 285 mm.). Chloroform containing from 1% to 10% of acetone eluted only traces of yellow resin. Chloroform containing from 12% to 80% of acetone eluted a total of 8.590 g. of colorless foam in a single broad peak. The center fractions of the peak were combined (5.685 g.). Paper chromatographic examination in the system toluene–propylene glycol revealed the presence of a contaminant which was assumed to be the 3-acetate, so this material was dissolved in 10 cc. of 95% ethanol and 100 cc. of *N* ethanolic potassium hydroxide was added. After standing overnight, concentration *in vacuo*, dilution with water, and acidification, thorough extraction with ethyl acetate yielded 4.990 g. of yellow foam. This was chromatographed on 200 g. of silica gel (38 × 270 mm.). Chloroform containing from 20% to 40% of acetone eluted 4.299 g. as a single, fairly sharp peak (twelve 500-cc. fractions). Most of this material resisted all attempts at crystallization, but it was assumed to consist essentially of the desired IV, as treatment with concentrated hydrochloric acid yielded 19:8-lactone XVIII (see below).

From two of the center fractions of the above peak, a crystalline product was obtained, and repeated recrystallization from methanol-ether gave 438 mg. of clusters of glistening prisms, m.p. 223–225° with foaming, following decrepitation at 195–210°. $[\alpha]_D^{25}$ +3° ± 2° (10.35 mg. in 2.0 cc. of 95% ethanol, α + 0.03°). *Anal.* Found: C, 62.22; H, 7.20. This was first thought to be IV, but it was quite different from authentic IV, subsequently prepared from 3β,5,14,21-tetrahydroxy-20-oxo-5β,14β-pregnan-19-oic acid (XVII) (*cf.* B), and treatment with concentrated hydrochloric acid gave a product (m.p. 263–264°. *Anal.* Found: C, 63.52; H, 6.90. Weight loss, 3.76. Dried at room temp.) which was not identical with the 19:8-lactone XVIII.

B. *From 3β,5,14,21-tetrahydroxy-20-oxo-5β,14β-pregnan-19-oic acid* (XVII). To a suspension of 50 mg. of XVII, m.p. 235–237°, in 5 cc. of water was added a solution of 43 mg. of periodic acid (H_5IO_6) in 5 cc. water. After 3 days, the crystals had disappeared and the solution was extracted with five portions of 50 cc. of ethyl acetate, yielding 46 mg. of colorless foam. Three successive crystallizations from acetone-hexane gave 40.3 mg. of IV as clusters of needles.

(36) For a similar observation *cf.* Ref. 12.

(37) In a preliminary experiment, 50 mg. of XIII furnished 49.0 mg. of crude XV. Chromatography over 5 g. of Florisil gave, by eluting with chloroform, 33.1 mg. of a colorless resin, representing pure XV. All attempts at crystallization failed.

(38) For method, *cf.* J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291, v. p. 2319 (1957).

(39) Dried at room temperature.

(40) Dried at 100°.

The crystals foamed without melting at approximately 125–135° and the resulting solid foam melted at 179–181°. $[\alpha]_D^{24}$ +3° ± 2°; M_D^{24} +11° ± 8° (10.74 mg. in 2 cc. of chloroform containing 5% of ethanol, α + 0.03°).

Anal. Calcd. for $C_{20}H_{30}O_7$ (382.44): C, 62.81; H, 7.91. Found: C, 62.34; H, 8.43. Weight loss, 2.36.

3β-Acetoxy-5,14-dihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid dimethyl ester (V) *from 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid* (IV). To approximately 20 mg. of IV, m.p. 179–181° (*cf.* preceding expt.), in 2 cc. of acetone was added an excess of freshly prepared ethereal diazomethane. After 5 min., the solution was evaporated to dryness, leaving a partly crystalline resin. This was dissolved in 1 cc. of pyridine and, after the addition of 0.5 cc. of acetic anhydride, the solution was kept overnight. Subsequently, 10 cc. of 3*N* hydrochloric acid was added and, after standing for 15 min., the mixture was extracted with four 25-cc. portions of ether. The ether extract was washed with *N* hydrochloric acid, water, and a saturated aqueous solution of sodium chloride. After drying, the ether was evaporated, leaving 22.8 mg. of a crystalline residue. Recrystallization from ether–petroleum ether and acetone-water gave 12.0 mg. of transparent rods; m.p. 165° (sharp). $[\alpha]_D^{21}$ + 78° ± 2°; M_D^{21} +355° ± 9° (7.90 mg., α + 0.62°). Lit.[17]: m.p. 164–165°. $[\alpha]_D^{15}$ +72.9° ± 2° (chloroform).

Strophanthidinic acid 19:8-lactone (XX) *from strophanthidinic acid* (II).[18] A solution of 500 mg. of II,[41] m.p. 180–185°, in 5 cc. of methanol was evaporated *in vacuo* to form a brittle foam which quickly dissolved on adding 10 cc. of concd. hydrochloric acid. The solution was allowed to stand overnight whereby it turned yellow. Subsequent dilution with water to a volume of 100 cc. produced a flocculant precipitate which was removed by filtration. The filtrate was extracted with four 100-cc. portions of ethyl acetate and the extract was then washed with water and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation to dryness gave 403.4 mg. of a colorless crystalline residue. On recrystallizing repeatedly from acetone–petroleum ether and acetone-water, finally 276.1 mg. of XX resulted as colorless transparent plates; m.p. 225–230°, when placed on block at room temperature; m.p. 234–236° when placed on block at 220°. Legal test positive. Lit.[18]: m.p. 235–236°.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.47): C, 68.63; H, 7.51. Found: C, 68.74; H, 7.52. Weight loss, 3.83.

3β,5,8,21-Tetrahydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XXI) *from strophanthidinic acid 19:8-lactone* (XX). A solution of 898 mg. of XX, m.p. 238–240°, in 100 cc. of methylene chloride was cooled in a salt-ice bath (approximately −20°).[42] A stream of oxygen containing approx. 2.5% of ozone was passed through for 1 hr., after which time the solution had assumed a persisting, although not very intense, blue color. After allowing it to warm to room temperature, 10 cc. of glacial acetic acid and 1 g. of zinc dust were added, and the mixture was stirred and heated on a steam bath until the starch-iodide test had become negative (approximately 1 hr.). Filtration, washing of the solids with acetone, and evaporation of the filtrate to dryness gave a residue which was taken up in acetone. After renewed filtering and evaporating to dryness, 925.8 mg. of a colorless foam resulted. This was taken up in 10 cc. of ethanol and 200 cc. of ethyl acetate and the solution was shaken with three 10-cc. portions of *N* sodium carbonate and then with 10 cc. each of water and saturated aqueous sodium chloride. The aqueous phases were re-extracted with ethyl acetate. From the carbonate phase was isolated in the usual fashion 61.8 mg. of acidic material representing a yellow resin. The combined ethyl acetate extracts yielded, after drying and evaporating to dryness, 669.5 mg. of neutral product as colorless foam.

One-fourth of the neutral material was taken up in 10 cc. of methanol, followed by the addition of 10 cc. of 0.1*M* potassium carbonate in 50% methanol. After standing for 1 hr., 20 cc. of water was added and the mixture was extracted with three 100-cc. portions of ethyl acetate. The ethyl acetate extracts were washed with *N* sodium carbonate and with water. From the aqueous phases was isolated in the usual fashion 46.3 mg. of acidic material as a yellow resin. The ethyl acetate phase yielded, after drying and evaporating to dryness, 109.3 mg. of neutral product as colorless resin. Crystallization from acetone-ether gave 50.1 mg. of yellowish prisms, m.p. 220–224°, which produced rapidly a positive blue tetrazolium test. By repeated recrystallizations from acetone-ether and acetone-hexane the m.p. was raised to 229–231°. $[\alpha]_D^{18}$ +126° ± 3°; M_D^{18} +477° ± 12° (17.45 mg. in 2.0 cc. of chloroform containing 5 drops of ethanol, α + 2.20°).

Anal. Calcd. for $C_{21}H_{30}O_6$ (378.45): C, 66.64; H, 7.99. Found[43]: C, 66.75; H, 8.34.

3β,5,8-Trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XVIII). A. *From amorphous 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid* (IV). The amorphous material from the reaction of impure III with hydrogen peroxide in acetic acid (see above), 3.652 g. of pale yellow foam dissolved at once on addition of 25 cc. of concd. hydrochloric acid. After standing overnight, dilution with 175 cc. of water and extraction with six 200-cc. portions of ethyl acetate, 3.370 g. of brown brittle foam was obtained. This was chromatographed on 200 g. of silica gel (38 × 280 mm.). Chloroform containing up to 10% of acetone eluted 563.4 mg. of resinous material which could not be crystallized. Chloroform containing 10% to 50% of acetone then eluted 2.581 g. of material as a single broad peak of twenty 500-cc. fractions. On dissolving in acetone and adding ether, eleven of these fractions, totaling 1.932 g. crystallized. Recrystallization from acetone-ether-hexane gave a total of 1.089 g. of crystalline fractions with melting points in the range 260–270°. These fractions were combined and recrystallized from acetone-ether to give 840.4 mg. of colorless prisms, m.p. 272–274°. The analytical sample melted at 273–274° (effervescence). $[\alpha]_D^{24}$ +107° ± 2°; M_D^{24} +391° ± 8° (9.50 mg. in 2.0 cc. of 95% ethanol, α + 1.02°).

Anal. Calcd. for $C_{20}H_{28}O_6$ (364.42): C, 65.91; H, 7.75. Found: C, 65.51; H, 7.64.

B. *From crystalline 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid* (IV). A solution of 19.2 mg. of crystalline IV, m.p. 176–180°, in acetone was evaporated *in vacuo* yielding a white foam to which was added 1 cc. of concd. hydrochloric acid. After standing overnight, the yellow solution was diluted with 9 cc. of water, whereby it became colorless. It was then extracted with five 25-cc. portions of ethyl acetate and the combined extracts were washed with water and saturated aqueous sodium chloride. After drying and evaporating the solvent, 17.3 mg. of a colorless resin resulted which crystallized from acetone-ether-hexane; 13.9 mg. of yellowish crystals, m.p. 268–271°. The solution of the latter in acetone was decolorized by treatment with Norit. Addition of ether to the filtered and concentrated

(41) The strophanthidinic acid (II) used in this experiment was prepared from strophanthidin (I) by a new method as follows: To 1 g. of crystalline I in 10 cc. of methanol were added 2 cc. of 30% hydrogen peroxide and 2 drops of saturated aqueous ferrous ammonium sulfate. After standing for 4 days, the mixture was worked up by partitioning between *M* sodium carbonate and ethyl acetate. The ethyl acetate phase yielded 236.2 mg. of neutral material. From the carbonate phase resulted 827.4 mg. of acidic product which was recrystallized from acetone-water, yielding 530.3 mg. of II as colorless prisms, m.p. 180–185° (effervescence); Legal test positive.

(42) In a preliminary experiment the solution was cooled in Dry Ice–acetone, but the ozonization did not proceed well. For the use of methylene chloride as an ozonolysis solvent, *cf.* G. Slomp, *J. Org. Chem.*, 22, 1277 (1957).

(43) Dried at 60°.

solution gave colorless rods of constant m.p. 277° (sharp). The mixture m.p. with the preceding analytical sample (method A) was 275–277°.

C. *From 3β,5,8,21-tetrahydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone* (XXI). A total of 17.4 mg. of XXI, m.p. 229–231°, was suspended in a solution of 80 mg. of periodic acid (H_5IO_6) in 2 cc. of water. After standing for 3 days, all crystals had disappeared. An amount of solid sodium bicarbonate was added to the clear solution sufficient to produce alkalinity to litmus. Extraction with ethyl acetate yielded no neutral product. The combined aqueous phases were acidified to Congo Red and the acid material was extracted with four 10-cc. portions of ethyl acetate. After drying and evaporating the combined extracts, 16.3 mg. of a crystalline residue was obtained. Recrystallization from acetone-hexane gave 14.8 mg. of minute granular crystals, m.p. 271–274°. The mixture melting point with the analytical sample (method A) was 271–274°.

Infrared analysis[44]: The sample obtained by method C was compared with the analytical sample obtained by method A. These substances produced identical spectra in the following regions, 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$, 1500–1280 cm.$^{-1}$, 1400–650 cm.$^{-1}$ The spectra were obtained from potassium bromide disks using Perkin-Elmer Spectrophotometers (Model 21) with sodium chloride and calcium fluoride prisms.

3β-Acetoxy-5,8-dihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XIX) *from 3β,5,8-trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone* (XVIII). A solution of 50 mg. of XVIII, m.p. 273–274° (analytical sample, prepared by method A; see above), in 2 cc. of pyridine and 1 cc. of acetic anhydride was left at room temperature for 44 hr. Addition of 50 cc. of 3*N* hydrochloric acid was followed, after 15 min., by extraction with ethyl acetate. After washing with 3*N* hydrochloric acid and with water, the ethyl acetate extract was dried and evaporated *in vacuo*, leaving 49.1 mg. of crystalline residue. Recrystallization from acetone-hexane and then from acetone-water gave 30.1 mg. of XIX as fan-like clusters of needles, m.p. 274° (sharp), depressed on admixture with XVIII. $[\alpha]_D^{24}$ +93° ± 2°; M_D^{24} +379° ± 8° (10.73 mg., α 1.00°).

Anal. Calcd. for $C_{22}H_{30}O_7$ (406.46): C, 65.00; H, 7.44. Found: C, 64.97; H, 7.38. Weight loss, 0.42.

8-Hydroxy-3-oxo-21-nor-Δ⁴-pregnene-19,20-dioic acid 19:8-lactone (XXII) *from 3β,5,8-trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone* (XVIII). A solution of 10 mg. of chromic anhydride in 5 cc. of 90% acetic acid was added, in five 1-cc. portions at half-hour intervals, to 50 mg. of XVIII, m.p. 274–275° (prepared by method A; see above), dissolved in 5 cc. of glacial acetic acid. After standing for 4 days, the reaction mixture was evaporated *in vacuo*. The residue was taken up in ethyl acetate and washed with *N* sulfuric acid and with water. Drying and evaporation of the ethyl acetate left 50 mg. of colorless crystalline residue. To this were added 5 cc. of absolute ethanol, 100 mg. of Girard's reagent T and 0.5 cc. of glacial acetic acid. After refluxing for 1 hr., the solution was diluted with ice water to 50 cc. and extracted with ethyl acetate, yielding 10.2 mg. of resinous, nonketonic material. The aqueous phase was made acid to approximately *p*H 1 by the addition of 5 cc. of concd. hydrochloric acid. After standing overnight, extraction with ethyl acetate yielded 33.4 mg. of crystalline ketonic fraction. Successive recrystallization from acetone-ether and acetone-water gave 16.9 mg. of XXII as long, slender, shining needles, m.p. 237–239° (heated from 230°), depressed on admixture with XI. $[\alpha]_D^{24}$ +110° ± 2°; M_D^{24} +379° ± 8° (7.89 mg., α + 0.87°). λ_{max}^{alc} 244 mμ, ε 13800.

Anal. Calcd. for $C_{20}H_{24}O_5$ (344.39): C, 69.75; H, 7.02. Found: C, 69.84; H, 7.32. Weight loss, 2.15. Residue, 0.55.

(44) Courtesy of Mrs. Beatrice S. Gallagher, Division of Steroid Metabolism, Sloan-Kettering Institute for Cancer Research in New York.

21-Diazo-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone (XXIII) *from 8-hydroxy-3-oxo-21-nor-Δ⁴-pregnene-19,20-dioic acid 19:8-lactone* (XXII). The sodium salt was prepared from a solution of 195 mg. of XXII, m.p. 237–239°, in 10 cc. of ethanol by adding 47.6 mg. of sodium bicarbonate in 2 cc. of water and evaporating to dryness from the frozen state. The dried salt was suspended in 10 cc. of dry benzene containing 5 drops of pyridine, and this mixture was cooled until partly frozen, whereupon 2 cc. of oxalyl chloride was added. After standing for 15 min., the reaction mixture was frozen in Dry Ice and evaporated to dryness *in vacuo*. Addition of 5 cc. of dry benzene, freezing, and evaporating again left an odorless residue. This was taken up in 10 cc. of dry benzene and filtered under nitrogen pressure through sintered glass into ice cold ethereal diazomethane, which was freshly prepared from 10 g. of methylnitrosourea[33] and dried over sodium. The residue of salts was washed with dry benzene and the reaction mixture was left at room temperature for 1 hr. and was finally evaporated to dryness *in vacuo*, yielding 266.8 mg. of yellow oil. This was chromatographed over 20 g. of alumina (activity I–II, 15 × 130 mm.). Benzene and benzene-ether eluted 131.6 mg. of crystalline XXIII. Successive recrystallization from acetone-hexane and acetone-water gave 96.8 mg. of XXIII as pale yellow needles with no definite melting point. The crystals foamed without melting at 145–155° and the foam liquefied at 198–205°. $[\alpha]_D^{25}$ +220° ± 2°; M_D^{25} +810° ± 8° (9.99 mg.; α + 2.20°). λ_{max}^{alc} 247 mμ, ε 23,400.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C,[34] 68.78; H,[34] 6.83; N,[35] 7.21. Weight loss, 0.73.

In repeated runs of this experiment, the chromatographic purification yielded a second, more polar product, m.p. 272–274°, which has not yet been identified.[36]

8-Hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone [*"19:8-Lactoprogesterone"*] (XXIV) *from 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone* (XXIII). A solution of 30 mg. of the analytical sample of the diazo ketone XXIII in 10 cc. of chloroform was shaken for 2 min. with 1 cc. of 48% hydriodic acid (Baker's Analyzed Reagent). The chloroform layer was then shaken successively with three 5-cc. portions of saturated aqueous sodium iodide and with 5 cc. of *N* sodium thiosulfate. After drying over sodium sulfate, evaporation of the chloroform *in vacuo* left 29.5 mg. of colorless crystalline residue. Recrystallization from acetone-hexane gave 25.5 mg. of colorless needles, m.p. 156–159°. Repeated recrystallization from acetone-water yielded 18.8 mg. of XXIV as long shining needles; constant m.p. 162–163°. $[\alpha]_D^{22}$ +147° ± 2°; M_D^{22} +504° ± 7° (11.07 mg., α + 1.63°). λ_{max}^{alc} 244 mμ, ε 14,900.

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.65. Found: C, 73.25; H, 7.75. Weight loss, 0.18. Residue, 0.24. (Corr. for residue: C, 73.43; H, 7.77.)

21-Acetoxy-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone [*"19:8-Lactocortexone acetate"*] (XXV) *from 21-diazo-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone* (XXIII). A solution of 53 mg. of the analytical sample of the diazo ketone XXIII in 4 cc. of glacial acetic acid was heated on the steam bath for 45 min. and was then evaporated to dryness *in vacuo*, leaving 53 mg. of yellow foam. On suspending in ether and adding 10 drops of acetone, the product slowly crystallized; yield: 45.9 mg.; m.p. 177–179°. Recrystallization from acetone–water gave 37 mg. of XXV as colorless needles, m.p. 181–183°. The analytical sample, derived from a repeat experiment, melted at 183–184°. $[\alpha]_D^{22}$ +159° ± 2°; M_D^{22} + 643° ± 8° (11.17 mg., α + 1.78°). λ_{max}^{alc} 244 mμ, ε 12,900.

Anal. Calcd. for $C_{23}H_{28}O_6$ (400.45): C, 68.98; H, 7.05. Found[39]: C, 68.78; H, 6.92. Residue, 0.25. (Corr. for residue: C, 68.99; H, 7.02.)

8,21-Dihydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone [*"19:8-Lactocortexone"*] (XXVI) *from 21-acetoxy-8-hydroxy-3,20-dioxo-Δ⁴-pregnen-19-oic acid 19:8-lactone* [*"19:8-*

Lactocortexone acetate"] (XXV). To a solution of 40 mg. of XXV, m.p. 183–184°, in 1 cc. of methylene chloride was added 2.5 cc. of 0.05*M* potassium carbonate in 75% methanol.[38] After 5 min., 1 cc. of water and a piece of Dry Ice were added, and the mixture was concentrated *in vacuo* to about 1 cc., yielding a crop of colorless needles. After filtering and washing the crystals (28.2 mg.), the filtrate was extracted with ethyl acetate, yielding 7.5 mg. of crystalline residue. These two portions were combined and chromatographed over 5 g. of Florisil (10 × 115 mm.). Chloroform containing from 2% to 25% of acetone eluted a total of 31.6 mg. of crystalline material which was recrystallized from acetone-water and acetone-hexane to give 24.2 mg. of XXVI as clusters of minute needles, m.p. 199–201°, depressed on admixture with XVI. $[\alpha]_D^{21}$ +158° ± 3°; M_D^{21} +566° ± 10° (9.95 mg., α + 1.57°). λ_{max}^{ale} 244 mμ, ϵ 14,000.

Anal. Calcd. for $C_{24}H_{26}O_5$ (358.42): C, 70.37; H, 7.31. Found[39]: C, 70.54; H, 7.50. Residue, 1.38.

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Isolation, Purification, and Structural Identity of an Alfalfa Root Saponin

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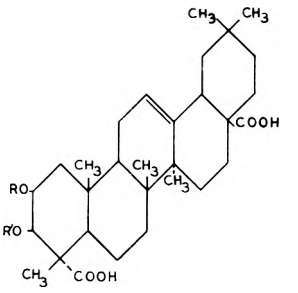
The isolation and structural identity of a pure alfalfa root saponin nucleus was accomplished. The probable structural formula was shown by experimentation to be a β-linked D-glucoside of 2β-hydroxy-Δ^{12}-oleanene-23,28-dioic acid; the aglycone is known as medicagenic acid. Specific enzyme hydrolysis was used to establish the linkage involved in the glucose attachment. Other evidence for the reported structure was prepared from chemical constants, elemental analysis, hydroxyl determinations, infrared interpretations and comparisons, and an NMR study.

In the last fifteen years the water soluble saponins isolated from alfalfa (Medicago sativa) have been indicated as a factor in inhibiting growth of chicks[2] and contributing to ruminant bloat.[3,4] From current structural investigations of these saponins isolated from alfalfa tops has come valuable information confirming the presence of a number of hexose and pentose sugars attached in some order to a triterpenoid nucleus.[5,6] The final absolute structure of the aglycone was reported in 1957 and is now known as medicagenic acid.[7]

Previous structural investigations[5–7] have not included the isolation and structural determination of a pure saponin but have concentrated on the individual identity of the monosaccharides and the triterpenoid nucleus following hydrolysis. It was therefore considered expedient to attempt the isolation, purification, and structural determination of a compound representative of a composite of carbohydrate and sapogenin from alfalfa. Such a compound would help establish the proper sequence of hexoses and pentoses in some saponin formations, furnish information on the glycosidic linkage and permit the complete structural proof of component parts. The information obtained should be useful in a better understanding of saponin formation and suggest a useful method for synthesis of these products.



I R, R' = H
II R, R' = CH_3CO
III R = H, R' = β-D-GLUCOSE

Figure 1

EXPERIMENTAL

Saponin isolation and purification. Preliminary investigations of the occurrence of saponins in alfalfa plants showed a potentially rich concentration in the roots. This portion of the plant body was therefore selected for this study.

Samples of alfalfa roots from Ranger and Lahontan varieties were gathered as plowed, cleaned of leaf material, and dried in a forced-draft oven until the roots became brittle. These dried roots were then ground to a fine powder and stored until needed.

The saponin isolation from root powder follows:

Four hundred and fifty grams of this powder was placed in a 4-l. steel beaker together with 1300 ml. of water and 1500 ml. of 95% ethanol. The slurry was maintained at 80° on a hot plate under constant agitation for 6 hr. This mixture was filtered with gentle suction through a large Buchner funnel so packed that it retained about a quarter of an inch

(1) P. S. Gisler, present address: Aerojet General, Sacramento, Calif.

(2) D. W. Peterson, *J. Biol. Chem.*, **183**, 647 (1950).

(3) H. H. Cole, C. F. Huffmann, M. Kleiber, T. M. Olsen, and A. F. Schalk, *J. Animal Sci.*, **4**, 183 (1945).

(4) M. Henrici, *Onderstepoort J. Vet. Research*, **25**, 45 (1952).

(5) E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, *J. Am. Chem. Soc.*, **76**, 2271 (1954).

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(7) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. R. Thompson, *J. Am. Chem. Soc.*, **79**, 5292 (1957).

bed of Hyflo-supercel on a good grade qualitative paper. The filtrate was then brought just under a boil (90°) and acidified with 360 ml. of concentrated hydrochloric acid. This approximately 12% solution was maintained near boiling for 20 min. Upon cooling the filtrate to room temperature with constant stirring, a light brown gelatinous precipitate formed. Complete precipitation was effected by allowing the mix to stand quietly at room temperature for 24 hr. The precipitate was collected by gentle suction on a filter paper. Care was taken to remove the filter cake from the paper while still moist.

The partially dried residue was completely dissolved in 125 ml. of hot 95% ethanol and treated repeatedly with activated carbon and filtered through a carbon retentive paper until the filtrate assumed a pale yellow color. To this ethanol solution was added 150 ml. of distilled water resulting in the formation of a white gelatinous precipitate. Following this treatment the gelatinous product was removed by filtration and the water precipitation process repeated. Two water treatments gave a nearly white gelatinous residue. The last traces of color were removed by taking the precipitate up in a minimum of 95% ethanol and treating twice as before with activated carbon. The clear colorless alcoholic solution was evaporated under a dry air stream. The resulting product was a fine white powder that was easily ground to any desired mesh.

This procedure prepared 1 g. of pure white dry saponin for every 100 g. of dry root powder used. It should be noted that this yield was significantly higher than that obtained from alfalfa tops.[5] The prepared saponin was vacuum dried at 50° for 8 hr. A sample of this product melted sharply at 255° ± 1° and gave an $(\alpha)_D^{26}$ of +70° in absolute ethanol.

The isolation and purification procedure for the aglycone. Continued hydrolysis under reflux using 12% hydrochloric acid resulted in the isolation of the sapogenin. The procedure for this hydrolysis follows:

Three grams of purified saponin were placed in a round bottom flask fitted with a reflux condenser. To this residue was added 400 ml. of a 50% ethanol-water solution containing a 12% concentration of hydrochloric acid. Boiling chips were added and the solution refluxed for 60 hr. Following this hydrolysis the solution was concentrated by means of a clean dry air stream to 50 ml., added to 100 ml. of hot ethanol, and treated repeatedly with activated carbon until a light straw yellow solution was obtained. Following a single water precipitation, the partially dried white gelatinous precipitate was taken up in 150 ml. of hot ethanol and treated twice more with activated carbon, whereupon a clear colorless solution resulted. The pure aglycone was recovered by evaporation, air dried, and redissolved in a minimum of hot 95% ethanol. Recovery from cold ethanol gave 1.2 g. of white microcrystals, the crystalline nature being confirmed by an x-ray diffraction study. A sample of these crystals selected for analysis was dried at 100° for 4 hr. They exhibited a sharp melting point at 352–353° and gave an $(\alpha)_D^{25}$ of +106° in absolute ethanol.

Determination of sapogenin structure. As preliminary constants obtained for the purified aglycone indicated the nucleus to be medicagenic acid, it was first chosen for further analyses.

Anal. Calcd. for $C_{28}H_{42}(OH)_2(COOH)_2$: C, 71.7; H, 9.16; O, 19.12; neut. equiv., 251.2. Found: C, 71.7; H, 9.17; O, 19.08; neut. equiv., 253, 255.7.

The value 253 was obtained by adding an excess of 0.1*N* sodium hydroxide under reflux and back titrating with standard 0.05*N* hydrochloric acid; the value of 255.7 by direct titration in aqueous ethanol using 0.1*N* sodium hydroxide.

A diacetate derivative of medicagenic acid was also prepared. The preparation of the diacetate duplicated a procedure already reported.[5] A sample of the crystalline diacetate dried at 100° for 2 hr. melted sharply at 207° and gave an $(\alpha)_D^{27}$ of +92° from chloroform.

To aid in confirming the number and position of functional groups on these nuclei, infrared and NMR spectrograms were prepared for the sapogenin and its diacetate.

Infrared spectrograms for these compounds were obtained from potassium bromide pellets using a Perkin-Elmer Infracord spectrophotometer. The graph obtained for the acid showed strong absorbances at 3.9, 5.9, and 2.85 μ indicative of carboxyl and hydroxyl loadings. Interpretation of the curve also suggests that the hydroxyl groups are axial because of the absorptive band in the 9–10 μ region. A double bond is most probably located such that there is only one hydrogen attached to the double bonded carbon as suggested by significant absorption bands between 11.5 and 12.5 μ.[8] The spectrogram obtained for the diacetate showed a significant decrease in hydroxyl absorbance and increased absorbance at 7.3 and 8 μ brought about by the acetate loadings.

The above infrared interpretations for the sapogenin nucleus loadings were properly confirmed when the infrared spectrograms of these compounds were shown to be exactly identical with the infrared charts of medicagenic acid and its diacetate supplied by WURDD[9].

A nuclear magnetic resonance spectrogram of the diacetate of medicagenic acid was prepared in deuterochloroform with a sweep rate of 1×10^{-5} and a chart rate of 4″/min., using a frequency of 60 mc. Characteristically sharp bands at 116 and 124 cps. were immediately evident and were indicative of the two acetate loadings. A broad signal was obtained at 500 cps. typical of carboxylic acid protons. Signals centering around 317 cps. were classified as characteristic of one olefinic proton and two protons attached in equatorial configuration with the acetate groups on the six-membered ring. Electronic integration of this spectrogram showed that the two sets of low field signals for the five protons considered above are in ratio of 2 to 3. The assignment of the two carboxyl protons, one olefinic proton, and two protons adjacent to acetate loadings is offered as supporting evidence in confirming the absolute structure for both medicagenic acid and its diacetate.

Determination of saponin structure. Following confirmation of the sapogenin, the saponin structure was further investigated. An infrared spectrogram from a potassium bromide pellet was prepared. An interpretation of the curve showed an increase in hydroxyl loadings evident from an increased absorbance at 2.85 μ over that exhibited by medicagenic acid. The curve also suggested the presence of a lactone structure due to enhanced absorbance at 8 and 8.5 μ, with a glycosidic attachment predicted because of the strong absorption in the 9–10 μ region.

In addition to the melting point and rotation data the following analytical data were recorded for the saponin nucleus:

Anal. Calcd. for $C_{28}H_{42}(COOH)_2(OH)(OC_6H_{11}O_5)$: C, 65.0; H, 8.4; O, 26.5. Hydroxyl det'm.: 12.4 corres. to 5 OH groups. Calcd. for $C_{28}H_{42}(COOH)_2(OH)(OC_5H_9O_4)$: C, 66.2; H, 8.5; O, 25.2. Hydroxyl det'm.: 10.4 corres. to 4 OH groups. Found: C, 64.88; H, 8.40; O, 26.63. Hydroxyl det'm.: 12.11.

The essential features of the hydroxyl acetylation is described in the literature.[10] One exception was the use of an indicator for end point detection prepared from one part by weight of Cresol Red with 3 parts by weight of Thymol Blue.

Determination of the linkage and specific sugar. In order to establish the linkage and determine the exact sugar present, the following procedures were used:

One gram of very finely ground saponin and 25 milligrams of pure β-D-glucosidase suspended in 25 ml. of water in a large test tube was mounted in a water bath at 37° ± 0.5° under constant agitation for 12 hr. The mixture was removed

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., Wiley, New York (1958).

(9) Western Utilization Research and Development Division, Agricultural Research Service, Albany 10, Calif.

(10) J. S. Fritz and G. H. Schenk, *Anal. Chem.* **31**, 1808–12 (1959).

and centrifuged at 30,000 G for 15 min. The clear supernatant solution was deionized by passing it through a mixed resin bed composed of amberlite IR-120 and amberlite IR-4B. The deionized filtrate was reduced under vacuum to 5 ml. A 2-ml. portion of this concentrate was tested by a standard orcinol method for hexose.[11] Although the test was not quantitative, it was clearly evident that the sugar was a hexose.

As noted in the literature[12] pure β-D-glucosidase is generally considered very specific for hydrolyzing normal β-linked D-aglucones. Therefore, the confirmation of a hexose by the orcinol test coupled with the fact that β-D-glucosidase will not hydrolyze β-linked D-fructose or D-mannose might be considered sufficient to indicate the presence of β-D-glucose. However, as some doubt exists as to whether this enzyme may also hydrolyze β-D-galactose under favorable conditions, the following confirmatory experiment to identify the sugar was completed:

To the remaining 3 ml. of filtrate were added 0.4 g. of phenylhydrazine, 0.6 g. of sodium acetate and 0.5 ml. of a saturated bisulfite solution. The volume was made up to 5 ml. and the solution immersed in a boiling water bath. An osazone of the sugar formed between 4 and 5 min. The time for osazone formation coincided exactly with that established for glucosazone,[13] as well as with time of osazone formation in a known glucose solution treated simultaneously in an identical manner. A galactose solution run under similar conditions did not form osazone crystals until 19 min. had elapsed.

Microscopic examination of the osazone crystals indicated that the unknown gave crystals that were identical with glucosazone and differed significantly from those formed for galactose.[14] As a result of these experimentations, the presence of glucose was confirmed in the saponin.

CONCLUSIONS

On the basis of the results recorded, it is expected that the pure root saponin isolated was a β-linked glucoside of 2β-hydroxy-Δ^{12}-oleanene-23,28-dioic acid (Medicagenic acid). Because of the difficulty encountered in the acid hydrolysis of glucose it is predicted that glucose is initially attached to the triterpene nucleus in a majority of alfalfa root saponins of this type regardless of the sugar chain complexity. This conclusion was suggested in that several different impure water soluble saponins isolated in initiating this research were all reduced by controlled hydrolysis to the same saponin nucleus reported in this paper.

Surface contact enzyme hydrolysis using pure β-D-glucosidase not only proved that a β-linkage for D-glucose was involved, but that the glucosidic attachment was probably free of further substitution or unusual binding to the aglycone.[12] This latter evidence was strengthened when the hydroxyl group determination presented evidence of five free hydroxyl groups in the saponin which is expected when a normal glucoside linkage exists.

Alfalfa roots have been found to be an excellent source for the isolation of saponins of this type or for isolating pure medicagenic acid. Should these compounds prove valuable as intermediates, alfalfa root powder would be a practical source material.

Acknowledgment. We wish to acknowledge the assistance of Dr. C. Blincoe for his professional advice on biochemical methods and R. M. Maffi for laboratory assistance. The authors are also indebted to Mr. C. R. Van Atta of Western Regional Laboratories for supplying infrared spectrograms of medicagenic acid and its diacetate for comparison studies and to Dr. LeRoy Johnson of Varian Associates for the NMR spectrogram and its interpretation.

RENO, NEV.

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(12) M. Dixon and C. E. Webb, *Enzymes*, Academic Press, New York (1958).

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., Wiley, New York (1956).

(14) W. Z. Hassid and R. M. McCready, *Ind. & Eng. Chem., Anal. Edition*, **14**, 683–6 (1942).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. L.[2,3] Conversion of 12-Ketosapogenins to 11β,12β-Epoxypregnanes

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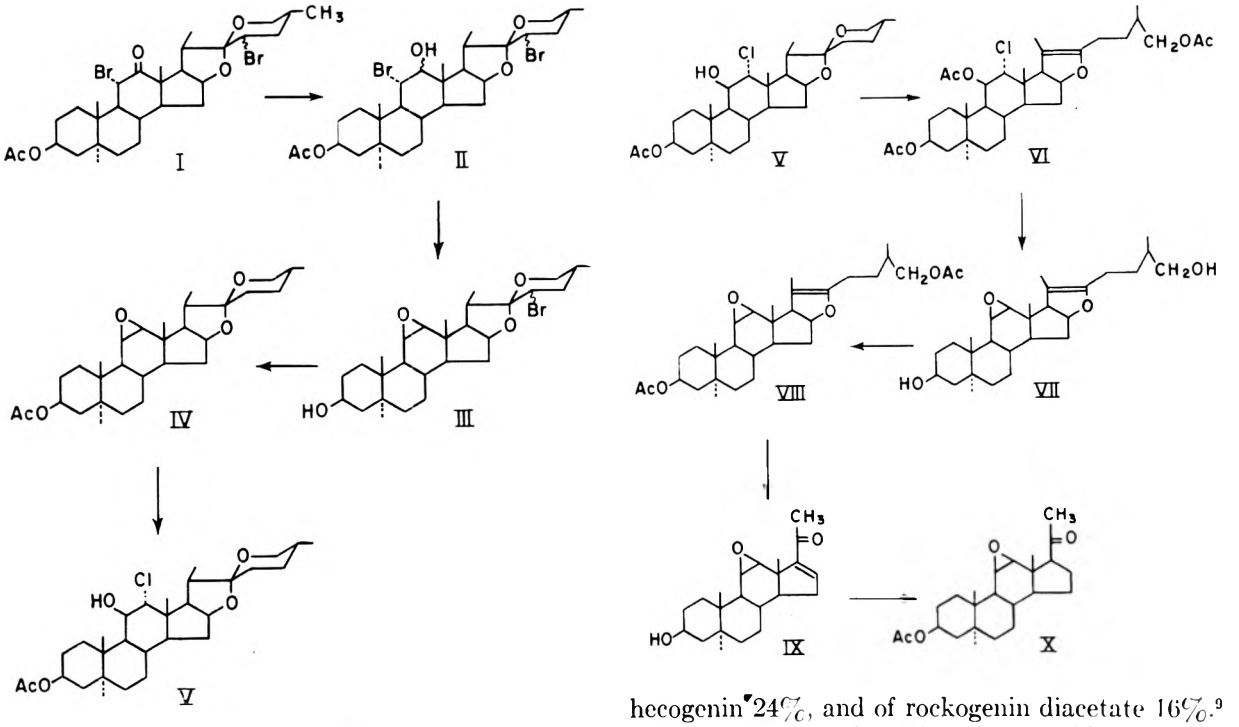
Hecogenin was converted to 11β,12β-epoxytigogenin (IV), and then to 3β-acetoxy-11β,12β-epoxy-5α-pregnane-20-one (X). Gentrogenin or gentrogenin-correllogenin mixtures were converted to 11β,12β-epoxydiosgenin (XV) and then to 11β,-12β-epoxy-3β-acetoxy-5-pregnene-20-one (XXI).

The elegant researches of Fried and his associates have demonstrated that 12-halosteroids have physiological activities comparable to those of corresponding 9-halosteroids.[4] Probably the most available route to such compounds are *via* the

(1) Eastern Utilization Research and Development Division, Agricultural Division, Agricultural Research Service, U. S. Department of Agriculture, Philadelphia 18, Pennsylvania. Article not copyrighted.

(2) Previous paper in this series, Steroidal Sapogenins. XLIX, *J. Org. Chem.*, **23**, 1741 (1958).



11β,12β-epoxides.[5] We wish to report at this time on the preparation of 3β-acetoxy-11β,12β-epoxy-5α-pregnan-20-one, X, derived from hecogenin, and the corresponding Δ^5-analogue, XXI, derived from gentrogenin.

11α,23ξ-Dibromohecogenin acetate[6] was conveniently reduced with sodium borohydride in a refluxing mixture of methylene chloride and methanol. The crude bromohydrin, a mixture of II and its 12α epimer, was obtained quantitatively and was treated with refluxing methanolic potassium hydroxide. The crude product, of which the chief constituent was the 23-bromo-11β,12β-epoxide, III, was treated with a zinc-copper couple in refluxing ethanol.[6,7] As was anticipated from the previous work of Cornforth, Osbond, and Phillipps,[8] the debrominated epoxide, IV, was not the sole product. Hecogenin, derived from the 12α-hydroxy-11α-bromo epimer,[8] was separated from the mixture by use of Girard's Reagent T. On acetylation of the nonketonic fraction, the insoluble 3β-acetoxy-11α,12β-epoxytigogenin, IV, was easily separated from the soluble rockogenin diacetate by crystallization. Based on the dibromide I, the yield of the desired epoxide IV was 53%, of hecogenin 24%, and of rockogenin diacetate 16%.[9] Attempts to pseudomerize the epoxide IV with refluxing acetic anhydride in the presence of pyridine hydrochloride[10] or acetic anhydride–acetic acid at 180°[11] were unsuccessful. As long as the 11β,12β-oxide ring was intact, there was no attack on the side chain.[12] After prolonged heating, cleavage of the oxide ensued and then side chain attack took place in the usual manner. On treatment of IV with hydrochloric acid in dioxane, the 11β,12β-oxide reacted smoothly to give the known 11β-hydroxy-12α-chloro-derivative, V.[13] On treating V with acetic anhydride containing 0.1% acetic

(3) Presented in part at the 134th National Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(4) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(5) L. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, pp. 684–5.

(6) J. Elks, G. H. Phillipps, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956).

(7) Use of zinc–acetic acid resulted in opening of the epoxide.

(8) J. W. Cornforth, J. M. Osbond, and G. H. Phillipps, *J. Chem. Soc.*, 907 (1954).

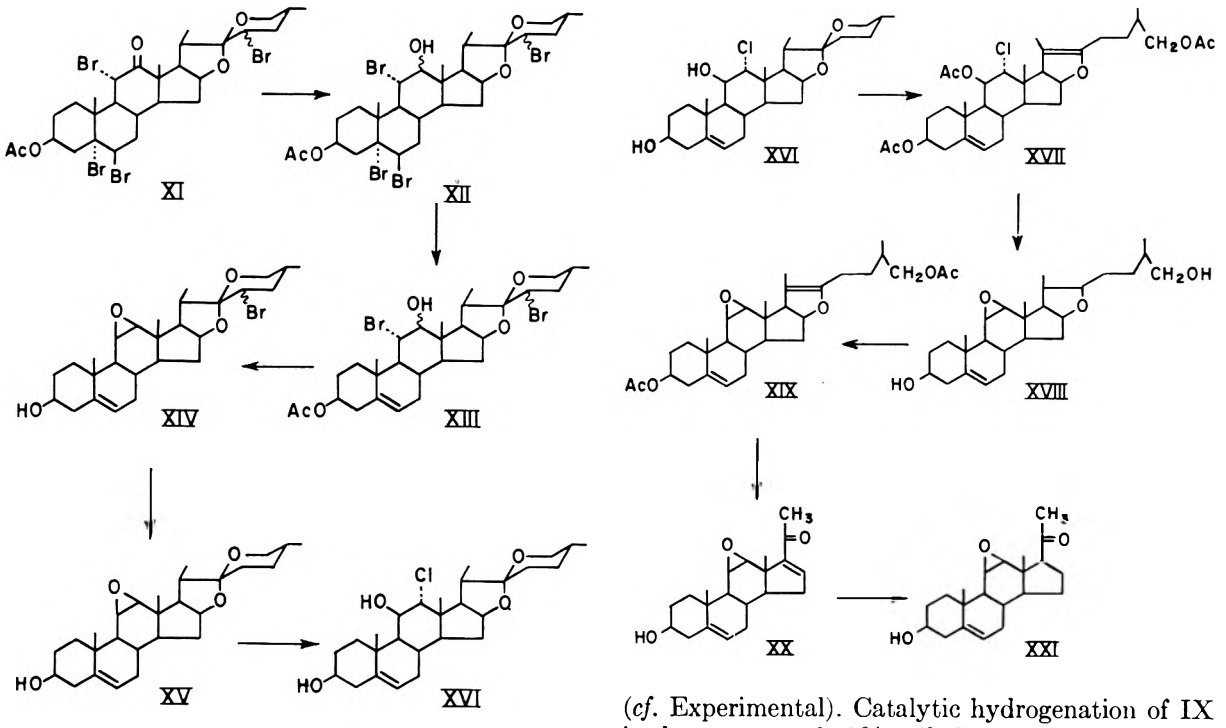
(9) During the sodium borohydride reduction of I, a substantial, although minor, fraction of the *cis*-12α-hydroxy-11α-bromo epimer is formed, *cf. J. Am. Chem. Soc.*, **78**, 3752 (1956). The *cis* epimer cannot form an epoxide[8] [*cf.* also *J. Am. Chem. Soc.*, **57**, 224 (1935)]. The rockogenin diacetate may originate as a result of reduction of the 11α-bromo moiety prior to reduction of the ketone.

(10) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **76**, 4618 (1954).

(11) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **79**, 6481 (1957).

(12) It seems well established that coordination of the ring F oxygen with a Lewis acid, thus yielding a positively charged intermediate, is a requisite for pseudomerization. The resistance of IV to pseudomerization could be explained by assuming that the oxide preferentially coordinates with a Lewis acid to give a positively charged species which would inhibit formation of a similar charge on the F ring oxygen. Recently we have shown that amines can inhibit catalytic hydrogenation of ring F, *J. Am. Chem. Soc.*, **82**, 1444 (1960), a reaction which also requires coordination of the F ring oxygen with an acid. However, the 12-ketosapogenins, wherein the 12-ketone would presumably coordinate more readily with a Lewis acid than the epoxide oxygen, show no inhibition of pseudomerization, thus weakening the above rationalization.

(13) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1241 (1953).



acid at 170°,[14] V was converted to 3β,11β,26-triacetoxy-12α-chloropseudotigogenin, VI, with surprising rapidity. The pseudotriacetate, VI, was not isolated in crystalline form but was characterized by infrared spectroscopy which indicated absence of characteristic spiroketal bands,[15a,b] presence of a band at 1685 cm.$^{-1}$ characteristic of pseudosapogenins[16] and absence of hydroxyl bands. Attempts to convert VI to the desired epoxypregnene, IX, *via* standard oxidation and alkaline hydrolysis techniques[17] were unsuccessful.[18] Treatment of VI with refluxing methanolic potassium hydroxide gave 11β,12β-epoxy-3β,26-dihydroxypseudotigogenin, VII. Compound VII was not crystalline and was characterized by its infrared spectrum and subsequent reactions. Acetylation of VII followed by standard chromium trioxide oxidation and hydrolysis with potassium hydroxide in *t*-butyl alcohol gave 3β-acetoxy-11β,12β-epoxy-5α-pregn-16-ene-20-one, IX, in 50% yield based on VII and 25% over-all yield based on I. The epoxypregnene IX was characterized by its carbon and hydrogen analysis, and the infrared and ultraviolet spectra are in agreement with the assigned structure (*cf.* Experimental). Catalytic hydrogenation of IX in the presence of 10% palladium-alumina gave the saturated pregnane, X.

A similar series of reactions were successfully conducted with gentrogenin[19] (12-ketodiosgenin). Gentrogenin tetrabromide,[20] XI, was reduced with sodium borohydride to give the bromohydrin XII which on treatment with sodium iodide in ethanol regenerated the Δ^5-double bond, giving XIII. Alkaline treatment followed by use of the zinc-copper couple gave a mixture of 11β,12β-epoxy diosgenin, XV, and gentrogenin, in a ratio of approximately 4 to 1 respectively. We were unable to find significant quantities of any 12-hydroxy compound. The yield of XV from XI was 78%. Treatment of the epoxide XV with hydrochloric acid in dioxane gave the chlorohydrin XVI as a gummy, noncrystalline compound. Without isolation, it was pseudomerized to give XVII which was then hydrolyzed and converted to 3β-acetoxy-11β,12β-epoxy-5,16-pregnadiene-20-one, XX, by the same route used in the hecogenin series. The crystalline pregnadiene XX was characterized by correct analytical values and infrared and ultraviolet spectra in agreement with the assigned structure (*cf.* Experimental). Catalytic hydrogenation of XX under mild conditions gave the saturated pregnene XXI. The conversion of the 11β,12β-epoxy diosgenin XV to the pregnadiene XX took place in 65% yield. The above reactions were conducted with the pure 25D-isomer, gentrogenin, as the starting material. It is more convenient to work with the naturally occurring 25D and 25L mix-

(14) The reaction required only 2.5 hr. for completion, in contrast to the 10–17 hr. normally required for complete pseudomerization.[11]

(15)(a) C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953); (b) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.*, **75**, 158 (1953).

(16) A. Hayden, P. Smeltzer, and I. Scheer, *Anal. Chem.*, **26**, 550 (1954).

(17) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).

(18) Among other reasons, treatment of the product of chromium trioxide oxidation of VI with potassium hydroxide in *t*-butyl alcohol failed to regenerate the 11β,12β-epoxide.

(19) H. A. Walens, S. Serota, and M. E. Wall, *J. Org. Chem.*, **22**, 182 (1957).

(20) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **79**, 3228 (1957).

tures,[19,21a,b] which on side chain cleavage give the same 16-dehydropregnene. The series XI to XX conducted with the 25D and 25L mixtures gave yields of the same order as those in which the pure 25D isomer was used. By means of available procedures, particularly the elegant Syntex method for 21-acetoxylation,[22] compounds IX, X, XX, and XXI should be excellent points of departure for elaboration of a variety of active steroid hormones.[23]

EXPERIMENTAL

11β,12β-Epoxytigogenin acetate (IV). 11α,23ξ-Dibromohecogenin acetate I was prepared in the usual manner.[6] Fifty grams of I was dissolved in 600 ml. of methanol and 200 ml. of methylene chloride and the solution heated to reflux. A refluxing solution of 23 g. of sodium borohydride in 200 ml. of methanol was added to this as quickly as possible (about 10–15 min.). The solution was refluxed an additional 15 min. and then the methylene chloride was distilled. The remaining solution was cooled to room temperature by the addition of 1.4 l. of ethanol. Twenty-five grams of potassium hydroxide was added and the mixture was stirred for 3 hr. and then allowed to stand overnight at room temperature. The solution was concentrated to about 600 ml. and then poured into 1500 ml. of water. The product was extracted with ether, three portions of 350 ml., and the ether layers combined. The ether was washed with water, dried over sodium sulfate, and evaporated *in vacuo* at room temperature. The residue was dissolved in 1 l. of ethanol and treated with a zinc-copper couple[6] (200 g. of zinc and 1350 ml. of 15% w./v. copper sulfate) at reflux for 3 hr. The reaction mixture was filtered while hot and the filter cake washed with methylene chloride, two 100-ml. portions. The combined filtrates were then evaporated to dryness *in vacuo*, giving 34 g. of product. Infrared analysis showed that this product contained some ketone, some dihydroxy, and some epoxy material. The mixture (8.4 g.) was dissolved in 175 ml. ethanol containing 5% acetic acid, 4 g. Girard's Reagent T was added, and the solution was refluxed for 1.5 hr. The solution was cooled to room temperature and then poured into a separatory funnel containing 400 ml. of ice and water and 5 g. of sodium carbonate. The aqueous layer was extracted with three 300-ml. portions of ether and the ether layers were combined. The ether was then washed with five 400-ml. portions of water, the last two washes giving no precipitate when acidified with hydrochloric acid. The ether was then dried over sodium sulfate and evaporated to dryness, giving 6.5 g. of crystalline material. This was acetylated in pyridine–acetic anhydride at room temperature for 16 hr. The product was isolated in the usual manner and infrared analysis showed the presence of an epoxide (875 cm.$^{-1}$) as well as some diacetoxy material. The mixture was crystallized from methanol–methylene chloride, giving 4.9 g. of 11β,12β-epoxytigogenin acetate, IV. Concentration of the mother liquors did not yield any further crystalline material; however, 1.5 g. of rockogenin diacetate was obtained upon evaporating the solvent. The aqueous layers from the Girard Reagent T separation were acidified and the ketonic material was recovered, giving 2.0 g. of hecogenin. IV was identified by infrared analysis (1735, 1248 cm.$^{-1}$ acetate, normal F-ring bands, and 875 cm.$^{-1}$ epoxide, no hydroxy or ketone bands) and melting point 203–206° (lit.,[13] m.p. 205–207°).

3β-Acetoxy-11β,12β-epoxy-16-pregnen-20-one (IX). One gram of IV was dissolved in 100 ml. of dioxane, 20 ml. of 3*N* hydrochloric acid and 5 ml. of water were added, and the resulting one phase solution was stirred for 1 hr. Seventy milliliters of water was added with stirring over a 10-min. period. Material started to precipitate and the mixture was allowed to stand for an additional hour. The precipitate was filtered off, the mother liquor was diluted with additional water and refiltered. The combined filter cakes were air dried, giving 1.1 g. of 12α-chloro-11β-hydroxytigogenin acetate (V). Infrared analysis showed bands at 3650 (hydroxyl), 1735, 1245 (acetate), normal F-ring bands, and absence of the 875 cm.$^{-1}$ (epoxide) band.

Nine grams of V was placed in a flask, 23 ml. of acetic anhydride containing 0.1% acetic acid was added, the flask sealed and then heated in a bath at 170° for 2.5 hr. The flask was cooled and the acetic anhydride was evaporated off *in vacuo*. Attempts to crystallize the product were fruitless. Infrared analysis agreed with VI, showing no F-ring bands, strong acetate bands (1736, 1250 cm.$^{-1}$), and double bond (1685 cm.$^{-1}$). VI was dissolved in 500 ml. of methanol, 5 g. of potassium hydroxide was added, and the solution was allowed to stand at room temperature overnight. The solution was poured into 1 l. of water and extracted with three 500-ml. portions of ether. The ether layers were combined and washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in 20 ml. of pyridine and 15 ml. of acetic anhydride, and allowed to stand overnight at room temperature. The product was isolated in the usual manner, giving 9.2 g. of 11β,12β-epoxypseudotigogenin diacetate (VIII), identified by infrared analysis.

Two grams of VIII was dissolved in 30 ml. of acetic acid and cooled to 15° in an ice bath. Fifteen milliliters of 50% acetic acid–water containing 0.8 g. of chromium trioxide was cooled to 10° and then added dropwise with stirring to the steroid solution, the addition taking 10 min. The reaction mixture was allowed to come to room temperature and then stirred for an additional 1 hr. The mixture was drowned in three volumes of water and the steroid was isolated by ether extraction. The residue was dissolved in 50 ml. of *t*-butyl alcohol, 1 g. of potassium hydroxide and 2 ml. of water were added and the mixture was shaken at room temperature for 3 hr. The reaction mixture was drowned in 100 ml. of water and product was isolated by ether extraction. The ether was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was acetylated in 5 ml. of pyridine and 3 ml. of acetic anhydride overnight at room temperature. The product (IX) was isolated by drowning in water and extraction with ether, giving 1 g. of colored resin. The resin was chromatographed on Florisil (20 g.), the desired product being eluted over a wide range, starting with benzene and ending with chloroform, giving 0.7 g. of acetoxy-11β,12β-epoxy-5α-pregn-16-en-20-one (IX). The analytical sample was crystallized from heptane, then from hexane, m.p. 182–184°, $[\alpha]_D^{25}$ 103.5, log ε 3.98.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.18; H, 8.66. Found: C, 73.96; H, 8.51.

The infrared spectrum showed bands at 1735 and 1248 (acetate), 1668 (conj. ketone), and 875 cm.$^{-1}$ (epoxide).

Hydrogenation of 3β-acetoxy-11β,12β-epoxy-5α-pregn-16-en-20-one (IX). Three grams of IX and 1 g. of 10% palladium on alumina were added to 200 ml. of ether, and hydrogenated for 3 hr. at 50 p.s.i.g. of hydrogen. The solution was filtered to remove the catalyst and the product isolated by evaporating the ether. The residue was crystallized from methanol and then from petroleum ether (b.p. 35–60°), giving 3β-acetoxy-11β,12β-epoxy-5α-pregnene-20-one (X), m.p. 113.5–114.5°, no absorption in the ultraviolet, bands at 1735 and 1248 (acetate), 1710 (20-ketone), 875 cm.$^{-1}$ (epoxide), and no band for conjugated carbonyl.

(21)(a) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, 81, 411 (1959); (b) O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, 81, 439 (1959).

(22) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, 80, 250 (1958).

(23) Because of scarcity of starting materials and a shifting in research orientation, our laboratory is not contemplating further work in this area.

Preparation of 12ξ-hydroxy-5α,6β,11α,23-tetrabromodiosgenin 3β-acetate (XI). Twenty grams of 5α,6β,11α,23ξ-tetrabromogentrogenin 3-acetate in 600 ml. of methanol and 250 ml. of methylene chloride was heated at reflux temperature. Ten grams of sodium borohydride in 100 ml. methanol was also heated to reflux temperature and was then added to the steroid solution portionwise over a time interval of about 4 min. Heating at reflux was continued for 15 min. The reaction mixture was then poured into 2 l. of water and the steroid recovered by three extractions with ether (500 ml.). The ether solution was washed with 3*N* hydrochloric acid, sodium bicarbonate, and distilled water, and dried over sodium sulfate. The ether was evaporated *in vacuo* at room temperature to give 20 g. of 12ξ-hydroxy,-5α,6β,11α,23ξ-tetrabromodiosgenin 3β-acetate (XII). Infrared showed no 12-ketone band, presence of hydroxyl (3420) and acetate (1735 and 1248 cm.$^{-1}$). The product was not purified at this stage.

12ξ-Hydroxy-11α,23ξ-dibromodiosgenin 3β-acetate (XIII). Twenty grams of XII was dissolved in 500 ml. ethanol, 25 g. of sodium iodide was added, and the solution was refluxed for 30 min. The ethanol solution was poured into 1500 ml. of water. Ethyl ether (600 ml.) was added and the two phase system was washed with just enough sodium thiosulfate to decolorize the system. The layers were separated and the aqueous layer was reextracted with ether. The ether portions were combined, washed with water, dried over sodium sulfate, and the dry ether solution evaporated *in vacuo* at room temperature, giving 16 g. of 12ξ-hydroxy-11α,23ξ-dibromodiosgenin 3β-acetate (XIII). The infrared spectrum had the characteristic 23-bromosapogenin fingerprint[24] and hydroxyl (3600) and acetate (1734 and 1248 cm.$^{-1}$) peaks.

Preparation of 11β,12β-epoxydiosgenin (XV). Sixteen grams of XIII was dissolved in 600 ml. ethanol and 8 g. potassium hydroxide was added. The solution was stirred for 3 hr. and then allowed to stand for 20 hr. The product was isolated by pouring the solution into 1500 ml. of water and then extracting with three 600-ml. portions of ether. The ether layers were combined and washed with water to remove any residual base, then the ether was dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was then dissolved in 500 ml. ethanol and treated with a zinc-copper couple prepared from 60 g. of zinc and 450 ml. of 15% aqueous copper sulfate solution. The mixture was refluxed with stirring for 3 hr. and then filtered while hot. The filter cake was washed with additional hot ethanol. The alcoholic solution was diluted with two volumes of water and then extracted with ether (3 × 500 ml.). The ether portions were combined, washed with water, dried over sodium sulfate, and evaporated to dryness; yield 11 g. Infrared showed this to be a mixture of ketone and epoxide. The mixture was separated by two methods.

(a) *Girard T Reagent.* Eleven grams of the mixture was dissolved in 250 ml. ethanol containing 12.5 ml. acetic acid. Six grams of Girard T Reagent was added and the solution was refluxed for 1 hr. The solution was poured into 750 ml. of ice and water which was saturated with sodium carbonate. Two 800-ml. portions of ether were used to extract the aqueous mixture. The ether fractions were combined and washed with three portions of water, the last wash giving no precipitate upon being acidified with hydrochloric acid. The ether was then taken to dryness, giving 8.5 g. of crude 11β,12β-epoxydiosgenin (XV). The aqueous washes were acidified, allowed to sit overnight, and the precipitate filtered off, giving 1.9 g. of gentrogenin.

(b) *Partition chromatography.* A partition column, 2 inches in diameter and 36 inches long, was prepared by the slurry technique using 250 g. of Celite and 100 ml. of phenyl cellosolve. The steroid mixture, as the acetate, 2.2 g., was dissolved in 250 ml. of heptane and placed on the column. All the heptane used was saturated with phenyl cellosolve. The column hold-up was approximately 500 ml. Steroid appeared after an additional 250 ml., and all the nonketonic steroid was off after another 300 ml. The column was clean after another 500 ml. of solvent was passed through it. The ketonic fraction amounted to 0.3 g. and the nonketonic fraction amounted to 1.87 g., giving a total of 2.17 g. recovered.

The analytical sample of XV acetate was crystallized from methanol, acetone, and finally hexane, giving long rods, m.p. 186–189°, $[\alpha]_D^{25}$ −83.7 (dioxane). Infrared analysis showed a shoulder at 3030 (Δ^5), 1738, 1245 (acetate), normal F-ring bands, 875 cm.$^{-1}$ (oxide).

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.72; H, 8.85.

Preparation of 11β,12β-epoxy-3β-hydroxy-5,16-pregnadiene-20-one (XXI). Two grams of XV was dissolved in 100 ml. of dioxane, containing 20 ml. of 3*N* hydrochloric acid and 4 ml. of water. The solution was stirred for 1 hr., then 200 ml. of water was added, and stirring continued for 1 hr. A viscous gummy residue resulted. The product (XVI) was isolated by ether extraction in the usual manner and the ether was evaporated *in vacuo*, giving a resin. Without further purification, the resin was placed in a 50-ml. flask, 5 ml. of acetic anhydride containing 0.1% acetic acid was added, the flask sealed, and heated at 170° for 2 hr. The reaction mixture was cooled to room temperature and the acetic anhydride–acetic acid solvent was evaporated *in vacuo*, giving a glassy residue (XVII). The residue was dissolved in 40 ml. of methanol, 2 g. of potassium hydroxide was added, and the solution sat overnight at room temperature. The reaction mixture was poured into 120 ml. of water and then extracted with ether. The ether was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo* at room temperature.

The residue (XVIII) was dissolved in 10 ml. of pyridine and acetylated with 2.5 ml. of acetic anhydride at room temperature overnight. The diacetate XIX was isolated in the usual manner. Attempts to crystallize the compound were fruitless. Infrared showed peaks at 875 (oxide), 1735 and 1250 (diacetate), 1685 cm.$^{-1}$ (pseudosapogenin), and lack of F-ring bands.

The steroid (XIX) was dissolved in 50 ml. of acetic acid and the solution was cooled to 15°. Eight-tenths of a gram of chromium trioxide in 30 ml. of 50% acetic acid–water was cooled to 10° and then added to the steroid solution dropwise, with stirring, over a period of 15 min. The temperature of the reaction was maintained at 15° or less during the addition. The mixture was allowed to come to room temperature and stirred for 1 hr. The reaction mixture was drowned in 100 ml. water and extracted with ether (3 × 60 ml.). The ether was neutralized with sodium carbonate solution, washed with water, dried over sodium sulfate, and evaporated *in vacuo* at room temperature. The residue was dissolved in 50 ml. of *t*-butyl alcohol, 1 g. of potassium hydroxide in 2 ml. of water was added, and the mixture was stirred vigorously for 3 hr. The reaction mixture was poured into 200 ml. of water and extracted with ether, using the usual work-up. Evaporation to dryness *in vacuo* gave 1 g. of semicrystalline 11β,12β-epoxy-3-hydroxy-5,16-pregnadiene-20-one (XX). The analytical sample was recrystallized from acetone, hexane, and then methanol; m.p. 240–250° (sublimes off slide), $[\alpha]_D^{25}$ −29.0 (dioxane), log ε 3.92.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 76.79; H, 8.59. Found: C, 76.11; H, 8.96.

Infrared analysis (potassium bromide disk) showed bands at 3460 (hydroxyl), 1655 (conj. ketone), 875 (epoxide), and 808 cm.$^{-1}$ (Δ^6).

Hydrogenation of 11β,12β-epoxy-3β-hydroxy-5,16-pregnadiene-20-one (XX). Three tenths of a gram of a 2% palladium–carbon catalyst was placed in 25 ml. of ethanol and allowed to absorb hydrogen at atmospheric pressure. When the hydrogen uptake ceased, 0.320 g. of XX was added and the hydrogenation proceeded at atmospheric pressure and

(24) M. E. Wall and H. W. Jones, *J. Am. Chem. Soc.*, 79, 3222 (1957).

room temperature. The hydrogenation was stopped after 15 min., at which time the hydrogen uptake was 1.1 moles. The solution was filtered to remove the catalyst and the ethanol was evaporated. The product, 11β,12β-epoxy-3β-hydroxy-5-pregnen-20-one (XXI) was crystallized from hexane, then methanol, m.p. 174–179°, no ultraviolet absorption. Infrared analysis (potassium bromide disk) showed bands at 3400 (hydroxy), 1697 (20-ketone), 875 (epoxy), and 808 cm.$^{-1}$ (Δ^5).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

Monosaccharide Sulfates. I. Glucose 6-Sulfate. Preparations, Characterization of the Crystalline Potassium Salt, and Kinetic Studies[1]

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Speed of preparation and yield and purity of product are improved when glucose is sulfated directly using pyridine–sulfur trioxide in *N,N*-dimethylformamide. Purification of a directly sulfated glucose mixture ultimately leads to the crystalline, nonhygroscopic potassium salt of the 6-sulfate.

Two unequivocal syntheses of glucose 6-sulfate are described involving the removal of the protecting groups from 1) barium 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-sulfate and 2) barium 1,2;3,5-di-*O*-benzylidine-α-D-glucofuranose 6-sulfate.

Kinetic studies on the hydrolysis of the pure potassium salts of glucose 6-sulfate and ethyl sulfate were made, adapting the recently reported colorimetric determination of sulfate ions with barium chloranilate. The energy of activation for acid hydrolysis was determined for each compound. The effect of nitrogenous bases upon the hydrolysis of sulfate from unpurified glucose sulfate in buffered, slightly acid, or basic solution was determined.

Although glucose 6-sulfate has been known in varying degrees of purity for about forty years,[2–8] no one has succeeded in preparing a crystalline metallic salt. Soda and Egami[9] investigated the products of the direct sulfation of glucose and found, in addition to the 6-sulfate, a disulfate, which they concluded was the 1,6-sulfate. More recently, Dodgson and Spencer[10] reported a means of purifying the product of directly sulfated glucose by repeated recrystallization of the brucinium salt. Lloyd[11] has described a definitive synthesis for glucose 6-sulfate.

This paper describes first, some modifications of the direct method of synthesis and two indirect syntheses for glucose 6-sulfate, and, subsequently, characterization of the crystalline potassium salt and kinetic studies on the hydrolysis of the ester sulfate.

The most common direct sulfation procedure employs chlorosulfonic acid in chloroform-pyridine as the sulfating agent,[5] and results in a product which contains about 15% of glucose disulfate,[12] unless the purification technique of Dodgson and Spencer[10] is employed, in which case most of the disulfate is removed.

A more recent method[8] uses pyridine-sulfur trioxide in pyridine but gives a product containing up to 30% disulfate.[13] Furthermore, the use of barium carbonate does not insure complete removal of the pyridinium ion during the neutralization step.

The method finally worked out[14] for the direct sulfation of glucose employed pyridine–sulfur trioxide, with *N,N*-dimethylformamide as a solvent. The method minimizes polysulfation produced to a large extent by the heterogeneity of

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(1)(a) Abstracted from the dissertation submitted by Kenneth B. Guiseley to the Graduate School of Syracuse University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) Presented at the Cleveland Meeting of the American Chemical Society, April 1960 (Abstracts of that meeting, p. 1D). (c) This investigation was supported by a research grant (RG-4997(C3)) from the National Institutes of Health, Public Health Service.

(2) C. Neuberg and L. Liebermann, *Biochem. Z.*, **121**, 326 (1921).

(3) H. Ohle, *Biochem. Z.*, **131**, 601 (1922).

(4) T. Soda, *Biochem. Z.*, **135**, 621 (1923).

(5) T. Soda, *Bull. Chem. Soc. Japan*, **8**, 37 (1933).

(6) T. Soda and W. Nagai, *J. Chem. Soc. Japan*, **59**, 135 (1938).

(7) E. G. V. Percival and T. H. Soutar, *J. Chem. Soc.*, 1475 (1940).

(8) R. B. Duff, *J. Chem. Soc.*, 1597 (1949).

(9) T. Soda and F. Egami, *J. Chem. Soc. Japan*, **63**, 465 (1942).

(10) K. S. Dodgson and B. Spencer in *Methods of Biochemical Analysis*, Vol. IV, edited by D. Glick, Interscience, New York, 1957, pp. 211 ff.

(11) A. G. Lloyd, *Nature*, **183**, 109 (1959).

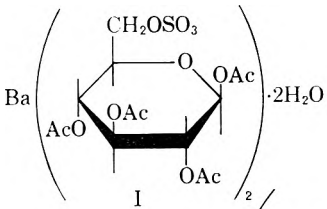
(12) T. Soda and H. Egami, *J. Chem. Soc. Japan*, **61**, 683 (1940).

(13) K. S. Dodgson and B. Spencer, *Biochem. J.*, **57**, 310 (1954).

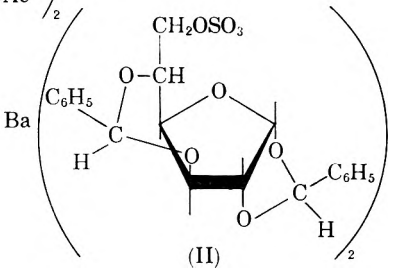
(14) Previously sulfamic acid was tried as a sulfating agent since it was known [M. E. Cupery, *Ind. Eng. Chem.*, **30**, 627 (1938)] to sulfate primary alcohols preferentially unless a suitable base was present [R. L. Burwell, Jr., *J. Am. Chem. Soc.*, **71**, 1769 (1949)]. However, as we later realized, the solvent, *N,N*-dimethylformamide, was basic enough to catalyze the sulfation of secondary alcohols, with the result that the products contained glucose disulfate. In addition, it was difficult to remove ammonium ion during neutralization and barium sulfamate after precipitation. Because of these factors, the method was not pursued further.

Duff's[8] procedure, and eliminates the involved chloride ion removal characteristic of chlorosulfonic acid sulfations. As a result, the method is faster than either of the other two, gives a product which is purer than that made by Duff's method, and, while giving a yield at least comparable to that of the chlorosulfonic method, is easier to perform.[15]

In the quest for pure glucose 6-sulfate, two definitive syntheses were achieved. The first involved sulfation of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose, and removal of the protective acetyl groups after isolation of the crystalline barium 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-sulfate (dihydrate) (I).



I



(II)

Shortly after this work was completed, Lloyd[11] reported a similar synthesis involving the same intermediate, but using different techniques.

In the second unequivocal synthesis, 1,2;3,5-di-*O*-benzylidene-α-D-glucofuranose (obtained directly from glucose[16]) was sulfated and the resulting barium 1,2;3,5-di-*O*-benzylidene-α-D-glucofuranose 6-sulfate (II) treated with dilute acid to remove the benzylidene residues.

Although both procedures were significant as definitive syntheses, they were not practical as preparative methods since the overall yields from glucose were less than 5%.

When the mixture of products from the direct sulfation of glucose was subjected to paper chromatography (1-butanol - ethanol - water - ammonia, 40:12:20:1[17]), a separation into three components resulted. The R_f values of 0.33, 0.20, and 0.10 corresponded to glucose, glucose 6-sulfate, and glucose disulfate, respectively. The spots for the sulfate salts had the same R_f, regardless of the salt used—barium, potassium, brucinium, and others.

Purification on a macro scale was attempted, using a cellulose column and essentially the same developing solution used with the paper strips, but as it was too time-consuming to prepare large quantities of pure glucose 6-sulfate in this manner, the chromatographic method was not further studied. However, a small quantity of the disulfate was isolated by this technique.

Because the definitive syntheses and the column chromatography method could not be conveniently scaled up, the recrystallization of brucinium glucose 6-sulfate (from direct sulfation) was reexamined as a means of preparing several grams of the pure substance. In our hands, the water-ethanol solvent pair used by Dodgson and Spencer[10] had been ineffectual in removing the disulfate, and was replaced by water-acetone, a solvent mixture used by Soda[4] only a few years after glucose "monosulfate" was first prepared. After only three recrystallizations, 98 mole per cent brucinium glucose 6-sulfate was obtained. From this the potassium salt was prepared in the conventional manner and dried by lyophilization. Subsequently, an aqueous solution of the salt deposited crystals upon spontaneous evaporation of the water. The crystalline potassium glucose 6-sulfate was anhydrous and non-hygroscopic in contrast to the amorphous potassium salt prepared by precipitation in ethanol.[10]

Hydrolytic studies were made on both purified and unpurified directly sulfated glucose. The course of the reaction was followed using the colorimetric sulfate method of Bertolacini and Barney[18] with suitable modifications.

Kinetic studies were made on the hydrolysis of sulfate from the purified potassium glucose 6-sulfate; for comparison, similar studies were made with potassium ethyl sulfate. Pseudo-first order rate constants were determined at three temperatures, and the energy of activation calculated for each compound from an Arrhenius plot. To show the dependence of the rate constants upon the substrate and acid concentrations, each was varied while holding the other and the temperature constant.

The rapid hydrolysis of part of the ester sulfate in unpurified glucose sulfate (direct sulfation) at *p*H 5.1 in the presence of hydrazine,[12] led to a means of analysis for the disulfate.

EXPERIMENTAL[19]

Pyridine-sulfur trioxide was prepared in essentially the same manner described in *Inorganic Syntheses*[20] except that

(15) After this work was completed we noted that sulfur trioxide-*N*,*N*-dimethylformamide complex in an excess of dimethylformamide was used in the homogeneous sulfation of chitosan [M. L. Wolfrom and T. M. Shen Han, *J. Am. Chem. Soc.*, **81**, 1764 (1959)].

(16) H. B. Wood, Jr., H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **79**, 3862 (1957).

(17) S. Suzuki, N. Takahashi, and F. Egami, *Biochim. et Biophys. Acta*, **24**, 444 (1957).

(18) R. J. Bertolacini and J. E. Barney II, *Anal. Chem.*, **29**, 281 (1957).

(19)(a) All melting points are uncorrected. (b) Microanalyses were performed at the Spang Microanalytical Laboratory, Ann Arbor, Mich. (c) All evaporations *in vacuo* were carried out with a Rinco Rotating Evaporator, Model 1007 4 IN.

Sulfan B (General Chemical Division, Allied Chemical and Dye Corporation's brand of stabilized sulfur trioxide) was used in place of chlorosulfonic acid in order to prepare the compound free from both chloride and sulfate ions. In a 5-l., three necked flask, equipped with a dropping funnel, thermometer (extending nearly to the bottom), and electric stirrer (loose-fitting glass seal) were placed about 2.25 l. of dry, alcohol-free chloroform and 200 ml. (*ca.* 2.5 moles) of anhydrous pyridine. During the dropwise addition of 80 ml. (1.92 moles) of Sulfan B, the temperature was kept between 0° and 10°. The product was filtered off by suction, washed with 500 ml. of ice-cold, dry, alcohol-free chloroform, and aspirated under a rubber dam. It was dried in a vacuum desiccator over concentrated sulfuric acid by continuous aspiration to yield about 235 g. (80%).

Chlorosulfonic acid was purified by distilling the practical grade material in an all-glass apparatus, using the fraction boiling at 156–158°.

Paper chromatography was carried out on Whatman No. 1 paper, using the solvent mixture of Suzuki *et al.*[17]: 1-butanol, ethanol, water, ammonia: 40:12:20:1. The chromatograms were run in the ascending manner with either glucose or a salt of glucose 6-sulfate spotted alongside to give reference points. After completion of a run, the strips were quickly dried in an oven at 115° and sprayed with a 3% solution of *p*-anisidinium chloride in butanol. Color was developed by heating the sprayed paper at 110–115° for *ca.* 10 minutes.

Direct sulfation procedures. A. *Chlorosulfonic acid in pyridine.* The method of Dodgson and Spencer[10] was followed exactly and gave a 16.5% yield of brucinium glucose 6-sulfate.

B. *Pyridine–sulfur trioxide in pyridine.* Duff's method[8] was followed exactly, giving a gummy product which proved to consist mainly of the pyridinium salt, rather than the expected barium salt of glucose 6-sulfate. Conversion to the barium salt was effected by dissolving the sticky pyridinium salt in water, and adding barium hydroxide solution to *p*H 7.5. Concentration *in vacuo* removed the liberated pyridine and water. This process of neutralization and evaporation was repeated until the sirupy product, when dissolved in water, became neutral. After removal of the barium sulfate by centrifugation, the solution was concentrated to a syrup, and the product precipitated by pouring the syrup slowly into 850 ml. of absolute ethanol. After standing overnight, the barium glucose sulfate was filtered off, washed with ether to facilitate drying, aspirated under a rubber dam, and dried over phosphorus pentoxide *in vacuo;* Yield, 11.4 g. (59.5%). Polysulfation is indicated by high barium analysis.

Anal. Calcd. for $Ba(C_6H_{11}O_9S)_2$: Ba, 20.95. Found: Ba, 25.3.

