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1,5-Hydrogen Transfer during Diazonium Ion Decomposition[1,2]

THEODORE COHEN, RAYMOND M. MORAN, JR., AND GERALDINE SOWINSKI

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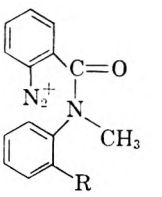
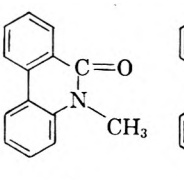
Thermal decomposition of diazonium salt XIIa derived from *o*-amino-*N*,*N*-dimethylbenzamide produced *N*-methylbenzamide (XIIIa) and formaldehyde in equivalent amounts, in addition to a lower yield of *N*-methylphthalimidine (XV). Under similar conditions, the diazonium salt XIIb derived from *o*-amino-*N*,*N*-dibenzylbenzamide gave higher yields of *N*-benzylbenzamide (XIIIb) and benzaldehyde. These results are explained in terms of a 1,5-hydride transfer from the *N*-alkyl group to the positive carbon formed by diazonium ion decomposition. The newly formed cation can then undergo either hydrolysis to an aldehyde and a dealkylated amide or it can suffer internal electrophilic substitution to yield a phthalimidine.

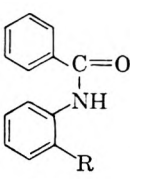
N-Alkylphenanthridones can be conveniently prepared by Pschorr type ring closures of appropriate diazonium salts.[3-7] For example, *N*-methylphenanthridone (II) is prepared by thermal or copper catalyzed decomposition of the diazonium salt Ia derived from *o*-amino-*N*-methylbenzanilide.[5,5] In addition, a number of substituted *N*-methylphenanthridones have been prepared from diazonium ions like I having various substituents *meta* and *para* to the nitrogen in the anilide ring.[4,6] However, when *ortho* substituents are present in this ring, closure to a phenanthridone fails to occur. In these cases, the reaction takes a different course; the diazonium function is replaced by hydrogen and the *N*-methyl group is lost. Thus Ib–g all decompose to the substituted benzanilides IIIb–g.[8,9]



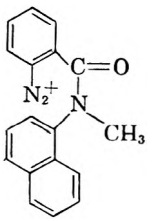
Ia. R = H
b. R = CH_3
c. R = OCH_3
d. R = Cl
e. R = NO_2
f. R = CO_2CH_3
g. R = CO_2H



II



III



IV

The same pattern is followed in the case of the diazonium ion IV, derived from 2-amino-*N*-methylbenz-1′-naphthalide. Upon decomposition, this ion undergoes demethylation rather than ring closure.[8] A case of *N*-deethylation has also been reported.[9]

This interesting behavior suggests two questions: (i) What is the role of the *ortho* substituent in preventing ring closure? (ii) What is the mechanism of the *N*-dealkylation reaction?

In order to answer the first of these questions it is necessary to consider the detailed course of the ring closure reaction. There is considerable evidence that thermal decompositions of diazonium ions in acid solution occur heterolytically to

(1) Taken, in part, from the Master's thesis of Raymond M. Moran, Jr., at the University of Pittsburgh, 1959.

(2) This work was supported, in part, by a grant from the National Science Foundation.

(3) A. Pictet and A. Gonset, *Arch. sci. phys. et nat.*, [4], **3**, 37 (1897).

(4) H. S. Forrest, R. D. Haworth, A. R. Pinder, and T. S. Stephens, *J. Chem. Soc.*, 1311 (1949).

(5) R. A. Heacock and D. H. Hey, *J. Chem. Soc.*, 1508 (1952).

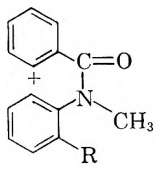
(6) R. A. Heacock and D. H. Hey, *J. Chem. Soc.*, 4059 (1952); 3 (1953).

(7) T. R. Govindachari and N. J. Arumugam, *J. Sci. Ind. Res.*, 13B, 694 (1954).

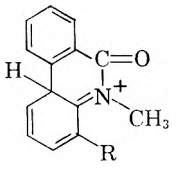
(8) D. H. Hey and D. G. Turpin, *J. Chem. Soc.*, 2471 (1954).

(9) T. R. Govindachari and N. J. Arumugam, *J. Sci. Ind. Res.*, 14B, 250 (1955).

produce carbonium ions.[10] Therefore, it is likely that such decomposition of the diazonium ion Ia yields the carbonium ion Va by loss of nitrogen. This is probably followed by an internal electrophilic substitution into the activated anilide ring to produce the intermediate VIa (one resonance structure is shown). Loss of a proton from VIa reestablishes the aromatic system and yields II.



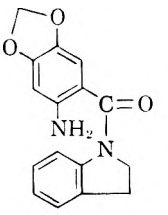
Va. R = H
b. R = CH_3



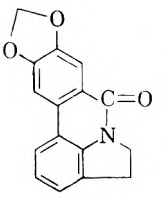
VIa. R = H
b. R = CH_3

However, when a group larger than hydrogen is in the *ortho* position of the anilide ring, the intermediate VI is expected to be destabilized by serious nonbonded repulsion between this substituent and the *N*-methyl group. For example, the two methyl groups of VIb are held almost in the same plane and therefore resemble spatially the methyl groups of 1,8-dimethylnaphthalene. The strain in the latter compound, due to nonbonded repulsion, has been estimated to be 7.6 kcal. per mole.[11]

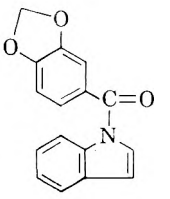
Strong evidence for this hypothesis would be provided by a demonstration that a diazonium ion in which the two methyl groups of Ib were tied together by a covalent bond could be successfully ring closed. This would lead to an intermediate possessing, as VIb does, a substituent in the *ortho* position of the anilide ring but lacking much of the nonbonded repulsion of VIb. Fortunately, the literature already carries an account of a reaction of this type. In connection with work on the structural proof of alkaloids, Humber *et al.*[12] have thermally decomposed the diazonium salt derived from *N*-(2-amino-4,5-methylenedioxybenzoyl)-2,3-dihydroindole (VII) and have obtained the ring closed product (VIII). This constitutes the first authentic case of a ring closure of a diazonium ion prepared from an *o*-aminobenzanilide possessing an *ortho* substituent in the anilide ring.[13] The fact that the ring-closed product is accompanied by a large amount of the abnormal product *N*-(3,4-methylenedioxybenzoyl)pyrrole (IX) probably indicates that some strain is still present in the transition state for ring closure (*vide infra*).



VII



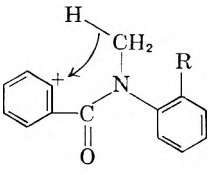
VIII



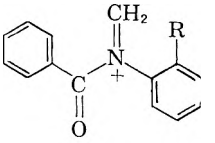
IX

In order to answer the second question concerning the nature of the dealkylation reaction, we must consider the fact that dealkylation is accompanied by replacement of the nitrogen of the diazonium group by hydrogen. It seems reasonable to assume *a priori* that the hydrogen is supplied by the *N*-alkyl group, as this would provide a starting point for the process by which the carbon-nitrogen bond is destroyed. The fact that no product has ever been reported in which the nitrogen has been replaced by hydrogen and yet in which the *N*-alkyl group is still intact (for example, Ib yields no *N*-methylbenztoluide) indicates further that the reduction of the diazonium function is an intramolecular process. The formation of IX during decomposition of the diazonium ion derived from VII also provides evidence for this viewpoint.

The most favorable mode of reduction in this case would probably involve the transfer of a hydride ion from the *N*-methyl group to the positive carbon of the benzene ring as in *X*. Many examples are known of hydride transfers to carbonium ions,[14] and evidence has recently been presented that intermolecular hydride ion transfer processes are involved in the reduction of diazonium ions by alcohols,[15a] ethers,[15b] and tertiary amines[15b] under certain conditions. In the present case, the hydride transfer is favored by the proximity of the hydrogen to the carbonium ion and by the relative stability of the positive ion (XI) which is generated. The latter ion would be expected to hydrolyze to formaldehyde and a substituted benzanilide. The identity of the carbon fraction lost in this reaction has, however, never been investigated.



X



XI

Because our hypothesis assigns no role to the *N*-phenyl group which was present in all of the compounds which have been previously found to

(10) For a summary of the evidence and recent references, see D. F. DeTar, *Org. Reactions*, **9**, 405 (1957).

(11) J. Packer, J. Vaughn, and E. Wong, *J. Am. Chem. Soc.*, **80**, 905 (1958).

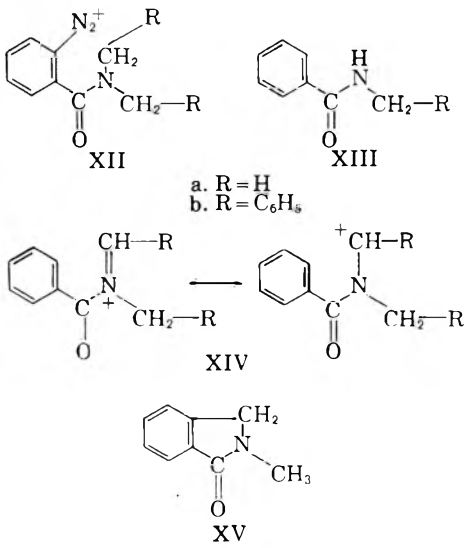
(12) L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima, and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).

(13) A number of earlier claims have been disputed by Hey and Turpin.[8]

(14) For references to some recent examples, see H. B. Henbest, *Ann. Rep.*, **53**, 144 (1956).

(15)(a) D. F. DeTar and T. Kosuge, *J. Am. Chem. Soc.*, **80**, 6072 (1958); (b) H. Meerwein, H. Allendörfer, P. Beekman, F. Kunert, H. Morschel, F. Pawellek, and K. Wunderlich, *Angew. Chem.*, **70**, 211 (1958).

undergo the dealkylation reaction,[8,9] the replacement of this phenyl by an alkyl group, while simplifying the experimental procedures, was not expected to interfere with the dealkylation reaction. We have thus carried out the thermal decomposition in acid solution of the diazonium salts XIIa and XIIb prepared from the easily accessible compounds *o*-amino-*N*,*N*-dimethylbenzamide and *o*-amino-*N*,*N*-dibenzylbenzamide, respectively. In agreement with the hypothesis, XIIa produced formaldehyde, isolated as its dimedone derivative, and *N*-methylbenzamide (XIIIa) in the same yield (9.9%) while XIIb produced benzaldehyde, isolated as its 2,4-dinitrophenylhydrazone, and *N*-benzylbenzamide (XIIIb), again in comparable yields (17.7% and 14.7%, respectively). The higher yield of dealkylation products obtained in the dibenzyl case was expected on the basis of the stability of the presumed intermediate (XIVb) afforded by delocalization of the positive charge over the benzene ring. In both cases, phenols, arising by the more usual replacement of the nitrogen by the hydroxyl group of water, were the main products.



XII XIII

a. R = H
b. R = C_6H_5

XIV

XV

In addition to these products, a fourth substance was isolated in the case of XIIa. This compound was eluted from alumina in the same fraction as XIIIa but could be separated cleanly from the latter by rechromatographing the mixture on a Florisil column. A clue to the identity of this material, m.p. 115–118°, was provided by an examination of its infrared spectrum which exhibited a carbonyl band at 1675 cm.$^{-1}$ As amides usually absorb at much lower frequencies unless a part of a five-membered ring, it appeared likely that the substance was a lactam. This was confirmed by the demonstration that the compound is *N*-methylphthalimidine (XV), identical with an authentic sample[16] prepared by reduction of *N*-methylphthalimide with zinc in hydrochloric acid.[17]

(16) G. Graebe and A. Pictet, *Ann.*, **247**, 302 (1888).

The formation of *N*-methylphthalimidine (XV) in this reaction is consistent with the proposed mechanism. Because of the proximity of the partially positive methylene carbon to the benzene ring, XIVa can undergo an internal electrophilic substitution to produce XV. This ring closure reaction must compete with the hydrolysis of XIVa which yields formaldehyde and *N*-methylbenzamide (XIIIa).[18]

1,5-Hydride transfers of the type proposed here are commonly encountered in the chemistry of medium size ring compounds.[20] In addition, several examples of nontransannular 1,5-hydride transfers have recently appeared in the literature. These include the acid-catalyzed conversion of 1-hydroxy-3,3-diphenyl-1H,3H-naphtho[1,8-c,d]pyran to 8-benzhydryl-1-naphthoic acid,[21] the reduction of a ketone by a carbinol amine in a degradation product of ajaconine,[22] the acid-catalyzed interconversion of normal and isosapogenins,[23] and the decomposition of 1,3,3-trimethylcyclohexyl hydroperoxide to a bicyclic ether induced by benzoyl chloride in pyridine.[24] The formation of tazettine upon methylation of haemanthidine[25] can also be nicely explained by a 1,5-hydride transfer. One of these examples[24] is especially analogous to our conversion of the diazonium salt (XIIa) to *N*-methylphthalimidine (XV) in that the hydride transfer is closely followed or concomitant with

(17) We have re-examined the report by Graebe and Pictet[16] that *N*-methylphthalimidine (XV) forms in ether a hydrochloride of melting point, 120°, identical with the melting point of the free "base". We have confirmed the fact that such a precipitate is indeed formed when a saturated solution of hydrogen chloride in ether is added to an ethereal solution of XV. However, this precipitate was shown to be unchanged XV by infrared analysis. Similar behavior has been observed in this laboratory with another neutral compound; unpublished observations of Jack L. Pinkus.

(18) Abramovitch, Hey, and Long[19] have reported the isolation of a compound, m.p. 185°, from the decomposition of the diazonium salt derived from 1-amino-*N*-methyl-2-naphthanilide in addition to the product of demethylation, 2-naphthanilide. The elemental analysis and infrared spectrum of the 185° material are consistent with those expected for the compound that would be formed by hydride transfer, followed by electrophilic substitution of the positive methylene group into the naphthalene nucleus, in an analogous manner to the formation of *N*-methylphthalimidine (XV) from XIIa.

(19) R. Abramovitch, D. Hey, and R. Long, *J. Chem. Soc.*, 1781 (1957).

(20) V. Prelog, *Angew. Chem.*, **70**, 145 (1958); A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., and G. W. Wood, *J. Am. Chem. Soc.*, **79**, 3900 (1957).

(21) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, **81**, 935 (1959).

(22) D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.*, 280 (1958).

(23) R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, **80**, 6693 (1958).

(24) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, **80**, 6686 (1958).

(25) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2590 (1958).

the formation of a bond between the hydride donor and acceptor atoms.

A hydrogen *atom* transfer cannot be definitely excluded by these results, but a free radical decomposition of diazonium salts in strong acid solution seems considerably less likely than an ionic decomposition.[10] We are now seeking experimental evidence concerning this point.

EXPERIMENTAL[26]

o-Nitro-N,N-dimethylbenzamide. A mixture of 30 g. (180 mmoles) of Eastman *o*-nitrobenzoic acid, 24 g. (200 mmoles) of thionyl chloride, and 200 ml. of purified anhydrous dioxane[27] was heated on a steam bath with stirring until hydrogen chloride and sulfur dioxide were no longer evolved (*ca.* 2 hr.). The dioxane solution of the *o*-nitrobenzoyl chloride was added dropwise to a stirred solution containing 50 g. of 25% aqueous dimethylamine (12 g. of dimethylamine, 270 mmoles), 7.2 g. of sodium hydroxide, and 60 ml. of purified dioxane.[27] After the reaction mixture had cooled to within 20° of room temperature, the mixture was diluted to twice its original volume with water and extracted with four 50-ml. portions of methylene chloride. The extract was washed twice with water, dried over sodium sulfate, and evaporated to dryness. Upon cooling, the oily residue yielded a yellow solid. After drying this in a vacuum desiccator for 1 hr., there was obtained 31.2 g. (89% yield) of *o*-nitro-*N,N*-dimethylbenzamide, m.p. 77.2–78.0, reported[28] m.p. 78°.

o-Amino-N,N-dimethylbenzamide hydrochloride. A solution of 15 g. (77 mmoles) of *o*-nitro-*N,N*-dimethylbenzamide in 150 ml. of absolute ethyl alcohol was mixed with a small quantity of Raney nickel[29] and shaken in a Parr apparatus under 3 atm. of hydrogen for 3 hr. Hydrogen uptake was very slow after the first hour. The total pressure drop was 18.4 lbs. per sq. inch, calcd.: *ca.* 19.9 lbs. per sq. inch. Filtration from the catalyst and evaporation of the alcohol yielded 9.34 g. (80.3%) of light red oil.

The hydrochloride was prepared in benzene. After two recrystallizations from isopropyl alcohol, the compound partially decomposed at 190° but did not melt below 300°. The analytical sample was prepared by repeated recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{13}N_2OCl$: C, 53.86; H, 6.49; N, 13.96. Found: C, 54.17; H, 6.31; N, 14.47.

For structural proof, a small quantity of this hydrochloride was hydrolyzed by heating its solution in 6*N* sulfuric acid for 1 hr. on a steam bath. The solution was brought to cloudiness with dilute sodium hydroxide and extracted with three portions of ether. The extract was dried over sodium sulfate and evaporated. One recrystallization of the solid residue from hot water gave anthranilic acid, m.p. 143–144°, alone or mixed with an authentic sample.

Deamination of o-amino-N,N-dimethylbenzamide. A stirred solution of 2.00 g. (10 mmoles) of *o*-amino-*N,N*-dimethylbenzamide hydrochloride in 20 ml. of 3*N* sulfuric acid was cooled to 0° and treated dropwise with a saturated aqueous solution of sodium nitrite. The addition was continued until the reaction mixture gave an immediate blue color with starch-iodide paper. In order to destroy excess nitrous acid, urea was added until nitrogen evolution ceased. Decomposition of the diazonium salt commenced with nitrogen evolution when the reaction solution was warmed rapidly on a water bath to 50°. During a 1-hr. period, the temperature was gradually raised to 70°. Although nitrogen was no longer being visibly evolved, the reaction mixture was finally heated on a steam bath for 10 min. to insure complete decomposition. The solution was cooled in ice and extracted with eight 20-ml. portions of methylene chloride. The aqueous layer was treated with excess 10% alcoholic dimedone solution and allowed to remain overnight. Filtration yielded 280 mg. (9.9% yield) of adduct, m.p. 162–167°. After one recrystallization from ethanol, the solid weighed 191 mg., m.p. 186.5–188.5°, alone or mixed with an authentic sample of the dimedone adduct of formaldehyde.

The aqueous acidic filtrate, on treatment with base and chloroform extraction, yielded 50 mg. of unreacted *o*-amino-*N,N*-dimethylbenzamide.

The dried (Drierite) methylene chloride extract was concentrated under reduced pressure and the last traces of solvent were removed under a stream of nitrogen. The residue, a mixture of yellow solid and oil weighing 1.40 g., was dissolved in a minimum of hot benzene and cooled. The precipitate, m.p. 115–137°, after three recrystallizations from benzene, was still light yellow and weighed 330 mg., m.p. 164–166.5°. The infrared spectrum in chloroform exhibited characteristic absorption at 3150 cm.$^{-1}$ (O—H) and 1620 cm.$^{-1}$ (C=O). This was shown to be *N,N*-dimethylsalicylamide by hydrolysis of a portion in 12*N* sulfuric acid to salicylic acid, m.p. 154–155°, alone or mixed with an authentic sample. A further crop of 170 mg. of this amide was obtained from the chromatography (see below). The total yield of the phenolic product was therefore 30.3%. In previous runs, it had been ascertained that this compound cannot be separated from the nonphenolic products by alkaline extraction. This is probably due to strong internal hydrogen bonding between the phenolic hydrogen and the amide oxygen.