C. *Pyridine-sulfur trioxide in N,N-dimethylformamide.* By warming to about 50°, 21.6 g. (0.12 mole) of anhydrous D-glucose was dissolved in 300 ml. of anhydrous dimethylformamide in a 1-l., three necked flask equipped with an air condenser and drying tube, ground glass stirrer, and dropping funnel. With stirring, a solution of 19.0 g. (0.12 mole) of pyridine–sulfur trioxide in about 125 ml. of dry dimethylformamide was added to the solution (at room temperature) over a period of 1.5 hr. Stirring was continued for an additional hour, after which, the dimethylformamide was removed *in vacuo* at less than 35°, and the resulting syrup taken up in 125 ml. of water. Barium hydroxide was added to *p*H 10.0, then carbon dioxide to a *p*H of 7.5. Concentration, *in vacuo*, removed water and liberated pyridine. The paste was taken up in 100 ml. of water. If the *p*H of the suspension were under 7.0, more barium hydroxide was added to bring the *p*H to 7.0–7.5, the water was evaporated *in vacuo*, and the process repeated until neutrality was permanent. After warming the suspension to 40°, barium sulfate was centrifuged off, and the solution treated with charcoal. The *p*H was checked and brought to 7.0 with barium hydroxide, if necessary. After concentration of the solution to a medium-thick syrup *in vacuo*, the product was precipitated as follows: methanol was added to the syrup a few milliliters at a time, with swirling, to redissolve the precipitated barium glucose sulfate. When it appeared that solution would not be possible after the addition of another increment, about 500 ml. of methanol was added in one portion. The flask was stoppered and shaken vigorously for about half a minute. The flask was placed on an automatic shaker overnight to "digest" the fine white precipitate of barium glucose sulfate. The resulting granular product was filtered off by suction, washed once with methanol and twice with ether, then dried *in vacuo* over phosphorus pentoxide. A second fraction could usually be obtained from the filtrate after the ether washings had been mixed in. Yield: first fraction, 16.6 g. (40%); second fraction, 5.8 g. (14%).

Anal. Calcd. for $Ba(C_6H_{11}O_9S)_2$: Ba, 20.95. $Ba(C_6H_{11}O_9S)_2 \cdot 2H_2O$: Ba, 19.85. Found: Ba, 1st fraction 19.8; 2nd fraction, 18.7. Despite the apparently good analysis, paper chromatography showed the presence of three compounds: glucose, glucose 6-sulfate, and glucose disulfate.

Pure brucinium α-D-glucose 6-sulfate. Twenty-five grams of crude barium glucose 6-sulfate was dissolved in 175 ml. of water, and the solution passed over an Amberlite IR-120 column (1.5 × 40.0 cm.), hydrogen-ion form, at the rate of 3.0 ml. per min. Ethanolic brucine was added to the combined effluent and rinsings to *p*H 6.0. After removal of the ethanol *in vacuo*, the water solution was washed twice with 75-ml. portions of chloroform, then twice with 50-ml. portions of ether. The solution was concentrated to 150–200 ml., *in vacuo*, and warmed to about 40°. Acetone was added to incipient cloudiness, while the solution was kept close to 40°. Upon slow cooling, and finally refrigeration, rosettes of very fine crystals formed. These were filtered off, washed with 90% acetone, then acetone, and allowed to air-dry. Three recrystallizations of this brucinium salt, performed in the same manner (x g. of brucinium salt dissolved in $3x$ ml. of water, warmed to 40°, and treated with approximately $12x$ ml. of acetone) with one charcoal treatment, yielded 15.2 g. (30.5%, based on crude barium salt) of product which, as shown in the next section, proved to be 98 mole per cent pure brucinium glucose 6-sulfate. $[\alpha]_D^{20}$ −1.57° (5 min.) → −6.53° (equi.) (*c.* 4.835, in water).

Analytical method for the quantitative determination of disulfate in purified brucinium α-D-glucose 6-sulfate. A 0.4144-g. sample of brucinium α-D-glucose 6-sulfate was weighed into a 10-ml. volumetric flask and dissolved in about 3 ml. of warm water. To this was added 4 ml. of 1*M* acetate buffer (*p*H 5.1) and 1.2 ml. of 1*M* hydrazine in aqueous acetic acid (*p*H 5.1). The mixture was diluted to the mark with water, mixed well, and incubated at 37.5° ± 0.5° for 30 hr. A 5-ml. aliquot was then analyzed as follows: The aliquot, contained in a 20-ml. beaker, was neutralized to *p*H 4.0 on the *p*H meter, using 0.64*N* hydrochloric acid (a little over 2 ml. was required). Five milliliters of a 1:1 mixture of 0.05*M* potassium hydrogen phthalate buffer and 95% ethanol was added and the *p*H readjusted to 4.0 with acid. The solution was transferred to a 25-ml. volumetric flask. After rinsing the electrodes into the beaker with about 1 ml. of water and 5 ml. (pipet) of 95% ethanol, the rinsings were transferred to the flask, the beaker rinsed into the flask with 5 ml. (pipet) more of 95% ethanol, and the flask made up to the mark with water. A blank was prepared similarly from a 5-ml. aliquot of a solution containing 40 ml. of 1*M* acetate buffer, *p*H 5.1, and 12 ml. of 1*M* hydrazine in acetic acid (*p*H 5.1) in a total volume of 100 ml. To each 25-ml. volumetric flask was added 0.050 g. of barium chloranilate.[18] The flasks were shaken once a minute for 15 min., the solutions centrifuged to clarity, and the per cent transmittance read on a Fisher Electrophotometer (or other suitable instrument) using the 525B green filter on the D scale. From a standard curve prepared from known concentrations of sulfate, the amount of sulfate liberated was determined, and

(20) W. C. Fernelius, *Inorganic Syntheses*, Vol. II, McGraw-Hill, New York, 1946, p. 173.

from that, the mole per cent of disulfate in the sample. (As hydrazine barely catalyzes the hydrolysis of sulfate from the 6-position, but does cause quantitative hydrolysis of sulfate from the 1-position of the 1,6-disulfate under the conditions employed, the amount of sulfate liberated is proportional to the amount of disulfate present.)

Crystalline potassium β-D-glucose 6-sulfate. To a solution of 15.0 g. of pure brucinium α-D-glucose 6-sulfate in 500 ml. of water, was added 1*N* potassium hydroxide to *p*H 9.5. The mixture was chilled in an ice bath for a few minutes, after which the precipitated brucine was filtered off. The filtrate was washed twice with chloroform, 100 ml., 80 ml., then twice with ether, 100 ml., 80 ml., and concentrated *in vacuo* to about 35 ml. Absolute ethanol was added to incipient cloudiness. If a gelatinous precipitate formed, it was centrifuged off. On standing, potassium β-D-glucose 6-sulfate crystallized out. This was filtered off and washed with 50–60% ethanol, then ethanol. As the compound was not hygroscopic, as contrasted with the amorphous form,[10] it could be air-dried. One recrystallization yielded 4.20 g. (65%, based on brucinium salt), m.p. 170–173° dec. $[\alpha]_D^{20}$ +16.46° (after 5 min.) → +37.35° (equi.) (*c* 2.983, in water).

Anal. Calcd. for $KC_6H_{11}O_9S$: K, 13.11; C, 24.16; H, 3.72; S, 10.75. Found: K, 12.99; C, 24.13; H, 3.68; S, 10.85.

Its density, determined by the flotation method, was 1.816 ± 0.004 g./ml.

X-ray powder diffraction data (nickel-filtered Cu Kα radiation): 12.50 (2), 6.544, 5.746, 5.698, 4.861 (1, strongest), 4.668, 4.651, 4.568, 4.518 (3), 4.110, 3.974 (1) 3.882, 3.703 (4), 3.666, 3.465, 3.329, 3.264, 3.177, 3.117, 3.008, 2.980, 2.958, 2.898, 2.851, 2.818, 2.810, 2.776, 2.724, 2.673 (5), 2.555.

Barium 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose 6-sulfate (I). To a solution of 5.22 g. (0.015 mole) of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[21] in 20 ml. of anhydrous pyridine contained in a 50-ml. glass-stoppered flask, was added 2.39 g. (0.015 mole) of pyridine-sulfur trioxide in one portion. The mixture was shaken until solution was complete. After standing at room temperature overnight, the reaction mixture was dissolved in 50 ml. of water, and the solution neutralized (*p*H 7.5) with aqueous barium hydroxide. The resulting suspension was concentrated to dryness *in vacuo*, and the residue taken up in 60 ml. of water. (The *p*H was adjusted to 7.0 with barium hydroxide, if acidic; the neutralization and evaporation steps were repeated until the suspension had a *p*H of 7.0 upon being taken up in water.) Insoluble inorganic salts were removed by centrifugation and the solution treated with charcoal, if necessary. The solution was concentrated *in vacuo* to a thick syrup which was redissolved in 30–40 ml. of methanol. Ether was added to cloudiness and the solution chilled until crystallization was complete. After being washed with methanol-ether, 1:1, and ether, the product was dried *in vacuo* over phosphorus pentoxide. Recrystallization by evaporation of a 98% ethanol solution of the compound (method of Ohle[3]) gave 2.3 g. (30%) of white crystals, m.p. 105–106° dec., $[\alpha]_D^{20}$ + 11.8° (*c*. 2.995, in water).

Anal. Calcd. for $Ba(C_{14}H_{19}O_{13}S)_2 \cdot 2H_2O$: Ba, 13.36; C, 32.71; H, 4.12; S, 6.24. Found: Ba, 13.35; C, 32.32; H, 3.80; S, 6.18.

X-ray powder diffraction data (nickel-filtered Cu Kα radiation): 11.7 (1, strongest), 9.24 (3), 8.20 (5), 6.53 (4), 5.77, 5.01, 4.70, 4.47, 4.31, 4.09, 3.848 (2), 3.614, 3.462, 3.366, 3.272, 3.152, 3.023, 2.936.

Barium glucose 6-sulfate from I. A solution of 1.00 g. of barium 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-sulfate (dihydrate) (I) in 10 ml. of absolute methanol, was cooled to 0° and saturated with dry ammonia.[22] After the solution had stood overnight at room temperature, the methanol and ammonia were removed *in vacuo* and a few milliliters of absolute ethanol evaporated from the residue to insure dryness. Following this, the residue was washed three times with absolute ethanol in order to remove acetamide, then taken up in 20 ml. of water. The solution was treated with charcoal, filtered, and concentrated *in vacuo*. Addition of absolute methanol gave 0.35 g. (53%) of product after filtering, washing, and drying.

Anal. Calcd. for $Ba(C_6H_{11}O_9S)_2 \cdot 2H_2O$: Ba, 19.85. Found: Ba, 19.02.

The x-ray diffraction pattern of the brucinium salt made from this barium salt was identical with that of the standard (see below).

1,2;3,5-Di-O-benzylidene-α-D-glucofuranose was prepared according to the method of Wood, Diehl, and Fletcher.[18] Recrystallization of the compound from ethyl acetate gave crystals melting at 160–161° as reported. However, when the reaction was scaled up by a factor of four, the melting point of the product could not be raised over 155–157°, neither by this method of recrystallization, nor the ammoniacal methanol method of Wolfrom and Tanghe.[23]

Barium 1,2;3,5-di-O-benzylidene-α-D-glucofuranose 6-sulfate (II). A solution of 3.11 g. (0.0087 mole) of 1,2;3,5-di-*O*-benzylidene-α-D-glucofuranose in 24 ml. of anhydrous pyridine was shaken in a 50-ml. glass-stoppered flask with 1.67 g. (0.0105 mole, *ca.* 20% excess) of pyridine-sulfur trioxide until solution was complete (10 min.). After an additional 10 min., the solution was poured into 20 ml. of cold water, and barium hydroxide solution was added to *p*H 8.2. Carbon dioxide was bubbled in to *p*H 7.5 and the solvents were removed *in vacuo*. The paste was treated with 50% ethanol to dissolve the product, and the *p*H adjusted to 7.0. Insoluble barium salts were centrifuged off and the resulting solution concentrated to a paste again (*in vacuo*). The neutralization-evaporation procedure was repeated until the *p*H of the solution was 7.0. The solution was dried until it solidified, then dried *in vacuo* over phosphorus pentoxide. The yield was 3.00 g. (68%) of amorphous material melting at 134–139° dec.

Anal. Calcd. for $Ba(C_{20}H_{19}O_9S)_2$: Ba, 13.62: C, 47.65; H, 3.80; S, 6.36. Found: Ba, 13.46; C, 47.95; H, 3.86; S, 6.18.

Barium glucose 6-sulfate from II. The protective benzylidene groups were removed by hydrolysis in dilute acid. In a typical experiment, 2.7 g. (0.00268 mole) of barium dibenzylidene-glucose 6-sulfate was placed in a 100-ml. round bottomed flask with 50 ml. of 1% acetic acid containing 5% ethanol. The mixture was refluxed for a total of 1.25 hr. Solution was complete after 1 hr., indicating that the reaction was nearly over, since the product, but not the starting material, was soluble in so aqueous a medium. After cooling, the solution, now milky with a suspension of benzaldehyde, was washed with three 30-ml. portions of ether, then concentrated to dryness *in vacuo*. The crude product, free from both benzaldehyde and acetic acid, was dissolved in a little water, treated with charcoal, filtered, neutralized to *p*H 7.0 with barium hydroxide solution, and concentrated to a syrup *in vacuo*. Absolute ethanol was added to precipitate the product. After standing overnight, it was filtered off, dried *in vacuo* over phosphorus pentoxide, and weighed: 1.1 g. (59.5%).

The brucinium salt was prepared as above to yield 0.5 g. (23%, based on barium salt) of fine white crystals with m.p. 182° dec. Its X-ray diffraction pattern was taken as a standard for brucinium α-D-glucose 6-sulfate (nickel-filtered Cu Kα radiation): 9.50, 8.54 (5), 7.92, 7.36, 6.90, 6.39 (5), 5.99, 5.66, 5.32 (5), 4.68 (1, strongest), 4.41, 4.14, 4.01, 3.797 (3), 3.636 (2), 3.490 (5) 3.370, 3.242, 3.126 (4), 2.994.

Anal. Calcd. for $C_{29}H_{38}O_{13}N_2S \cdot 2H_2O$: C, 50.43; H, 6.13; N, 4.06; S, 4.64. Found: C, 50.19; H, 6.11; N, 3.75; S, 4.24.

(Removal of the protecting groups from barium 1,2; 3,5-di-*O*-benzylidene-α-D-glucofuranose 6-sulfate by hydro-

(21) E. C. Horning, *Org. Syntheses*, Coll. Vol. III, 432 (1955).

(22) B. Helferich and J. Becker, *Ann.*, **440**, 16 (1924).

(23) M. L. Wolfrom and L. J. Tanghe, *J. Am. Chem. Soc.*, **59**, 1597 (1937).

TABLE I
KINETIC DATA

Substrate	Temp., ±0.1°	Substrate, (Mole/l.)	HCl, (Mole/l.)	Pseudo-1st Order Rate Constants, Min.$^{-1}$ (least squares)
Potassium glucose 6-sulfate	37.0	0.0600	0.487	$3.37 \pm 0.17 \times 10^{-6}$
	52.0	0.0600	0.503	$2.95 \pm 0.15 \times 10^{-5}$
	70.0	0.0600	0.495	$3.36 \pm 0.16 \times 10^{-4}$
	70.0	0.0287	0.490	$3.62 \pm 0.18 \times 10^{-4}$
	52.0	0.0600	1.24	$8.37 \pm 0.42 \times 10^{-5}$
Potassium ethyl sulfate	37.0	0.0600	0.485	$1.08 \pm 0.05 \times 10^{-6}$
	52.0	0.0600	0.519	$1.10 \pm 0.06 \times 10^{-5}$
	70.0	0.0600	0.505	$1.22 \pm 0.06 \times 10^{-4}$
	70.0	0.030	0.499	$1.26 \pm 0.10 \times 10^{-4}$
	52.0	0.0600	1.23	$2.89 \pm 0.29 \times 10^{-5}$

genolysis in aqueous ethanol over palladium black[24] at 1–2 atm. of hydrogen, failed. However, when the free acid was used, hydrogen uptake was observed, but was believed to be due to hydrogenation of the benzaldehyde produced by hydrolysis.)

Separation of the products of direct sulfation of glucose by column chromatography. Solka-Floc was washed twice with about four to five times its weight of the following solvent mixture: 1-butanol-ethanol-water, 40:12:20. A slurry of the washed cellulose was then poured into a column and packed by passing the solvent mixture through, under 3–4 p.s.i. air pressure until the effluent was colorless, and the cellulose had completely settled.

A trial run was made on a cellulose column 1.29 × 29 cm. A solution containing 0.1 g. of the crude product was prepared as follows: The mixture was dissolved in 1 ml. of water; to this was added 0.6 ml. of ethanol, followed by butanol to a point just short of cloudiness. This solution was placed on the column and eluted with the solvent mixture described above, under gravity. Fractions (3-ml.) were collected on a Rinco Automatic Fraction Collector, and analyzed by paper chromatography:

Fraction No.	Material Present
0–13	—
14–20	Glucose
21–39	Glu-6-SO_4
40–70	Glu-diSO_4

Because the method seemed successful, a larger column (3.0 × 78 cm.) was prepared. A solution of the mixture [5 g. of the crude product in 20 ml. of water, plus 12 ml. of absolute ethanol, then butanol to incipient cloudiness (*ca.* 10 ml.)] was placed on the column and eluted. That the solution contained too much material for separation was demonstrated by a break-through of unresolved starting material (1.9 g., 38%) in the volume 500–1000 ml. The attempted separation was repeated with 1.5 g. of the mixture dissolved in 15 ml. of water + 9 ml. of ethanol + 10 ml. of butanol. Again, there was a break-through of unresolved components, occurring this time in the range 700–820 ml. Various groups of fractions were collected and combined. The solvent was evaporated from the last group of fractions collected (2030–2650 ml.) to yield 0.12 g. of material with an analysis corresponding to 26.1% barium. Ba glu-mono-SO_4 requires 20.95% Ba. Ba glu-di-$SO_4 \cdot 3H_2O$ requires 26.0% Ba.

Kinetic studies on pure potassium glucose 6-sulfate and potassium ethyl sulfate. Hydrolysis of sulfate was followed colorimetrically.[18] The solutions were thermostated to ±0.1°. The exact concentration of acid was determined by titrating aliquots of the solution after a run had been made, and subtracting the contribution of the bisulfate ion produced by the hydrolysis.

Materials. Potassium ethyl sulfate (Eastman Kodak, white label, 10 g.) was purified by dissolving it in water (100 ml.), adding barium hydroxide solution to *p*H 9.0, and centrifuging off the resulting barium sulfate. The clear, sulfate-free solution was passed over an Amberlite IR-120 column, hydrogen-ion form, to remove barium ion. The effluent was neutralized to *p*H 7.2 with potassium hydroxide solution, concentrated to about 25 ml. *in vacuo*, and lyophilized.

Anal. Calcd. for $KC_2H_5O_4S$: K, 23.8. Found: K, 23.1.

Potassium glucose 6-sulfate was prepared by addition of potassium hydroxide solution to pure brucinium glucose 6-sulfate (17 g.) dissolved in water (700 ml.), followed by adequate washings with chloroform and ether. For the kinetic runs, the crystalline material was not yet available. Instead, the solution of potassium glucose 6-sulfate was concentrated to *ca.* 60 ml. *in vacuo*, and lyophilized to give 6.7 g. of pure material.

Anal. Calcd. for $KC_6H_{11}O_9S.H_2O$: K, 12.36. Found: K, 12.43.

Barium chloroanilate was used as supplied by Fisher Scientific Company.

Procedure. The following general method was used in the kinetic determinations having substrate concentration equal to 0.0600*M* and acid concentration 0.5*M*: The desired amount of substrate (0.9490 g. of potassium glucose 6-sulfate; 0.4927 g. of potassium ethyl sulfate) was weighed into a 50-ml. volumetric flask and dissolved in a little water. To the solution was added 25.0 ml. of 1*M* hydrochloric acid and sufficient water to dilute the contents to volume. After thorough mixing, the flask was thermostated. Analyses were made at appropriate time intervals by neutralizing a 5-ml. aliquot contained in a 20-ml. beaker, with 1.2*M* ammonium hydroxide to a *p*H of 2.5–2.8 (*ca.* 2 ml. required), then with 0.12*M* ammonium hydroxide to *p*H 3.0. Five milliliters of 1:1 0.05*M* potassium hydrogen phthalate buffer and 95% ethanol was then added, and the *p*H very carefully adjusted to 4.12–4.15 with the 0.12*M* ammonium hydroxide (accurate *p*H control was very essential). The solution was transferred to a 25-ml. volumetric flask. The electrodes were rinsed off into the beaker with about 1 ml. of water, then 5 ml. of 95% ethanol (pipet). This was transferred to the volumetric flask, and the beaker again rinsed into the flask with 5-ml. more alcohol (pipet). The solution was then diluted to volume with water. A blank was prepared similarly from a 5 ml. aliquot of 0.5*M* hydrochloric acid. (This blank, thus prepared, was also used for diluting purposes; see below.) To each 25-ml. volumetric flask was added 0.050 g. of barium chloranilate. The flasks were shaken once a minute for 15 min., the solution centrifuged to clarity, and the per cent transmittance read on a Fisher Electrophotometer (or other suitable instrument), using the 525B green filter on the D scale. From a standard curve prepared from known concentrations of sulfate, the amount

(24) E. C. Horning, *Org. Syntheses*, Coll. Vol. III, 685 (1955).

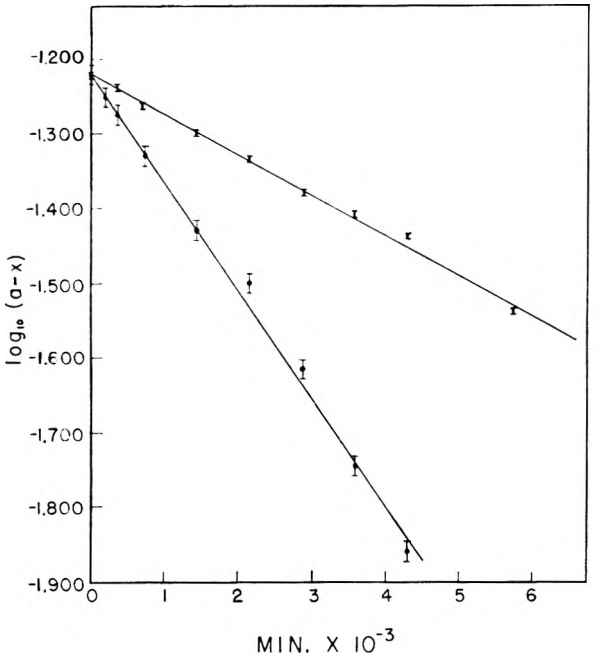


Fig. 1. First order plot (least squares) for hydrolysis of sulfate from 0.0600*M* K glu 6-SO_4 (∓) and 0.0600*M* K $C_2H_5SO_4$ (I) in 0.5*M* HCl at 70.0°

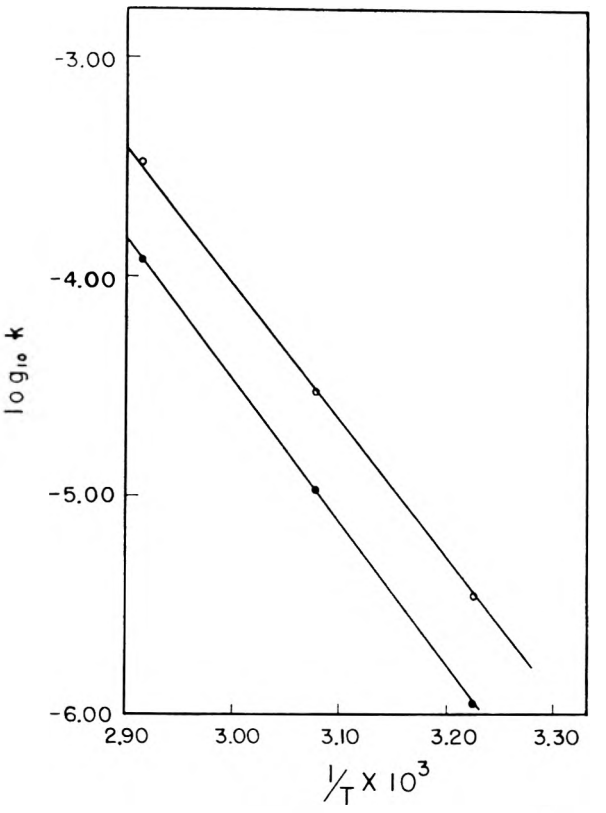


Fig. 2. Arrhenius plot for hydrolysis of sulfate from K glu 6-SO_4 (○) and K $C_2H_5SO_4$ (●) in 0.5*M* HCl

of sulfate liberated was determined. If an aliquot was known to contain an amount of sulfate greater than the upper limit of the standard curve, a dilution was made as follows: Following the neutralization of the sample, and dilution to 25 ml., an aliquot of suitable size was withdrawn and placed in another (dry) 25-ml. volumetric flask. After dilution to volume with prepared blank, this solution was treated with barium chloranilate in the usual manner, an appropriate factor being used when calculating the amount of sulfate present in the original 5-ml. aliquot of reaction mixture.

In the other two sets of kinetic runs, certain modifications were made: For 0.030*M* substrate in 0.5*M* hydrochloric acid, half as much substrate was used; the amount of acid and method of analysis were unchanged. For 0.0600*M* substrate in 1.25*M* hydrochloric acid, the acid added initially, was 2.5*M* (25 ml.), the amount of substrate being the same as before. For analysis of this mixture, 2 ml. was pipetted from the reaction flask and added to 3 ml. of water contained in a 20-ml. beaker. From here on, the method was as described above.

Hydrolytic studies on unpurified glucose sulfate. A. *At pH 5.1.* In a typical experiment, 1.6214 g. of impure glucose sulfate was dissolved in 15 ml. of water, and the solution passed over an ice-water jacketed Amberlite IR-120 column, hydrogen-ion form (1.0 × 13.5 cm.). The free acid was thoroughly removed from the column with water. The effluent was neutralized to *p*H 7.0 with sodium hydroxide solution, then concentrated to a few milliliters *in vacuo*. The solution of sodium glucose sulfate was transferred quantitatively to a 25-ml. volumetric flask and diluted to volume with water. To prepare a solution for hydrolytic study, the following solutions were combined in a 25 ml. volumetric flask, and diluted to volume with water: 8 ml. of the sodium glucose sulfate solution, 10 ml. of 1*M* acetate buffer, *p*H 5.1, 3 ml. of 1*M* catalyst (hydrazine, semicarbazide, imidazole, *dl*-serine, or L-glutamine) adjusted to *p*H 5.1. Final concentrations were: substrate, 0.060*M*, catalyst, 0.120*M*, buffer, 0.40*M*. Blanks were prepared similarly, omitting the glucose sulfate solution; a control was prepared by omission of the catalyst. The flasks were immersed in a constant temperature bath, 37.5 ± 0.1°. At intervals, 5-ml. aliquots were withdrawn and analyzed by the method described in an earlier section (determination of disulfate) for the case of the *p*H 5.1 acetate buffer.

B. *At pH 8.9.* Conditions were the same as in part A, except that the buffer stock solution was 1*M* ammonium chloride–ammonium hydroxide, and the catalyst stock solutions were adjusted to *p*H 8.9 with ammonium hydroxide. The analyses were made as before, except that 0.22*M* hydrochloric acid was used to lower the *p*H of the aliquot to 4.0. Also, suitable blanks and controls were run.

RESULTS AND DISCUSSION

Kinetic studies on pure potassium glucose 6-sulfate and pure potassium ethyl sulfate. The results of the kinetic studies are given in Table I.

Figure 1 shows a typical least squares plot of the data for one of the kinetic runs, while in Fig. 2, the temperature dependence of the sulfate hydrolysis is shown for both potassium glucose 6-sulfate and potassium ethyl sulfate. From the latter curves, the activation energies were calculated and found to be 29 kcal per mole for the glucose 6-sulfate anion, and 30 kcal per mole for the ethyl sulfate anion.

A rough comparison can be made between the rates of hydrolysis of phosphate and sulfate from the 6-position of glucose. Robison[25] found the first order rate constant for the hydrolysis of phosphate from glucose 6-phosphate in 1*M* hydrochloric acid at 100° to be 2.2×10^{-4} min.$^{-1}$. By extrapola-

(25) R. Robison, *Biochem. J.*, **26**, 2191 (1932).

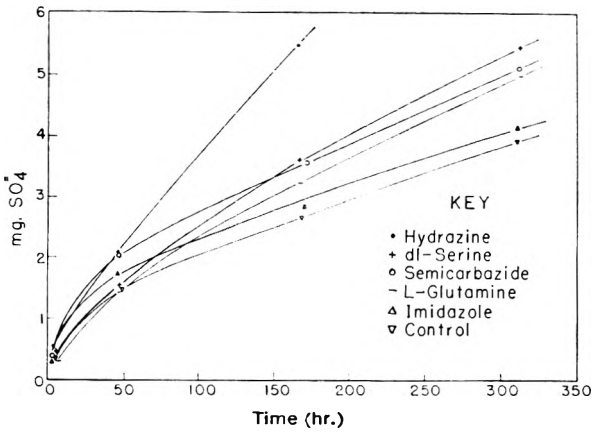


Fig. 3. Hydrolysis of impure Na glu 6-SO_4 (0.06M) in the presence of some nitrogenous bases (0.12M), in 0.40M acetate buffer (pH 5.1) at 37.5°

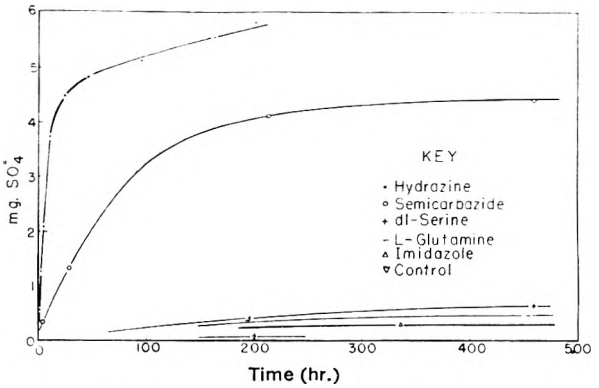


Fig. 4. Hydrolysis of impure Na glu 6-SO_4 (0.06M) in the presence of some nitrogenous bases (0.12M), in 0.40M ammonium buffer (pH 8.9) at 37.5°

tion of the Arrhenius plot, the rate constant for the hydrolysis of glucose 6-sulfate in 0.5M hydrochloric acid at 100° can be found. As, at the concentrations used, the rate was roughly proportional to the concentration of acid, this value can be doubled to give an approximate value for the rate constant at 100° in 1M hydrochloric acid: 1.97×10^{-2} min.$^{-1}$, which is about two orders of magnitude as great as the value for the phosphate. It will be interesting to compare more of these as more data become available.

Hydrolytic studies on unpurified glucose 6-sulfate (ca. 15% disulfate). The results of these preliminary studies are shown in Figs. 3 and 4. As already reported by Soda and Egami,[12,26] hydrazine and semicarbazide were very effective in catalyzing the hydrolysis of sulfate from the disulfate impurity at pH 5.1, but much less so in the case of the 6-sulfate (major constituent of the unpurified material). At pH 5.1, the other bases examined showed very little activity. At pH 8.9, there was a general hydrolysis brought about by the base, although imidazole, L-glutamine, semicarbazide, and *dl*-serine exhibited a small catalytic effect. Hydrazine again showed a strong tendency to accelerate the hydrolytic process.

X-ray crystallographic data on pure potassium β,D-glucose 6-sulfate. From a Weissenberg picture of a single crystal of potassium β-D-glucose 6-sulfate, taken and interpreted by William O. Roberts, the lattice constants of the unit cell (monoclinic) were tentatively assigned the following values: a_0 = 12.99 Å, b_0 = 7.71 Å, c_0 = 5.77 Å, β = 106.6°. From the density of the compound, 1.816 ± 0.004 g./cc., it followed that there were two molecules per unit cell. However, when d values were obtained from the powder pattern, using a recording diffractometer, *hkl* values could be assigned to only half the d values. There is evidence that grinding causes a partial phase change. More work is currently underway to determine if this is the case.

Polarimetric studies on pure brucinium α-D-glucose and pure potassium β-D-glucose 6-sulfate. Polarimetric readings were obtained at several times during the mutarotation of these two compounds and a plot of $\log_{10}(\alpha_\infty - \alpha)$ *vs.* t, made for each. Extrapolation to zero time gave rotational values of +14.2° for potassium β-D-glucose 6-sulfate and −1.28° for brucinium α-D-glucose 6-sulfate at 20°. After taking into account the rotation of the brucinium ion, the relatively amounts of α- and β-forms in the equilibrium mixture were found to be 81.5% and 18.5%, respectively.

NOTE ADDED IN PROOF: Two significant contributions on monosaccharide sulfates appeared in the December issue of the Journal of the Chemical Society, S. Peat *et al.*, *J. Chem. Soc.*, 4761 (1960) and D. Grant and A. Holt, *J. Chem. Soc.*, 5026 (1960).

(26) H. Egami, *J. Chem. Soc. Japan*, **59**, 1034 (1938).

SYRACUSE 10, N. Y.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Reaction of Ethyl 5-*O*-Benzoyl-1-thio-β-L-arabinoside with Silver Benzoate and with Mercuric Acetate

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Ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside (I) reacts in boiling acetonitrile solution with silver benzoate to give 1,5-di-*O*-benzoyl-α-L-arabinose (II). The structure of this product is shown through conversion to 1,5-di-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose (IV) and 5-*O*-benzoyl-2,3-*O*-di-*p*-nitrobenzoyl-α-L-arabinosyl bromide (V) and through conversion of V to IV by silver benzoate.

With mercuric acetate in acetonitrile at room temperature ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside (I) is transformed to 1-*O*-acetyl-5-*O*-benzoyl-α-L-arabinose (VI). The nature of this product is clarified through its behavior with periodate, stability in aqueous pyridine and conversion through 1-*O*-acetyl-5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose (VII) to V.

In recent communications it has been shown that aldose dialkyl dithioacetals[2,3] and an alkyl 1-thioaldopyranoside[2] react with the silver salts of various carboxylic acids to give 1-*O*-acylaldoses. Likewise, 5-*O*-benzoyl-2-deoxy-D-ribose diisopropyl dithioacetal has been found to condense with chloromercuri-6-benzamidopurine to give (after removal of the protecting groups) 2′-deoxyadenosine and its anomer.[4] We have now extended this investigation to a representative of a third class of 1-thioaldose derivatives, an alkyl 1-thioaldofuranoside.

Ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside (I) was prepared through partial demercaptalation of 5-*O*-benzoyl-L-arabinose diethyl dithioacetal using the process which Reist, Hart, Goodman and Baker[5] described for its enantiomorph. Condensation of this substance with silver benzoate in boiling acetonitrile led to the isolation in 33% yield of a crystalline di-*O*-benzoylpentose. The ring structure of this substance was demonstrated through benzoylation which gave α-L-arabinofuranose tetrabenzoate (III). That the newly introduced benzoyl group was located at C_1 was ascertained through *p*-nitrobenzoylation to the crystalline ester IV and conversion of this with hydrogen bromide to a crystalline *O*-benzoyl-di-O-*p*-nitrobenzoyl-L-arabinosyl bromide (V), the loss of one benzoyl group in the last step clearly indicating its location at C_1.

Since the reaction of ethyl 1-thio-β-D-glucopyranoside with silver mesitoate is not stereospecific,[2] giving both anomeric 1-*O*-mesitoyl-D-glucopyranoses, it is not possible to decide *a priori* whether II is an α- or a β-anomer. However, condensation of the bromide V with silver benzoate should give the *trans*, or α-L-, ester IV regardless of the anomeric configuration of the bromide.[6] This condensation was carried out and the crystalline product found to be identical with that obtained from the *p*-nitrobenzoylation of the 1,5-di-*O*-benzoyl-L-arabinose. The latter is, therefore, the α-L-anomer depicted by II.

It is of interest to contrast the behavior of ethyl 5-*O*-benzoyl-1-thio-β-L-arabino*furanoside* (I) with that of ethyl 1-thio-β-D-gluco*pyranoside* toward silver benzoate.[2] With the furanoside, one hour in boiling acetonitrile with an excess of silver benzoate served to give, as stated earlier, a 33%

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(2) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).

(3) C. Pedersen, H. W. Diehl and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3425 (1960).

(4) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 5210 (1960).

(5) E. J. Reist, P. A. Hart, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 5176 (1959).

(6) R. S. Tipson, *J. Biol. Chem.*, **130**, 55 (1939).

yield of the *trans* product II. Three hours in boiling acetonitrile with an excess of silver benzoate was required to desulfurize the 1-thiopyranoside and the product, 1-*O*-benzoyl-β-D-glucopyranose (isolated as its tetraacetate), was obtained in only 6.2% yield. The role, if any, of neighboring groups in this type of reaction is not known although it should be observed that ethyl 1-thio-β-D-glucopyranoside is a *trans*-glycoside while I is a *cis*-glycoside. However, it seems from the present work that alkyl 1-thioaldofuranosides may be more reactive toward silver benzoate than alkyl 1-thioaldopyranosides.

In the condensation of ethyl 1-thio-β-D-glucopyranoside with silver benzoate 2-*O*-benzoyl-D-glucose as its tetraacetate was isolated[2] in 5% yield and evidence found for the formation of a trace of free D-glucose. Both anomeric 1-*O*-benzoyl-D-glucopyranoses had doubtless been formed, the *cis* ester, however, undergoing acyl migration under the conditions of the reaction. With the more stable mesitoyl group, both anomeric 1-*O*-mesitoyl-D-glucopyranoses were isolated.[2] A considerable quantity of crystalline by-product was found after the formation of the *trans* ester 1,5-di-*O*-benzoyl-α-L-arabinose (II). This proved to be heterogeneous and efforts to resolve the mixture were unsatisfactory; it seems likely that products derived from the migration of the 1-*O*-benzoyl group of 1,5-di-*O*-benzoyl-β-L-arabinose may have been present.

In contrast to silver benzoate, mercuric acetate reacts rapidly with ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside (I) in acetonitrile at room temperature to give, in 34% yield, a mono-*O*-acetyl-mono-*O*-benzoyl-L-arabinose. This ester reduced 1.03 molar equivalents of sodium metaperiodate at room temperature during twenty-four hours and was stable in 20% aqueous pyridine. These facts, together with the analogy provided by II, indicate the *trans* ester structure VI.[7] *p*-Nitrobenzoylation of VI gave an *O*-acetyl-*O*-benzoyl-di-*O*-*p*-nitrobenzoyl-L-arabinose which was converted to the bromide V, identical with that obtained from IV.

The rotation of the 5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-L-arabinosyl bromide (V), $[\alpha]_D^{20}$ −40.0° in chloroform, indicates that it is probably the α-L-anomer V. It may be noted that Ness and Fletcher[8] found 2,3,5-tri-*O*-benzoyl-α-D-arabinosyl bromide to be the predominant anomer formed when methyl α-D-arabinofuranoside tribenzoate is treated with hydrogen bromide.[9]

(7) The *cis* ester 1,3,5-tri-*O*-benzoyl-α-D-ribose is readily converted to 2,3,5-tri-*O*-benzoyl-D-ribose by aqueous pyridine: R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 4710 (1956). For a general discussion of this rearrangement see H. G. Fletcher, Jr., *Record Chem. Progr. Kresge-Hooker Sci. Libr.*, 19, 147 (1958).

(8) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).

(9) The "normal" anomer in the arabino*pyranose* series is, however, β.

EXPERIMENTAL[10]

1,5-Di-O-benzoyl-α-L-arabinose (II) *from ethyl 5-O-benzoyl-1-thio-β-L-arabinoside* (I). To a solution of 2.00 g. of ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside[11] in 30 ml. of acetonitrile was added 3.08 g. (2.01 molar equivalents) of silver benzoate. The mixture was refluxed and stirred for 1 hr. and then cooled and filtered, the solid being washed several times with fresh acetonitrile. Solvent was removed from the combined filtrate and washings and the residue dissolved in dichloromethane. After filtration through decolorizing carbon the solution was concentrated to give 2.84 g. of brownish sirup which was dissolved in 50 ml. of benzene and adsorbed on a column of 50 g. of alumina ("Woelm," Grade III, acid-washed). Elution with 500 ml. of benzene, followed by removal of solvent, afforded 879 mg. of sirup which crystallized spontaneously. Recrystallized twice from a mixture of ether and pentane, the nearly pure product (470 mg., 20%) melted at 111–115° and had $[\alpha]_D^{20}$ −31.2° in chloroform. Two further recrystallizations from the same solvent mixture gave pure 1,5-di-*O*-benzoyl-α-L-arabinose: m.p. 113–115°, $[\alpha]_D^{20}$ −34.4° ($CHCl_3$, *c* 1.21).

Anal. Calcd. for $C_{19}H_{18}O_7$ (358.33): C, 63.68; H, 5.07. Found: C, 63.33; H, 5.19.

Further elution of the alumina with benzene-ether (1:1, 500 ml.) gave a second fraction (1.1 g.) which, from ether-pentane afforded 800 mg. of crystalline material melting as 95–105° and rotating $[\alpha]_D^{20}$ +36.1° in chloroform. Attempts to obtain a homogeneous product from this were unsuccessful. A sample (100 mg.) was *p*-nitrobenzoylated to give 73 mg. of 1,5-di-*O*-benzoyl-2,3-di-*p*-nitrobenzoyl-α-L-arabinose identical with the ester prepared from pure 1,5-di-*O*-benzoyl-α-L-arabinose as described later in this paper. The total yield of 1,5-di-*O*-benzoyl-α-L-arabinose in this reaction is therefore at least 33%.

α-L-Arabinofuranose tetrabenzoate (III) *from 1,5-di-O-benzoyl-α-L-arabinose* (II). Pure 1,5-di-*O*-benzoyl-α-L-arabinose (120 mg.) was benzoylated in the usual manner with benzoyl chloride (0.30 ml.) in pyridine (1 ml.) to give, after removal of the reagents, a sirup which, from ether-pentane solution, afforded 150 mg. (79%) of α-L-arabinofuranose tetrabenzoate, melting at 114–118°. After recrystallization from ethanol it melted at 115–118° and showed $[\alpha]_D^{20}$ −28.1° ($CHCl_3$, *c* 1.06). An authentic sample of α-L-arabinofuranose tetrabenzoate, prepared through the condensation of 2,3,5-tri-*O*-benzoyl-α-L-arabinosyl bromide with silver benzoate as described earlier by Ness and Fletcher[8] for its enantiomorph, showed m.p. 115–117° and $[\alpha]_D^{20}$ −28.5° ($CHCl_3$, c 1.56). A mixed melting point was undepressed.

Anal. Calcd. for $C_{33}H_{26}O_9$ (566.54): C, 69.96; H, 4.63. Found: C, 69.99; H, 4.72.

1,5-Di-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinose (IV). Pure 1,5-di-*O*-benzoyl-α-L-arabinose (110 mg.) was added to a solution of 200 mg. of *p*-nitrobenzoyl chloride in 2 ml. of pyridine. The mixture was kept at room temperature for 3 hr. and a crystalline mass then precipitated through the addition of *ca.* 15 ml. of water. The crude product was washed successively with water and methanol; recrystallization from benzene-pentane then afforded 190 mg. (94%) of fine needles melting at 170–172°. After one further recrystallization the ester melted at 171–172° and showed $[\alpha]_D^{20}$ −9.6° in chloroform (*c* 1.09).

Anal. Calcd. for $C_{33}H_{24}N_2O_{13}$ (656.54); C, 60.37; H, 3.68; N, 4.27. Found: C, 60.56; H, 3.86; N, 4.18.

5-O-Benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinosyl bromide (V) *from 1,5-di-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinose* (IV). 1,5-Di-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose (100 mg.) was dissolved in 5 ml. of dichloro-

(10) Melting points are corrected.

(11) Using the method of Reist, Hart, Goodman, and Baker (ref. 5), the yields of this compound varied unaccountably from 30–67%.

methane and the solution treated with 1 ml. of a 30% solution of hydrogen bromide in glacial acetic acid. The reaction mixture was kept at room temperature for 30 min., diluted with dichloromethane and washed successively with water, saturated aqueous sodium bicarbonate and water. Moisture was removed with granular sodium sulfate and the solution, after filtration through decolorizing carbon, concentrated *in vacuo*. Dissolved in a mixture of benzene and pentane (1:1), the residue crystallized as short needles: 57 mg. (61%), m.p. 160–161°. Recrystallization failed to change this value. The pure bromide showed $[\alpha]_D^{20}$ −40.0° in U.S P. chloroform (*c* 0.73) and could be recovered unchanged from this solvent.

Anal. Calcd. for $C_{26}H_{19}BrN_2O_{11}$ (615.35): C, 50.75; H, 3.11; N, 4.56; Br, 12.99. Found: C, 50.95; H, 3.05; N, 4.74; Br, 12.68.

1,5-Di-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinose (IV) *from 5-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinosyl bromide* (V). A solution of the bromide V (76 mg.) in 10 ml. of dry benzene was stirred with 150 mg. of silver benzoate for 30 min. at room temperature. The mixture was then filtered through decolorizing carbon, the filtrate evaporated *in vacuo* and the residue crystallized from benzene-pentane to give 51 mg. (62%) of 1,5-di-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose, melting at 169–170°; the substance failed to depress the melting point of a sample prepared through the *p*-nitrobenzoylation of 1,5-di-*O*-benzoyl-α-L-arabinose.

1-O-Acetyl-5-O-benzoyl-α-L-arabinose (VI) *from ethyl 5-O-benzoyl-1-thio-β-L-arabinoside* (I). To a stirred solution of 5.0 g. of ethyl 5-*O*-benzoyl-1-thio-β-L-arabinoside in 125 ml. of acetonitrile was added 5.90 g. (1.1 molar equivalents) of mercuric acetate. The salt dissolved within a few minutes and then a precipitate began to form. The mixture was stirred for 2 hr., filtered and the filtrate concentrated *in vacuo*. After solution in dichloromethane the residue was treated with hydrogen sulfide and the solution filtered through decolorizing carbon. Evaporation of the filtrate afforded a partly crystalline mass (5.53 g.) which was recrystallized from 50 ml. of ether to yield 2.12 g. of crude 1-*O*-acetyl-5-*O*-benzoyl-α-L-arabinose. After two recrystallizations from a mixture of ethyl acetate and pentane the pure ester (1.70 g., 34%) was obtained as plates melting at 117–118°, $[\alpha]_D^{20}$ −49.3° (*c* 0.53). The substance failed to mutarotate in 20% aqueous pyridine and could be recovered unchanged after 24 hr. in this solvent mixture. In aqueous solution it reduced 1.03 molar equivalents of sodium periodate in 24 hr. at room temperature.

Anal. Calcd. for $C_{14}H_{16}O_7$ (296.27): C, 56.75; H, 5.44. Found: C, 56.77; H, 5.47.

1-O-Acetyl-5-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinose (VII). To a solution of 1.25 g. of *p*-nitrobenzoyl chloride in 10 ml. of pyridine was added 500 mg. of 1-*O*-acetyl-5-*O*-benzoyl-α-L-arabinose. After standing at room temperature overnight the mixture was diluted with water and the product extracted with dichloromethane. The extract was washed successively with 3*N* sulfuric acid, saturated aqueous sodium bicarbonate and water. Moisture was removed with granular sodium sulfate and the solution filtered through decolorizing carbon. Removal of solvent left an amorphous residue; dissolved in a mixture of benzene (10 ml.) and pentane (10 ml.) this yielded 750 mg. (75%) of 1-*O*-acetyl-5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose as very pale yellow prisms melting at 149–151°, $[\alpha]_D^{20}$ +38.6° in chloroform. A further recrystallization failed to change this melting point but raised the rotation to $[\alpha]_D^{20}$ +39.7° ($CHCl_3$, *c* 0.82).

Anal. Calcd. for $C_{28}H_{22}N_2O_{13}$ (594.48): C, 56.57; H, 3.73; N, 4.71. Found: C, 56.83; H, 3.65; N, 4.70.

5-O-Benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinosyl bromide (V) *from 1-O-acetyl-5-O-benzoyl-2,3-di-O-p-nitrobenzoyl-α-L-arabinose* (VII). 1-*O*-Acetyl-5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose (295 mg.) was dissolved in 8 ml. of dichloromethane and 2 ml. of a 30% solution of hydrogen bromide in glacial acetic acid added. Mutarotation ceased after 3 min. at 20°; after 23 min. the solution was diluted with 15 ml. of dichloromethane and washed successively with water, saturated aqueous sodium bicarbonate and water. Moisture was removed with granular sodium sulfate, the solution filtered through decolorizing carbon and solvent removed *in vacuo*. From its solution in a mixture of 10 ml. of benzene and 10 ml. of pentane the residue afforded 230 mg. (75%) of 5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinosyl bromide melting at 160–161° either alone or in admixture with a sample prepared as described earlier from 1,5-di-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α-L-arabinose.

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[CONTRIBUTION NO. 1633 FROM THE STERLING CHEMISTRY LABORATORY, AND THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. L. Phospholipids of Sponges[1,2]

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The phospholipid fractions of two sponges, *Lissodendoryx isodyctialis* and *Speciospongia vesparia*, have been isolated and characterized. That from *L. isodyctialis* was found to consist of sphinegosine phosphate fatty acid esters, free of choline and sugars; the other, from *S. vesparia*, was a lecithin containing aldehyde in an enol ether linkage.

The study of the phospholipids of marine invertebrates has been continued as an extension of our comparative studies on the composition and evolution of the lipids of these organisms. In the previous report[5] the importance of isolation fol-

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(2) Taken in part from the dissertation submitted in 1958 by R. A. Landowne to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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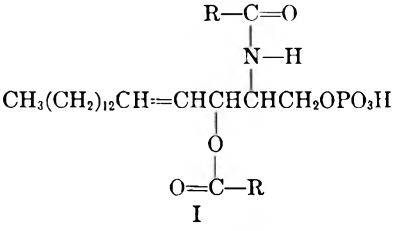
lowed by structural determination of the complex lipids was pointed out, as simple analysis for nitrogen and phosphorus can be misleading in the case of the atypical phospholipids of some marine organisms. The present work offers another example of the importance of characterization of phospholipids in this field, because both types of material studied here differ in structure from those previously described in ways not detectable by nitrogen and phosphorus analysis alone.

Lissodendoryx isodyctialis. The sponge, *L. isodyctialis*, collected from the waters around Bermuda, was extracted for lipids by standard methods[6] and its phospholipid content isolated. When purified by precipitation from glacial acetic acid this fraction was found to have a typical nitrogen to phosphorus ratio of 1:1 but exhibited both ester (5.8 μ) and amide (6.1 μ) carbonyl bands in the infrared. The high melting point (181.5–183°), insolubility in ether, and its stability to air and moisture were indicative of a sphingoside, and the persistence of the ester infrared absorption through purification steps tended to rule out the presence of glycerides in the mixture. Hydrolysis yielded no detectable choline. If choline had been present in the original molecule, it was not lost during extraction of the organism, as normal choline-containing sphingomyelin was obtained from the anemone *A. elegantissima* by the same procedures used here.[5] Nor did hydrolysis yield carbohydrate (Molisch and Fehlings tests) even though the material resembled cerebrosides by its insolubility in acetic acid. Sphingosine, identified by infrared comparison with the known triacetyl derivative, was isolated. Two moles of fatty acid (calculated as C_{16} acids) were obtained per molecule of sphingoside, the molecular weight of the sphingoside being based on the assumption of one nitrogen and phosphorus atom per molecule. Analysis of the fatty acids, as their methyl esters, by gas chromatography[7] showed a mixture ranging from C_{10} to C_{22}. Many of the minor components appeared to be branched chain acids; the major components were palmitate (38%) and palmitoleate (17%).

Hydrogenation cleaved the fatty acid ester linkage to yield 66% of theoretical yield (based on C_{16}) of free fatty acid. This behavior is typical of the reactions of allylic esters[8] and indicates that most, if not all, of the fatty acid was esterified at the allylic hydroxyl group of sphingosine. Hydrogenation of sphingosine esters does not give quantitative yields of acids; Carter[9] *et al.* isolated only 80% of acetic acid from sphingosine triacetate and in our experience the yield of acetic acid was somewhat less than this.

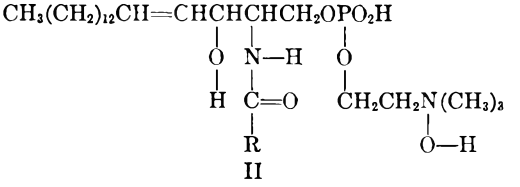
Evidence for a monophosphate ester grouping was obtained by study of the action of alkaline phosphatase.[10] This enzyme liberated 10.5% of the phosphate in thirty minutes, while simple hydrolysis at the same *p*H liberated 4.3%. Lack of material made more complete studies impossible, but it is felt that a monophosphate ester is the most likely structure present.

Consideration of the above evidence leads to the proposal of structure I for the phospholipid from *L. isodyctialis*.



I

This structure best accomodates the amide, allylic ester and phosphate linkages, taking into consideration also the normal sphingomyelin structure II.[11]



II

The name acylsphingomyelin phosphatidic acid is suggested for this new subclass of natural products.[12]

The only previous report of an acyl sphingomyelin known to us is that of Thannhauser and Reichel[13] who treated a beef brain sphingomyelin fraction with esterase and obtained free fatty acids. Their sphingomyelin fraction, however, was not purified by washing with acetic acid as in the present work, and more recent findings have indicated that hydrolecithins are ether insoluble and contaminate sphingomyelin fractions.[14] The possibility that the esterase-liberated fatty acids from their material originated from impurities certainly

(5) W. Bergmann and R. A. Landowne, *J. Org. Chem.*, **23**, 1241 (1958).

(6) W. R. Bloor, *J. Biol. Chem.*, **17**, 377 (1914); **22**, 133 (1915).

(7) S. R. Lipsky and R. A. Landowne, *Biochim. Biophys. Acta*, **31**, 336 (1959).

(8) H. Adkins and R. L. Shriner, *Organic Chemistry*, H. Gilman, Ed., John Wiley and Sons, New York, 1943, vol. I, 2nd ed., p. 799.

(9) H. E. Carter, W. P. Norris, F. J. Glick, G. E. Phillips, and R. Harris, *J. Biol. Chem.*, **170**, 269 (1947).

(10) L. A. Heppel, *Methods in Enzymology*, S. P. Colowick and N. O. Kaplan, Eds., Academic Press, New York, 1955, vol. II, p. 530.

(11) H. E. Carter, F. J. Glick, W. P. Norris, and G. E. Phillips, *J. Biol. Chem.*, **142**, 449 (1942).

(12) The term "phosphatidic acid" follows from the accepted nomenclature for the glycero-phosphatides that do not contain a nitrogen base in ester linkage with the phosphate and are therefore phosphate mono-esters.

(13) S. J. Thannhauser and M. Reichel, *J. Biol. Chem.*, **135**, 1 (1940).

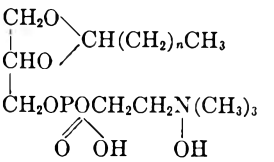
(14) E. Baer, D. Buchnea, and A. G. Newcombe, *J. Am. Chem. Soc.*, **78**, 232 (1956).

exists, since no confirmation by isolation of a purified product free of normal sphingomyelin and hydrolecithins has been reported.

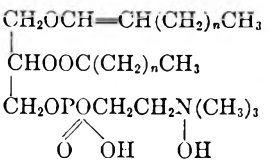
Speciospongia vesparia. The major phospholipid component was an aldehydogenic lecithin.[15] The material was surprisingly insoluble in ethanol, and precipitation by ethanol from petroleum ether aided its purification and made it evident that the ester group as detected by its infrared absorption and later established by hydrolysis was not due to impurities. The purified phospholipid also gave a rapid fuchsin-aldehyde test. It was free of amino nitrogen but contained a mole of choline for each mole of nitrogen and of phosphorus. Hydrolysis gave aldehydes, acids, choline, and glycerol phosphate. The aldehyde was shown to arise from an enol ether by hydrogenation of the intact molecule followed by hydrolysis. Here, no free aldehyde could be found, but a stable glyceryl ether was isolated instead (as the salt of its phosphate ester). Whether the enol ether linkage was α or β (at C_1 or C_2 of the glycerol) was not determined.

Both the aldehydes and esters were isolated after hydrolysis, and from elementary analyses the average chain length of each moiety was eighteen carbon atoms. Gas chromatography of the methyl esters showed a mixture of components from C_{10} to C_{24} with no one particular ester predominating. The aldehydes were also a complex mixture. The 2,4-dinitrophenylhydrazones were not crystalline for this reason. Unsaturation was relatively high in that there was 0.77 double bond per mole of phospholipid in addition to the double bond of the enol ether.

An acetal phospholipid (III) isolated as a minor constituent from the sea anemone *A. elegantissima* was previously reported.[5] Aldehyde-containing compounds of this type were first noted by Feulgen and Bersin[16] and later confirmed by Thannhauser *et al.*[17] to be present in mammalian tissue. Other structures were proposed which included hemiacetal[18] and enol ether[19,20] attachment of the aldehyde moiety (IV). These investigators preferred to discount the existence of the acetal structure in nature. Our present finding in the sponge *S. vesparia* of an aldehyde-containing phospholipid (IV) which did not have the acetal linkage, even though similar isolation and identification procedures were used, makes it seem quite certain that both acetals and enol ethers, and perhaps even other types, exist in nature.



III



IV

A comparison of the optical rotation for the several plasmalogens that have been reported is quite interesting although its interpretation is not particularly clear. While the sea anemone acetal plasmalogen[5] (III) had a negative rotation similar to Rapport's enol ether plasmalogen[19] and opposite to that of Thannhauser's acetal compound,[17] the sponge plasmalogen herein reported (IV) has a positive rotation even though it is structurally similar to Rapport's compound. It seems unwise at this point to attribute these rotational discrepancies to species differences. It should be pointed out that all natural lecithins have a positive rotation, and there is no apparent reason to expect the replacement of a fatty acid by an aldehyde (be it in the α- or β-position) to alter significantly the rotation of these compounds. Thus, a positive rotation for the aldehydogenic lecithins (IV) seems consistent with other data.

EXPERIMENTAL[21]

Isolation of L. isodyctialis phospholipid. The air-dried tissue (228 g.) was homogenized in a Waring blendor in eight portions with 200 ml. of 2:1 (v./v.) chloroform-methanol solvent mixture per portion. The residual tissue was centrifuged, divided into two parts, and homogenization was repeated with 200 ml. of chloroform for each part. The homogenate was centrifuged again and the supernatants were combined and washed with 10 volumes of water by the Folch method.[22] The chloroform extract (1.5 l.) was filtered and then added to 5.25 l. of acetone and refrigerated overnight.

The flocculent phospholipid precipitate was centrifuged and taken up in 150 ml. of chloroform. The solution was filtered and the phospholipids reprecipitated by adding the solution to 525 ml. of acetone. This process was repeated using 40 ml. of chloroform and 160 ml. of acetone. The precipitate was dried under a stream of nitrogen to yield 2.25 g. (1.0%) of light tan powder.

Purification. The phospholipid was stirred and ground in 100 mg. portions with 10 ml. of glacial acetic acid. The acetic acid insoluble fraction (50%) was filtered and washed twice with 10 ml. of acetone to remove acetic acid. The acetic acid filtrate was mixed with 14 volumes of acetone and let stand a few hours. Phospholipid, now acetic acid insoluble and identical with the original acetic acid insoluble fraction, precipitated and was filtered and washed with acetone. The

(15) A minor constituent (0.01%) was also isolated by precipitation with ethyl ether from petroleum ether solution. It was apparently a phospholipoprotein in that it had a N/P ratio of 12.6/1.

(16) R. Feulgen and T. Bersin, *Z. Physiol. Chem.*, **260**, 217 (1939).

(17) S. J. Thannhauser, N. F. Boncoddo, and G. Schmidt, *J. Biol. Chem.*, **188**, 417 (1951).

(18) E. Klenk and H. Debuch, *Z. Physiol. Chem.*, **299**, 66 (1955).

(19) M. M. Rapport, B. Lerner, N. Alonzo, and R. E. Franzl, *J. Biol. Chem.*, **225**, 859 (1957).

(20) G. V. Marinetti and J. Erbland, *Biochim. Biophys. Acta*, **26**, 429 (1957); G. V. Marinetti, J. Erbland, and E. Stotz, *J. Am. Chem. Soc.*, **80**, 1624 (1958).

(21) P, N, C, and H analyses by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Choline was determined in this laboratory gravimetrically as the reineckate.

(22) J. Folch, I. Ascoli, M. Lees, and J. A. Meath, *J. Biol. Chem.*, **191**, 833 (1951).

purification yield was 88%, m.p. 181.5–183° dec.; $[\alpha]_D^{27°}$ = +13.3° (1.25% in pyridine, α = +0.166°).

Anal. Calcd. for $C_{50}H_{98}NO_7P$: N, 1.64; P, 3.62. Found: N, 1.73; P, 3.73. N/P = 1.02.

Paper chromatography by the method of Bevan *et al.*[23] showed only one phosphorus positive spot which remained at the origin. The compound gave negative Molisch and Fehlings tests for sugar after acid hydrolysis. The ninhydrin test was negative but strongly positive after hydrolysis.

Acid hydrolysis and isolation of the esters. The sphingoside (101 mg.) was mixed with 90 ml. of 2*N* methanolic hydrochloric acid (anhydrous) and refluxing was begun. After 16 hr., 25 mg. of undissolved, unchanged starting material was filtered from the cooled solution, and the filtrate was extracted with three 50-ml. portions of petroleum ether (b.p. 30–60°). The petroleum ether was washed twice with 50 ml. of water and dried over anhydrous sodium sulfate overnight. Removal of the drying agent by filtration and the solvent by evaporation left 41 mg. of a mixture of methyl esters, m.p. 30–33°. The yield from the material that treated was 85% based on 2 moles of palmitate per mole of hydrolyzed sphingoside. Gas liquid chromatography of the mixture showed at least fourteen peaks from C_{19} to C_{22} with palmitate and palmitoleate being the two most abundant components, in concentrations of 38% and 17%, respectively.

Characterization of the nitrogen base. The sphingoside (202 mg.) was refluxed with 68 ml. of 2*N* methanolic sulfuric acid for 3.5 hr. The solution was filtered to remove 6 mg. of starting material and extraction with four 50-ml. portions of petroleum ether removed the esters. Methanolic potassium hydroxide (30%) was added to make the solution alkaline to phenolphthalein. Potassium sulfate was filtered and the solution was re-acidified with 1 drop of glacial acetic acid before being concentrated to a volume of 25 ml. at 50° in a rotary evaporator. An equal volume of water was added, and the solution was made alkaline again before extracting the free base three times with 50 ml. of ethyl ether. The ether was washed twice with 25 ml. of water, dried with anhydrous sodium sulfate, and evaporated to yield 49 mg. (50%) of crude base.

The base was acetylated overnight with 1 ml. of pyridine and 1 ml. of acetic anhydride. Two milliliters of water was then added to the mixture and the brown oil that floated to the top was removed and dried *in vacuo* at room temperature. Recrystallization from acetone was partially successful, m.p. 50–60°. The infrared spectrum was identical with both natural[24] and synthetic[25] triacetyl sphingosine.

Hydrogenolysis. A microhydrogenation apparatus[26] was used to hydrogenate 84.7 mg. (0.1 mmole) of sphingoside, dissolved in 1 ml. of pyridine, and diluted with 5 ml. of benzene. The catalyst was 48.5 mg. of 5% palladium on charcoal. The reaction was stirred at room temperature under hydrogen at atmospheric pressure. The catalyst was then filtered off and the solvents removed in a rotary evaporator. The residue was taken up in 3 ml. of chloroform and 12 ml. of acetone was added. This precipitated 42 mg. of a mixture of hydrogenated starting material and the deacylated compound. The filtrate was taken to dryness and the residue extracted with acetone to leave an additional 10 mg. of insoluble product. The acetone solution was taken to dryness and the residue (30 mg.) extracted with ether. The ether extract contained 17 mg. of free fatty acid equivalent to 0.066 mmole of palmitic acid.

Enzymatic hydrolysis. A finely ground sample of sphingoside (52 mg.) was shaken for 10 min. in 10 ml. of water to obtain a nearly homogeneous mixture. Ten milliliters of 0.1*M* sodium borate solution ($Na_2B_4O_7.10H_2O$) was added to bring the mixture to *p*H 9. A 15% magnesium chloride solution (0.5 ml.) and 0.1 ml. of enzyme solution containing 0.19 mg. (760 units) of alkaline phosphatase (Mann Laboratories, New York, N. Y.) was then added. The mixture was incubated at 36° in a water bath for 30 min., and then 3 ml. of 10% trichloroacetic acid was added to quench the reaction. The procedure was repeated with 32 mg. of sphingoside but without the enzyme. An enzyme blank was run by repeating the procedure without the phospholipid sample. Phosphorus was determined on all solutions by a modification of the Fiske-Subbarow procedure[27] using amidol[28] as the reducing agent. The optical density was determined at 550 mμ in a Bausch and Lomb colorimeter. Standards were obtained by adding magnesium phosphate in place of enzyme and/or lipid.

RESULTS

Solution	O.D.[a]	P Added, Calcd.	Free P, Found
Standard I	0.23	0.05 mg.	0.05 mg.
Standard II	0.46	0.10	0.10
Standard III	0.91	0.20	0.20
Enzyme blank	0.04	—	0.009
Lipid blank	0.76	3.7	0.16
Lipid sample	1.46[b]	6.0	0.63[c]

[a] After subtracting blank with water as zero. [b] Read at half-dilution. [c] After subtracting enzyme blank.

The yield of hydrolyzed phosphate was 4.3% without enzyme, and 10.5% with the enzyme.

Isolation and purification of S. vesparia phospholipids. The frozen tissue was defrosted for 24 hr. at room temperature and 2.3 kg. was shredded and homogenized in ten portions with a total of 2.1 l. of chloroform-methanol solvent mixture (2:1, v./v.). The tissue was filtered from the extract and rehomogenized with 1.2 l. more of chloroform. All filtrates were combined and 1.5 l. of methanol was added to obtain a homogeneous extract. The dried residual tissue was 0.31 kg.

The extract was washed by the Folch procedure[22] in two 3 l. batches, with 20 l. of water for each portion. After 4.5 hr., fresh water was substituted and washing continued for 13.5 hr. more. The chloroform extract was concentrated to 0.70 l. at 60° and 20 mm. pressure, and then added to 2.45 l. of acetone. This mixture was kept at 5° for 2 days.

One milliliter of saturated ethanolic magnesium chloride ($MgCl_2.6H_2O$) was added to coagulate the phospholipids which were centrifuged and collected by washing the centrifuge bottles with 30 ml. of chloroform. Reprecipitation with 320 ml. of acetone then followed and the precipitate was dissolved in 35 ml. of petroleum ether. This solution was added to 175 ml. of ethyl ether to yield a small precipitate (10 mg.). The combined acetone-chloroform mother liquors were taken to dryness at 60° and 20 mm. to yield 6.5 g. of lipid material which was acetone soluble except for 20 mg. This acetone insoluble fraction was also ether insoluble and was therefore combined with the first ether insoluble fraction. The total yield was 0.01% of the dry weight.

The ether–petroleum ether solution was taken to dryness and the residue found to be completely soluble in 100% ethyl ether. The ether was removed, and the lipid reprecipitated from 75 ml. of chloroform with 525 ml. of acetone. The phospholipid was taken up in 100 ml. of petroleum ether

(23) T. H. Bevan, G. I. Gregory, T. Malkin, and A. G. Poole, *J. Chem. Soc.*, 841 (1951).

(24) K. Mislow, *J. Am. Chem. Soc.*, **74**, 5155 (1952).

(25) D. Shapiro and K. Segal, *J. Am. Chem. Soc.*, **76**, 5894 (1954).

(26) C. L. Ogg and F. J. Cooper, *Anal Chem.*, 21, 1400 (1949).

(27) C. H. Fiske and Y. Subbarow, *J. Biol. Chem.*, **66**, 375 (1925).

(28) R. J. L. Allen, *Biochem. J.*, **34**, 858 (1940).

and the solution dried over anhydrous sodium sulfate. The yield of a gummy amorphous material was 2.93 g. (0.92%). Quantitative precipitation from petroleum ether with an equal volume of ethanol gave a powdery, light brown material. Paper strip chromatography according to the method of Bevan *et al.*[23] gave only one phospholipid spot which was negative to ninhydrin but indicative of a lecithin, according to its R_f value of 0.92. It gave a positive fuchsin-aldehyde test with mercuric acetate. The test was negative without the mercury salt. The infrared showed a strong carbonyl peak at 5.78 μ and the melting behavior was also typical of the lecithins with softening occurring at 90°, and meniscus formation at 210–220°. $[\alpha]_D^{24°} = +12.6°$ (1.11% in chloroform, $\alpha = +0.14°$).

Anal. Calcd. for $C_{48}H_{98}NO_8P$: P, 3.65; N, 1.65; choline, 14.3. Found: P, 3.65; N, 1.60; choline, 14.9. N:P:choline = 0.97:1:1.04.

The ether insoluble fraction had an infrared spectrum similar to the major phospholipid fraction. Its melting behavior was also similar.

Anal. Found: P, 1.05; N, 6.01. N:P = 12.6:1.

No further identification was attempted.

Quantitative hydrogenation of the plasmal lecithin. An 18.9-mg. sample of the phospholipid (23.9 μM) was dissolved in 8 ml. of *n*-butyl ether after the platinum catalyst (19 mg.) was reduced in the microhydrogenation apparatus.[26] At 22° and 754 mm., the sample required 1.04 ml. of hydrogen or 0.946 ml. at STP (42.2 μM). The number of double bonds was 1.77 per mole of phospholipid.

Alkaline hydrolysis of hydrogenated phospholipid. The compound (500 mg.) was dissolved in 75 ml. of *n*-butyl ether and hydrogenated over platinum in a Parr shaker for 21 hr. The catalyst was then filtered off and the solvent removed at 2 mm. and room temperature. The residue was dissolved in 30 ml. of ethyl ether and 30 ml. of 0.5*N* methanolic potassium hydroxide was added. This cloudy mixture was shaken in a stoppered flask at room temperature for 21 hr. Water (20 ml.) was then added and the mixture extracted twice with 25 ml. of ether. The ether extract was washed twice with 10 ml. of water and dried over sodium sulfate. The solvent was evaporated to yield an oil containing a white solid. The oil was removed by dissolving it in 10 ml. of ether leaving 30 mg. (17%) of the solid whose infrared spectrum was typical of a fatty acid salt.

Anal. Calcd. for $C_{18}H_{35}O_2K$: C, 67.08; H, 10.86. Found: C, 67.13; H, 10.45.

The alcoholic solution was filtered, acidified with 1 ml. of concd. hydrochloric acid, and extracted again with three 25-ml. portions of ether. The extract was washed twice with 10 ml. of water and dried. This solution of fatty acids was esterified with diazomethane distilled with the ether from a solution of 1.2 g. of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide, slowly added to 30% ethanolic potassium hydroxide. The excess diazomethane was allowed to evaporate with the ether and the methyl esters remaining were combined with the ether soluble methyl esters first extracted from the alkaline hydrolysis mixture. The yield was 142 mg. (76%).

The material filtered from the alkaline hydrolysis mixture contained phosphorus. It was taken up in 2 ml. of chloroform and precipitated with 8 ml. of acetone. The precipitate was dissolved in 1 ml. each of pyridine and benzene and reprecipitated with 8 ml. of acetone. The dried powder had no carbonyl band in the infrared and had a strong hydroxyl peak typical of a glyceryl ether phosphate. The yield was 25 mg. (8%).

Anal. Calcd. for $C_{21}H_{43}O_6PK_2$: C, 50.40; H, 8.60. Found: C, 49.47; H, 8.83.

Acid hydrolysis. The lecithin (84 mg.) was dissolved in 1 ml. of chloroform, and 2 ml. of concd. hydrochloric acid and 8 ml. of ethanol were added. This mixture was allowed to stand over a few milligrams of mercuric acetate for 24 hr., after which time hydrolysis seemed complete, as the solution was almost clear. The solution was then filtered and extracted three times with 10 ml. of petroleum ether. The solvent was removed from the extract, the residual oil taken up in 2 ml. of ethanol and 2 ml. of 2,4-dinitrophenylhydrazine reagent added. A precipitate formed immediately but the mixture was refrigerated overnight. The 2,4-dinitrophenylhydrazones were centrifuged and dissolved in benzene. The benzene solution was passed through an alumina column to purify the 2,4-dinitrophenylhydrazones. The benzene was removed to yield a red oil which could not be successfully crystallized. The yield was 25 mg. (53%).

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

A Unique Fatty Acid from *Limnanthes douglasii* Seed Oil: The C_{22} Diene

M. O. BAGBY, C. R. SMITH, JR., T. K. MIWA, R. L. LOHMAR, AND I. A. WOLFF

Received July 6, 1960

The C_{22} dienoic fatty acid of *Limnanthes douglasii* seed oil (representing 10% of the total fatty acid) is shown to be the previously unknown *cis*-5-*cis*-13-docosadienoic acid.

An earlier paper from this laboratory[2] reports that the major components of seed oil from *Limnanthes douglasii* are *cis*-5-eicosenoic, *cis*-5-docosenoic, *cis*-13-docosenoic acids, and a C_{22} acid of undetermined structure. This paper reports the isolation and characterization of the remaining component as a previously unknown docosadienoic acid.

Concentration of the docosadienoic acid. A concentrate of the C_{22} diene acid (I) was obtained by low temperature crystallization of mixed free acids from heptane and subsequent countercurrent distribution (Fig. 1 and Table I).

(1) One of the laboratories of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

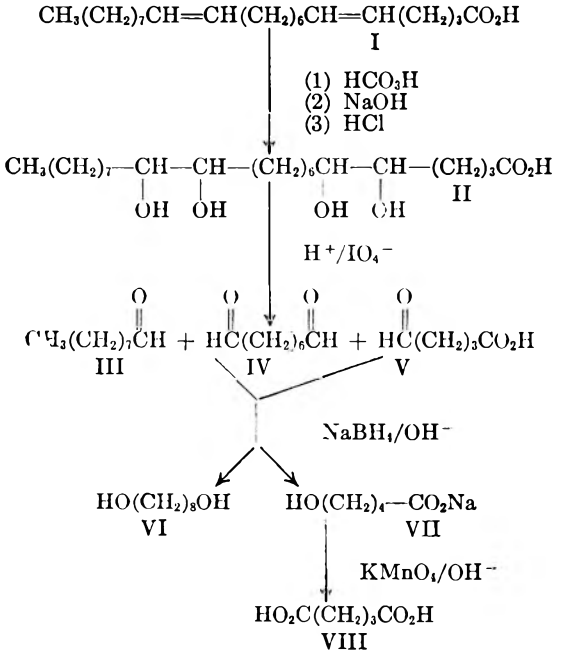
(2) C. R. Smith, Jr., M. O. Bagby, T. K. Miwa, R. L. Lohmar, and I. A. Wolff, presented before the Division of Organic Chemistry, 137th Meeting American Chemical Society, Cleveland, Ohio, April 5–14, 1960. C. R. Smith, Jr., M. O. Bagby, T. K. Miwa, R. L. Lohmar, and I. A. Wolff, *J. Org. Chem.*, **25**,1770 (1960).

TABLE I

GAS CHROMATOGRAPHIC ANALYSIS OF METHYL ESTERS OF FRACTIONS DERIVED FROM *Limnanthes douglasii* FATTY ACIDS

Type of Acid	Equivalent Chain Length[a] Apiezon-L	Equivalent Chain Length[a] Resoflex-446	% Acid Heptane Soluble	% Acid Countercurrent Distribution (Transfer Number) 310	330	350	390	336–394
C_{12} Saturated	12.0	12.0	0.1					
C_{14} Saturated	14.0	14.0	0.2					
C_{16} Saturated	16.0	16.0	1				0.8	0.1
C_{16} Monoene	15.7	16.4	2				—	—
C_{17} Saturated	17.0	17.0	0.5				—	—
C_{18} Saturated	18.0	18.0	—	—	0.5		—	0.1
C_{18} Monoene	17.7	18.4	7					
C_{18} Diene	17.6	19.0	3	0.3	0.2		3.1	0.5
C_{18} Triene	17.6	19.8	3					
C_{19} Unsaturated	18.7	—	—	—	—		1.3	0.2
C_{20} Saturated	20.0	20.0	—	0.6	—		—	—
C_{20} Monoene	19.7	20.4	13	7.3	34.5	19.7	0.7	17.2
C_{2x} Unknown	19.4	20.6	3	0.2	—	—	—	1.6
C_{22} Monoene	21.7	22.4	5	72.3	9.6	—	—	—
C_{22} Diene[b]	21.6	23.0	1					
C_{22} Unknown (diene)	21.4	22.6	60	2.2	55.6	80.3	82.6	80.2
C_{24} Unknown	23.4	24.6	1	16.3	—	—	—	—

[a] According to T. K. Miwa, K. L. Mikolajczak, F. R. Earle, and I. A. Wolff, in a paper presented before the Division of Analytical Chemistry, 137th Meeting American Chemical Society, Cleveland, Ohio, April 5–14, 1960. T. K. Miwa, K. L. Mikolajczak, F. R. Earle, and I. A. Wolff, *Anal. Chem.*, **32**,1739 (1960). [b]This diene is not discussed in the text.