The combined mother liquors from the recrystallizations of the *N,N*-dimethylsalicylamide were concentrated and chromatographed on a column (2 × 56 cm.) containing 153 g. of Woelm alumina (neutral, activity grade No. 1). Elution with ether yielded 240 mg. of white solid, m.p. 45–101°. Elution with ethanol produced 173 mg. of crude *N,N*-dimethylsalicylamide, m.p. 147–157°. One recrystallization from benzene raised the m.p. to 154–157°. A portion (140 mg.) of the solid, m.p. 45–101°, was rechromatographed on Florisil (30 g.). Elution with benzene-ether (1:1) yielded 69 mg. of white solid, m.p. 69–79°. The melting point was raised to 77–80° by recrystallization from benzene–petroleum ether (b.p. 64–66°) and was undepressed when mixed with an authentic sample of *N*-methylbenzamide, whose preparation is described below. The infrared spectrum of this substance was also identical with that of the authentic sample. The overall yield of this compound was 9.9%. It was shown in control experiments that very little of this material is lost by hydrolysis in the 3*N* sulfuric acid. On further elution with the same benzene-ether solution, three fractions containing minute traces of oil were obtained followed by a number of fractions containing in all 65 mg. of white solid, m.p. 93–118°. Recrystallization from benzene–petroleum ether (b.p. 64–66°) gave colorless rhombic crystals, m.p. 115–118°. The mixture melting point with authentic *N*-methylphthalimidine, m.p. 112–114°, prepared as below, was 114–116°. The infrared spectrum of this compound which had a strong carbonyl peak at 1675 cm.$^{-1}$ in chloroform and 1685 cm.$^{-1}$ in carbon disulfide was identical with that of the authentic sample. Of the material placed on the Florisil column, 45% was thus *N*-methylphthalimidine. Of the 241 mg. of the mixture, m.p. 45–101°, obtained from the alumina column, 111 mg. was *N*-methylphthalimidine, representing an overall yield of 7.6%.

N-Methylphthalimidine (XV). A modification of the method of Graebe and Pictet[16] was used. A mixture of 3.00

(26) Melting points were determined on a Kofler block unless the capillary method is specifically stated, in which case they are uncorrected. Infrared spectra were determined with a Perkin-Elmer model 21 spectrophotometer with sodium chloride optics. Microanalyses are by Mr. Otho Harris.

(27) A. Vogel, *Practical Organic Chemistry*, Longmans, Green and Co., London, 1951, p. 175.

(28) L. Van Scherpenzeel, *Rec. trav. chim.*, **20**, 181 (1901).

(29) Ref. 27, p. 807.

g. (19 mmoles) of *N*-methylphthalimide[30] and 9.7 g. (149 mmoles) of zinc dust in 50 ml. of concd. hydrochloric acid was heated to reflux and then allowed to cool. The mixture of white precipitate and zinc was filtered, mixed with a small amount of water and filtered free of zinc. Sodium carbonate solution was added to the filtrate until a slight cloudiness appeared. The mixture was extracted with methylene chloride and the dried (sodium sulfate) extract was evaporated to yield 1.17 g. (42%) of pale yellow solid, m.p. 112–114° (lit.[30] m.p. 120°). Several recrystallizations from benzene–petroleum ether (b.p. 64–66°) failed to remove a slight quantity of persistent impurity. The infrared spectrum was identical to that reported by Theilacker and Schmidt.[31]

When an ether solution of hydrogen chloride was added to an ether solution of *N*-methylphthalimidine, an instant precipitate appeared,[16] m.p. 120–122°. The infrared spectrum of this compound was identical with that of *N*-methylphthalimidine itself. This treatment apparently removed the trace of impurity mentioned above.

N-Methylbenzamide (XIIIa). Benzoyl chloride was added dropwise to a solution prepared by dissolving methylamine hydrochloride and excess sodium hydroxide in water. The resulting solid, capillary m.p. 79–79.5° (lit.[32] m.p. 80°), was recovered unchanged after refluxing for 1 hr. in 3*N* sulfuric acid, conditions under which the diazonium salt decomposition was carried out.

o-Nitro-N,N-dibenzylbenzamide. A solution of *o*-nitrobenzoyl chloride, prepared as above, in purified dioxane was added dropwise to a mechanically stirred solution of 5.91 g. (30 mmoles) of dibenzylamine and 1.2 g. (30 mmoles) of sodium hydroxide in 60 ml. of dioxane. After the reaction heat had subsided, the mixture was diluted to twice its original volume with water and extracted with four portions of methylene chloride. The extract was washed twice with water to remove dioxane, dried over sodium sulfate, and evaporated. The residue, m.p. 80–89°, was recrystallized twice from ethanol to yield 6.0 g. (58% yield), capillary m.p. 104–105°.

o-Amino-N,N-dibenzylbenzamide. A mixture of 5.6 g. (16 mmoles) of *o*-nitro-*N,N*-dibenzylbenzamide, dissolved in 150 ml. of absolute ethanol, and a small quantity of Raney nickel was shaken in a hydrogen atmosphere for 4 hr. The decrease in hydrogen pressure was equal to that calculated for the reduction of the nitro group. Filtration of the nickel and evaporation of the alcohol produced 5.05 g. (99% yield) of crude product, m.p. 115–125°. The analytical sample was prepared by two recrystallizations from ethanol, capillary m.p. 131.5–132.5°.

Anal. Calcd. for $C_{21}H_{20}N_2O$: C, 79.70; H, 6.37; N, 8.85. Found: C, 79.83, 79.89; H, 6.67, 6.45; N, 8.92, 9.11.

Deamination of o-amino-N,N-dibenzylbenzamide. As this compound is insoluble in aqueous sulfuric acid, the diazotization was carried out in a medium of 2*N* sulfuric acid in acetic acid, prepared by diluting 27.8 ml. of concd. sulfuric acid to 500 ml. with glacial acetic acid. A solution of 1.28 g. (4.1 mmoles) of the amine in 20 ml. of this medium was cooled to 16° and diazotized by stepwise addition, with stirring, of solid sodium nitrite. The addition was stopped when 1 drop of reaction mixture turned starch-iodide paper an intense blue color. During the addition, the solution changed from colorless, through red, to greenblack. In order to decompose excess nitrous acid a small quantity of solid urea was added until nitrogen evolution ceased. The cold reaction mixture was diluted with water (19 ml.) until the first permanent cloudiness appeared, warmed to steam bath temperature, and heated for 1 hr. on the steam bath. At this time nitrogen was no longer being evolved. Upon cooling, a deep red oil separated. The mixture was made homogeneous by the addition of 23.5 ml. of 2*N* sulfuric acid in acetic acid. To a one quarter aliquot of this solution was added an excess of a saturated solution of 2,4-dinitrophenylhydrazine in acetic acid. After 5 hr., the precipitate was removed by filtration and dried. The solid weighed 52 mg., m.p. 235–239°, undepressed on admixture with an authentic sample of benzaldehyde-2,4-dinitrophenylhydrazone, m.p. 236–240°. The overall yield of benzaldehyde was thus 17.7%.

The remaining three quarters of the reaction mixture was dissolved in methylene chloride and extracted with four portions of 0.5*N* sodium hydroxide. (No acidic products could be obtained from this basic extract by acidification and ether extraction). The methylene chloride was dried over sodium sulfate and evaporated under reduced pressure. The red oily residue was dissolved in a minimum of benzene and adsorbed on an alumina column (2 × 20 cm., 126 g. of Fisher alumina). Elution with benzene–ether (3:2) produced 181 mg. of white solid, m.p. 60–80°. One recrystallization from benzene–petroleum ether (b.p. 64–66°) gave 95 mg. of white crystals, m.p. 104–105°, alone or mixed with an authentic sample of *N*-benzylbenzamide (XIIIb), prepared as below. The infrared spectrum was also identical with that of the authentic sample. This represents a 14.7% yield of *N*-benzylbenzamide in this deamination. The absence of acidic reaction products indicated that none of the *N*-benzylbenzamide was lost by hydrolysis during the reaction.

Further elution with ethanol–ether (1:1) produced 330 mg. of gum, which was not investigated further. Upon elution with ethanol–ether (5:1), 132 mg. of crude solid, m.p. 130–140°, was obtained. Three recrystallizations from alcohol brought the m.p. to 146–148°. This compound exhibits carbonyl absorption in the infrared spectrum at 1618 $cm.^{-1}$ (chloroform) and is very probably *N,N*-dibenzylsalicylamide, since it was hydrolyzed by heating in 12*N* sulfuric acid for 4 hr. to salicylic acid, m.p. 154–155°, alone or mixed with an authentic sample. The total yield of crude *N,N*-dibenzylsalicylamide was 13.6%.

N-Benzylbenzamide (XIIIb). A mixture of 4.9 g. (46 mmoles) of benzylamine, 2.44 g. (17 mmoles) of benzoyl chloride and 10 ml. of water in an Erlenmeyer flask was shaken vigorously during periodic addition of 10 ml. of 20% sodium hydroxide solution. The resulting solid was filtered, washed with water and dried. One recrystallization from benzene–petroleum ether (b.p. 64–66°) gave 2.8 g. (80%) of *N*-methylbenzamide as colorless needles, capillary m.p. 104–105.5° (lit.[33] m.p. 105–105.5°).

Acknowledgment. We wish to thank Dr. H. Yajima for calling this problem to our attention.

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(30) J. Breslauer and A. Pictet, *Ber.*, **40**, 3784 (1907); C. Graebe and A. Pictet, *Ber.*, **17**, 1174 (1884).

(31) W. Theilacker and W. Schmidt, *Ann.*, **597**, 102 (1955).

(32) H. E. French and R. J. Adams, *J. Am. Chem. Soc.*, **43**, 657 (1921).

(33) E. Beckmann, *Ber.* **37**, 4136 (1904).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE UNION CARBIDE PLASTICS CO.]