The heptane-soluble concentrate was shown by gas-liquid chromatography to contain 60% of the unusual C_{22} diene acid (Table I). A 560-transfer counter-current distribution of the concentrate in an acetonitrile-hexane[3] system effected an enrichment of the unusual C_{22} diene; however, the C_{20} monoene present was not resolved from the mixture (Table I). The C_{22} diene concentrate, of about 80% purity, was obtained by combining material from transfers 336 to 394 (Table I).

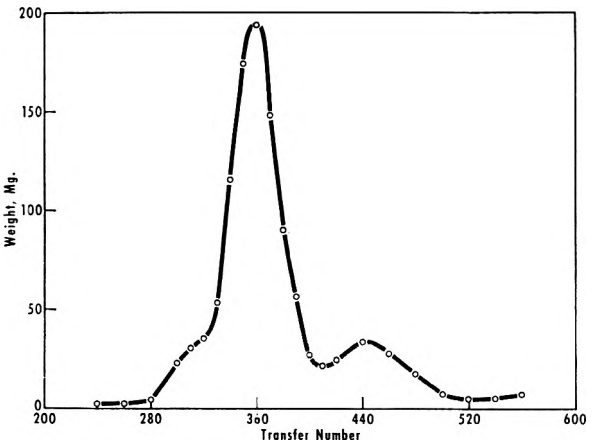


Fig. 1. Countercurrent distribution of heptane-soluble acids (−55°) from *Limnanthes douglasii* seed oil

The presence of two double bonds was confirmed by iodine value (Wijs) and quantitative hydrogenation; however, alkali isomerization[4] failed to yield appreciable (< 2%) conjugation. Treatment with lipoxidase[5] indicated no methylene interrupted *cis*-unsaturation.

The C_{22} acid was isolated by hydroxylating the concentrate with performic acid[6] and subsequent solvent extraction. The high yield of tetrahydroxy acid, contrasted to the low yields reported for the oxidation of linoleic acid,[6,7] was probably due to the greater separation of the double bonds.

(3) C. R. Scholfield, J. Nowakowska, and H. J. Dutton, *J. Am. Oil Chemists' Soc.*, **37**, 27 (1960).

(4) American Oil Chemists' Society, *Official and Tentative Methods*, 2nd ed., revised 1959, Cd 7-58.

(5) J. MacGee, *Anal. Chem.*, **31**, 298 (1959).

(6) D. Swern and G. B. Dickel, *J. Am. Chem. Soc.*, **76**, 1957 (1954).

Characterization of tetrahydroxy acid. The purified tetrahydroxydocosanoic acid (II) was subjected to oxidative cleavage by acid-periodate.[8] The steam-volatile aldehyde (III) was isolated by extracting the aqueous aldehyde mixture with petroleum ether and subsequent steam distillation of the residue from the extraction. The 2,4-dinitrophenylhydrazone (2,4-DNP) of III was identical with that prepared from authentic nonanal. The nonsteam-volatile aldehyde mixture (IV and V) was reduced with sodium borohydride.[9] The diol (VI) was removed from the alkaline solution by continuous extraction with ethyl ether. The identity of VI as 1,8-octanediol was established by mixed melting point determinations using the authentic diol and its bisphenylurethane derivative. The remaining fragment (VII) was oxidized by alkaline permanganate,[10] and the product was identified as glutaric acid (VIII) by mixed melting point, gas chromatography, and x-ray diffraction. These cleavage products, with the infrared and near infrared[11] spectra, clearly establish the structure of the C_{22} diene as the previously unknown *cis*-5-*cis*-13-docosadienoic acid.

DISCUSSION

The *cis*-5-*cis*-13-docosadienoic acid found in *Limnanthes* oil appears to be unique. No other dienoic acids with hexylene interrupted unsaturation appear to have been recorded as triglyceride constituents in natural sources. The variance from the common conjugated and methylene interrupted unsaturation[12] has not previously been reported for vegetable oil sources of docosadienoic acid; in fact, only two other docosadienoic acids have been reported: the $\Delta^{13,16}$-isomer from rapeseed oil[12] and the $\Delta^{10,13}$-isomer from ox liver[13] phosphatides. The 5,13-docosadienoic acid did not form a conjugated acid by treatment with alkali. De Surville *et al.* and other workers[14] have shown that even ethylene interrupted unsaturation is difficult to conjugate with alkali. Koyama and Toyama[15a] report that on treatment with alkali 9,12,18- or 9,15,18-eicosatrienoic acid[15b] from the seed oil of *Podocarpus nagi* forms only a conjugated diene instead of conjugated triene. Acids containing ethylene interrupted unsaturation have been reported in fish oils[16–18] and ox liver lipid[19]; however, later work[20] seems to discredit earlier reports.

By analogy with established precedent[21] the tetrahydroxydocosanoic acids, which have not been previously reported, have the d*ithreo*structure. The 5,6-dihydroxyeicosanoic acids likewise have the *threo*structure. An interesting phenomenon is the occurrence of two C_{22} monoenes with Δ^5- and Δ^{13}- unsaturation together with the 5,13-docosadienoic acid; whereas, petroselinic acid (Δ^6 containing oils are reported to contain oleic and 9,12-octadecadienoic acid[12] rather than the $\Delta^{6,9}$ acid.

EXPERIMENTAL

General methods. Gas chromatographic analyses were carried out with a Burrell Kromo-Tog K-5[22] gas chromatographic instrument. The columns were of U-shaped glass tubing 1.25 to 2.75 meters in length, 1/8 to 1/4 inch inner diameter, and packed with LAC-2R-446 (a polyester of diethylene glycolpentaerythritol and adipic acid) or Apiezon L (a hydrocarbon grease) supported by Johns-Manville Celite 545. The carrier gas was helium and the operating temperature ranged from 185° to 250°, depending on the column liquid phase and the sample. For quantitative determinations of composition, the areas under the peaks were measured by the instrument's automatic integrator. Mixtures of acids were analyzed as their methyl esters. Except where noted, methyl esters were prepared by refluxing the acids 2 hr. under nitrogen in excess 1% sulfuric acid in methanol. Esters were isolated by ether extraction in the usual manner; unchanged acids were removed by washing the ethereal solutions of esters with 5% potassium carbonate. When desired for characterization work, fractionated esters were saponified by refluxing 0.5 hr. with 2*N* ethanolic potassium hydroxide.

Preparation of mixed fatty acids. Coarsely ground seeds of *Limnanthes douglasii* were extracted overnight in a Soxhlet apparatus with petroleum ether (b.p. 33–57°). The bulk of the solvent was evaporated on a steam bath under nitrogen and the remainder was removed *in vacuo* with a rotating evaporator.

A 24.2-g. portion of *Limnanthes* oil was refluxed 30 min. with 150 ml. of 2*N* ethanolic potassium hydroxide. The unsaponifiable material was removed and the free fatty acids (22.9 g.) were obtained in the usual manner.

Low-temperature crystallization. Mixed fatty acids (17.8 g.) were dissolved in 415 ml. of heptane, and the solution was cooled slowly to −55°. After standing 1.5 hr., the mixture was filtered using a filter stick. The solvent was removed yielding 2.7 g. of heptane-soluble acids, iodine

(7) A. F. McKay, N. Levitin, and R. N. Jones, *J. Am. Chem. Soc.*, **76**, 2383 (1954).

(8) F. D. Gunstone, *J. Chem. Soc.*, **1954**, 1611.

(9) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

(10) W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

(11) R. T. Holman, S. Ener, and P. R. Edmonson, *Arch. Biochem. Biophys.*, 80, 72 (1959) and references therein.

(12) T. P. Hilditch, *Chemical Constitution of Natural Fats*, 3rd ed., John Wiley and Sons, New York, 1956.

(13) E. Klenk and H. J. Tomoschat, *Z. physiol. chem.*, **308**, 165 (1957).

(14) B. M. A. de Surville, D. E. A. Rivett, and D. A. Sutton, *J. Chem. Soc.*, **1957**, 3304, and references therein.

(15) (a) Y. Koyama and Y. Toyama, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **78**, 1223 (1957). (b) Y. Toyama, Private communication.

(16) Y. Toyama and T. Yamamoto, *Mem. Fac. Eng. Nagoya Univ.*, **3**, 122 (1953).

(17) Y. Toyama and T. Shimo-Oka, *Mem. Fac. Eng. Nagoya Univ.*, **5**, 319 (1953).

(18) T. Aoyagi, *Pharm. Bull. Tokyo*, **5**, 224 (1957).

(19) T. Shimo-Oka and Y. Toyama, *Mem. Fac. Eng. Nagoya Univ.*, **6**, 48 (1954).

(20) Y. Toyama, Y. Iwata, and K. Fujimura, *Fette, Seifen., Anstrichmittel*, **61**, 846 (1959).

(21) F. D. Gunstone, *An Introduction to the Chemistry of Fats and Fatty Acids*, John Wiley and Sons, New York, 1958, pp. 104–109.

(22) Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

value 143. Gas chromatographic analysis of the methyl esters of the combined heptane-soluble acids indicated 60% C_{22} unknown and 13% C_{20} monoene (Table I).

Fractionation by countercurrent distribution. Methyl esters (7.3 g.) of the heptane-soluble acids were subjected to a 560-transfer countercurrent distribution in a 200-tube automatic Craig-Post apparatus. The solvent system used was mutually saturated acetonitrile and hexane[3] (8:1). The methyl esters were divided evenly among the first four tubes and 40 ml. of acetonitrile (full in the decant position) was placed in each of the remaining tubes. The automatic operation of the instrument introduced 5 ml. of equilibrated hexane to tube O at each transfer stage. As the upper phase progressed past tube 200, it was decanted into an automatic fraction collector, combining two transfers per tube, and was successively collected until 180 fractions had been obtained. The weight distribution plot obtained by evaporating solvent, under reduced pressure, from the contents of selected tubes is shown in Fig. 1. Gas chromatographic analyses of significant fractions are indicated in Table I. On the basis of these analyses, it was not deemed practical to resolve the C_{20} monoene-C_{22} unknown mixture further, and fractions 336 through 394 were combined, yielding 3.7 g. Gas chromatographic analysis of the combined fractions indicated 80.2% of C_{22} unknown, Table I. Free acids were obtained by the usual saponification procedure followed by acidification; these liquid acids gave a neutral equivalent (neut. equiv.) of 327, an iodine value (I.V.) of 141, and a hydrogenation number (H.N.) of 172. Theoretical values for a mixture consisting of 82% C_{22} diene and 17% C_{20} monoene are: neut. equiv., 328; I.V., 136; and H.N., 182.

An 81-mg. portion of the above acid concentrate was hydrogenated in ethanol with a platinum oxide catalyst at room temperature and atmospheric pressure. The suspended catalyst was removed by filtration and after the solvent was removed by evaporation, 76 mg. of white crystals, melting at 72.0–76.5°,[23] was obtained. Recrystallization from 100 ml. of acetone at 0° yielded 50 mg. of crystals, melting at 76.5–78.0°. On recrystallization from ethanol, 32 mg. was obtained, melting point and mixed melting point with authentic docosanoic (behenic) acid (m.p. 78.5–79.0°) was 78–79°.

The infrared spectrum of the concentrate indicated no *trans* unsaturation (little absorption at 10–11 μ), and the near infrared spectrum[11] indicated a *cis*-iodine value of 141 (Wijs iodine values 141).[24] Ultraviolet absorption spectra[4] indicated no conjugated unsaturation before alkali treatment and less than 2% after treatment. Reaction with lipoxidase[5] did not indicate methylene interrupted *cis*-unsaturation.

Hydroxylation[6] of C_{22} diene concentrate. Performic acid was prepared by mixing 0.3 ml. of 30% hydrogen peroxide with 3 ml. of 90% formic acid at room temperature. After 1 hr., the performic acid concentration was 6.0% (determined on a small scale by Wheeler's method[25]).

The C_{22} diene acid concentrate (0.325 g.; 1 mmole) was added at once with stirring and the temperature was maintained between 25 and 30°. After 2 hr., 2 mmoles of performic acid had been used, with no consumption during an additional 0.5 hr. The reaction mixture was diluted with 15 ml. of water and poured over ice; the product was removed by extracting with ether (three times). The combined ether extract was washed with water and dried over sodium sulfate. The viscous liquid (0.383 g.) obtained upon removing the ether was refluxed 1 hr. under nitrogen with 10 ml. of *N* aqueous sodium hydroxide. After diluting the solution with water (50 ml.) and acidifying to Methyl Orange with 2*N* hydrochloric acid, the acids were removed by ether extraction (5 × 100 ml.). The combined ether extract (containing suspended solids) was washed sparingly with cold water and concentrated to *ca.* 125 ml. The mixture was chilled on solid carbon dioxide, and the precipitate was collected on filter paper and dried under reduced pressure, yielding 0.240 g. a white solid (A) melting at 127–132°. The filtrate was evaporated, yielding 0.075 g. of a yellowish solid (B) melting at 71–83°. Fraction A was recrystallized first from 100 ml. of ether and then from 10 ml. of ethyl acetate to yield 0.191 g. of II, melting at 129–131°.

Anal. Calcd. for $C_{22}H_{44}O_6$: C, 65.3; H, 11.0. Found: C, 65.0; H, 10.9.

Fraction B was recrystallized from chloroform:ether (1:1) to yield 0.012 g. melting at 89–112°. The filtrate residue was recrystallized twice from hexane, yielding 0.024 g. melting at 78–81°. This product was presumed to be *threo*-5,6-dihydroxyeicosanoic acid.

Periodate oxidation[8] of the tetrahydroxybehenic acid. A 1.21 g. portion (3 mmoles) of II was suspended in 70 ml. of ethanol and a solution of 1.61 g. of sodium periodate in 75 ml. of *N* sulfuric acid was added. The mixture was heated at 40° for 35 min. with occasional stirring. Suspended solids dissolved slowly leaving only a trace insoluble. The reaction mixture was filtered and collected in 250 ml. of cold water.

Identification of steam-volatile aldehyde. The aqueous solution was extracted (three 100-ml. portions) with pentane-hexane (b.p. 33–57°), and the combined petroleum ether extract was washed with water.

After most of the petroleum ether was removed by distillation (maximum temperature 47°), the residue was steam distilled. The steam volatile aldehyde (III) was treated with 0.60 g. of 2,4-dinitrophenylhydrazine.[26] After dilution with water, the 2,4-dinitrophenylhydrazone was taken up in ether. The crude product (1.00 g.), melting at 84–90°, was chromatographed on paper[27] simultaneously with the 2,4-dinitrophenylhydrazone of authentic nonanal; both had R_f 0.87. By a combination of chromatography on alumina (eluting with benzene) and recrystallizations from ethanol, 0.08 g. melting at 100–103° was obtained from 0.20 g. of crude 2,4-dinitrophenylhydrazone. The mixed melting points with the authentic 2,4-dinitrophenylhydrazone of nonanal (m.p. 103–104°), decanal (m.p. 104–105°), and undecanal (m.p. 104.5–105.5°) were 101–104°, 94–98°, and 85–90°, respectively, thus confirming III to be nonanal.

Sodium borohydride reduction[9] of nonsteam-volatile aldehyde mixture. The remaining aqueous solution of aldehydes (containing IV and V) was extracted with ether, and after removal of most of the ether, the residue was neutralized to indicator paper with 0.2*N* sodium hydroxide, and 150 ml. of 0.25*M* pH 9 sodium borate buffer was added. Sodium borohydride (0.091 g. in 110 ml. water) solution was added dropwise over 30 min. with stirring, and after standing overnight, the alkaline solution was diluted with water and extracted continuously with ether. Removal of the ether under reduced pressure yielded a solid (VI, 0.364 g.) melting at 40–54°.

The aqueous alkaline solution was evaporated to dryness under reduced pressure and reserved for characterization of the ω-hydroxy acid (VII).

Characterization of VI. A portion (0.32 g.) of VI was heated 10 min. at 60–65° with 110 ml. of *N* sodium hydroxide. The solution was diluted with water and continuously extracted with ether, yielding 0.22 g. of a semisolid. The product was recrystallized twice from benzene, yielding 0.13 g., melting at 57–58°; mixed melting point with

(23) Melting points were determined with a Fisher-Johns block and are uncorrected.

(24) Infrared spectrum was measured on undiluted acid in a 0.088-mm. cell with a Baird-Atomic model KM1 recording spectrophotometer. Near infrared spectrum was measured in carbon tetrachloride solution with a Cary model 14 PM spectrophotometer.

(25) D. H. Wheeler, *Oil & Soap*, 9, 89 (1932).

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

(27) D. F. Meigh, *Nature*, 170, 579 (1952).

authentic 1,8-octanediol[28] (m.p. 57.5–58.0°) was 57.5–58.0°. A portion of the diol was treated with 0.2 ml. of phenyl isocyanate and with 2 drops of pyridine as a catalyst. The excess reagents were removed under reduced pressure yielding 0.086 g., melting at 169.0–171.5°. The product was recrystallized from ethyl acetate and ethyl acetate–hexane, yielding 0.025 g. with a melting point and a mixed melting point with the authentic bisphenylurethane derivative of 1,8-octanediol (m.p. 172–173°) of 170–172°.

Characterization of the ω-hydroxy acid (VII). A portion of VII (0.40 g.) was dissolved in 20 ml. of water and 0.50 g. of potassium permanganate, and 0.8 ml. of 10% sodium hydroxide was added with stirring. After 30 min. at 20–25° and 2 hr. at 30–35°, the excess permanganate was destroyed by addition of sodium bisulfite, and the reaction mixture was filtered with suction. The filtrate was concentrated, acidified with 2*N* hydrochloric acid, and extracted with ether. The ether extract was evaporated to dryness, and the residue was extracted with hot benzene. After removal of the benzene, the product was recrystallized successively from benzene, chloroform, and chloroform-benzene yielding 0.007 g of VIII, melting at 90–95°; mixed melting point with authentic glutaric acid (m.p. 96.5–97.5°) was 92–96°. The x-ray diffraction pattern of the product was identical to authentic glutaric acid. The methyl esters, prepared with diazomethane,[29] of the combined mother liquor residue consisted of 93% glutaric acid as determined by gas chromatography.

(28) Suberic acid was reduced to 1,8-octanediol as outlined by R. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

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PEORIA, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE UNIVERSITY]

Preparation and Reactions of *sym*-Tetraphenyldisilane

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The preparation of *sym*-tetraphenyldisilane (I) is discussed. Various reactions of I have been studied in an attempt to correlate the reactions of *sym*-tetraphenyldisilanediol with those of the carbon analog. A series of novel difunctional disilanes was prepared from I and their reactions studied. A useful quantitative method for the estimation of silicon-silicon and silicon-hydrogen bonds is discussed in detail.

The number of known organosilicon compounds containing one or more silicon-silicon bonds is small compared to the number of compounds containing only one silicon atom or isolated silicon atoms. The majority of these disilanes or polysilanes are fully substituted by alkyl or aryl groups. Some *sym*-difunctional disilanes have been encountered as biproducts in the industrial preparation of chlorosilanes.[1]

An accidental encounter with a *sym*-difunctional disilane is reported in connection with the study of steric effects in organosilicon chemistry.[2] It was found that hexachlorodisilane reacted with four moles of *o*-tolyllithium to give *sym*-tetra-*o*-tolyldisilanediol, subsequent to hydrolysis, whereas hexaphenyldisilane could be obtained by the corresponding reaction with phenyllithium.

Attempts to prepare *sym*-dichlorotetraphenyldisilane by the action of four moles of phenylmagnesium bromide on hexachlorodisilane failed as did the attempted introduction of six phenyl groups by the use of the Grignard reagent.[3]

It was discovered that chlorodiphenylsilane is coupled by the action of magnesium to form *sym*-tetraphenyldisilane.[4] This reaction is comparable

$$2(C_6H_5)_2SiHCl + Mg \longrightarrow (C_6H_5)_2SiHSiH(C_6H_5)_2 + MgCl_2$$

to the coupling reaction of chlorotriphenylsilane with magnesium.[5] This type of coupling may involve the highly reactive silyl Grignard reagent which was likewise considered to be an intermediate in the reaction of cyclohexylmagnesium bromide with chlorotriphenylsilane.[6]

The preparation of *sym*-tetraphenyldisilane is very sensitive to the effectiveness of the initiation. This may be performed by the addition of ethyl iodide in much the same way as difficult preparations of Grignard reagents are initiated. Table I

(1) M. Kumada and M. Yamaguchi, *J. Chem. Soc., Japan, Ind. Chem. Sect.*, **57**, 175 (1954); *Chem. Abstr.*, **49**, 11542 (1955); M. Kumada and M. Kuriyagawa, Japanese Patent **7223** (1954); *Chem. Abstr.*, **50**, 10125 (1956).

(2) H. Gilman and G. N. R. Smart, *J. Org. Chem.*, **15**, 720 (1950).

(3) H. Gilman and G. D. Lichtenwalter, *J. Org. Chem.*, **24**, 1588 (1959); W. O. Schumb and C. M. Saffer, *J. Am. Chem. Soc.*, **61**, 363 (1939).

(4) H. Gilman and W. Steudel, *Chem. & Ind.*, 1094 (1959).

(5) H. Gilman, D. J. Peterson, and D. Wittenberg, *Chem. & Ind.*, 1479 (1958); M. V. George, D. J. Peterson, and H. Gilman, *J. Am. Chem. Soc.*, **82**, 403 (1960).

(6) T. G. Selin and R. West, *Tetrahedron*, **5**, 97 (1959).

TABLE I

Preparation of *sym*-Tetraphenyldisilane		
G.-atom Mg/mole $(C_6H_5)_2SiHCl$	Time of Reaction (hr.)	Yield, %
0.55	40	12
0.55	120	—[a]
2.00	20	45–55
3.00	16	45
2.00[b]	24	30
2.00[c]	96	<11

[a] The product did not crystallize on prolonged standing. [b] The chlorodiphenylsilane was heated in the presence of magnesium for four hours instead of the normal 30 min. [c] The period of preheating was 5 min. [d] The product was not isolated and the yield represents the percent consumption of chlorodiphenylsilane after the total reaction time.

shows the effect of variation of some experimental factors on the yield of product. The extent of reaction was determined by the removal of aliquots from the reaction mixture and titrating the amount of acid liberated on hydrolysis. The yields given are those of pure crystalline material obtained. The remainder of the material was a viscous oil which did not give crystalline fractions on chromatography.

It is evident from the data presented in Table I that the shorter reaction time favors the formation of the higher yield. A shorter reaction time is a consequence of a more effective initiation and this apparently is dependent on the time of preheating before the solvent, tetrahydrofuran, is added and on the amount of magnesium present. The silyl Grignard reagent, if formed, is consumed immediately as evidenced by the negative Color Test I[7] throughout the reaction.

The *sym*-tetraphenyldisilane gives a positive test for silicon-hydrogen bond with silver nitrate[8] and behaves as a trisubstituted silane against copper (II) chloride in pyridine[9] by giving a green color after prolonged standing only. The compound reacts very rapidly with dilute base to give three moles of hydrogen per mole of compound.

Attempts to hydrolyze *sym*-tetraphenyldisilane directly to *sym*-tetraphenyldisilanediol led to the formation of hexaphenylcyclotrisiloxane and octaphenylcyclotetrasiloxane. Under milder conditions it was possible to isolate the intermediate diphenylsilanediol which is known to undergo dehydration to either hexaphenylcyclotrisiloxane or octaphenylcyclotetrasiloxane under the given conditions.[10] No reaction occurred under acid conditions, and rapid cleavage was caused under slightly basic conditions.

$$(C_6H_5)_2SiHSiH(C_6H_5)_2 \xrightarrow{OH^-} [(C_6H_5)_2Si(OH)_2] \xrightarrow{OH^-} [(C_6H_5)_2SiO]_4$$

$$(C_6H_5)_2SiHSiH(C_6H_5)_2 \longrightarrow (C_6H_5)_2Si(OH)_2 \longrightarrow [(C_6H_5)_2SiO]_3$$

It was thus necessary to proceed by way of the *vic*-dihalo-tetraphenyldisilane which may be hydrolyzed under mild conditions[10] thus preventing cleavage of the silicon-silicon bond.

$$(C_6H_5)_2SiHSiH(C_6H_5)_2 + 2X_2 \xrightarrow{[-2HX]} (C_6H_5)_2SiXSiX(C_6H_5)_2 \xrightarrow{[H_2O]} (C_6H_5)_2SiOHSiOH(C_6H_5)_2$$

The *sym*-dichlorotetraphenyldisilane may be prepared in chloroform or carbon tetrachloride containing small amounts of ether. Chloroform in the absence of ether is undesirable since crystallization could not be induced in preparations performed in the absence of ether. It is conceivable that the ether acts as a hydrogen chloride acceptor and thus facilitates the reaction.

The *sym*-dibromotetraphenyldisilane may, however, be prepared by the addition of bromine in carbon tetrachloride in the absence of ether. The reaction may also be performed by the addition of *N*-bromosuccinimide by the normal type procedure used for this reagent.[11]

Attempts to prepare these compounds directly from dichlorodiphenylsilane or dibromodiphenylsilane by the action of one gram-atom of alkali metal per mole of dihalosilane led to the formation of perphenylated silicohydrocarbons by reactions similar to those first described by Kipping.[12] The use of lithium amalgam,[13] which reacts with dibromodiphenylgermane to give *sym*-dibromotetraphenyldigermane,[14] likewise caused the complete reduction of a fraction of the dihalodiphenylsilane rather than the desired partial reduction of all. A less active metal such as zinc did not react with diphenyldichlorosilane under the conditions employed.

The structure of the *sym*-dichlorotetraphenyldisilane was confirmed by the preparation of the known *sym*-di-*p*-tolytetraphenyldisilane[15] by the action of two moles of *p*-tolyllithium on one mole of dihalodisilane.

The dihalotetraphenyldisilanes could be hydrolyzed under mildly acid conditions to the *sym*-tetraphenyldisilanediol. Under mildly alkaline conditions, ammonium carbonate monohydrate in acetone,[16] condensation to a disiloxanediol occurred, whereas octaphenylcyclotetrasiloxane was formed under strongly alkaline conditions:

(7) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).
(8) A. Stock, *Z. Electrochem.*, **32**, 341 (1926).
(9) H. Gilman, H. G. Brooks, and M. B. Hughes, *J. Org. Chem.*, **23**, 1398 (1958).
(10) C. A. Burkhard, *J. Am. Chem. Soc.*, **67**, 2173 (1945).
(11) E. Campaigne and B. F. Tullar, *Org. Syntheses*, **33**, 96 (1953).
(12) F. S. Kipping and J. E. Sands, *J. Chem. Soc.*, 830 (1921).
(13) G. Wittig and L. Pohmer, *Ber.*, **89**, 1334 (1956).
(14) H. H. Zeiss, private communication.
(15) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **75**, 3762 (1953).
(16) T. Takiguchi, *J. Org. Chem.*, **24**, 989 (1959).

$$(C_6H_5)_2SiXSiX(C_6H_5)_2 \xrightarrow{[H_2O]} (C_6H_5)_2SiOHSiOH(C_6H_5)_2 \text{ (acid or neutral cond.)}$$

$$(C_6H_5)_2SiXSiX(C_6H_5)_2 \xrightarrow{[H_2O]} (C_6H_5)_2SiOH(C_6H_5)_2SiOSi(C_6H_5)_2Si(C_6H_5)_2OH \text{ (weakly alkaline cond.)}$$

$$(C_6H_5)_2SiXSiX(C_6H_5)_2 \xrightarrow{[H_2O]} [(C_6H_5)_2Si(OH)_2] \longrightarrow [(C_6H_5)_2SiO]_4 \text{ (strongly alkaline cond.)}$$

Confirmatory evidence for the structure of the compound was obtained by utilizing strongly alkaline conditions on a quantitative scale.

The infrared spectrum of the *sym*-tetraphenyldisilanediol showed the presence of hydrogen bonding both in the solid state and in solution. The spectrum was identical in many respects to that of diphenylsilanediol, although the intramolecular hydrogen bonded O—H stretching frequency was at a higher frequency for the *sym*-tetraphenyldisilanediol than for diphenylsilanediol. This indicates that the hydroxyl groups in the former compound are closer to each other in the *cis*-form than they are in the latter compound.

A chief interest in this compound rested in the possible preparation of a silicon analog of an epoxy compound. It would likewise be interesting to see if the *vic*-silicoglycol underwent a pinacol-pinacolone type rearrangement. A wide variety of conditions was employed to effect the preparation of the epoxy type or the rearrangement, but the conditions which effected dehydration did so by an intermolecular route to a cyclic siloxane and not by an intramolecular route nor by rearrangement. Neither ice-cold concentrated sulfuric acid[17] nor 50% boiling phosphoric acid[18] caused any dehydration. The starting material was recovered unchanged. Preparation and pyrolysis of the phenylthiourethan did not effect the desired epoxy formation.[19] A procedure utilized in the steroid field for the preparation of 3,9-oxy compounds from the corresponding diols involves heating the diol with pyridine in the presence of *p*-toluenesulfonyl chloride.[20] This method gave a good yield of the cyclic siloxane described later. Attempted dehydration in benzene containing a catalytic amount of *p*-toluenesulfonic acid failed; and unchanged starting material was recovered.[21] More forcing conditions such as heating the compound in a dimethylformamide solution[22] of oxalic acid caused dehydration to the cyclic disiloxane. An unsuccessful attempt to effect the acetal formation with chloral, a typical reaction of *vic*-glycols,[23] likewise failed in the absence or in the presence of *p*-toluenesulfonic acid. The cyclic disiloxane was formed in both cases.

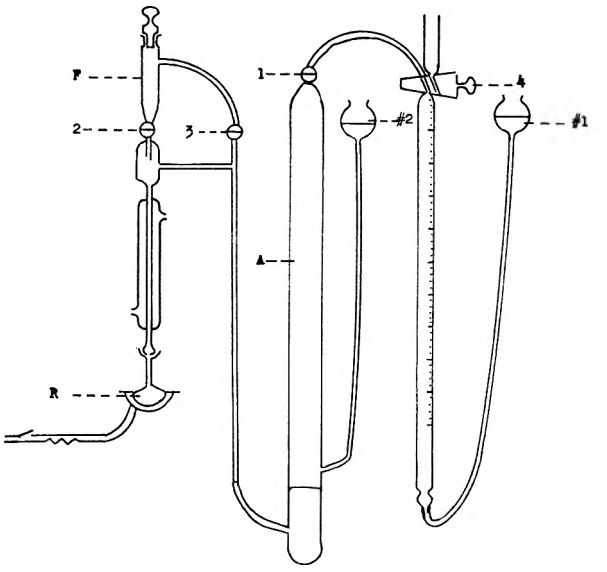

Fig. 1. Apparatus for determination of hydrogen values

From these observations it may be concluded that *sym*-tetraphenyldisilanediol behaves quite differently from benzopinacol which readily undergoes the pinacol-pinacolone rearrangement and dehydration to form epoxytetraphenylethylene.

Intermolecular dehydration is best performed in boiling formic acid. The compound isolated is a siloxane of the structure shown:

$$2(C_6H_5)_2SiOHSiOH(C_6H_5)_2 \xrightarrow{[-2H_2O]} \begin{matrix} Si(C_6H_5)_2Si(C_6H_5)_2 \\ O \qquad\qquad O \\ Si(C_6H_5)_2Si(C_6H_5)_2 \end{matrix}$$

This compound was of interest in connection with the identification of various products isolated but not identified by Kipping[12] in an oxidation of octaphenylcyclotetrasilane.

In connection with the identification of the compounds discussed in this investigation there was developed a refined technique for the quantitative estimation of silicon-hydrogen or silicon-silicon groups in an organosilicon compound. The method was first described with little detail by Kipping[24] for the estimation of the silicon-silicon group. The procedure was later modified and extended to the estimation of the silicon-hydrogen group and it

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(18) W. M. Dehn and K. E. Jackson, *J. Am. Chem. Soc.*, **55**, 4286 (1933); G. A. Hill and E. W. Flosdorf, *Org. Syntheses*, **5**, 91 (1925).

(19) Erdman, Thesis, Rostock, 1910, p. 65. [V. Grignard, "Traité de Chimie Organique," Masson, Paris, 1941, Ref. 171, p. 79].

(20) H. Heymann and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

(21) E. J. Salmi, *Ber.*, **71B**, 1803 (1938).

(22) D. Vorlander, *Ber.*, **30**, 2266 (1897).

(23) O. Wallach, *Ann.*, **193**, 40 (1878); M. Renoll and M. S. Newman, *Org. Syntheses*, **28**, 73 (1948).

(24) F. S. Kipping, *J. Chem. Soc.*, 848 (1921).

is for this purpose the method has been used most widely for rate studies or otherwise.[25]

An experimental set-up similar to that described in the literature[26] was used. The inability of highly substituted silanes to hydrolyze was reconfirmed for compounds having high steric hindrance. Thus, it was noted that tri-*o*-tolylsilane and tri-*o*-xenylsilane failed to liberate any more than a trace of hydrogen even after 24 hours of heating in refluxing wet piperidine, and the starting material was recovered essentially quantitatively. It appears that the use of the method for the determination of silicon-silicon groups is not limited sterically to the same extent as is the determination of the silicon-hydrogen bond. Thus, *sym*-tetra-*o*-tolyldisilanediol undergoes ready cleavage with the liberation of one mole of hydrogen per mole of compound. Table II represents the determinations carried out on the compounds discussed in this investigation. The term "hydrogen value" refers to the number of milliliters of gas (at S. T. P.) liberated per gram of compound.

TABLE II

"HYDROGEN VALUES" OF VARIOUS COMPOUNDS

Compound	H-value found, ml./g.	H-value calcd., ml./g.
$(C_6H_5)_2SiHSiH(C_6H_5)_2$	195	183
$(C_6H_5)_2SiOHSiOH(C_6H_5)_2$	59	56
$[(C_6H_5)_2Si(C_6H_5)_2SiO_2]$	59.5	59
$(C_6H_5)_2SiClSiCl(C_6H_5)_2$	52	51.5

The method may be modified to distinguish between silicon-silicon and silicon-hydrogen groups. A determination of the compound containing both groups is first performed, and another sample of the compound is chlorinated or brominated (under conditions which do not effect silicon-silicon bond cleavage) to convert the silicon-hydrogen bonds to silicon-halogen bonds. The silicon-silicon group is then determined separately for this compound and the difference between the two determinations is due to silicon-hydrogen bonds.

EXPERIMENTAL[27]

Reaction of hexachlorodisilane with phenylmagnesium bromide. The Grignard reagent was prepared by a conventional procedure from 80 g. of bromobenzene and 13.4 g. of magnesium in 300 ml. of ether. A 1-ml. sample was assayed to contain 1.66 mmoles of Grignard reagent per ml. Part of this solution (240 ml., containing 0.400 mole of Grignard reagent) was added dropwise to 26.8 g. of hexachlorodisilane (0.1 mole) in 50 ml. of ether. The solution was stirred well and cooled in ice during the initial part of the reaction. The solution was stirred for 24 hr. after complete addition of the reagent and since Color Test I[7] was still positive, the solution was heated under reflux for another 24 hr. The Color Test was negative and the ether was distilled while petroleum ether (b.p. 60–70°) was added. The total volume of solvents which had been removed was 500 ml. To the remaining suspension of magnesium bromide and chloride was added 100 ml. of benzene and the magnesium halides were removed by filtration under nitrogen pressure. The filtrate was concentrated and the remaining oil distilled under reduced pressure; at 2 mm. pressure there were collected 5 g. of biphenyl, vapor temp. 100–120°, identified by infrared spectra and mixed melting point with an authentic sample, and 6 g. (24%) of dichlorodiphenylsilane at 136–138°/2 mm. At still lower pressures were collected 7 g. (22%) of tetraphenylsilane, b.p. 165–166°/0.07 mm., and a residue which did not crystallize on prolonged standing.

Preparation of sym-tetraphenyldisilane. A mixture of 218 g. of chlorodiphenylsilane (1 mole) and 48 g. of magnesium (2 g.-atoms) was heated in a 1 l. flask equipped with a condenser (topped by a nitrogen inlet), a stirrer, and an addition funnel containing 300 ml. of tetrahydrofuran, distilled from sodium wire and lithium aluminum hydride under a nitrogen atmosphere. The heating at 70° was continued for 30 min. and 50–100 ml. of tetrahydrofuran were introduced. If the reaction did not start spontaneously within 5 min. there was added 5 drops of ethyl iodide. The magnesium turned black and heat was generated. The heating mantle was removed and the reaction allowed to proceed for 16–20 hr. at room temperature, while the remaining tetrahydrofuran was added. The extent of reaction may be determined by removing an aliquot of the reaction mixture which has been allowed to settle and adding this to 25 ml. of water and titrating the liberated acid with 0.1*N* sodium hydroxide. The suspension was decanted through a glass wool plug into 500 ml. of 1*N* ice-cooled hydrochloric acid which was stirred rapidly. To the resulting aqueous suspension was added 200 ml. of ether and the aqueous layer was separated and extracted with two 100-ml. portions of ether. The combined organic layers were shaken with 300 ml. of saturated sodium chloride solution and dried over calcium chloride. The solvents were removed and the remaining oil seeded with a small amount of *sym*-tetraphenyldisilane. Crystallization was allowed to proceed for 24 hr. and the solids collected on a Büchner funnel and washed with small amounts of ice-cooled ethanol. The solid was recrystallized from 4:1 petroleum ether (b.p. 60–70°)-benzene to give 87 g. of pure *sym*-tetraphenyldisilane (47%), m.p. 79–80°.

From the mother liquors of the precipitation was obtained another 48 g. of tetraphenyldisilane by distillation, b.p. 175–177°/0.05 mm. (Total yield 145 g. or 74%).

Anal. Calcd. for $C_{24}H_{22}Si_2$: C, 78.64; H, 6.05; Si, 15.31. Found: C, 78.42; H, 6.11; Si, 15.32.

Hydrolysis of sym-tetraphenyldisilane by sodium ethoxide at 0°. A solution of 0.6 g. of *sym*-tetraphenyldisilane in 30 ml. of ethanol was cooled to 0° and 25 ml. of 0.5*M* sodium ethoxide was added dropwise. A gas was evolved during the 30-min. addition period. To the resulting solution was added 100 ml. of saturated ammonium chloride solution and the aqueous layer was extracted with ether which was dried over Drierite and concentrated. A total of 0.5 g. of a white solid, m.p. 159.5–160°, was collected (70%).

Anal. Calcd. for $C_{12}H_{12}SiO_2$: Si, 12.97. Found: Si, 12.97, 12.87. Infrared spectrum: (chloroform solution) 3650, 3300, 3025, 1600, 1420, 1130, 1120 cm^{-1}.

By comparison with an authentic sample (infrared spectra and mixture melting point) prepared by conventional

(25) A. Stock and C. Somieski, *Ber.*, **49**, 111 (1916); F. P. Price, *J. Am. Chem. Soc.*, **69**, 2600 (1947); H. Gilman and G. E. Dunn, *J. Am. Chem. Soc.*, **73**, 3404 (1951); H. Gilman, G. E. Dunn, G. S. Hammond, *J. Am. Chem. Soc.*, **73**, 4499 (1951); R. West, *J. Am. Chem. Soc.*, **76**, 6015 (1954); L. Kaplan, K. E. Wilzbach, *J. Am. Chem. Soc.*, **74**, 6152 (1952) and **77**, 1297 (1955); J. E. Baines and U. C. Eaborn, *J. Chem. Soc.*, 4023 (1955).

(26) G. Fritz and G. Grabe, *Z. anorg. Chem.*, **299**, 302 (1959).

(27) All reactions involving organometallic compounds were carried out in an atmosphere of dry, oxygen-free nitrogen, and all melting points are uncorrected.

procedures[10] it was concluded that this compound was diphenylsilanediol. A second preparation from *sym*-tetraphenyldisilane was performed under conditions by which it was possible to measure the amount of gas liberated. It was found that 2.97 moles of gas, per mole of starting material, was liberated; theory 3.00.

Hydrolysis of sym-tetraphenyldisilane by wet piperidine. To a solution of 1.8 g. of *sym*-tetraphenyldisilane in 20 ml. of piperidine was added 1 ml. of water while external cooling to 0° was provided. There was an immediate evolution of hydrogen, 3.0 moles per mole of compound. The solvents were removed under an air-jet and the resulting oil was chromatographed to yield 1.2 g. of solid, m.p. 186–187°. Infrared spectra[28] and mixed melting point identified this compound as octaphenylcyclotetrasiloxane (62%). Trace amounts of hexaphenylcyclotrisiloxane were identified in one fraction of the eluates.

Preparation of sym-dichlorotetraphenyldisilane. To a solution of 10 g. of *sym*-tetraphenyldisilane in 100 ml. of carbon tetrachloride, containing 25 ml. of diethyl ether, was added chlorine gas through a bubbler. The flask was protected from the atmosphere by a calcium chloride drying tube. The addition was continued for 4 hr. and the solvents were removed at reduced pressure (a water aspirator protected by a calcium chloride drying tube) after dry nitrogen had been passed through the bubbler for another 3 hr. to remove the major portion of the hydrogen chloride. The solid crystallized immediately and was recrystallized from benzene–petroleum ether (b.p. 60–70°), 1:1. There was obtained a total of 10.6 g. of recrystallized material, m.p. 114.5–115°. The compound was recrystallized twice from hexane, before analysis, without change in melting point; yield 86%.

Anal. Calcd. for $C_{24}H_{20}Si_2Cl_2$: C, 66.20; H, 4.63; Si, 12.89; Cl, 16.28. Found: C, 65.96, 66.10; H, 4.40, 4.28; Si, 12.72, 12.78; Cl, 17.10.

Preparation of sym-dibromotetraphenyldisilane. To a solution of 5 g. of *sym*-tetraphenyldisilane (0.0136 mole) in 50 ml. of carbon tetrachloride was added 4.35 g. of bromine (0.0272 mole) in 40 ml. of carbon tetrachloride. The reaction mixture was cooled in an ice bath throughout the addition. The bromine was consumed very readily and it was not until the last drop of bromine solution was added that a slightly yellow color developed. Stirring was continued for another 16 hr. after complete addition and the reaction mixture was allowed to heat to room temperature. On addition of 75 ml. of pentane, the solid *sym*-dibromotetraphenyldisilane precipitated. The solid was filtered off and dried *in vacuo* for 4 hr., m.p. 154.5–155.5° after one recrystallization from a 1:1 mixture of benzene-petroleum ether (b.p. 60–70°). Additional fractions were collected giving a total yield of 87%.

This compound was also prepared by the reaction of 4.8 g. of *N*-bromosuccinimide (0.027 mole) containing 0.1 g. of benzoyl peroxide with 4.0 g. of *sym*-tetraphenyldisilane (0.011 mole) in 40 ml. of refluxing benzene. The solution was heated for 2 hr. after complete addition and then cooled to room temperature. The succinimide was filtered off (2 g. or 75% of theory). The benzene was removed under reduced pressure and 25 ml. of petroleum ether (b.p. 60–70°) was added. Cooling for 16 hr. caused the precipitation of 3.9 g. of *sym*-dibromotetraphenyldisilane, 68%.

Attempted direct preparation of sym-dichlorotetraphenyldisilane. To 50.6 g. of dichlorodiphenylsilane in 100 ml. of tetrahydrofuran was added 1.4 g. of lithium metal. A reaction was evidenced by the yellow coloring of the metal. The reaction was allowed to proceed for 48 hr. at which time the lithium had been consumed. The white precipitate which had separated was filtered off and extracted in a Soxhlet apparatus with toluene. From the extracts were obtained 8 g. of octaphenylcyclotetrasilane (22%), m.p. 315–317°.[29] From the ether filtrates were recovered dichlorodiphenylsilane by distillation, b.p. 128–130°/2 mm. 20 g., 39%. The remaining oils did not crystallize on standing and consisted of diphenylsilylene polymers.

Reaction of dichlorodiphenylsilane with zinc (attempted). A 50-g. sample of dichlorodiphenylsilane was added to a suspension of 15 g. of finely powdered zinc in 200 ml. of refluxing ether. The reaction mixture was stirred for 48 hr. while the ether was heated to reflux. There was no visual sign of reaction and an aliquot indicated that none of the chlorosilane had reacted. Distillation of the filtrate from the zinc yielded 40 g. of dichlorodiphenylsilane, b.p. 128–130°/2 mm.; 80% recovery.

Reaction of dichlorodiphenylsilane with lithium amalgam. Lithium amalgam was prepared from 0.3 g. of lithium (0.0435 g.-atom)in an open Schlenk tube in a slow current of hydrogen. Mercury, 100 g., was heated to 145° and the lithium was added slowly through one of the inlets in the tube. The temperature was raised to 210° after complete addition and the suspension was swirled occasionally during a 10-min. period. The tube was cooled and there was introduced 11 g. of dichlorodiphenylsilane (0.040 mole) in 30 ml. of ether. The tube was cooled in a Dry Ice acetone bath and sealed under an atmosphere of nitrogen. The Schlenk tube was mounted in a Parr hydrogenation apparatus and shaken for 70 hr. (130 rpm). The tube was cooled and opened. The contents of the tube were filtered through a fluted filter and the mercury washed with tetrahydrofuran. The mercury contained a large proportion of unchanged lithium amalgam as evidenced by the evolution of hydrogen on hydrolysis. The organic layer was evaporated and since no solid separated on standing, the oil was distilled to give 4.0 g. of dichlorodiphenylsilane (36% recovery) and various oils, 4.5 g., from which was obtained in a 52% yield hexaphenylcyclotrisiloxane, identified by mixed melting point and infrared spectra.

Reaction of dibromodiphenylsilane with lithium amalgam. Dibromodiphenylsilane was prepared from diphenylsilane and bromine in 73% yield, b.p. 180°/12 mm. A portion (15 g.) of this was added to lithium amalgam prepared as described in the previous experiment (0.0435 mole/0.0432 g.-atom). The reaction was carried out in an identical manner to yield by work-up under anhydrous conditions 1.5 g. of lithium bromide (47%). The organic layer did not yield any *sym*-dibromotetraphenyldisilane. A mixture of octaphenylcyclotetrasiloxane and hexaphenylcyclotrisiloxane was obtained by chromatography and a small amount of octaphenylcyclotetrasilane, m.p. 315–317°, 2.6 g. (31%). By distillation there was obtained 30% unchanged dibromodiphenylsilane, b.p. 180–185°/12 mm.

Preparation of sym-di-p-tolyltetraphenyldisilane. A 1*M* solution of *p*-tolyllithium was prepared from 17.7 g. of *p*-bromotoluene and lithium in a total of 100 ml. of ether. A portion of this solution (21 ml.; 0.99*M* by analysis) was added to a solution of 2.20 g. (0.005 mole) *sym*-dichlorotetraphenyldisilane in 40 ml. of ether. The solution was stirred for 24 hr. at room temperature, and 100 ml. of saturated aqueous ammonium chloride was added. The product which was insoluble in ether was obtained by filtration. Recrystallization from benzene-chloroform 1:1, yielded 1.74 g. of *sym*-di-*p*-tolyltetraphenyldisilane (70%), m.p. 248–249°. The compound was identified by mixed melting point and comparison of infrared spectra with an authentic sample.

Hydrolysis of sym-dichlorotetraphenyldisilane. A solution of 3.8 g. of *sym*-dichlorotetraphenyldisilane (0.0088 mole) in 15 ml. of toluene was added to a well-stirred emulsion of 70 ml. of water and 20 ml. of *tert*-amyl alcohol. The mixture was stirred for 1 hr. at room temperature and for 3 hr. at 0°. The product was obtained from the dried organic layer, which had been combined with ether extracts of the

(28) C. W. Young and P. C. Servais, C. C. Currie, and M. J. Hunter, *J. Am. Chem. Soc.*, **70**, 3758 (1948).

(29) H. Gilman, D. J. Peterson, A. W. Jarvie, H. J. S. Winkler, *J. Am. Chem. Soc.*, **82**, 2076 (1960).

aqueous layer (three 100-ml. portions), by removal of the solvents. Recrystallization from benzene-petroleum ether (b.p. 60–70°) gave an 83% yield of *sym*-tetraphenyldisilanediol, 3.2 g., m.p. 139–140°.

Anal. Calcd. for $C_{24}H_{22}Si_2O_2$: C, 72.32; H, 5.57; Si, 14.08. Found: C, 71.86, 71.96; H, 5.34, 5.34; Si, 13.96, 14.06.

Hydrolysis in acetone with ammonium carbonate monohydrate of 2 g. of *sym*-dichlorotetraphenyldisilane at 50° for 1 hr. and in the refluxing solvent for another hour yielded ammonium chloride which was filtered off and identified by qualitative analysis. The filtrate yielded a small fraction of *sym*-dihydroxytetraphenyldisilane, 0.3 g. (16%), m.p. 138–139° and 1.1 g. of 1,5-dihydroxy-1,1,2,2,4,4,5,5-octaphenyltetrasiladisiloxane-3, m.p. 118–119°, H-value 58.5 ml./g. Calcd. for $C_{48}H_{42}Si_4O_3$, 57.5 ml./g.

Anal. Calcd. Si, 14.42. Found: 13.93, 14.02.

Hydrolysis of *sym*-dichlorotetraphenyldisilane in 10% piperidine-water on a quantitative scale gave a hydrogen value of 52 ml./g. Calcd. for this compound is 51.5. From the hydrolysis mixture was isolated a compound which was identified as octaphenylcyclotetrasiloxane by melting points and infrared spectra.

Attempted dehydrations of sym-tetraphenyldisilanediol. A suspension of 2 g. of *sym*-tetraphenyldisilanediol in 30 ml. of 88% formic acid was heated to boiling for 30 min. The solution was cooled and poured on 100 ml. of an ice water slurry. The white crystalline compound which was collected on filtration was recrystallized from benzene-petroleum ether (b.p. 60–70°), 1.8 g. or 95% yield, m.p. 219–220°.

Anal. Calcd. for $C_{48}H_{40}Si_4O_2$: C, 75.75; H, 5.30; Si, 14.75. Found: C, 75.55, 75.75; H, 5.30, 5.36; Si, 14.60, 14.81.

A finely ground sample of *sym*-tetraphenyldisilanediol was added to 20 ml. of concentrated sulfuric acid which had been cooled to 0°. The suspension was stirred for 0.5 hr. and then poured on cracked ice. Extraction of the resulting suspension with ether and drying of the combined extracts gave a colorless solution which on concentration yielded a solid melting at 137–139° and having an infrared spectrum identical with the starting material. The yield of recovered *sym*-tetraphenyldisilanediol was 65%.

Dehydration of 0.3 g. of diol in 50% phosphoric acid heated to reflux in the presence of an equal volume of toluene, after an initial 10-min. period of heating without toluene, resulted in the recovery of 40% of the starting material containing traces of the linear disiloxane melting at 118–119°.

An 0.5-g. sample of *sym*-tetraphenyldisilanediol was heated with 1 ml. of phenyl isothiocyanate for 5 min. producing a clear solution. A white solid precipitated on cooling the solution and adding petroleum ether (b.p. 60–70°). The solid was collected on a filter and washed with 50% ethanol in order to remove phenylisothiocyanate. The product was recrystallized from benzene-petroleum ether (b.p. 60–70°), m.p. 137–138°, 0.35 g., or 70% recovery.

A solution of 0.4 g. of the diol in 6 ml. of dried pyridine containing 0.8 g. of *p*-toluenesulfonyl chloride was left standing at room temperature for 44 hr. The solution was then heated on a steam bath for 30 min. and cooled in an ice bath. Part of the solvent was evaporated and the remaining oil was chromatographed to yield 0.38 g. of solid, m.p. 219–220°, identified as the cyclic siloxane by its infrared spectrum and mixture melting point with an authentic sample.

A solution of 1 g. of the diol in 50 ml. of benzene containing a trace of *p*-toluenesulfonic acid was refluxed briskly for 4 hr. Any water in the refluxing vapors would have been removed by means of the Deen-Stark trap used. Evaporation of the solvent left the unchanged starting material behind (75% recovery).

A mixture of 1.0 g. of oxalic acid and 0.3 g. of the diol was dissolved in 2 ml. of dimethylformamide and heated in the refluxing solvent for 30 min. The reaction mixture was poured on ice to remove the solvent and the acid. The solid which separated was filtered off and washed with ethanol. Recrystallization yielded the pure cyclic siloxane in 68% yield, m.p. 220–221.°

Chloral hydrate was dehydrated by heating in boiling benzene for 3 hr. The water was separated by azeotropic distillation and collected in a Deen-Stark trap. The benzene solution was cooled and a trace of *p*-toluenesulfonic acid was introduced together with 2.0 g. of the diol. The solvent was brought to a brisk boil which was continued for 20 hr. The solution was concentrated to 5 ml. and chromatographed to yield 1 g. of the cyclic siloxane, m.p. 220–221°.

Determination of hydrogen values. The hydrogen value of a compound may be calculated from the molecular weight and the number of silicon-silicon bonds (n) and silicon-hydrogen bonds (m) in the molecule: H-value = $\frac{22.400\,(n + m)}{\text{Mol. Wt.}}$. The hydrogen evolved from silicon-hydrogen bonds is usually evolved more rapidly than that from a silicon-silicon bond.

It is advantageous to use the amount of compound which would liberate a total of 10–15 ml. of hydrogen. Usually 0.1–0.2 g. of compound suffices for the determination. The compound is weighed out directly into the dried flask R and three boiling stones are added. The ball joint at R is greased with Lubriseal and clamped closed. Leveling bulb No. 2 is placed in such a postion that the mineral oil surface is at the same level as the side-arm of the reservoir A. Stopcock 2 is closed and stopcock 3 is opened while 10 ml. of wet piperidine (containing 10% of water by volume) is introduced into the addition funnel F. The addition funnel (F) is closed and stopcock 2 is opened to allow the piperidine to flow into the reaction flask. Stopcocks 2 and 3 are closed immediately after the piperidine has drained out of the addition funnel. The heating mantle under R is turned on and the flow of water through the condenser started. The evolved gases will bubble through the mercury at the bottom of A and displace the mineral oil in A into the leveling bulb No. 2. The heat is left on until no more bubbles pass through the mercury (3–15 hr.). The gas is moved from A into the measuring burette by raising leveling bulb No. 2 and lowering No. 1 while stopcocks 1 and 4 are set in such a position as to allow the gas to flow into the burette. If more than 50 ml. of gas is collected this should be measured off in two portions. Measuring the gases is accomplished by raising leveling bulb No. 1 until the mineral oil inside the bulb is at the same level as the oil inside the burette. If it appears necessary to check whether more gas will be evolved on prolonged heating, it is advisable to lower the leveling bulb No. 2 slowly to its lower position since a sudden change in pressure accompanied thereby will cause the piperidine to boil more rapidly and displace more gas in the condenser than normally. The pressure at the time of reading the volume should be noted as should the temperature of the gas. From the amount of gas evolved, the pressure, the weight of the compound, and the temperature, the hydrogen value of the compound can be calculated if the volume of gas liberated from refluxing an equal volume of wet piperidine is known. This amount of gas is called the "empty value". A choice in calculating the hydrogen value may be made: either the empty value may be converted to S.T.P. and subtracted from the value observed, corrected to S.T.P.; or the empty value may be converted from the conditions under which it was observed to the conditions at which the determination of the hydrogen value was made (V_{empty}) and subtracted from this before the remaining volume is corrected to S.T.P. The volume thus found should be corrected to S.T.P. taking into account the temperature, the pressure, and the vapor pressure of the wet piperidine at the temperature of the condenser:

$$\text{H-value found} = \frac{(V_{found} - V_{empty}) \cdot 273 \cdot (P_{mm.} - 11)}{g_{cpd.} \cdot \text{Temp.}_{observed}\,(K^\circ) \cdot 760}$$

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AMES, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY]

Organoboron Compounds. XIII. Boronic Acids with Neighboring Unsaturated Groups[1]

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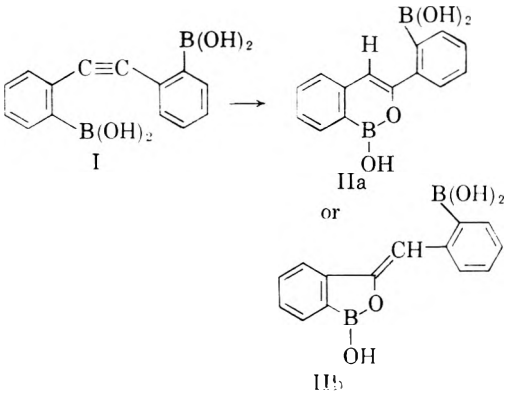
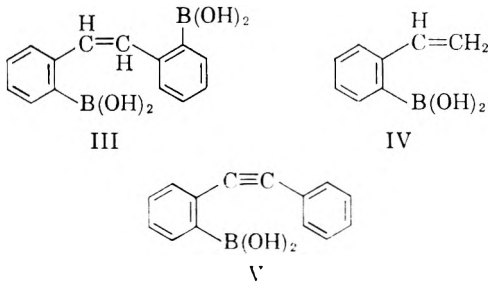
2,2′ Stilbenediboronic acid, 2-vinylbenzeneboronic acid, and 2-tolanboronic acid are described. None of these compounds isomerizes under conditions which convert 2,2′-tolandiboronic acid to a heterocyclic compound (II).

2,2′-Tolandiboronic acid (I) readily isomerizes in an alkaline medium or in solutions containing potassium acid tartrate to give a heterocyclic compound, which has been formulated as either IIa or IIb.[4]



In order to gain further information concerning the reactions of boronic acid groups with neighboring unsaturated linkages, we prepared 2,2′-stilbenediboronic acid (III), 2-vinylbenzeneboronic acid (IV), and 2-tolanboronic acid (V) and subjected them to conditions which would effect the transformation of I to II. Particular attention was directed to 2-tolanboronic acid, for should this compound yield a product analogous to II, it would be possible by oxidative degradation to determine whether the hetero-ring was five- or six-membered.



Neither the stilbenediboronic acid nor the vinylbenzeneboronic acid yielded isolable rearrangement products under the conditions examined. In each case the major portion of the boronic acid was recovered unchanged, as shown by the infrared spectrum. The vinyl group in 2-vinylbenzeneboronic acid possessed normal reactivity with respect to polymerization. Like 4-vinylbenzeneboronic acid[5] compound IV yielded when warmed with azobisisobutyronitrile a brittle polymer, which was insoluble in ether or benzene but soluble in alkaline solutions.

More surprising, no isomerization was observed with 2-tolanboronic acid.[6] This fact shows that both boronic acid groups in 2,2′-tolandiboronic acid must play a role in the isomerization and suggests that the reaction may involve concerted donation of a proton by one boronic acid group and a hydroxide ion by the other (which is complexed with hydroxide or tartrate ion) to the two carbon atoms joined by the triple bond. Models indicate that a

(1) For the previous paper in this series see R. L. Letsinger and S. B. Hamilton, *J. Org. Chem.*, 25, 592 (1960).

(2) National Science Foundation Undergraduate Summer Research Participant.

(3) National Science Foundation Predoctoral Fellow.

(4) R. L. Letsinger and J. R. Nazy, *J. Am. Chem. Soc.*, 81, 3013 (1959). Product II is unusual in that, though formally a boronate ester, it resists hydrolysis in acidic, neutral and weakly alkaline media and titrates as a monoboronic acid. The recently demonstrated stability of the six-membered heterocyclic B-O-C system in 9,10-boroxarophenanthrene [M. J. S. Dewar and R. Dietz, *J. Chem. Soc.*, 1344 (1960)] increases the plausibility of structure IIa.

(5) R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, 81, 3009 (1959).

(6) A small amount of 2-bromo-2′-tolanboronic acid was isolated from one of the reactions used in the preparation of 2,2′-tolandiboronic acid (see Ref. 4). The structure, deduced from the mode of formation and analyses of the compound and its dihydrobenzoboradiazole derivative (ref. 4), is strongly supported by the ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 287,306; shoulders at 272,297 mμ), which is almost superposable upon the spectrum of 2,2′-tolandiboronic acid Like 2-tolanboronic acid, this compound did not isomerize when warmed in an alkaline, aqueous-alcoholic solution.

concerted process of this type would not be excluded on geometrical grounds in the case of the *trans*-2,2′-stilbenediboronic acid.[7] It is therefore apparent that reaction of a boronic acid group with a neighboring alkene group is less favored than reaction with a neighboring alkyne group.

2,2′-Stilbenediboronic acid and 2-tolanboronic acid were prepared from the corresponding bromo compounds in the manner by which 2,2′-tolandiboronic acid was made from 2,2′-dibromotolan. This involved metal-halogen interchange with butyllithium, boronation with *n*-butyl borate, and hydrolysis. 2-Vinylbenzeneboronic acid was obtained both by reaction of 2-vinylphenylmagnesium chloride with *n*-butyl borate and by dehydrobromination of 2-(1-bromoethyl)benzeneboronic anhydride with quinoline. The latter reaction gave much the better yield. By contrast, it may be noted that both boronation of 4-vinylphenylmagnesium chloride[5,8] and dehydrobromination of 4-(1-bromoethyl)benzeneboronic anhydride[9] afforded satisfactory yields of 4-vinylbenzeneboronic acid.

The structures of the boronic acids are based on the synthetic paths, analyses, formation of derivatives (with *o*-phenylenediamine or by oxidation with hydrogen peroxide), and spectral data. The marked similarity in the infrared and ultraviolet spectra of 2,2′-tolandiboronic acid and 2-tolanboronic acid is particularly significant. Neither I nor V absorbed appreciably in the 10–11 μ region, indicating the absence of *trans*-stilbenes. Their infrared spectra differed primarily in that 2-tolanboronic acid showed a strong band at 14.6 μ, indicative of a compound with an unsubstituted phenyl group. In the ultraviolet both compounds exhibited maxima and shoulders in the 270–310 mμ region of the type expected for tolan compounds.

EXPERIMENTAL

All organometallic reactions were carried out with efficient stirring in a nitrogen atmosphere. Butyllithium was prepared from butyl bromide.[10] Unless otherwise specified, the boronic acid was isolated from the reaction of *n*-butyl borate with the organolithium compound by adding dilute hydrochloric acid to the reaction mixture. The ether layer was combined with an ether extract of the aqueous layer and extracted several times with dilute sodium hydroxide solution. On acidification of the alkaline solution the boronic acid precipitated. It was collected either by filtration or ether extraction and recrystallized from alcohol-water solutions. Dihydrobenzoboradiazole derivatives were prepared by heating the boronic acids with *o*-phenylenediamine in toluene as previously described.[11] Melting points were taken on a Fisher-Johns block. Infrared spectra were taken with a Baird spectrometer with the sample in potassium bromide unless otherwise specified. Ultraviolet spectra were obtained with a Cary recording spectrophotometer. Carbon, hydrogen, and nitrogen analyses were made by Miss H. Beck; boron analyses were obtained by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

2,2′-Stilbenediboronic acid (III) (J. N.). A solution containing 8.35 g. (0.0247 mole) of *trans*-2,2′-dibromostilbene[4] in 35 ml. of ether was added to 65 ml. of 0.759*M* butyllithium (0.049 mole) in ether at ice temperature and the mixture was stirred for 30 min.

A 25-ml. aliquot of the reaction mixture was pipetted into a Dry Ice-ether slurry. Subsequent acidification and isolation of the carboxylic acid yielded 1.37 g. (83%) of crude 2,2′-stilbenedicarboxylic acid; m.p. 241–247°. After recrystallization from ethanol a sample melted at 260–262° (lit.,[12] m.p. 263–265°); λ_{max} 5.90 μ. The structure of the acid was further verified by preparation of the dimethyl ester by heating the acid in methanol with a catalytic amount of sulfuric acid; m.p. 100–101.5° (lit.,[12] m.p. 101–102°); λ_{max} 5.80 μ. The formation of the known dicarboxylic acid on carbonation demonstrated that 2,2′-lithiostilbene had been produced in good yield.

The major portion (75 ml.) of the dilithiostilbene solution was cooled to −75° and treated with a solution of *n*-butyl borate (9.75 g., 0.0423 mole) in ether. A rise in temperature to −55° was noted. The mixture was cooled to −75°, stirred for an hour, allowed to warm to 0° and hydrolyzed with dilute hydrochloric acid. Conventional work-up yielded 4.34 g. (87%) of 2,2′-stilbenediboronic acid, m.p. 198–205°. After recrystallization it melted at 205–210°; $\lambda_{max}^{ethanol}$ 302 mμ (log ϵ 3.55), 238 mμ (log ϵ 2.94). A strong band at 3.0 μ and the absence of a bond between 14 and 15[13] μ indicated that the compound was an acid rather than an anhydride. The neutralization equivalent of the diboronic acid (titration in presence of mannitol) was 133; that calculated for $C_{14}H_{14}B_2O_4$, 134.0. A dihydrobenzoboradiazole derivative[11] was prepared and found to melt at 270–274°.

Anal. Calcd. for $C_{26}H_{22}B_2N_4$: N, 13.60. Found: N, 13.35.

2-Ethylbenzeneboronic anhydride (T.S.). 2-Ethylphenylmagnesium bromide, prepared from 14.6 g. of magnesium and 105 g. of 2-ethylbromobenzene in 200 ml. of ether, was cooled to 0° and added slowly to a well stirred solution containing 183 g. of *n*-butyl borate in 100 ml. of ether at −75°. After 2 hr. of stirring the mixture was allowed to warm to room temperature, hydrolyzed with 200 ml. of dilute sulfuric acid, worked up as usual, and dried at 80° to give 64 g. (85% based on bromobenzene) of 2-ethylbenzeneboronic anhydride, m.p. 117–117.5°. The absence of a band between 2.8 and 3.2 μ and the presence of a strong band at 14.45 μ in the infrared spectrum showed that the product was an anhydride.[13]

Anal.[14] Calcd. for C_8H_9OB: H, 6.87; B, 8.20. Found: H, 6.61; B, 7.92.

A dihydrobenzoboradiazole derivative melted sharply at 75°.

Anal. Calcd. for $C_{14}H_{15}N_2B$: N, 12.62. Found: N, 12.90.

(7) The 2,2′-stilbenediboronic acid described in this paper must be preponderantly, if not exclusively, the *trans* isomer, as it was prepared from *trans*-2,2′-dibromotolan (ref. 4) and exhibited an absorption band at 10.36 μ, which is characteristic of *trans*-stilbene compounds. With respect to a concerted addition involving the alkene bond and groups in the 2,2′-positions, however, it should be noted that the aromatic rings must be twisted out of the plane of the —CH=CH-atoms in order for the reaction to occur. The consequent loss in resonance energy could be reflected in a relatively high activation energy for the process.

(8) H. Normant and J. Braun, *Compt. rend.*, **248**, 828 (1959). See also J. Cazes, *Compt. rend.*, **247**, 2019 (1958), for the preparation of 4-vinylbenzeneboronic acid by means of a Grignard reaction.

(9) A. K. Hoffman and W. M. Thomas, *J. Am. Chem. Soc.*, **81**, 580 (1959).

(10) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 352 (1951).

(11) R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, **80**, 5411 (1958).

(12) P. Ruggli and R. E. Meyer, *Helv. Chim. Acta*, **5**, 28 (1922).

(13) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *J. Am. Chem. Soc.*, **86**, 3611 (1958).

2-Vinylbenzeneboronic acid (IV) (T. S.). A mixture of 20 g. of 2-ethylbenzeneboronic anhydride, 26.7 g. of *N*-bromosuccinimide, and 0.15 g. of benzoyl peroxide in 350 ml. of carbon tetrachloride was refluxed for 3.5 hr., then cooled, and filtered. The filtrate was concentrated and the solid which separated was recrystallized twice from heptane to give 11.7 g. (42%) of 2-(1-bromoethyl)benzeneboronic anhydride; m.p. 148.5–150°; λ_{max} 7.4, 14.43 μ (anhydride band).

Anal. Calcd. for $(C_8H_8OBrB)_3$: B, 5.13%. Found. B, 4.84%.

A mixture of 10 g. of this anhydride and 20 g. of freshly distilled quinoline was heated at 130–135° with occasional stirring for 30 min. Following hydrolysis and acidification the boronic acid was taken up in ether and subsequently recrystallized from water. There was obtained 3.7 g. (54% based on the bromoethylbenzeneboronic anhydride) of 2-vinylbenzeneboronic acid; m.p. 108–109°; λ_{max} 3.05 (v. strong, O—H), 5.5 (weak, =CH_2), 6.12 (weak, C=C), 7.42 (v. strong, B—O), and 10.05 and 10.9 μ (weak and strong, respectively, vinyl hydrogens); $\lambda_{max}^{50\%\ C_2H_5OH}$ 247 mμ (log ϵ 4.14).

Anal.[14] Calcd. for $C_8H_9O_2B$: H, 6.13; B, 7.31. Found: H, 6.15; B, 6.89.

The dihydrobenzoboradiazole derivative melted sharply at 93.5°.

Anal. Calcd. for $C_{14}H_{13}N_2B$: N, 12.73. Found: N, 13.01.

2-Vinylbenzeneboronic acid was also prepared *via* a Grignard reaction. In this case 6.9 g. of 2-chlorostyrene in 15 ml. of tetrahydrofuran (dried by distillation from lithium aluminum hydride) was added dropwise over a 10-min. period to 2.3 g. of magnesium and 1 ml. of bromoethane in 3 ml. of tetrahydrofuran. After 35 min. of refluxing the mixture was cooled to about −70°, whereupon 23 g. of *n*-butyl borate in 50 ml. of tetrahydrofuran was rapidly added. After 30 min. of stirring the mixture was warmed to room temperature and worked up as in the previous cases to give 0.20 g. (3%) of 2-vinylbenzeneboronic acid, identical in melting point and infrared spectrum to the product obtained from the dehydrobromination reaction.

For polymerization, a solution of 0.390 g. of 2-vinylbenzeneboronic acid and 0.0039 g. of azobisisobutyronitrile in 5 ml. of benzene was heated at 75° for 14 hr. The resulting white gel was washed with several 15-ml. portions of ether to give 0.290 g. (74%) of ether insoluble polymer. The polymer did not soften below 300°.

2-Bromostilbene dibromide (T.F.). 2-Bromobenzaldehyde (90 g.) in 150 ml. of ether was added dropwise to a solution of benzylmagnesium chloride, prepared from 22.4 g. of magnesium and 93 g. of benzyl chloride, in 700 ml. of ether. After standing overnight the mixture was hydrolyzed with aqueous acetic acid. The ether layer was separated, washed with 10% sodium bicarbonate solution, dried, and evaporated to give 105 g. of a liquid alcohol ($\lambda_{max}^{CHCl_3}$ 2.8 μ). A 40-g. portion of this product was dehydrated by heating with 80 g. of potassium acid sulfate for 7 hr. Following hydrolysis the ether layer was filtered to remove a small amount of insoluble material and evaporated. The residual oil (23.4 g.) did not absorb in the 2 to 3 μ region of the infrared. It was taken up in carbon tetrachloride and treated with 5 ml. of bromine in 20 ml. of carbon tetrachloride. After 30 min. at reflux temperature, the solvent was removed at reduced pressure. The residual brownish solid (25.5 g., m.p. 130–140°) was washed with sodium bisulfite solution, decolorized with Norite, and recrystallized from chloroform to give colorless, crystalline 2-bromostilbene dibromide, m.p. 179–181°.

Anal. Calcd. for $C_{14}H_{11}Br_3$: C, 40.13, H, 2.65. Found: C, 40.63; H, 2.61.

2-Bromotolan (T. F.). An attempt to dehydrobrominate the bromostilbene dibromide by a solution of potassium hydroxide in ethylene glycol at 160–170° was not promising since the product showed an infrared band at 10.4 μ, indicative of some debromination to a bromostilbene. Application of Nazy's procedure[4] for purification of 2,2′-dibromotolan to this material did not yield a pure alkyne. As an alternative the dehydrobromination was accomplished by means of potassium *t*-butoxide. In this case 13.7 g. of 2-bromostilbene dibromide was added to a solution of potassium *t*-butoxide prepared from 4.1 g. of potassium and 500 ml. of *t*-butyl alcohol. After the mixture had been refluxed for 4 hr. it was poured into 700 ml. of water and extracted with ether. Distillation of the extract afforded 5.33 g. (63%) of 2-bromotolan; b.p. 155–160° (0.7 mm.); $\lambda_{max}^{CHCl_3}$ 4.5 μ (—C≡C—).

Anal. Calcd. for $C_{14}H_9Br$: C, 65.39; H, 3.53. Found: C, 65.65; H, 4.18.

2-Tolanboronic acid. (V) (T. F.). Butyllithium (150 ml. of 0.118*N* ether solution) was added over an hour to 2.0 g. of 2-bromotolan dissolved in 50 ml. of ether at 0°. The solution was then cooled to −75° and 2.44 g. of *n*-butyl borate in 20 ml. of ether was rapidly added. After two additional hours the mixture was allowed to warm up and was hydrolyzed and worked up as usual to give 0.70 g. of colorless boronic acid, m.p. 126–130°; after recrystallization from ethanol-water the sample weighed 0.53 g. (31% yield) and melted at 158–160°. Subsequent recrystallizations yielded the analytical sample, m.p. 160–161°; $\lambda_{max}^{ethanol}$ 279 mμ (log ϵ 3.36), 297 mμ (log ϵ 3.28).

Anal. Calcd. for $C_{14}H_{11}O_2B$: H, 4.98; B, 4.87. Found: H, 4.69; B, 4.56.

Oxidation of 2-tolanboronic acid (T. F.). Hydrogen peroxide (5 ml. of 30% solution) was added to a solution of 92 mg. of 2-tolanboronic acid in an acetic acid (5 ml.), ethanol (5 ml.), and water (2 ml.) mixture. After 30 min. the solution was poured into 80 ml. of water. White crystals of the hydroxytolan slowly separated when the solution was allowed to stand in the cold; weight, 45 mg. (56%); m.p. 69–70°; λ_{max}^{KBr} 2.95 μ (sharp); no band between 5 and 6 μ; $\lambda_{max}^{C_2H_5OH}$ 296 mμ, log ϵ 4.18.

Anal. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.62; H, 5.47.

Attempted isomerizations. The boronic acids were heated in 20 ml. of 50 to 60% ethanol-water solutions at reflux temperature; then the solutions were cooled, acidified, concentrated at reduced pressure, and filtered. The precipitates were dried and analyzed by their infrared spectrum. In every case the spectrum of the product was essentially the same as that of the reactant. By contrast, 2,2′-tolandiboronic acid was converted to compound II (70% recovery of an organoboron compound, 90% isomerization) by heating in 50% alcohol-water for 3 hr. at *p*H 9.

Compound	Weight, Mg.	Reflux Time (hr.)	*p*H	% Recovery
III	200	7	10[a]	65
IV	150	3	9	84
V	190	3	10	80
V	152	6.5	9.5[b]	79

[a] The solution also contained sodium tartrate—from 0.836 g. of tartaric acid. [b] From 0.72 g. of tartaric acid.

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(14) As characteristic of aromatic boronic acids, the boron compounds reported in this paper left a black ash after analysis, indicating incomplete carbon combustion. Consequently, all carbon analyses were 1–6% lower than the theoretical value and were of no diagnostic value.

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Reduction of Polymers Using Complex Metal Hydrides. II

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A study of the reaction between acylating and alkylating agents and the reaction mixtures obtained from the reduction of simple ketones and esters with complex metal hydrides is described. Pure poly(allyl alcohol) was prepared by the reduction of poly(methyl acrylate) with lithium aluminum hydride using sodium potassium tartrate in the isolation procedure. A number of other ester-containing vinyl polymers were also reduced with lithium aluminum hydride, acetylated directly, and then hydrolyzed to the pure hydroxyl-containing polymers. These polymers were also reduced with lithium borohydride. In these cases, acetylation was not required for product isolation.

Although a number of articles in recent years have described the reduction of polymers containing pendant ester groups, no general, simple method to achieve this end has as yet appeared. Rånby[1] reported the reduction of poly(butylacrylate), but has not yet published his experimental details. Houel reported the reduction of both poly(methyl acrylate)[2] and poly(methyl methacrylate),[3] using a solution of lithium aluminum hydride in tetrahydrofuran. After hydrolysis of the reaction mixture with water, the precipitated solids were stirred with hot *m*-cresol and the resulting slurry was extracted with dilute hydrochloric acid to remove the suspended inorganic solids. It was claimed that the poly(allyl alcohol) so obtained was insoluble in all organic solvents except pyridine and *m*-cresol. Shulz and co-workers[4] have also reported the reduction of poly(methyl acrylate) with lithium aluminum hydride in tetrahydrofuran. Their method of isolation was not given, but they report their higher molecular weight products to be soluble only in mixtures of hydrochloric acid with methanol, dioxane, or tetrahydrofuran. No analyses were given. Marvel and co-workers reported the reduction of a butadiene–methyl acrylate copolymer[5] and of poly(dimethyl itaconate)[6] with lithium aluminum hydride in tetrahydrofuran, using ethyl acetate to decompose the excess hydride, followed by 2*N* sulfuric acid to dissolve the inorganic solids. Almost complete (93%) reaction was claimed for the poly(dimethyl itaconate) reduction. The product was soluble in a water–dioxane mixture, although it contained some ash. A patent granted to Imperial Chemical Industries, Ltd.[7] claimed the reduction of poly(methyl acrylate) and poly(methyl methacrylate) with lithium aluminum hydride in tetrahydrofuran. After hydrolysis of the reaction mixture with water, the product was isolated by treatment of the precipitated solids with dilute hydrochloric acid. The poly(allyl alcohol) was reported to be insoluble in all solvents. Poly(methyl methacrylate), on the other hand, has presented no difficulties, its reduced product being soluble in a 1:1 methanol–tetrahydrofuran mixture.

In a continuation of the work at these Laboratories on the reduction of polymers with complex metal hydrides,[8] the problem of ester reduction was reinvestigated to see whether a general, reproducible method for the reduction of polymeric esters to the corresponding hydroxylated polymers could be found. From the results obtained by the previous investigators, and concurrently here, it became apparent that complete reduction of poly(methyl acrylate) could be accomplished by lithium aluminum hydride in tetrahydrofuran, the dimethyl ether of diethylene glycol (diglyme) or *N*-methylmorpholine. Difficulty arose, however, in the isolation of the product. The hydroxylated polymer was easily rendered insoluble by intermolecular etherification in acid media.[6] It also formed a strong complex with aluminum hydroxide, which made isolation of an ash-free polymer very difficult. It was found, for example, that the procedure given in Belgian Patent 571,019[7] gave a product, containing an appreciable amount of ash, soluble in a methanol–dilute hydrochloric acid mixture. All attempts to remove the aluminum hydroxide by *p*H control, precipitation, or dialysis were futile. Treatment with sodium hydroxide solution at a *p*H of 12 to remove the aluminum as the soluble aluminate reprecipitated the aluminum-containing polymer. Dialysis of the methanol–hydrochloric acid solution did not effect purification, since the aluminum ion would not pass through the cellophane membrane. The method reported by Marvel and co-workers[6] and by Houel[2] also gave samples of poly(allyl alcohol) containing some aluminum which could not be removed by the methods just mentioned.

(1) B. G. Rånby, Makromdec. Chem., **42**, 1 (1960).
(2) B. Houel, *Compt. rend.*, **246**, 2488 (1958).
(3) J. Petit and B. Houel, *Compt. rend.*, **246**, 1427 (1958).
(4) R. C. Shulz, P. Elzer, and W. Kern *Chimia*, (Switz.) **13**, 237 (1959)
(5) C. S. Marvel, R. M. Potts, and C. King, *J. Am. Chem. Soc.*, **77**, 177 (1955).
(6) C. S. Marvel and J. H. Shepherd, *J. Org. Chem.*, **24**, 599 (1959).
(7) Belgian Patent **571,019**, Imperial Chemical Industries, Ltd. (1958).
(8) H. L. Cohen and L. M. Minsk, *J. Org. Chem.*, **24**, 1404 (1959).

Potassium sodium tartrate complexes strongly with aluminum ions and an aqueous solution of this reagent has been used to hydrolyze lithium aluminum hydride reduction mixtures. The aluminum and lithium salts dissolve in the aqueous phase, leaving the reduced organic product in the organic solvent. Addition of a concentrated solution of potassium sodium tartrate to the poly(methyl acrylate) reduction mixture in *N*-methylmorpholine caused precipitation of the inorganic salts as a hydrated solid, while the reduced polymer dissolved in the aqueous *N*-methylmorpholine which resulted from the addition of the tartrate solution. The pure reduced product could then be isolated by conventional means. It was soluble in methanol or in pyridine, each containing at least 5% of water, and remained in solution on further addition of water until about a 1:1 mixture resulted. Substitution of diethyleneglycol dimethyl ether or tetrahydrofuran for *N*-methylmorpholine necessitated dilution of the reduction mixture with an equal volume of methanol prior to the addition of the aqueous tartrate solution. The use of *N*-methylmorpholine was, therefore, simpler and preferable.

An ethylene–diethyl maleate copolymer was also successfully reduced by lithium aluminum hydride in *N*-methylmorpholine using the tartrate method for isolation. On the other hand, the products from the reductions of poly(acetoxymethyl vinyl ketone), poly(butyl acetoxyacrylate) and the methyl acrylate–maleic anhydride copolymer precipitated with the inorganic salts on addition of the tartrate solution, and therefore could not be isolated in an ash-free state.

In an attempt to find a general procedure for the reduction of ester polymers and the subsequent isolation of soluble products, acetylation of the reduced polymers was tried next. Treatment of the dried solids, precipitated by the addition of water to a reduction mixture, with acetyl chloride in the presence or absence of pyridine usually gave insoluble products. When the precipitated solids were heated at high temperatures (140°) with acetic anhydride, dark, soluble products could sometimes be isolated; usually, however, separation of the polymer solution from the aluminum salts could not be achieved.

One would expect that the addition of an excess of acylating reagent to the unhydrolyzed reaction mixture from a lithium aluminum hydride reduction of a ketone or an ester would acylate the reduced compound. No reports, however, concerning this type of reaction could be found in the literature. Cautious addition of an excess of acetyl chloride or acetic anhydride to the reduction mixtures from ethyl valerate and pentanone-3 did, indeed, give good yields of *n*-amyl acetate and 3-pentyl acetate, respectively. Addition of these acylating reagents to the mixture obtained from the reduction of ethyl valerate with the sodium borohydride–aluminum chloride complex also gave amyl acetate, but in lower yield. Sodium borohydride reduction of 3-pentanone, followed by reaction with an excess of acetic anhydride, gave a moderate yield of 3-pentyl acetate. The addition of isopropyl acetate, or, preferably, isopropenyl acetate,[9] to an unhydrolyzed lithium aluminum hydride reduction mixture of ethyl valerate, followed by distillation of the volatile constituents, also gave, *via* the ester interchange reaction, amyl acetate in moderate yield. A similar *trans*-esterification has recently been reported by Stapp and Rabjohn.[10]

Methyl amyl ether and methyl 3-pentyl ether, respectively, were obtained in moderate yield by the addition of excess methyl sulfate to the lithium aluminum hydride reduction mixture of ethyl valerate and 3-pentanone. Methyl *p*-toluenesulfonate and hexyl bromide, on the other hand, did not alkylate the reduced products. Alkylation attempts with methyl sulfate on reduction mixtures, obtained when sodium borohydride was used on ketones, or when the sodium borohydride–aluminum chloride complex was used on esters, were also unsuccessful. All of these reactions with simple organic compounds were run in diethyleneglycol dimethyl ether.

The addition of an excess of acetic anhydride to a poly(methyl acrylate) reduction mixture in diethyleneglycol dimethyl ether gave a gel, which broke up on heating to higher temperatures (110–140°) with stirring, and precipitated a fine white powder. The supernatant liquid was a solution of the soluble poly(allyl acetate) which was almost free from inorganic salts. The acetate could be isolated by conventional means and freed from any residual inorganic matter by extraction of a chloroform solution with dilute hydrochloric acid. By using this procedure, poly(methyl acrylate), poly(acetoxymethyl vinyl ketone), poly(butyl acetoxyacrylate), and a maleic anhydride–methyl acrylate copolymer were converted completely to the acetates of the corresponding reduced polymers which could be saponified with sodium hydroxide, preferably in methoxy ethanol solution. The acylated polymers and their hydrolyzed derivatives were usually colored.

Tetrahydrofuran could also serve as the solvent for the reduction, although when used, it had to be removed by distillation, after the addition of acetic anhydride, in order to attain temperatures high enough to effect acetylation. *N*-Methylmorpholine, on the other hand, could not be used. At low temperatures, no acetylation resulted, while at higher temperatures, cross-linked, insoluble

(9) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, 41, 2920 (1949).

(10) P. Stapp and N. Rabjohn, *J. Org. Chem.*, 24, 1798 (1959).

products were formed. With all of these solvents, acetyl chloride gave insoluble products.

While the acetylation procedure described was a general method for the isolation of the reduced polymers, it was tedious and usually gave colored products. Work was therefore continued toward a simpler method. It was found that lithium borohydride in diethyleneglycol dimethyl ether solution reduced polymeric esters, anhydrides, and lactones at temperatures above 100°. Following reduction, the cooled reaction mixture was poured into dilute aqueous acetic acid. Poly(allyl alcohol), from poly(ethyl acrylate) precipitated in relatively pure form. The products derived from the reduction of poly(acetoxymethyl vinyl ketone), poly(butyl acetoxyacrylate) and the methyl acrylate–maleic anhydride copolymer dissolved. Dialysis removed the inorganic materials completely so that the polymeric derivative could be isolated by evaporation of the water. The products in all cases were colorless.

The acetylated polymers, when free from aluminum salts, were soluble in acetone, chloroform, dioxane, tetrahydrofuran and dimethylformamide. They were insoluble in methanol, ether and water. The poly(allyl alcohol) prepared was soluble in methanol, acetone and pyridine containing 10–45% of water. No pure solvent for this material could be found. The other hydroxyl polymers were soluble in water and water–methanol mixtures containing up to 40% of methanol. They were insoluble in dimethylformamide and dimethyl sulfoxide.

Infrared analysis of the hydroxyl polymers indicated that reduction was complete.

The viscosities of the original and reduced polymers are included in Table II. Although an exact comparison of relative degree of polymerization cannot be made from the respective viscosities of different types of polymers, run in different solvent systems, the much lower viscosities of some of the reduced polymers would appear to indicate that some degradation had taken place. This is because hydroxyl-containing polymers usually have higher viscosities than the esters derived from them.

It may be concluded from the work described in this and the preceding paper[8] that the complex metal hydrides are as useful for the reduction of polymeric materials as they are for simple organic compounds. The difficulties encountered due to the lower reactivities and limited solubilities of most polymers can usually be overcome by the proper choice of hydride, solvent, reaction conditions and isolation procedures.

EXPERIMENTAL

Starting materials. *N*-Methylmorpholine, diethyleneglycol dimethyl ether and tetrahydrofuran were purified by refluxing over sodium, then fractionating through a glass, helix-packed column. Lithium aluminum hydride, sodium borohydride, lithium borohydride (Metal Hydrides, Inc.), and aluminum chloride (Merck Analytical Grade) were used as purchased. The other reagents were Eastman Kodak White Label Grade, fractionated before use.

A methyl acrylate–maleic anhydride copolymer was made by copolymerizing the ingredients in acetone solution. It contained 72 mole % of methyl acrylate. The ethylene–diethyl maleate copolymer was made by the reaction of an ethylene–maleic anhydride copolymer (Monsanto Chemicals) with ethanol in the presence of sulfuric acid and benzene. Analysis showed esterification was not complete, the composition being calculated at about 40% diester and 60% monoester. This derived polymer was soluble in *N*-methylmorpholine, while the original polymer was not.

Reactions. To conserve printing space, only representative reactions are given. Data for the simple organic compounds are given in Table I. Data for the polymer reactions are given in Table II. Method B is identical with the procedure described in the previous paper.[8]

TABLE I

REDUCTION AND ACYLATION OF SIMPLE COMPOUNDS

Compound Reduced	Reducing Agent	Acylating or Alkylating Agent	Yield, %
3-Pentanone	[a]	[d]	65[m]
3-Pentanone	[b]	[c]	57
3-Pentanone	[b]	[d]	70
3-Pentanone	[b]	[f]	15
3-Pentanone	[b]	[g]	30
3-Pentanone	[b]	[h]	78
3-Pentanone	[b]	[i]	60
3-Pentanone	[a]	[i]	0
3-Pentanone	[b]	[j]	0
3-Pentanone	[b]	[l]	0
3-Pentanone	[b]	[k]	0
Ethyl valerate	[b]	[d]	90
Ethyl valerate	[c]	[d]	70
Ethyl valerate	[b]	[g]	75
Ethyl valerate	[b]	[i]	78[p]
Ethyl valerate	[c]	[i]	0
Ethyl valerate	[b]	[j]	0

[a] Sodium borohydride. [b] Lithium aluminum hydride. [c] Sodium borohydride–aluminum chloride. [d] Acetyl chloride. [e] Acetic anhydride. [f] Ethyl acetate. [g] Isopropyl acetate. [h] Isopropenyl acetate. [i] Methyl sulfate. [j] Hexyl bromide. [k] Methyl *p*-toluenesulfonate. [l] Benzyl chloride. [m] B.p. 131–132°. *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.7; H, 10.75; acetyl, 33.1. Found: C, 65.0; H, 11.1; acetyl, 33.5. [p] B.p. 99.5–100.5°, n_D^{20} 1.3870. *Anal.* Calcd. for $C_6H_{14}O$: C, 70.5; H, 13.7. Found: C, 70.5; H, 13.3.

Analytical values given in Table II are the averages of at least two determinations, each of which agreed within 0.4 unit. Yields given for the simple organic compounds are of pure products boiling in the range given in Table I and the Experimental. In most cases, they represent the results of only one experiment, and especially in the case of the ethers, can probably be increased by better isolation procedures.

Reduction of ethyl valerate by lithium aluminum hydride, followed by acetylation with acetyl chloride. A solution of 39 g. (0.3 mole) of ethyl valerate in 100 ml. of diethyleneglycol dimethyl ether was added, dropwise, with stirring, to a solution of 7.6 g. (0.2 mole) of lithium aluminum hydride in 150 ml. of diethyleneglycol dimethyl ether. Following addition, the mixture was heated 0.5 hr. on a steam bath, then cooled. Acetyl chloride (80 g.) (1.0 mole) was added, dropwise, giving an exothermic reaction. Following addition, the mixture was refluxed for an additional hour on a steam bath, then distilled up to 155°. The distillate was washed with

TABLE II

Original Polymer and Viscosity	Reducing Agent	Method of Isolation	Analysis	Calcd.	Found	Yield, %	Hydrolysis	Calcd.	Found	Yield, %
Methyl acrylate $\eta = 0.60^a$	$LiAlH_4$	A	C	62.2	61.9	85				
			H	10.3	10.2					
			Methoxyl	0	<1					
			η	—	0.76[b]					
Methyl acrylate	$NaBH_4$-$AlCl_3$	A	C	62.2	61.8	80				
			H	10.3	10.2					
			Methoxyl	0	<1					
Methyl acrylate	$LiAlH_4$	C	C	60.0	59.9	70	C	62.2	61.5	48
			H	8.0	7.8		H	10.3	10.3	
			Acetyl	43.0	41.3		Acetyl	0	1.0	
			Methoxyl	0	<1					
			Ash	0	0.1					
Methyl acrylate	$LiAlH_4$	D	C	60.0	56.0	50	C	62.2	61.2	75
			H	8.0	8.1		H	10.3	10.1	
			Acetyl	43.0	44.3		Acetyl	0	0.5	
Methyl acrylate $\eta = 0.60^a$	$LiBH_4$	E	C	62.2	61.7	85				
			H	10.3	10.1					
			Methoxyl	0	<1					
			η	—	0.65					
Methyl methacrylate	$LiAlH_4$	B	C	66.8	65.9	70				
			H	11.0	11.0					
			Methoxyl	0	<1					
			Ash	0	0.1					
Ethylene-diethyl malcate	$LiAlH_4$	A	C	62.0	61.5	75				
			H	10.3	10.1					
			Ethoxyl	0	0.0					
			Ash	0	0.0					
Acetoxymethyl vinyl ketone	$LiAlH_4$	C	C	55.8	55.8	90	C	54.6	54.3	85
			H	7.0	7.2		H	9.1	9.1	
			Acetyl	50.0	46.5		Acetyl	0	<1	
Acetoxymethyl vinyl ketone $\eta = 0.43^a$	$LiBH_4$	E	C	54.8	55.1	85				
			H	9.1	8.9					
			Acetyl	0	0.5					
			η	—	0.26[e]					
Methyl acrylate-maleic anhydride[c]	$LiAlH_4$	C	C	58.8	58.4	65	C	59.5	58.7	40
			H	7.7	7.6		H	9.9	9.8	
			Acetyl	43.0	44.2		Acetyl	0	0.6	
Ethyl acrylate-maleic anhydride[d] $\eta = 0.26^a$	$LiBH_4$	E	C	58.1	57.1	85				
			H	9.6	10.0					
			Ethoxyl	—	0.5					
			η	—	0.58[e]					
Butyl α-acetoxy-acrylate	$LiAlH_4$	C	C	53.1	52.3	50	C	48.8	49.1	52
			H	6.4	6.6		H	8.1	7.7	
			Acetyl	54.5	52.3		Acetyl	0	<1	
Butyl α-acetoxy-acrylate $\eta = 0.64^a$	$LiBH_4$	E	C	48.8	49.3	85				
			H	8.1	7.6					
			η		0.12[c]					

[a] In acetone. [b] In 80% v/v aqueous methanol. [c] 72 Mole % methyl acrylate. [d] 64 Mole % ethyl acrylate. [e] In water.

water and redistilled, giving a fraction, b.p. 148.5–149.0°, n_D^{20} 1.4014, weighing 35 g. (90%).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.7; H, 11.75. Found: C, 64.6; H, 11.5.

Reduction of 3-pentanone, followed by reaction with methyl sulfate. A solution of 52 g. (0.6 mole) of 3-pentanone in 200 ml. of diethyleneglycol dimethyl ether was reduced with a solution of 7.6 g. (0.2 mole) of lithium aluminum hydride in 200 ml. of diethyleneglycol dimethyl ether. A solution of 80 g. (0.67 mole) of distilled dimethyl sulfate was then added, dropwise, with stirring. Following addition, the mixture was heated 3 hr. on a steam bath. The complex was decomposed by the cautious addition of 100 ml. of 2*N* sulfuric acid and the mixture steam distilled. The distillate was extracted with ether, dried over sodium sulfate and distilled, giving 36 g. (60%) of product, b.p. 88.5–89.0°, n_D^{20} 1.3864.

Anal. Calcd. for $C_6H_{14}O$: C, 70.6; H, 13.7. Found: C, 71.0; H, 13.9.

Reduction of 3-pentanone, followed by reaction with isopropenyl acetate. A solution of 43 g. (0.5 mole) of 3-pentanone in 100 ml. of diethyleneglycol dimethyl ether was reduced by 5.6 g. (0.15 mole) of lithium aluminum hydride in 150 ml. of diethyleneglycol dimethyl ether. Isopropenyl acetate (100 g., 1 mole) was then added. The stirred mixture was slowly distilled on a steam bath until no more acetone came over. The reaction complex was treated with 1 l. of water and then steam distilled. The distillate was extracted with ether, dried and distilled; yield, 50 g. (77%), b.p. 131–132°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.7; H, 10.75; acetyl, 33.1. Found: C, 64.7; H, 11.0; acetyl, 32.5.

Reduction of poly(methyl acrylate) with lithium aluminum hydride. Method A. To a refluxing, stirred suspension of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of purified *N*-methylmorpholine, under nitrogen, was added, dropwise, over a period of 2 hr., a solution of 8.6 g. (0.1 mole)

of poly(methyl acrylate) ($\{\eta\}$ = 0.60, 0.25 g./100 ml. in acetone) in 100 ml. of *N*-methylmorpholine. After addition, the mixture was stirred under reflux for an additional 3 hr. Then, while still hot, a solution of 30 g. of potassium sodium tartrate in 150 ml. of water was added, dropwise, and very cautiously, until the excess hydride had been decomposed. Following addition of all the tartrate solution, the mixture was stirred hot for an additional hour and allowed to cool.

The filtered solution was evaporated to dryness on a steam bath under vacuum, leaving a soft residue. This was stirred with a mixture of 90 ml. of methanol and 10 ml. of water for 3 hr. Most of the solid dissolved, giving a viscous solution. Some granular powder remained and was centrifuged off. The polymer was precipitated in acetone. The purification process was repeated, giving 5 g. (85%) of a tough resin after vacuum drying over phosphorus pentoxide.

Anal. Calcd. for C_3H_6O: C, 62.2; H, 10.3; methoxyl, 0. Found: C, 61.9; H, 10.3; methoxyl, <1; ash, 0.3; $\{\eta\}$ = 0.76.

Reduction of poly(methyl acrylate), acetylation with acetic anhydride and hydrolysis. Preparation of poly(allyl acetate). Method C. A solution of 8.6 g. (0.1 mole) of poly(methyl acrylate) in 100 ml. of tetrahydrofuran was added, dropwise, under nitrogen, to a refluxing solution of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran over a period of 1 hr. Following addition, the mixture was refluxed and stirred for an additional 2 hr., then cooled.

Acetic anhydride (250 ml.) was added, dropwise, to the mixture, cautiously at first, until all the excess lithium aluminum hydride had reacted. The mixture was then heated slowly with stirring, and the tetrahydrofuran was allowed to distill until the internal temperature reached 110°. The mixture became exceedingly thick. After stirring at 110° for 1 hr., the mixture became much more fluid and a fine, white precipitate was left. Heating was continued for a total of 3 hr.

The cooled mixture was filtered, the filter cake being washed with acetone. The combined washings were evaporated to dryness on a steam bath under vacuum. The residue, after solution in acetone, was precipitated in ether. This procedure was repeated twice to give an analytical sample; yield, 7 g. of a soft polymer which hardened somewhat on vacuum drying.

Anal. Calcd. for $C_5H_8O_2$: C, 60.0; H, 8.0; acetyl, 43. Found: C, 60.0; H, 7.9; acetyl, 41.4; methoxyl, >2; ash, 0.1.

Reduction of poly(methyl acrylate), followed by reaction with isopropenyl acetate. Method D. A solution of 8.6 g. of poly(methyl acrylate) in 100 ml. of diethyleneglycol dimethyl ether was added, dropwise, under nitrogen, with heating over a period of 1 hr. to a stirred solution of 3.8 g. (0.1 mole) of lithium aluminum hydride in 100 ml. of diethyleneglycol dimethyl ether. Following addition, the mixture was heated and stirred at 110° for 3 hr.

Isopropenyl acetate (100 g.) was then added, dropwise, with stirring. Following addition, the temperature was raised to 135° for 2 hr., 20 ml. of material being allowed to distill. The mixture was then cooled and decomposed by the addition of a solution of 20 g. of sodium potassium tartrate in 100 ml. of water. After the stirred mixture had been heated to boiling and allowed to cool, the mixture was centrifuged. The supernatant liquid was evaporated to dryness on a steam bath under vacuum, dissolved in a mixture of acetone, and methanol, and precipitated in ether, giving 5 g. of a soft, amber solid after drying.

Anal. Calcd. for $C_5H_{10}O_2$: C, 60.0; H, 8.0; acetyl, 43. Found: C, 56.1; H, 8.1; acetyl, 44.4.

Hydrolysis of this product gave 2.3 g. of a tan solid.

Anal. Calcd. for C_3H_6O: C, 62.2; H, 10.3. Found: C, 61.2; H, 10.1; acetyl, 0.5.

Reduction of poly(butyl α-acetoxyacrylate) with lithium borohydride. Method E. A solution of 9.3 g. (0.05 mole) of poly(butyl α-acetoxyacrylate) in 100 ml. of diethyleneglycol dimethyl ether was added dropwise over a period of 1 hr. to a stirred solution of 2.5 g. of lithium borohydride in 200 ml. of diethyleneglycol dimethyl ether kept at 100° under nitrogen. Following addition, the mixture was heated to 115° for an additional 2 hr., then allowed to cool to room temperature.

The reaction mixture was then poured slowly into 1 l. of water containing 50 ml. of acetic acid, giving a clear solution which was dialyzed overnight. The undialyzed material was filtered, then evaporated to dryness on a steam bath under vacuum. The residue was dissolved in 20 ml. of distilled water giving a clear viscous solution which was precipitated into acetone to give a white powder. The product was vacuum dried; yield, 3.3 g., soluble in water, but insoluble in methanol, acetone and ether.

Anal. Calcd. for $C_3H_6O_2$: C, 48.8; H, 8.1. Found: C, 49.2, 49.4; H, 7.5, 7.7; N, 0.12.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE ARMOUR INDUSTRIAL CHEMICAL COMPANY]

Phase Properties of Mixtures of 9- and 10-Oxo-octadecanoic Acids and of 9- and 10-Hydroxyoctadecanoic Acids[1]

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Pure homolog-free samples of 9- and 10-oxo- and the corresponding hydroxyoctadecanoic acids have been prepared and phase diagrams for mixtures of the isomers have been established. That for the oxo acids is a simple eutectic system; that for the hydroxy acids shows compound formation at a 1:1 ratio of the components. On the basis of these diagrams the identity of various preparations of the four compounds reported in the literature is discussed. Evidence for preferential reactivity at the 9- or 10-position of the eighteen-carbon fatty-acid molecule which is based upon conclusions regarding the identity of the oxo or hydroxy acids is invalidated.

A number of reports in the literature present evidence for a directive influence during reactions of unsaturated or epoxy eighteen-carbon fatty acids which results in preferential reactivity at the 9- or 10-position of the molecule. For the most part, this evidence is based on isolation of a preponderance of a substance identified as 9- or 10-oxo- or 10-hydroxyoctadecanoic acid.

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(2) Address communications to this author.

In an investigation of the constitution of stearolic (9-octadecynoic) acid, Baruch[3] produced an oxo-octadecanoic acid melting at 76°. Through the Beckmann rearrangement of the oxime of this oxo acid, substances identified as nonanoic acid, octylamine, decanedioic acid, and 9-aminononanoic acid were isolated. Baruch concluded therefrom that only 10-oxo-octadecanoic acid was produced by the hydration of stearolic acid. Robinson and Robinson[4] repeated this work and obtained, after recrystallization of the sodium salt, oxo-octadecanoic acid freezing at 70.90°. In order to estimate the composition of this product, which was assumed to be a mixture of the 9- and 10-isomers, these authors synthesized the pure oxo acids and determined the freezing points of synthetic mixtures. On the basis of the partial phase diagram, the original product was estimated to contain 42.4% of the 9-isomer. The apparent difference in reactivity at the 9- and 10-positions was ascribed to the inductive influence of the carboxyl group. Myddleton, Bercham, and Barrett[5] also produced an oxo-octadecanoic acid through the reaction of stearolic acid with mercuric acetate. This oxo acid, purified according to the procedure of Robinson and Robinson, melted at 76°. It was believed to be 10-oxo-octadecanoic acid.

In a review of earlier work on the sulfation of oleic (9-octadecenoic) acid, Tomecko and Adams[6] reached the conclusion that a major product after hydrolysis of the sulfate is 10-hydroxyoctadecanoic acid. This conclusion was based on melting-point data obtained with mixtures of pure synthetic positional isomers and on the fact that the melting point of the hydroxy acid obtained by sulfation of oleic acid was in the range of 80–85° in most cases.

Through catalytic hydrogenation of methyl 9,10-epoxyoctadecanoate followed by chromic oxide oxidation of the resulting hydroxy acid, Ross, Gebhart, and Gerecht[7] obtained a major amount of an oxo acid melting at 71° and a small amount of an oxo acid melting at 81.5°. The 71° compound yielded decanedioic acid upon Beckmann rearrangement of the oxime and was identified as 10-oxo-octadecanoic acid. The 81.5° compound was believed to be the 9-isomer. By the same process, Mack and Bickford[8] obtained only the 71° compound; no product melting at 81.5° was isolated. These authors concluded that a strong directional force favors rupture of the C—O bond at the 9-position.

Jungermann and Spoerri[9] produced a mixture of chlorohydrins by hydrochlorination of methyl 9,10-epoxyoctadecanoate. Fractional crystallization yielded chlorohydroxyoctadecanoates in a 3:1 ratio. These were converted to oxo acids by removal of chlorine with zinc amalgam and oxidation of the hydroxyl group with chromic oxide. There were obtained a compound melting at 72° described as 10-oxo-octadecanoic acid and one melting at 80° said to be 9-oxo-octadecanoic acid. The apparent preponderance of the 10-isomer was attributed to an inductive effect during reaction of the epoxide with hydrogen chloride.

Other work in the same general area of chemistry has shown no evidence of directive influences. Rockett[10] obtained formoxyoctadecanoic acid through the reaction of oleic acid with formic and perchloric acids. Conversion to the hydroxy acid followed by oxidation with chromic oxide yielded the oxo acid. This was converted to the oxime which then was subjected to the Beckmann rearrangement. Elution chromatography showed equal amounts of azelaic (nonanedioic) and sebacic (decanedioic) acids. No evidence for inductive or field effects during formoxylation was found. Fore and Bickford[11] hydrogenated both *cis*-9,10-epoxyoctadecanol and its actate, oxidized the resulting hydroxy compounds to oxo acids, converted these to the oximes, and through the Beckmann rearrangement obtained mixtures of dibasic acids which were resolved chromatographically. Here again the evidence showed no directive influence.

The contradictory nature of the literature reviewed above, discrepancies in reported melting points of compounds assumed to be pure,[12] and complete disregard of phase properties of the mixtures which might result from the various reactions discussed lead to the work which is presented here. Binary mixtures of fatty acids or derivatives of fatty acids generally form eutectics or minimum-melting mixtures.[13] Frequently, evidence of compound formation also exists, usually as an incongruent melting point in the phase diagram. On theoretical grounds, it is not possible to effect total separation of the components of such systems by fractional crystallization. In order to clarify the several points in question, high-purity samples of 9- and 10-oxo-octadecanoic acids and DL-9- and DL-10-hydroxyoctadecanoic acids were synthesized and phase diagrams of the two sets of positional isomers were established.

(3) J. Baruch, *Ber.* 27, 172 (1894).
(4) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 2204 (1926).
(5) W. W. Myddleton, R. G. Bercham, and A. W. Barrett, *J. Am. Chem. Soc.*, 49, 2264 (1927).
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(10) J. Rockett, *J. Am. Chem. Soc.*, 78, 3191 (1956).
(11) S. P. Fore and W. G. Bickford, *J. Org. Chem.*, 24, 620 (1959).
(12) T. F. Grey, J. F. McGhie, and W. A. Ross, *J. Chem. Soc.*, 1502 (1960).
(13) A. E. Bailey, *Melting and Solidification of Fats*, Interscience Publishers, Inc., New York, 1950, Chapter IV.

EXPERIMENTAL

Materials. Dimethyl azelate, dimethyl sebacate, heptylmalonic, and octylmalonic esters were fractionated on a Podbielniak column and those fractions that contained only one component, as indicated by gas chromatographic analysis, were retained. Heptylmalonic acid, m.p. 96–97°,[14] and octylmalonic acid, m.p. 113–114°, were obtained by hydrolysis of the corresponding homolog-free esters.[15]

Methyl hydrogen azelate and sebacate, prepared by the Organic Syntheses method,[16] were converted by reaction with thionyl chloride to 8-carbomethoxyoctanoyl chloride, b.p. 95–99° (0.15 mm.), and 9-carbomethoxynonanoyl chloride, b.p. 117–122° (0.6 mm.).

9- and 10-Oxo-octadecanoic acids. The procedure of Bowman and Fordham[17] was employed for the preparation of these keto acids. The following preparation of 10-oxo-octadecanoic acid is typical of the method.

To a solution of 109 g. of dihydropyran[18] in 200 ml. of dry benzene containing 2 drops of concentrated sulfuric acid, 111.1 g. of octylmalonic acid was added in portions, with stirring and cooling below 30°. When a clear solution was obtained, the reaction mixture was allowed to stand at room temperature for 0.5 hr., then stirred with 4 g. postassium hydroxide pellets for 0.5 hr. The acid-free benzene solution was decanted and the solvent and excess dihydropyran removed under vacuum below 30°.

The residual ester in 500 ml. of dry benzene was added dropwise, with cooling and stirring, to 24 g. of a 50% sodium hydride-oil suspension in 500 ml. of dry benzene. When all the hydride had reacted (about 2 hr.), 117.3 g. of 9-carbomethoxynonanoyl chloride in 300 ml. of dry benzene was added dropwise (temperature ~20°). The reaction mixture gelled near the end of the addition. After 1.5 hr. stirring at room temperature, 10 ml. of acetic acid was added and the mixture refluxed overnight to hydrolyze and decarboxylate the β-ketoester.

The reaction mixture was washed twice with water, the solvent removed, and low-boiling material distilled at 1 mm. (up to a bath temperature of 190°). The residue was refluxed 3 hr. in 10% methanolic potassium hydroxide and acidified with dilute hydrochloric acid, and the filtered solid was air-dried and crystallized from *n*-heptane to give 109 g. (73% yield) of 10-oxo-octadecanoic acid, m.p. 80–81°. Two crystallizations from acetonitrile gave m.p. 81–82°; semicarbazone, from 95% alcohol, m.p. 117–118°; methyl ester, m.p. 46–47°.

In an analogous manner 9-oxo-octadecanoic acid, m.p. 80–81°, was prepared in 63% yield; semicarbazone, from 95% alcohol, m.p. 110–111°; methyl ester, m.p. 47–48°.

DL-*9- and* DL-*10-hydroxyoctadecanoic acids.* The hydroxy acids were prepared by hydrogenation of methanolic solutions of methyl 9- and 10-oxo-octadecanoate in the presence of Raney nickel as described by Bergström *et al.*[19] DL-10-Hydroxyoctadecanoic acid, m.p. 79–80°; hydrazide, m.p. 115–116°; methyl ester, m.p. 54–55°. DL-9-Hydroxyoctadecanoic acid, m.p. 76–77°; hydrazide, m.p. 113–114°; methyl ester, m.p. 50–51.5°.

Phase studies. The thaw-melt method[20] was used for the study of phase changes. Synthetic mixtures were prepared, melted, and, when cool, ground in an agate mortar prior to use. Observations were made through an Ernst Leitz polarizing microscope fitted with an electrically heated hot stage. Temperatures were measured by means of a calibrated thermometer with 0.2° graduations. Liquidus temperatures were reproducible within less than 0.1°; solidus curves are approximations, as it is not possible to locate the solidus accurately by the thaw-melt technique. Precise temperature values are significant only in relation to other values obtained in this work; other techniques and equipment may yield values which differ by as much as 1°.

RESULTS AND DISCUSSION

The phase diagram for the binary system of 9-oxo- and 10-oxo-octadecanoic acids is shown in Fig. 1. This diagram represents a simple eutectic system with solid-solution formation and limited miscibility in the solid state. The points on the liquidus curve represent experimentally determined temperatures. The approximate solidus is represented by the broken lines. The eutectic lies at or close to the 1:1 ratio of the two components.

The phase diagram for the system of 9-hydroxy- and 10-hydroxyoctadecanoic acids, Fig. 2, is strikingly different from that of the oxo acids. A maximum occurs at the 1:1 ratio of the two components which is at a temperature higher than the melting point of either component. This maximum is the result of compound formation between the two hydroxy acids (actually between two racemic modifications). In this system eutectics occur between the 1:1 compound and each of the pure components; also solid solutions are formed with limited miscibility in the solid state.

With this knowledge of the two binary systems which have been described, it is now possible to comment on previous work involving 9- and 10-oxo- and 9- and 10-hydroxyoctadecanoic acids. In Table I are listed melting-point values reported in the literature together with values obtained in the present work for the pure compounds and for the 9- + 10-oxo eutectic and the 9- + 10-hydroxy compound. With due allowance for differences in experimental techniques, and the fact that most of these temperature readings are uncorrected, it is still obvious that the melting point of the substance which several authors describe as 10-oxo-octadecanoic acid (71–76°) does not agree with that of the synthetic material (82–83°) It also seems probable from the phase diagram that the lower-melting material is the 1:1 eutectic mixture (m.p. 73.2°) and that this mixture has resulted, directly or indirectly, from a completely random reaction of the eighteen-carbon fatty-acid chain at the 9- and 10-positions. With 10-hydroxyoctadecanoic acid the interpretation of the data in the literature is somewhat less clear-cut, as there is not so great a difference between the melting point of the synthetic material (79–82°) and that the 1:1 compound (82.6°). However, it is significant that in general the melting points of the products described as the 10-hydroxy acid, which are obtained from eighteen-carbon acids by one of the several pro-

(14) Temperatures are uncorrected.

(15) G. M. Robinson, *J. Chem. Soc.*, **125**, 228 (1924).

(16) S. Swann, R. Oehler and R. J. Buswell, *Org. Syntheses*, Coll. Vol. II, 276 (1944).

(17) R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 3945 (1952).

(18) Generously supplied by the Quaker Oats Company, Chicago, Ill.

(19) S. Bergström, G. Aulin-Erdtman, B. Rolander, E. Stenhagen, and S. Ostling, *Acta Chem. Scand.*, **6**, 1157 (1952).

(20) H. Rheinboldt, *Ber.*, **74**, 756 (1941); H. Lettré, H. Barnbeck, and W. Lege, *Ber.* **69**, 1151 (1936).

cedures described earlier, are higher than that of the synthetic material. This fact is in agreement with the possibility that these procedures have actually led to the 1:1 compound formed between 9- and 10-hydroxyoctadecanoic acids. This compound is indistinguishable from the pure 10-isomer on the basis of melting point alone, and none of the earlier investigators reported a mixed-melting point determination with the synthetic 10-hydroxy acid.

It is now possible to discount almost completely all evidence for a directive effect presented in earlier work. Baruch's[3] claims to have found only those products of the Beckmann rearrangement which coincide with those expected from 10-oxo-octadecanoic acid are not confirmed by the results of Robinson and Robinson.[4] These authors definitely obtain a mixture of the 9- and 10-isomers (m.p. 70.9°) and conclude that more of the latter is formed. However, it is difficult to defend their quantitative results based on thermal analysis. Fatty acids derived from natural sources, unless rigorous purification procedures are followed, always contain minor amounts of impurities which will carry over to derivatives and exert a significant effect upon the melting points. This argument is substantiated by the work of Myddleton and co-workers[5] whose purified "10-ketostearic acid" (from stearolic) melted at 76°. In each instance, the actual product is, we believe, the eutectic mixture of the 9- and 10-positional isomers.

As part of their studies of mixtures of hydroxy-octadecanoic acids, Tomecko and Adams[6] determined melting and solidification points of two mixtures of the synthetic 9- and 10-isomers. Two points are not sufficient to give even an indication of the nature of the phase diagram, but these authors did correctly conclude that the melting points of such compounds are not reliable criteria of purity. However, they incorrectly concluded that the major product of the sulfation of oleic acid or olive oil is 10-hydroxyoctadecanoic acid since in most cases the melting point lies in the 80–85° range. It is obvious from the complete liquidus curve that the 1:1 compound will also fit this melting range, and we believe that it is the actual product of the reaction.

The oxo-octadecanoic acid melting at 71° obtained by Ross, *et al.*[7] and Mack and Bickford[8] through hydrogenation of 9,10-epoxyoctadecanoic acid (or ester) followed by oxidation of the hydroxy acid is without question the 1:1 eutectic mixture of the 9- and 10-isomers. The fact that Ross was able to isolate sebacic acid after Beckmann rearrangement of the oxime does not preclude the presence also of azelaic acid. These two dibasic acids form a eutectic system[32] from which, starting with a 1:1 mixture, it is theoretically possible to separate only the 10-carbon acid by fractional crystallization.[33]

The oxo-octadecanoic acid of Jungermann and Spoerri[9] melting at 72°, which was produced from one of their chlorohydrin fractions, is also probably the eutectic mixture. This invalidates the conclusion that the two possible chlorohydrins are produced in a 3:1 ratio. Without knowledge of the binary system of the two chlorohydrins, it is not possible to predict whether either can be separated by the crystallization process, and no conclusions regarding the ratio of products should be drawn. There is no reason to believe that the hydrochlorination of 9,10-epoxyoctadecanoic acid is not a random process.

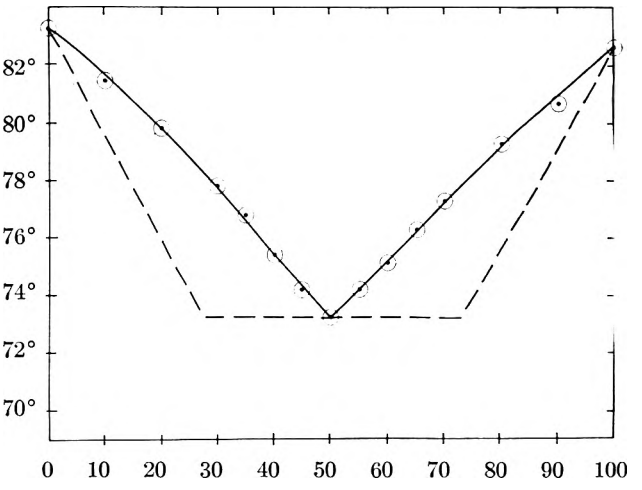

Fig. 1. The system 9-oxo-octadecanoic acid–10-oxo-octadecanoic acid

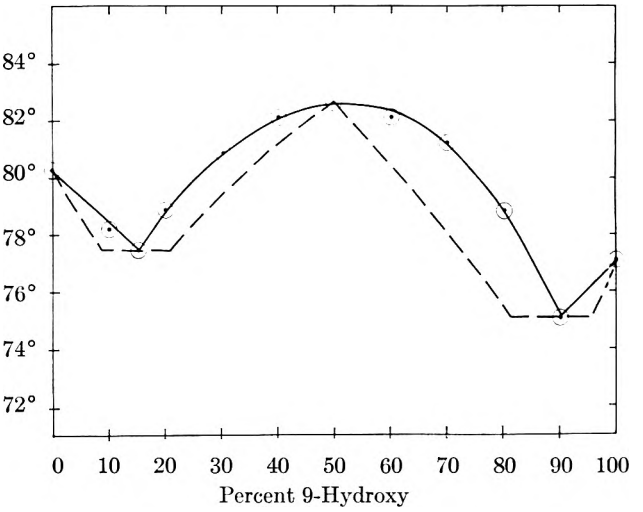

Fig. 2. The system 9-hydroxyoctadecanoic acid—10-hydroxy-octadecanoic acid

Although no claims for a directive influence in the formoxylation of oleic acid were made by Knight, Koos, and Swern,[31] these authors produced hydroxyoctadecanoic acid which, after repeated crystallization, melted at 81.5–82.5° and which showed no depression when mixed with an "authentic sample" of 10-hydroxyoctadecanoic acid. The reference sample was prepared by hydrogenation of

TABLE I

MELTING POINTS OF OXO- AND HYDROXYOCTADECANOIC ACIDS[a]

	Literature Values	Present Work
9-Oxo	*83*,[4,21] 81.5,[8] *81.7–81.9*,[19] 80,[9] *81*[12]	*82.6*
10-Oxo	76,[3,5] 74,[22] *82* (cor),[4] *82–82.8*,[23] 71,[8] *83*,[24] *82.4–82.6*,[19] 72,[8,9] *81–82*[12]	*83.2*
9- + 10-Oxo eutectic		*73.2*
9-Hydroxy	*74–75*,[6] *75.4–75.9*,[19] *70–72*[12]	*77.1*
10-Hydroxy	84–86,[25] 81–81.5,[26] 83–84,[27] *84.5*,[28] 81–82,[6] 85,[29] 82.5,[30] *79.2–79.5*,[19] 81.5–82.5,[31] 80,[9] *78–79*[12]	*80.3*
9- + 10-Hydroxy 1:1 compound		*82.6*

[a] Those in italics are for synthetic preparations.

9,10-epoxyoctadecanoic acid. Both materials are, we believe, the 1:1 compound formed by the 9- and 10-isomers.

On the basis of what has been presented, we conclude that there is no basis in the work of others which we have discussed for the belief that eighteen-carbon fatty acids which contain unsaturation or an epoxy group at the 9–10 position react in other than a random manner at these two positions.

CHICAGO, ILL.

(21) O. Behrend, *Ber.*, **29**, 806 (1896).

(22) A. A. Shukoff and P. V. Schestakoff, *J. prakt. Chem.*, **67**, 414 (1903).

(23) C. R. Fordyce and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 3368 (1933).

(24) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).

(25) M. C. Saytzeff and A. Saytzeff, *J. prakt. Chem.*, [2], **35**, 384 (1887).

(26) A. C. Geitel, *J. prakt. Chem.*, [2], **37**, 82 (1888).

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(28) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **127**, 175 (1925).

(29) L. G. Radcliffe and W. Gibson, *J. Soc. Dyers Colourists*, **39**, 4 (1923).

(30) G. V. Pigulevskii and Z. Y. Ruboshko, *J. Gen. Chem. (U.S.S.R.)*, **9**, 829 (1939); *Chem. Abstr.*, **34**, 378 (1940).

(31) H. B. Knight, R. E. Koos, and D. Swern, *J. Am. Chem. Soc.*, **75**, 6212 (1953).

(32) D. F. Houston and W. A. van Sandt, *Ind. Eng. Chem., Anal. Ed.*, **18**, 538 (1946).

(33) A private communication from Dr. David B. Howton, University of California Medical Center, Los Angeles, California, reports the unequivocal confirmation of the conclusion that a 1:1 mixture of 9- and 10-hydroxyoctadecanoic acids results from the catalytic hydrogenation of *cis*-9,10-epoxyoctadecanoic acid. This was accomplished through the following sequence of reactions: epoxy → hydroxy → oxo → oximino, followed by Beckmann rearrangement of the oximes, hydrolysis of the amides and esterification of the mixture of mono- and dibasic acids. Gas-liquid chromatography of the mixture of esters yielded equimolar amounts of azelaic and sebacic and of capric and pelargonic esters.

Notes

A department for short papers of immediate interest.

Acrylic and Methacrylic Anhydrides

T. K. Brotherton, J. Smith, Jr., and J. W. Lynn

Received July 26, 1960

Acrylic and methacrylic anhydrides have been prepared directly from the corresponding acids through the use of dehydrating agents such as acetic anhydride,[1] and indirectly from the reaction of the sodium salts of the acids with the corresponding acid chlorides.[2] The former method is complicated by the formation of difficultly separable mixed anhydrides and polymeric by-products and the latter process requires a separate synthesis of the acid chloride. A procedure similar to one previously described[3] for the preparation of amino acid anhydrides, which were not isolated but used *in situ*, has been used for the preparation of polymer-free acrylic and methacrylic anhydrides.

The process involves the addition of thionyl chloride or phosgene (gaseous or liquid) to a nonaqueous solution of a carboxylic acid and at least an equivalent of triethylamine at −5 to 20°. Triethylammonium chloride precipitates during the acid chloride addition and either carbon dioxide when phosgene is used or sulfur dioxide when thionyl chloride is used is evolved on warming the solution to room temperature. After removal of the salt by filtration the resulting clear solution which contains the anhydride can be used *per se* in syntheses or the solvent can be removed and a refined product isolated. Comparable results were obtained when either benzene, acetone, or ethyl ether was used as solvent with acid concentrations of 10 to 35%.

EXPERIMENTAL[4]

Experimental data from several runs using different reaction conditions are summarized in Table I.

Typical acrylic anhydride preparation. A solution of 144 g. (1.95 moles) of acrylic acid in 1296 g. of benzene was treated with 202 g. (2 moles) of triethylamine at 0 to 10° over a period of 10 min. Hydroquinone (1.4 g.) was present in the solution as a polymerization inhibitor. With vigorous agitation, 99 g. (1 mole) of gaseous phosgene was added through a sparger placed near the bottom of the reactor. The phosgene addition was completed in 65 min. with the temperature of the reaction mixture being maintained at 0 to 10° by external cooling. The resulting mixture was allowed to warm to room temperature and the triethylammonium chloride removed by filtration. The clear benzene filtrate was flash-distilled yielding 95 g. of crude product which was fractionally distilled through a column furnishing 89 g. (72.3%) of refined acrylic anhydride with a boiling point of 68°/9.7 mm. and n_D^{30} 1.4438.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.76. Found: C, 57.31; H, 4.82.

Typical methacrylic anhydride preparation. The same general procedure was used as described for the preparation of acrylic anhydride except methacrylic acid was used in place of acrylic acid. A solution of 172 g. (2.0 moles) methacrylic acid, 202 g. (2.0 moles) of triethylamine, and 1.72 g. of hydroquinone in 1400 g. of benzene was treated with 99

TABLE I

Preparation of Anhydrides

Acid,[b] moles	TEA,[a] moles	Phosgene Feed: Form	Feed rate, moles/hr.	Moles	Temp.	Solvent	% Soln. by wt. of acid	% Yield of anhydride
Acrylic								
2.0	2.0	Liq.	1.5	1.0	−6 to 0	Acetone	35	73
1.95	2.0	Gas	2.0	1.0	5 to 18	Ether	25	50
1.95	2.0	Gas	0.82	0.82	−5 to 0	Ether	10	66
Methacrylic								
2.0	2.0	Gas	1.0	1.0	0 to 10	Benzene	11	90
Acrylic		Thionyl Chloride Feed						
1.95	2.0	Liq.	1.2	1.0	0 to 5	Benzene	10	60

[a] Triethylamine. [b] Containing 0.1% hydroquinone polymerization inhibitor.

(1) W. G. Lowe and W. D. Kenyon, U. S. Patent 2,319,-070.

(2) C. Moreu, *Ann. Chim. and Phys.*, 7, 2,167 (1894); British Patent 538,310; W. N. Haworth, H. Gregory, and L. F. Wiggins, *J. Chem. Soc.*, 483 (1946); A. A. Berlin and T. A. Makarova, *Zhur. Obschei. Khim.* (*J. Gen. Chem.*), 21 1267 (1945); *Chem. Abstr.*, 46, 1996d (1952); C. E. Barnes, U. S. Patent 2,308,581.

(3) M. Brenner, Z. P. Zimmermann, P. Quitt, W. Schneider, and A. Hartmann, *Helv. Chem. Acta.* 40, 604 (1957).

(4) All temperatures are uncorrected.

g. (1.0 mole) of gaseous phosgene. Distillation of the benzene solution furnished 139 g. (90.3%) of methacrylic anhydride with a boiling point of 82°/9.4 mm. and n_D^{30} 1.4492.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.30; H, 6.50. Found: C, 61.98; H, 6.45.

RESEARCH DEPARTMENT
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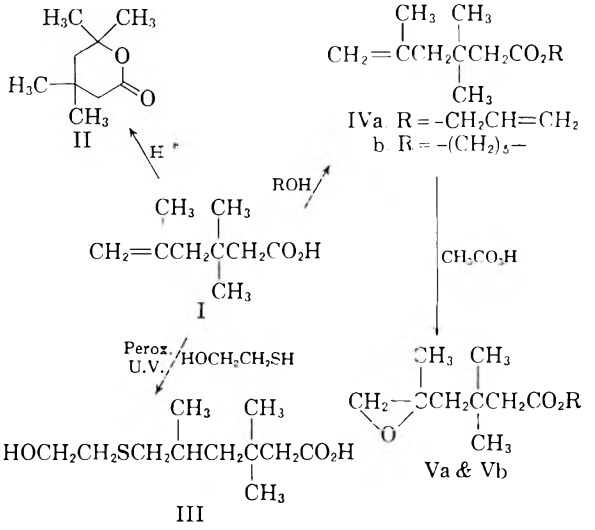
Some Derivatives of 3,3,5-Trimethyl-5-hexenoic Acid

JOHN W. LYNN

Received August 11, 1960

Alkali fusion of isophorone to give 3,3,5-trimethyl-5-hexenoic acid (I)[1] provides a facile synthesis of this terminally unsaturated acid. A variety of novel materials may be derived from I by simple procedures as is shown schematically below.



EXPERIMENTAL[2]

3,3,5-Trimethyl-5-hexenoic acid (I). The method of Finch[1] was employed to furnish a 41% yield of I (b.p. 121°/9 mm., n_D^{30} 1.4495, 98.6% purity by sodium hydroxide titration).

4,4,6,6-Tetramethylvalerolactone (II). A mixture of 156 g. (1.0 mole) of I, 1.6 g. of *p*-toluenesulfonic acid and 300 ml. of benzene was refluxed for 36 hr. The cooled mixture was neutralized with sodium acetate, filtered, and distilled to furnish an 89% yield of II (b.p. 99°/6 mm. n_D^{30} 1.4457, d_{20}^{20} 0.9667, 97.7% purity by saponification).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.25. Found: 69.1; H, 10.48.

9-Hydroxy-7-thia-3,3,5-trimethylnonanoic acid (III). A mixture of 172 g. (1.1 moles) of I, 78 g. (1.0 mole) of 2-mercaptoethanol and 1.26 g. of benzoyl peroxide was stirred at 70° for 10 hr. under irradiation from a General Electric Company Sunlamp. The reaction mixture was stripped of volatiles to a flask temperature of 205° at 1.5 mm. The residual amber oil amounted to 39% of III (n_D^{30} 1.5047).

Anal. Calcd. for $C_{11}H_{22}O_3S$: C, 56.1; H, 9.41; S, 13.66. Found: C, 56.48; H, 9.36; S, 14.8.

Allyl 3,3,5-trimethyl-5-hexenoate (IVa). A mixture of 75.3 g. (0.46 mole) of I, 58 g. (1.0 mole) of allyl alcohol, 1.35 g. of *p*-toluenesulfonic acid and 265 ml. of benzene was refluxed for 11 hr. while water was removed azeotropically. The mixture was washed with 10% sodium carbonate solution and water and then distilled to furnish an 84% yield of IVa (b.p. 83°/4.5 mm., n_D^{30} 1.4460, d_{20}^{20} 0.9084, 99.3 purity by saponification).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.50; H, 10.2. Found: C, C, 73.34; H, 10.17.

1,5-Pentamethylene bis(3,3,5-trimethyl-5-hexenoate) (IVb). A mixture of 234 g. (1.5 moles) of I, 52 g. (0.5 mole) of 1,5-pentanediol, 1.4 g. of *p*-toluenesulfonic acid, and 400 ml. of benzene was refluxed for 28 hr. while water was removed azeotropically. The mixture was neutralized with sodium acetate, filtered, and distilled to furnish a 95% yield of lactone II (based on excess I) and a 98% yield (based on glycol) of IVb as a residual oil (n_D^{30} 1.4620, d_{20}^{20} 0.9521.

Anal. Calcd. for $C_{23}H_{40}O_4$: C, 72.70; H, 10.51. Found: C, 72.62; H, 10.50.

Allyl 5,6-epoxy-3,3,5-trimethylhexanoate (Va). To 218 g. (1.11 moles) of IVa was added with cooling to maintain 40° temperature 346 g. of 26.8% peracetic acid in ethyl acetate over 2-hr. period. The mixture was stirred for an additional 6 hr. at 40° to complete reaction. The mixture was fed into refluxing ethylbenzene to remove acetic acid and excess peracetic acid and was then distilled to furnish 81 g. of refined product (b.p. 93°/5 mm., n_D^{30} 1.4499).

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 68.0; H, 9.45. Found: C, 68.3; H, 9.7.

1,5-Pentamethylene bis(5,6-epoxy-3,3,5-trimethylhexanoate) (Vb). The procedure described above was employed to furnish a pale yellow residual oil (n_D^{30} 1.4650) whose infrared spectrum exhibited strong epoxide absorption and no unsaturation.

Acknowledgment. The author is grateful to Mr. J. Smith, Jr. for technical assistance and to Mr. P. S. Starcher for synthesis of the epoxides.

UNION CARBIDE CHEMICAL CO.
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Reactions of Active Methylene Compounds in Pyridine Solution. IV. A New Synthesis of β-Hydroxypropionitriles

M. AVRAMOFF AND Y. SPRINZAK

Received July 18, 1960

In the previous parts of this series[1] reactions of hydrocarbons of the cyclopentadiene type have been discussed. In particular,[1b] the high reactivity observed in pyridine solution in the presence of benzyltrimethylammonium hydroxide made possible the use of lower temperatures in the reaction with aldehydes and thereby the isolation of primary reaction products, *e.g.* carbinols of structure I from fluorene,

(1) H. Finch, K. E. Furman, and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 4299 (1951).

(2) All temperatures are uncorrected.

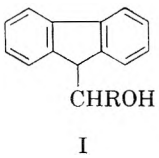
(1) (a) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 5449 (1958); (b) E. Ghera and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 4945 (1960); (c) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 4953 (1960).

TABLE 1

HYDROXYMETHYLATION OF $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!\!CH\text{—}CN$

No.	R_1	R_2	Temp.	Time, hr.	Yield, %	Recrystallization Solvent	M.P.	Formula	Calcd. C	Calcd. H	Found C	Found H
1	C_6H_5	C_6H_5	25	22	94	Benzene–pet. ether (b.p. 60–90°)	65	$C_{15}H_{13}NO$	80.69	5.87	80.80	5.84
2	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$[a,b]	25	24	92	Heptane	97	$C_{17}H_{17}NO$	81.24	6.82	81.16	6.89
3	C_6H_5	α-$C_{10}H_7$[a,c]	25	18	95	Benzene-heptane	126–128	$C_{19}H_{15}NO$	83.49	5.53	83.45	5.63
4	C_6H_5	$C_6H_5CH_2$[d]	0	2	93	Ethyl acetate–pet. ether	89–90	$C_{16}H_{15}NO$	80.98	6.37	81.21	6.42
5	C_6H_5	α-$C_{10}H_7CH_2$[d]	25	16	95	Benzene	146–148	$C_{20}H_{17}NO$	83.59	5.96	83.61	5.96
6	$C_6H_5CH_2$	α-$C_{10}H_7$[d]	25	6	87	Benzene	122–124	$C_{20}H_{17}NO$	83.59	5.96	83.35	6.01
7	p-ClC_6H_4	p-$ClC_6H_4CH_2$[e,f]	25	48	44	Heptane	89–90	$C_{16}H_{13}Cl_2NO$	62.74	4.28	62.98	4.43
8	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4CH_2$[e,g]	25	48	45	Ether–pet. ether	75–76	$C_{18}H_{19}NO_3$	72.70	6.44	72.45	6.46
9	C_6H_5	$(C_6H_5)_2CH$[d]	25	16	91	Benzene-heptane	161–162	$C_{22}H_{19}NO$	84.31	6.11	84.25	6.22
10	$C_6H_5CH_2$	$C_6H_5CH_2$[h]	25	24	0							

[a] Prepared according to the procedure of J. G. Burr, Jr., and L. S. Ciereszko [*J. Am. Chem. Soc.*, **74**, 5426 (1952)]. [b] M.p. 45–46°; reported 46.5–47° [R. F. Brown and N. M. van Gulick, *J. Am. Chem. Soc.*, **77**, 1083 (1955)]. [c] M.p. 94.5–96°; reported 95–96° [C. J. Collins, L. S. Ciereszko, and J. G. Burr, Jr., *J. Am. Chem. Soc.*, **75**, 405 (1953)]. [d] Ref. 3. [e] Prepared according to the procedure of Avramoff and Sprinzak.[3] [f] M.p. 90–91°; reported 91–92° [P. Weiss, M. G. Cordasco, and L. Reiner, *J. Am. Chem. Soc.*, **71**, 2650 (1949)]. [g] M.p. 117–118°; reported 117–118° [H. Köling and H. Lettré, Schenley Laboratories, Inc., U. S. Patent **2,691,044**, October 5, 1954]. [h] H. Cassirer, *Ber.*, **25**, 3018 (1892).



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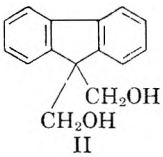

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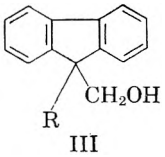
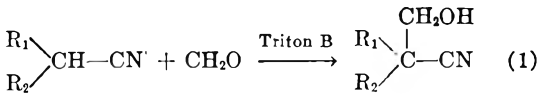


III

rather than their dehydration products. While formaldehyde reacted with fluorene with particular ease, affording both carbinol I (R = H) and glycol II, these products were accompanied by a considerable amount of a resinous material, presumably arising from the polymerization of dibenzofulvene, the dehydration product of the carbinol. The reaction occurred smoothly, however, with 9-alkylfluorenes, affording the corresponding hydroxymethylfluorenes (III) in quantitative yield.

The hydroxymethylation reaction has now been extended to acetonitrile derivatives[2] (Table I), including diarylacetonitriles and aryl-arylmethylacetonitriles.[3] Treatment of these compounds with paraformaldehyde in pyridine solution in the presence of Triton B affords α,α-disubstituted β-hydroxypropionitriles (Equation 1).



(1)

in yields ranging from 44 to 95%. It appears that the presence of an α-aryl group is essential for reaction to occur, as is indicated by the failure of dibenzylacetonitrile (No. 10) to react under the general reaction conditions. The reaction products, all of which are new compounds, were identified by elementary analysis and by their infrared spectra, showing the typical OH and C≡N absorption bands in the 2.8 and 4.5 μ regions. The reaction product from diphenylacetonitrile (No. 1) was also identified by its benzoate ester.

Tertiary nitriles are known to be very resistant to hydrolysis.[4] Alkaline conditions could not be applied to the β-hydroxynitriles in question, as these are transformed, by reversal of their mode of formation and in complete analogy with β-hydroxyacids,[5] to the corresponding acetonitriles. Thus, prolonged refluxing of α,α-diphenyl-β-hydroxypropionitrile (No. 1) in ethanolic potassium hydroxide resulted in its conversion to diphenylacetic acid. A large quantity of the intermediate diphenylacetonitrile was isolated when the hydroxynitrile was kept at room temperature under similar conditions. α-Phenyl-α-benzyl-β-hydroxypropionitrile (No. 4) was the only hydroxynitrile that could be hydrolyzed to the corresponding hydroxy-acid under acid conditions.

(2) Phenylacetonitrile has been reported to form, by interaction with formaldehyde in methanolic sodium methoxide, a viscous oil, considered to be the hydroxymethylated nitrile: the product was dehydrated, without isolation, to α-phenylacrylonitrile (J. F. Walker, E. I. du Pont de Nemours and Co., U. S. Patent 2,478,990, August 16 1949). A recent publication reports the formation of α,c-diphenyl-α,α'-bishydroxymethylglutaronitrile, $NCC(C_6H_5)(CH_2OH)$-$CH_2C(C_6H_5)(CH_2OH)CN$, from the same reagents in toluene and sodium methoxide [H. Jäger, *Arch. Pharm.*, 289, 165 (1956)].

(3) Chosen for their ready accessibility [M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, 80, 493 (1958)].

(4) See, *e.g.*, S. Rovira, *Ann. chim.* (*Paris*), [11], 20, 660 (1945).

(5) See, *e.g.*, C. S. Rondestvedt, Jr., and M. E. Rowley, *J. Am. Chem. Soc.*, 78, 3804 (1956).

EXPERIMENTAL[6]

Pyridine was dried and a 40% solution of Triton B was prepared as described previously.[1a] The condensation reactions were performed in an atmosphere of nitrogen, the details being given in part II.[1b]

Hydroxymethylation of the nitriles (Table I). Triton B (0.5 ml.) was added to an ice cold, stirred solution of 0.005 mole of the nitrile in 10 ml. of pyridine, containing paraformaldehyde (0.6 g.; 0.02 mole) in suspension, and the stirred mixture was left at the appropriate temperature for the period indicated. The crude product obtained after treatment of the reaction mixture as described previously[1b] crystallized on trituration with petroleum ether. One recrystallization afforded the pure product.

β,β-Diphenyl-β-cyanoethyl benzoate. Refluxing α,α-diphenyl-β-hydroxypropionitrile (No. 1) with an excess of benzoyl chloride in pyridine solution for 30 min. gave the benzoate, m.p. 110° (from heptane).

Anal. Calcd. for $C_{22}H_{17}NO_2$: N, 4.28. Found: N, 4.23.

Alkaline hydrolysis of α,α-diphenyl-β-hydroxypropionitrile (No. 1). A solution of the nitrile (1.0 g.) in 20 ml. of ethanol and 2 g. of potassium hydroxide was refluxed for 20 hr. The acid fraction afforded 0.7 g., m.p. 130–140°. Recrystallization from 50% ethanol and then from a benzene-heptane mixture gave diphenylacetic acid, m.p. 139–142° and mixed m.p. 140–144°.

Reverse aldol reaction of α,α-diphenyl-β-hydroxypropionitrile (No. 1). A solution of the nitrile (1.0 g.) in 20 ml. of ethanol and 0.5 g. of potassium hydroxide was kept at room temperature for 48 hr. The mixture obtained after dilution with water was extracted several times with ether. The ethereal extract was washed with water, dried and evaporated to give 0.95 g. of residue, which was chromatographed on acid-washed alumina. The fraction (0.48 g.) obtained by elution with a 4:1 petroleum ether-benzene mixture was identified as diphenylacetonitrile, m.p. and mixed m.p. 72–75° (from petroleum ether). A fraction (0.35 g.) collected by elution with a 1:1 mixture of the same solvents proved to be the starting material.

α-Phenyl-α-benzyl-β-hydroxypropionic acid. One gram of the corresponding nitrile (No. 4) was refluxed for 30 hr. with a mixture of acetic acid (25 ml.), water (5 ml.), and concd. sulfuric acid (3 ml.). The mixture was poured into water, made alkaline with sodium hydroxide, the precipitate filtered, washed with water and with ether, then suspended in dilute hydrochloric acid, and extracted with ether. Evaporation of the dried ether solution afforded 0.35 g., m.p. 184–188°. Recrystallized from toluene, the acid melted at 190–193° (lit.[7] m.p. 188–189°).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.30; H, 6.45.

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(6) Melting points are corrected. Infrared spectra were determined in chloroform solution on a Perkin-Elmer Infracord.

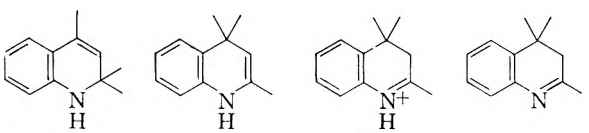
(7) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, 74, 1730 (1952).

The Structure of "Acetone Anil," 2,2,4-Trimethyl-1,2-dihydroquinoline

I. W. Elliott, Jr., and Peter Yates

Received July 5, 1960

The condensation product of aniline with two molar equivalents of acetone has been given the trivial name "acetone anil" although it is in fact a dihydroquinoline. The weight of evidence favors the structure 2,2,4-trimethyl-1,2-dihydroquinoline (I), but an alternative 2,4,4-trimethyldihydroquinoline formulation (II) has not been rigorously excluded from consideration as the structure of "acetone anil."[1] Ultraviolet spectroscopy has been used to support the assignment of structure I; Johnson and Buell[2] have pointed out the similarity of the ultraviolet spectrum of "acetone anil" to that of *o*-aminostyrene and have concluded that structure I is correct. Craig and Gregg[3] have criticized the validity of this argument on the grounds that the ultraviolet spectrum of "acetone anil" does not eliminate the possibility that the compound is a



I II III IV

1,4-dihydroquinoline derivative;[4] they considered, however, that the similarity of its ultraviolet spectrum in acid solution to those of 1,2-dihydronaphthalene and its 4-methyl derivative provided compelling evidence for the 1,2-dihydroquinoline structure, I. It may be pointed out in turn that the evidence from the ultraviolet spectrum in acid solution is itself ambiguous in that, were "acetone anil" a 1,4-dihydroquinoline derivative, protonation would be expected to occur on carbon[8,9] giving a species, III, whose spectrum might resemble that observed. As the structure of "acetone anil" was of interest to us in connection with another investigation, we have attempted to accumulate further evidence on which to base a decisive choice between I and II.

The infrared spectrum of "acetone anil" in chloroform solution shows a medium strength NH band at 2.95 μ. Witkop's results in connection with imine-enamine tautomerism[9] indicate that, were "acetone anil" a 2,4,4-trimethyldihydroquinoline, the imine form IV would largely predominate and only a very weak NH band would be observed. Further, the band of "acetone anil" at 6.04 μ, which is absent in the spectrum of its hydrogenation product and may be assigned to the double bond, is not shifted to lower wave lengths in the spectrum of "acetone anil" hydrochloride. A compound of either structure II or IV would be expected to give rise to the protonated species III with concomitant shift of the double bond band to shorter wave lengths.[8,9] Thus the infrared data favor structure I for "acetone anil."[10]

The proton magnetic resonance spectra for "acetone anil" and its acetyl and dihydro derivatives have now been recorded.[11] "Acetone anil" shows, in addition to the series of peaks due to the aromatic hydrogen atoms, four bands with τ values[12]; 4.78, 6.40, 8.06 (doublet, J $\sim$ 1.0 c/s.) and 8.81; the areas of these bands were in the approximate ratio 1:1:3:6. They may be assigned respectively to the vinyl, amine, single methyl, and *gem*-dimethyl hydrogen atoms of *either* I *or* II; but cannot be interpreted in terms of structure IV. In accordance with these assignments the band in the τ = 6.4 region is absent in the spectrum of the acetyl derivative, while a new singlet appears in the τ = 8.0 region which is attributable to the hydrogen atoms of the acetyl group. Also, the dihydro compound fails to show a band in the τ = 4.5–5.0 region, and shows a new, highly split multiplet centered about τ = 7.1, which may be assigned to a single hydrogen at the 4-position of I (or the 2 position of II), together with other changes in the region τ = >8.0. Unfortunately, these spectra do not permit a choice between I and II.

Although the spectral evidence taken as a whole favors structure I, we considered it important to seek chemical evidence in addition. Earlier experiments directed towards the oxidative degradation of "acetone anil" led to unidentified products.[13] The acetyl derivative of "acetone anil" has now been oxidized with the permanganate-periodate

(1) See D. Craig, *J. Am. Chem. Soc.*, **60**, 1458 (1938), for leading references to early work.

(2) W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, **74**, 4517 (1952).

(3) D. Craig and E. C. Gregg, Jr., *J. Am. Chem. Soc.*, **75**, 2252 (1953).

(4) It may be noted, however, that the spectra of compounds considered to be 1-methyl-4-cyano-1,4-dihydroquinoline[5] [λ_{max} 230 mμ (log ϵ 3.93); 302 mμ (log ϵ 3.95)] and 1-methyl-4-(α-cyano-α-aralkyl)-1,4-dihydroquinolines[6] are markedly different from those of "acetone anil" and other compounds which have been assigned 1,2-dihydroquinoline structures.[2,7] Nevertheless, this cannot be considered as decisive, as the position of the double bond in these presumed 1,4-dihydroquinoline derivatives has not been proved unequivocally.

(5) A. Kaufmann and A. Albertini, *Ber.*, **42**, 3776 (1909).

(6) N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.*, **74**, 3671 (1952).

(7) K. Sutter-Kostič and P. Karrer, *Helv. Chim. Acta*, **39**, 677 (1956).

(8) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(9) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

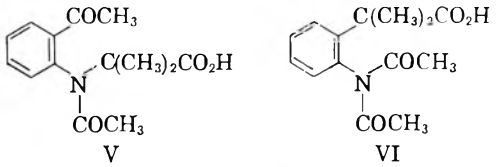
(10) The possibility that I might protonate on carbon cannot be completely eliminated and thus this conclusion is still not completely rigorous. However, such protonation would appear *a priori* less likely for I than for II.

(11) We thank Mr. T. J. Curphey for these measurements.

(12) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

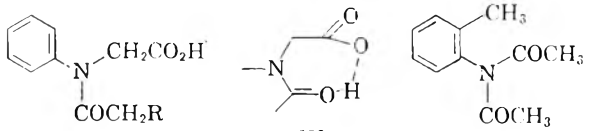
(13) P. Kalnin, *Ann.*, **523**, 118 (1936).

reagent[14] to give a crystalline product, m.p. 194–195°, with the formula $C_{14}H_{17}NO_4$. This product could be either V or VI, derived from I or II, respectively. A choice can be made between these



V VI

possibilities on the basis of the fact that the oxidation product gives a positive iodoform test, showing it to have structure V. The infrared spectrum (Nujol) of the oxidation product confirms this structural assignment, having bands at 5.71 μ (carboxylic acid), 5.89 μ (aromatic ketone), and 6.17 μ (tertiary amide). These may be compared with the bands of *N*-acetyl-*N*-phenylglycine (VII) at 5.75 μ (carboxylic acid) and 6.18 μ (tertiary amide)[15] and of *N*-phenacetyl-*N* phenylglycine (VIII) at 5.71 μ (carboxylic acid) and 6.11 μ (tertiary amide).[16] The combination of the unusually low wave length of the carboxylic acid bands and the unusually high wave length of the amide bands[17] in the spectra of these compounds may be interpreted in terms of *monomeric* structures, with intramolecular hydrogen bonding between the carboxylic acid and the amide carbonyl groups (*cf.* IX).[18] The infrared spectrum of the oxidation



VII. R = H
VIII. R = C_6H_5

IX X

product is not, however, in accord with structure VI. Thus, the *N*,*N*-diacetyl derivative of *o*-toluidine, X, shows a poorly resolved doublet in its spectrum at 5.78–5.83 μ,[19] while the amide band in the spectrum of the oxidation product falls at a considerably longer wave length.[20] The structure of "acetone anil" is therefore established as I.[21]

EXPERIMENTAL[22]

"Acetone anil" (I) was prepared by the method of Vaughan[23] and was obtained as a pale yellow oil, b.p. 131° (6 mm.) [lit.[23] b.p. 133–138° (13 mm.)]; $\lambda_{max}^{CHCl_3}$ 2.95, 6.04 μ; τ 4.78, 6.40, 8.06 (doublet, J ~ 1 c./s.), 8.81. The *hydrochloride* was prepared by the procedure of Craig[1] and after recrystallization from ethanol-ether had m.p. 212–213° (lit.[1] m.p. 212–213°); λ_{max}^{Nujol} 6.04 μ. The *acetyl derivative* was prepared by the method of Cliffe[24] and was obtained as a yellow oil, b.p. 172° (18 mm.) [lit.[24] b.p. 175° (23 mm.)], which slowly solidified; recrystallization of the solid from petroleum ether gave yellow prisms, m.p. 54–55° (lit.[24] m.p. 54°); $\lambda_{max}^{C_2H_5OH}$ 243 mμ (log ϵ 4.41), 285 mμ (log ϵ 3.63); $\lambda_{max}^{CHCl_3}$ 5.98 μ; τ 4.65, 8.03, 8.13, 8.63.

Dihydro derivative of "acetone anil." A solution of 2.09 g. (0.01 mole) of the hydrochloride of "acetone anil" in 125 ml. of ethanol was hydrogenated at atmospheric pressure over platinum. The catalyst was filtered and the solution was concentrated to afford 1.7 g. of colorless prisms, m.p. 207–209°; a mixture melting point with the starting material was depressed. The product was dissolved in water and treated with dilute aqueous sodium hydroxide. The resulting suspension was extracted with ether, and the ether solution was evaporated to leave an oil which slowly crystallized at 0°. Recrystallization of the solid gave the dihydro derivative of "acetone anil" as colorless prisms, m.p. 42–43° (lit.[25] m.p. 41°); $\lambda_{max}^{C_2H_5OH}$ 248 mμ (log ϵ 4.03), 302 mμ (log ϵ 3.42); $\lambda_{max}^{CHCl_3}$ 2.94 μ; τ 6.60, 7.10 (multiplet), 8.33, 8.58, 8.78, 8.85.

Hydrogenation of the acetyl derivative of "acetone anil." A solution of 2.15 g. of the acetyl derivative of "acetone anil" in 125 ml. of ethanol was hydrogenated at atmospheric pressure over platinum. The reduction was stopped after the uptake of 1.1 molar equivalents of hydrogen. The solution was filtered from the catalyst and evaporated to small volume. The residual oil solidified after storage in a vacuum desiccator. The solid was recrystallized from petroleum ether to give the dihydro compound as flat, colorless prisms, m.p. 87–88°; $\lambda_{max}^{C_2H_5OH}$ 210 mμ (log ϵ 4.31), 253 mμ (log ϵ 4.09); $\lambda_{max}^{CHCl_3}$ 6.05 μ.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.63; H, 8.92; N, 6.40.

Oxidation of the acetyl derivative of "acetone anil": Formation of V. To 15 g. of potassium periodate stirred in 600 ml. of water was added 0.4 g. of potassium permanganate, 5 g. of potassium carbonate, and 3 g. of the acetyl derivative of "acetone anil." The reaction mixture was stirred for 5 hr.; it was then treated with sodium bisulfite until the color of the solution became light yellow and extracted with ether containing a small quantity of dichloromethane until the organic layer was colorless. The extract was evaporated to a dark oil, and this was redissolved in ethanol. On being cooled and scratched the solution slowly deposited 0.2 g. of

(14) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955); E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).

(15) A. Gierer, *Z. Naturforsch.*, **86**, 654 (1953).

(16) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949. p. 155.

(17) Tertiary amides with a phenyl group on the nitrogen atom usually absorb *ca.* 5.92 μ: L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd., London, 2nd ed., 1958, p. 213.

(18) Similar interpretations have been made of anomalies in the spectra of *o*-methoxy aromatic carboxylic acids: S. Marburg, Ph.D. thesis, Harvard, 1960; J. W. Huffman, *J. Org. Chem.*, **24**, 1759 (1959); *cf.* E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, **75**, 4585 (1953).

(19) For the infrared spectra of other compounds of this type, see B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3861 (1952); F. C. Uhle, C. M. McEwen, Jr., H. Schröter, C. Yuan, and B. W. Baker, *J. Am. Chem. Soc.*, **82**, 1200 (1960).

(20) Hydrogen bonding of this type illustrated in IX would not be expected for VI since this would require the formation of a much larger ring. Intramolecular hydrogen bonding of the carboxylic acid with the nitrogen atom in VI would tend to lower, rather than to raise, the wave length of the amide band relative to the wave lengths of the amide bands of X.