A New Synthesis of β-Cyanoesters

CAROL K. SAUERS AND ROBERT J. COTTER

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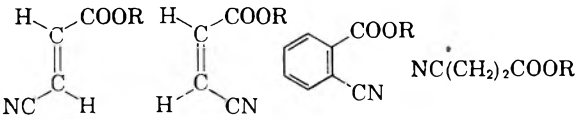
Alkyl and aryl β-cyanoacrylates, ethyl β-cyanopropionate, and ethyl *o*-cyanobenzoate have been prepared by simultaneous dehydration and esterification of the appropriate amic acids with chloroformate esters and triethylamine.

Alkyl β-cyanoacrylates (I and II, R = alkyl) and their derivatives possess a variety of uses which have been disclosed in the patent literature.[1] β-Cyanoesters in general have found use in the synthesis of 2-pyrrolidones, *e.g.* the recent hydrogenation and ring closure of ethyl 3-cyano-2-carboethoxypropionate to 3-carboethoxy pyrrolidone.[2] Wide application of the β-cyanoesters has been hampered by the lack of convenient methods for their preparation. Previous syntheses of these materials have suffered from low yields, expensive starting materials and the hazards attending the use of hydrogen cyanide. Thus, methyl *trans*-β-cyanoacrylate (I, R = CH_3) was prepared from methyl α-chloroacrylate in 31% yield by the concurrent addition of hydrogen cyanide and loss of hydrogen chloride.[3] The product was contaminated with a small amount of the *cis* isomer (II, R = CH_3).[4] A less attractive method for laboratory use involves the addition of gaseous hydrogen cyanide to methyl propiolate.[5] The product was reported to be *trans* and the yield was 25%. Substituted β-cyanoacrylates have been prepared by dehydration of the cyanohydrins formed from acetoacetic esters[6]; this general method has not been applied to the synthesis of the unsubstituted β-cyanoacrylic esters.

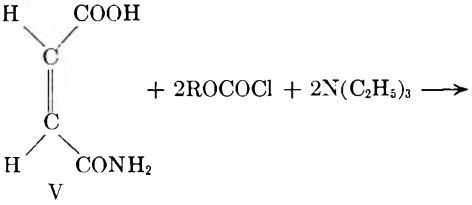
Ethyl *o*-cyanobenzoate (III, R = C_2H_5) has been prepared from ethyl anthranilate by diazotization and treatment with cuprous cyanide.[7] Dimethyl 2,5-dicyanoterephthalate has been obtained from the corresponding dibromo compound by treatment with cuprous cyanide.[8] β-Cyanopropionates



I II III IV

have also been prepared from the appropriate halogen esters.[9]

We have developed a method for the synthesis of the cyanoesters, II, III, and IV in good yields. The starting materials are the corresponding amic acids obtained by the reaction of the appropriate five-membered ring anhydrides with ammonia. Treatment of a solution made from maleamic acid[10] (V) and two equivalents of triethylamine in dichloromethane at 0–5° with two equivalents of ethyl chloroformate resulted in an immediate, mild exothermic reaction. Carbon dioxide was evolved and triethylamine hydrochloride precipitated. A 91% yield of ethyl β-cyanoacrylate which possessed the appropriate infrared spectrum and elemental analysis was obtained (see Equation 1). In a similar



V

$$\text{II} + \text{ROH} + 2CO_2 + 2[HN(C_2H_5)_3]^+Cl^- \quad (1)$$

experiment, methyl chloroformate, triethylamine, and maleamic acid at 0–5° gave a 64% yield of a solid, m.p. 30–31°, which had an elemental analysis and infrared spectrum corresponding to methyl β-cyanoacrylate. The synthesis of β-cyanoacrylates from maleamic acid (*cis* unsaturation) at 0–5° suggested that the double bond in the acrylate products possesses the *cis* configuration. The major product obtained by Crawford, McLeish, and Wood[3] from methyl α-chloroacrylate and sodium cyanide was synthesized and was shown to be different from the methyl β-cyanoacrylate prepared above. The assignment of the *trans* configuration by these workers to their major product[4] thus appears to be correct. These assignments have been

(1) (a) D. T. Mowry, U. S. Patent **2,437,231** (1948) [*Chem. Abstr.*, **42**, 5272 (1948)]; (b) G. F. D'Alelio, U. S. Patents **2,531,408** (1950) [*Chem. Abstr.*, **45**, 1812 (1951)]; **2,850,486** (1958); **2,850,487** (1958).

(2) W. M. Byrd, Jr., Dissertation Abst., **20**, 517 (1959). See also C. F. Koelsch and C. H. Stratton, *J. Am. Chem. Soc.*, **66**, 1883 (1944).

(3) J. W. Crawford, N. McLeish, and T. K. Wood, U. S. Patent **2,293,967** (1942).

(4) The *cis* and *trans* structural assignments were made on the basis of boiling point comparisons but no rigorous proof of structure was reported.

(5) P. Kurtz, *Ann.*, **572**, 23 (1951).

(6) D. T. Mowry and A. G. Rossow, *J. Am. Chem. Soc.*, **67**, 926 (1945).

(7) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5381 (1958).

(8) E. A. Lawton and D. D. McRitchie, *J. Org. Chem.*, **24**, 26 (1959).

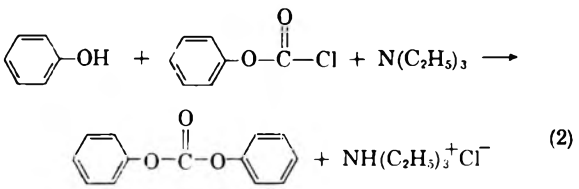
(9) M. Protiva, V. Rečicha, and J. O. Jílek, *Chem. Listy*, **44**, 231 (1950).

(10) R. S. Robinson and E. L. Humburger, U. S. Patent **2,459,964** (1949), Example 1: *Chem. Abstr.*, **43**, 3843 (1949).

confirmed by the NMR spectra of both isomers which have been studied by another group.[11] Both the *cis* and *trans* isomers of methyl β-cyanoacrylate absorb in the 960–970 cm.$^{-1}$ region of their infrared spectra. Absorption in this region can indicate the presence of *trans* unsaturation.[12] However, the intensity of the absorption at 965 cm.$^{-1}$ for the *trans* compound is much greater than that of the *cis* compound. These same observations have been made for the *cis* and *trans* isomers of ethyl β-cyanoacrylate. Therefore, assignment of the structure of the β-cyanoacrylate isomers based on infrared data alone could be misleading.

The use of phosgene and ethanol in the above synthesis in place of ethyl chloroformate gave a fair yield of ethyl *cis*-β-cyanoacrylate although no attempt was made to maximize the yield under these conditions. When the amount of tertiary amine used in this modification of the synthesis was insufficient to neutralize completely the hydrogen chloride produced, chlorinated products were obtained. These products, presumably chloro derivatives of β-cyanopropionates, could be dehydrochlorinated with triethylamine to yield mainly ethyl *trans*-β-cyanoacrylate (I, R = C_2H_5).

The behavior of the alkyl chloroformates and triethylamine toward maleamic acid was paralleled by phenyl chloroformate; phenyl *cis*-β-cyanoacrylate was prepared in 43% yield. A substantial amount of diphenyl carbonate was also obtained, presumably from the reaction of phenyl chloroformate with the phenol produced in the reaction. (See Equation 2.) The reaction of aryl chloroformate–pyridine complexes with phenol to produce

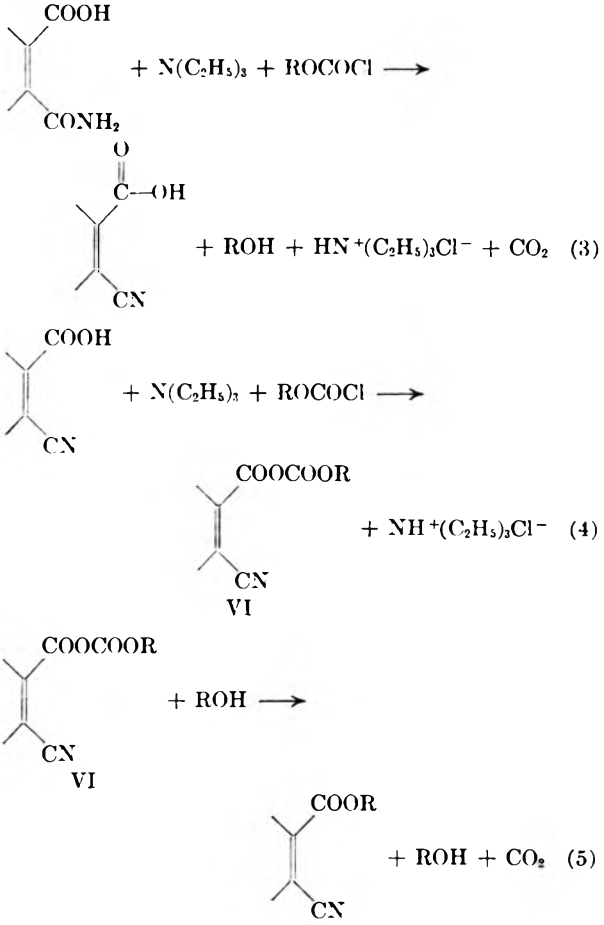


(2)

diphenyl carbonate has been previously reported.[13] Other amic acids gave good yields of the corresponding ethyl cyanocarboxylates when subjected to the ethyl chloroformate–triethylamine reagent. Thus, ethyl β-cyanopropionate (IV, R = C_2H_5) and ethyl *o*-cyanobenzoate (III, R = C_2H_5) were synthesized from succinamic acid and phthalamic acid in yields of 69% and 84%, respectively.

The ready availability of many five-membered ring anhydrides from Diels-Alder reactions of maleic anhydride provides a variety of starting materials to which the above synthesis of cyanoesters will probably be applicable. Most of the cyanoesters would be difficult to obtain by previous methods.

The detailed course of the formation of cyanoesters by the method described above is unknown. One possibility is a stepwise dehydration of the amide group to the nitrile-carboxylic acid (Equation 3) followed by the formation of a mixed carboxylic-carbonic anhydride[14] (Equation 4). Subsequent nucleophilic attack of the alcohol formed in Equation 3 upon this material (VI) would yield the product (Equation 5).