(21) Other chemical evidence has been adduced very recently in favor of this structure: J. P. Brown, *Chem. & Ind.*, 233 (1960).

(22) Melting points and boiling points are uncorrected.

(23) W. R. Vaughan, *Org. Syntheses*, **Coll. Vol. III**, 329 (1955).

(24) W. H. Cliffe, *J. Chem. Soc.*, 1327 (1933).

(25) G. Reddelien and A. Thurm, *Ber.*, **65**, 1511 (1932).

colorless crystals which were collected and washed with ether. This product melted at 187°; after several recrystallizations from alcohol and passage through a column of alumina, it had m.p. 194–195°; λ_{max}^{Nujol} 3.75–3.95, 5.71, 5.89, 6.17 μ.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.35; N, 5.54.

Diacetyl derivative of o-toluidine (X). This was prepared by the method of Sudborough[26] and obtained as an oil, b.p. 142–143° (9 mm.) [lit.[26] b.p. 152–153° (20 mm.)]; λ_{max}^{Nujol} 5.78–5.83 μ (poorly resolved doublet).

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(26) J. J. Sudborough, *J. Chem. Soc.*, **79**, 533 (1901).

Configurations of the Isophorone Oximes

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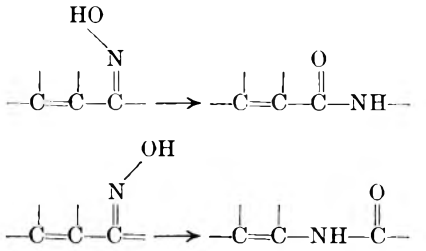
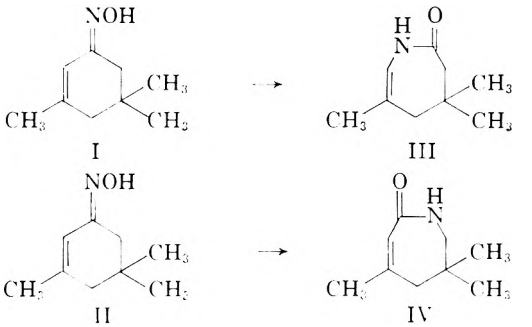
Received November 30, 1959

The Beckmann rearrangement has not only been a useful synthetic tool but has proved of great value in determining the configurations of *syn* and *anti* aldoximes and ketoximes.[1] Previous work has been virtually exclusively limited to the study of oximes of saturated carbonyl compounds with a few references to rearrangement of α,β-unsaturated ketoximes.[2-10] The latter type should be especially valuable for configuration determination since only an ultraviolet spectrum might be necessary to distinguish between the products. Thus, *syn*-α,β-unsaturated ketoximes lead to α,β-unsaturated amides or lactams while the *anti*-isomers give acylated enamines or enamine lactams. The two types of products might be expected to have markedly different ultraviolet absorption maxima but which should be reasonably constant from compound to compound. Also, if the unsaturated and saturated lactams and/or oximes can be related (reduction or oxidation), the configurations of the saturated oximes are simultaneously determined.



We attempted to use this method to assign the proper structure to a C-ring steroid lactam.[9] Although the isophorone (3,5,5-trimethyl-2-cyclohexenone) oximes and resulting lactams were excellent models for the steroid case from the standpoint of both ring size and substitution, the evidence which had been presented suggested that the configurations had been incorrectly assigned,[5] a premise shown to be true by the present work.

The existence of the two oximes of isophorone was a subject of controversy in the early chemical literature.[11-15] It was assumed[12,15] that their formation was due to a double bond isomer present in some preparations of isophorone. Apparently the concept[16] of *syn*- and *anti*-oximes was slow to gain acceptance. Finally, Montgomery and Dougherty[5] repeated the separation of the two isomers, demonstrated their interconvertibility, and isolated a Beckmann rearrangement product in low yield from each. We have repeated and confirmed this work and have greatly improved the yield in the Beckmann rearrangement of the *anti*-oxime by using the polyphosphoric acid method of Horning.[4]

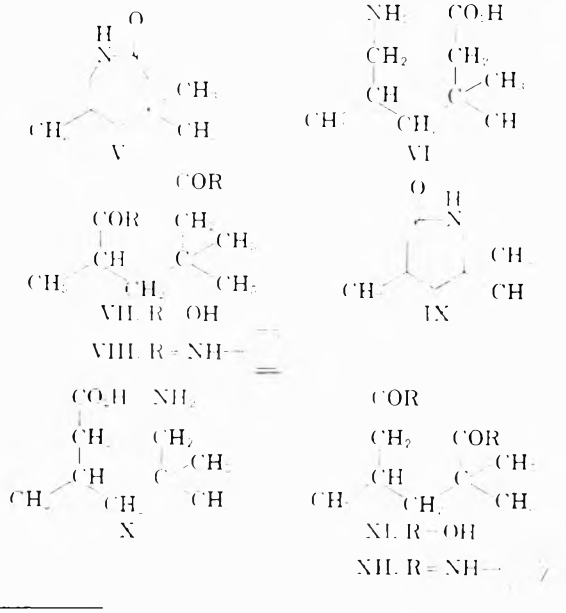


That the two oximes were really *syn*- and *anti*-isomers of an α,β-unsaturated ketone was shown by their nearly identical ultraviolet spectra.[5] The additional question arises in a reaction proceeding in low yield as to whether the product truly represents the configuration of the starting material. However, when a good yield is obtained, either the product is related directly to the starting material or isomerization of the starting material is essentially complete before reaction takes place. Since, in the

(1) A. H. Blatt, *Chem. Rev.*, **12**, 215 (1933); B. Jones, *Chem. Rev.*, **35**, 335 (1944).
(2) A. H. Blatt and J. F. Stone, Jr., *J. Am. Chem. Soc.*, **53**, 4134 (1931).
(3) R. C. Morris and A. V. Snider, U. S. Patent 2,462,009 (Feb. 15, 1949).
(4) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).
(5) R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, **17**, 823 (1952).
(6) C. S. Barnes, D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 2339 (1952).
(7) G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).
(8) F. J. Donat and A. L. Nelson, *J. Org. Chem.*, **22**, 1107 (1957).
(9) R. H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1959).
(10) J. Romo and A. Romo de Vivar, *J. Am. Chem. Soc.*, **81**, 3446 (1959).
(11) E. Knoevenagel, *Ann.*, **297**, 185 (1897).
(12) J. Bredt and R. Rübel, *Ann.*, **299**, 160 (1898).
(13) W. Kerp and F. Müller, *Ann.*, **299**, 193 (1898).
(14) L. Wolff, *Ann.*, **322**, 351 (1902).
(15) A. W. Crossley and C. Gilling, *J. Chem. Soc.*, **95**, 19 (1909).
(16) A. Hantzsch and A. Werner, *Ber.*, **23**, 11 (1890).

present case, oxime I gave a good yield of lactam III, either the two are related or oxime I isomerized to oxime II and then rearranged to lactam III. However, if the latter situation applied, then rearrangement of oxime II *under the same conditions* would also give a good yield of lactam III. In fact, though, oxime II led to a poor yield of lactam IV and the material isolated from the mother liquors of this reaction was shown by infrared spectra to be a mixture of lactams III and IV. Thus, we may surely conclude that a proof of the structures of lactams III and IV demonstrates the configuration of oximes I and II respectively.

In a parallel series of experiments, each lactam was successively hydrogenated to a trimethyloxohexamethylenimine, hydrolyzed to an aminotrimethyl-hexanoic acid and oxidized[17] to a trimethylhexanedioic acid. These changes are shown by formulas III → V → VI → VII and IV → IX → X → XI. The final products are known compounds of unambiguous structure[18,19] so that identification of the acid eventually obtained from oxime I with 2,4,4-trimethyl-hexanedioic acid and that from oxime II with 2,2,4-trimethylhexanedioic acid established the configurations of the oximes. In addition, the results show that a seven-membered enamine lactam has an ultraviolet absorption maximum about 20 mμ higher than the corresponding α,β-unsaturated lactam so that the spectra constitute a firm basis for distinguishing between two α,β-unsaturated six-membered ketoximes. Even when only one oxime can be obtained, absorption by the resulting lactam in the 240 mμ region would be excellent evidence for an *anti*-oxime, while absorption in the 220 mμ region would enable the conclusion that a *syn*-oxime was the starting material.



The saturated lactams V and IX have been previously reported.[20] They were prepared by Beckmann rearrangement of dihydroisophorone (3,3,5-trimethylcyclohexanone) oxime and subsequent fractional crystallization. The melting points recorded were α: m.p. 111–112°, β: m.p. 82–84°. When our pure lactams prepared from III and IV showed m.p. 110–111° and m.p. 109–110° (m.p. 114–115°, polymorph) respectively, we repeated the work of Wallach[20] and isolated his α-lactam, m.p. 108–109° (m.p. 112–114°, polymorph). Not only the formation of a polymorph on melting but the infrared spectrum showed this to be identical with lactam IX. The so-called β-form may be presumed to be a mixture of V and IX (mixed m.p. 80–86°).

Lactam mixtures from both isophorone[3] and dihydroisophorone[21] have been claimed in patents but no attempt was made to separate the isomers. The lactams were converted to amino acids,[3,21] again giving mixtures.

EXPERIMENTAL[22]

Isophorone oxime. Redistilled isophorone (13.8 g., 0.1 mole) and 8.7 g. (0.125 mole) of hydroxylamine hydrochloride were dissolved in 20 ml. of pyridine and 100 ml. of 95% ethanol. The solution was heated under reflux for 1.5 hr., concentrated to a small volume and diluted with 100 ml. of water. The resultant oil crystallized on standing. The yield of isophorone oxime, m.p. 74–79°, was 15.1 g. (98%).

A systematic fractional crystallization from aqueous methanol gave approximately equal quantities of the less soluble *anti*-oxime I, m.p. 102–104° (lit.[5], m.p. 101.8–102.4°) and the more soluble *syn*-oxime II, m.p. 77–78.5° (lit.[5], m.p. 78.2–78.5°).

4,5-Dihydro-4,4,6-trimethyl-2(3H)-azepinone (III). *anti*-Oxime (15.00 g.) in 150 ml. of polyphosphoric acid was heated at 131–135° for 10 min. The solution was poured into 1 l. of water and continuously extracted overnight with ether. The ether was dried over potassium carbonate and distilled and the residue washed well with water giving 10.74 g. (72%) of enamine lactam III, m.p. 89–91°. Crystallization from aqueous methanol yielded small needles, m.p. 92–93° (lit.[5], m.p. 90.1–90.7°); $\lambda_{max}^{CH_3OH}$ 237 mμ, ε 7,200.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.75; H, 9.97; N, 9.14.

6,7-Dihydro-4,6,6-trimethyl-2(5H)-azepinone (IV). *syn*-Oxime (2.06 g.) in 40 ml. of polyphosphoric acid was heated at 132–135° for 10 min. and the reaction mixture worked up

(17) O. Wallach, *Ann.*, **343**, 40 (1905).

(18) S. F. Birch and E. A. Johnson, *J. Chem. Soc.*, 1493 (1951).

(19) G. B. Payne, *J. Org. Chem.*, **24**, 719 (1959).

(20) O. Wallach, *Ann.*, **346**, 249 (1906).

(21) A. V. Snider and R. C. Morris, U. S. Patent 2,462,008 (Feb. 15, 1949).

(22) We would like to thank R. T. Dillon, H. W. Sause, and their associates for analyses (samples dried overnight at room temperature under high vacuum) and spectra (ultraviolet in methanol, infrared in chloroform). Melting points are uncorrected.

We are indebted to W. M. Selby and R. L. Johnson for hydrogenations and to E. G. Daskalakis and Miss S. Glanville for cellulose column partition chromatography. The solvent systems used for paper chromatography (ascending) were BAW: *n*-butyl alcohol–acetic acid–water 5:2:3, MPW: methyl ethyl ketone–pyridine–water 60:15:25 and PAW: isopropyl alcohol–concd. ammonium hydroxide–water 7:1:2.

as described above. The residue from ether extraction was crystallized three times from petroleum ether (b.p. 60–80°) yielding 0.44 g. (21%) of the α,β-unsaturated lactam IV as long prisms, m.p. 112–113° (lit.[6], m.p. 108.8–109.1°); $\lambda_{max}^{CH_3OH}$ 218 mμ, ε 11,800.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.77, H, 9.98; N, 9.29.

4,4,6-Trimethyl-2-oxohexamethylenimine (V). Lactam III (14.0 g., 0.091 mole) in 50 ml. of acetic acid was hydrogenated over 5% palladium on carbon at room temperature and atmospheric pressure. Hydrogen uptake stopped at 106% of one molar equivalent (3 hr.). The filtrate after removal of catalyst was concentrated to dryness and the residue slurried with a little cold petroleum ether (b.p. 60–80°) to give the saturated lactam V as irregular prisms, 12.8 g. (90%), m.p. 109–111°. A sample was sublimed for analysis at 90° (0.01 mm.), m.p. 110–111°; $\lambda_{max}^{CH_3OH}$ 202.5 mμ, ε 6,500.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.03. Found: C, 69.53; H, 10.88; N, 9.18.

6-Amino-3,3,5-trimethylhexanoic acid (VI). Lactam V (1.55 g., 0.01 mole) in 30 ml. of 48% hydrobromic acid was heated under reflux for 24 hr. The solution was concentrated to dryness, the residue taken up in water and the amino acid liberated by passage through an Amberlite IR-45 ion exchange column. Concentration of the ninhydrin positive fractions to dryness yielded 1.30 g. (75%) of compound VI, m.p. 180–181°. Crystallization from methanol–ethyl acetate gave glistening plates, m.p. 181.5–183°; R_F .79 (BAW), .55 (MPW).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.70; H, 11.08; N, 8.18.

2,4,4-Trimethylhexanedioic acid (VII). Amino acid VI (1.56 g., 0.009 mole) was dissolved in 10 ml. of water and 2.25 ml. of 4*N* sodium hydroxide added. The solution was treated with 1.90 g. (0.012 mole) of potassium permanganate in 35 ml. of water and the temperature maintained at 25–30° by external cooling. After the exothermic reaction had subsided, the mixture was allowed to stand at room temperature for 1 hr., heated on the steam bath for 15 min., and the manganese dioxide removed by filtration through Celite. The filter cake was washed thoroughly with boiling water, the combined filtrates acidified to *p*H 1 with 12*N* hydrochloric acid and the solution continuously extracted overnight with ether. Distillation of the ether gave 1.51 g. of an oily solid; R_F .41 (s), .55 (w), .62 (w) (PAW). The product was purified by partition chromatography on a cellulose column using the PAW system. The fractions containing only R_F .41 material were combined, concentrated to dryness, the residue dissolved in water and passed through a Dowex 50 ion exchange column to convert the ammonium salt to the free acid. Concentration of the effluent to dryness gave 0.74 g. (44%) of acid VII, m.p. 66–69°. Two crystallizations from water yielded chunky prisms, m.p. 72–73.5° (lit.[17], m.p. 68.5–69.5).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.59; H, 8.95.

The acid VII was converted to the acid chloride by refluxing in thionyl chloride and the crude acid chloride treated with aniline in benzene to yield the dianilide VIII, granules from benzene, m.p. 164–165° (lit.,[17] m.p. 162.8–163.3°).

4,6,6-Trimethyl-2-oxohexamethylenimine (IX). Lactam IV (6.54 g., 0.0427 mole) was hydrogenated in 80 ml. of acetic acid over pre-reduced platinum catalyst. Hydrogen uptake stopped after 98% of one molar equivalent had been absorbed (6 hr.). Work-up as described for lactam V gave 4.91 g. (75%) of the desired product, m.p. 107–110°. The analytical sample was sublimed at 90° (0.01 mm.). The material began to melt at 109°, resolidified at 111° and remelted sharply at 114–115°. On cooling and remelting, the sample had m.p. 109–110° with no resolidification; $\lambda_{max}^{CH_3OH}$ 202.5 mμ, ε 6,700.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.03. Found: C, 69.62; H, 10.97; N, 9.39.

6-Amino-3,5,5-trimethylhexanoic acid (X). The procedure described for compound VI was followed using 1.55 g. (0.01 mole) of lactam IX and yielded 1.25 g. (72%) of the desired amino acid, m.p. 150–152°. Crystallization from methanol–ethyl acetate gave fine needles, m.p. 154–155°; R_F .75 (BAW), .58 (MPW).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.48; H, 10.94; N, 8.49.

2,2,4-Trimethylhexanedioic acid (XI). The procedure for the oxidation of compound VI was followed using 1.04 g. (0.006 mole) of amino acid X and 1.27 g. (0.008 mole) of potassium permanganate and yielded 1.03 g. of an oily solid; R_F .41 (s), .59 (w), .70 (tr) (PAW). Purification was carried out as under VIII. The crude acid XI, 0.61 g. (54%), had m.p. 97.5–100°. Crystallization from water gave plates, m.p. 100–101.5° (lit.,[17] m.p. 100.1–100.5°).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.61; H, 8.55.

As described above, the acid XI gave the dianilide XII, small prisms from benzene, m.p. 172–173° (lit.,[17] m.p. 169.4–169.8°).

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Improved Preparations of Fluorenone Oxime and 9-Fluorylamine

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In an investigation on the so-called[1] tetrafluorenylhydrazine,[2] a large quantity of 9-fluorylamine was used. This long-known substance has almost always been prepared from fluorene by successive oxidation, oximation, and reduction, following old procedures.[3] An early suggestion by Wislicenus[4] that fluorenone oxime might better be made by direct nitrosation of fluorene has not been acted on.

Wislicenus' reaction has now been studied, using not only ethereal potassium ethoxide as he recommended, but also other solvents and bases. Results are presented in Table I, where each experiment represents use of 15 g. of pure fluorene. A convenient procedure is described using potassium hydroxide in butyl alcohol.

Reduction of fluorenone oxime in acetic acid with zinc dust, added in portions, as heretofore recommended, was vigorous, messy, and difficult to control, and a considerable amount of acetylaminofluorene was formed. These difficulties were easily overcome by using dilute acetic acid and granu-

(1) It is probable that the compound is really a β-aza analog of α,γ-bisdiphenylene-β-phenylallyl; C. F. Koelsch, *J. Am. Chem. Soc.*, **79**, 4439 (1957).

(2) S. Goldschmidt, *Ann.*, **456**, 161 (1927); Chu and Weismann, *J. Am. Chem. Soc.*, **76**, 3787 (1954).

(3) J. Schmidt and J. Söll, *Ber.*, **40**, 4257 (1907). J. Schmidt and H. Stützel, *ibid.*, **41**, 1243 (1908); C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 1499 (1933); S. Schulman, *J. Org. Chem.*, **14**, 382 (1949).

(4) W. Wislicenus and M. Waldmuller, *Ber.*, **41**, 3334 (1908).

TABLE I

NITROSATION OF FLUORENE

Solvent	Base	Yield of oxime, %
$(C_2H_5)_2O$, C_6H_6[a]	KOC_2H_5	77,[b] 81[c]
C_2H_5OH	KOH	32
C_4H_9OH	KOH	71
C_4H_9OH	KOH[d]	5
C_4H_9OH	KOH[e]	80, 82, 83
C_4H_9OH	NaOH	11
C_4H_9OH	$NaOC_4H_9$	18
$CH_3CH(OC_3H_7)_2$[f]	KOH	30

[a] Wislicenus conditions. [b] No stirring. [c] Vigorous stirring. [d] 50% aqueous solution. [e] Solvent partially distilled after solution of base to remove water. [f] An excellent solvent for many base-catalyzed reactions. C. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Org. Chem.*, 15, 918 (1950).

lated zinc, added all at once, as described in the present note.

EXPERIMENTAL

A solution of 100 g. of 85% potassium hydroxide in 500 ml. of butyl alcohol was boiled for 2 hr. under a 20-cm. column with a fractionating head to remove about 30 ml. of water, butyl alcohol being returned. Then 166 g. of technical fluorene was added. This was followed by dropwise addition during 10 min. of 125 ml. (110 g., calcd. 103 g.) of butyl nitrite,[5] and the mixture was boiled for 10 min. It was then diluted with water (two 500-ml. portions) and partially distilled to remove butyl alcohol. The aqueous residue was cooled and extracted with 100 ml. of ligroin,[6] then acidified with acetic acid. There was obtained 143 g. (73%) of fluorenone oxime, m.p. 175–184°, used without purification for reduction. Recrystallization from acetic acid gave tan needles, m.p. 187–188° corresponding to reported values.

A solution of 150 g. of oxime in 450 ml. of warm acetic acid was diluted with 150 ml. of water and heated to about 100°. Then 110 g. of 20 mesh granulated zinc was added, resulting in a smooth reaction which kept the mixture boiling for about 20 min. The mixture was boiled for an additional 20 min., and then decanted from the little remaining zinc into a hot solution of 450 ml. of hydrochloric acid in 1250 ml. of water. Cooling gave gray needles which were pressed on a filter, washed with three 100-ml. portions of ether, and dried. The resulting 9-fluorylamine hydrochloride formed white needles of excellent purity that darkened at 210°, m.p. 220° dec. (reported, 216–217°); yield 128 g. (76%). The yield was raised to 90% by working over the mother liquors, but this was uneconomical.

9-Fluorylamine, m.p. 60–62° was obtained by treatment with base of the salt. It was interesting to discover that although it could be distilled at 20 mm. in quantities of less than 1 g., attempted distillation of larger quantities resulted in much decomposition with formation of dibiphenylene-ethane, -ethylene, and resin.

(5) Butyl nitrite was prepared by adding a slight excess of iced sulfuric acid in portions to a separatory funnel containing ice and 1 equivalent each of butyl alcohol and concentrated aqueous sodium nitrite, with shaking after each addition. The lower layer was discarded, and the product was washed with a little dilute sodium carbonate and stored over solid potassium carbonate; yield, 94%. Preparation of 2 moles of nearly pure butyl nitrite in this way required only a few minutes, and the product kept well. Samples more than 2 years old gave as good results as fresh ones.

(6) This extraction removed 65 g. of dark oil containing 19 g. of fluorene, 35 g. of crude butylidenefluorene (b.p. 200–240°, m.p. 55°, dibromide m.p. 93–94° dec.) and 8 g. of black resin, probably corresponding to impurities in the technical fluorene used.

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Spectral Evidence for the Structures of the Nitrofluorescein Isomers

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In 1905 Bogert and Wright[1] reported that condensation of 4-nitrophthalic acid with resorcinol yields a nitro derivative of fluorescein. One might expect from this reaction two isomeric products differing in the position of the nitro group (Fig. 1), which would result from the condensation of one or the other carboxyl groups of 4-nitrophthalic acid. The authors, however, have not indicated the existence of such isomers.

In 1942 Coons and co-workers[2] repeated the above reaction with the eventual aim of obtaining a derivative of fluorescein which could be used as a fluorescent label for antibody proteins. They apparently believed the crude product to be 4′-nitrofluorescein (Fig. 1b). In 1950, however, Coons

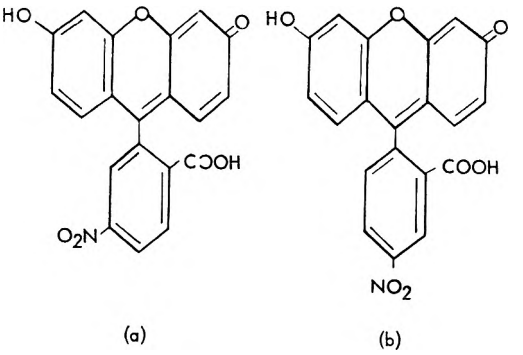

Fig. 1. (a) 5′-nitrofluorescein; (b) 4′-nitrofluorescein

and Kaplan[3] found the product to be a mixture of two isomers and succeeded in separating them by fractional crystallization of the 3,6-diacetates. They called the isomer which was less soluble in benzene-ethanol mixture "nitrofluorescein diacetate I," and the more soluble one "nitrofluorescein diacetate II." Henceforth all other derivatives prepared from these compounds received designations of I or II, respectively. No attempt has been made to determine the position of the nitro group in either isomer, but the separation of the two

(1) R. T. Bogert and R. G. Wright, *J. Am. Chem. Soc.*, 27, 1310 (1905).

(2) A. H. Coons, H. J. Creech, R. N. Jones, and E. Berliner, *J. Immunol.*, 45, 159 (1942).

(3) A. H. Coons and M. H. Kaplan, *J. Exp. Med.*, 91, 1 (1950).

TABLE I

COMPARISON OF INFRARED ABSORPTION BANDS[a]

Nitrofluorescein I	MNX	Nitrofluorescein II	PNX
1032 cm.$^{-1}$ (m)	1032 cm.$^{-1}$ (m)	—	—
Nitrofluorescein I Diacetate	MNX Diacetate	Nitrofluorescein II Diacetate	PNX Diacetate
—	—	703 cm.$^{-1}$ (m)	703 cm.$^{-1}$ (m)
Dichloronitrofluorane I	*p*-$NO_2PhCOOH$	*p*-NO_2PhCHO	
875 cm.$^{-1}$ (s)	872 cm.$^{-1}$ (s)	—	
828 cm.$^{-1}$ (m)	825 cm.$^{-1}$ (w)	—	
742 cm.$^{-1}$ (s)	—	740 cm.$^{-1}$ (s)	
Dichloronitrofluorane II	*m*-$NO_2PhCOOH$	*m*-NO_2PhCHO	
826 cm.$^{-1}$ (v.s.)	826 cm.$^{-1}$ (s)	826 cm.$^{-1}$ (m)	
812 cm.$^{-1}$ (m)	811 cm.$^{-1}$ (m)	812 cm.$^{-1}$ (s)	
735 cm.$^{-1}$ (s)	—	732 cm.$^{-1}$ (s)	

[a] The infrared spectra were determined with a Perkin-Elmer Infracord Spectrophotometer. The samples were Nujol mulls.

isomers was found to be the best way for the purification of the product. De Repentigny and James[4] devised an efficient separation of aminofluoresceins I and II prepared by the catalytic hydrogenation of the nitro derivatives. They used chromatography on a kieselguhr column in phosphate buffer, with a mixture of *n*-butyl alcohol and cyclohexane as eluent. In this system isomer II was found to be the more mobile component.

The structural similarity of the two isomers is reflected in their physical properties, which include absorption spectra—visible as well as infrared. However, it was found in our laboratory that when the nitrofluoresceins were converted into their 3,6-dichloroderivatives, their infrared spectra showed distinct differences in the fingerprint region. Some of these differences proved to be analogous to those in the spectra of structurally related compounds, namely *p*- and *m*-nitrobenzoic acid and *p*- and *m*-nitrobenzaldehyde. On the other hand, spectra of the original nitrofluorescein isomers were compared with those of independently prepared *p*- and *m*-nitrophenyl derivatives of 3,6-dihydroxyxanthene (PNX and MNX, respectively), and of the corresponding diacetates. This comparison is shown in Table I and in Fig. 2.

From these data it is evident that in the region of 810–830 cm.$^{-1}$ the spectrum of dichloronitrofluorane I shows a close similarity to the spectra of *m*-nitrobenzoic acid and *m*-nitrobenzaldehyde, while it is markedly different from the spectra of *p*-nitrobenzoic acid and *p*-nitrobenzaldehyde in that region. On the other hand, the spectrum of dichloronitrofluorane II has a strong band near 870 cm.$^{-1}$, in common with that of *p*-nitrobenzoic acid. Further, the 1000 cm.$^{-1}$ region in the spectrum of nitrofluorescein I is similar to that of *m*-nitrophenyl-3,6-dihydroxyxanthene while near 700 cm.$^{-1}$ there is a similarity between the spectrum of nitrofluorescein II diacetate and that of *p*-nitrophenyl-3,6-dihydroxyxanthene diacetate.

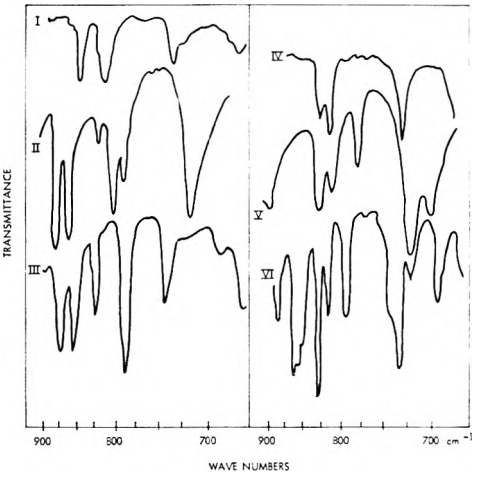

Fig. 2. Infrared spectra. I. *p*-$NO_2C_6H_4CHO$; II. *p*-$NO_2C_6H_4COOH$; III. dichloronitrofluorane I; IV. *m*-$NO_2C_6H_4CHO$; V. *m*-$NO_2C_6H_4COOH$; VI. dichloronitrofluorane II

In the absence of other evidence, the above-mentioned similarities of infrared data suggest that the structure shown in Fig. 1a (5′-nitrofluorescein) can be assigned to nitrofluorescein I, and the structure in Fig. 1b, (4′-nitrofluorescein), to nitrofluorescein II.

EXPERIMENTAL[5]

3,6-Dichloronitrofluorane I. A suspension of 10 g. (0.0265 mole) of nitrofluorescein I in 15 ml. of phosphorus oxychloride was heated to 100° for 0.5 hr. Then 12 g. (0.0517 mole) of phosphorus pentachloride was added, and the mixture maintained at 100° for 0.5 hr. After the evolution of hydrogen chloride had ceased, the mixture was poured slowly and with vigorous stirring into 1.5 l. of water and then heated

(4) J. De Repentigny and A. T. James, *Nature*, **174**, 927 (1954).

(5) The melting points were determined on a Fisher-Johns apparatus and are uncorrected. Microanalyses were done in part by Dr. H. A. Bright at the National Bureau of Standards, Washington, D. C., and in part by Mr. J. F. Alicino, Metuchen, N. J.

to boiling for 10 min. The solid precipitate was filtered with suction, redissolved in 1.5 l. of boiling water, filtered again hot, and dried. The yield of the crude product was 10 g. (92%). Several recrystallizations from 1:1 absolute ethanol-benzene gave a white crystalline solid,[6] m.p. 221–222.5°.

Anal. Calcd. for $C_{20}H_9O_5NCl_2$: C, 58.0; H, 2.2; N, 3.4; Cl, 17.1. Found: C, 58.2; H, 2.6; N, 3.1; Cl, 17.3.

3,6-Dichloronitrofluorane II. This material was prepared from nitrofluorescein II, using a procedure analogous to that described above. The yield of the crude product was 9 g. (82%), and the recrystallized material[5, 7] melted at 215–216°.

Anal. Calcd. for $C_{20}H_9O_5NCl_2$: C, 58.0; H, 2.2; N, 3.4; Cl, 17.1. Found: C, 58.1; H, 2.4; N, 3.1; Cl, 17.0.

3,6-Dihydroxy-9-(m-nitrophenyl)-xanthene (MNX) and its diacetate. A mixture of 3.8 g. (0.025 mole) of *m*-nitrobenzaldehyde and 5.5 g. (0.050 mole) of resorcinol was fused at 195–200° and maintained at that temperature for 3 hr. during which the mixture hardened into a dark mass. The melt was ground in the mortar and heated on a steam bath with 15 ml. of 6*N* hydrochloric acid for 1 hr. The solid was filtered, dissolved in *N* sodium hydroxide, and reprecipitated with *N* hydrochloric acid. The product, m.p. 185–188° dec., showed blue fluorescence in alkaline solution which was quenched on acidification.

One gram of the product was dissolved in 5 ml. of pyridine and treated with 5 ml. of acetic anhydride. The solution was heated on a steam bath for 0.5 hr., left at room temperature overnight, and then poured into iced water. The resulting precipitate was filtered and dried. After the diacetate had been recrystallized several times from acetone-ethanol, it melted at 185–190° dec. It was found to be hygroscopic.

Anal. Calcd. for $C_{23}H_{17}O_7N.1^1/_2H_2O$: C, 61.89; H, 4.51. Found: C, 62.30; H, 4.05.

3,6-Dihydroxy-9-(p-nitrophenyl)-xanthene (PNX) and its diacetate. These compounds were prepared, using *p*-nitrobenzaldehyde and resorcinol as starting materials, by the procedures described above. Both products did not melt below 300° and were hygroscopic.

Anal. (diacetate) Calcd. for $C_{23}H_{17}O_7N.H_2O$: C, 63.16; H, 4.38; N, 3.20. Found: C, 63.68; H, 3.97; N, 3.21.

Acknowledgment. The author wishes to thank Mr. P. Berrigan for his assistance in the preparation of some of the compounds.

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(6) A γ-lactone form was indicated by the strong infrared absorption band at 1760 cm.$^{-1}$ (*cf.* ref. 7), lack of color and fluorescence, and low solubility in water and alkalis.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, Inc., New York, 1954, p. 159.

The Preparation of Oxetanones

JAMES L. HARPER[1,2] AND CHARLES T. LESTER[3]

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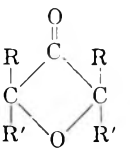
Within recent years several oxetanones have been synthesized.[4] We wish to report that we have completed the synthesis of 2,4-dimethyl-2,4-diethyl-3-oxetanone[5] (Ia) and 2,2,4,4-tetraphenyl-3-oxetanone[4b] (Ib) by the method used to synthesize 2,2,4,4-tetramethyl-3-oxetanone[4c,f] (Ic).



Ia. R = CH_3; R′ = C_2H_5
Ib. R,R′ = C_6H_5
Ic. R,R′ = CH_3

Included in this report are descriptions of the synthesis of 2,2,4,4-tetramethyl-3-oxetanol (II) and 2,2,3,4,4-pentamethyl-3-oxetanol (III). Both of these have been prepared from Ic.

EXPERIMENTAL[6]

The preparation of 2,5-dimethyl-2,5-diethyltetrahydro-3-furanone (IV). The procedure of Richet[7] gave 145 g. (70%) of ketone, b.p. 190–195°, from 209 g. of 3,6-dimethyl-4-octyne-3,6-diol.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.59. Found: C, 70.65; H, 10.75.

The preparation of 2,5-dimethyl-2,5-diethyltetrahydro-furan-3,4-dione (V). Thirty-one grams of IV was added dropwise to a suspension of 24 g. of selenium dioxide in 400 ml. of dioxane and 20 ml. of water. The mixture was stirred and heated to reflux temperature during the addition of IV and for 12 hr. thereafter. The selenium was removed by filtration and the dioxane evaporated under reduced pressure. The residue was dissolved in ether and the solution stored over Drierite. After filtration and evaporation of the solvent, the residue was purified by distillation, yielding 27 g. (68%) of V, b.p., 56–63° at 1 mm.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.31; H, 8.82. Several attempts to prepare V by way of the dibromo derivative[4c] of IV were unsuccessful.

The preparation of 2,4-dimethyl-2,4-diethyl-3-oxetanol-3-carboxylic acid. (VI). A procedure previously described for rearranging a diketone[4c] was followed. This produced 5.7 g. (30%) of VI from 17.7 g. of V. After several crystallizations from carbon tetrachloride, the acid melted at 127–128°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 59.46; H, 8.92; neut. equiv., 202. Found: C, 59.69; H, 8.77; neut. equiv., 200.4.

The preparation of Ia. The lead tetraacetate oxidation of VI was employed as in the preparation of Ic.[4c] A yield of 4.2 g. (60%) of Ia, b.p., 133–134° resulted from the oxidation of 10 g. of VI. Ia solidified on cooling; m.p. of resublimed product, 56–57°.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.87; H, 10.26. Found: C, 70.46; H, 9.90. The oxetanone readily formed a 2,4-dinitrophenylhydrazone derivative,[8] m.p., 135–136°.

(1) Taken from the Ph.D. Dissertation of James L. Harper, Emory University, 1957.

(2) Tennessee Eastman Fellow, 1956–57.

(3) To whom inquiries should be sent.

(4)(a) J. T. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952). (b) G. B. Hoey, D. O. Dean, and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 391 (1955). (c) B. L. Murr, G. B. Hoey, and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 4430 (1955). (d) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955). (e) G. A. Bailey, G. I. Poos, R. Walker, and S. M. Chermeda, *J. Am. Chem. Soc.*, **78**, 4814 (1956). (f) C. Sandris and G. Ourisson, *Bull. Soc. Chim., France*, 958 (1956). (g) J. Maxwell, Ph.D. dissertation, Emory University, 1957.

(5) No effort has been made to resolve this or any related compounds into the various stereoisomers.

(6) All melting and boiling points are uncorrected. Microanalyses were done by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(7)(a) H. Richet, R. Dulon, and G. Dupont, *Bull. Soc. Chim., France*, 693 (1947). (b) H. Richet, *Ann. chim.*, [12] **3**, 317 (1948).

Anal. Calcd. for $C_{15}H_{20}O_5N_4$: N, 16.66. Found: N, 16.33. The infrared spectrogram of Ia showed a strong carbonyl absorption at 5.5 μ. This is characteristic of the spectrograms of the other oxetanones.[4b,c]

Preparation of Ib. Ib has been prepared by the oxidation of tetraphenylallene[9] and tetraphenylacetone.[4b] The synthesis reported here started with the preparation of 128 g. (50% yield) of 1,1,4,4-tetraphenyl-2-butyne-1,4-diol from 225 g. of benzophenone and acetylene by the procedure of Dupont.[10] The procedure of Tichamolow and Druchinin[11] was used to convert 5 g. of the diol into 2.5 g. (50% yield) of 2,2,5,5-tetraphenylfurandione. The procedure described above for the preparation of VI was used to convert 2 g. of the dione into 1.9 g. (93% yield) of 2,2,4,4-tetraphenyl-3-hydroxyoxetane-3-carboxylic acid, m.p., 189–90°.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.52; H, 5.61. Ib was prepared as indicated above for Ia, 1.1 g. (63% yield) from 2 g. of the hydroxy acid. The purified tetraphenyloxetanone melted at 199–200° and did not depress the melting point of a sample prepared by the oxidation of tetraphenylacetone.[4b]

The preparation of II. (a) A solution of 4 g. of Ic in 50 ml. of anhydrous ether was added dropwise with stirring to a suspension of 1 g. of lithium aluminum hydride in 100 ml. of dry ether. After heating at reflux temperature for 1 hr. the excess lithium aluminum hydride was decomposed with water and the two phase system placed in a continuous ether extractor for 8 hr. The ether layer was separated and the ether evaporated at reduced pressure. The crude residue was crystallized from petroleum ether (b.p. 00–00°) to yield 2.3 g., 58% of II, m.p., 101–102°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.61; H, 10.78. Found: C, 64.49; H, 10.89.

(b) A solution of 4 g. of Ic in 50 ml. of dry ether was added dropwise to a solution of isopropylmagnesium bromide made from 3.9 g. of isopropyl bromide and 1 g. of magnesium in 100 ml. of dry ether. The addition was accompanied by a steady evolution of gas. After the addition was plete, the solution was stirred for 15 min. and then 50 ml. of a saturated aqueous solution of ammonium chloride was added. The two phase mixture was placed in a continuous ether extractor for 8 hr. Separation of the ether layer, evaporation of the ether under reduced pressure, and crystallization of the residue from petroleum ether gave 0.8 g. (20%) of II, m.p. and mixture m.p. with sample prepared as described in (a) above, 101–102°.

The preparation of III. In a manner identical with the procedure described in (b) above 4 g. of Ic and an excess of methylmagnesium iodide were used to prepare 1.1 g., (25% yield) of III, m.p., 129–130°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.66; H, 11.11. Found: C, 66.66; H, 11.17.

Acknowledgment. We wish to thank the Tennessee Eastman Company and the Richard K. Whitehead Foundation for their generous support of this research. We also thank the Air Reduction Chemical Company for generously supplying us with the dimethylhexynediol and dimethyloctynediol used in the synthesis of the oxetanones.

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(8) S. M. McElvain, *The Characterization of Organic Compounds*, Macmillan, New York, 1953, p. 205.

(9)(a) D. Vorlander and C. Siebert, *Ber.*, **39**, 1024 (1906). (b) D. Vorlander and P. Weinstein, *Ber.* **56B**, 1122 (1923).

(10) G. Dupont, Compt. rend., **150**, 1524 (1910).

(11) P. A. Tichamolow and A. E. Druchinin, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 869–872 (1937).

Derivatives of Tetrahydropyran

C. P. J. GLAUDEMANS

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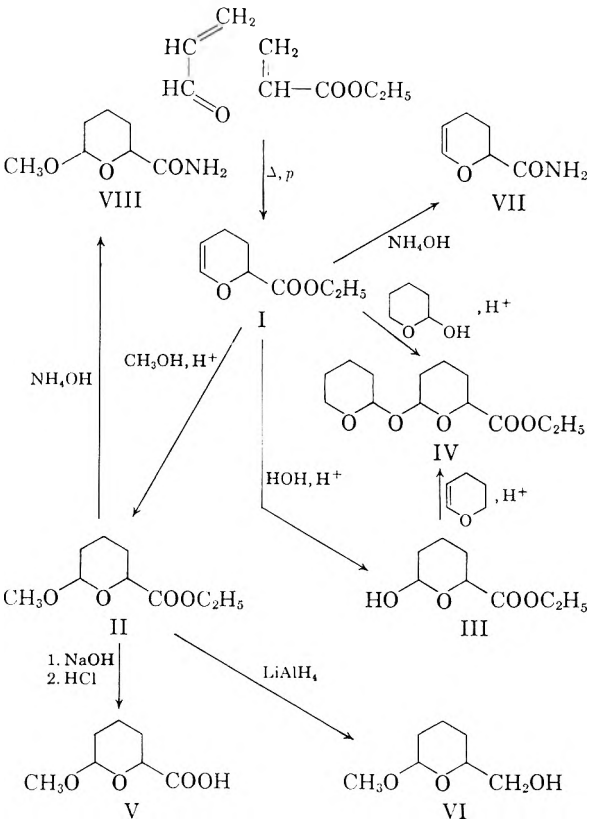
In connection with some kinetic studies, several derivatives of tetrahydropyran were desired. Their preparations are described below.

All derivatives were prepared from ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate which was obtained in poor yield, similarly to the method of Smith *et al.*,[1] from the Diels-Alder addition of ethyl acrylate to acrolein. The structure of the addition product was established by 1) carbon-hydrogen analysis, and by 2) conversion to the known amide.[1]

In the 3,4-dihydro-2*H*-pyran series, it is known that addition of ROH to the $\Delta^{5,6}$-double bond yields a product having the alkoxy radical attached to the C_6, the hydrogen radical attached to the C_5.[2] No structure proof of the herein described derivatives was undertaken, but when VI was hydrolyzed with aqueous sulfuric acid (1*N*), the resulting product had a positive Fehling reaction, indicating



(1) C. W. Smith, D. G. Norton, S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5270 (1951).

(2) R. Paul, *Bull. Soc. Chim.* [5], , 971 (1934); L. E. Schniepp and H. H. Geller, *J. Am. Chem Soc.*, **68**, 1646 (1946); G. F. Woods, and D. N. Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947); G. F. Woods and H. Sanders, *J. Am. Chem. Soc.*, **68**, 2111 (1946).

that in II, V, and VI the methoxy group is attached to the C_6. The fact that *IV* was obtained both by the addition of 2,3-dihydro-4*H*-pyran to *III*, as well as by the addition of tetrahydro-2-hydroxypyran to *I*, is additional evidence for the type of link shown in *IV*.

I has been obtained by Whetstone and Ballard[3] by the oxidation of 3,4-dihydro-2*H*-pyran-2-carboxaldehyde with silver oxide followed by treatment of the silver salt with ethyl iodide.

EXPERIMENTAL

Preparation of ethyl 3,4-dihydro-2H-pyran-2-carboxylate (I). Ethyl acrylate (160 ml.), acrolein (92 ml.), and hydroquinone (2.52 g.) were heated in a closed vessel (initial pressure 13.5 atm.) to 189° and kept at this temperature for 78 min. The products were crudely distilled. Fractional redistillation yielded ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate (I) b.p. 73.5–76°/7 mm. (7 ml.). Infrared analysis showed the presence of an ester (doublet) and an isolated double bond (1650 $cm.^{-1}$).

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.54; H, 7.69. Found: C, 61.50; H, 8.21.

The derived 3,4-dihydro-2*H*-pyran-2-carboxamide (VII) had a m.p. of 114–114.5° (hot stage, sublimation).

Preparation of ethyl tetrahydro-6-methoxypyran-2-carboxylate (II). Ice cold *I* (6 ml.) was mixed with ice cold methanol (2.5 ml.) and concd. aqueous hydrochloric acid was added (1 drop). After 5 hr. (3 hr. at room temperature) the mixture was neutralized (sodium bicarbonate), filtered, and distilled. The ethyl tetrahydro-6-methoxypyran-2-carboxylate (II) boiled at 81°–81.5°/2.5 mm., n_D^{25} 1.4422; yield, approximately 6 ml.

The infrared spectrum retained the ester doublet, and showed the absence of the double bond.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.45; H, 8.52. Found: C, 57.25; H, 8.76.

The derived tetrahydro-6-methoxypyran-2-carboxamide (VIII) had a m.p. of 161–162° (hot stage). Profound sublimation started around 130°, the sublimed crystals melting at 159°–160°.

Preparation of ethyl tetrahydro-6-hydroxypyran-2-carboxylate (III). Compound *I* (8 ml.) was mixed with water (14 ml.), acetone (10 ml.), tetrahydrofuran (30 ml.), and concd. aqueous hydrochloric acid (1.7 ml.). It was stirred for 1 hr. and deionized by Dowex 1X-4 anion exchange resin (bicarbonate form). Concentration *in vacuo* gave an oil. Distillation yielded ethyl tetrahydro-6-hydroxypyran-2-carboxylate (III) b.p. 114–115.7°/1 mm. (1.3 ml.), n_D^{24} 1.4586. The infrared spectrum showed hydroxyl, no water, no double bond.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.20; H, 8.05. Found: C, 54.89; H, 8.17% H.

Preparation of ethyl tetrahydro-6-[tetrahydropyran-2-oxy]-pyran-2-carboxylate (IV). Compound *III* (1.1 ml.) was mixed with 2,3 dihydro-4*H*-pyran (1.3 ml.) and concd. aqueous hydrochloric acid was added (1 drop). The mixture was left at room temperature for 3 hr., neutralized with aqueous sodium bicarbonate, and distilled to yield ethyl tetrahydro-6-[tetrahydropyran-2-oxy]pyran-2-carboxylate (IV) b.p. 142–144°/1 mm., n_D^{25} 1.4650; yield: approximately 1 ml.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.48; H, 8.53. Found: C, 60.25; H, 8.32% H.

The infrared spectrum showed no hydroxyl, no double bond, and an ester (doublet). When *I* was allowed to react with tetrahydro-2-hydroxypyran (acid catalysis), a product was obtained with boiling point 145–148°/2 mm., which had an infrared spectrum identical with that of *IV*, n_D^{25} 1.4648.

Preparation of tetrahydro-6-methoxypyran-2-carboxylic acid (V). Saponification of *II* (1 ml.) with sodium hydroxide (0.25 g.) in ethanol water (3 ml., 50/50 v./v.) for 1 hr., followed by acidification (6*N* hydrochloric acid), dilution with water (25 ml.), extraction by ether, and concentration of the dried (with sodium sulfate) ether layer, yielded an oil. Paper chromatography of the product, tetrahydro-6-methoxypyran-2-carboxylic acid, in ethyl acetate–acetic acid–formic acid–water (18:3:1:4) followed by spraying with an aqueous solution of Chlorophenol Red (0.8%), showed a bright yellow spot, $R_f = 0.80$.

Preparation of tetrahydro-6-methoxypyran-2-methanol (VI). Compound *II* (6 ml.) dissolved in absolute tetrahydrofuran (10 ml.) was added dropwise to a solution-suspension of lithium aluminum hydride (10 g.) in absolute tetrahydrofuran (160 ml.) while stirring. Stirring was continued overnight, and the mixture was refluxed for 6 hr. The hydride was decomposed by the dropwise addition of ethyl acetate followed by aqueous tetrahydrofuran to the reaction mixture at room temperature. Water was added (total of 450 ml.) and the slurry was filtered. Tetrahydrofuran was removed *in vacuo* and the aqueous solution was adjusted to 2*N* with sodium hydroxide, left for 2 hr. and continuously extracted with ether (4 days). The dried extract was concentrated *in vacuo* and the residual oil was distilled to yield tetrahydro-6-methoxypyran-2-methanol (VI). b.p. 70–75°/1.8 mm. (1.25 ml.), n_D^{25} 1.4535.

Anal. Calcd. for $C_7H_{14}O_3$: C, 56.55; H, 9.58. Found: C, 56.53; H, 9.53.

The infrared spectrum showed a hydroxyl peak, no water and no carbonyl.

When VI was heated on the steambath with aqueous sulfuric acid (1*N*) for 2 hr., the resulting hydrolysate had a positive Fehling reaction.

Acknowledgment. Technical assistance by Messrs. E. H. Hicks and G. F. Goodley is gratefully acknowledged.

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(3) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, 73, 5280 (1951).

Cyclization of 1,5-Diphenyl-1,3,5-pentanetrione with Ethyl Oxalate. 3,5-Dibenzoyl-1,2,4-cyclopentanetrione and Its Quinoxaline[1]

ROBLEY J. LIGHT[2] AND CHARLES R. HAUSER

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Recently,[3,4] the terminal methyl group of benzoylacetone was benzoylated to form triketone I. This triketone has now been cyclized with ethyl oxalate by sodium ethoxide in refluxing ethanol to

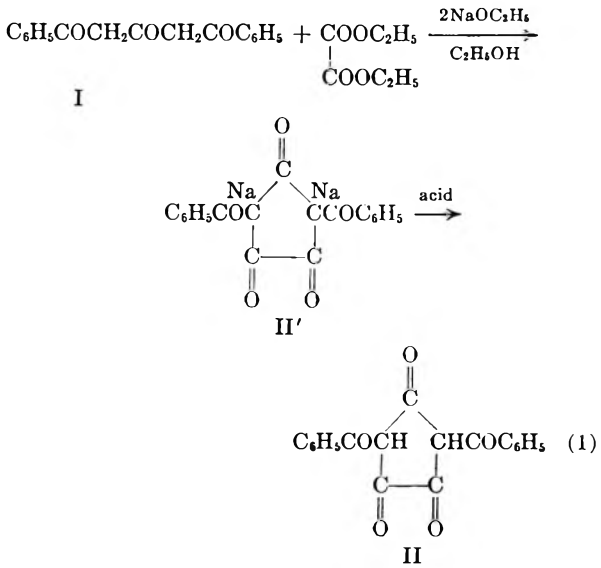
(1) Supported in part by Grant CY-4455 from the National Institutes of Health.

(2) National Science Foundation Predoctoral Fellow, 1958–60.

(3) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, 80, 6360 (1958).

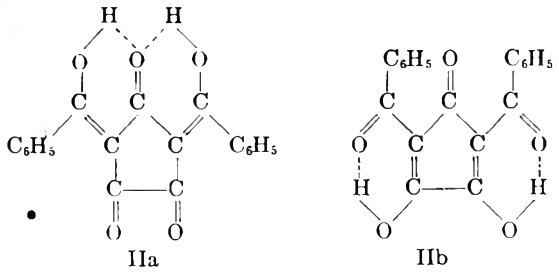
(4) R. J. Light and C. R. Hauser, *J. Org. Chem.*, 25, 538 (1960).

give II. The reaction presumably involves a two-fold Claisen type of acylation to produce the disodio salt II′, from which II is liberated by acid (Equation 1).



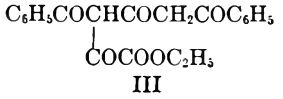
(1)

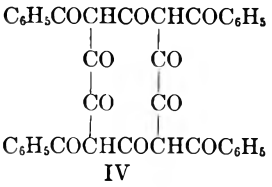
The infrared spectrum of II indicated an enol-chelate type of structure similar to that proposed for ordinary β-diketones[5] and for 1,3,5-triketones.[4] Two possible tautomers would be IIa and IIb. The compound showed strong infrared bands at 6.29 μ and 6.51 μ, characteristic of such an enol-chelate ring,[4,5] and a strong band at 5.82 μ containing a shoulder at 5.76 μ. It is not clear whether this last absorption would arise from the α-diketone structure shown in IIa or the single free carbonyl shown in IIb, either of which are conjugated with the enol-chelate rings. Five-membered ring ketones absorb in the region 5.71–5.75 μ, but are shifted to 5.83 μ on conjugation with a double bond.[6] Some cyclic α-diketones were observed to produce a double band near 5.65 μ, in contrast to a single absorption band found at 5.78–5.85 μ for other α-diketones,[7] but none of these diketones were conjugated.



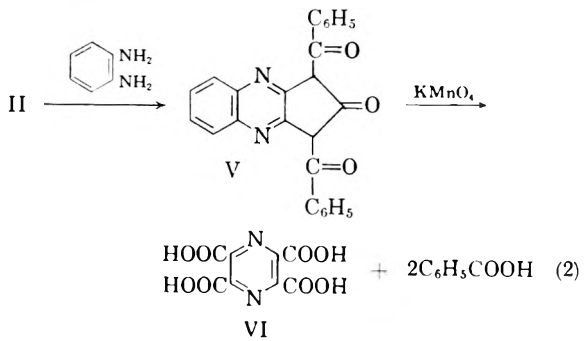
That the compound isolated was the cyclic product II (or a tautomer) was supported by its analysis, molecular weight, and neutralization equivalent. The last determination gave a value of one half of the molecular weight indicating that the dilute sodium hydroxide employed converted II to its disodio salt II′ (see equation 1). The acidity of II was also demonstrated by its solubility in sodium bicarbonate, in which triketone I was insoluble.

These data were not in agreement with the possible monoacylation product III, the anion of which was presumably formed as an intermediate, or with the unlikely ten-membered cyclic product IV which would have the same calculated analysis as II but twice the molecular weight. Neither were the data in agreement with products that might have arisen from two molecules of I and one of ethyl oxalate or from one molecule of I and two of the ester.





The structure of the product was confirmed as II by further cyclization with *o*-phenylenediamine to form quinoxaline V, which was oxidized to give pyrazinetetracarboxylic acid (VI) and benzoic acid (Equation 2).



(2)

The tetracarboxylic acid VI was shown to be identical with an authentic sample of this compound prepared by the oxidation of phenazine.

A cyclization similar to that shown in Equation 1 has previously been realized with dicarbethoxyacetone and ethyl oxalate by sodium ethoxide to form the ditriacyl derivative VII.[8] Also certain ketones have been condensed with excess ethyl oxalate to form glyoxalates of 1,2,4-cyclopentanetriones.[9]

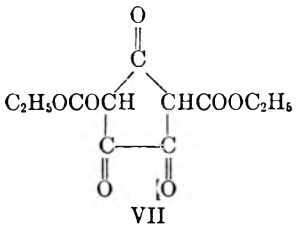
(5) See L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, New York, N. Y., 1958, p. 142.

(6) See ref. (5), pp. 148–9.

(7) K. Alder, H. K. Schäfer, H. Esser, H. Krieger, and R. Reubke, *Ann.*, **593**, 23 (1955). See also ref. (5), p. 141.

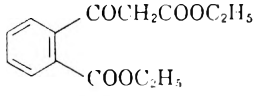
(8) E. Rimini, *Gazz. chim. ital.*, **26**, **2**, 374 (1896); W. Wislicenus and F. Melms, *Ann.*, **436**, 101 (1924); J. H. Boothe, R. G. Wilkinson, S. Kushner, and J. H. Williams, *J. Am. Chem. Soc.* **75**, 1732 (1953).

(9) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 84 (1954).

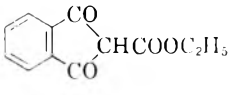


VII

A related acylation not involving ethyl oxalate is the intramolecular cyclization of VIII by sodium ethoxide to form IX.[10]

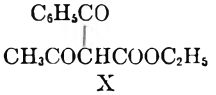


VIII



IX

Such acylations of carbanions of dicarbonyl compounds with ethyl ester groups to form triacyl derivatives are of interest, since the equilibrium between most open chain di- and triacyl carbanions in the presence of ordinary ethyl esters, sodium ethoxide, and ethanol is generally on the side of the diacyl anion. For example, triacyl compound X, which may be prepared by the benzoylation of the anion of acetoacetic ester with benzoyl chloride, undergoes cleavage with ethanolic sodium ethoxide to form the anion of ethyl benzoylacetate and ethyl acetate.[11]



X

EXPERIMENTAL[12]

3,5-Dibenzoyl-1,2,4-cyclopentanetrione (II). A solution of 0.15 mole of sodium ethoxide was prepared by adding 3.5 g. (0.15 g.-atom) of sodium to 250 ml. of absolute ethanol in a 500-ml. three-necked flask equipped with a stirrer, a water condenser, and a Drierite drying tube. To this stirred solution was added 10 g. (0.0375 mole) of 1,5-diphenyl-1,3,5-pentanetrione (I) as a solid through a powder funnel, followed by 5.5 g. (0.0375 mole) of ethyl oxalate. The reaction mixture was refluxed for 5 hr., and most (about 200 ml.) of the ethanol was then removed by distillation. The residual slurry was poured into 500 ml. of ice and water containing 20 ml. of concd. hydrochloric acid, and the resulting suspension was shaken with ether in a separatory funnel. The undissolved solid was then removed by filtration and was combined with the ether layer from the filtrate. This suspension was shaken with aqueous sodium bicarbonate, dissolving all the solid. The bicarbonate layer was separated and washed with ether, and the ethereal layers were combined and dried over Drierite. The solvent was removed and the residue was recrystallized from 95% ethanol to yield 2.8 g. (28%) of recovered I, m.p. 110–114° (recorded[4] m.p. 106–110° and 110–115°). The aqueous bicarbonate layer was acidified and the precipitate collected on a Büchner funnel and dried in a vacuum desiccator to yield 5.4 g. (45%) of crude II, m.p. 140–150°. Recrystallization from acetone produced 4.1 g. (34%) of II, m.p. 154–156°. Essentially the same recovery was obtained by recrystallization of the crude product from 95% ethanol, but decomposition occurred slowly in hot ethanol. Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 71.25; H, 3.78; mol. wt., 320; neut. equiv., 160.2. Found: C, 71.34; H, 3.90; mol. wt., 279, 280, 317, 333, av. 302 (Rast); neut. equiv., 160.5, 160.1.

The infrared spectrum in the carbonyl and enol-chelate region[5] showed strong bands at 5.82 μ, 6.29 μ, and 6.51 μ, and a shoulder at 5.76 μ. Only a weak band was present at 2.82 μ, attributable to moisture in the potassium bromide. Ultraviolet spectrum: λ_{max} = 241 mμ, 298 mμ, 351 mμ; log ϵ = 4.33, 4.07, 4.22; λ_{min} = 267 mμ, 315 mμ; log ϵ = 3.98, 4.05. A red color was produced with ethanolic ferric nitrate.

Approximately the same yield of II was obtained when the reaction was repeated employing 0.113 mole of sodium ethoxide. The yield was not improved by removing the ethanol as an azeotrope with benzene before acidification. The usual forcing conditions employing excess of the ester were not studied.

1,3-Dibenzoyl-2-oxo-cyclopenteno[4,5-b]quinoxaline (V). A 1.5-g. (0.0047 mole) sample of 2,5-dibenzoyl-1,3,4-cyclopentanetrione (II) was dissolved in 45 ml. of hot 95% ethanol. To this solution was added rapidly a solution of 0.6 g. (0.006 mole) of *o*-phenylenediamine in 30 ml. of hot 95% ethanol. The reaction mixture was heated on the steam bath for several minutes, allowed to cool slowly to room temperature, and stored in the refrigerator overnight. The solution was filtered, and the solid was recrystallized from benzene to give 0.6 g. (32%) of V, m.p. 268–271°. An analytical sample melted at 271–274°.

Anal. Calcd. for $C_{25}H_{16}N_2O_3$: C, 76.52; H, 4.11; N, 7.14. Found: C, 76.40; H, 4.38; N, 7.15.

The infrared spectrum in the carbonyl and enol-chelate region[5] showed a medium band at 5.97 μ, and strong bands at 6.15 μ and 6.34 μ. Only a weak band was present at 2.85 μ, attributable to moisture in the potassium bromide. Ultraviolet spectrum: λ_{max} = 301 mμ; log ϵ = 4.44; λ_{min} = 265 mμ; log ϵ = 4.23.

Oxidation of quinoxaline V. A hot solution of 5.2 g. (0.033 mole) of potassium permanganate in 25 ml. of water was added dropwise to a slurry of 1.2 g. (0.003 mole) of V in 20 ml. of hot aqueous 5% potassium hydroxide. The last of the permanganate was rinsed in with 20 ml. of water, and the mixture was heated on the steam bath for 2 hr. After adding a few drops of ethanol to destroy the excess permanganate, the mixture was filtered and the solid manganese dioxide was washed with two 20-ml. portions of water. The filtrate was concentrated to 15 ml. on the hot plate, cooled, and acidified dropwise with concentrated hydrochloric acid. The precipitate, which consisted of a mixture of benzoic acid and the dipotassio salt of VI,[13] was collected on a filter funnel and washed with water. The benzoic acid was removed by suspending the solid in hot 95% ethanol and filtering. The solvent was removed from the ethanol filtrate leaving 0.65 g. (90%) of crude benzoic acid, m.p. 116–121°. One recrystallization from water raised the melting point to 120–121°, which was not depressed by mixing with an authentic sample of benzoic acid.

The solid that was not dissolved in hot ethanol was recrystallized from 10 ml. of 20% hydrochloric acid to yield 0.15 g. (20%) of pyrazinetetracarboxylic acid (VI), m.p. 195-

(10) W. Wislicenus, *Ann.*, 246, 349 (1888).

(11) See C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, I, 298 (1942).

(12) Melting points were taken on a Fisher-Johns melting point apparatus which had been calibrated with melting point standards. Infrared spectra were determined with a Perkin-Elmer Infracord by the potassium bromide pellet method. Ultraviolet spectra were determined with a Warren Spectracord spectrophotometer using 2 × 10^{-5} *M* solutions in 95% ethanol with a 1-cm. sample cell. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(13) F. D. Chattaway and W. G. Humphrey, *J. Chem. Soc.*, 645 (1929).

199° dec. (reported[13] m.p. 205° dec.). The melting point was not depressed on admixture with an authentic sample of the acid prepared as described below, and the infrared spectra of the two samples were identical.

Independent synthesis of pyrazinetetracarboxylic acid (VI). A hot solution of 20.6 g. (0.13 mole) of potassium permanganate in 100 ml. of water was added dropwise to a slurry of 1.8 g. (0.01 mole) of phenazine in 20 ml. of hot water containing one pellet of potassium hydroxide. The reaction and work up were carried out as described above for the oxidation of V, except that the filtrate and washings from the manganese dioxide were concentrated to only 50 ml. before acidification. The crude precipitate was washed with ethanol and recrystallized from 25 ml. of 20% hydrochloric acid to yield 0.7 g. (27%) of VI, m.p. 199–202° dec. (reported[13] m.p. 205° dec.).

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The Synthesis of Substituted Indanes by the Cyclialkylation Reaction

L. AMES, E. CHAITMAN, AND F. GRANT

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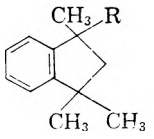
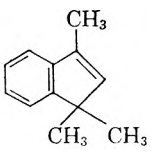
The cyclialkylation reaction of Bruson and coworkers has recently provided a unique approach to the synthesis of highly substituted β-tetralones.[1] In this manner, 1,1,4,4-tetramethyltetralone has been prepared by the alkylation of benzene with 2,2,5,5-tetramethyltetrahydrofuranone. We have been interested in the synthesis of *ortho*-substituted ditertiaryalkylbenzenes from the oxidative cleavage products of compounds of this type. In this connection, it was of interest to determine whether the isomeric ketone of unknown structure also formed in the above condensation could provide an additional source of starting material for the preparation of these substituted benzenes. To this end, we have obtained evidence which, together with the data previously presented, confirms the formulation of this compound as 1,3,3-trimethyl-1-acetylindane (I).



I. R = $COCH_3$
II. R = COOH
III. R = $OCOCH_3$
IV. R = OH



V

$C_6H_5C(CH_3)_2CH_2COC(CH_3)_2OH$

VI

$C_6H_5C(CH_3)_2CH_2C(CH_3)(OH)COCH_3$

VII

The basic permanganate oxidation of the isomeric ketone has been reported to result in a crystalline monocarboxylic acid—$C_{13}H_{16}O_2$.[1] We have synthesized 1,3,3-trimethyl-1-indanecarboxylic acid (II) and demonstrated its identity with this oxidation product. The sequence of reactions leading to this acid are as follows. Neophylmagnesium chloride was carbonated to yield β-phenylisovaleric acid. Treatment with thionyl chloride and ring closure with aluminum chloride resulted in 3,3-dimethylindan-1-one, which added methylmagnesium iodide to give, after dehydration, 1,1,3-trimethylindene (V). Treatment of V with formic acid in sulfuric acid, following the procedure of Koch and Haaf,[2] resulted in the desired acid. The latter reaction appears to be the first application of this method to the carboxylation of an aryl-substituted double bond.

Additional support for structure I for the isomeric ketone came from the perbenzoic acid oxidation of this material. The acetate (III) was detected in the infrared spectrum of the crude oxidation mixture but was not isolated. 1,1,3-Trimethylindene (V), the dehydration product of the intermediate tertiary alcohol (IV), was isolated and identified as a product of the saponification of the oxidation mixture.

The origin of the isomeric ketone can be rationalized by a rearrangement and cyclization of the ketol (VI) which has previously been isolated and identified as a product of the cyclialkylation reaction and which is the logical precursor of the 1,1,4,4-tetramethyltetralone. Rearrangement of the type VI to VII has been described in a closely related system.[3]

EXPERIMENTAL[4]

β-Phenylisovaleric acid. The Grignard reagent prepared from 338 g. (2.0 moles) of neophyl chloride (b.p. 93°–94°/10 mm.) and 50.0 g. (2.0 moles) of magnesium turnings in 750 cc. of anhydrous ether was poured onto an excess of Dry Ice. The acid was isolated and recrystallized from 1:1 benzene-petroleum ether (b.p. 30–60°) yielding 144.3 g. (41%) of β-phenylisovaleric acid, m.p. 57°–58° (lit.,[5] m.p. 58°–58.5°).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.14; H, 7.92. Found: C, 74.84; H, 7.93.

3,3-Dimethylindan-1-one. The acid chloride derived by heating at reflux for 3 hr., 125 g. (0.70 mole) of β-phenylisovaleric acid and 100 g. (0.84 mole) of thionyl chloride, followed by removal of the excess thionyl chloride, was heated at reflux for 15 hr. with 93.3 g. (0.70 mole) of anhydrous aluminum chloride in 200 cc. of 3:1 petroleum ether (b.p. 30°–60°)-carbon disulfide. Water was added and the neutral material isolated and fractionally distilled. A 53% yield (59.0 g.) of 3,3-dimethylindanone, b.p. 86°–89°/1.7 mm., was obtained. The semicarbazone melted at 205°–206° (lit.,[6] m.p. 205°–207°).

Anal. Calcd. for $C_{12}H_{15}N_3O$: N, 19.34. Found: N, 19.58.

1,1,3-Trimethylindene. A dry ethereal solution of 48.0 g. (0.30 mole) of 3,3-dimethylindan-1-one was added dropwise with stirring to the Grignard reagent prepared from 56 g. (0.40 mole) of methyl iodide and 9.7 g. (0.40 mole) of mag-

(1) H. A. Bruson, F. W. Grant, and E. Bobko, *J. Am. Chem. Soc.*, **80**, 3633 (1958).

(2) H. Koch and W. Haaf, *Angew. Chem.*, **70**, 311 (1958).

(3) A. M. Khaletskii, *J. Gen. Chem.* (*U.S.S.R.*) **15**, 524 (1945), *Chem. Abstr.*, **40**, 4696 (1946).

(4) All melting and boiling points are uncorrected.

(5) A. Hoffman, *J. Am. Chem. Soc.*, **51**, 2545 (1929).

(6) K. v. Auwers, *Ber.*, **54**, 994 (1921).

nesium turnings in anhydrous ether. The tertiary alcohol formed was not isolated but dehydrated during the workup. 1,1,3-Trimethylindene (43.2 g., 98%) was recovered by distillation, b.p. 58°–62°/1.6 mm. (lit.,[7] b.p. 94°/15 mm.).

Anal. Calcd. for $C_{12}H_{14}$: C, 91.10; H, 8.90. Found: C, 90.97; H, 9.03.

1,3,3-Trimethyl-1-indanecarboxylic acid. 1,1,3-Trimethylindene (2.0 g., 0.013 mole) and 5 g. of 90% formic acid were added to 45 g. of concd. sulfuric acid at 0°–5°. After 1 hr. at 0°–5° the dark red solution was poured into water. 1,3,3-Trimethyl-1-indanecarboxylic acid (0.3 g., 12%) was isolated and recrystallized from petroleum ether to m.p. 129°–130°. This material had an infrared spectrum identical with, and did not depress the melting point of the acid, m.p. 131°–132°, obtained by the permanganate oxidation of the isomeric ketone.[1]

Peracid oxidation of the isomeric ketone. The isomeric ketone (40 g., 0.20 mole) was added to 23.2 g. (0.17 mole) of perbenzoic acid in 350 cc. of chloroform at 0°–5° and kept in the dark at this temperature for 1 week. The solution was allowed to stand for an additional month at 20° in the dark. The crude oxidation product showed a peak at 5.73 μ in its infrared spectrum consistent with the presence of ester carbonyl absorption. Saponification of 16.9 g. of the crude oxidation mixture and fractional distillation of the neutral products resulted in 2.9 g. (15%) of 1,3,3-trimethylindene, b.p. 110°–120°/18 mm., identified by comparison of its infrared spectrum with that of the synthetic sample prepared above.

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(7) J. Colonge and P. Garnier, *Bull. soc. chim. France*, 436, 1948.

Isolation of the 1,4- and the 6,3-Lactones of D-Glucaric Acid[1]

R. J. Bose, T. L. Hullar, Bertha A. Lewis, and F. Smith

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Oxidation of D-glucose or starch with nitric acid yields D-glucaric acid (saccharic acid)[2] which is readily isolated as the acid potassium salt.[2,3] Removal of the potassium ions followed by evaporation afforded the monolactone of D-glucaric acid.[2] This product which was originally thought to be the 6,3-lactone[4] and which played a major role in the conversion of D-glucose into L-gulose[5] was subsequently proved[6] to be a mixture by isolating and proving the structure of the two lactones, the 1,4-lactone having m.p. 98° and $[\alpha]_D$ + 34°, and the 6,3-lactone having m.p. 149° and $[\alpha]_D$ + 45°.[7] The separation was facilitated by making use of the fact that the 1,4-lactone crystallizes as a monohydrate which is readily soluble in acetone, whereas the 6,3-lactone which crystallizes in the anhydrous form is almost insoluble in acetone.

More recently the 1,4-lactone has been shown to have anti-β-D-glucuronidase activity[8] and, as it may be a useful chemotherapeutic agent in the cure of bladder cancer,[9] there have been many requests for samples of the D-glucaro-1,4-lactone. This publication is prompted by our reinvestigation of the preparation of the 1,4-monolactone which has brought to light some simplification in procedure and an improvement in the yield. The improvement in yield has resulted from making use of the observation that when an aqueous solution of potassium hydrogen D-glucarate is boiled for thirty minutes the salt of the 1,4-lactone is generated,[10] whereas the simplification follows from the use of a cation exchange resin to remove the potassium ions from the boiled solution containing the potassium salt of D-glucaro-1,4-lactone.[11]

EXPERIMENTAL

Preparation of D-glucaro-1,4- and 6,3-lactones. Corn starch or soluble starch was oxidized to D-glucaric acid by nitric acid. Nitric acid (1 l. of concentrated acid in 2 l. of water) was added to the starch (220 g.) in a 4-l. glass beaker. A few crystals of sodium nitrite were added to catalyze the oxidation and the solution was heated on the steam bath. The beaker was removed from the heat during the vigorous evolution of brown gases which usually occurred after about 2 to 4 hr. of heating. When the gas evolution had subsided, the brownish yellow solution was heated on the steam bath for 16 to 18 hr., the solution being allowed to evaporate to about a quarter of the original volume. The solution, which was light yellow, was diluted with water (0.5 volume) and concentrated under reduced pressure (bath temp. 50–55°), water being added repeatedly to remove residual nitric acid. After most of the nitric acid was removed, the yellow solution was neutralized with solid potassium carbonate and then acidified to *p*H 4 with acetic acid. The potassium hydrogen D-glucarate was allowed to crystallize for 3 days at 5°, recovered by filtration, and dried in the air (yield, 130 g.). The crude salt was recrystallized from boiling water,[12] charcoal being added to effect decolorization; yield 90 g., $[\alpha]_D^{25}$ +5.2° (c 1.3, water).

A suspension of pure, recrystallized potassium hydrogen D-glucarate (129 g.) in water (525 ml.) was gently refluxed for 35 min[10]. The solution which had become yellow was

(1) Paper No. 4553, Scientific Journal Series, Minnesota Agricultural Experiment Station.

(2) O. Sohst and B. Tollens, *Ann.*, **245**, 1 (1888).

(3) E. Fischer, *Ber.*, **23**, 2611 (1890).

(4) K. Rehorst and H. Scholz, *Ber.*, **69**, 520 (1936).

(5) E. Fischer and O. Piloty, *Ber.*, **24**, 521 (1891).

(6) F. Smith, *J. Chem. Soc.*, 571, 633 (1944).

(7) *Cf.* M. Sutter and T. Reichstein, *Helv. Chim. Acta*, **21**, 1210 (1938).

(8) G. A. Levvy and C. A. Marsh, *Advances in Carbohydrate Chem.*, **14**, 413 (1959).

(9) E. Boyland, D. M. Wallace and D. C. Williams, *Brit. J. Cancer*, **11**, 578 (1957); E. Boyland, *Ciba Foundation Symposium* (*Carcinogenesis Mechanisms of Action*) **1958**, 218.

(10) G. A. Levvy, *Biochem. J.*, **52**, 464 (1952).

(11) *Cf.* H. Zinner and W. Fischer, *Ber.*, **89**, 1503 (1956).

(12) The heating in boiling water should be as brief as possible, otherwise the potassium hydrogen glucarate undergoes transformation.

cooled and kept at 5° for 12 hr. The liquid was separated by filtration, and the unchanged crystalline potassium hydrogen D-glucarate was suspended in water (300 ml.) and treated as before. The crystals from the second treatment were recovered and again treated with water (300 ml.) as above. The crystalline potassium hydrogen D-glucarate (18.0 g.) which separated after this third heating and cooling was not treated further.

The yellow solutions from the above three heat treatments of the potassium hydrogen salt were combined and deionized by passing through a column of Amberlite IR-120[13] cation exchange resin (H form). The acidic effluent from the cation exchange column was concentrated under reduced pressure (bath temp. 30–35°). The resulting thick, yellow sirup was stirred with a 1:1 mixture of water and acetone (50 ml.) and concentrated in an air stream. Crystallization commenced shortly after the heavy, viscous sirup was seeded with a mixture of D-glucaro-1,4- and 6,3-lactones. The crystallization was continued for 4 days under the air stream. The crystalline matrix was triturated with acetone (100 ml.) and the crystalline 6,3-lactone separated by filtration and washed with acetone (300 ml.). The yield of D-glucaro-6,3-lactone was 15.2 g. (17.6% of the potassium salt converted); m.p. 138–142°, $[\alpha]_D^{23}$ +58.5° (c 1.3, water) changing to $[\alpha]_D^{27}$ +23.7° (87 days).

The combined yellow acetone filtrate and washings were concentrated in an air stream and seeded with the 1,4-lactone. Crystallization was allowed to proceed to completion. After about 4 weeks the crystalline mass was triturated with ethyl acetate (125 ml.) and washed by decantation first with ethyl acetate and then with diethyl ether. The yield of D-glucaro-1,4-lactone was 56.0 g. (64% of the potassium salt converted); m.p. 90–100°, $[\alpha]_D^{27}$ +43.6° (c 1.2, water) changing to +27° in 8 days.

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(13) A product of the Rohm and Haas Co., Philadelphia, Pa.

p-Vinylbenzoic Acid

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Several preparations of *p*-vinylbenzoic acid have been reported.[1-4] All are four- to six-step syntheses of low over-all yields (10–20%). A recently published[4] synthesis from ethylbenzene gave a yield of 24% of material of doubtful purity.

The preparation of *p*-vinylbenzoic acid reported here is a three-step synthesis from an ordinary molding-grade polystyrene. The yield, 18%, is only average compared to that of the other methods, but the simplicity of the procedure moderates this objection considerably. Polyvinylacetophenone was prepared by Friedel-Crafts acetylation of polystyrene. Thermal depolymerization yielded *p*-vinylacetophenone, and hypochlorite oxidation of the ketone gave *p*-vinylbenzoic acid.