The dehydration of carboxamides to nitriles with phosgene and pyridine is known.[15] However, the preferred conditions for this reaction are more vigorous than those employed in this cyanoester synthesis. Furthermore, benzamide was only slightly dehydrated to benzonitrile with ethyl chloroformate and triethylamine under conditions which gave a high yield of ethyl *o*-cyanobenzoate from phthalamic acid. The reaction of mixed carbonic-carboxylic anhydrides with alcohols to give esters has been studied by Tarbell and Price.[14a] Again the conditions were more vigorous than those

(11) We are indebted to Professor E. J. Corey for informing us of these conclusions and for permission to mention them here in advance of their publication.

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York (1954), p. 31.

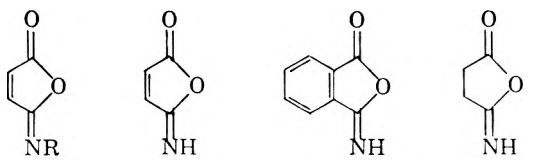
(13) German Patent 116,386 (1900); *cf. Friedlander*, 6, 1160.

(14) (a) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957); (b) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

(15) P. M. Brown, D. B. Spiers, and M. Whalley, *J. Chem. Soc.*, 2882 (1957).

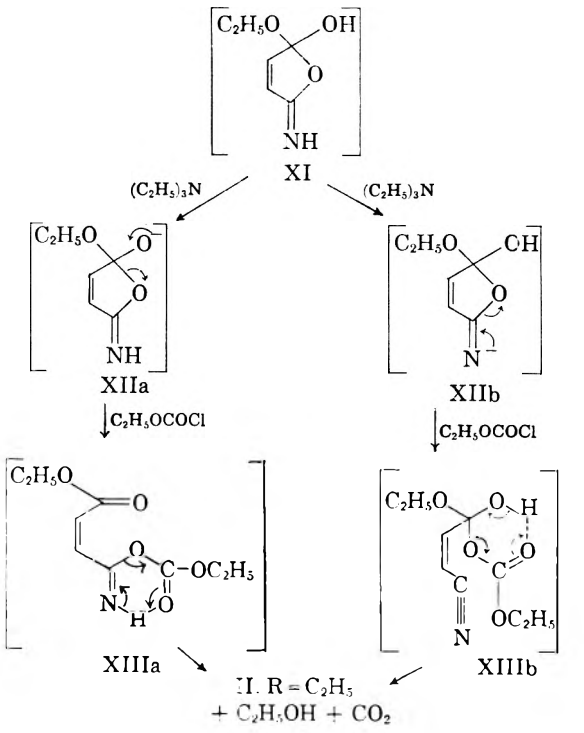
employed in this cyanoester synthesis. When the mixed anhydride from benzoic acid and ethyl chloroformate was prepared in the presence of ethanol and the undistilled product compared with the mixed anhydride prepared without ethanol, no differences were noted. When the sample prepared in the presence of ethanol was distilled under reduced pressure, nothing distilled at 1 mm. until the pot temperature reached 140°. At that temperature the pressure increased to 4 mm., a vigorous bubbling started, and some material which may have contained ethyl benzoate was carried over. This material resulted from the pyrolytic decomposition of the mixed anhydride.[16] These results appear to rule out the mechanism shown in Equations 3-5 for this synthesis.

The necessary proximity of the acid and amide group for good reactivity in this synthesis is emphasized by the failure of terephthalamic acid to give ethyl *p*-cyanobenzoate. This experiment indicates that interaction[17] of the reacting groups is probably a requirement for facile reaction. Furthermore, the related synthesis of *N*-substituted isomaleimides (VII) from *N*-substituted maleamic acids suggests that the isoimides VIII, IX, and X may be intermediates in these reactions.[18] In the synthesis of ethyl *cis*-β-cyanoacrylate, formation



VII VIII IX X

of isomaleimide (VIII) would require one mole each of triethylamine and ethyl chloroformate and would yield one mole of ethanol. Addition of this ethanol to the carbonyl group of isomaleimide would yield a species (XI) that could lose a proton in either of two ways by attack of the second mole of triethylamine. The ions (XIIa, XIIb) could both undergo ring-opening as indicated, to yield *O*-anions which could react with the second mole of ethyl chloroformate. The intermediates formed in this step should be capable of facile decomposition through the indicated *quasi*-six membered ring transition states[19] (XIIIa, XIIIb) to yield the observed products. A choice between these two possible mechanistic routes cannot be made on the basis of the available evidence.



EXPERIMENTAL[20]

Starting materials. Maleamic acid was prepared by the method of Robinson and Humburger.[10] It was not necessary to bubble ammonia into the solution of maleic anhydride. Instead, ammonia was run in over the surface of the solution at 60–75° and was absorbed until the theoretical quantity had been added. The yields obtained were in the range of 90–97% of white crystals, m.p. 165–168°, (lit.[10] m.p. 166°).

Phthalamic acid and succinamic acids were obtained by reaction of the appropriate anhydrides with concd. aqueous ammonia followed by acidification.[21]

Terephthalamic acid was prepared by the method of Kattwinkel and Wolffenstein.[22]

Methyl cis-β-cyanoacrylate. To 95 g. (0.83 mole) of maleamic acid in 1 l. of dichloromethane at 0–5°, 170 g. (1.7 mole) of triethylamine was added with stirring. The mixture was cooled to 0–5° and 170 g. (1.8 moles) of methyl chloroformate was added dropwise with stirring while the temperature was maintained below 5°. Carbon dioxide was evolved during the addition and for a short time after it was completed. The mixture was allowed to remain for 16 hr. at room temperature. Triethylamine hydrochloride was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue was taken up in ether and filtered to remove the remainder of the amine salt. The ether was removed under reduced pressure and the residue was added to water and allowed to crystallize at 5°. The crystals were collected and dried under vacuum; 59 g. (64%), m.p. 30–31°, was obtained. The infrared spectrum

(16) T. B. Windholz, *J. Org. Chem.*, **23**, 2044 (1958); A. Einhorn, *Ber.*, **42**, 2772 (1909); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(17) M. L. Bender, F. Chloupek, and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5380, 5384 (1958).

(18) Robert J. Cotter, Carol K. Sauers, and John M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

(19) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Henry Holt Co., New York, 1959, p. 500–504.

(20) Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord Spectrophotometer, model 137. Vapor phase chromatographic analyses were obtained on a Perkin-Elmer Vapor Fractometer, model 154-C. Microanalyses were performed by Drs. G. Weiler and F. Strauss, Oxford, England, and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(21) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1793 (1925).

(22) P. Kattwinkel and R. Wolffenstein, *Ber.*, **37**, 3221 (1904).

of a liquid film of this product possessed absorption at 2220 cm.$^{-1}$ (w), 1730 cm.$^{-1}$ (s) and 1630 cm.$^{-1}$ (m) indicating the presence of the nitrile, ester, and double bond groups, but no strong absorption near 970 cm.$^{-1}$ Vapor phase chromatography showed no contamination with the methyl *trans*-β-cyanoacrylate prepared below. Upon admixture of this product with the *trans* isomer the melting point was depressed below 25°.

Anal. Calcd. for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.94; H, 4.43; N, 12.65.

Methyl trans-β-cyanoacrylate The method of Crawford, McLeish, and Wood[3] (Example I) was followed with the following modifications. After the addition of the sodium cyanide solution the reaction mixture was allowed to stir for *ca.* 16 hr. at room temperature. At the end of this time the organic layer was separated from the aqueous layer and the aqueous layer extracted with several portions of dichloromethane. When the aqueous layer was not extracted completely, the yield of the product was very low. The dichloromethane extracts and the organic layer from the reaction mixture were combined and the solvents removed by distillation at atmospheric pressure. The residue was distilled through a short Vigreux column, yielding 32% b.p. 85–88° (35 mm.) of a clear liquid which solidified on cooling. Recrystallization from 1:1 1-propanol-water afforded white crystals, m.p. 32–34° (lit.[5] m.p. 34°). The retention time of this material on a Carbowax column at 140° and 25 p.s.i. was 2.9 min. The retention time of methyl *cis*-β-cyanoacrylate prepared above was 9.3 min. under the same conditions. The infrared spectrum of the *trans* isomer was similar to that of the *cis* isomer with the addition of a strong absorption band at 965 cm.$^{-1}$

Ethyl cis-β-cyanoacrylate. This compound was prepared by essentially the same procedure as the one used for methyl *cis*-β-cyanoacrylate except that ethyl chloroformate was used in place of methyl chloroformate. The product was obtained in 100% yield by distillation of the residue obtained from the ether solution through a Vigreux column. It distilled at 50–54° (0.2 mm.) n_D^{25} 1.4491 and was shown to be 91.4% pure by vapor phase chromatography on a silicone column (Perkin-Elmer column "C") at 190° and 25 p.s.i. The retention time was 2.65 min. The infrared spectrum of a liquid film showed bands at 2220 cm.$^{-1}$ (w), 1730 cm.$^{-1}$ (s), 1630 cm.$^{-1}$ (w), 980 cm.$^{-1}$ (very weak) indicative of the ethyl *cis*-β-cyanoacrylate structure.

An analytical sample redistilled through a semimicro column boiled at 53–54° (0.15 mm.), n_D^{26} 1.4510.

Anal. Calcd. for $C_6H_7O_2N$: C, 57.60; H, 5.64; N, 11.20. Found: C, 57.74; H, 5.62; N, 11.20.

When only 1 mole each of ethyl chloroformate and triethylamine per mole of maleamic acid was used, the yield of ethyl *cis*-β-cyanoacrylate was 33% based on maleamic acid and no other product was isolated.