The low-yield step in the various published syntheses of *p*-vinylbenzoic acid has been the formation of the vinylic double bond. The necessary high temperature or prolonged reaction time causes polymerization of the product. The negative group, carboxy, alkoxycarbonyl, or cyano, on the ring of the styrene molecule renders it more sensitive to polymerization. Previously this low-yield step has been the fourth or fifth reaction in the sequence, which makes it particularly objectionable. The double-bond formation in the present synthesis does not afford a better yield, but it occurs in the second step. Furthermore, the first step, acetylation of polystyrene, can be conducted on a large scale with little additional effort.

The preparation of polyvinylacetophenone and its depolymerization have been described,[5] but the yield reported for the pyrolysis could not be repeated. Heat transfer to the partially pyrolyzed polymer in the spherical flask was poor. A special pyrolysis tube overcame this problem somewhat. This apparatus probably could be used to advantage in many pyrolysis reactions which leave a nonvolatile residue. Redistillation of the pyrolysis product gave *p*-vinylacetophenone contaminated with *p*-methylacetophenone which boils a few degrees lower. Recrystallization from *n*-heptane constituted the best purification.

Excess hypochlorite causes increased polymer formation in the oxidation reaction. Consequently, the potassium hypochlorite was standardized by titration with thiosulfate in a conventional iodometry procedure, and only the calculated amount was used. The conventional recrystallization of *p*-vinylbenzoic acid from aqueous alcohol does not remove the contaminating polymeric acid. The monomer is highly soluble in ethyl ether; the polymer is quite insoluble in ether. Filtration affords the separation, and the low temperature of this process prevents further polymerization. Titration of the double bond of *p*-vinylbenzoic acid with bromine was found to be a better measure of purity than melting point.

EXPERIMENTAL

Polyvinylacetophenone. This polymer was prepared in 91% yield by a modification[6] of the published[5] procedure with carbon tetrachloride as solvent. An equivalent of aluminum chloride and a 10% excess of acetyl chloride were used. The dried polymer–aluminum chloride complex was decomposed in dilute hydrochloric acid and ice. The polymer was washed thoroughly with water but not reprecipitated.

(1) C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.*, 68, 722 (1946); C. S. Marvel and C. G. Overberger, *J. Am. Chem. Soc.*, 67, 2250 (1945).

(2) W. S. Emerson, J. W. Heyd, V. E. Lucas, E. C. Chapin, G. R. Owens, and R. W. Shortridge, *J. Am. Chem. Soc.*, 68, 674 (1946).

(3) E. D. Bergmann and J. Blum, *J. Org. Chem.*, 24, 549 (1959).

(4) E. R. Bissell and R. E. Spenger, *J. Org. Chem.*, 24, 1146 (1959).

(5) W. O. Kenyon and G. P. Waugh, *J. Polymer Sci.*, 32, 83 (1958).

(6) C. C. Unruh, *J. Appl. Polymer Sci.*, 2, 358 (1959).

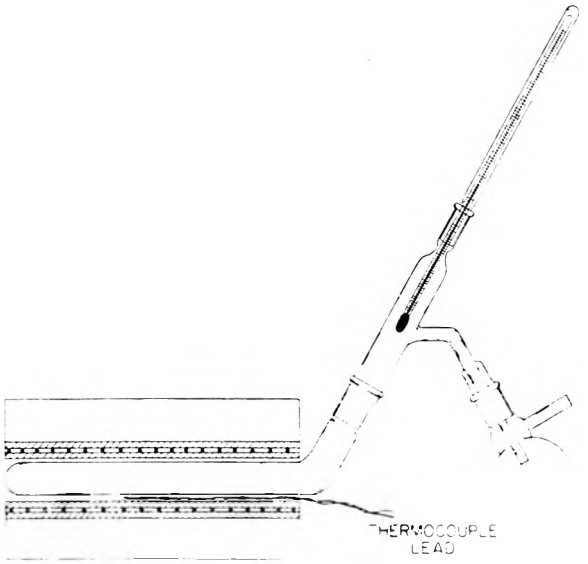

Fig. 1. Pyrolysis apparatus

p-Vinylacetophenone. Into the pyrolysis tube illustrated in Fig. 1 was charged 35 g. of polyvinylacetophenone. The tube, with a thermocouple attached, was placed in a stationary combustion furnace inclined about 30° upward toward the opening. The heating zone of the furnace was 12 in. long and extended an inch beyond the polymer charge at the outlet end of the tube. The thermocouple output activated a regulator which registered and controlled the furnace temperature. The furnace was heated to 200° to soften the polymer, vacuum was applied, and the temperature was raised to 400° for depolymerization. The temperature of the distilling product was in the vicinity of 100° at 1–2 mm. The receiver was cooled in ice. When the pyrolysis was completed (60–90 min.), the tube was removed from the furnace, cooled, and recharged. This process was repeated several times before the accumulation of nonvolatile pyrolysis products had to be removed. A total of 110 g. of polymer was pyrolyzed to give 70 g. of crude distillate. The oil was redistilled, in the presence of a small amount of hydroquinone, at 75–80° (0.3 mm.). The 48 g. of crystalline distillate was recrystallized from 40 ml. of *n*-heptane at 0°. The yield was 33 g. (30%); m.p. 34–35°.

If desired, the pyrolysis can be conducted in a flask immersed in a molten metal or salt bath at 400° with a somewhat reduced yield.

p-Vinylbenzoic Acid.[7] To 31 g. (0.21 mole) of *p*-vinylacetophenone in 150 ml. of dioxane was added dropwise, with stirring, 530 ml. (0.63 mole) of a 1.19*M* solution of potassium hypochlorite[8] over a 45-min. period. The temperature was maintained at 35° with slight cooling. The mixture was stirred an additional 30 min. at 35°. The small amount of excess hypochlorite was discharged by the addition of 1 ml. of acetone as indicated by acidic iodide solution. The mixture was cooled, extracted with one portion of ether, and the aqueous phase was added to 75 ml. of concentrated hydrochloric acid mixed with ice. The product was recovered by filtration and washed with cold water. The damp cake was dissolved in 150 ml. of warm ethanol containing a little hydroquinone, and hot water was added to incipient crystallization. Crystallization was completed at 5°. The acid was dried *in vacuo* at room temperature; yield, 27 g.

This acid was warmed in 150 ml. of ethyl ether to dissolve the monomeric acid. Filtration through Perlite removed the polymeric material, and 600 ml. of petroleum ether was added to the filtrate. Crystallization was completed at 5°. The product was collected and washed with the same mixed solvent. Bromine titration of the double bond[9] indicated 100.0% vinylbenzoic acid. The melting point was 138–141°; yield, 21 g. (67%).

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(7) The hypochlorite oxidation of *p*-vinylacetophenone was mentioned by W. J. Dale and B. D. Vineyard before the Division of Organic Chemistry at the 137th Meeting, ACS, Cleveland, Ohio, April 1960.

(8) M. S. Newman and H. L. Holmes, *Org. Syntheses*, Coll. Vol. II, 428 (1943).

(9) This analysis was a "dead-stop" end-point titration with pyridinium bromide perbromide as titrant and mercuric acetate as catalyst, developed and performed by E. P. Przybylowicz and A. D. Baitsholts, of these Laboratories.

The Reaction of 9,10-Dihydro-9,10-ethano-9-anthranol and 2,6-Di-*t*-butylphenol with Lithium Aluminum Hydride

John S. Meek and Constantine Bouboulis

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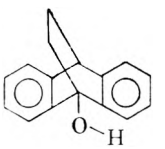
Lithium aluminum hydride when treated with excess methyl, ethyl or isopropyl alcohol liberates four equivalents of hydrogen while *t*-butyl and *t*-amyl alcohols liberate but three equivalents.[1] Two compounds which might liberate only two equivalents of hydrogen are the bridgehead alcohol (I) prepared in these laboratories and 2,6-di-*t*-



butylphenol.[2] These compounds were tested and it was found that compound I was comparable with *t*-butyl alcohol and liberated three equivalents of hydrogen. However, 2,6-di-*t*-butylphenol was found to be of the next order of hindrance and it liberated only two equivalents of hydrogen.

As no precipitate was formed, it is likely that the evolution of only two equivalents of hydrogen is due to the inability of three 2,6-di-*t*-butylphenoxide groups to fit around an aluminum atom rather than to insolubility of the complex causing precipitation before a third equivalent of the phenol could react.

Aqueous sodium hydroxide solutions do not dissolve 2,6-di-*t*-butylphenol, but it seems doubtful that the lowered acidity of this hindered phenol would cause it to be unreactive with the bis-2,6-

(1) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, 80, 5372 (1958).

(2) During the course of a visit at Colorado, Professor H. C. Brown suggested that compound I would be considerably more hindered than *t*-butyl alcohol in its reaction with lithium aluminum hydride.

di-*t*-butylphenoxyaluminohydride ion rather than a steric factor. After this complex with the phenol had been formed, the addition of compound I did not liberate a third equivalent of hydrogen. This showed that I does not exchange with the phenol in the complex ion as such an exchange would lead to the tris-9,10-dihydro-9,10-ethano-9-anthroxy-aluminohydride ion as was formed with I acting directly on lithium aluminum hydride.

Methanol liberated hydrogen slowly from the bis-2,6-di-*t*-butylphenoxyaluminohydride ion and, while not quite two equivalents of hydrogen were evolved, no further hydrogen was released upon the addition of hydrochloric acid. This evolution of hydrogen by methanol may be due to exchange or two methoxide ions may be small enough to fit around the aluminum atom together with the 2,6-di-*t*-butylphenoxide ions.

The next stage of hindrance where an excess of a hydroxyl compound would liberate only one equivalent of hydrogen from lithium hydride might be found with an alcohol such as I if substituents were in the 1,8-positions. If bulky enough presumably they could even completely shield the hydroxyl group.

EXPERIMENTAL

Starting materials. The 2,6-di-*t*-butylphenol was a gift of the Ethyl Corporation. The 9,10-dihydro-9,10-ethano-9-anthrol was prepared by condensing anthrone dissolved in pyridine with ethylene at 180° under pressure of about 1500 to 3000 p.s.i. This solvent seems more satisfactory than aqueous sodium hydroxide and dioxane, which were used in our original procedure.[3]

Measurement of hydrogen evolution. A quantitative hydrogenation apparatus was used and solutions were injected with graduated hypodermic syringes. One milliliter of 0.78*M* solution of lithium aluminum hydride in tetrahydrofuran was added to an excess of methanol and 89 ml. of hydrogen was evolved at 25° and 630 mm. When the bridgehead alcohol was used, 66.2 ml. of hydrogen was evolved. A second solution gave 94 ml. of hydrogen with excess methanol and 49 ml. with excess hindered phenol. The values reported are the averages of three runs. No precipitate was observed on mixing either the phenol or the alcohols with the lithium aluminum hydride.

The oxyalumino hydrides. A solution of lithium aluminum hydride in tetrahydrofuran was added to a solution of the alcohol until evolution of hydrogen ceased. Removal of the solvent under reduced pressure gave a white solid whose spectrum in a potassium bromide pellet showed a greatly reduced hydroxyl peak when compared with the starting alcohol. The complex with water gave the starting alcohol back quantitatively with the evolution of hydrogen. Methanol and ethanol also released hydrogen from the complex.

In a similar manner the phenol complex was isolated but on exposure to air quickly turned to a yellow oil. The complex on heating at 80° bubbled and became a yellow oil. The complex liberated hydrogen when treated with water or methanol.

In another experiment 0.80 ml. of a stock solution of lithium aluminum hydride (about 0.75 mmole) was added to a fifty fold excess of methanol and 80.4 ml. of hydrogen was liberated. Next 0.80 ml. of the stock solution was added to 1 g. of 2,6-di-*t*-butylphenol in 8 ml. of tetrahydrofuran and 62.6 ml. of hydrogen was evolved, partly because of drying the solvent and partly from reaction with the phenol. A second addition of 0.80 ml. of the stock solution then liberated 40.6 ml. of hydrogen from the dried solution of excess phenol. After this evolution of hydrogen had ceased, the addition of 1 ml. of methanol liberated an additional 41.4 ml. of hydrogen. This came off slowly over a period of 4 hr. A final addition of hydrochloric acid liberated no further hydrogen.

In a similar experiment the addition of 2 g. of the alcohol I to the phenol complex did not liberate any hydrogen while subsequent addition of methanol did.

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(3) J. S. Meek, V. C. Godefroi, and W. B. Evans, abstracts, 123rd meeting of the American Chemical Society 27M, 1953. See also M. Wilhelm and D. Y. Curtin, *Helv. Chim. Acta*, 40, 2129 (1957).

Some Alkoxyorganosilanes[1]

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Received September 1, 1960

In the course of an investigation of organosilicon polymers containing bulky organic groups, we have prepared several organoalkoxysilanes whose synthesis and properties have not been reported elsewhere. Each of the compounds was obtained from the well known condensation of an aryl Grignard reagent with either an alkoxysilane or an alkoxychlorosilane.

Two of the new compounds, 4-chlorophenylethoxydiphenylsilane and 4-chlorophenylethoxydimethylsilane, were prepared for an investigation of the synthesis of monomers of the type $(C_2H_5OSiR_2C_6H_4)_4Si$, where R is methyl or phenyl. Treating either compound with silicon tetrachloride in the presence of sodium in diethyl ether failed to initiate a reaction. When boiling toluene was used as the solvent, considerable cleavage of the ethoxyl groups occurred and pure products could not be isolated from the reaction mixture.

The other new compounds—diethoxymethyl-1-naphthylsilane, diisopropoxymethyl-1-naphthylsilane, diethoxymethyl-2-naphthylsilane, and 2-biphenylyldiethoxymethylsilane—were prepared for an investigation of the effect of bulky pendant aromatic groups on the formation of siloxane chains. Also used in this investigation was 4-biphenylyldiethoxymethylsilane whose preparation has been described elsewhere.[2] An attempt to prepare 9-

(1) This research was supported by the United States Air Force under Contract AF 33(616)-3675, monitored by the Materials Laboratory, Wright Air Development Division, Wright-Patterson Air Force Base, Ohio.

(2) L. W. Breed, *J. Org. Chem.*, 25, 1198 (1960).

anthryldiethoxymethylsilane was not successful. Although the Grignard reagent of 9-bromoanthracene in tetrahydrofuran was obtained in good yield, a condensation with chlorodiethoxymethylsilane could not be effected.

Initial attempts to prepare the second group of monomers utilized dialkoxychloromethylsilanes in the condensation with the aryl Grignard reagents. 2-Naphthylmagnesium bromide and 2-biphenylylmagnesium bromide failed to condense preferentially with the silicon-attached chlorine in chlorodiethoxymethylsilane. Considerable hydrolyzable chlorine remained, particularly in the naphthyl derivative, but methyltriethoxysilane, condensed with 2-naphthylmagnesium bromide, gave a pure product with no loss of yield.

For polymer preparation a two-step procedure was followed. First the monomers were hydrolyzed in a mixture of ethanol and benzene in the presence of hydrochloric acid. The hydrolysis products were then treated with a catalytic amount of sodium hydroxide at 145° for five hours following a method similar to that described by Hyde[3] and Andrianov[4] for preparing linear siloxanes. During the second procedure cleavage products, naphthalene and biphenyl, were obtained as sublimates in the reaction flask.

The molecular weights of the polymers from diethoxymethyl-2-naphthylsilane and 4-biphenylyldiethoxymethylsilane did not differ greatly from the molecular weight of a polymer prepared from diethoxymethylphenylsilane under similar conditions (see Table I). All values were in the neighborhood of 2000, outside the limit of precise determination by the cryoscopic methods. In the case of the materials prepared from 2-biphenylyldiethoxymethylsilane and diethoxymethyl-1-naphthylsilane, however, molecular weights were less, the bulky pendant groups interfering with the growth of the siloxane chain. This effect is not surprising in view of the reported steric effects in the hydrolysis and condensation of silane monomers with bulky substituents such as *t*-butyl and trimethylsilylmethyl.[5–7]

All the biphenylyl- and naphthylsiloxanes were solids at room temperature. The product obtained from 4-biphenylyldiethoxymethylsilane melted rather sharply near 100°. The others became somewhat tacky below their melting points, and softened over a greater range. Only the latter polymer was a solid before the alkali treatment, the others were tacky semisolids.

(3) J. F. Hyde, U. S. Patent 2,542,334 (1951).

(4) K. A. Andrianov, *Organic Silicon Compounds*, Moscow, 1955. (United States Department of Commerce, Office of Technical Services Translation), p. 763.

(5) L. H. Sommer and L. J. Tyler, *J. Am. Chem. Soc.*, 76, 1030 (1954).

(6) L. H. Sommer, R. M. Murch, and F. A. Mitch, *J. Am. Chem. Soc.*, 76, 1619 (1954).

(7) D. Seyferth and E. G. Rochow, *J. Polymer Sci.*, 18, 543 (1955).

TABLE I

MOLECULAR WEIGHTS AND SOFTENING POINTS OF POLYMERIC SILOXANES

Polymer from:	Molecular Weight	Softening Point
Methylphenyldiethoxysilane	2020 1890	Liquid
2-Biphenylylmethyldiethoxysilane	880 910	55
4-Biphenylmethyldiethoxysilane	2130 2620	100
Methyl-1-naphthyldiethoxysilane	1190 1260	65
Methyl-2-naphthyldiethoxysilane	1800 1840	55

EXPERIMENTAL

4-Chlorophenylethoxydiphenylsilane. In a 3-l. flask were placed 26.4 g. (1.1 g.-atoms) of magnesium turnings, 20 g. of *p*-bromochlorobenzene, and 100 ml. of diethyl ether. To the mixture a solution containing 171.4 g. (total 1 mole) of *p*-bromochlorobenzene, 272.4 g. (1 mole) of diethoxydiphenylsilane, and 400 ml. of diethyl ether was added dropwise over a 3.5-hr. period. The product was refluxed 22 hr., cooled, filtered and stripped to remove the solvents. Fractional distillation of the residue at 0.25 mm. gave 38.5 g. of diethoxydiphenylsilane boiling at 104–108° and 169 g. (49.9%) 4-chlorophenyldiphenylethoxysilane boiling at 158–160°, d_4^{25} 1.038; n_D^{25} 1.4938.

Anal. Calcd. for $C_{10}H_{15}ClOSi$: C, 56.40; H, 7.04; Cl, 16.50; Si, 13.10; MR_D, 60.33. Found: C, 56.20; H, 6.93; Cl, 16.47; Si, 13.12; MR_D, 60.22.

4-Chlorophenylethoxydimethylsilane. In a similar procedure, 26.4 g. (1.1 g.-atoms) of magnesium turnings, 191.4 g. (1.0 mole) of *p*-bromochlorobenzene, and 148.2 g. (1.0 mole) of diethoxydimethylsilane in 500 ml. ether gave 123 g. (57.3%) of 4-chlorophenyldimethylethoxysilane boiling at 65–68° at 0.25 mm., d_4^{25} 1.132; n_D^{25} 1.5887.

Anal. Calcd. for $C_{20}H_{19}ClOSi$: C, 71.20; H, 5.65; Cl, 11.47; Si, 8.26; MR_D, 99.97. Found: C, 71.09; H, 5.52; Cl, 11.47; Si, 8.26; MR_D, 100.00.

9-Anthrylmagnesium bromide. In a 250-ml. flask were placed 0.5 g. (0.021 g.-atom) of magnesium turnings, 2.57 g. (0.01 mole) of 9-bromoanthracene, 20 ml. of tetrahydrofuran, and a small crystal of iodine. The mixture was heated 2 hr., cooled, and filtered through glass wool into 15% hydrochloric acid. The product, recrystallized from benzene, gave 1.2 g. (67%) anthracene melting 212–215°.

9-Anthryldiethoxymethylsilane (attempted). A 250-ml. flask was charged with 1.46 g. (0.06 g.-atom) of magnesium turnings, 1.0 g. of 9-bromoanthracene, 10 ml. of tetrahydrofuran, and a crystal of iodine. A mixture containing 6.71 g. (0.03 mole, total) of 9-bromoanthracene, 5.05 g. (0.03 mole) of methylchlorodiethoxysilane, and 25 ml. of tetrahydrofuran was added dropwise over a period of 45 min. Heating, which was required throughout the addition, was continued for 4.5 hr. At the end of the heating period 40 ml. of methylcyclohexane was added, and a part of the tetrahydrofuran was removed by distillation. A dark-colored oil remained which was insoluble in benzene and solidified on cooling. No 9-anthryldiethoxymethylsilane was obtained in attempts to purify the crude product.

In similar trials no product was obtained when the reaction mixture was refluxed 16 hr. or when the tetrahydrofuran was replaced with di-*n*-butyl ether and the mixture refluxed for 14 hr. at 142°.

Diethoxymethyl-1-naphthylsilane. 1-Naphthylmagnesium bromide, prepared from 32.5 g. (0.157 mole) of 1-bromonaphthalene and 5.8 g. (0.239 g.-atom) of magnesium

turnings in 43.2 g. (0.6 mole) of tetrahydrofuran and diluted with 85 ml. of tetrahydrofuran, was cooled to 6° with an ice bath and treated with 30.3 g. (0.18 mole) of methylchlorodiethoxysilane. The temperature of the mixture was not allowed to exceed 10° during the addition. After the addition was complete, the product was refluxed 1 hr., diluted with heptane, concentrated by distillation, and filtered. Fractional distillation gave 23.6 g. (58%) of diethoxymethyl-1-naphthylsilane boiling at 114–115° at 0.1 mm., n_D^{28} 1.5393; d_4^{28} 1.039.

Anal. Calcd. for $C_{15}H_{20}O_2Si$: Si, 10.79; MR_D, 78.46. Found: Si, 10.44; MR_D, 78.42.

In a repetition of the experiment with 0.7 mole of 1-bromonaphthalene, the bromide and the silane were added to the reaction mixture concomitantly. The yield of methyl-1-naphthyldiethoxysilane boiling at 100° at 0.05 mm. was 36%.

Diisopropoxymethyl-1-naphthylsilane. When 5.9 g. (0.24 g.-atom) of magnesium was treated with a mixture of 41.4 g. (0.2 mole) of 1-bromonaphthalene, 47.2 g. (0.24 mole) of methylchlorodiisopropoxysilane, and 43.2 g. (0.6 mole) of tetrahydrofuran, diisopropoxymethyl-1-naphthylsilane (37.5%) was obtained boiling 137–143° at 2.7 mm., n_D^{25} 1.5165, d_4^{25} 0.996.

Anal. Calcd. for $C_{17}H_{24}O_2Si$: Si, 9.74; MR_D, 87.72. Found: Si, 9.99; MR_D, 87.46.

Diethoxymethyl-2-naphthylsilane. A mixture of 20.0 g. of 2-bromonaphthalene, 24.9 g. (0.145 mole) of chlorodiethoxymethylsilane, and 20 ml. of ethyl ether was added dropwise to a flask containing 5.0 g. (0.121 mole, total) of 2-bromonaphthalene, 5 ml. of ether, and 5.0 g. (0.206 g.-atom) of magnesium turnings. The contents of the flask were heated under reflux and stirred for 19 hr., and then cooled and filtered. Distillation at 0.5 mm. gave 15.1 g. of unchanged 2-bromonaphthalene between 70° and 99°. Fractional distillation of the remainder of the material gave about 4 g. (13%) of impure diethoxymethyl-2-naphthylsilane boiling 138–138.5° at 2.5 mm., n_D^{25} 1.5518, d_2^{25} 1.066.

Anal. Calcd. for $C_{15}H_{20}O_2Si$: Si, 10.79; MR_D, 78.46. Found: Si, 11.37; MR_D, 78.01.

The product fumed in air and gave a positive Beilstein test. Titration of a hydrolyzed aliquot indicated that the product contained 5.32 weight per cent chlorine, or that about one-third of the material was chloroethoxymethyl-2-naphthylsilane.

A product of about the same purity and in about the same yield was obtained when the reaction was carried out in tetrahydrofuran.

Repetition of the procedure with 25.0 g. of methyltriethoxysilane in place of the methylchlorodiethoxysilane gave 4.6 g. (15%) of diethoxymethyl-2-naphthylsilane boiling 140–144° at 2.2 mm., n_D^{26} 1.5407, d_4^{26} 1.042. About 17 g. of 2-bromonaphthalene was recovered unchanged.

Anal. Found: Si, 10.93; MR_D, 78.53.

2-Biphenylylmethyldiethoxysilane. When 9.6 g. (0.40 g.-atom) of magnesium was treated with a mixture of 76.7 g. (0.33 mole) of 2-bromobiphenyl, 67.5 g. (0.40 mole) of chlorodiethoxymethylsilane, and 71.3 g. (0.99 mole) of tetrahydrofuran and the product was worked up similarly, 42.1 g. (45%) 2-biphenyldiethoxymethylsilane boiling 102° at 0.04 mm. was obtained, n_D^{25} 1.5334, d_4^{25} 1.094.

Anal. Calcd. for $C_{15}H_{22}O_2Si$: Si, 9.81; MR_D, 85.27. Found: Si, 9.84; MR_D, 84.64.

Titration of a hydrolyzed aliquot indicated that the product contained 0.36 weight per cent hydrolyzable chlorine.

Hydrolysis procedure. A mixture of 5 ml. of 95% ethyl alcohol, 5 ml. of coned. hydrochloric acid, and 10 ml. of the silane monomer was refluxed 2 hr., diluted with 15 ml. of benzene, and refluxed for an additional 4 hr. The product, washed with water until it was neutral, was heated to 100° *in vacuo* to remove the solvents.

Rearrangement of the siloxanes with sodium hydroxide. Five grams of the polymer and 0.2 g. of 50% sodium hydroxide was heated at 145° for 5 hr. The cooled product, diluted with 20 ml. of benzene, was washed with portions of water until the washings were neutral, and then heated at 100° overnight *in vacuo*. In each case a cleavage product, either naphthalene or biphenyl, was collected as a sublimate during the initial heating period. Although no attempt was made to recover the decomposition products quantitatively, the solid material recovered usually represented about 5% of the organic groups present in the polymer.

Polymer molecular weights given in Table I were determined cryoscopically in benzene, K_f = 5.32. Softening points of the four polymers were determined as follows: A few milligrams of the sample was placed between two-micro cover glasses on a Fisher-Johns melting point apparatus heated at the rate of 5°/min. A slight pressure was applied on the top cover glass, and the temperature at which the material flowed freely between the plates was recorded. These results are also recorded in Table I.

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Reactions of Triphenylsilyllithium with Triaryl Phosphates

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Recent publications[1,2] from this laboratory described the reactions of triphenylsilyllithium with trialkyl phosphates. High yields of alkyltriphenylsilanes were realized when the reactions were carried out in a 1:1 mole ratio. The use of three equivalents of triphenylsilyllithium in attempts to utilize all three alkyl groups of tri-*n*-butyl phosphate in this reaction, however, resulted in the isolation of considerable amounts of hexaphenylisildane together with other products.[2] A mechanism involving the displacement of a butoxyl group, and the subsequent cleavage of the intermediate silylphosphorus compound by triphenylsilyllithium, was proposed to account for the formation of the disilane.

The reactions of triphenylsilyllithium in various ratios with triaryl phosphates, likewise gave sizeable amounts of hexaphenyldisilane. After hydrolysis, the reaction mixtures had pronounced phosphine-like odors, as did the 3:1 reactions of triphenylsilyllithium with tri-*n*-butyl phosphate.[2] Thus, it appears as though a similar mechanism is involved in these reactions.

This reaction path is not surprising since carbon-metallic compounds react with substances having the P—O—R linkage *via* displacements of —O—R groups from phosphorus.[3] Furthermore, resonance

(1) M. V. George, B. J. Gaj, and H. Gilman, *J. Org. Chem.*, **24**, 624 (1959).

(2) H. Gilman and B. J. Gaj, *J. Org. Chem.* (in press).

(3) For references to reactions of this type, see the publication cited in ref. (2) of this paper.

interaction between oxygen and the aryl group should also favor the displacement mechanism in spite of the steric factors involved.

At room temperature, the reaction of three equivalents of triphenylsilyllithium with triphenyl phosphate afforded 27% of hexaphenyldisilane and 52% of triphenylsilanol subsequent to hydrolysis. All of the organosilyllithium compound was consumed as evidenced by a negative Color Test I.[4] When six equivalents of this reagent were employed, these products were isolated in 33 and 41% yields, respectively, together with hexaphenyldisiloxane (3%) and triphenylsilane (14%). The hydrolysis of unchanged triphenylsilyllithium probably accounts for the formation of the last-mentioned product. These results can best be explained *via* the following reaction scheme:

$$(C_6H_5)_3SiLi + (C_6H_5O)_3PO \longrightarrow C_6H_5Li + (C_6H_5)_3SiP(O)(OC_6H_5)_2$$
I.

$$(C_6H_5)_3SiLi + (C_6H_5)_3SiP(O)(OC_6H_5)_2 \longrightarrow (C_6H_5)_6Si_2 + LiP(O)(OC_6H_5)_2$$
II.

$$(C_6H_5)_3SiLi + (C_6H_5)_3SiP(O)(OC_6H_5)_2 \longrightarrow C_6H_5OLi + ((C_6H_5)_3Si)_2P(O)OC_6H_5$$
III.

$$(C_6H_5)_3SiLi + ((C_6H_5)_3Si)_2P(O)OC_6H_5 \longrightarrow (C_6H_5)_6Si_2 + (C_6H_5)_3SiP(O)(Li)(OC_6H_5)$$
IV.

$$(C_6H_5)_3SiLi + ((C_6H_5)_3Si)_2P(O)OC_6H_5 \longrightarrow C_6H_5OLi + ((C_6H_5)_3Si)_2PO$$
V.

$$(C_6H_5)_3SiLi + ((C_6H_5)_3Si)_3PO \longrightarrow (C_6H_5)_6Si_2 + ((C_6H_5)_3Si)_2P(O)Li$$
VI.

Since Color Test I was negative in the 3:1 reaction, and hexaphenyldisilane was isolated in only 27% yield, it is evident that at least some of the ester molecules are undergoing displacement of all three phenoxide groups. If this were not so, the yield of the disilane should have been nearer to 67% than to 33%, and the yield of triphenylsilanol would have been somewhere around 33% or less. The fact that less than one-third of the silicon appeared as hexaphenyldisilane in this reaction, indicates that a considerable amount of III and V, as well as their cleavage products (IV and VI) were formed. There is nothing to prevent two or three displacements from occurring, except possibly steric factors.

The cleavage of a triphenylsilyl group from I, III or V would be expected to occur with relative ease, based on considerations presented earlier.[2] However, the removal of a triphenylsilyl group from anions such as IV and VI, or the displacement of a phenoxide group from II, IV or VI would not be expected to occur readily. Such reactions would involve anionic attack at positions of high electron density. This may account for the failure to realize more than 33% of the disilane from the reaction employing six equivalents of triphenylsilyllithium at room temperature.

Hydrolysis of the silylphosphorus intermediates (I, III, IV, V, VI), accounts for the isolation of triphenylsilanol from these reactions, as well as for the phosphine-like odors noticed after hydrolysis. Using IV as an example, this hydrolysis may be formulated as follows:

$$(C_6H_5)_3SiP(O)(Li)(OC_6H_5) \xrightarrow{H_2O} (C_6H_5)_3SiOH + H_2P(O)(OC_6H_5) + LiOH$$
IV. VII.

Hydrolytic reactions of this type are well-known.[5]

Although products of type VII were not isolated from these reactions, the fact that the phosphine-like odors were carried into the organic layer after hydrolysis indicates strongly that they exist in the reaction mixtures.

In order to determine whether or not forced conditions might cause cleavage of a second triphenylsilyl group from intermediates of type IV and VI, the reaction using six equivalents of triphenylsilyllithium was repeated under reflux conditions for 21 hours. Color Test I was negative after this time. The products isolated were: hexaphenyldisilane, hexaphenyldisiloxane, 4-triphenylsilylbutanol, triphenysilanol, and phenol (isolated as the tribromoderivative), in yields of 39.6, 11.8, 3.75, 30, and 81%, respectively. The slight increase in yield of hexaphenyldisilane together with the high yield of phenol suggests that placing a second negative charge on phosphorus *via* this reaction is possible, but not readily accomplished, and that all three phenoxide groups are capable of displacement in this reaction.

Similar results were obtained from reactions employing either two or three equivalents of triphenylsilyllithium with tri-*p*-tolyl phosphate. The former reaction gave 35.8% of hexaphenyldisilane together with triphenylsilanol, (47.8%) and recovered ester (14.9%). The 3:1 reaction afforded the disilane, triphenylsilanol, triphenylsilane, and *p*-cresol in yields of 33, 45.2, 3.8, and

(4) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(5) See, for example: G. Fritz, *Z. Naturforsch*, **8b**, 776 (1953); G. Fritz, *Z. anorg. u. allegem. Chem.*, **280**, 332 (1955); W. Keeber and H. W. Post, *J. Org. Chem.*, **21**, 509 (1956); G. Fritz and H. O. Berkénhoff, *Z. anorg. u. allegem. Chem.*, **289**, 250 (1957); F. Fehér, G. Kulbörsch, A. Blüneke, H. Keller, and K. Lippert, *Chem. Ber.*, **90**, 134 (1957); G. W. Parshall and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **81**, 6273 (1959).

57.2%, respectively. These yields are also consistent with the proposed mechanism.

EXPERIMENTAL[6]

Reaction of triphenylsilyllithium with triphenyl phosphate (3:1). A solution of 4.20 g. (0.0133 mole) of triphenyl phosphate in 10 ml. of tetrahydrofuran was added to a stirred solution of 0.04 mole of triphenylsilyllithium[7] in 90 ml. of the same solvent. The reaction was mildly exothermic and a suspension developed after the first few ml. of solution had been added. Upon complete addition, Color Test I[4] was negative, hence the mixture was hydrolyzed with water in a hood (strong phosphine-like odor). Filtration and thorough washing with water and diethyl ether left 2.8 g. (27%) of hexaphenyldisilane, melting point and mixed m.p. 362–364°. The phenol was extracted from the organic layer with 10% sodium hydroxide solution and discarded.

The solvents were removed from the dried organic layer, which still smelled strongly of phosphine, to leave an oily solid. Crystallization from cyclohexane gave in several crops, 5.73 g. (52%) of triphenylsilanol, identified by mixed melting point and infrared spectra.

Reaction of triphenylsilyllithium with triphenyl phosphate (6:1). A mixture of 0.12 mole of triphenylsilyllithium and 6.32 g. (0.02 mole) of triphenyl phosphate in 250 ml. of tetrahydrofuran was stirred at room temperature for 2 days to give a brown suspension. Color Test I was pale green. The mixture was hydrolyzed with 100 ml. of dilute hydrochloric acid, filtered, and the insoluble material was washed thoroughly with water and diethyl ether to leave 10.2 g. (33%) of hexaphenyldisilane, melting point and mixed m.p. 363–365°.

The layers of the filtrate, which had a pronounced phosphine-like odor, were separated and the organic layer was washed with 10% sodium hydroxide to remove phenol, then dried over sodium sulfate. Removal of the solvents by distillation and treatment of the residue with cyclohexane afforded 11.25 g. (34%) of triphenylsilanol, m.p. 149–152° (mixed melting point and infrared spectra). The material in the cyclohexane filtrate oiled upon further concentration, hence the solvent was removed and the residue passed through a column of alumina. Elution with 600 ml. of petroleum ether (b.p. 60–70°) gave 4.5 g. (14%) of triphenylsilane, m.p. 42–44° (identified by mixed melting point and infrared spectra). The next 600 ml. of the same solvent gave 0.8 g. (3%) of hexaphenyldisiloxane, m.p. 224–226° after two crystallizations from cyclohexane. Ethyl acetate then eluted 2.5 g. of triphenylsilanol, m.p. 152–154°, (total yield, 13.25 g., 41%).

Reaction of triphenylsilyllithium with triphenyl phosphate (6:1) at reflux. The preceding reaction was repeated using the same quantities of material; however, the mixture was refluxed gently for 21 hr., at the end of which time, Color Test I was negative. The mixture was worked up as in the previous reaction to give 12.3 g. (39.6%) of hexaphenyldisilane, melting point and mixed m.p. 366–368°.

The solvents were removed from the dried organic layer and the residue was chromatographed on alumina to give 3.9 g. (11.8%) of hexaphenyldisiloxane, melting point and mixed m.p. 226–228°, after crystallization of the material eluted with petroleum ether (b.p. 60–70°) and benzene from cyclohexane. The first 30 ml. of ethyl acetate eluates gave an oil, which when recrystallized from petroleum ether (b.p. 60–70°), afforded 1.5 g. (3.75%) of 4-triphenylsilylbutanol, m.p. 107–109° (mixed melting point and infrared spectra). Further elution with the same solvent gave, after recrystallization from cyclohexane, 9.95 g. (30%) of triphenylsilanol and *ca.* 2 g. of an oil whose infrared spectrum indicated it to be a mixture of triphenylsilanol and 4-triphenylsilylbutanol. This material was not worked up any further.

The basic extract of the organic layer was acidified and extracted with diethyl ether. Drying and removing the ether gave, upon bromination, 16 g. (81%) of tribromophenol, m.p. 92–94° (mixed melting point).

Reaction of triphenylsilyllithium with tri-p-tolyl phosphate (2:1). A mixture of 0.04 mole of triphenylsilyllithium and 7.37 g. (0.02 mole) of tri-*p*-tolyl phosphate in 110 ml. of tetrahydrofuran was stirred overnight at room temperature (12 hr.) then hydrolyzed with 10% hydrochloric acid. Filtration and washing gave 3.7 g. (35.8%) of hexaphenyldisilane, melting point and mixed m.p. 365–367°.

The organic layer was separated and washed with 10% sodium hydroxide to remove the *p*-cresol, then dried. The dried organic layer was distilled to remove solvent and the residue was dissolved in cyclohexane. Concentration afforded 4.78 g. (43.3%) of triphenylsilanol, m.p. 152–154° (mixed melting point). Further concentration gave an oil which had a pronounced phosphine-like odor. Passage through a short column of alumina gave a trace of hexaphenyldisiloxane, m.p. 222–224° (mixed melting point); 1.1 g. (14.9%) of recovered tri-*p*-tolyl phosphate, m.p. 74–76° (mixed melting point); and 0.5 g. (4.5%) of triphenylsilanol, m.p. 152–154° (after crystallization from cyclohexane).

Reaction of triphenylsilyllithium with tri-p-tolyl phosphate (3:1). A mixture of 0.06 mole of triphenylsilyllithium in 100 ml. of tetrahydrofuran was allowed to react for 3 hr. with a solution of 7.37 g. (0.02 mole) of tri-*p*-tolyl phosphate in 50 ml. of the same solvent. Hydrolysis with 100 ml. of water followed by acidification and filtration gave 5.15 g. (33%) of hexaphenyldisilane, melting point and mixed m.p. 360–364°.

The separated organic layer was extracted with 10% sodium hydroxide, then dried. The basic extract was acidified and extracted with diethyl ether and the ether extracts were dried. Solvent removal from the ether extract left an oil which was distilled to give 3.7 g. (57.2%) of *p*-cresol, b.p. 95–97° (20 mm.), identified by infrared spectra. A considerable amount of distillation residue remained and attempts to distill it at a lower pressure led to decomposition by charring and fuming.

The neutral organic layer was chromatographed on alumina to give 0.6 g. (3.8%) of triphenylsilane, identified by infrared spectra, and 7.5 g. (45.2%) of triphenylsilanol, m.p. 152–154° (mixed melting point).

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(6) Melting points and boiling points are uncorrected. All reactions were carried out in oven-dried glassware under an atmosphere of dry, oxygen-free nitrogen. The tetrahydrofuran was dried by refluxing over sodium wire for at least 24 hr., followed by distillation into a refluxing suspension of lithium aluminum hydride under dry nitrogen. It was then distilled immediately before use from this suspension.

(7) Prepared by the lithium cleavage of hexaphenyldisilane according to the reported procedure of H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958).

The Structures of the Polymers and Cyclic Dimers Obtained from Diorganovinylsilanes

JAMES W. CURRY

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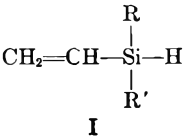
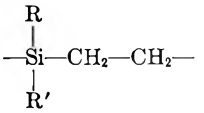
In 1956 Curry[1] reported the polymerization and cyclization of certain diorganovinylsilanes (I)



I

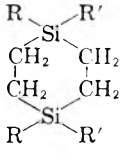
a. R = R′ = CH_3
b. R = R′ = C_2H_5
c. R = R′ = C_6H_5
d. R = CH_3; R′ = C_6H_5

via Si-H addition. The resulting products were designated as polysilethylenes (II) and 1,4-disil-



II a–d

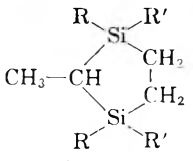
acyclohexanes (III) on the basis of infrared spectral analysis. Subsequently, however, it was called to our attention[2] that certain of these structural



IIIa, b, c, d

assignments might not be correct. Accordingly, in an effort to gain additional information, new samples of the materials were prepared and studied by NMR spectroscopy.

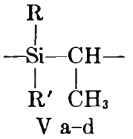
For the dimethylvinylsilane cyclic dimer, the results indicated the presence of both structure IIIa and the five-membered ring compound, 1,1,2,3,3-pentamethyl-1,3-disilacyclopentane (IVa). There was found in the nmr spectrum, at relatively



IVa, b, c, d

low field, a doublet, arising from the protons of the C-methyl group in IVa. The observed splitting was due to spin coupling with the proton at the tertiary carbon atom. The next peak was attributed to the equivalent methylene groups in IIIa, and at slightly higher field was a peak from the protons of the CH_2 groups in IVa. Next, there appeared two signals from the two pairs of nonequivalent methyls attached to silicon in IVa, the one pair being above the plane of the five-membered ring, and the other pair, below the plane of the ring. A third CH_3—Si peak at somewhat higher field represented the equivalent methyl groups in IIIa. Finally, a low, broad pattern appearing at still higher field was due to the tertiary proton in IVa. The pattern would normally appear as a quartet because of splitting by the protons of the attached methyl group. In this case, however, the first peak of the quartet was obscured by the CH_3—Si resonance from IIIa. By comparing the areas of the two CH_2 peaks, it was possible to determine that the cyclic dimer consists of 27% IIIa and 72% IVa.

The corresponding polymer was shown to be predominantly polydimethylsilethylene (IIa), although the presence of a small amount of the alternate structure (Va) was also indicated. In the



V a–d

nmr spectrum there was a low intensity signal from the methyl protons in CH_3—CH, split into a doublet by the proton at the tertiary carbon. At higher field there was a single peak arising from the equivalent CH_2 groups in IIa, and at still higher field there appeared the CH_3—Si resonance. From the relative areas of the three sets of signals the composition of the polymer was estimated approximately as 75% IIa and 25% Va.

Examination of the spectrum from the diethylvinylsilane cyclic dimer revealed the presence of a very small amount of 1,1,3,3-tetraethyl-2-methyl-1,3-disilacyclopentane (IVb). The tertiary proton present therein gave rise, at high field, to a weak signal, which was split into a quartet by the attached methyl group. Thus, from the evidence it was concluded that the major component is 1,1,4,4-tetraethyl-1,4-disilacyclohexane (IIIb). The resonance peaks were not, however, sufficiently well defined to permit a quantitative estimate of the relative amounts of the two isomers. Interestingly enough, the multiplicity of CH_2 peaks in the spectrum indicated that the individual protons in these groups are not equivalent and suggested that compound IIIb may exist in a fixed conformation (chair form).

The spectrum of the polymer from diethylvinylsilane was difficult to interpret because all of the resonance peaks were crowded into a small region. However, no quartet, which would be expected from the tertiary proton in Vb, could be found, and it was concluded, therefore, that IIb best represents the structure of this product.

(1) J. W. Curry, *J. Am. Chem. Soc.*, **78**, 1686 (1956).
(2) A. J. Barry, Dow Corning Corp., private communication.

Spectral analysis of the diphenylvinylsilane cyclic dimer showed clearly the presence of 1,1,3,3-tetraphenyl-2-methyl-1,3-disilacyclopentane (IVc) to the exclusion of the other possible isomer (IIIc). The expected quartet and doublet from HC—CH_3 appeared at relatively low and high field, respectively, and bracketed neatly the single resonance peak from the two equivalent methylene groups.

The results from the related polymer were not so definite. However, the apparent absence of a doublet signal from CH_3—CH indicated that Vc is probably not present, thereby suggesting that the most likely structure is IIc.

The spectrum of the methylphenylvinylsilane cyclic dimer showed a split phenyl signal at low field, indicating the presence of both of the two possible structures. At high field were observed, successively, an incompletely resolved multiplet due to all the methylene groups present, a group of low peaks, probably from CH_3—CH, and another multiplet due to non-equivalent protons in the CH_3—Si groups. The multiple splittings were attributed to *cis* and *trans* isomers of both IIId and IVd. By comparing the relative areas of the two portions of the phenyl signal, it was established that this dimeric material is a 60:40 mixture of the two ring structures. However, the resonance peaks from CH_2 and CH_3—CH were not sufficiently well resolved to permit a conclusion as to which isomer constitutes the larger portion.

On the basis of the meager information available from the spectrum of the methylphenylvinylsilane polymer, structure IId is favored over the isomeric Vd, although the latter cannot be completely ruled out. Even in carbon tetrachloride solution the resonance peaks were viscosity broadened, and while the small quartet pattern from CH_3—CH did not appear to be present in high field, it might have been obscured by the other broad signals near this region.

In summary, the NMR evidence, while not always clear cut, did show that both five- and six-membered ring structures are represented among the various cyclic dimers, and in the main, appeared to reaffirm the earlier assigned[1] polysilethylene structure for the polymers.

EXPERIMENTAL[3,4]

Nuclear magnetic resonance spectra. The NMR spectra were determined using the Varian Associates High Resolution Spectrometer (V-4300-C), operated at 60 mc. and 14090 gauss. The spectra of all of the polymers and of diphenylvinylsilane cyclic dimer were run in carbon tetrachloride solution. The other cyclics (liquids) were run without solvent.

Physical properties. In Tables I and II are listed certain physical properties. The values shown have either not been reported previously or constitute revisions of those recorded earlier.[1]

TABLE I

Reaction product	n_D^{25}	d_4^{25}	R_D, Calcd.	R_D, Found
Dimethylvinylsilane:				
Polymer	1.4903	0.8827	0.3263	0.3277
Diethylvinylsilane:				
Polymer	1.4988	0.8970	0.3276	0.3272

TABLE II

Reaction Product	Mol. Wt., Calcd.	Mol. Wt., Found	Average Degree of Polymerization
Dimethylvinylsilane:			
Polymer	—	2340, 2190, 2110	25.6
Cyclic Dimer	172	178, 177	—
Diethylvinylsilane:			
Polymer	—	992, 980	8.6
Cyclic Dimer	228	239, 237	—
Diphenylvinylsilane:			
Polymer	—	647, 661	3.1
Methylphenylvinylsilane:			
Polymer	—	847, 864	5.8
Cyclic Dimer	297	283, 286	—

Acknowledgment. The author gratefully acknowledges the financial support of this work by the Dow Corning Corporation. He also wishes to thank Mr. LeRoy F. Johnson of Varian Associates, Palo Alto, Calif., and Mr. Paul C. Lauterbur of Mellon Institute of Industrial Research, Pittsburgh, Pa., for their aid in running and interpreting the nmr spectra discussed in this paper.

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(3) Calculated specific refractivities were computed from bond refractivity values listed in the following references: A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *Chem. & Ind. (London)*, 358 (1950), and A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954).

(4) All molecular weight determinations were carried out cryoscopically in benzene.

An Evaluation of the Gilman-Haubein Determination of Alkyllithium

KENNETH C. EBERLY

Received August 18, 1960

The question arose concerning the application of the double titration of Gilman and Haubein[1] to assay of pure butyllithium under oxygen- and moisture-free conditions. It was felt that quantitative experiments were in order to confirm the method.

(1) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515–16 (1944).

EXPERIMENTAL

Butyllithium solution was prepared under conditions as dry and air-free as possible. In a 1-l. flask fitted with condenser, stirrer, graduated dropping funnel, batch thermometer, argon inlet, and water bath, 33.20 g. of Foote's 52.5% lithium dispersion (2.500 g.-atoms) was dispersed in 500 ml. of sulfuric acid-washed, sodium-dried heptane (Phillips' 99%) in a gentle current of argon. In the course of 55 min. 115.7 g. (1.250 moles) of 1-chlorobutane (n_D^{20} 1.4019) was added dropwise, the batch temperature varying between 35 and 43°. The slurry was stirred for another 30 min. at 35°, then quickly discharged into a baked, argon-filled, 28-oz. beverage bottle (capped under a slight positive pressure of argon). After the whole had settled for 100 hr. 512 ml. of colorless butyllithium solution was forced with argon pressure into a second baked, lamp nitrogen-filled, 28-oz. beverage bottle (capped under slight positive pressure of lamp nitrogen).[2]

One gallon of anhydrous ether (Baker and Adamson) was treated with 25 g. of sodium ribbon; then it was confined under argon for 50 days. Benzyl chloride (Baker and Adamson, reagent) was distilled in vacuum over phosphorus pentoxide, then stored over anhydrous calcium chloride under argon.

Exactly 1.00 ml. of clear butyllithium solution titrated 8.87 ml. of 0.19850*N* hydrochloric acid to the faintest Methyl Orange change.

Three 60-ml. bottles with serum caps were baked at 110°, then flushed with argon (using #19 and #20 hypodermic needles) until cool. Exactly 1.5 ml. of benzyl chloride and 10, 20, and 30 ml. of dry ether (from hypodermic syringes and needles baked at 110° and cooled over phosphorus pentoxide) were charged through the serum cap, respectively. After mixing, 1.00 ml. of colorless butyllithium solution was charged to each bottle through the serum cap. After reacting for 2 min., 5 ml. of water was added to each. Each was titrated with 0.19850*N* hydrochloric acid, first against phenolphthalein then Methyl Orange (faintest change). The titrations against Methyl Orange were 0.40, 0.43, and 0.46 ml., respectively.

The above experiment was repeated using lamp nitrogen instead of argon as the flushing agent. The titrations were 0.34, 0.37, and 0.40 ml., respectively.

Ten milliliters of sodium-dried ether contained enough oxygen, moisture, and ethanol to destroy butyllithium equivalent to 0.03 ml. of 0.19850*N* hydrochloric acid.

One milliliter of ball-milled lithium butoxide dispersion in dry heptane (titn., 4.07 ml. of 0.19850*N* hydrochloric acid) was treated with 1.8 ml. of dry benzyl chloride and 10 ml. of dry ether at 45–50° for 2 min. After dilution with water the titration remained unchanged.

CALCULATIONS AND CONCLUSIONS

Taking the best figure from a determination in lamp nitrogen, 8.87 ml. (total titn.) − 0.34 ml. (titn. after BzCl) + 0.03 ml. (ether corr.) × 100%/ 8.87 ml. (total titn.) or 96.5% of the base in the colorless butyllithium solution was destroyed by benzyl chloride. Since lithium butoxide is unaffected by benzyl chloride in ether in 2 min. at 45–50°, it is reasonable to believe that 96.5% of the total base in the clear butyllithium solution was carbon-bound lithium. One could assume that if butyllithium free from lithium butoxide and hydroxide could be prepared, benzyl chloride in absolutely dry and oxygen-free ether would destroy all of the alkalinity in it. The author feels that the method of Gilman and Haubein for assay of alkyllithium is most reliable.

Acknowledgment. The author is indebted to Dr. F. W. Stavely of the Firestone Research Laboratories for his interest in this work and to Mr. Harold A. Kerry of the American Potash and Chemical Corporation for much valuable advice.

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(2) Lamp nitrogen is almost completely dry and free from oxygen while commercial argon is not. However, lamp nitrogen reacts fairly rapidly with lithium dust at room conditions to yield lithium nitride, but it has no effect upon butyllithium over a period of 8 months.

A Study of Reaction Variables in Aromatic Chlorination by Antimony Pentachloride[1]

PETER KOVACIC AND ALLEN K. SPARKS[2]

Received August 4, 1960

Our previous investigations[3] on aromatic chlorination by antimony pentachloride have been concerned primarily with the reaction mechanism. This report presents a study of reaction variables in the chlorination of aromatic compounds, particularly chlorobenzene, by antimony pentachloride. The aspects dealt with include solvent and catalytic effects, mode of addition, temperature, and time. In addition, the practicality of chlorination by this method was investigated.

The presence of nitrobenzene as a solvent in the chlorobenzene reaction, while ineffective in altering the isomer distribution significantly, necessitated the use of more drastic conditions to effect chlorination. Pyridine inhibited the reaction completely. These effects are attributed to the formation of addition compounds from antimony pentachloride and the solvents, resulting in deactivation of the metal halide. In fact, solid separated initially from solution in both cases, in accord with reports that antimony pentachloride forms complexes with pyridine[4] and nitrobenzene.[5] With titanium tetrachloride solvent, it is not known whether the increased temperature required for reaction is due to complexing or to a concentration influence.

(1) Part IX of a series on "Reactions of Metal Halides with Organic Compounds"; from the Ph.D. thesis of A. K. Sparks, Case Institute of Technology, 1960.

(2) Allied Chemical Corporation Fellow, 1958–1960.

(3)(a) P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, **76**, 5491 (1954); (b) P. Kovacic and A. K. Sparks, *J. Am. Chem. Soc.*, **82**, 5740 (1960).

(4) J. C. Hutton and H. W. Webb, *J. Chem. Soc.*, 1518 (1931).

(5) T. Maki and M. Yokote, *J. Soc. Chem. Ind., Japan*, **39** (suppl.), 442 (1936); *Chem. Abstr.*, **31**, 4499 (1937).

TABLE I

SOLVENT AND CATALYTIC EFFECTS

Solvent or Catalyst	Mole	C_6H_5Cl, Mole	$SbCl_5$, Mole	Time, hr.	Temp.	Dichlorobenzene Yield, %	*o*	*m*	*p*
—	—	2	0.5	2	41–59	82	15	1	84
$TiCl_4$	1	1	.25	3.1	80–92[a]	66	20	1	79
$C_6H_5NO_2$	1	1	.25	6.2	70–102[a]	76	16	1	83
C_5H_5N	1	1	.25	2.5	124	0	—	—	—
$TiCl_4$	0.5	0.5	.125	2.0	82–84	68[b]	—	—	—
$C_6H_5NO_2$	.5	.5	.125	2.0	82–84	67[b]	—	—	—
$AlCl_3$	.01	2	.5	1.2	24–38	81	16	1	83
$CuCl_2$	.02	2	.5	2.6	42–50[a]	93	16	1	83

[a] Hydrogen chloride was first detected at the lower temperature. [b] Isomer distribution not determined.

In an investigation of possible catalytic effects, no alteration in the isomer distribution of the chlorinated aromatic compound resulted from the concomitant use of small amounts of aluminum chloride or cupric chloride.

The mechanism which has been proposed[3b] for aromatic chlorination by antimony pentachloride is consistent with the observed solvent and catalytic effects.

The mode of addition significantly affects the *ortho/para* ratio, as shown by a decrease from 0.18 for dichlorobenzene from the usual method to 0.065 when chlorobenzene is added to antimony pentachloride. This is probably due to further chlorination of dichlorobenzene during the "reverse addition," entailing a difference in the rates of reaction for the various isomers. The *ortho* isomer is reported[6] to be more reactive than the *para* toward electrophilic reagents.

Increased temperatures produced an increase in the *ortho/para* ratio, as would be expected. It is noteworthy that at mild temperatures prolonging the reaction time resulted in essentially a quantitative yield of dichlorobenzene.

TABLE II

VARIATION OF TIME, TEMPERATURE, AND ORDER OF ADDITION[a]

Time, hr.	Temp.	Dichlorobenzene Yield, %	B.P.	*o*	*m*	*p*
2	41–59	82	170–172	15	1	84
51[b]	25–59	99	171–173	16	1	83
1.3	102–128	81	171–172.6	22	1	77
1.3[c]	23–35	57[d]	170–173	6	1	93

[a] Chlorobenzene (2 moles) and antimony pentachloride (0.5 mole). [b] 3 hr. at 34–59° and the remainder at room temperature. [c] Chlorobenzene was added to antimony pentachloride during 1 hr. of reaction time. [d] Trichlorobenzene (10 g.), b.p. 193–210°, was also obtained.

Since aromatic chlorination by antimony pentachloride produces an isomer distribution different[3] from that obtained by the usual method (chlorine gas-catalyst), the practicality of the antimony pentachloride method was investigated and shown to be promising. By direct distillation of the reaction mixture, by-product antimony trichloride was separated from the chlorinated aromatic product, then treated with chlorine, and the regenerated antimony pentachloride was recycled satisfactorily.

EXPERIMENTAL[7]

Materials. Chlorobenzene (Matheson Coleman and Bell) was dried over sodium sulfate. Commercial toluene was distilled, b.p. 109.4–109.6°, through a 60-cm., helix-packed column. Commercial nitrobenzene was distilled, b.p. 93° (17 mm.), through a 12-in. column. The other materials were commercial products which were used directly.

General procedure. The method is previously described.[3b] In some cases, in place of steam distillation, extraction with dilute hydrochloric acid was used, followed by fractional distillation of the organic phase.

Antimony pentachloride-toluene-aluminum chloride. Toluene (2 moles), containing anhydrous aluminum chloride (0.05 mole), was allowed to react with antimony pentachloride (0.5 mole) at 14–27° according to the general procedure. Fractionation of the steam-volatile material yielded 44 g. of chlorotoluene[8] (*ortho*, 51%; *meta*, 2%; *para*, 47%), and 1.4 g. of dichlorotoluene, b.p. 194–195° (infrared spectrum used in identification).

Antimony pentachloride and chlorobenzene. Regeneration of antimony pentachloride. After the reaction of antimony pentachloride (0.5 mole) with chlorobenzene (2 moles) at 34–59° for 3 hr., the mixture was allowed to stand at room temperature for an additional 48 hr. Direct distillation[9] yielded 71.2 g. (99%) of dichlorobenzene (*o*/*m*/*p* = 16/1/83). Treatment of the residual antimony trichloride with chlorine gas effected the regeneration of antimony pentachloride which was allowed to react with chlorobenzene at 30–37° for 3 hr., yielding 65 g. of dichlorobenzene (83% *para* by m.p.–f.p. determination).

Analytical methods—The infrared and melting point-freezing point methods of analysis have been described.[3]

Acknowledgment. We are grateful to the National Science Foundation for support of part of this work.

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(6) E. H. Huntress, *Organic Chlorine Compounds*, Wiley Inc., New York, 1948, p. 119.

(7) Boiling points are uncorrected.

(8) A similar isomer distribution (*o*/*m*/*p* = 47/2/51) is obtained[3b] in the absence of aluminum chloride.

(9) Direct distillation has also been used[3b] with the reaction mixture from fluorobenzene.

Even-Numbered *n*-Acyl and *n*-Alkyl Ferrocenes

EDWIN L. DEYOUNG[1]

Received August 1, 1960

The Friedel-Crafts acylation with acid chlorides and aluminum chloride was one of the first reactions to be carried out with ferrocene.[2] About a dozen each of *n*-acyl- and *n*-alkyl ferrocenes with various chain lengths have since been prepared.[3-5]

TABLE I

PROPERTIES OF FERROCENES

Substituent	Color	Yield	B.P. or Solvent	M.P.[a] or n_D^{20}	Calcd. C	Calcd. H	Found C	Found H
			ACYL SUBSTITUTED					
1-Ethanoyl-[b]	Red	—	Methanol	81–83°	—	—	—	—
1-Butanoyl-	Red	72%	144–146°/1.5 mm.	1.6073	65.6	6.3	65.8	6.2
1-Hexanoyl-	Orange	88%	161–163°/1.5 mm.	1.5843	67.6	7.0	67.4	7.0
1-Octanoyl-	Orange	91%	Methanol	26–27°	69.2	7.7	69.1	7.4
1-Decanoyl-	Red	84%	203–204°/1.6 mm.	1.5513	70.6	8.2	70.8	8.2
1-Dodecanoyl-	Orange	79%	Methanol	36–37°	71.7	8.6	71.7	8.5
1,1′-Dihexanoyl-	Orange	67%	Methanol	38–39°	69.1	7.8	68.8	7.7
			ALKYL SUBSTITUTED					
1-Ethyl-[c]	Red	67%	107–108°/5 mm.	1.6011	—	—	—	—
1-Butyl-[c]	Red	7%	180°/3/5 mm.	1.5701	—	—	—	—
1-Hexyl-	Orange	93%	139–40°/1.5 mm.	1.5602	71.1	8.1	71.2	8.1
1-Octyl-	Orange	71%	154–155°/1.0 mm.	1.5490	72.5	8.7	72.6	8.7
1-Decyl-	Orange	90%	183–184°/1.4 mm.	1.5399	73.6	9.2	73.9	9.3
1-Dodecyl-	Yellow	96%	Methanol	35–36°	74.6	9.6	74.6	9.6
1,1′-Dihexyl-	Orange	86%	189°/1.6 mm.	1.5320	74.6	9.6	74.8	9.9

[a] Uncorrected. [b] From A. N. Nesmeyanov, E. G. Perevalova, R. V. Goloonya, and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954). [c] From Ref. 3.

To complete an even-numbered series of *n*-acyl and *n*-alkyl ferrocenes, eleven new ferrocenes through dodecyl were synthesized in good yields by the methods of Rausch.[5] After purification by either distillation through a 60 × 8-mm. spinning-band column or recrystallization from methanol, the products were red to yellow liquids and low-melting solids. Table I lists the measured properties.

All of the acyl derivatives showed carbonyl infrared absorption at about 6 μ. The monosubstituted ferrocenes showed infrared absorption bands at 9 to 10 μ.[6]

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(1) Present address: RB&P Chemical & Supply Co., 1640 N. 31st St., Milwaukee 8, Wis.

(2) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

(3) K. L. Rinehart, R. J. Corby, and P. E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957).

(4) A. N. Nesmeyanov and N. S. Kochetkova, *Doklady Akad. Nauk S.S.S.R.*, **109**, 543 (1956).

(5) M. D. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 1016 (1957).

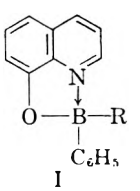
(6) M. Rosenblum, *Chem. & Ind.*, 953 (1958).

8-Quinolinol Derivatives of Borinic Acids

JAMES E. DOUGLASS

Received August 23, 1960

In 1955, Letsinger and Skoog reported that diarylborinic acids react with ethanolamine to form crystalline products.[1] Attempts in this laboratory to prepare such derivatives of several aralkylborinic acids were not uniformly successful, and thus attention was turned to the problem of finding a suitable reagent for making derivatives of these acids. As ethanolamine and 8-quinolinol have in common the critical reactive grouping, HO—C—C—N=, the latter was considered as a possible reagent, and indeed it was found to react with both diaryl- and aralkylborinic acids to form yellow crystalline products (I) which are readily isolated and characterized.[2] Each of the reported compounds (Table I) shows an intense green fluorescence under ultraviolet light.



I

(1) R. L. Letsinger and I. Skoog, *J. Am. Chem. Soc.*, **77**, 2491 (1955).

(2) R. Neu [*Z. anal. Chem.*, **142**, 335 (1954)], in an article describing the use of diphenylborinic acid as a reagent for identifying certain 5-hydroxyflavones, mentioned that this acid also reacts with 8-quinolinol.

TABLE I

8-QUINOLINOL DERIVATIVES OF $C_6H_5—\underset{\displaystyle R}{\underset{|}{B}}—OH$

R	M.P.[a]	Formula	Carbon[b]		Hydrogen[b]		Boron[c]		Neut. Equiv.[d]	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
C_2H_5	152–153	$C_{17}H_{16}BNO$	78.21	78.09	6.17	6.14	4.14	4.10	261	262
i-C_3H_7	87	$C_{18}H_{18}BNO$	78.56	79.23	6.60	6.58	3.93	3.88	275	275
t-C_4H_9	108–109	$C_{19}H_{20}BNO$	78.91	78.65	6.97	7.29	3.74	3.70	289	291
$C_6H_5CH_2$[e]	133–133.5	$C_{22}H_{18}BNO$	81.75	81.27	5.62	5.66	3.35	3.34	323	325
C_6H_5	204–205[f]	$C_{21}H_{16}BNO$	81.47	81.84	5.22	5.30	3.50	3.48	309	308

[a] Melting points are corrected. [b] Analyses by Drs. Weiler and Straus, Oxford, England. [c] Boron analyses by the method described by J. M. Thoburn, Dissertation, Northwestern University, 1954. [d] By titration with perchloric acid in glacial acetic acid; sample dissolved in acetic acid–acetic anhydride (4 to 1). [e] This compound does form a crystalline aminoethyl ester, m.p. 211–213°; reported[5] m.p. 208–212.5°. [f] Reported[2] m.p. 203°.

The 8-quinolinol derivatives are stable in air (no indication of decomposition over a period of several months) and resist hydrolysis in neutral aqueous ethanol (as judged by the persistence of strong fluorescence for several weeks).

Each of these compounds has an absorption maximum in chloroform in the region 397–405 mμ (ϵ 2700–3100). These data, joined with those of Moeller and Cohen, who found that the 8-quinolinol chelates aluminum, gallium, indium, and thallium have λ_{max} in the same region (390–401 mμ),[3] indicate that absorption near 400 mμ is characteristic of the 8-quinolinol chelates of all the Group III-A elements.

EXPERIMENTAL

Boronic acids. The previously reported ethylphenylborinic acid[4] and benzylphenylborinic acid[5] were prepared as described by Torssell[4]; the previously unreported isopropylphenylborinic acid was prepared similarly. Diphenylborinic acid was prepared by the method of Povlock and Lippincott.[6]

t-Butylphenylborinic acid. As conventional methods for the preparation of unsymmetrically substituted borinic acids[7] failed to give detectable amounts of this acid, its synthesis will be described in some detail.

A solution of *t*-butylmagnesium chloride (0.1 mole) in 45 ml. of dry tetrahydrofuran was added dropwise to a well stirred solution of 10.4 g. (0.10 mole) of benzeneboronic anhydride (triphenylboroxin)[8] in 150 ml. of dry tetrahydrofuran cooled to 0° and under an atmosphere of dry nitrogen. After the addition was complete (about 30 min.), stirring at 0° was continued for 1 hr. The mixture was then hydrolyzed with 100 ml. of 3*M* hydrochloric acid, the two layers were separated, and the solvent was evaporated under reduced pressure from the organic layer to give 2.6 g. (16%) of crude product.[9]

8-Quinolinol derivatives. An equivalent amount of 8-quinolinol (in a 20% solution of 95% alcohol) was added to a solution of the crude borinic acid (about 0.5 g. of acid per 10 ml. of 95% alcohol); in most cases the product crystallized immediately and in high yield. The crude derivatives were recrystallized from 95% alcohol, with the exception of the diphenyl derivative which was more conveniently recrystallized from methanol-tetrahydrofuran (3 to 1).

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5-Substituted Derivatives of 3-Methylpyrrolidinone-2

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Received August 18, 1960

In the light of a recent investigation[4] in which is described a concomitant addition and cyclization between acrylic esters and diethyl acetamidomalonate to form 2-pyrrolidinone derivatives, it became of interest to prepare various carboxylic acid derivatives utilizing one or both of the carboxyl groups of the pyrrolidinone prepared from diethyl acetamidomalonate and ethyl methacrylate as indicated in Fig. 1.

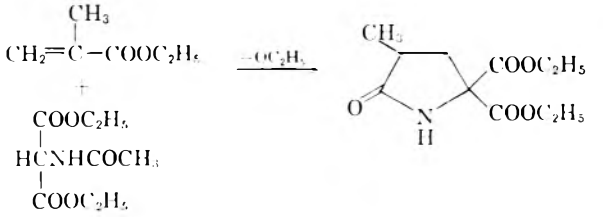

Figure 1

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(4) G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5023 (1958).

TABLE I

5-SUBSTITUTED DERIVATIVES

3-Methylpyrrolidinone-2	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	M.P.[a]	Yield, %
Intermediates					
5,5-Dicarbethoxy-	$C_{11}H_{17}NO_5$	5.76	5.75, 5.71	111–113	91
5-Carboxy-	$C_6H_9NO_3$	9.79	9.80, 9.82	153–156 (lit. 175°)[c]	55
5-Carbethoxy-	$C_8H_{13}NO_3$	8.18	8.02, 8.03	55–57	64
Diamides					
5,5-Dicarbohydrazino-	$C_7H_{14}N_6O_3$	32.54	31.90, 31.99	183–184	92
5,5-Diallylcarbamyl-	$C_{13}H_{19}N_3O_3$	15.84	16.05, 16.01	205–210/0.05 mm.[b]	65
5,5-Di-β-diethylaminoethylcarbamyl-	$C_{19}H_{36}N_3O_3$	18.26	18.21, 18.20	215–217/0.03 mm.[b]	79
5,5-Di-γ-methoxypropylcarbamyl-	$C_{15}H_{27}N_3O_5$	12.76	12.38, 12.35	202–205/0.05 mm.[b]	65
Monoamides					
5-Carbohydrazino-	$C_6H_{10}N_3O_2$	26.74	26.36, 26.78	149–150	71
5-β-Dimethylaminoethylcarbamyl-	$C_{10}H_{19}N_3O_2$	19.70	19.07, 19.28	152–154	82
5-γ-Dimethylaminopropylcarbamyl	$C_{11}H_{21}N_3O_2$	18.49	18.14, 17.95	135–138	45
5-β-Morpholinoethylcarbamyl-	$C_{12}H_{21}N_3O_3$	16.46	16.19, 16.20	152–154	82
Esters					
5-*N*,*N*-Dimethylcarbamylcarbomethoxy-	$C_{10}H_{16}N_2O_4$	12.27	12.01, 11.95	150–152	72
5-*N*,*N*-Diallylcarbamylcarbomethoxy-	$C_{14}H_{20}N_2O_4$	9.99	9.92, 9.93	80–82	62
Misc.					
Spirobarbituric acid-5,5′-	$C_8H_8N_4O_4$	19.90	19.85, 19.87	269–272	64

[a] All readings are uncorrected. [b] Boiling points. [c] J. Fillman and N. Albertson, *J. Am. Chem. Soc.*, 74, 4969 (1952).

The 5-mono- and 5,5-dicarboxylic esters (IV, I) were conveniently converted to the mono- and diamides by heating with the corresponding amine. It was expedient in the synthesis of monoamides to prepare the intermediate ester (IV) from the monocarboxylic acid (III) which could be easily separated from the reaction mixture.

The monoesters (XIII, XIV) were prepared from the corresponding 3-methyl-5-carboxypyrrolidinone-2 (III) using the appropriate chloroacetamide and triethylamine.

Listed in Table I are the compounds prepared.

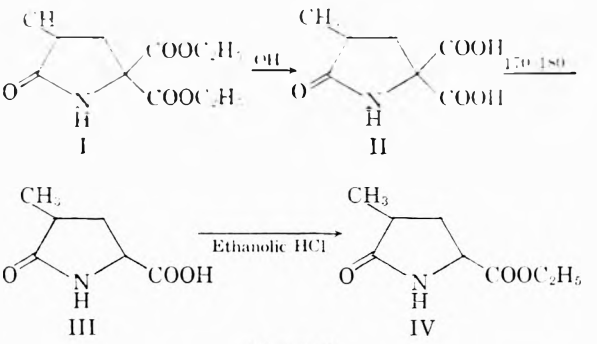

Figure 2

EXPERIMENTAL

3-Methyl-5,5-dicarbethoxypyrrolidone-2 (I). Two hundred and seventy-five grams of ethyl methacrylate were added to a mixture of 655 g. of diethyl acetamidomalonate in 1500 ml. of ethanol containing 6.9 g. of dissolved sodium metal and the mixture refluxed for 5–6 hr. The condenser was then set for downward distillation and the ethanol removed with the aid of a steam bath. The last traces of solvent were removed by application of a water aspirator to leave a solid residue. The residue was taken up in 1 l. of boiling benzene and filtered free from insoluble sodium ethoxide and methacrylate polymer. On cooling the filtrate 576 g. of 3-methyl-5,5-dicarbethoxypyrrolidinone-2 (I) precipitated, m.p. 108–110°. Concentration of the mother liquor yielded 83 g. more of I. A sample recrystallized for analysis melted at 113–115°.

3-Methyl-5-carboxypyrrolidinone-2 (III). A solution of 240 g. of potassium hydroxide in 750 ml. of water was added dropwise to a warm solution of 315 g. of 3-methyl-5,5-dicarbethoxypyrrolidinone-2 (I) in 750 ml. of ethanol. The mixture was refluxed for 20 hr. and then concentrated to 300 ml. under reduced pressure. The residue was cooled to 0° and then treated with 360 ml. of concd. hydrochloric acid and 200 ml. of acetone. The potassium chloride which precipitated was filtered and the filtrate was concentrated to 200 ml. *in vacuo* at room temperature. The 3-methyl-5,5-dicarboxypyrrolidinone-2 (II) which precipitated from the solution was collected (185 g., crude) and the filtrate cooled to precipitate 35 g. more of II, m.p. 158–159°. The melting point was accompanied by effervescence. The crude dicarboxylic acid was fused at 170–180° for 2 hr. and the residue taken up in 150 ml. of ethanol. A small amount of potassium chloride which remained insoluble was removed by filtration and the filtrate was concentrated to one half its original volume and cooled. Petroleum ether (b.p. 30–60°) was added to aid in precipitating 90 g. of 3-methyl-5-carboxypyrrolidinone-2 (III). Two recrystallizations from ethanol gave an analytical sample, m.p. 153–156°.

3-Methyl-5-carbethoxypyrrolidinone-2 (IV). A solution of 35 g. of 3-methyl-5-carboxypyrrolidinone-2 (III) in 200 ml. of ethanol saturated with anhydrous hydrogen chloride was allowed to stand at room temperature for 2 days. The solvent was then removed *in vacuo* with the aid of a steam bath and the residue was taken up in benzene and washed with an aqueous solution of potassium carbonate. The organic layer was dried over anhydrous potassium carbonate and distilled to collect 3-methyl-5-carbethoxypyrrolidinone-2 (IV), b.p. 120–126° at 0.1 mm. The distillate solidified on standing and was rubbed with petroleum ether (b.p. 30-

60°) to a fine crystalline solid, m.p. 55–57° which weighed 26.6 g.

3-Methyl-5,5-dicarbohydrazinopyrrolidinone-2 (V). A mixture of 24.3 g. of I, 15 g. of 64% aqueous hydrazine hydrate and 100 ml. of ethanol was refluxed for 2 hr. The reaction mixture was cooled to precipitate 20.0 g. of 3-methyl-5,5-dicarbohydrazinopyrrolidinone-2 (V). The product was recrystallized from a mixture of water-ethanol, m.p. 183–184°.

3-Methyl-5-carbohydrazinopyrrolidinone-2 (VI). The same procedure as described above was employed using 8.5 g. of the monocarboxylic ester (IV), 8.0 g. of 64% aqueous hydrazine hydrate in 50 ml. of ethanol to give 5.5 g. of 3-methyl-5-carbohydrazinopyrrolidinone-2 (VI). Recrystallization from an ethanol-ether mixture gave a product melting at 149–150°.

3-Methyl-5,5-diallylcarbamylpyrrolidinone-2 (VII). A mixture of 23.4 g. of I and 25 g. of allylamine were refluxed for 8 hr. at which time the unchanged amine was recovered by distillation. The residue was distilled under high vacuum and the fraction boiling at 195–210° at 0.05 mm. was collected. Redistillation of the oil gave an analytically pure sample of VII, b.p. 205–210° at 0.05 mm.

3-Methyl-5,5-di-β-diethylaminoethylcarbamylpyrrolidinone-2 (VIII). A mixture of 24.3 g. of I and 30 g. of *N,N*-diethylethylenediamine was heated on an oil bath at 150° for 2 hr. The unchanged amine was removed under reduced pressure and the residue distilled to collect 25.0 g. of VIII, b.p. 215–217° at 0.03 mm.

3-Methyl-5,5-di-γ-methoxypropylcarbamylpyrrolidinone-2 (IX). This compound was prepared in the manner described in the preceding experiment. A viscous amber oil, b.p. 202–205° at 0.03 mm., having a tendency to solidify on standing was obtained.

3-Methyl-5-β-morpholinoethylcarbamylpyrrolidinone-2 (X). Ten grams of IV and 30 g. of 4-β-aminoethylmorpholine were heated on an oil bath at 150° for 3 hr. The unchanged 4-β-aminoethylmorpholine was removed *in vacuo* and the residue taken up in ethanol and cooled to precipitate 12.0 g. of the product (X), m.p. 151–154°. One recrystallization from ethanol gave an analytically pure sample, m.p. 152–154°.

3-Methyl-5-β-dimethylaminoethylcarbamylpyrrolidinone-2 (XI). The same procedure was employed as described directly above. Ten grams of IV and 25 g. of *N,N*-dimethylethylenediamine yielded 7.4 g. of the product XI, m.p. 152–154° after recrystallization from alcohol.