Preparation of ethyl cis-β-cyanoacrylate with ethyl chloroformate prepared in situ. Phosgene, 114 g. (1.15 moles), was dissolved in 600 ml. of dichloromethane at 0° and 54 g. (1.17 moles) of ethanol was added with gentle stirring. Then 57 g. (0.5 mole) of maleamic acid in a solution of 116 g. (1.15 mole) of triethylamine and 140 ml. dichloromethane was added dropwise with stirring while the reaction was cooled with an ice salt bath. Another 116 g. of triethylamine was added dropwise with stirring and the reaction was stirred overnight during which time it came to room temperature. One liter of cold 10% sodium hydroxide solution was added and the aqueous layer was saturated with sodium chloride. The organic layer was separated and the dichloromethane and triethylamine were recovered by distillation. The residue was distilled through a short Vigreux column and the main fraction, b.p. 59–62° (0.4 mm.), was collected, 35.2 g. (56%). The infrared spectrum indicated that ethyl *cis*-β-cyanoacrylate prepared in this manner was contaminated by a small amount of the *trans* isomer.

In another experiment an excess of phosgene was bubbled into a solution of 57 g. (0.5 mole) of maleamic acid, 46 g. (1.0 mole) of ethanol and 101 g. (1.0 mole) of triethylamine in 1 l. of dichloromethane. The solution was allowed to remain for *ca.* 48 hr. at room temperature and the triethylamine hydrochloride was removed by filtration and by washing the filtrate with water. After the solvent was removed the residue was distilled, 40 g., b.p. 40–70° (0.4 mm.). This material contained several halogen-containing compounds as was shown by positive Beilstein tests on several fractions obtained by vapor phase chromatography. The material not used in the analyses was dehydrohalogenated with a mixture of 20 ml. of triethylamine and 80 ml. of ether. After removal of the amine salt and the solvent, the product was distilled under reduced pressure (0.4–0.5 mm.). Three fractions were collected: 10.1 g., b.p. 42–43°; 5 g., b.p. 43–49°; 5 g., b.p. 49–53°. The infrared spectra of these fractions exhibited strong absorption at 975 cm.$^{-1}$ The first fraction was redistilled for analysis, b.p. 37–38° (0.23 mm.), n_D^{25} 1.4480.

Anal. Calcd. for $C_6H_7O_2N$: C, 57.60; H, 5.64; N, 11.20. Found: C, 57.57; H, 5.76; N, 11.23.

Phenyl cis-β-cyanoacrylate. This compound was prepared by essentially the same procedure as the one used for methyl *cis*-β-cyanoacrylate except that phenyl chloroformate was used in place of methyl chloroformate. The crude residue obtained after distilling the methylene chloride [26 g., (75%), m.p. 39–50°] was passed through a column of Florisil in benzene. The benzene eluates were evaporated and the residue recrystallized from 1:1 pentane-ether. Eight grams (23%) of phenyl *cis*-β-cyanoacrylate was obtained, m.p. 54–56°.

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.40; H, 4.21; N, 8.28.

The mother liquor from the recrystallization was evaporated and a sample of the residue (17 g.) subjected to vapor phase chromatography. This crude material contained 56% diphenyl carbonate, 2.3% phenol, 40% phenyl *cis*-β-cyanoacrylate and 1.6% of an unknown component. Thus, the total yield of phenyl *cis*-β-cyanoacrylate was 14.8 g. or 43%.

The infrared spectrum of the phenyl *cis*-β-cyanoacrylate showed absorption at 2200 cm.$^{-1}$ (w), 1730 cm.$^{-1}$ (s), 1600 cm.$^{-1}$ (m), 1620 cm.$^{-1}$ (s), 955 cm.$^{-1}$ (w) and 685 cm.$^{-1}$ (s).

Ethyl β-cyanopropionate. This compound was prepared by essentially the same procedure as the one used for methyl *cis*-β-cyanoacrylate. The starting materials were succinamic acid (m.p. 153–157°) and ethyl chloroformate. After removing the methylene chloride from the product, the residue was distilled through a semimicro column; 69% of a clear liquid was obtained, b.p. 54.3–55.5° (0.35 mm.), n_D^{25} 1.4228 (lit.[23] for ethyl β-cyanopropionate, b.p. 221°). The infrared spectrum of a liquid film possessed absorption at 2260 cm.$^{-1}$ (w), 1740 cm.$^{-1}$ (s), and no absorption from 1600–1700 cm.$^{-1}$ A weak broad band had appeared at 960 cm.$^{-1}$

Anal. Calcd. for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 56.63; H, 7.03.

Ethyl o-cyanobenzoate. This compound was prepared by essentially the same procedure as the one used for methyl *cis*-β-cyanoacrylate. The starting materials were phthalamic acid and ethyl chloroformate. After removal of the methylene chloride, the residue was taken up in ether and filtered to remove the remainder of the amine salt. After removal of the ether under reduced pressure, the crude product remained. Recrystallization from benzene-pentane yielded 84% of white crystals, m.p. 62–65°. Ethyl *o*-cyanobenzoate has a reported m.p. 66.5–67°,[9] 70°.[24] The infrared spectrum of a melted film possessed absorption at 1725 cm.$^{-1}$ (s) and 2220 cm.$^{-1}$ (w).

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(23) O. Dalmer, C. Diehl, E. Feske, and H. Pieper, German Patent 597,305 (1934); *Chem. Abstr.*, **28**, 5078 (1934).

(24) G. Muller, *Ber.*, **19**, 1491 (1886).

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.02. Found: C, 68.72; H, 5.43; N, 7.92.

Reaction of terephthalamic acid with ethyl chloroformate and triethylamine. A solution of terephthalamic acid (1.4 g., 0.0085 mole) and triethylamine (1.72 g., 0.017 mole) in 20 ml. of dichloromethane was cooled to 0–5° and 1.9 g. (0.018 mole) of ethyl chloroformate was added. Stirring was continued for 3.5 hr. at room temperature after the addition. The mixture was filtered to remove triethylamine hydrochloride and the solvent was removed under reduced pressure. The residue was washed several times with ether. The ether-insoluble material (1.4 g.) melted at 140–155°. The ether-soluble material (0.2 g.) melted with decomposition at 90–95°. The infrared spectra and melting points of these products preclude the presence of more than a trace of ethyl *p*-cyanobenzoate which has a reported melting point of 50°.[25]

Mixed anhydride of benzoic and ethylcarbonic acids prepared in presence of ethanol. A stirred solution of 12.2 g. (0.1 mole) of benzoic acid, 4.6 g. (0.1 mole) of ethanol and 10.1 g. (0.1 mole) of triethylamine in 100 ml. of dichloromethane was stirred at 0° while ethyl chloroformate (10.8 g., 0.1 mole) was added dropwise over 30 min. The temperature was kept below 0° during the addition. After the addition the external cooling bath was removed and the reaction mixture was stirred for 3 hr. The mixture was filtered and the filtrate washed with water, 5% sodium carbonate solution, water and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent removed under reduced pressure. The clear, colorless liquid which remained, n_D^{25} 1.4930, showed absorption in the carbonyl region of its infrared spectrum (liquid film) at 1775 cm.$^{-1}$ (s) and 1715 cm.$^{-1}$ (w). The spectrum was identical with that for the mixed anhydride of benzoic and ethyl carbonic acids (n_D^{25} 1.4941) obtained by the procedure described above[14] except that no ethanol was added and the reaction time was 1 hr. An attempt was made to distill the crude product in a semimicro distilling apparatus. A vacuum of 1 mm. was applied and the distillation pot heated slowly. Nothing distilled until the temperature of the pot reached 140°; then the pressure rose to 4 mm. and vigorous decomposition of the product began.

Dehydration of benzamide with ethyl chloroformate and triethylamine. A solution of 2.8 g. (0.023 mole) of benzamide in 25 ml. of acetone and 2.3 g. (0.023 mole) of triethylamine was cooled to 0–5°. Ethyl chloroformate (2.5 g., 0.023 mole) was added dropwise with stirring. After the addition, the cooling bath was removed and the reaction was stirred at room temperature for 3 hr. The reaction mixture was diluted with water and extracted three times with dichloromethane. The dichloromethane extracts were dried over magnesium sulfate and solvent was removed under vacuum. An infrared spectra of the solid residue (2.4 g.) indicated traces of benzonitrile. The residue was washed with ether which left a white solid (2.0 g.), m.p. 119–121.5°. Recrystallization from aqueous ethanol raised the melting point to 123–125°. A mixture melting point with the starting benzamide (m.p. 125–127.8°) was 124–127°.

Acknowledgment. We are indebted to Miss Olive M. Garty for the vapor phase chromatographic analyses and to Mr. William Birch and Mr. J. T. Commerford for technical assistance. We are especially indebted to Dr. J. M. Whelan, Jr. for many helpful discussions of this work.

BOUND BROOK, N. J.

(25) K. H. Slotta and R. Kethur, *Ber.*, **71**, 335 (1938).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE UNION CARBIDE PLASTICS CO.]

The Synthesis of *N*-Substituted Isomaleimides

ROBERT J. COTTER, CAROL K. SAUERS, AND JOHN M. WHELAN

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N-Alkyl and *N*-aryl substituted isomaleimides and bisisomaleimides have been prepared by dehydration of the corresponding *N*-substituted maleamic acids with *N,N'*-dicyclohexylcarbodiimide, ethyl chloroformate-triethylamine, and trifluoroacetic anhydride–triethylamine. *N*-Substituted isomaleimides were isomerized to the symmetrical *N*-substituted maleimides in the presence of sodium acetate or triethylammonium acetate. An improvement in the synthesis of *N*-alkyl maleimides is also reported.

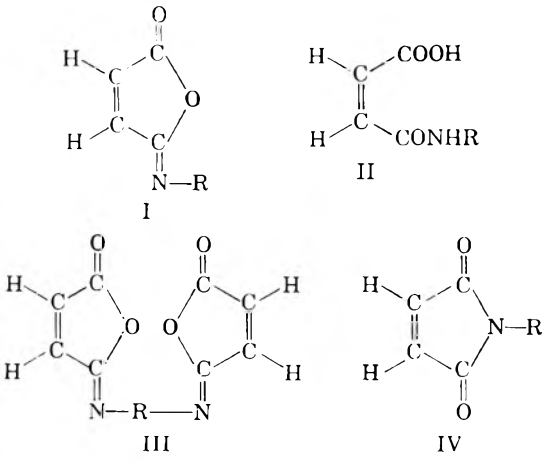
The synthesis of three isomaleimides has been previously recorded in the literature. Piutti[1] has claimed the preparation of *N*-(*p*-methoxyphenyl)isomaleimide (I, R = *p*-$CH_3OC_6H_5$—) and *N*-(*p*-ethoxyphenyl)isomaleimide (I, R = *p*-$C_2H_5OC_6H_5$—) by acetyl chloride dehydration of the corresponding maleamic acids (II). Roderick[2] has recently shown that the compounds obtained by Piutti do not possess the isomaleimide structure but instead are the α-chloro-*N*-(*p*-alkoxyphenyl)-succinimides. Tsou, Barrnett, and Seligman[3] have dehydrated *N*-(4-hydroxy-1-naphthyl)maleamic acid with trifluoroacetic anhydride and obtained *N*-(4-hydroxy-1-naphthyl)isomaleimide. This is the only substantiated example of an isomaleimide in the literature. Attempts[3] to prepare other isomaleimides using the trifluoroacetic anhydride reagent were unsuccessful. Mild dehydration of phthalanilic acid with acetyl chloride was shown to give the hydrochloride of *N*-phenylisophthalimide which on careful treatment with potassium hydroxide solution allowed the isolation of *N*-

(1) (a) A. Piutti, *Atti. reale accad. Lincei, Classe sci. fis mat. e nat.*, [5] **18**, II, 312 (1909); *Chem. Abstr.*, **4**, 2451 (1910); (b) A. Piutti and E. de'Conno, *Mem. reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] **8**, 793 (1911); (c) L. H. Flett and W. H. Gardner, "*Maleic Anhydride Derivatives*, John Wiley & Sons, Inc., New York, N. Y., 1952, p. 108.

(2) W. R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957).

(3) K. C. Tsou, R. J. Barrnett, A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).

phenylisophthalimide.[4] Roderick[2] has shown that this method is inapplicable to the synthesis of *N*-substituted isomaleimides. Thus, no general method for the synthesis of *N*-substituted isomaleimides has been previously available. In contrast to the



lack of syntheses for isomaleimides, maleimides (IV) have been prepared by a variety of methods,[5] and their possible utility has been extensively investigated.

We wish to describe two syntheses for *N*-substituted isomaleimides (I) and bisisomaleimides (III) which we believe to be general in scope. The starting materials are the corresponding maleamic acids. The first method employs *N,N'*-dicyclohexylcarbodiimide, a reagent which has found application in the synthesis of amides[6] from carboxylic acids and amines. With simple carboxylic acids, the carbodiimides either dehydrate the acids to the corresponding anhydrides or react to form acyl ureas.[7] However, when *N*-phenylmaleamic acid was treated with *N,N'*-dicyclohexylcarbodiimide in dichloromethane at 25°, neither of these products was isolated. Instead, a yellow, crystalline compound isomeric with *N*-phenylmaleimide (IV, R = C_6H_5—) was obtained in 93% yield. We have assigned the *N*-phenylisomaleimide structure (I, R = C_6H_5—) to this material. This compound absorbed strongly in its infrared spectrum at 1791 cm.$^{-1}$ because of the five-membered ring lactone and at 1680 cm.$^{-1}$ because of the carbon-nitrogen double bond. This type of absorption in the infrared is identical with that reported for *N*-(4-hydroxy-1-naphthyl)isomaleimide.[3] It also possessed an elemental analysis corresponding to a molecular formula of $C_{10}H_7O_2N$. The ultraviolet spectrum, measured in dichloromethane, showed absorption at 228 mμ (ϵ = 8600) and 345 mμ (ϵ = 4010). These data are all consistent with the isomaleimide structure. None of the symmetrical *N*-phenylmaleimide (IV, R = C_6H_5—) could be isolated from this reaction. *N,N'*-Dicyclohexylcarbodiimide was also used to prepare *N*-*n*-butylisomaleimide, *N,N'*-hexamethylenebisisomaleimide, bis(4-*N*-phenylisomaleimido)-methane, *N*-(*o*-chlorophenyl)isomaleimide, and *N*-(*o*-tolyl)isomaleimide. The spectral data and elemental analyses for all of these compounds are consistent with the *N*-substituted isomaleimide structure. The yields obtained by this synthesis for *N*-alkyl isomaleimides were about 50%, whereas the *N*-aryl isomaleimides were obtained in yields of 89–100%. As this synthesis has been successful for the preparation of *N*-alkyl and *N*-aryl isomaleimides and bis-isomaleimides, we believe the method to be a general one.

The second synthetic method for isomaleimides employed triethylamine and ethyl chloroformate. Treatment of a solution of *N*-phenylmaleamic acid and triethylamine in dichloromethane at 0–5° with ethyl chloroformate, gave a 46% yield of *N*-phenylisomaleimide. Similarly, *N*-*n*-butylisomaleimide was prepared in yields of 77–90% by this method. None of the isomeric *N*-*n*-butylmaleimide could be detected in the freshly prepared, purified product by vapor phase chromatographic analysis. The ethyl chloroformate–triethylamine reagent also dehydrated bis(4-*N*-phenylmaleamic acid)methane to the corresponding bisisomaleimide in 47% yield.

All of the *N*-substituted isomaleimides that have been prepared are crystalline solids except for *N*-*n*-butylisomaleimide. The aromatic compounds are yellow or yellow-orange in color. The solid isomaleimides are stable compounds and may be stored indefinitely in a dry atmosphere. In the presence of moisture they slowly hydrolyze to the expected maleamic acids. The only liquid isomaleimide that has been prepared, *N*-*n*-butylisomaleimide, slowly decomposed on standing at room temperature, but it could be stored under dry nitrogen at 0° with little decomposition.

Hydrolysis of these *N*-substituted isomaleimides is catalyzed by acids and may be autocatalytic. The failure of trifluoroacetic anhydride dehydration of *N*-substituted maleamic acids to yield *N*-substituted isomaleimides (except for the synthesis of *N*-(4-hydroxy-1-naphthyl)isomaleimide) may be due to the instability of isomaleimides in the presence of acids. We have found that adding

(4) (a) P. H. van der Muelen, *Rec. trav. chim.*, **15**, 282 (1896). (b) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **21**, 339 (1902). (c) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *J. Am. Chem. Soc.*, **50**, 474 (1928).

(5) (a) N. E. Searle, U. S. Patent **2,444,536** (1948); *Chem. Abstr.*, **42**, 7340 (1948). (b) H. W. Arnold and N. E. Searle, U. S. Patent **2,462,835** (1949). (c) L. E. Coleman, Jr., J. F. Bork, and H. Dunn, Jr., *J. Org. Chem.*, **24**, 135 (1959). (d) D. H. Marrian, *J. Chem. Soc.*, 1515 (1949). (e) P. Kovacic and R. W. Hein, *J. Am. Chem. Soc.*, **81**, 1187 (1959).

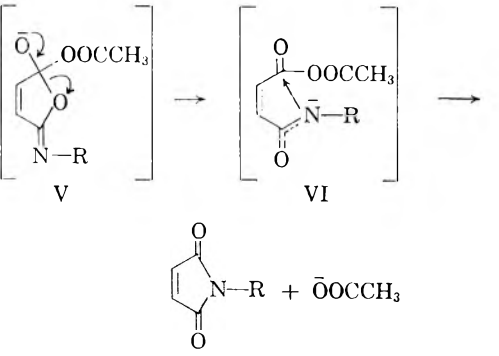
(6) (a) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955); (b) J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).

(7) (a) H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953); (b) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

enough triethylamine to neutralize completely the trifluoroacetic acid that was formed allowed the isolation of *N*-phenylisomaleimide in 50% yield from the reaction of *N*-phenylmaleamic acid with trifluoroacetic anhydride. These conditions may provide another general synthesis for isomaleimides. The fact that only *N*-(4-hydroxy-1-naphthyl)-isomaleimide could be prepared by dehydration with trifluoroacetic anhydride alone indicates that this isomaleimide and/or its protonated form possesses added stability which provides resistance to the hydrolysis reaction.[8,9] This stabilization would slow down the subsequent hydrolysis step, thus allowing isolation of the isomaleimide from the acid solution.

It was mentioned earlier that acetyl chloride has been employed for the dehydration of amic acids but that recent work indicated it possessed no utility for the preparation of isomaleimides from maleamic acids. We have found that acetyl chloride with added triethylamine to neutralize the acidic by-products dehydrated *N*-substitued maleamic acids to the symmetrical *N*-substituted maleimides. For example, *N*-*n*-butylmaleimide was obtained in 39% yield by dehydration of *N*-*n*-butylmaleamic acid with this reagent. Thus, acetyl chloride appears to give only the symmetrical product in the dehydration of maleamic acids[2] although the isoimides are obtained from phthalamic acids[4] with this reagent. In addition, dehydration of *N*-*n*-butylmaleamic acid with acetic anhydride–triethylamine either at 0–5° or in refluxing benzene (80°) gave *N*-*n*-butylmaleimide, although a small amount of the corresponding isomaleimide was formed in the reaction run at 0–5°. The symmetrical *N*-substituted maleimides are also formed in the acetic anhydride–sodium acetate dehydrations of *N*-substituted maleamic acids.[5] The use of triethylamine instead of sodium acetate with acetic anhydride for the synthesis of *N*-alkyl maleimides usually gave better yields.