3-Methyl-5-γ-diethylaminopropylcarbamylpyrrolidinone-2 (XII). The same procedure was employed as is described above. Ten grams of IV and 30 g. of *N,N*-dimethyl-1,3-diaminopropane yielded 6.0 g. of XII, m.p. 135–138°.

3-Methyl-5-N,N-dimethylcarbamylcarbomethoxypyrrolidinone-2 (XIII). A mixture of 10 g. of 3-methyl-5-carboxypyrrolidinone-2 (III), 20 g. of α-chloro-*N,N*-dimethylacetamide,[5] and 7.0 g. of triethylamine in 50 ml. of toluene was refluxed for 6 hr. The reaction was then stripped of its solvent under reduced pressure and the unchanged chloroacetamide distilled *in vacuo*. The residue was then dissolved in 25 ml. of ethanol and chilled to precipitate 11.5 g. of the crystalline product XIII, m.p. 148–151°. Recrystallization from ethanol gave an analytically pure sample, m.p. 150–152°.

3-Methyl-5-N,N-diallylcarbamylcarbomethoxypyrrolidinone-2 (XIV). The same procedure was employed as described above. Seven grams of III and 20 g. of α-chloro-*N,N*-diallylacetamide in the presence of 6.5 g. of triethylamine in 50 ml. of toluene yielded 8.5 g. of the crystalline product XIV, m.p. 78–81°. Recrystallization from a mixture of ethanol-ether gave a pure product, m.p. 80–82°.

Spirobarbituric acid-5,5-(3-methylpyrrolidinone-2) (XV). Three grams of magnesium turnings were dissolved in 75 ml. of methanol by refluxing for 1 hr. A mixture of 20 g. of I and 10 g. of urea dissolved in 100 ml. of methanol was added to the methanolic magnesium solution. The reaction was refluxed for 15 min. at which time the spirobarbituric acid derivative began to precipitate. Refluxing was continued for 15 min. more before cooling the mixture and collecting the product on a Buchner funnel. The precipitate was washed with ethanol and water to give 11.7 g. of XV, m.p. 269–272° with browning at 250°.

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Synthesis of Potential Antiviral Agents. Part II. Pyridine Derivatives

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Received July 14, 1960

In Part I compounds directly related to isatin-β-thiosemicarbazone were examined,[1] in this, formylpyridine derivatives have been investigated, some of which have detectable antiviral activity (4-formylpyridine thiosemicarbazone has approximately 10% the antivaccinial activity of isatin-β-thiosemicarbazone). The order of antivaccinial action of the formylpyridine thiosemicarbazones is 4>3>2; this is not the same as the order of chemical reactivity, *i.e.*, 2>4>3. Replacement of the formyl hydrogen atom by a methyl group abolishes activity, as acetylpyridine thiosemicarbazones are inactive. In both groups of compounds the 2-derivatives are the most toxic. Quaternization of 4-formylpyridine thiosemicarbazone results in loss of activity, as also does quaternization of *p*-dimethylaminobenzaldehyde thiosemicarbazone; but ferric chloride oxidation, which forms the corresponding 2-amino-4-pyridyl thiodiazole I, does not affect the antivaccinial activity. Therefore, this cyclization may be reversible *in vivo*. Modification of the side chain produces the usual effects, as substitution in the 2′-position or replacement of sulfur by oxygen, *i.e.*, 2-, 3-, and 4-formylpyridine semicarbazones, results in inactive compounds.

The most notable structural difference between *N*-alkylisatin-β-thiosemicarbazones, which show pronounced antivaccinial and antivariola activity,[2] and the less active formylpyridine thiosemicarbazones, is the absence of an α-carbonyl group in the latter. The α-carbonyl group of isatin-β-thiosemicarbazone has been shown to be essential for the retention of antivaccinial activity,[3] and is also involved in the formation of an intramolecular hydrogen bond with the 2′-imino hydrogen atom. Therefore, two pyridine derivatives were prepared which could possess related intramolecularly bonded structures.

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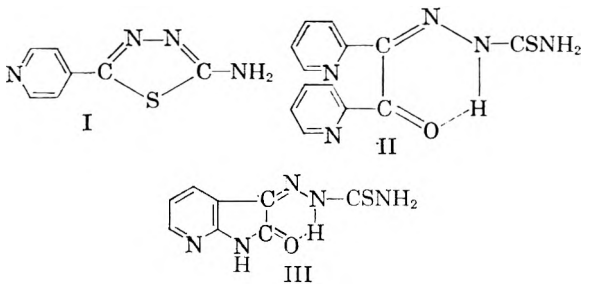

I II III

Infrared spectra of α-pyridilmonothiosemicarbazone II and 7-pyrisatin-β-thiosemicarbazone III showed lowering and broadening of the 2′-imino N—H and carbonyl stretching frequencies characteristic of hydrogen bonding, and dilution studies indicated that this was mainly intramolecular, but neither II nor III possess antivaccinial activity. This finding is perhaps not surprising in the case of II as benzilmonothiosemicarbazone is also inactive, but the lack of activity of III suggests that isatin and pyridine derivatives exert their antivaccinial effects by completely different routes.

EXPERIMENTAL

Spectra. Compounds were examined as potassium bromide discs and in solution in chloroform, a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock salt prism being used.

Test of antiviral activity. Groups of mice infected intracerebrally with about 1,000 LD 50 of the IHD strain of neurovaccinia virus were treated with doses of 125 mg./kg. and the survival times were compared with those of a control group of mice which were similarly infected but left untreated.[4] Compounds which gave no significant reduction of the mean reciprocal survival time at this dose were considered to be inactive.

Thiosemicarbazones of 2-, 3- and 4-formylpyridine and 2-, 3- and 4-acetylpyridine were prepared by standard methods and had melting points in agreement with those reported.[5, 6]

4-Formylpyridine-2′-phenylthiosemicarbazone. Equimolar quantities of 2-phenylthiosemicarbazide[7] and 4-formylpyridine were refluxed for 1 hr. in ethanol. The product which separated on cooling was recrystallized from ethanol, m.p. 207°.

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 61.4; H, 4.7; N, 22.1; S, 12.6. Found: C, 61.2; H, 4.8; N, 21.6; S, 12.4.

4-Formylpyridiniumthiosemicarbazonemethiodide. To a hot solution of 12.5 g. of 4-formylpyridinium methiodide[8] in 100 cc. of water was added 4.6 g. of thiosemicarbazide in an equal volume of hot water. A yellow product 12.3 g., m.p. 251°, was obtained on cooling, which after recrystallization from water had a melting point of 252°.

Anal. Calcd. for $C_8H_{11}N_4SI$: C, 33.3; H, 3.5; N, 17.3. Found: C, 33.1; H, 3.5; N, 17.7.

4-Formyltrimethylanilinium iodide thiosemicarbazone was obtained as pale yellow plates, m.p. 209°, by a similar method.

Anal. Calcd. for $C_{11}H_{17}N_4SI$: C, 36.2; H, 4.7; S, 8.8. Found: C, 36.2; H, 4.6; S, 9.0.

α-Pyridilmonothiosemicarbazone. α-Pyridil 21.2 g. and thiosemicarbazide 9.1 g. were heated under reflux in 200 cc. ethanol for 24 hr. The product was removed from the hot reaction mixture, washed well with hot water and crystallized from butyl alcohol, m.p. 212°.

Anal. Calcd. for $C_{13}H_{11}N_5SO$: C, 54.6; H, 3.9; S, 11.5. Found: C, 54.6; H, 3.8; S, 11.7.

7-Pyrisatin-β-thiosemicarbazone was prepared from 7-pyrisatin[9] in the usual manner,[3] recrystallization from aqueous ethanol gave yellow needles which decomposed at 285°.

Anal. Calcd. for $C_8H_7N_5SO$: C, 43.4; H, 3.2; S, 14.5. Found: C, 43.2; H, 3.2; S, 14.3.

2-Amino-4-pyridylthiodiazole. Ferric chloride 30 g. was added to 15.9 g. of finely ground 4-formylpyridinethiosemicarbazone in 300 cc. water at 85° and stirred vigorously for 0.5 hr.[10] The reaction mixture was filtered and the filtrate concentrated to 100 cc. and chilled, giving the hydrochloride of the base as white plates, m.p. 260°. Treatment with 2*N* ammonium hydroxide solution gave a yellow amorphous precipitate, m.p. 225°, which was raised to 226° on crystallization from ethanol.

Anal. Calcd. for $C_7H_6N_4S$: C, 47.1; H, 3.4; N, 31.5; S, 18.4. Found; C, 47.2; H, 3.4; N, 31.6; S, 18.2.

Acknowledgment. The author thanks Dr. D. J. Bauer for the antivaccinial assay data, Dr. H. Kägi for a gift of 7-pyrisatin and Miss Carole Brown and Miss Toinette Smalley for assistance.

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(4) D. J. Bauer, *Brit. J. Exp. Path.*, **39**, 480 (1958).

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Naphthoquinone Chemistry. 6H,11H-Benzo[*f*]pyrido[*a*]benzimidazole-6,11-dione

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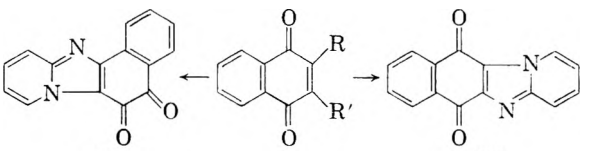
Received July 18, 1960

In Part I of these studies,[1] it was shown that 2,3-dichloro-1,4-naphthoquinone (I. R = R′ = Cl) reacted with 2-aminopyridine to yield the angular quinone II. This same product was produced[1] by the reaction of 2-aminopyridine with either



II I III

2-acetamido-3-chloro-1,4-naphthoquinone (I. R = Cl, R′ = NHAc) or 3,4-dichloro-1,2-naphthoquinone.

However, the reaction of 2-aminopyridine with 2-hydroxy(or ethoxy or acetoxy)-3-chloro-1,4-naphthoquinone (I. R = OH, or OC_2H_5 or OAc, R′ = Cl) took a different course, and the *linear* quinone III was produced. Although the formation of III

(1) W. L. Mosby and R. J. Boyle, *J. Org. Chem.*, **24**, 374 (1959).

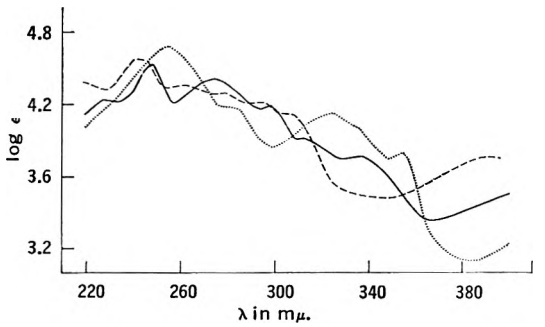


Fig. 1. The ultraviolet spectra in ethanol of Compound II (----), Compound III (———), and of 2,3-Phthaloylpyrrocoline (.....)

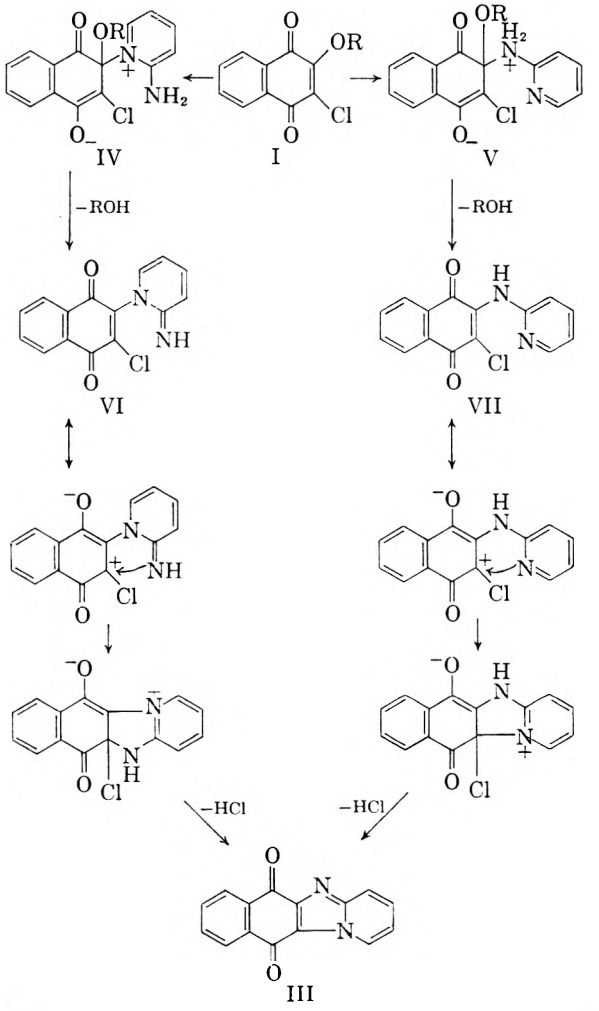
was less efficient (the yield of pure product is ~34%) than that of II, and required more vigorous reaction conditions, the quinone was easily isolated, and it did not appear to be accompanied by any of the angular isomer (II). The linear quinone formed golden-tan needles having distinctly different melting point, infrared and ultraviolet spectra from those of the angular isomer. A mixture melting point of II with III showed an appreciable depression. That the new quinone was indeed the linear isomer, and not the second possible angular isomer (see Part I),[1] was demonstrated by the reduction of III to the known[2] 1,2,3,4-tetrahydro derivative, and by the failure of III to form a phenazine when treated with *o*-phenylenediamine. The linear quinone had erroneously been reported[3] to be the product of the reaction of I (R = R′ = Cl) with 2-aminopyridine.

Fig. 1 shows the ultraviolet absorption spectra of the quinones II and III compared with that of the known[4] 2,3-phthaloylpyrrocoline.

As mentioned, rather vigorous conditions (refluxing ethyleneglycol dimethyl ether) were required for the production of III. Refluxing the reactants in ethyl acetate for many hours failed to produce III, and the naphthoquinone (I. R = Cl, R′ = OC_2H_5) was recovered. Under these same conditions 2-acetoxy-3-chloro-1,4-naphthoquinone also failed to form III, but, unlike the ethoxy homolog, it suffered hydrolysis to the red 2-aminopyridine salt of 2-chloro-3-hydroxy-1,4-naphthoquinone. As 2-hydroxy- and 2-hydroxy-3-chloro-1,4-naphthoquinones are known to be reasonably strong acids, it is not surprising that the products of their reaction with 2-aminopyridine (in ethyl acetate or toluene) are merely the 2-aminopyridine salts. These red salts are stable to recrystallization, but treatment with acetic anhydride readily yields the corresponding acetoxy-1,4-naphthoquinones. However, when the initially formed red salt of 2-hydroxy-3-chloro-1,4-naphthoquinone and 2-aminopyridine is heated in ethyleneglycol dimethyl ether the red color quickly changes to brown, and III is produced.

The formation of III appears to be a curiously circumscribed reaction. Attempts to replace 2-aminopyridine with 2-aminopyrimidine or 2-aminopyrazine gave only carbonaceous matter and not the aza homologs of III. Also, 2-aminopyridine failed to react with 2,3-bismethylthio-1,4-naphthoquinone (I. R = R′ = SCH_3) or with 2-acetamido-3-methoxy-1,4-naphthoquinone (I. R = $NHCOCH_3$, R′ = OCH_3) to produce III, and the quinones were recovered. Efforts to prepare III by treating 2-aminopyridine with 2-bromo-1,4-naphthoquinone yielded mixtures of dark intractable products, and under these conditions, 1,4-naphthoquinone itself is rapidly and efficiently converted into triphthaloylbenzene.[5]

From the information available, one may draw certain inferences concerning the mechanism of the reaction producing III. In the earlier study[1] of the reactions of 2,3-dichloro-1,4-naphthoquinone



(2) W. L. Mosby, *J. Org. Chem.*, **24**, 419 (1959).

(3) P. Truitt, J. E. Cooper, and F. M. Wood, *J. Am. Chem. Soc.*, **79**, 5708 (1957).

(4) R. V. Acharya, B. Suryanarayana, and B. D. Tilak, *J. Sci. Ind. Research*, **14B**, 394 (1955); *Chem. Abstr.*, **50**, 12971 (1956).

(5) R. Pummerer, A. Pfaff, G. Riegelbauer, and E. Rosenhauer, *Ber.*, **72**, 1623 (1939).

(6) L. F. Fieser, *J. Am. Chem. Soc.*, **48**, 2922 (1926).

leading to II, both 1,2- and 1,4-addition mechanisms were considered. It seems evident, however, that III could not be formed by 1,2-addition of aminopyridine to the quinone carbonyl groups. One can envision four possible structures for the initial reaction intermediate produced by 1,4-addition and attachment of either the ring nitrogen or the amino group to the carbon atom of II bearing either the chlorine or the oxygen function. Insomuch as Fieser has shown[6] that 2-ethoxy-3-chloro-1,4-naphthoquinone yields the 2-anilino-3-chloro compound when treated with aniline, structures IV and V appear more attractive for the initial intermediate than do the two alternative possibilities. The formation of III could then occur from either IV or V by the paths shown. Now VI and VII could, *a priori*, also be produced by the 1,4-addition of 2-aminopyridine to 2,3-dichloronaphthoquinone, and in Part I[1] it was remarked that if such were the case, it is curious that III was not produced instead of II. As III is produced in the present reactions, it seems probable that VI (or VII) is not an intermediate in the formation of II, and this lends weight to the probability that the reaction of 2-aminopyridine and 2,3-dichloronaphthoquinone occurs by a 1,2- and not a 1,4-addition mechanism.

While the foregoing may provide a useful working hypothesis, it is in no way a complete explanation of the problem. Left unexplained, for example, are the curious differences in the behavior of I (R = Cl, R′ = OH, OCH_3, or $OCOCH_3$) and 2-acetamino-3-chloro-1,4-naphthoquinone,[1] and the nonreactivity of I (R = OCH_3, R′ = $NHCOCH_3$, or R = R′ = SCH_3) with 2-aminopyridine.

EXPERIMENTAL[7]

6H,11H-Benzo[f]pyrido[a]benzimidazole-6,11-dione (III). A mixture of 2.36 g. of 2-ethoxy-3-chloro-1,4-naphthoquinone,[8] 2.00 g. of 2-aminopyridine, and 5 ml. of dry ethyleneglycol dimethyl ether ("Diglyme") was stirred and boiled under reflux for 20 hr., then was diluted with water and filtered. The dark solid (2.28 g.) was dissolved in acetic acid, diluted with water, refiltered, and washed well with water and methanol. Vacuum sublimation of this material, (weight 1.60 g.) gave 1.08 g. of yellow-brown needles. Crystallization from chlorobenzene gave 0.85 g. (34.3% yield) of golden-tan needles, m.p. 297–298°, λ_{max} 227, 242.5*, 248, 275, 298, 312, and 336 mμ (ϵ 17,450, 26,570, 34,140, 25,900, 15,450, 8,320, 3,735).

This same product was obtained by this procedure when the ethoxychloronaphthoquinone was replaced by either hydroxychloro- or acetoxychloronaphthoquinone.

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.57; H, 3.25; N, 11.29; O, 12.80. Found: C, 72.45; H. 3.41; N, 10.93; O, 12.80.

1,2,3,4-Tetrahydro-6H,11H-benzo[f]pyrido[a]benzimidazole-6,11-dione. Hydrogenation of I in ethanol over Adams catalyst, and air-oxidation of the resulting hydroquinone produced the tetrahydro compound, which crystallized from acetonitrile in yellow needles, m.p. 251–252°, having an infrared spectrum identical with that of the material prepared[2] by another route.

2-Aminopyridine salt of 2-chloro-3-hydroxy-1,4-naphthoquinone. A solution of 2.09 g. of 2-chloro-3-hydroxynaphthoquinone and 1.00 g. of 2-aminopyridine in 45 ml. of ethyl acetate was stirred and boiled for 0.25 hr., then cooled and filtered. The bright red solid weighed 2.84 g. (100% yield) and melted at 174–176°. A sample crystallized twice from acetonitrile formed brick red microcrystals, m.p. 178.4–179.4°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_3$: C, 59.50; H, 3.63; Cl, 11.72; N, 9.25; O, 15.85. Found: C, 59.48; H, 3.55; Cl, 11.71; N, 9.13; O, 16.00.

Acknowledgment. The author is indebted to Dr. J. L. Gove for the infrared spectra, Mr. A. M. Ferri for the ultraviolet spectra, and Mr. O. E. Sundberg and his associates for the microanalyses.

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(7) All melting-points were taken in Pyrex capillaries using a Hershberg melting-point apparatus and Anschütz thermometers.

(8) L. F. Fieser and R. H. Brown, *J. Am. Chem. Soc.*, **71**, 3609 (1949).

A Convenient Preparation of the 1-Methyl Betaines of Pyridine Carboxylic Acids

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The 1-methyl betaines of the various pyridine carboxylic acids have been prepared in many ways. For example, pyrolysis of methyl *iso*-nicotinate has afforded the 1-methyl betaine of isonicotinic acid[2] in fair yield. The various betaines have also been prepared by methylation of the acid with methyl iodide followed by treatment with silver oxide,[3] and by methylation with methyl sulfate followed by treatment with barium hydroxide.[4] Ion exchange columns have also been used. The methiodides of the three pyridine carboxylic acids were converted to the corresponding betaines by passing the solutions through a quaternary ammonium resin in the hydroxide form.[5]

These preparations suffer from several disadvantages. Those that use silver oxide invariably afford dark solutions and betaines that are difficult to purify. The use of strong base hydroxide exchange columns on the acid salts necessitates the use of very dilute solutions, for the heat of neutralization of the strong base with the acid salt liberates a considerable amount of heat. This latter

(1) Ohio Oil Company Fellow, 1958–1959. The authors are grateful to the Research Committee of the Graduate School for support from funds granted by the Wisconsin Alumni Research Foundation.

(2) M. L. Black, *J. Phys. Chem.*, 59, 670 (1955).

(3) A. Kirpal, *Monatsh.*, 24, 519 (1903).

(4) F. A. Hoppe-Seyler, *Z. Physiol. Chem.*, 222, 105 (1933).

(5) R. W. Green and H. K. Tong, *J. Am. Chem. Soc.*, 78, 4896 (1956).

problem is particularly serious for homarine, which is very temperature sensitive and decarboxylates readily, with the formation of dark solutions.

The best solution to the problem is to use a strong base ion-exchange resin to hydrolyse an ester rather than to neutralize the acid salts. The heating problem mentioned above is eliminated, as the saponification of the ester salt is not particularly exothermic. The procedure has the added advantage in that the ester methiodides can be easily purified by recrystallization before use, in contrast to the methiodides of the free acids which are difficult to separate from unreacted acid.

The eluate from passage of the ester methiodide through a strong base hydroxide column is neutral, colorless, and iodide free. Evaporation of the aqueous solutions using a rotary evaporator at room temperature readily affords the hydrated betaines in colorless crystalline form of high purity and in high yield.

EXPERIMENTAL[6]

1-Methyl betaine of isonicotinic acid. A solution of 5.00 g. (17.0 mmoles) of 1-methyl-4-carbomethoxy pyridinium iodide, m.p. 189–191° dec.,[7] in 50 ml. of water was passed through a 2 cm. × 15 cm. column of Dowex-1 in the hydroxide form. The column was eluted with 50 ml. of water and the neutral, colorless, iodide free eluate evaporated on a rotary evaporator at room temperature to a semisolid paste. To this was added 10 ml. of ethanol and the white solid filtered, giving 2.08 g., m.p. 286–289° (immediate decrepitation and loss of water when the sample was placed in the melting point apparatus, decomposition at the melting point). The addition of a few milliliters of ether to the mother liquor afforded an additional 0.28 g., m.p. 286–288°. Total yield 89.5%. Reported[2] m.p. 264° (anhydrous).

Anal. Calcd. for $C_7H_7O_2N \cdot H_2O$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.31; H, 5.63; N, 8.97.

Picrate of 1-methyl betaine of isonicotinic acid. To a solution of the betaine in alcohol was added a saturated alcoholic solution of picric acid, giving a yellow picrate, m.p. 214–216°; reported[4] m.p. 215–217°.

Anal. Calcd. for $C_{13}H_{10}O_9N_4$: C, 42.63; H, 2.75; N, 15.30. Found: C, 42.87; H, 2.74; N, 15.49.

Trigonelline. A solution of 5.00 g. (17.0 mmoles) of 1-methyl-3-carbomethoxy pyridinium iodide, m.p. 128–130° dec.[8] in 50 ml. of water was passed through a 2 cm. × 15 cm. column of Dowex-1 in the hydroxide form. The column was eluted with 50 ml. of water and the neutral, colorless, iodide free eluate evaporated on a rotary evaporator at room temperature to a semisolid paste. To the paste was added 10 ml. of ethanol and the white crystalline solid filtered off, giving 1.70 g., m.p. 230–233° (immediate decrepitation and loss of water when the sample was placed in the melting point apparatus, decomposition at the melting point). The addition of a few milliliters of ether to the mother liquor gave an additional 0.60 g., m.p. 230–233°. Total yield 87.4%. Reported[9] m.p. 218°.

Anal. Calcd. for $C_7H_7O_2NH_2O$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.80; H, 6.02; N, 9.01. Several analyses of the trigonelline hydrate were made by several microanalytical laboratories. The first two analyses were high in carbon by about 0.40%. The third sample was recrystallized from alcohol and was low in carbon by 0.39%, and is the one reported here.

Trigonelline picrate. To an alcoholic solution of trigonelline was added a saturated solution of picric acid in alcohol, giving a yellow picrate, m.p. 204–205°, reported[9] 205–206°.

Anal. Calcd. for $C_{13}H_{10}O_9N_4$: C, 42.63; H, 2.75; N, 15.30. Found: C, 42.76; H, 2.74; N, 15.52.

Homarine. A solution of 5.00 g. (17.0 mmoles) of 1-methyl-2-carbethoxy pyridinium iodide, m.p. 108–109,[8] in 50 ml. of water was passed through a 2 cm. × 18 cm. column of Dowex-1 in the hydroxide form and eluted with 50 ml. of water. The neutral, colorless, iodide free eluate was evaporated on a rotary evaporator at room temperature to a semisolid paste. To the paste was added 10 ml. of ethanol and the betaine filtered off to give 0.80 g. To half of the mother liquor was added a small amount of ether giving an additional 0.55 g., making the yield 58%. The material does not have a melting point, but slowly carbonizes when heated. Solutions of this betaine must not be heated or decomposition takes place.

Anal. Calcd. for $C_7H_7O_2N$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.31; H, 4.95; N, 9.98.

Homarine picrate. To the other half of the mother liquor mentioned above was added a saturated alcoholic picric acid solution to give an orange picrate, m.p. 158–160°, reported[4] 155–160°.

Anal. Calcd. for $C_{13}H_{10}O_9N_4$: C, 42.63; H, 2.75; N, 15.30; Found: C, 42.47; H, 2.84; N, 14.76.

Acknowledgment. Analyses were made by Scandinavian Microanalytical Labs., Box 1257, Copenhagen 5, Denmark; Spang Microanalytical Labs., P.O. Box 1111, Ann Arbor, Mich.; and Hufmann Microanalytical Laboratories, 3830 High Court, P.O. Box 125, Wheatridge, Colo.

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(6) All melting points are uncorrected. All melting points were taken by placing the samples in the melting point apparatus approximately 10° before the melting point to minimize premature decomposition.

(7) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958).

(8) E. M. Kosower, J. A. Skorcz, W. M. Schwarz, Jr., and J. W. Patton, *J. Am. Chem. Soc.*, **82**, 2188 (1960).

(9) E. Schulze, *Z. physiol. Chem.*, **60**, 155 (1909).

Preparation of Polyvinylamine Perchlorate[1]

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The synthesis of poly(vinylamine) and its derivatives has been detailed by Reynolds and Kenyon.[3] Since various other derivatives of poly(vinylamine) (V) were of interest as potential constituents of propellants, the synthesis of the polymer was under-

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(2) The authors are indebted to Dr. E. C. Horswill, Mr. P. McWain, and Mr. A. Reife for assistance in the early stages of this investigation.

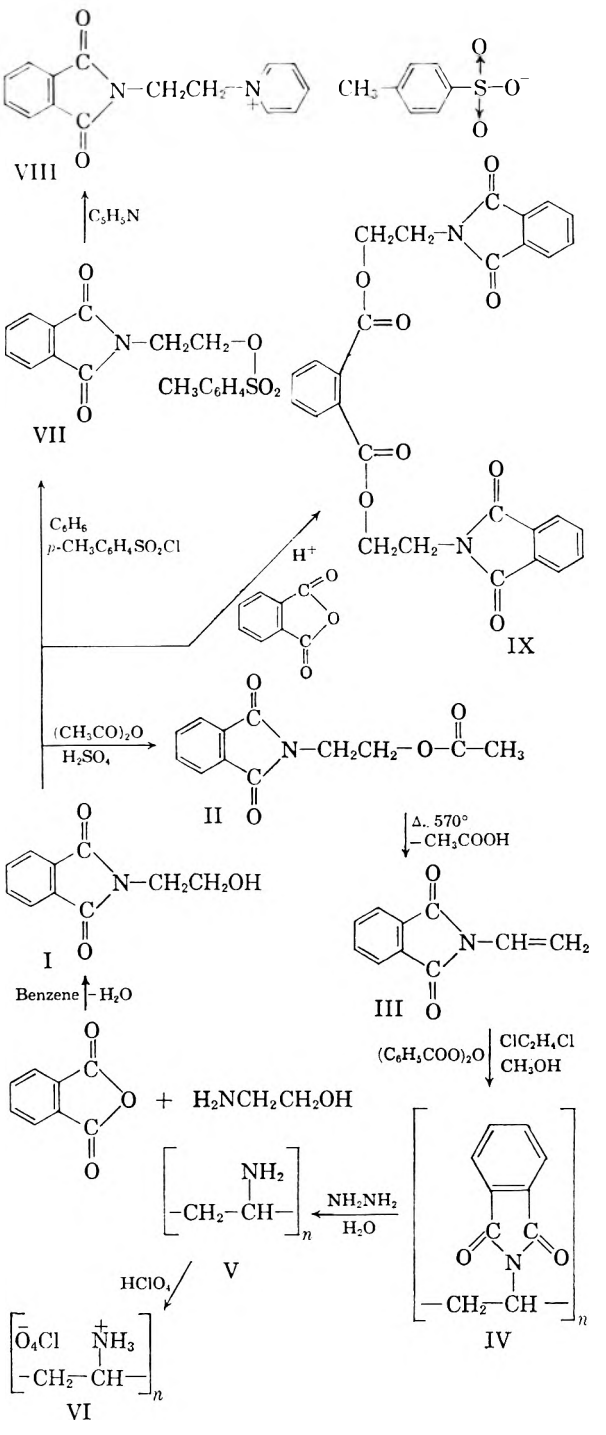
(3) D. D. Reynolds and W. O. Kenyon, *J. Am. Chem. Soc.*, 69, 911 (1947).

taken following the general method of Reynolds and Kenyon.

In our hands, the preparation of 2-phthalimidoethyl acetate (II) described by Hanford and Stevenson[4] was improved and simplified by elimination of the laborious distillations of the intermediate, 2-phthalimidoethanol (I), and the final product. The intermediate was not isolated but was directly acetylated and the 2-phthalimidoethyl acetate was isolated by crystallization in 90% yield after removal of the acetylation by-products by distillation.

The 2-phthalimidoethyl acetate was pyrolyzed[4] and the resulting *N*-vinylphthalimide (III) was polymerized[3] following known techniques in an over-all yield of about 70% for the two steps. Hydrazinolysis of the poly(*N*-vinylphthalimide) (IV) was effected following the method of Reynolds and Kenyon[3] but their method for preparation of the hydrogen halide salts was modified for the synthesis of the perchloric acid salt of poly(vinylamine) (VI). Thus, the hydrazinolysis mixture was diluted with water and steam-distilled to remove the excess hydrazine. The resulting solution was acidified with perchloric acid and the insoluble phthalhydrazide was filtered. After dialysis of the filtrate, the solution was treated with Amberlite IRA-400 (OH^-) resin and reacidified with perchloric acid. Lyophilization of the resulting solution (*p*H 3.0) after freezing afforded a product that contained less perchloric acid than required by stoichiometry. The deficiency was eliminated by dissolving the solid in water and treating with the calculated amount of the acid. Lyophilization then gave poly(vinylamine perchlorate) (VI) with the correct analytical composition. The light-brown, hygroscopic, polymeric perchlorate salt had physical properties similar to the halide salts[3] except that it could be detonated by strong heating or by a firm hammer blow on a steel anvil. The molecular weight, 90,000 (D. P. 630), was determined using a light-scattering technique.

During the course of this investigation, two new compounds, 2-phthalimidoethylpyridinium *p*-toluenesulfonate (VIII) and bis(2-phthalimidoethyl) *o*-phthalate (IX) were isolated, originally as by-products and subsequently by direct synthesis. The former (VIII) was the major product if 2-phthalimidoethanol (I) was treated with pyridine and *p*-toluenesulfonyl chloride while the latter (IX) could be isolated if the tosylation of I containing traces of phthalic anhydride was accomplished in the absence of pyridine.



EXPERIMENTAL

2-Phthalimidoethyl acetate (II). Phthalic anhydride (148 g., 1 mole) and 300 ml. of benzene were stirred and heated just under reflux while adding 2-aminoethanol (61.9 g., 1.01 moles) dropwise. The water formed was removed with a phase-separating head during 20 hr. of refluxing. To the slightly cooled, clear solution was added 4 ml. of 95% sulfuric acid and a simple distillation head was substituted for the original head. Then, as 450 g. of acetic anhydride was added, the heat of the reaction was employed to distill the benzene. Distillation was continued with the application of heat until the temperature of the reaction mixture reached 150° and its volume was about 400 ml. Cooling overnight (5°) afforded crystals which were filtered, washed with water and dried. A single crystallization from ethanol-water afforded pure 2-phthalimidoethyl acetate; yield 202 g. (a further 8 g. could be recovered from the mother liquor for an over-all yield of 90%), m.p. 88.5–89.0° (lit.,[4] m.p. 88–89°).

(4) W. E. Hanford and H. B. Stevenson, U. S. Patent 2,276,840 (1942).

If desired, the intermediate, 2-phthalimidoethanol (I), could be isolated by cooling the benzene solution (above); yield 190 g. (99%), m.p. 126–127° (lit.,[5] m.p. 126–127°).

Poly(vinylamine perchlorate) (VI). Following Hanford and Stevenson,[4] the 2-phthalimidoethyl acetate was passed through a packed tube heated at 570°. The *N*-vinyl-phthalimide (III) obtained, m.p. 85.5–86.5° (lit.,[4] m.p. 85–86°), in 75% yield was polymerized with dibenzoyl peroxide in methanol-1,2-dichloroethane (15/85, v/v) following the method of Reynolds and Kenyon.[3] The nearly quantitative yields of white, finely divided poly(*N*-vinylphthalimide) (IV) were treated with hydrazine following the method of Reynolds and Kenyon.[3] Thus, the polymer (120 g., 0.69 mole) was added in portions to 180 ml. of hydrazine hydrate (85%) stirred at 100° under nitrogen. After 24 hr., the solution was cooled, diluted with an equal volume of water, and steam-distilled until no additional hydrazine could be detected[6] in the distillate. After acidification to *p*H 4 with perchloric acid, the mixture was filtered and dialyzed against water. The dialyzate was concentrated under reduced pressure to 200 ml. and treated successively with three 100-ml. portions of Amberlite IRA-400 (OH^-) resin. The solution was adjusted to *p*H 3.0 with dilute perchloric acid. The solid product obtained on lyophilization contained less chlorine than calculated for the desired product. The denciency was determined by the analysis, and after dissolving the polymer in water, the required amount of perchloric acid (about 5% of the total) was added and the product was again recovered by lyophilization; yield 48 g. (49%) of light-brown, hygroscopic poly(vinylamine perchlorate) (VI); analytical sample dried under reduced pressure over sodium hydroxide.

Anal. Calcd. for $C_2H_5N\cdot HClO_4$: C, 16.74; H, 4.21; N, 9.76; Cl, 24.70. Found: C, 16.83; H, 4.29; N, 9.70; Cl, 24.95.

Properties of poly(vinylamine perchlorate). The molecular weight was determined by Dr. Quentin Van Winkle of the Department of Chemistry of The Ohio State University employing a B-S Light Scattering Photometer (Phoenix Precision Instrument Co., Philadelphia). From measurements in 0.1*M* sodium chloride a value of 90,000 was obtained. This molecular weight resulted from calculations employing the value of C/τ at infinite dilution as determined by the linear extrapolation of the data obtained at finite concentrations.

Poly(vinylamine perchlorate) is very soluble in water and ethanol, dissolves very slowly in acetone but not in ethyl acetate, benzene, or ether. On heating in a test tube, the salt melts and then explodes with a small flash of light leaving a small carbonaceous residue. The polymer also can be detonated by a firm hammer blow on a steel anvil but has been pulverized (caution) in small amounts with a mortar and pestle.

Bis(2-phthalimidoethyl) o-phthalate (IX). 2-Phthalimidoethanol (206 g., 1.08 mole), which had been purified by three wasteful recrystallizations from ethanol (95%), was dissolved in 1.5 l. of refluxing benzene containing 2 ml. of 95% sulfuric acid. Phthalic anhydride (80 g., 0.54 mole) was added in portions to the refluxing solution and the water formed (10 ml.) was removed with a phase-separating head during 20 hr. On cooling and diluting with an equal volume of absolute ethanol, crystals formed which were filtered, washed with water, and dried (110°); yield 220 g. (80%), m.p. 161–162°. The analytical sample (m.p. 164–165°) was obtained by a single crystallization from acetone-ethanol.

Anal. Calcd. for $C_{28}H_{20}N_2O_8$: C, 65.62; H, 3.93; N, 5.47; mol. wt., 512. Found: C, 65.68; H, 3.82; N, 5.43; mol. wt., 511 (Rast).

2-Phthalimidoethylpyridinium p-toluenesulfonate (VIII). 2-Phthalimidoethyl *p*-toluenesulfonate (VII) was prepared following the procedure of Peacock and Dutta[7] in 90% yield (m.p. 142–143°). This sulfonate (30 g.) was refluxed for 5 hr. with 150 ml. of dry pyridine and the solution on cooling deposited crystals (VIII) which were washed with ether and dried; yield 36.5 g. (99%), m.p. 205–206°.

Anal. Calcd. for $C_{22}H_{20}N_2O_5S$: C, 62.25; H, 4.75; N, 6.60; S, 7.55; neut. equiv., 424. Found: C, 62.31; H, 4.70; N, 6.64; S, 7.57; neut. equiv., 427.

The pyridinium compound (VIII) was originally isolated as the major product during an attempt to prepare the tosylate (VII) employing a mixture of pyridine and *p*-toluenesulfonyl chloride.

If the 2-phthalimidoethanol employed for the synthesis of the sulfonate derivatives was contaminated with phthalic anhydride, small amounts of the bis(2-phthalimidoethyl) *o*-phthalate could be isolated by pouring the crude pyridinium compound into water which left the phthalate as an insoluble residue. The phthalate derivative could also be recovered under similar circumstances from the mother liquors formed during the crystallization of the 2-phthalimidoethyl *p*-toluenesulfonate. The only way found to avoid the appearance of this contaminant in the sulfonate derivatives was to effect the condensation of the phthalic anhydride with a slight excess of the 2-aminoethanol.

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(5) S. Gabriel, *Ber.*, **21**, 566 (1888).

(6) F. Feigl, *Spot Tests in Organic Analysis*, 5th English Ed., Elsevier, New York, 1956, p. 297.

(7) D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, 1303 (1934).

Glycyliminodiacetic Acid

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The literature contains few examples of peptides of an imino acid other than those derived from proline. Attempts in this laboratory to prepare β-alanyliminodipropionic acid[2] and α-alanyliminodiacetic acid[3] were unsuccessful, but the simplest member of the series, glycyliminodiacetic acid, $NH_2CH_2CON(CH_2COOH)_2$, has now been obtained.

The conversion of carbobenzoxyglycinehydrazide[4] to the azide and the coupling of the latter with the dimethyl ester of iminodiacetic acid[5] gave a syrup, which was saponified to the crystalline carbobenzoxyglycyliminodiacetic acid. Hydrogenolysis produced glycyliminodiacetic acid.

Possible by-products of the azide coupling are derivatives of the isocyanate resulting from a Curtius rearrangement of the azide. For example, Nyman and Herbst,[6] in attempting to condense the azide of carbobenzoxy-L-valine hydrazide with L-valine ethyl ester, obtained the substituted urea, formed by interaction of the isocyanate with the valine ester. A similar substituted urea was ap-

(1) From the M.S. thesis of Shirley Shyluk, University of Delaware, 1958.

(2) G. L. Ford, M.S. thesis, University of Delaware, 1951.

(3) T. E. Majewski, M.S. thesis, University of Delaware, 1953.

(4) S. Simmonds, J. I. Harris, and J. S. Fruton, *J. Biol. Chem.*, **188**, 259 (1951).

(5) J. V. Dubsky, *Ber.*, **50**, 1694 (1917).

(6) M. A. Nyman and R. M. Herbst, *J. Org. Chem.*, **15**, 117 (1950).

parently obtained by Majewski[3] in the attempted reaction of the azide from carbobenzoxy-α-alaninehydrazide with the dimethyl ester of iminodiacetic acid. In the current work the coupling of the azide from carbobenzoxyglycinehydrazide with the same imino ester gave small amounts of a presumed isocyanate polymer, $(C_6H_5CH_2OCONHCH_2NCO)_x$.

The carbodiimide method of coupling was investigated because of its prior use[7] in a notable case of imino coupling in the penicillin synthesis. In the present work, a simple model, the reaction of carbobenzoxyglycine[8] with di-*n*-propylamine in the presence of dicyclohexylcarbodiimide[9] gave crystalline carbobenzoxyglycine-di-*n*-propylamide. When carbobenzoxyglycine was treated with iminodiacetic acid dimethyl ester in the presence of a quaternized carbodiimide,[10] a syrup was obtained having similar properties to that from the azide coupling.

With phthalyl as the protective group on the glycine, crystalline coupling products could be obtained in good yields. Phthalylglycine[11] and iminodiacetic acid dimethyl ester reacted in the presence of either dicyclohexylcarbodiimide or a quaternized carbodiimide to give crystalline phthalylglycyliminodiacetic acid dimethyl ester. The same ester (or free acid) was formed from the reaction of phthalylglycylchloride[12] with the imino ester (or acid). However, the use of phthalyl compounds had the disadvantage that removal of the phthalyl group from phthalylglycyliminodiacetic acid caused dehydration of the peptide with the formation of 1-carboxymethyl-2,5-diketopiperazine. A dehydration on hydrazinolysis of other glycyl peptides was observed by Emerson.[13]

EXPERIMENTAL

Carbobenzoxyglycyliminodiacetic acid dimethyl ester. To a solution of 8.0 g. (0.036 mole) of carbobenzoxyglycinehydrazide[4] in 42 ml. of glacial acetic acid were added 200 ml. of water, 18 ml. of 5*N* hydrochloric acid and 200 ml. of ether, then dropwise with stirring at 0° a concentrated aqueous solution of 2.52 g. (0.037 mole) of sodium nitrite. The azide was purified and coupled with 0.036 mole of the dimethyl ester of iminodiacetic acid[5] by the general procedures outlined by Erlanger and Brand.[14] The product was 7.12 g. (56% yield, based on the hydrazide) of a syrup which could not be crystallized nor further purified by chromatography. It was eluted as one band from silica with varying proportions of chloroform and carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{20}N_2O_7$: N, 7.95; OCH_3, 17.62. Found: N, 8.22; OCH_3, 16.90.

A syrup of similar properties resulted in 55% yield from the reaction of carbobenzoxyglycine[8] (0.01 mole) with iminodiacetic acid dimethyl ester hydrochloride (0.01 mole) in acetonitrile in the presence of triethylamine (0.01 mole) and 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)carbodiimide metho-*p*-toluenesulfonate.[10]

During the azide coupling described above, a precipitate (1.43 g.) separated from the ether layer while the azide was being washed. This substance, which decomposed at 247–252°, was soluble only in dimethylformamide. The analysis and lack of solubility suggested that it was an impure polymer of the isocyanate formed from the rearrangement of the azide.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: N, 13.58. Found: N, 13.16.

Carbobenzoxyglycyliminodiacetic acid. An ethanol solution of 6.08 g. of the dimethyl ester was saponified in the usual way.[15] The yield of acid, m.p. 155–159° dec., was 75%. It was recrystallized from water to constant melting point (159–160° dec.).

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.84; H, 4.97; N, 8.64; neut. equiv., 162. Found: C, 52.03; H, 5.29; N, 8.65; neut. equiv., 162.

Glyciliminodiacetic acid. The hydrogenolysis of a solution of 1.0 g. (0.003 mole) of carbobenzoxyglycine[8] in 10 ml. of methanol containing 4 drops of glacial acetic acid was conducted as usual[14] with a total of 0.05 g. of palladium on charcoal as catalyst. After recrystallization from water-methanol (6:5), 0.48 g. (69% yield) of product, m.p. 153–155° was obtained. It separated as a hydrate.

Anal. Calcd. for $C_6H_{10}N_2O_6.H_2O$: C, 34.61; H, 5.81; N, 13.46; neut. equiv., 208. Found: C, 34.44; H, 6.09; N, 13.43; neut. equiv., 207.

Phthalylglycyliminodiacetic acid. To a mixture of 17.59 g. (0.0787 mole) of phthalylglycyl chloride[12] and 21.99 g. (0.165 mole) of finely ground dried iminodiacetic acid (prepared from the disodium salt) in a pressure bottle containing a magnetic stirrer was added 50 ml. of dry dioxane. The bottle was sealed, evacuated, filled with nitrogen (at 5 p.s.i.) and heated slowly with stirring to 50°, kept at this temperature for 3 hr., then heated slowly to 90° for 20 hr. After addition of 200 ml. of hot water and cooling, 18.16 g. (72% yield) of the product, m.p. 215.5–216.5°, separated. When recrystallized from water, it melted at 216–217° with effervescence.

Anal. Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.54; H, 4.01; N, 8.73.

Phthalylglycyliminodiacetic acid dimethyl ester. By the reaction of 0.99 g. (0.005 mole) of iminodiacetic acid dimethyl ester hydrochloride[6] in 10 ml. of pyridine with 1.12 g. (0.005 mole) of phthalyl glycyl chloride[12] in an ice bath for 2 hr. during stirring followed by shaking at room temperature overnight, a 90% yield of crude product was obtained, m.p. 191–192.5°. After recrystallization from dimethylformamide, it melted at 193–193.5°.

Anal. Calcd. for $C_{16}H_{16}N_2O_7$: OCH_3, 17.8. Found: OCH_3, 17.7.

The same ester was obtained by three other methods in the yields (crude) indicated: (a) from phthalylglycine[11] and iminodiacetic dimethyl ester in tetrahydrofuran with dicyclohexylcarbodiimide as condensing agent, 80%; (b) from the same reactants as in (a) with 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)carbodiimide metho-*p*-toluene sulfonate,[10] 60%; (c) from phthalylglycylchloride[12] in tetrahydrofuran with 2 equivalents of iminodiacetic acid dimethyl ester, 96%.

(7) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1262 (1957).

(8) H. E. Carter, R. L. Frank, and H. W. Johnston, *Org. Syntheses*, Coll. Vol. III, 168 (1955).

(9) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(10) J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

(11) E. Drechsel, *J. prakt. Chem.*, [2], **27**, 418 (1883).

(12) J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.*, **71**, 1856 (1949).

(13) O. H. Emerson, U. S. Patent 2,498,665, Feb. 28, 1950.

(14) B. F. Erlanger and E. Brand, *J. Am. Chem. Soc.*, **73**, 3508 (1951)

(15) J. S. Fruton, *Advances in Protein Chemistry*, Vol. 5, M. L. Anson, J. T. Edsall, and K. Bailey, eds., Academic Press, Inc., New York, 1949, p. 28.

N-Carboxymethyldiketopiperazine. Hydrazinolysis under standard conditions[12] was not successful, but could be accomplished in the following way. A mixture of 2.303 g. (0.01 mole) of phthalylglycyliminodiacetic acid, 10 ml. of ethanol, 10 ml. of 1*N* piperidine in ethanol (0.01 mole), and 10 ml. of 1*N* hydrazine hydrate in ethanol was heated in a pressure tube at 100° for 40 min. with occasional shaking. After the removal of the solvent, the residue was treated with 18.81 ml. of 0.5315*N* hydrochloric acid (0.01 mole) and 50 ml. of water. The phthalhydrazide was filtered, the filtrate evaporated *in vacuo* and the residue crystallized from water, giving 1.326 g. (70% yield) of product, m.p. 165–171°. After four recrystallizations from water the melting point was 174.5–175.5° dec.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.96; H, 4.79; N, 16.34.

Carbobenzoxyglycine di-n-propylamide. A mixture of 2.02 g. (0.02 mole) of di-*n*-propylamine, 2.09 g. (0.01 mole) of carbobenzoxyglycine,[8] 2.04 g. (0.01 mole) of dicyclohexylcarbodiimide,[9] and 5.7 ml. of acetonitrile was shaken for 36 hr. After removal of the precipitate, the filtrate was evaporated, taken up in ethyl acetate and washed with acid, water, bicarbonate, and water. The yield of product from the organic layer was 1.46 g. (50%). After recrystallization from ethyl acetate the substance melted at 146–147°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: N, 10.42. Found: N, 10.13.

Phthalylglycine di-n-propylamide. The reaction of phthalylglycylchloride and di-*n*-propylamine in pyridine gave a 71% yield of product melting at 104–105° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.61; H, 7.04; N, 9.88.

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Pyridylethylated *d*-α-Methylphenethylamines

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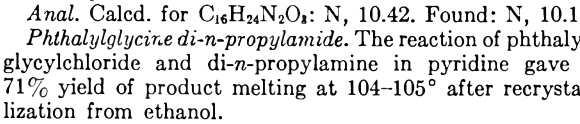
Received June 16, 1960

Our explorations[1,2] of derivatives of *d*-α-methylphenethylamine are herein extended to pyridylethylated products of the type I.



Other work[3,4] has shown that the pyridylethyl substituent, particularly the 4-pyridylethyl group, promotes central nervous system depression. It was therefore of interest to assess the effect of this radical on the analeptic activity of *d*-α-methylphenethylamine. Conversion of this amine to a secondary amine (*N*-methyl)[5] or to a tertiary amine (*N*-methyl, *N*-benzyl)[6] has been associated with significant retention of analeptic properties.

The examination of I as acyl- and arylamides[1] was suggested by "reverse" chelidamic acid[7] structures.

Pyridylethylation of *d*-α-methylphenethylamine[8] proceeded readily[9] in acetic acid following the method of Levine,[10] to give compounds 1, 7, and 9.[11] In the preparation of compound 9, some *N*-*d*-α-methylphenethylacetamide was obtained as a side product.

The amino nitrogen of I R = H, although hindered to a large degree, was readily acylated or arylated. In an effort to obtain the corresponding *N*-methylpiperidylethyl analogs of I, preliminary trials of hydrogenation of compound 3 failed. This work, however, is being pursued further.

Pharmacology. Using the reduction of motor activity as an indicator of effect on the central nervous system,[12] the analeptic activity of the *d*-α-methylphenethylamine was retained with compound 1, and depressant effects were observed with compounds 7 and 9. Compounds 4 and 5 also gave depressant effects. Other significant activity was 3+ hypotension[13] and anesthesia (ED_{50} = 9.7 mg./ml.)[14] with compound 4, and potentiation of adrenalin[14] with compounds 3 and 7.

EXPERIMENTAL[15]

N-d-α-Methylphenethyl-2-(5-ethyl-2-pyridyl)ethylamine (Compound 9). A mixture of one-third mole each of *d*-α-methylphenethylamine, 2-vinyl-5-ethylpyridine, and acetic acid in 80 ml. of methanol was heated under reflux for 8 hr. and distilled. After removal of low boiling fractions, a forerun was collected at 128–140° (0.3 mm.), and the product

(1) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(2) S. L. Shapiro, I. M. Rose, F. C. Testa, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5646 (1959).

(3)(a) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958); (b) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 386 (1959).

(4) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(5)(a) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, 1955, p. 532; (b) K. Soehring and G. Ergenzinger, *Arzneimittel-Forsch.*, **5**, 478 (1955).

(6)(a) B. Simkin and L. Wallace, *Current Therap. Research*, **2**, 33 (1960); (b) Y. Matsushima, *Nippon Yakurigaku Zasshi*, **53**, 926 (1957) [*Chem. Abstr.*, **52**, 20638c (1958)].

(7) D. G. Markees, *J. Org. Chem.*, **23**, 1030 (1958).

(8) Under somewhat similar conditions, 4-vinylpyridine did not react with isopropylamine. E. Profft, *J. prakt. Chem.*, **4**, 19 (1956).

(9) For possible mechanism of reaction, see L. S. Luskin, M. J. Culver, C. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.*, **78**, 4042 (1956).

(10) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(11) For pyridine analogs of α-methylphenethylamine, see A. Burger, M. L. Stein, and J. B. Clements, *J. Org. Chem.*, **22**, 143 (1957).

(12) See ref. (1) and (3a) for method used. Noted significant activity is reported as compound no./LD_{min} mg./kg./test dose, mg./kg., s.c./% reduction (or increase) in activity: Increase, 1/75/10/166. Decrease, 4/1000/100/22; 5/>1000/100/26; 7/100/10/28; 9/75/10/30.

(13) For method of testing, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(14) For method of testing, see S. L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(15) Descriptive data shown in the table are not herein reproduced.

TABLE I

$PyCH_2CH_2—N(R)—CH(CH_3)CH_2C_6H_5$[a]

No.	R	M.P.[b,c] or B.P., (Mm.)	Yield,[d] %	Formula	Carbon,[e] % Calcd.	Carbon,[e] % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	120 (0.05)	66[g]	$C_{16}H_{20}N_2$	80.0	80.1	8.4	8.2	11.7	12.0
2	CH_3CO—	170–179 (0.16)	87	$C_{18}H_{22}N_2O$					9.9	10.1
3	[f]	151–152[c1]	85	$C_{19}H_{25}IN_2O$	53.8	54.0	5.9	6.0	6.6	6.8
4	*p*-$CH_3OC_6H_4CO$—	238–242 (0.03)	39	$C_{24}H_{26}N_2O_2$	77.0	77.0	7.0	6.7	7.5	7.0
5	*o*-$C_2H_5OC_6H_4CO$—	226–229 (0.03)	47	$C_{25}H_{28}N_2O_2$					7.2	6.8
6	TMB[h]	117–118[c2]	58	$C_{26}H_{30}N_2O_4$	71.9	71.7	7.0	7.2	6.5	6.0
7[a1]	H	128–134 (0.08)	53[g]	$C_{16}H_{20}N_2$	80.0	79.5	8.4	8.4	11.7	11.7
8[a1]	*o*-$C_2H_5OC_6H_4CO$—	103–106[c2]	57	$C_{25}H_{28}N_2O_2$	77.3	77.4	7.3	7.1	7.2	6.9
9[a2]	H	148–150 (0.4)	46[g]	$C_{18}H_{24}N_2$	80.6	80.7	9.0	9.1	10.4	9.8

[a] Py = 2-pyridyl unless otherwise indicated; [a1] Py = 4-pyridyl; [a2] Py = 5-ethyl-2-pyridyl. [b] Melting points are not corrected and were established on a Fisher-Johns melting point block. [c] Recrystallizing solvent; [c1] ethyl acetate; [c2] hexane-benzene. [d] Yields are expressed as recrystallized or distilled product. [e] Analyses are by Weiler and Strauss, Oxford, England. [f] Compound is methiodide of compound 2. [g] $[\alpha]_D^{20}$ in methanol: compound 1, +21.40; compound 7, +24.30; compound 9, +22.30. [h] TMB = 3,4,5-trimethoxybenzoyl.

(41.5 g.) was obtained, b.p. 148–150° (0.4 mm). The forerun, upon trituration with hexane, gave 2.4 g. (4.1%), m.p. 126–127°, not depressing the melting point of authentic *d*-α-methylphenethylacetamide.[16]

Compounds 1 and 7 were similarly prepared.

Acetamide of compound 1 (Compound 2). A mixture of 9.6 g. (0.04 mole) of compound 1 and 10 ml. of acetic anhydride was heated under reflux for 1 hr. When cool, after addition of 100 ml. of water, and treatment with base, the formed oil was extracted with 100 ml. of benzene and the product was obtained by distillation, 9.77 g. (87%), b.p. 170–179° (0.16 mm.).

A solution of 2.8 g. (0.01 mole) of this compound in 25 ml. of acetonitrile and 2 ml. of methyl iodide was refluxed for 2 hr., and upon cooling, yielded 3.6 g. (85%) of the methiodide (compound 3). Attempted hydrogenation[17] with rhodium on carbon afforded only unconverted reactant.

3,4,5-Trimethoxybenzamide of compound 1 (Compound 6). A solution of 9.6 g. (0.04 mole) of compound 1 in 35 ml. of benzene was added dropwise under stirring over 1 hr. to a solution of 4.6 g. (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 65 ml. of benzene while maintaining the temperature at 25–30°. When addition was complete, the reaction mixture was heated under reflux for 1 hr. and then stored at 20° for 24 hr. After extraction with dilute hydrochloric acid, and treatment with base, 8.6 g. (98%) of product was separated and recrystallized.

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(16) Ref. (1) reports m.p. 123–125°.

(17) S. L. Shapiro, K. Weinberg, T. Bazga, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5146 (1959).

Thiete Sulfone[1]

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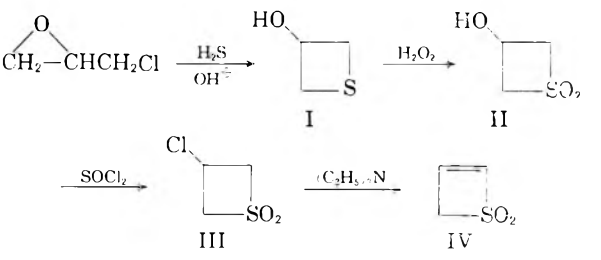
The synthesis and properties of five- and six-membered cyclic unsaturated sulfones have been described[2,3] but the four-membered cyclic unsaturated sulfones have been unreported.

The most simple four-membered cyclic unsaturated sulfone, thiete sulfone (thiete 1,1-dioxide), has been prepared according to the following reaction sequence:



Starting material, 3-thiethanol, (I),[4] was obtained by the addition of epichlorohydrin to a barium hydroxide solution saturated with hydrogen sulfide.[5] Oxidation of I in glacial acetic acid at room temperature gave the sulfone II in 56% yield. If the oxidation is carried out at 90–100°, the product is dimethyl sulfone which also is obtained by oxidation of I with potassium permanganate in acetone at 0°. The dimethyl sulfone probably arises from methylsulfonylacetic acid which is known to decarboxylate readily.[6]

(1) Presented at the 137th Meeting, American Chemical Society, Cleveland, Ohio, April, 1960.

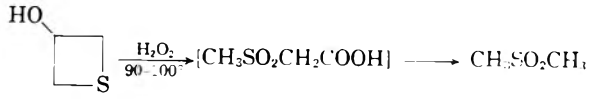
(2) For a brief review see A. Schöberl and A. Wagner, *Methoden der Organischen Chemie*, Vol. IX, Schwefel-, Selen-, Tellur-Verbindungen, E. Müller, ed., Georg Thieme, Stuttgart, 4th Ed., 1955, p. 236.

(3) L. Bateman and R. W. Glazebrook, *J. Chem. Soc.*, 2834 (1958); R. C. Krug, G. R. Tichelaar, and F. E. Didot, *J. Org. Chem.*, **23**, 212 (1958); R. C. Krug and T. Yen, *J. Org. Chem.*, **21**, 1441 (1956); E. A. Fehnel and P. A. Lackey, *J. Am. Chem. Soc.*, **73**, 2473 (1951); R. F. Naylor, *J. Chem. Soc.*, 2749 (1949).

(4) B. Sjöberg, *Svensk. Kem. Tid.*, **50**, 250 (1938).

(5) Modification of the method of B. Sjöberg, *Ber.*, **75**, 13 (1941).

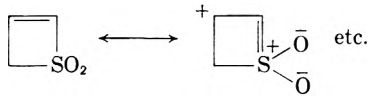
(6) E. Baumann and G. Walter, *Ber.*, **26**, 1131 (1893).



Conversion of II to III proceeded in good yield with thionyl chloride in 2,4,6-collidine. Yields were considerably lower in pyridine, presumably because of a greater amount of dehydrohalogenation by the stronger base. The chlorosulfone, III, is readily dehydrohalogenated by triethylamine at room temperature to yield the unsaturated sulfone, IV.

The structure of IV was confirmed by hydrogenation to the known thietane sulfone. Its NMR spectrum is in agreement with the structure.

It may be noted that the signal for the *beta* olefinic proton is at lower field than the *alpha* olefinic proton which suggests less electron density at the β- than the α-carbon. This may be a result of delocalization of the electrons in the system of the double bond and the sulfone group.



The infrared spectrum shows a C—H stretching frequency at 3165 cm.$^{-1}$ and a C=C stretching frequency at 1543 cm.$^{-1}$

Further work on the reactivity of IV is in progress.

EXPERIMENTAL[7]

3-Thietanol (I). A modified procedure of Sjöberg was used.[5] A mixture of 315 g. (1 mole) of barium hydroxide octahydrate and 1.8 l. of water was stirred and saturated with hydrogen sulfide at room temperature. The mixture was cooled in ice with continuous stirring and passage of hydrogen sulfide, and 92.53 g. (1 mole) of epichlorohydrin was added dropwise over 2 hr. After another hour at 50–55°, carbon dioxide was introduced until the precipitation of barium carbonate was complete. The precipitate was collected and washed with water. The combined filtrates and washings from four 1-mole runs were concentrated *in vacuo* on the steam-bath until oil began to separate. The oil was taken up in ether, and after drying and removal of the solvent, it was fractionated *in vacuo*. The 3-thietanol (142 g.; 39%), was collected at 51–52°/0.9 mm., $d_{25°}$ 1.2129, $n_D^{25°}$ 1.5408 (lit.[4] b.p. 57°/1.3 mm., $d_{20°}$ 1.2130, $n_D^{20°}$ 1.5433). A sample from a comparable preparation, b.p. 61–62°/2 mm., $n_D^{20°}$ 1.5476, gave the following analysis:

Anal. Calcd. for C_3H_6OS: C, 39.97; H, 6.71; S, 35.57. Found: C, 39.69; H, 6.73; S, 35.44.

The *3,5-dinitrobenzoate* melted at 112–113° after repeated crystallizations from 95% ethanol.

Anal. Calcd. for $C_{10}H_8O_6N_2S$: C, 42.25; H, 2.84; N, 9.86. Found: C, 41.99; H, 2.86; N, 9.72.

Treatment with excess methyl iodide in benzene in the cold gave *dimethyl 2-hydroxy-3-iodopropylsulfonium iodide* which melted at 110–110.5° after repeated crystallizations from absolute ethanol.

Anal. Calcd. for $C_5H_{12}OI_2S$: C, 16.05; H, 3.23; I, 67.86. Found: 16.28; H, 3.26; I, 67.88.

3-Thietanol 1,1-dioxide (II). To a stirred and ice cold solution of 22.5 g. (0.25 mole) of 3-thietanol in 75 ml. of glacial acetic acid, hydrogen peroxide, 58 g. (0.51 mole) of 30%, was added rapidly dropwise. After another 15 min. in the cold and 1 hr. at room temperature, the reaction was quenched with 450 ml. of water and the solution evaporated to dryness on the steam-bath. The residual oily, colorless solid afforded 17.3 g. (56.5%) of colorless needles, m.p. 99.5–102°, after two crystallizations from ethyl acetate. An analytical sample melted at 101–102°.

Anal. Calcd. for $C_3H_6O_3S$: C, 29.50; H, 4.96; S, 26.25. Found: C, 29.61; H, 4.71; S, 26.33.

The *3,5-dinitrobenzoate* melted at 197–198° after two crystallizations from 95% ethanol.

Anal. Calcd. for $C_{10}H_6O_8N_2S$. C, 37.98; H, 2.55; N, 8.86. Found: C, 38.08; H, 2.59; N, 8.82.

The *p-toluenesulfonate* was obtained as colorless prisms, m.p. 129–131°, from ethyl acetate.

Anal. Calcd. for $C_{10}H_{12}O_5S_2$: C, 43.46; H, 4.38; S, 22.90. Found: C, 43.55; H, 4.49; S, 23.25.

When the exothermic reaction with hydrogen peroxide was allowed to proceed without cooling and the solution then heated on the steam-bath for 3 hr., a 12% yield of *dimethyl sulfone* was isolated. The product was identical in melting point, 110.5–111.5°, (lit.[6] m.p. 109°), mixed melting point, 110–111°, and infrared spectrum with an authentic sample prepared by hydrogen-peroxide oxidation of dimethyl sulfide.

Oxidation with potassium permanganate in cold aqueous acetone resulted in a 2% yield of dimethyl sulfone.

3-Chlorothietane 1,1-dioxide (III). Thionyl chloride, 35.7 g. (0.3 mole), was added dropwise to a stirred suspension of 18.3 g. (0.15 mole) of II in 18.15 g. (0.15 mole) of dry *s*-collidine, the temperature being maintained at 25–30°. Stirring was discontinued after one-half of the reagent had been added when the mixture set to a solid mass. Most of the solid dissolved, when, after 45 min. at room temperature, the mixture was heated on the steam-bath for 30 min. The warm solution was poured onto ice and the solid product was collected, washed with cold water, and crystallized from water with decolorization with Norite; yield, 18.1 g. (86%) of large, colorless, prismatic needles, m.p. 136.5–137.5°.

Anal. Calcd. for $C_3H_5O_2ClS$: C, 25.63; H, 3.59; Cl, 25.22; S, 22.81. Found: C, 25.56; H, 3.96; Cl, 25.25; S, 23.51.

When the reaction was conducted under the same conditions using pyridine as the base, the yield of 3-chlorothietane 1,1-dioxide was 60%.

Thiete 1,1-dioxide (IV). A solution of 10.0 g. (0.071 mole) of III in 350 ml. of dry benzene at 40° was treated with 50 ml. of triethylamine. Triethylamine hydrochloride started to precipitate almost immediately and after 3 hr. at room temperature and overnight at 5°, the precipitate was collected and washed with benzene. Evaporation of the filtrate gave a very oily solid which was crystallized from ether containing a few milliliters of ethanol to obtain 6.0 g. (81%) of large, colorless needles, m.p. 48–50°. An analytical sample melted at 52–54°.

Anal. Calcd. for $C_3H_4O_2S$: C, 34.60; H, 3.87; S, 30.79. Found: C, 34.93; H, 4.07; S, 30.77.

Hydrogenation of IV in chloroform at 25 p.s.i. of hydrogen in the presence of 5% palladium on charcoal afforded *trimethylene sulfone*. The product was identical in melting point, 74–75° [lit.[8] m.p. 75°], mixed melting point, 74–76°, and infrared spectrum with an authentic sample prepared by hydrogen-peroxide oxidation of trimethylene sulfide.

The NMR spectrum of IV at 60 Mc. with tetramethylsilane as a standard shows a set of signals at 274 c.p.s. for the methylene (CH_2) protons which show about 2 cycle spin coupling to the adjacent olefinic proton and a little less than 1 cycle spin coupling to the other olefinic proton. The olefinic protons are at 408 (α) and 434 (β) c.p.s. and show a similar spin coupling to the protons of the methylene

(7) All melting points are uncorrected. Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

(8) E. Grishkevich-Trokhimovskii, *J. Russ. Phys. Chem. Soc.*, **48**, 880 (1916); *Chem. Zentr.*, 1923 III, 773.

group as well as a 5-cycle spin coupling between themselves. The spectrum was obtained by Varian Associates.

Compound IV exhibited no absorption in the ultraviolet between 220–420 mμ at a concentration of 10^{-3} *M*, infrared spectrum (potassium bromide): 697, 758, 851, 926, 954, 1062, 1136, 1188, 1250, 1290, 1435, 1543, 2994, 3049, 3165 cm.$^{-1}$

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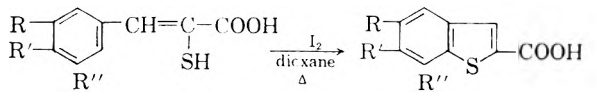
The Preparation of Some Alkoxybenzothiophene Derivatives[1]

E. CAMPAIGNE AND W. E. KREIGHBAUM[2]

Received August 11, 1960

In connection with earlier studies in this laboratory,[3,4] several mono-, di- and trialkoxyphenyl-α-mercaptoacrylic acids were prepared. Subjection of these compounds to mild ring-closure conditions (iodine in dioxane) provided, in most instances, the corresponding alkoxybenzothiophene-2-carboxylic acids.



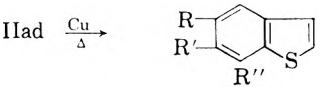
Iabcd IIabcd

a. R = CH_3O, R′ = H, R″ = H
b. R = H, R′ = CH_3O, R″ = H
c. R = C_2H_5O, R′ = C_2H_5O, R″ = H
d. R = CH_3O, R′ = CH_3O, R″ = CH_3O

The β-aryl-α-mercaptoacrylic acids (Ia–Id) were obtained by alkaline hydrolysis of the corresponding 5-(benzylidene)rhodanines.[3] Treatment of β-(3,4-diethoxyphenyl)- and β-(3,4,5-trimethoxyphenyl)-α-mercaptoacrylic acids (Ic and Id) with an excess of iodine in dioxane at 70° for several hours afforded 5,6-diethoxybenzothiophene-2-carboxylic acid (IIc) and 5,6,7-trimethoxybenzothiophene-2-carboxylic acid (IId) in fair to moderate yields. Interestingly enough, when β-(4-ethoxyphenyl)-α-mercaptoacrylic acid was subjected to ring-closure conditions only tars were obtained. Similarly, β-(2,4-dimethoxyphenyl)-α-mercaptoacrylic acid gave resinous material. The 4-methoxy derivative (Ib) produced the desired 6-methoxybenzothiophene-2-carboxylic acid (IIb) in extremely poor yield, while the 3-methoxy analog (Ia) produced a moderate yield of 5-methoxybenzothiophene-2-carboxylic acid (IIa).

Thus, it appears that the ring closure is related to direction of orientation of the substituent rather than degree of activation of the aryl ring. Apparently, intermolecular condensation becomes predominant when orientation is to the 3- and 5-positions, particularly in the highly activated 2,4-dialkoxy derivative. On the other hand, ring closure is facilitated by electron-releasing groups in the 3-position, which can activate the point of ring closure (*para*) to electrophilic attack.

In two cases (IIa and IId) the decarboxylated derivatives (IIIa and IIId) were prepared in almost quantitative yields using copper in quinoline.



IIIad

EXPERIMENTAL

Preparation of the 5-(alkoxybenzylidene)rhodanine derivatives. The procedure previously employed[3] was used to prepare the three new rhodanine derivatives described below.

5-(3,4,5-Trimethoxybenzylidene)rhodanine (IV). Twenty-five grams (0.128 mole) of 3,4,5-trimethoxybenzaldehyde (Aldrich) was refluxed for 30 min. with 17 g. of rhodanine in 150 ml. of glacial acetic acid using 40 g. of fused sodium acetate as catalyst. The hot mixture was poured into 1 l. of water and stirred. The precipitate was collected and dried in air to give 37 g. (93%) of material which was recrystallized from ethanol-dioxane as orange prisms melting at 202–203°.

Anal. Calcd. for $C_{13}H_{13}NO_4S_2$: S, 20.61. Found: S, 20.66.

5-(4-Ethoxybenzylidene)rhodanine (V). Five grams (0.033 mole) of *p*-ethoxybenzaldehyde was condensed with 5 g. of rhodanine in 40 ml. of glacial acetic acid using 10 g. of fused sodium acetate as described above. Isolating in the normal manner gave 8 g. (91%) of material which was recrystallized from ethanol as yellow needles melting at 225–226°.

Anal. Calcd. for $C_{12}H_{11}NO_2S_2$: S, 24.15. Found: S, 24.19.

5-(2,4-Dimethoxybenzylidene)rhodanine (VI). Twenty-five grams (0.156 mole) of 2,4-dimethoxybenzaldehyde (Eastman) and 20 g. of rhodanine were refluxed in 125 ml. of glacial acetic acid with 37 g. of fused sodium acetate as described above for the trimethoxy derivative. Isolating as before gave 40 g. (95%) of material melting at 269–270°. The analytical sample was recrystallized from ethanol-dioxane as yellow-orange needles melting at 271–272°.

Anal. Calcd. for $C_{12}H_{11}NO_3S_2$: S, 22.80. Found: S, 22.62.

Preparation of the β-(alkoxyphenyl)-α-mercaptoacrylic acids.

β-(3,4-Diethoxyphenyl)-α-mercaptoacrylic acid (Ic). Thirty-five grams (0.113 mole) of 5-(3,4-diethoxybenzylidene)rhodanine[5] (m.p. 199°) was stirred into a solution of 25 g. of sodium hydroxide in 160 ml. of water. The mixture was stirred at 70° for 30 min., chilled, filtered (Norit) and acidified by pouring into excess cold 10% hydrochloric acid. The precipitated material was collected and air-dried to give 27 g. (72%) of product which was recrystallized from petroleum ether (b.p. 30–60°) as orange prisms melting at 128–130°.

Anal. Calcd. for $C_{13}H_{16}O_4S$: S, 11.95. Found: S, 11.88.

β-(3,4,5-Trimethoxyphenyl)-α-mercaptoacrylic acid (Id). Thirty-five grams (0.11 mole) of 5-(3,4,5-trimethoxybenzylidene)rhodanine (IV) was hydrolyzed with 25 g. of sodium hydroxide in 160 ml. of water on the steam bath for 0.5 hr. Isolation and recrystallization from benzene gave 25 g. (82%) of orange needles melting at 158–159°.

Anal. Calcd. for $C_{12}H_{14}O_5S$: S, 11.85. Found: 11.80.

(1) Contribution No. 977 taken from a portion of a thesis submitted by W. E. K. in partial fulfillment of the requirements for the Ph.D. degree at Indiana University, June, 1960.

(2) Lubrizol Fellow, 1959–1960.

(3) E. Campaigne and R. E. Cline, *J. Org. Chem.*, 21, 32, 39 (1956).

(4) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, 26, 359, 363 (1961).

(5) F. C. Brown, C. K. Bradsher, S. M. Bond, and M. Potter, *J. Am. Chem. Soc.*, 73, 2357 (1951).

2,2'-Dithiobis(3,4,5-trimethoxyphenyl)acrylic acid. Id (2.7 g., 0.01 mole) was dissolved in 35 ml. of absolute ethanol and cooled to 0°. A stoichiometric amount of iodine (1.27 g., 0.005 mole) was added and the solution stirred at 0° for 2 hr. After dilution with 500 ml. of water, the precipitate was recrystallized from aqueous methanol and then from ethanol-benzene to give 2.5 g. (92%) of fine yellow leaflets melting at 186–187° dec.

Anal. Calcd. for $C_{24}H_{26}O_{10}S_2$: S, 11.86. Found: S, 11.88.

β-(4-Ethoxyphenyl)-α-mercaptoacrylic acid. Eight grams (0.019 mole) of 5-(4-ethoxybenzylidene)rhodanine (V) was hydrolyzed in 100 ml. of 10% sodium hydroxide on the steam bath for 0.5 hr. Isolation and recrystallization from acetone-ethanol gave 5 g. (62%) of orange prisms melting at 181–183° with gas evolution.

Anal. Calcd. for $C_{11}H_{12}O_3S$: S, 14.30. Found: S, 14.35.

β-(2,4-Dimethoxyphenyl)-α-mercaptoacrylic acid. Forty grams (0.144 mole) of 5-(2,4-dimethoxybenzylidene)rhodanine (VI), hydrolyzed with a warm solution of 40 g. of sodium hydroxide in 500 ml. of water gave 24 g. (65%) of material which melted at 221–222° dec. after one recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{12}O_4S$: S, 13.34. Found: S, 13.32.

Preparation of the alkoxybenzothiophene-2-carboxylic acids. 5,6-Diethoxybenzothiophene-2-carboxylic acid (IIc). Twenty-two grams (0.082 mole) of β-(3,4-diethoxyphenyl)-α-mercaptoacrylic acid (Ic) was dissolved in 750 ml. of dioxane and 30 g. (0.118 mole) of iodine was added. The solution was heated at 60–70° for 22 hr. and then poured into 6 l. of water, decolorized with saturated sodium bisulfite solution and stirred vigorously for a few minutes. The crude material was collected and dissolved in about 100 ml. of warm 10% sodium hydroxide solution. The strongly alkaline solution was treated with Norit and filtered to give a deep red solution (color due to impurities). Upon standing in the refrigerator overnight, 7 g. of pale pink crystals formed. The mother liquor was concentrated under an air stream and cooled to give an additional 2 g. of the sodium salt of 5,6-diethoxybenzothiophene-2-carboxylic acid. The salt was dissolved in 200 ml. of water and precipitated with dilute hydrochloric acid to give 7 g. (31%) of acid which was recrystallized from 95% ethanol as fine white needles melting at 245–246°.

Anal. Calcd. for $C_{13}H_{14}O_4S$: S, 12.04. Found: S, 11.89.

5,6,7-Trimethoxybenzothiophene-2-carboxylic acid (IId). A solution of 13.5 g. (0.05 mole) of β-(3,4,5-trimethoxyphenyl)-α-mercaptoacrylic acid (Id) and 20 g. (0.08 mole) of iodine in 400 ml. of dioxane was heated at 70° for 12 hr. with occasional swirling. The mixture was diluted with water to a volume of 2 l. and decolorized with 5% sodium bisulfite solution. After the mixture had been allowed to stand in the refrigerator for 4 days, the solid material was collected and recrystallized from dilute methanol to give 5 g. (37%) of flat rust-colored needles melting at 180–181°. Two additional recrystallizations from the same solvent failed to remove the color or change the melting point of the product.

Anal. Calcd. for $C_{12}H_{12}O_5S$: S, 11.87. Found: S, 11.75. Ultraviolet λ_{max} mμ/ε: 235/20,400, 295/18,500.

6-Methoxybenzothiophene-2-carboxylic acid (IIb). Two grams (0.0095 mole) of β-(4-methoxyphenyl)-α-mercaptoacrylic acid (Ib)[6] was dissolved in 75 ml. of dioxane. Three grams (0.0118 mole) of iodine was added and the mixture was refluxed for 15 hr. By pouring the reaction mixture into 500 ml. of water containing 2 g. of sodium bisulfite and treating the resulting tars with acetone, a small amount of acid was isolated which was recrystallized once from ethanol to give 0.15 g. (7.5%) of silvery platelets which melted sharply at 251°. (Perold and van Lingen[7] reported a melting point of 248.5–249.0° for 6-methoxybenzothiophene-2-carboxylic acid.) Attempts to repeat this synthesis have failed completely, only tars being obtained.

Anal. Calcd. for $C_{10}H_8O_3S$: S, 15.40. Found: S, 15.40.

5-Methoxybenzothiophene-2-carboxylic acid (IIa). Twenty grams (0.095 mole) of β-(3-methoxyphenyl)-α-mercaptoacrylic acid (Ia)[8] and 30 g. (0.118 mole) of iodine were refluxed for 18 hr. in 500 ml. of dioxane. The solution was cooled to room temperature and poured into 3 l. of cold water containing 60 ml. of saturated sodium bisulfite solution. The mixture was stirred well and the tan precipitate was collected and recrystallized as the sodium salt from 30% sodium hydroxide solution. The salt was dissolved in water and acidified with 10% hydrochloric acid to give 8 g. (40%) of product melting at 215–216°. The analytical sample melted at the same temperature after one recrystallization from dilute acetic acid.

Anal. Calcd. for $C_{10}H_8O_3S$: S, 15.40. Found: S, 15.36.

5,6,7-Trimethoxybenzothiophene (IIId). Five grams (0.0186 mole) of 5,6,7-trimethoxybenzothiophene-2-carboxylic acid (IId) was heated with 1.0 g. of copper powder in 25 ml. of quinoline until the temperature rose to 180–195°. The mixture was cooled to room temperature and stirred well with 100 ml. of isopropyl ether. The solution was filtered to remove the solid material and stirred vigorously with dilute hydrochloric acid until acid to Congo red. The ether layer was separated, concentrated on the steam bath and distilled under vacuum to give 4.5 g. (99%) of a colorless oil boiling at 147–150° (1.5 mm.).

Anal. Calcd. for $C_{11}H_{12}O_3S$: S, 14.30. Found: S, 14.23. Ultraviolet λ_{max} mμ/ε: 233/27,000; 262,269/8,750; 297,308/2,500.

Compound IIId forms a picrate, recrystallized from 95% ethanol as blood red needles, melting at 72.5°.

Anal. Calcd. for $C_{17}H_{15}N_3O_{10}S$: N, 9.26. Found: N, 9.38.

5-Methoxybenzothiophene (IIIa). Seven grams (0.084 mole) of the acid (IIa) was decarboxylated by heating with 0 5 g. of copper powder in 55 ml. of quinoline as described above. The crude material was isolated as before and steam-distilled to give 5.5 g. (99%) of beautiful white flakes melting at 43–44°.[9]

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(6) C. Gränacher, M. Gero, A. Ofner, A. Klopfenstein, and E. Schlatter, *Helv. Chim. Acta*, 6, 458 (1923).

(7) G. W. Perold and P. F. A. van Lingen, *Ber.*, 92, 293 (1959).

(8) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 1469 (1950).

(9) K. Fries, H. Herring, E. Hemmecke, and G. Siebert, *Ann.*, 527, 83 (1936).

The Preparation of Some Derivatives of 5,6-Dimethoxy- and 5,6-Methylenedioxybenzothiophene[1]

E. CAMPAIGNE AND W. E. KREIGHBAUM[2]

Received August 11, 1960

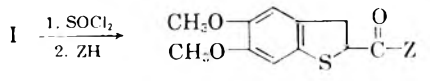
In connection with another problem,[3] several derivatives of 5,6-dimethoxy- and 5,6-methylene-

(1) Contribution No. 976, taken from a portion of a thesis submitted by W. E. K. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, June, 1960.

(2) Schering Research Fellow, 1958–1959. Lubrizol Fellow, 1959–1960.

(3) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, 26, 359 (1961).

dioxybenzothiophene-2-carboxylic acids (I and II) were prepared. Three ester and amide derivatives of I (IIIabc) were submitted for pharmacological testing.[4] Although the anticipated antiserotonin activity of these substances was slight or nil in all three cases,

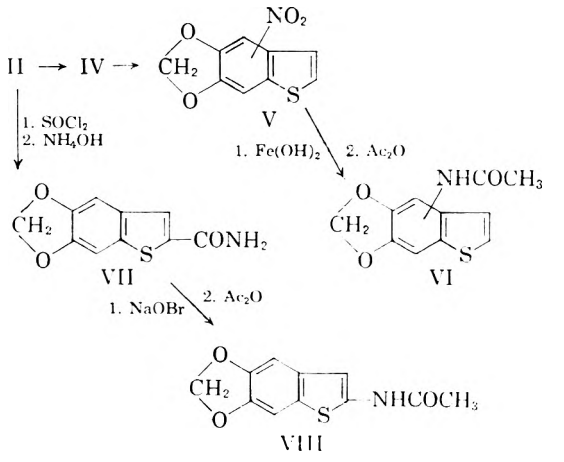


IIIabc

a. Z = N—$(CH_2)_4$—CH_2
b. Z = $NHCH_2CH_2$—$N(C_2H_5)_2$.HCl
c. Z = OCH_2CH_2—$N(C_2H_5)_2$.HCl

IIIa and IIIb were found to exhibit analgetic activity greater than that of aspirin, while IIIb but not IIIa showed diuretic activity in dogs. None of the compounds tested showed activity in bacteriological or antiviral screening.

Nitration of 5,6-methylenedioxybenzothiophene (IV),[3] the decarboxylated derivative of II, with nitric acid in acetic acid-acetic anhydride mixture gave a crystalline mononitro derivative (V) in nearly quantitative yield. Substitution did not occur at the expected 2-position (*cf.* Ref. 3). This was shown by conversion of V to the corresponding acetamide derivative (VI) and mixed melting point comparison of VI with an authentic sample of 2-acetamido-5,6-methylenedioxybenzothiophene (VIII) which was prepared unequivocally by the Hofmann rearrangement of II (VII).



EXPERIMENTAL

5,6-Dimethoxybenzothiophene-2-carbonyl chloride. A mixture of 16.5 g. (0.069 mole) of the acid (I)[5] 35 ml. of purified thionyl chloride and 375 ml. of dry benzene was refluxed for 3 hr. The acid dissolved slowly to form a clear amber solution which was then filtered through a Norit pad to remove traces of insoluble material. The benzene solution was chilled and the yellow crystals of the acid chloride were collected and dried in air. Concentration of the filtrate gave additional material. The total yield was 14 g. (79%) of odorless yellow needles melting at 171–172°.

Anal. Calcd. for $C_{11}H_9O_3SCl$: Cl, 13.81. Found: Cl, 13.89.

(4) Testing was performed in the laboratories of the Schering Corp., Bloomfield, N. J.

Preparation of the amides and ester of I. The acid chloride of I repeatedly demonstrated rather sluggish reactivity. This was first exemplified by the relatively high melting point of the odorless product, and later by the uncommonly vigorous conditions necessary to obtain some of the derivatives.

1-(5,6-Dimethoxy-2-benzothenoyl)piperidine (IIIa). A mixture of 2.4 g. (0.010 mole) of the acid (I) and 5 g. of purified thionyl chloride was suspended in 200 ml. of anhydrous ether. The mixture was allowed to stand for 2 days in a 250-ml. round bottomed flask fitted with a drying tube. The acid eventually dissolved to form a clear amber solution of the acid chloride. The ether was removed under vacuum; 50 ml. of benzene was added and removed in the same fashion until the odor of thionyl chloride had disappeared. The crude material thus obtained was treated with 2 g. (0.023 mole) of piperidine in 150 ml. of water containing 10 ml. of 10% sodium hydroxide solution. After the mixture had been shaken vigorously for 2 min., the precipitate was collected and recrystallized twice from aqueous ethanol to give 2.0 g. (65%) of transparent flakes which melted at 163–164°.

Anal. Calcd. for $C_{16}H_{19}NO_3S$: S, 10.50. Found: S, 10.45.

β-Diethylaminoethyl 5,6-dimethoxybenzothiophene-2-carboxamide hydrochloride (IIIb). Seven grams (0.027 mole) of the acid chloride of I and 3.2 g. (0.027 mole) of β-diethylaminoethylamine were refluxed overnight with 250 ml. of benzene. The cooled reaction mixture afforded a white precipitate which was collected and recrystallized from isopropanol to give 5 g. (47%) of light tan flakes melting at 185–186°.

Anal. Calcd. for $C_{17}H_{25}O_3N_2SCl$: Cl, 9.54. Found: Cl, 9.69.

β-Diethylaminoethyl 5,6-dimethoxybenzothiophene-2-carboxylate hydrochloride (IIIc). This compound was prepared from 7 g. (0.027 mole) of the acid chloride of I and 3.2 g. (0.027 mole) of β-diethylaminoethanol according to the procedure described in the preceeding experiment. Recrystallization from isopropyl alcohol gave 5 g. (49%) of colorless needles melting at 198–199°.

Anal. Calcd. for $C_{17}H_{24}O_4NSCl$: Cl, 9.48. Found: Cl, 9.42.

Nitration of 5,6-methylenedioxybenzothiophene. A solution of 3 g. (0.017 mole) of the benzothiophene (IV)[3] in 30 ml. of glacial acetic acid was added dropwise with stirring to a mixture of 50 ml. of acetic anhydride, 20 ml. of glacial acetic acid and 1.6 g. (0.018 mole) of 70% nitric acid maintained at 0–3°. The mixture was allowed to come to room temperature, whereupon 500 ml. of water was added with vigorous stirring. The yellow precipitate was collected, washed with ethanol and dried to give 3.7 g. (98%) of material melting at 234–235° (compound V). The analytical sample (golden-yellow threadlike needles from acetone) melted at 235–236°.

Anal. Calcd. for $C_9H_5O_4NS$: N, 6.27. Found: N, 6.38.

Reduction and acetylation of the mononitro-5,6-methylenedioxybenzothiophene (V). One gram (0.009 mole) of the finely divided nitro derivative was stirred into a suspension of ferrous hydroxide made by adding 30 ml. of concentrated ammonia to 20 g. of ferrous sulfate heptahydrate in a solution of 30 ml. of dioxane and 80 ml. of water. The mixture was stirred at 90–95° for 20 min. The resulting paste was filtered hot and the filtrate was treated with 20 ml. of acetic anhydride with vigorous stirring. The clear solution was chilled overnight to give a dark precipitate which was collected and recrystallized several times from dilute ethanol to give 0.3 g. (27%) of amber needles melting at 227–228° (compound VI).

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95; S, 13.62. Found: N, 6.16; S, 13.42.

5,6-Methylenedioxybenzothiophene-2-carboxamide (VII). Nine grams (0.04 mole) of I was converted to the acid chloride by refluxing 3 hr. with an excess (18 ml.) of thionyl chloride and 0.25 ml. of pyridine in 50 ml. of benzene. The benzene was removed under vacuum at room temperature; the crude acid chloride was dissolved in a small amount of

dioxane and poured into excess concentrated ammonia. After the mixture had been allowed to stand overnight, the tan precipitate was collected and dried to give 8.5 g. (94%) of (VII) which melted at 240–241° after one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{10}H_7NO_3S$: S, 14.50. Found: S, 14.23.

2-Acetamido-5,6-methylenedioxybenzothiophene (VIII). The amide prepared in the preceding experiment was subjected to the Hofmann hypobromite reaction according to the procedure of Vogel.[5] Eight grams (0.036 mole) of VII was treated with 30 ml. of a solution made by dissolving 8.4 ml. of bromine in 120 ml. of water containing 30 g. of sodium hydroxide. The mixture was warmed slightly until the reaction started and was then held at 80–90° for 45 min. The resulting suspension was diluted with 25 ml. of water and cooled to room temperature. Twenty milliliters (0.21 mole) of acetic anhydride was added with rapid stirring over a period of 20 min. and then the mixture was warmed at 60° for 0.5 hr. After the solution had been allowed to cool in the refrigerator overnight, the brown precipitate was collected and recrystallized from ethanol. The yield was 6 g. (70%) of red warty aggregates which melted at 241°. A mixed melting point with compound VI was depressed to 208–215°, and one with compound VII was depressed to 223–240°.

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95; S, 13.62. Found: N, 5.83; S, 13.98.

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(5) A. I. Vogel, *Practical Organic Chemistry*, Longmans, Green, Inc., N. Y., 3rd edition, 1956, p. 773.

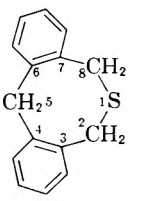
1-Thiadibenzo[*a*,*c*][3,6]cyclooctadiene and Other Cyclic *o*,*o*′-Bridged Diphenylmethanes[1]

DONALD D. EMRICK[2] AND WILLIAM E. TRUCE

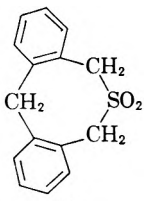
Received July 27, 1960

Regarding our studies on the preparation and geometry of various *o*,*o*′-bridged biphenyls and diphenylmethanes, it appears unlikely that further experimental work along these lines will be undertaken in the near future at this laboratory. Hence, the present data are being published in the hope that they may be of use to other workers, particularly since the stereochemistry of *o*,*o*′-bridged diphenylmethanes has yet to be demonstrated.

2,2′-Bis(bromomethyl)diphenylmethane, prepared from phthalic anhydride by the complex route of Bergmann and Pelchowicz,[3] was cyclized with methanolic sodium sulfide to the eight-membered ring 1-thiadibenzo[*a*,*c*][3,6]cyclooctadiene (I) approximately as readily as similar cyclization to the corresponding seven-membered sulfide in the biphenyl series occurred.[4] It was not necessary to use high dilution techniques in order to obtain good yields of the cyclic sulfide.



I



II

Oxidation of the sulfide (I) to the corresponding sulfone (II, 1-thiadibenzo[*a*,*c*][3,6]cyclooctadiene-1-dioxide) was readily accomplished with hydrogen peroxide in acetic acid. Alkylation of I with excess methyl iodide in ethanol produced a sublimable and water-insoluble coordination complex with an analysis corresponding to two g.-atoms of iodine per mole; the literature has described methyl iodide, haloform, and metal halide coordination complexes of sulfonium salts.[5]

Reduction of 2′-aminobenzophenone-2-carboxylic acid[6] to 2′-aminodiphenylmethane-2-carboxylic acid was accomplished *via* reduction by means of zinc dust (activated by copper) in ammonia.[7] Although stable indefinitely as carboxylate salts, the free 2′-aminodiphenylmethane-2-carboxylic acid cyclized slowly at room temperature (rapidly at 100°) to form the seven-membered ring cyclic lactam, indicating that this amino acid is more stable than 2′-aminobiphenyl-2-carboxylic acid and 2′-aminobiphenyl-2-acetic acid which have never been isolated, both cyclizing spontaneously to their six- and seven-membered cyclic lactams, respectively.[8]

EXPERIMENTAL[9]

1-Thiadibenzo[a,c][3,6]cyclooctadiene (I). A mixture of 10 g. (0.028 mole) of 2,2′-bis(bromomethyl)diphenylmethane,[3] 30 g. of sodium sulfide nonahydrate (0.125 mole), 80 ml. of water, and 1600 ml. of methanol were gently refluxed with stirring for 36 hr. The methanol was distilled and the residue was taken up in 500 ml. of cold water. The water-insoluble product was filtered off and recrystallized from a mixture of alcohol and benzene. The yield was 4.6 g. (72%), m.p. 194–195°.

Anal. Calcd. for $C_{15}H_{14}S$: C, 79.64; H, 6.19; mol. wt. 226. Found: C, 79.39; H, 6.14; mol. wt. 226.

A mercuric chloride coordination complex of the above sulfide was prepared by dissolving 1.00 g. of mercuric chloride in 10 ml. of hot absolute ethanol and adding quickly, with rapid stirring, a solution of 0.86 g. of the sulfide dis-

(1) Abstracted from the doctoral thesis submitted to Purdue University in 1956 by Donald D. Emrick.

(2) Present address: Research Department, The Standard Oil Company (Ohio), Cleveland 28, Ohio.

(3) E. D. Bergmann and Z. Pelchowicz, *J. Am. Chem. Soc.*, **75**, 4281 (1953).

(4) W. E. Truce and D. D. Emrick, *J. Am. Chem. Soc.*, **78**, 6130 (1956).

(5) N. V. Sidgwick, *The Chemical Elements and Their Compounds*, Vol. II, Oxford University Press, London, 1950; *Chem. Zentr.*, **69**, ii, 524 (1898) [Farbenfabriken vorm. Friedr. Bayer & Co., DRP 97207 (1897)].

(6) E. Beckmann and O. Liesche, *Ber.*, **56**, 1 (1923).

(7) E. D. Bergmann and E. Loewenthal, *Bull. soc. chim., France*, **19**, 66 (1952).

(8) L. Oyster and H. Adkins, *J. Am. Chem. Soc.*, **43**, 208 (1921); C. W. Muth, W. L. Sung, and Z. B. Papanastassiou, *J. Am. Chem. Soc.*, **77**, 3393 (1955).

(9) Boiling and melting points reported are uncorrected.

solved in 90 ml. of hot ethanol. Upon cooling, white crystals were obtained, m.p. 262–263°.

Four grams (0.0177 mole) of the above 1-thiadibenzo[*a,c*]-[3,6]cyclooctadiene were refluxed for 36 hr. with 30 ml. of absolute ethanol and 45 ml. (0.72 mole) of methyl iodide. Upon concentrating the reaction mixture down to a volume of 50 ml. with an air jet, white crystals were deposited upon standing overnight at −5°. Recrystallization from absolute ethanol produced white crystals (fluffy needles) which sublimed completely at 215–217°. In a sealed capillary, the crystals melted at 217°. The properties and analysis are consistent with a methyl iodide coordination complex of the sulfonium iodide.[6]

Anal. Calcd. for $C_{17}H_{20}SI_2$: I, 49.8. Found: I, 50.4.

1-Thiadibenzo[a,c][3,6]cyclooctadiene 1-dioxide (II). 1-Thiadibenzo[*a,c*][3,6]cyclooctadiene was prepared on a scale twice that described above. A mixture of 8.9 g. (0.039 mole) of this crude sulfide, 33 ml. (about 0.30 mole) of 30% hydrogen peroxide, and 130 ml. of glacial acetic acid was refluxed for 20 hr. The cooled mixture was poured into a cold solution of 87 g. of sodium hydroxide in 300 ml. of water and the resulting paste was allowed to cool to room temperature. Upon filtering off the crude sulfone and recrystallizing from an 80:20 benzene-toluene mixture, white crystals were obtained; yield 6.3 g. (61%), m.p. 258–259.

Anal. Calcd. for $C_{15}H_{14}SO_2$: C, 69.76; H, 5.43; mol. wt. 258. Found: C, 69.66; H, 5.40; mol. wt. 263.

Beckmann rearrangement of anthraquinone monoxime. The procedure for the reported successful Beckmann rearrangement of anthraquinone monoxime[8] was employed with poor results. A procedure patterned directly after the method used by Moore and Huntress[10] for the rearrangement of fluorenone oxime was employed successfully.

Anthraquinone monoxime (100 g.) was mixed with phosphorus oxychloride (200 ml.). A slurry of 125 g. of phosphorus pentachloride in 300 ml. of phosphorus oxychloride was cautiously added and the mixture was then refluxed for 5 hr. The phosphorus oxychloride (400 ml.) was distilled and the liquid residue was added to excess ice with vigorous stirring. The crude product was filtered off and dried; weight 94 g.; after recrystallization from acetic acid, m.p. 243–244°, literature[6] m.p. 245° for the cyclic amide.

Ninety grams of the cyclic amide from the above Beckmann rearrangement was refluxed with 90 g. of sodium hydroxide in 200 ml. of ethanol and 400 ml. of water for 6 hr. and was then poured into 1000 ml. of water, decolorized with 20 g. of Norite, cooled to 0°, and then acidified to yield yellowish-green crystals of 2′-aminobenzophenone-2-carboxylic acid; weight after recrystallization from 60% ethanol, 75 g.

Beckmann and Liesche[9] reported a melting point of 199° with decomposition and evolution of water to reform the Beckmann rearrangement amide, m.p. 245°. The recrystallized yellow 2′-aminobenzophenone-2-carboxylic acid, if placed in an initially cold melting point bath and then slowly heated, was found to change slowly to a gray solid (presumably the amide) melting at 243–244°. However, if the yellow crystals were placed in a preheated melting point bath at 180° and rapidly heated, it was found that the material melted with vigorous frothing at 191–194°, obviously expelling water; if these melted crystals were then allowed to solidify by standing for some time at room temperature, they were found to then melt at 243.5–244.5°, clearly indicating the conversion to the amide.

2-Aminodiphenylmethane-2-carboxylic acid and its lactam. The procedure of Bergmann and Loewenthal[7] for reducing benzophenone-2,2′-dicarboxylic acid to diphenylmethane-2,2′-dicarboxylic acid was found in this laboratory to be readily applicable to the reduction of the keto group of 2-benzoylbenzoic acid and 2′-aminobenzophenone-2-carboxylic acid.

A mixture of 75 g. (0.311 mole) 2′-aminobenzophenone-2-carboxylic acid, 450 ml. of concentrated ammonium hydroxide (sp. gr. 0.90), 150 ml. of water, 210 g. (3.12 g.-atoms) of zinc dust, and 4 ml. of an ammoniacal solution of 1*M* copper sulfate were gently refluxed with vigorous stirring for 20 hr. under a pressure slightly greater than atmospheric. Sodium carbonate solution (180 ml. of 10%) was added and refluxing with stirring was continued for an additional 20 hr. The resulting solution was filtered, the residue being extracted twice with hot 10% sodium carbonate solution. The combined filtrates were decolorized with 10 g. of Norite and acidified to give a crude grayish spongy mass of solid. Recrystallization from 80% ethanol gave nearly white crystals, m.p. 126–127°. The free acid slowly lactamized upon standing at room temperature while heating at 100–120°, or momentary heating to 190°, rapidly caused the formation of the internal seven-membered cyclic lactam of 2′-aminodiphenylmethane-2-carboxylic acid, m.p. 193–194°. The total yield of the free acid and lactam, collectively, was 75%. The experimental molecular weight was found to be 214, compared to a theoretical value of 209 for the monomeric amide.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.46; H, 5.28; N, 6.72 Found: C, 80.13; H, 5.06; N, 6.94.

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(10) F. J. Moore and E. H. Huntress, *J. Am. Chem. Soc.*, 49, 2618 (1927).

The Synthesis of 2-Mercaptoethanesulfonamide

Henry Lemaire and Martin Rieger[1]

Received July 25, 1960

As part of an investigation of mercaptoalkanesulfonic acids and related compounds,[2,3] the synthesis of 2-mercaptoethanesulfonamide (V) was undertaken. 2-Chloroethanesulfonyl chloride, (VI) available from previous work[2] was used in an attempt to prepare V *via* 2-chloroethanesulfonamide. However, both aqueous and anhydrous ammonia caused reaction of both chlorine atoms of VI. Dehydrochlorination of VI to ethenesulfonyl chloride and subsequent conversion to ethenesulfonamide[4,5] afforded such low yields that the addition of hydrogen sulfide was not attempted.

Conversion of 2-mercaptoethanesulfonic acid (I), also available from previous work,[3] to V requires the protection of the sulfhydryl group. Thioacetoxyethanesulfonyl chloride[5] was treated with dry ammonia but the resulting oil could not be purified. The desired synthesis of V was ac-

(1) Present address: Warner Lambert Research Institute, Morris Plains, N. J.

(2) C. Walling and W. F. Pease, *J. Org. Chem.*, 23, 478 (1958).

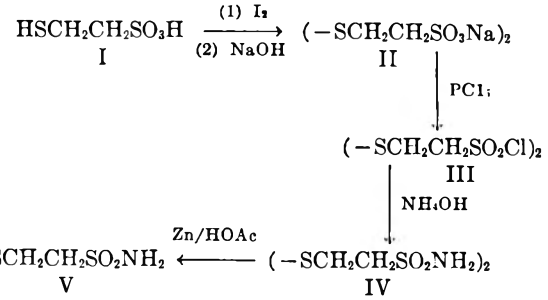
(3) C. H. Schramm, H. Lemaire, and R. H. Karlson, *J. Am. Chem. Soc.*, 77, 6231 (1955).

(4) C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, 76, 1926 (1954).

(5) P. W. Clutterbuck and J. B. Cohen, *J. Chem. Soc.*, 120 (1922).

(6) H. D. Porter and A. Weisberger, U. S. Patent 2,396,-879, March 19, 1946.

complished by protecting the sulfhydryl group through formation of the disulfide.



EXPERIMENTAL

Disodium-3,4-dithia-1,6-hexanedisulfonate (II). Iodine (39 g., 0.31 equivalent) was added to 250 ml. of a stock solution 2-mercaptoethanesulfonic acid (I) containing 54 g. (0.33 equivalent) of solute based on acidimetric titration.[7] A slight amount of iodine color remained undischarged. The disulfonic acid and the hydriodic acid were neutralized with 25.5 g. of sodium hydroxide (0.64 equivalent) in 25 ml. of water. The solution was then diluted with 380 ml. of methanol and treated with 1200 ml. of acetone. A copious precipitate was filtered, washed with acetone, and dried at 70°. It weighed 56.3 g. Recrystallization of 55.0 g. from 50 ml. of water gave 45 g. of wet crystals (not washed) which dried to 35.2 g. of (II) (65% yield).

Anal. Calcd. for $C_4H_8Na_2O_6S_4$: mol. wt., 326. Found[8]; 328.

3,4-Dithia-1,6-hexanedisulfonyl chloride (III). A dry mixture of 105 g. of II (0.32 mole) and 149 g. of phosphorus pentachloride (0.72 mole) was allowed to stand until it had turned molten and the heat of reaction had dissipated. Fumes were evolved and 24 g. was lost. An additional 93 g. of phosphorus oxychloride was removed by distillation at reduced pressure. The residue, 137 g., was taken up in 300 ml. of benzene, filtered to remove sodium chloride, and stripped to 95 g. of oily crystals. Filtration and washing with petroleum ether (b.p. 90–120°) gave 45 g. of III melting at 64°–72°. Mixing the mother and wash liquors gave more crystals which were dissolved in hot benzene filtered with Norite, and recovered by the addition of petroleum ether. This crop weighed 20 g. (total yield 0.204 mole, 63%) and melted at 68°–72°.

3,4-Dithia-1,6-hexanedisulfonamide (IV). Dithiahexanesulfonyl chloride (III), 20 g., was added to 200 ml. of concd. ammonium hydroxide with cooling to hold the temperature below 25°. The solid dissolved. The solution was concentrated to 100 ml. at reduced pressure, giving a precipitate which was filtered with great difficulty. The very finely divided powder was recrystallized from alcohol with Norite and again from alcohol to give 3.0 g. of crystals (17% yield) melting 146°–151°. Analysis by reduction showed a purity of 99%.

In another preparation the crude powder was recrystallized from water and three times from alcohol, the last time with Norite, to give platelets melting at 152.5°–154°.

Anal. Calcd. for $C_4H_{12}N_2O_4S_4$: S, 45.74. Found: S, 45.89.

2-Mercaptoethanesulfonamide (V). A solution of 7.0 g. (0.025 mole) of disulfonamide (IV) was prepared in a mixture of 50 ml. of water and 40 ml. of acetic acid at 90°. Eleven grams of 20-mesh zinc were added and the reduction mixture held at 90° for 45 min. The zinc was filtered off and the filtrate made up to 100 ml. Titration of an aliquot showed the presence of 50 mequivalents of mercaptan. Ten grams (63 mequivalents) of mercuric acetate in 20 ml. of water were added and the resulting precipitate was filtered and washed with ethanol. It was suspended in water and hydrogen sulfide passed in until the light colored solid had disappeared. Most of the mercuric sulfide suspension was removed by centrifuging and decantation. The rest was filtered on a Seitz K5 asbestos filter.

The solution of 2-mercaptoethanesulfonamide was concentrated at reduced pressure, leaving a small amount of oil. 1-Propanol was added and the solution again concentrated to an oil. Addition of petroleum ether gave 3.0 g. of crystals (yield 43%) which assayed 96% by iodometric titration.[8] A sharp melting point could not be obtained on this product.

RESEARCH AND DEVELOPMENT DIVISION
LEVER BROTHERS CO.
EDGEWATER, N. J.

(7) Iodometric titration showed only 0.31 equivalent of mercaptan. The discrepancy is probably due to disulfide formed in the solution by air oxidation.

(8) Samples of 100 mg. were dissolved in 20 ml. of water and 5 ml. of sulfuric acid. Titration showed the absence of mercaptan. One-half gram of powdered zinc was added and the reaction allowed to proceed for 30 min. (Similar results were obtained after 20 min. or 40 min.) The metallic zinc was removed, and the solutions were titrated with standard tenth normal iodine.

Oxidation of Dialkyl Sulfides with Nitric Acid

DAVID W. GOHEEN AND CLIFTON F. BENNETT

Received June 27, 1960

Many articles in the literature describe the oxidation of organic sulfides and sulfoxides to the corresponding sulfones. Oxidizing agents which are cited[1] are hydrogen peroxide, organic peroxides, per acids, potassium permanganate, sodium hypochlorite, hypochlorous acid, aqueous chlorine, chromic acid, oxygen, ozone, oxides of nitrogen, fuming nitric acid, ruthenium tetroxide,[2] and potassium persulfate.[3] Anodic oxidation also has been used.

For commercial processes, the above oxidizing agents are relatively costly and thus a search for an inexpensive oxidizing agent was undertaken. Nitric acid offers the advantage of economy over most of the other oxidants. Not only is the initial cost low but also the recovery of nitrogen oxides produced during oxidation and passage through a nitric acid tower assures very high recovery of the acid for re-use.

The oxidation of sulfides to corresponding sulfoxides with nitric acid[4,5] has been known to proceed smoothly and in good yield for many years. However, oxidation in high yield of the resulting sulfoxides to sulfones with nitric acid has heretofore not been realized at ordinary pressures.[6,7,8]

(1) C. M. Suter, *The Organic Chemistry of Sulfur*, John Wiley, New York, 1944, pp. 660–667.

(2) C. Djerassi and R. R. Engle, *J. Am. Chem. Soc.*, **75**, 3838 (1953).

(3) E. Howard, Jr., and L. S. Levitt, *J. Am. Chem. Soc.*, **75**, 6170 (1953).

(4) T. P. Hilditch, *J. Chem. Soc.*, 1618 (1908).

(5) E. Fromm, *Ann.*, **396**, 75 (1913).

(6) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3127 (1928).

(7) O. Beckmann, *J. Prakt. Chem.*, (2), **17**, 471 (1878).

(8) F. Beilstein and A. Kurbatow, *Ann.*, **197**, 75 (1879).

TABLE I

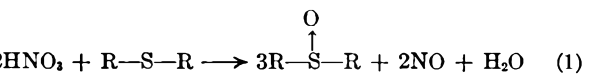
OXIDATION WITH NITRIC ACID

Material Oxidized	Quantity Oxidized, Mole	Quantity Nitric Acid, Moles	Reaction Temp.	Reaction Time, Min.	Sulfone Produced	M.P.	Yield, %
Dimethyl sulfide	1.00	3.0	122–148	85	Dimethyl	109	88
Diethyl sulfide	0.45	0.96	140	120	Diethyl	74	77
Di-*n*-propyl sulfide	.33	1.33	115–150	45	Di-*n*-propyl	26	97
Di-*n*-butyl sulfide	.33	1.33	96–120	60	Di-*n*-butyl	43	69
Di-*n*-octyl sulfide	.33	1.33	125–176	12	Di-*n*-octyl	73	83
Dimethyl sulfoxide	.42	0.64	120–150	240	Dimethyl	109	86

In the early literature there are several references to the use of nitric acid for oxidation of sulfides.[9–12] In all cases, ordinary nitric acid resulted in the formation of only the sulfoxide. In order to obtain the sulfone it was necessary to use fuming nitric acid or sealed tubes and long heating periods. Reaction details in these references are very sketchy and conversions to the sulfone were not complete.

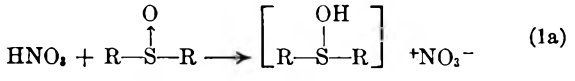
In contrast to these earlier methods, the procedure used in the present investigation gave high yields using ordinary concentrated nitric acid. The dialkyl sulfides and dialkyl sulfoxides which were examined in the present study were converted to the sulfones in yields approaching theoretical in many cases.

The reaction of nitric acid, as is the case with many other oxidizing agents, with sulfides proceeds in two steps, *viz.*,



$$2HNO_3 + R{-}S{-}R \longrightarrow 3R{-}\overset{\overset{O}{\uparrow}}{S}{-}R + 2NO + H_2O \quad (1)$$

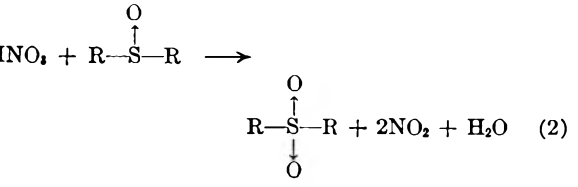
The sulfoxide formed immediately reacts with any excess nitric acid to form the hydroxy sulfonium nitrate,



$$HNO_3 + R{-}\overset{\overset{O}{\uparrow}}{S}{-}R \longrightarrow \left[R{-}\overset{\overset{OH}{|}}{S}{-}R\right]^{+}NO_3^{-} \quad (1a)$$

The oxidation proceeds so readily with most oxidizing agents that one must assume a low activation energy exists for the conversion of a sulfide to sulfoxide.

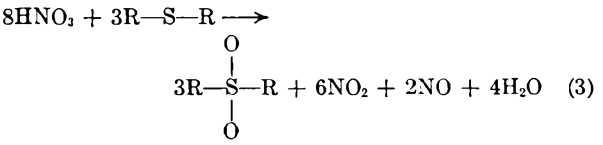
The second step of the oxidation, although in most cases is accompanied by a larger heat of reaction, proceeds with much greater difficulty:



$$2HNO_3 + R{-}\overset{\overset{O}{\uparrow}}{S}{-}R \longrightarrow R{-}\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}{-}R + 2NO_2 + H_2O \quad (2)$$

and thus the activation energy for the oxidation of sulfoxides to sulfones is probably very high.

It has been found that reaction (2) starts at about 120° and proceeds readily only at temperatures above 130° and then only with continuous application of heat. One must be dealing, in this case, with a large activation energy. The failure of previous investigators satisfactorily to oxidize sulfides to sulfones resulted because reaction temperatures were too low to overcome readily the high activation energies. It is fortunate that sulfoxides readily form the conjugate acid with nitric acid, as this allows the use of high temperatures at ordinary pressures without undue loss of nitric acid. The overall reaction of nitric acid with sulfides can best be summarized by adding equations (1) and (2) to give (3):



$$8HNO_3 + 3R{-}S{-}R \longrightarrow 3R{-}\overset{\overset{O}{|}}{\underset{\underset{O}{|}}{S}}{-}R + 6NO_2 + 2NO + 4H_2O \quad (3)$$

This is, of course, an oversimplification but most closely explains the stoichiometry which has been observed. In reaction (1), it has been found experimentally that most of the nitric acid is reduced to nitric oxide although a small amount of nitrogen dioxide is formed, and conversely, in reaction (2), the major part of the nitric acid is reduced to nitrogen dioxide with only a small portion appearing as nitric oxide.

The results obtained in this investigation demonstrate that sulfones can be readily prepared by an inexpensive oxidation and thus may become available commercially. High cost has, until now, been a large factor in retarding their commercial utilization. The oxidative process is especially adaptable to recovery and re-use of the nitric acid. The nitrogen oxides can be recovered and regenerated to nitric acid with at least 95% efficiency.

EXPERIMENTAL

Nitric acid, of any desired concentration, was combined with the sulfide in a molar ratio between 2.00 nitric acid:1.00 sulfide and 6.00 nitric acid:1.00 sulfide, and the mixture was heated at atmospheric pressure to a temperature of 120 to 180° until red-brown fumes ceased to evolve. Any water originally present in the acid was driven off during the heating. The addition of the nitric acid to the sulfide, or

(9) A. Saytzeff, *Ann.*, **139**, 354 (1866).
(10) A. Von Oefele, *Ann.*, **127**, 370 (1863).
(11) A. Saytzeff, *Ann.*, **144**, 148 (1867).
(12) N. Grabowsky, *Ann.*, **175**, 348 (1875).

vice versa, was found to be possible at any temperature between 0° and the boiling point of the higher boiling component.

Dialkyl sulfoxide was oxidized to the sulfone by combining it with nitric acid of any desired concentration at any temperature between 0° and the boiling point of the higher boiling component, and heating at atmospheric pressure until cessation of red fumes signified completion of the reaction.

The various oxidations are summarized in Table I.

CHEMICAL PRODUCTS DIVISION
CROWN ZELLERBACH CORPORATION
CAMAS, WASH.

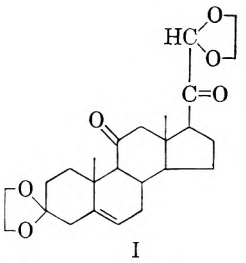
Steroidal Cyclic Ketals. XXII.[1] By-Products of the Ketalization of Cortisone and 11-Epihydrocortisone

SEYMOUR BERNSTEIN, MILTON HELLER, AND WILLIAM S. ALLEN

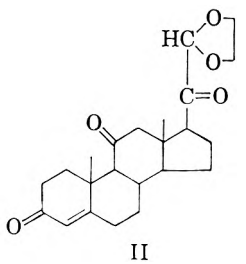
Recieved June 16, 1960

In view of the recent comment of Evans and co-workers[2] that a nonhydroxylic by-product was formed in substantial yield during the ketalization of 5α-dihydrocortisone, we wish to disclose certain similar experiences in the preparation of cortisone 3,20-bisethylene ketal[3] and 11-epihydrocortisone 3,20-bisethylene ketal.[4]

The combined mother liquors for several preparations of cortisone-3,20-bisethylene ketal[3] were evaporated and after crystallization from ethanol and then acetone, gave a new compound (I) whose elemental analyses indicated an empirical formula of $C_{25}H_{34}O_6$. There was no selective ultraviolet absorption. The infrared absorption spectrum, however, indicated the presence of two carbonyl functions, at least one ethylene ketal moiety, and a Δ^5-double bond, but no hydroxyl function. Treatment of I with sulfuric acid in methanol gave a new compound II, which obviously, from the ultraviolet and infrared absorption spectra and elemental analyses, was the result of removal of the 3-ethylene ketal group to form a Δ^4-3-one. This latter compound, moreover, still did not contain a hydroxyl group. The most convenient rationale for the by-product I was to assume it was the product of ordinary ketalization at the C3-one with a concomitant Mattox rearrangement[5] of the side chain. Since the only alcohol present in the reaction was ethylene glycol, this would necessitate that the final formulation of I would be 3,21-bisethylenedioxy-5-pregnene-11,20-dione, while II would be 21-ethylenedioxy-4-pregnene-3,11,20-trione (II).



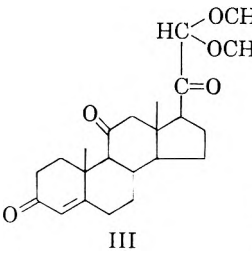
I



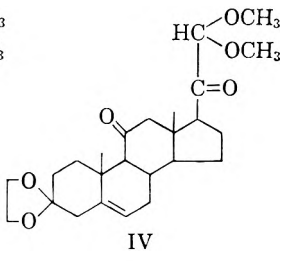
II

It was interesting to note the difficulty in removing the C21-ketal group in I which may be ascribed to the influence of the C11-carbonyl group. A similar influence has been previously found in the hydrolysis of a C20-ketal group in an 11-ketosteroid.[3,6-8] Also, the infrared absorption spectrum of I revealed the presence of carbonyl functions at 1712 and 1738 cm.$^{-1}$. The former band has been assigned to the C11-carbonyl group.[9] The assignment of the 1738 cm.$^{-1}$ band to the C20-carbonyl function implies that the band is markedly displaced from the normal 1706–1710 cm.$^{-1}$ region associated with such a group.[9,10] It would appear, then, that there is some interaction between the C20-carbonyl and the C21-ethylenedioxy groups analogous to the interaction in the 21-acetoxy-20-ketosteroids.[10]

It was thought that further confirmation of the postulated structure for I might be achieved by ketalization of 21,21-dimethoxy-4-pregnene-3,11,20-trione (III)[5] with an exchange reaction taking place at C21. Apparently no exchange reaction occurred at C21 since a new compound was obtained, presumably, 3-ethylenedioxy-21,21-dimethoxy-5-pregnene-11,20-dione (IV).



III



IV

When the mother liquors from the preparation of 11-epihydrocortisone-3,20-bisethylene ketal[4] were

(1) Paper XXI, W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 3223 (1956).

(2) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Phillips, *J. Chem. Soc.*, 1529 (1958).

(3) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(4) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

(5) V. R. Mattox, *J. Am. Chem. Soc.*, **74**, 4340 (1952).

(6) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1954).

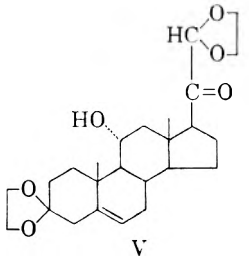
(7) J. A. Zderic and D. C. Limon, *J. Am. Chem. Soc.*, **81**, 4570 (1959).

(8) K. Tsuda, N. Ikekawa, and S. Nozoe, *Chem. and Pharm. Bull.* (Tokyo), **1**, 519 (1959), have recently illustrated the same sort of ketalization and Mattox rearrangement[5] while performing an exchange dioxolanation reaction on Reichstein's substance S. In this case where a C11-carbonyl group is not present, the C21-ketal group was easily hydrolyzed with dilute acid.

(9) R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, **72**, 956 (1950).

(10) R. N. Jones, V. Z. Williams, M. J. Whalen, and K. Dobriner, *J. Am. Chem. Soc.*, **70**, 2024 (1948).

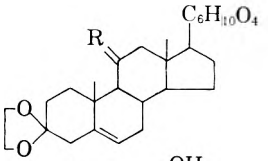
investigated, evidence for at least two by-products were obtained. Oxidation with chromium trioxide-pyridine of a crude glass isolated from the mother liquors gave in small yield compound I, indicating thereby that some 3,21-biscthylenedioxy-11α-hydroxy-5-pregnen-20-one (V) was in the glass. Direct crystallization of the crude glass from methanol, however, led to a different series of com-



V

pounds. The actual compound VIa isolated had, on the basis of elemental analyses, an empirical formula $C_{27}H_{40}O_7$. The infrared absorption spectrum showed the presence of a hydroxyl group, but no carbonyl absorption was observed. This compound could be easily acetylated to afford a derivative VIb with no hydroxyl absorption in the infrared. Furthermore, oxidation with chromic acid-pyridine (or in poorer yield with chromic acid-acetic acid) furnished a carbonyl compound VII with no hydroxyl absorption in the infrared. This set of experiments showed that the only hydroxyl grouping in VIa was most likely the 11α-ol originating from that in the starting material, 11-epihydrocortisone.

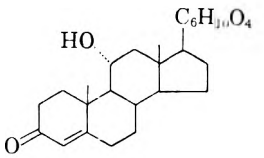
Hydrolysis of VIa with *p*-toluenesulfonic acid in acetone gave a Δ^4-3-ketone VIII, the analysis of which indicated that the side chain was unaltered in the acid treatment. It appeared to us from these series of reactions that no profound, unexplainable alterations of structure have occurred in the ring system in the synthesis of VIa from 11-epihydrocortisone. Rather, the side chain at C_{17} may be represented by the moiety, $C_6H_{10}O_4$.



VIa. R = 

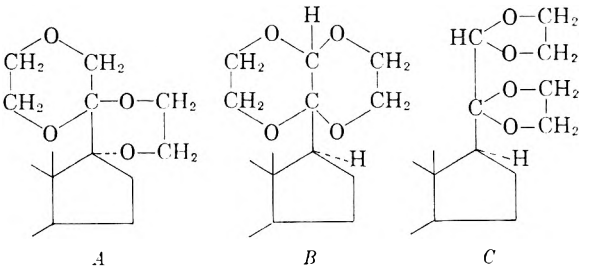
b. R = 

VII. R = O



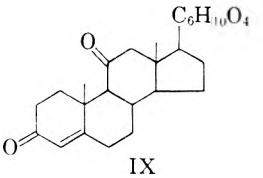
VIII

The infrared absorption spectrum of VIa indicated a high degree of 'C—O—C' absorption, but shed no light on other structural points in regard to the side chain. Hydrolysis studies also indicated the stability of the side chain toward acid. Conjecture, however, of the possible nature of the sidechain lead to the possibilities represented by *A* and *B*, formulations already proposed by Evans and co-workers.[2] The structure *A* is reminiscent of the bismethylenedioxy compounds synthesized by Beyler and associates.[11] In view of the Mattox rearrangement discussed above there is no *a priori* reason not to suggest a side chain moiety as illustrated by *C*.



A *B* *C*

In a series of experiments designed to prove rigorously the structure of the rearrangement product I, cortisone was treated at room temperature with an anhydrous hydrogen chloride solution of ethylene glycol. It was hoped that thereby compound II would be obtained. Surprisingly, a new compound IX resulted which by elemental and infrared spectral analyses appeared to contain a side chain similar to that found in VIa. Indeed, ketalization of the Δ^4-3-one group of IX by exchange dioxolanation[12] gave VII as indicated by a mixed melting point determination and by comparison of infrared spectra.



IX

A very small amount of a second product was isolated from the acidic ethylene glycol reaction on cortisone which had a very strained carbonyl absorption at 1749 cm.$^{-1}$ in its infrared spectrum. This was in addition to the expected absorption at 1711 cm.$^{-1}$ (11-carbonyl) and 1678 cm.$^{-1}$ (3-carbonyl). This was reminiscent of the spectra reported for 13α,21-epoxy-17β-methyl-18-nor-17α-4-pregnene-3,11-20-trione.[13] However, comparison with an authentic sample[13] of this compound showed the two compounds to be quite different in the fingerprint region of the infrared spectra.

In conclusion, it is felt that none of the suggested partial structures, *A*, *B* and *C*, for the side chain can be preferred in view of the method of formation and the resistance to acid hydrolysis. An attempt to hydrolyze a very small amount of VII with 60%

(11) R. E. Beyler, R. M. Moriarity, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(12) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 135 (1954).

(13) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **78**, 4814 (1956). We wish to thank Dr. Hirschmann for the sample of 13α,21-epoxy-17β-methyl-18-nor-17α-4-pregnene-3,11,20-trione.

formic acid[11] gave a crude glass with an infrared spectrum suggesting the formation of some formates. This interesting project was then unfortunately terminated in favor of other work.

EXPERIMENTAL

Melting points. All melting points are uncorrected. *Petroleum ether.* The fraction used unless otherwise noted had a b.p. 60–70° (Skellysolve B).

3,21-Bisethylenedioxy-5-pregnene-11,20-dione (I). *A.* Mother liquors from several cortisone bisethylene ketal[3] preparations were combined and evaporated. The resultant solid was dissolved in 200 ml. of warm ethanol and allowed to stand overnight. The precipitate was filtered and crystallized from acetone to give 0.68 g. of I, m.p. 173–175°. The analytical sample had a m.p. 178–182°; ν_{max}^{Nujol} 1738, 1712 and 1100 cm.$^{-1}$; $[\alpha]_D^{25}$ +44.° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.78, 69.85; H, 8.17, 8.16.

B.[14] Mother liquors from a ketalization[4] of 5.0 g. of 11-epihydrocortisone were evaporated to give 1.89 g. of glass. This was dissolved in 100 ml. of pyridine and poured into a slurry of 1.27 g. of chromium trioxide in 30 ml. of pyridine. After standing for 18 hr., at room temperature the reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried and evaporated to give an oil. Crystals formed after long standing of the oil dissolved in methanol. Filtration afforded 70 mg. of I, m.p. 182–184°. The infrared spectrum was identical to that of the sample prepared above in *A*.

21-Ethylenedioxy-4-pregnene-3,11,20-trione (II). A solution of 400 mg. of the 3,21-bisketal I in 40 ml. of methanol and 4.5 ml. of 8% (v/v) sulfuric acid was refluxed for 1 hr. Aqueous sodium bicarbonate was added until the solution was slightly basic. Addition of water gave a solid which was collected and dried to give 150 mg. of II, m.p. 145–151°. Recrystallization from acetone-petroleum ether raised the m.p. to 153–154°; $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,500); ν_{max}^{Nujol} 1728, 1710, 1676 and 1622 cm.$^{-1}$; $[\alpha]_D^{25}$ +226° (chloroform).

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.86, 71.60; H, 7.95, 8.18.

3-Ethylenedioxy-21,21-dimethoxy-5-pregnene-11,20-dione (IV). 21,21-Dimethoxy-4-pregnene-3,11,20-trione[5] (III, 1.0 g.) and *p*-toluenesulfonic acid (30 mg.) was added to a mixture of 35 ml. of benzene and 10 ml. of ethylene glycol. The mixture was refluxed and stirred with constant water removal for 5 hr. An additional 15 mg. of *p*-toluenesulfonic acid was added after 1 hr. A solution of potassium carbonate was added, the water layer was separated and extracted with benzene and the combined benzene extracts were evaporated. Repeated crystallization of the resultant solid from acetone-petroleum ether gave 0.415 g. of IV, m.p. 131.5–133°; ν_{max}^{Nujol} 1722 (shoulder), 1711 and 1080 cm.$^{-1}$; $[\alpha]_D^{25}$ +55° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.15; H, 8.57.

Isolation of compound VIa. Crystallization of the residue from the mother liquors of a preparation of 11-epihydrocortisone-3,20-bisethylene ketal gave VIa, m.p. 234–236°; ν_{max}^{Nujol} 3570 and 1100 cm.$^{-1}$; $[\alpha]_D^{25}$ −28° (chloroform).

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 68.04; H, 8.46. Found: C, 67.96; H, 8.53.

Acetylation of compound VIa (VIb). Acetylation of 500 mg. of crude VIa in 5 ml. of pyridine and 2.5 ml. of acetic anhydride in the usual manner gave 200 mg. of VIb after crystallization from acetone-petroleum ether, m.p. 233–236°; ν_{max}^{Nujol} 1730 and 1256 cm^{-1}.

Anal. Calcd. for $C_{29}H_{42}O_8$ (518.63): C, 67.16; H, 8.16; OAc, 9.54. Found: C, 67.35; H, 8.55; OAc, 9.59.

(14) This experiment was performed by R. Littell.

Compound VII. *A.* A solution of 1.0 g. of VIa in 100 ml. of pyridine was treated with a slurry of 800 mg. of chromium trioxide in 140 ml. of pyridine. After the mixture was allowed to stand for 18 hr. at room temperature, 0.8 g. of sodium bicarbonate was added. The pyridine was removed by steam distillation, and the resultant mixture was extracted with chloroform. The extract was dried and evaporated to give a glass. Crystallization from ether-petroleum ether yielded 770 mg. of VII, m.p. 172–174°. The analytical sample had a m.p. 173–174°; ν_{max}^{Nujol} 1708 and 1100 cm.$^{-1}$; $[\alpha]_D^{25}$ −16° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_4$ (474.57): C, 68.33; H, 8.07. Found: C, 68.28, 68.51; H, 8.18, 8.30.

B. A solution of 0.5 g. of chromium trioxide in 20 ml. of glacial acetic acid was added to a solution of 1.0 g. of VIa in 20 ml. of acetic acid. After standing for 18 hr. at room temperature, the solution was diluted with water. The resultant solid (0.74 g.) was collected and had a m.p. 154–157°. Further crystallization from acetone-petroleum ether gave a sample of VII identical in all respects to the sample described above in *A*.

C. A solution of 0.26 g. of IX and 10 mg. of *p*-toluenesulfonic acid in 20 ml. of 2-methyl-2-ethyl-1,3-dioxolane was refluxed and slowly distilled for 5 hr. Benzene was then added to the solution and it was washed with sodium bicarbonate. Removal of the solvent afforded a glass which was submitted to chromatography on Florisil.[15] Solid was collected from the acetone-petroleum ether (23:2) eluates and had a m.p. of 170–171° with no depression of melting point on mixture with the sample obtained from *A* above. The infrared spectra of the two samples were identical.

Compound VIII. A solution of 1.0 g. of VIa and 75 mg. of *p*-toluenesulfonic acid in 75 ml. of acetone was allowed to stand at room temperature for 18 hr. Water was added and the acetone was removed under reduced pressure at room temperature. The resultant collected solid (800 mg.) had a m.p. 243–246°. Crystallization from methanol gave VIII, m.p. 258–260°; $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 15,300); ν_{max}^{Nujol} 3700, 1672 and 1634 cm.$^{-1}$; $[\alpha]_D^{25}$ +63° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.61; H, 8.61.

The 3-(2,4-dinitrophenylhydrazone) of VIII prepared in the usual manner in glacial acetic acid had a m.p. 279–281°.

Anal. Calcd. for $C_{31}H_{40}O_9N_4$ (612.66): C, 60.77; H, 6.58; N, 9.15. Found: C, 60.75; H, 6.87; N, 8.53.

Compound IX. A slurry of 5.0 g. of cortisone in 40 ml. of ethylene glycol was added to 40 ml. of ethylene glycol saturated with hydrogen chloride. The mixture was stirred for 24 hr. at room temperature, and the solid (wt. 2.5 g., Fraction 1) was collected by filtration. The filtrate was diluted with water and the resultant solid was collected. Repeated crystallizations from acetone-water gave pure IX, m.p. 221.5–223°; $\lambda_{max}^{CH_3OH}$ 237–238 mμ (ε 15,500); ν_{max}^{KBr} 1710, 1682, 1627 and 1100 cm.$^{-1}$; $[\alpha]_D^{25}$ +142° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.82; H, 8.14.

The mother liquors from the above crystallization gave another 0.345 g. of IX, m.p. 217–219° upon partition chromatography on Celite[16] with the solvent system heptane:ethyl acetate:methanol:water (8:2:3:2).

Fraction 1 was subjected to partition chromatography on Celite[16] first with the solvent system, cyclohexane:dioxane:water (5:4:1). The second and third hold-back volumes were combined and evaporated, and again chromatographed with the solvent system heptane:ethyl acetate:methanol:

(15) Florisil is the trade-mark of the Floridin Co. for a synthetic magnesium silicate.

(16) This technique was described by S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959). Celite is Johns-Manville's registered trade-mark for diatomaceous silica products.

water (8:2:3:2). Concentration of the first part of the second hold-back volume gave 0.77 g. of IX, m.p. 220–221°. Concentration of the fourth hold-back volume gave 5 mg. of an unknown compound, m.p. 175–180° (not further purified); ν_{max}^{KBr} 1749, 1711, 1678 and 1618 cm^{-1}.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analytical data, William Fulmor and associates for the spectral and optical rotational data, and Charles Pidacks and associates for the partition chromatographic separations.

ORGANIC CHEMICAL RESEARCH SECTION
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Dehydration of a Steroidal β-Ketol with Chromatographic Adsorbents

ROY H. BIBLE, JR., AND NORMAN W. ATWATER

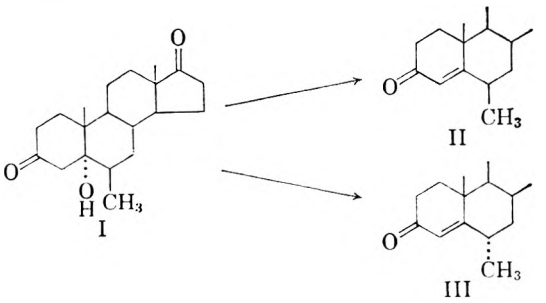
Received July 11, 1960

The preparation of steroidal 6-alkyl-Δ^4-3-ketones is usually accomplished by dehydration of the 6β-alkyl-5α-hydroxy-3-ketones which in turn arise from the action of an alkyl Grignard reagent on a 5α,6α-epoxide. A variety of basic and acidic conditions are available for the production of the 6α-alkyl derivatives[1] from this intermediate because of the great ease with which C_6 is epimerized subsequent to the dehydration step. For this same reason, however, the formation of the 6β-alkyl derivatives[2] has required careful attention to reaction conditions.

Quite by accident it was discovered that when the steroidal 5α-hydroxy-3-ketone system was chromatographed on Florisil[3] the eluates consisted of a mixture of dehydrated material along with the ketol. Further experiments in which the formation of the α,β-unsaturated ketone was followed by the appearance of its characteristic ultraviolet absorption demonstrated that the reaction was essentially complete after three hours at reflux in benzene in the presence of the Florisil. A good yield of 6β-methylandrost-4-ene-3,17-dione (II) was obtained from 6β-methyl-5α-hydroxyandrostan-3,17-dione (I)[1c] using these conditions.

This result led us then to attempt dehydration of I with the more strongly adsorbing aluminum oxide. In contrast to the previous case this reaction was quite fast and the only product isolated was 6α-methylandrost-4-en-3,17-dione (III).[4] Both procedures are characterized by the absence in the crude products of colored impurities thus allowing final crystallization with a minimum of loss.

Further examples of these methods will be described in forthcoming communications from this laboratory.



EXPERIMENTAL

6β-Methylandrost-4-ene-3,17-dione (II). A mixture of 5α-hydroxy-6β-methylandrostane-3,17-dione (I, 830 mg.),[1c] Florisil (8.3 g., 100–200 mesh), and benzene (166 ml.) was stirred at reflux temperature for 3 hr. The mixture was filtered and the solid was washed with ethyl acetate (500 ml.). Removal of the solvents from the combined filtrates followed by two recrystallizations of the resulting residue from aqueous methanol gave II; 570 mg.; m.p. 207–215°; $[\alpha]_D$ +135°; λ_{max} 241 mμ (ε 15,800). Reported[2a,5]: m.p. 207–212°; λ_{max} 242 mμ (ε 16,200); $[\alpha]_D$ +139°.

6α-Methylandrost-4-ene-3,17-dione (III). A. *By dehydration of ketol* I *with alumina.* Compound I (500 mg.) in benzene (100 ml.) was stirred at reflux temperature with basic aluminum oxide[6] (5.00 g., activity grade I) for 50 min. The mixture was filtered and the solid was washed with benzene (150 ml.). Removal of the solvent followed by one recrystallization of the resulting residue from aqueous methanol gave III; 250 mg.; m.p. 171–174°; $[\alpha]_D$ +181°. Reported[2a,5,7]: m.p. 164–167°; $[\alpha]_D$ +180°; λ_{max} 242 mμ (ε 15,650).

B. *By isomerization of the 6β-derivative* (II). A solution of Compound II (80 mg.) in ethanol (10 ml.) was refluxed with dilute sodium hydroxide (2 ml. of 0.1*N*) under nitrogen for 30 min. Dilution of the reaction mixture with water (200 ml.) containing dilute hydrochloric acid gave III; 46 mg.; m.p. 168.5–171.5°; λ_{max} 240 mμ (ε 14,520).

DIVISION OF CHEMICAL RESEARCH
G. D. SEARLE AND CO.
CHICAGO 80, ILL.

(1) (a) H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959); (b) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 3091 (1958); (c) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957); (d) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 436 (1939); *Chem. Abstr.*, **33**, 9309 (1939).

(2) (a) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 4717 (1958); (b) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 5362 (1952).

(3) A chromatographic magnesium silicate sold by the Floridin Co., Warren, Pa. Analysis: MgO, 15.5:; SiO_2, 84%; Na_2SO_4, 0.5%.

(4) An aqueous slurry of the Florisil was at least as basic as an aqueous slurry of the aluminum oxide thus demonstrating that this result was a consequence of the action of the adsorbent itself and not of the water soluble hydroxide.

(5) Compare also Ref. 1c; H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(6) A product of M. Woelm Eschwege supplied by Alupharm Chemicals.

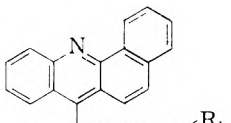
(7) Compare also V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957); O. S. Madaeva, M. I. Ushakov, and N. F. Koscheleva, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 213 (1940); *Chem. Abstr.*, **34**, 7292 (1940).

Synthetic Amebicides. V. 6-(Mono- and Dialkylaminoalkylamino)-3-methyl-7H-dibenz-[f,ij]isoquinoline-2,7(3H)diones[1]

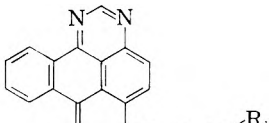
EDWARD F. ELSLAGER AND LESLIE M. WERBEL

Received August 4, 1960

A variety of amine derivatives of nitrogen heterocyclic compounds has been reported to possess activity against *Entamoeba histolytica*, the causative agent of amebiasis.[2] Among these, striking activity has been observed with polycyclic amines such as 7-aminobenz[c]acridines of general formula I[1,3] and 6-aminoanthrapyrimidines of structure II,[4] where Y represents an alkylene

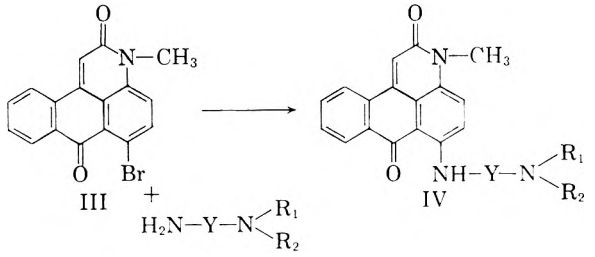


I



II

radical. In a search for polycyclic amines with antiamebic activity, we have synthesized a series of 6-(mono- and dialkylaminoalkylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)diones (IV) (Table I) for biological evaluation. These compounds were prepared by the condensation



of the commercially available[5] 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione (III) with the appropriate *N*-monoalkyl-or *N,N*-dialkylalkylenediamine utilizing xylene, pyridine or excess

(1) For previous paper in this series, see E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 451 (1958).

(2) For a summary of these studies, see E. F. Elslager in *Medicinal Chemistry*, A. Burger, ed., Interscience, New York, 1960, pp. 862–864.

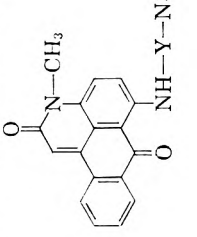
(3) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **79**, 4699 (1957); F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 223 (1958); P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles, and H. Najarian, *Antibiotics & Chemotherapy*, **8**, 37 (1958).

(4) W. R. Jones, J. K. Landquist, and N. Senior, *Brit. J. Pharmacol.*, **7**, 486 (1952).

(5) The authors express their appreciation to the Antara Chemicals Division of General Dyestuff Corp., New York for the generous supply of the 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione used in this work.

TABLE I

6-(MONO- AND DIALKYLAMINOALKYLAMINO)-3-METHYL-7H-DIBENZ[f,ij]ISOQUINOLINE-2,7(3H)DIONES[a]

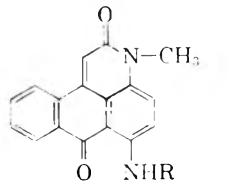


Y	NR_1R_2	M.P.	Yield purified, %	Procedure	Purification Solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_2-$	$N(C_2H_5)_2$	195–197	35	I[d]	A	$C_{23}H_{25}N_3O_2$	73.57	73.66	6.72	6.78	11.18	11.41
$-(CH_2)_3-$	$NHCH(CH_3)_2$	157–158 (s. 153)	43	I	A, B	$C_{23}H_{25}N_3O_2$	73.57	73.59	6.72	6.68	11.18	10.98
$-(CH_2)_3-$	$N(CH_3)_2$	168–170	76	II	B	$C_{22}H_{23}N_3O_2 \cdot H_2O$[c]	69.63	69.58	6.64	6.66	11.07	11.15
$-(CH_2)_3-$	$N(C_2H_5)_2$	175–176	42	I[d]	B	$C_{24}H_{27}N_3O_2$	74.01	73.83	6.99	7.16	10.79	10.63
$-(CH_2)_3-$	$N[(CH_2)_2]_2O$	204–205	30	I[d]	A	$C_{24}H_{25}N_3O_3$	71.44	71.17	6.25	6.22	10.41	10.84
$-(CH_2)_5-$	$N(CH_2)_5$	183–185 (s. 178)	22	III	B	$C_{27}H_{31}N_3O_2$	75.49	75.48	7.28	7.20	9.78	9.84
$-CH_2CHOHCH_2-$	$N(C_2H_5)_2$	189–191 (s. 185)	53	II	B	$C_{24}H_{27}N_3O_3$	71.09	70.54	6.71	6.76	10.36	10.48

[a] All compounds were orange-red or red solids. [b] A, Benzene; B, acetone. [c] Water determination (Karl Fischer); Calcd. 4.75, Found: 4.89. [d] A trace of cuprous chloride was added.

amine as the solvent. The *N*-monoalkyl- and *N,N*-dialkylalkylenediamines have been described previously.[3]

The 6-(mono- and dialkylaminoalkylamino)-3-methyl - 7H - dibenz[f,ij]isoquinoline-2,7(3H)-diones described in the present communication were tested by P. E. Thompson and co-workers of these laboratories against *E. histolytica in vitro*,[6] and when indicated, against acute intestinal amebiasis in rats,[7] amebic colitis in dogs[8] and amebic hepatitis in hamsters.[9] Although details of these test results will be presented elsewhere,[10] the following highlights might be mentioned here. The dibenzisoquinolinediones listed in Table I were amebicidal *in vitro* at concentrations of 2 to 67 μg./ml. and each was active against intestinal amebiasis in the rat. Five compounds were tested against amebic dysentery in dogs and all were active. One compound (Va) was tested against amebic hepatitis in hamsters and was found to be approximately as active as chloroquine. Com-



Va, R = $-(CH_2)_5N(CH_2)_5$
b, R = $-CH_3$

pound Vb,[11] which lacks the basic side chain, was inactive *in vitro* at 2000 μg./ml. and was ineffective against intestinal amebiasis in the rat at the M.T.D.

(6) For a description of test methods, see P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles, and A. R. Cook, *Antibiotics & Chemotherapy*, 5, 433 (1955).

(7) For a description of test methods, see P. E. Thompson, M. C. Dunn, A. Bayles, and J. W. Reinertson, *Am. J. Trop. Med.*, 30, 203 (1950).

(8) For a description of test methods, see P. E. Thompson and B. L. Lilligren, *Am. J. Trop. Med.*, 29, 323 (1949).

(9) For a description of test methods, see (a) P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, 31, 707 (1951); (b) J. W. Reinertson and P. E. Thompson, *Proc. Soc. Exp. Biol. Med.*, 76, 518 (1951).

(10) P. E. Thompson, to be published.

(11) Farbenfabriken Bayer Aktiengesellschaft, Brit. Pat. 486/1908 (Nov. 12, 1908).

EXPERIMENTAL[12]

Methods for preparing 6-(mono- and dialkylaminoalkylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)diones (Table I). Procedure I. 6-(3-Isopropylaminopropylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione. A mixture of 68 g. (0.2 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione and 130 g. (1.6 mole) of *N*-isopropylpropylenediamine was stirred and heated at approximately 120° for 24 hr. The red solution was cooled and poured into a mixture of 200 ml. of water and 40 g. of sodium hydroxide. Excess starting amine was removed by steam distillation, the residue was cooled, and the alkaline solution decanted from the gummy red solid. The crude product was extracted with warm 10% acetic acid, the extract was treated with decolorizing charcoal, filtered, and the red filtrate was made strongly alkaline with 20% sodium hydroxide solution. The alkaline solution was decanted and the residue crystallized from acetone or benzene.

Procedure II. 6-(3-Dimethylaminopropylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione. A mixture of 68 g. (0.2 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione, 40.8 g. (0.4 mole) of *N,N*-dimethylpropylenediamine and 350 ml. of xylene was heated under reflux for 24 hr. The red solid that separated was collected by filtration and dried *in vacuo* at 50° for 18 hr. The product was purified by extraction with 10% acetic acid and crystallization from acetone as outlined under procedure I above.

Procedure III. 3-Methyl-6-[5-(1-piperidyl)-amylamino]-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione. A mixture of 34 g. (0.1 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione, 34 g. (0.2 mole) of 1-(5-aminopentyl)piperidine, and 60 g. of dry pyridine was heated under reflux for 18 hr. The red reaction mixture was cooled, poured into a 5-l. three-neck flask containing 200 ml. of 2*N* sodium hydroxide solution, and steam distilled for 3 hr. Upon cooling, the alkaline supernatant liquid was decanted and the dark red oily residue extracted with 10% acetic acid. The deep red acid extract was treated with decolorizing charcoal, filtered, and made strongly alkaline with 20% sodium hydroxide solution. The aqueous supernatant layer was decanted from the dark red gum which separated and the gum slowly solidified. The crude product was crystallized from acetone.

Acknowledgment. The authors thank Dr. Loren M. Long and Dr. George Rieveschl, Jr., for advice and encouragement, Dr. Paul E. Thompson, Miss Anita Bayles, Dr. D. A. McCarthy and Miss B. Olszewski for the biological testing, Mr. Charles E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and associates for determination of the infrared and ultraviolet absorption spectra.

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(12) All melting points are uncorrected.

Communications TO THE EDITOR

The Structure of Nidulin

Sir:

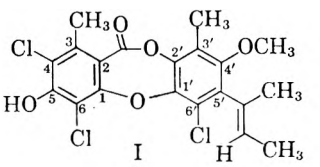
A recent examination of the NMR spectra of nidulin and its derivatives has indicated that, contrary to earlier reports,[1] the alkyl groups of ring B of nidulin consist of a methyl and *cis*-isobutenyl residue.[2]

An examination of the infrared spectra[3] of nidulin and certain of its derivatives in the hydroxyl stretching region now allows the assignment of structure I to nidulin.

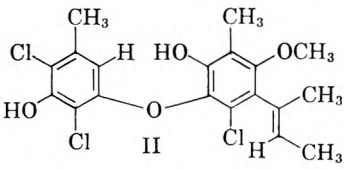
Nidulin (m.p. 178–180°,[1] isolated from the mycellial felts of *Aspergillus nidulans* and crystallized from heptane) has a single sharp hydroxyl band at 3516 cm.$^{-1}$ This can be assigned to the ring A phenolic hydroxyl which is known to be flanked by two *ortho*-chlorine substituents. That its frequency is 15–20 cm.$^{-1}$ lower than that expected[4] for *o*-chlorophenols is undoubtedly the result of the acid strengthening lactonic carbonyl group in the *para* position.

The spectrum of decarbonidulin II (m.p. 145–146.5°[1]) has absorption maxima of approximately equal intensity at 3532 cm.$^{-1}$ and 3556 cm.$^{-1}$ The former is due to the hydroxyl in ring A (raised to the expected frequency[4] because of the loss of the lactonic carbonyl group). The latter absorption is due to the new hydroxyl group in ring B. Its frequency, 3556 cm.$^{-1}$ is that expected for an *o*-phenoxy phenol.[5]

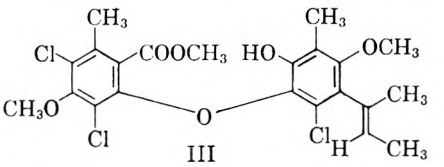
The spectrum of methyl *o*-methylnidulinate III (m.p. 154–160°[1]) has a single absorption at 3550 cm.$^{-1}$ Since a chlorine atom is at least as effective as an oxygen atom in the role of a hydrogen bond proton acceptor,[6] the absence of any appreciable O—H···Cl— absorption in the spectrum of methyl *O*-methylnidulinate excludes the possibility that a chlorine atom is attached at the 3′ position.



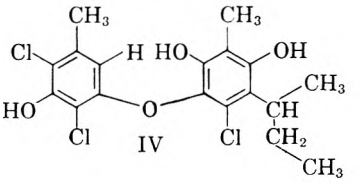
I



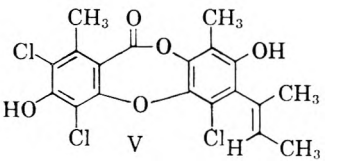
II



III



IV



V

The infrared spectrum of demethyldecarbodihydronidulin IV (m.p. 153–155°[8]) possesses three sharp, approximately equally intense bands at 3532 cm.$^{-1}$, 3565 cm.$^{-1}$ and 3614 cm.$^{-1}$ On the basis of the foregoing discussion the 3532 cm.$^{-1}$ and 3565 cm.$^{-1}$ bands are assigned to the 5 and 2′ hydroxyl groups, respectively. The band at 3614 cm.$^{-1}$, the frequency of a free phenolic hydroxyl group, implies that the second hydroxyl in ring B must be flanked by two groups which are incapable of acting as hydrogen bond proton acceptors. The only two such groups in ring B are the two alkyl residues.

Since the chlorine atom of ring B is not at 3′ and the second ring B hydroxyl is between two alkyl groups, the chlorine must be at 6′, the second ring B hydroxyl at 4′ and alkyl groups at 3′ and 5′.

The π-electrons of double bonds have been found to be excellent proton acceptors in hydrogen bonding.[9] Due to overwhelming steric reasons, the double bond of the isobutenyl group will not be in

(1) F. M. Dean, J. C. Roberts, and A. Robertson, *J. Chem. Soc.*, 1954, 1432.

(2) W. F. Beach and J. H. Richards, *J. Org. Chem.* (in press).

(3) All spectra were taken on a Beckman model IR7 spectrometer of 0.5% and 0.1% carbon tetrachloride solutions. No changes were observed on dilution in any case.

(4) A. W. Baker, *J. Am. Chem. Soc.*, 80, 3598 (1958); A. W. Baker and W. A. Kalding, *J. Am. Chem. Soc.*, 81, 5904 (1959).

(5) A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, 80, 5358 (1958).

(6) According to Badger's rule,[7] the energy of a hydrogen bond is proportional to the frequency shift of the OH stretching vibration, *cf.*, *e.g.*, L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N. Y., 490–495 (1960).

(7) R. M. Badger, *J. Chem. Phys.*, 5, 837 (1937).

(8) D. S. Noyce, personal communication.

(9) A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, 80, 5358 (1958).

the plane of the aromatic ring and should, therefore, be especially well situated for hydrogen bond interaction with an adjacent hydroxyl group. Nornidulin V (m.p. 182–184°[1]) shows absorption at 3516 cm.$^{-1}$ (the 5-hydroxyl in ring A), and at 3531 cm.$^{-1}$ due to the ring B hydroxyl at 4′. Since hydrogenation of the double bond in the isobutenyl residue (*cf.* the peak at 3614 cm.$^{-1}$ in demethyldecarbodihydronidulin) shifts this absorption 83 cm.$^{-1}$ to higher frequency, it is clear that the 4′ hydroxyl group in nornidulin interacts with the π-electrons of the isobutenyl group. However, in the spectrum of methyl *O*-methylnidulinate there is no absorption observed at 3531 cm.$^{-1}$ Since hydrogen bonding to the olefin should be at least competitive with hydrogen bonding to the ether oxygen,[6] the absence of interaction of the 2′ hydroxyl with an adjacent olefin, places the isobutenyl group at 5′. Thus, structure I is the only acceptable alternative for nidulin on the basis of the infrared evidence.

NOTE ADDED IN PROOF: A recent article[10] reaches structural conclusions different from those presented here. For reasons to be discussed in detail in a forthcoming publication, we feel these alternate conclusions are incorrect.

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(10) F. M. Dean, D. S. Deorha, A. D. T. Erni, D. W. Hughes, and J. C. Roberts, *J. Chem. Soc.*, 4829–37 (1960).