N-Substituted isomaleimides are isomerized to the corresponding *N*-substituted maleimides in the presence of sodium acetate or triethylammonium acetate. Thus, *N*-phenylmaleimide was formed in 90% yield when *N*-phenylisomaleimide was heated at 90° with sodium acetate and acetic anhydride. Treatment of a 0.003*M* solution of *N*-*n*-butylisomaleimide in benzene at reflux with two equivalents each of triethylamine and acetic acid for ninety minutes gave a mixture containing approximately 40% of *N*-*n*-butyl-isomaleimide and 60% of *N*-*n*-butylmaleimide. The same reagents isomerized *N*,*N*′-hexamethylenebisisomaleimide to *N*,*N*′-hexamethylenebismaleimide in 34% yield. Heat alone did not cause these isomerizations, as *N*-phenylisomaleimide was unaffected by heating in acetic anhydride without added sodium acetate. In addition, *N*-*n*-butylisomaleimide could be prepared from *N*-*n*-butylmaleamic acid by dehydration with ethyl chloroformate and triethylamine in benzene at reflux. The isomerization of isomaleimides to maleimides which is catalyzed by acetate ion may proceed through nucleophilic attack of the acetate ion on the carbonyl carbon of the isomaleimide. Subsequent ring opening (V) to the mixed anhydride followed by displacement of the acetate

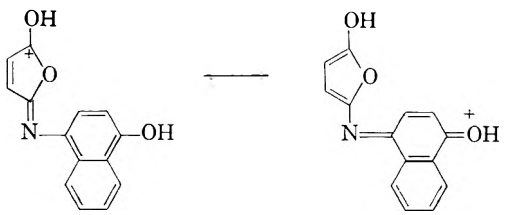


ion by the nitrogen of the amide ion (VI) would yield the maleimide. A similar acetate ion attack at the carbonyl carbon atom has been postulated for the acetate ion catalysis of the hydrolysis of phenyl acetate.[10]

The ease of isomerization of *N*-substituted isomaleimides to *N*-substituted maleimides under the conditions described above suggests the possibility that isomaleimides may be the primary dehydration products of maleamic acids when acetyl chloride–triethylamine and acetic anhydride–triethylamine (or sodium acetate) are employed. Isomerization of the isomaleimides to maleimides under the conditions of synthesis could account for the isolation of maleimides. The detection of a small amount of *N*-*n*-butylisomaleimide in the product of the dehydration of *N*-*n*-butylmaleamic acid with acetic anhydride–triethylamine at low temperatures (0–5°) indicated that the symmetrical maleimides are not the exclusive primary products of these dehydrations. This possibility cannot be resolved without a detailed study of the kinetic of the isomerization and dehydration reactions.

The formation of *N*-substituted isomaleimides by dehydration of *N*-substituted maleamic acids with *N*,*N*′-dicyclohexylcarbodiimide, ethyl chloro-

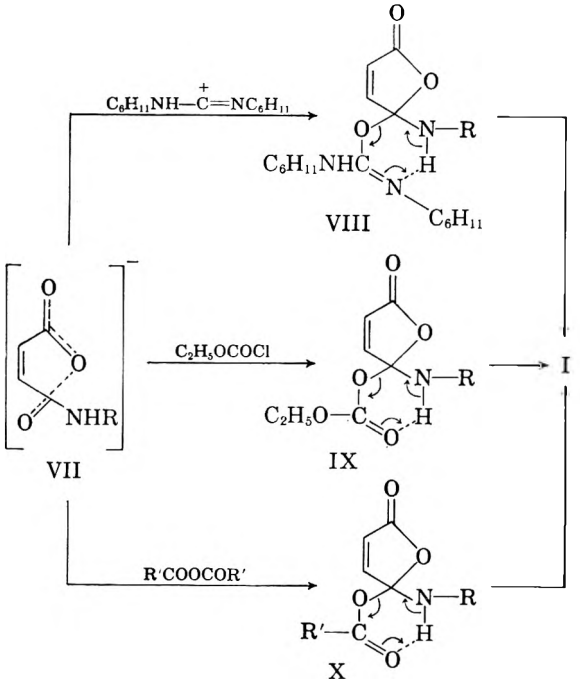
(8) Protonation of the carbonyl oxygen of *N*-(4-hydroxy-1-naphthyl)isomaleimide would give a species which would be stabilized by resonance, *viz.*:



(9) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1952, p. 268.

(10) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, 80, 5388 (1959).

formate–triethylamine, trifluoroacetic anhydride–triethylamine, and acetic anhydride–triethylamine probably proceeds by similar mechanisms. Donation of a proton from the maleamic acid to the tertiary base or to *N,N'*-dicyclohexylcarbodiimide[11] could lead to a ring-closed structure like VII. Further reaction with the dehydrating agents might lead to species like VIII, IX, and X which could decompose *via* the indicated *quasi* six-membered ring transition states into the isomaleimides. Internal catalysis by carboxylate ion in hydrolysis of



methyl hydrogen phthalate[12] and acyl salicylates[13] has been demonstrated. Interaction of the carboxylate anion of maleamic acids with the amide function to produce a species like VII is very probable. As the isomaleimide syntheses are carried out in nonaqueous media in the presence of acylating agents, hydrolysis of VII is avoided and dehydration takes place. The formation and decomposition of VIII, IX, and X through a cyclic transition state would explain the exclusive formation of the *N*-substituted isomaleimides in those reactions where no acetate ion is present to catalyze their isomerization to *N*-substituted maleimides.

EXPERIMENTAL[14]

N-n-Butylisomaleimide. Method A. Dehydration using ethyl chloroformate–triethylamine. Triethylamine (10.1 g., 0.1 mole) was added rapidly through a dropping funnel to a stirred slurry of *N-n*-butylmaleamic acid (17.2 g., 0.1 mole) in 100 ml. of anhydrous dichloromethane in a dry flask externally cooled by an ice salt bath. The resulting solution of triethylammonium *N-n*-butylmaleamate was cooled to 0–5° and ethyl chloroformate (11.9 g., 0.11 mole) was added dropwise at a rate slow enough to maintain the temperature below 5°. Carbon dioxide evolution and precipitation of triethylamine hydrochloride began almost immediately and continued throughout the addition. The reaction mixture was stirred for 1 hr. after the addition during which time it warmed to 20°. Triethylamine hydrochloride was removed by filtration and the filtrate was washed with water. After the organic layer was dried, the solvent was removed under reduced pressure and the residue distilled. The product, 12.1 g. (79%), b.p. 62–67° (1.0–1.2 mm.), n_D^{25} 1.4868–1.4870, was a clear, colorless liquid which developed a pale pink color on standing. The infrared spectrum of a liquid film possessed absorption at 1802 cm.$^{-1}$ (s) and 1698 cm.$^{-1}$ (s). When a 10% excess of triethylamine was used, the yield was raised to 90%. A sample purified by preparative vapor phase chromatography had n_D^{25} 1.4885. Its retention time on a silicone column at 190° and 25 p.s.i. was 5.0 min.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.98; H, 7.22; N, 9.25.

When the reaction was run on the same scale in 200 ml. of refluxing benzene for 1 hr., the yield was 65% of *N-n*-butylisomaleimide as determined by infrared and vapor phase chromatographic analyses. No *N-n*-butylmaleimide was detected in either the sample prepared at 0–5° or the sample prepared in refluxing benzene.

Ethyl N-n-butylmaleamate. It was necessary to use rigorously dried solvents for these dehydrations of *N-n*-butylmaleamic acid. When the solvents were not dry, ethyl *N-n*-butylmaleamate was formed at the expense of *N-n*-butylisomaleimide. However, this ester could also be prepared deliberately even with dry solvents by adding ethanol to the initial reaction mixture. The yields were in the 40–68% range, b.p. 125–128° (1.5 mm.), n_D^{25} 1.4761. Infrared absorption (liquid film) occurred at 3280 cm.$^{-1}$, 1732 cm.$^{-1}$ (s), 1640 cm.$^{-1}$, 1550 cm.$^{-1}$, and 675 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.94; H, 8.25; N, 7.10.

The dibromide of ethyl *N-n*-butylmaleamate was prepared by treating this ester with bromine in chloroform. It melted at 79–81° after recrystallization from ether.

Anal. Calcd. for $C_{10}H_{17}O_3NBr_2$: C, 33.45; H, 4.77; N, 3.89. Found: C, 33.34; H, 4.75; N, 3.46.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. To a slurry of 8.6 g. (0.05 mole) of *N-n*-butylmaleamic acid in 50 ml. of dichloromethane, a solution of 10.3 g. (0.05 mole) of *N,N'*-dicyclohexylcarbodiimide in 50 ml. of dichloromethane was added dropwise over a 20-min. period. A white, crystalline precipitate began to form when about half of the carbodiimide had been added. The mixture was stirred at room temperature for 3 hr., followed by removal of the precipitate by filtration. The precipitate was shown to be dicyclohexylurea by a mixture melting point with an authentic sample. The filtrate was concentrated and the residue was distilled to yield *N-n*-butylisomaleimide, 4 g. (52%), b.p. 80–83° (3 mm.), n_D^{25} 1.4890. The infrared spectrum of this product was identical with that obtained by Method A above.

N-n-Butylmaleimide. Method A. Dehydration using acetic anhydride–triethylamine. A solution of 17.3 g. (0.1 mole) of

(11) The first step in the reaction of carbodiimides with acids has been postulated to be donation of a proton to nitrogen. See reference 7a, p. 154.

(12) M. L. Bender, F. Chloupek, and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5384 (1958).

(13) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 3401 (1957); J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952); D. Davidson and L. Auerbach, *J. Am. Chem. Soc.*, **75**, 5984 (1953).

(14) Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infrared Spectrophotometer, model 137. Vapor phase chromatographic analyses were obtained on a Perkin-Elmer Vapor Fractometer, model 154-C. Microanalyses were performed by Drs. G. Weiler and F. Strauss, Oxford, England and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

N-*n*-butylmaleamic acid and 21 g. (0.21 mole) of triethylamine in 250 ml. of dichloromethane was cooled by an external ice salt bath. The mixture was stirred while 10.2 g. (0.1 mole) of acetic anhydride was added dropwise. After the addition, stirring was continued for 3 hr. followed by removal of the solvent under reduced pressure. The residue was dissolved in 1:1 ether-pentane and this solution was washed with water, dried and concentrated under reduced pressure. Distillation of the residue gave 8.5 g. (56%) b.p. 60–65° (1–2 mm.) of a clear liquid which showed absorption in its infrared spectrum at 1780 cm.$^{-1}$ (w) and 1698 cm.$^{-1}$ (s), indicating the maleimide structure. Vapor phase chromatographic analysis showed that this product contained 92.5% of *N*-*n*-butylmaleimide, 5.9% of *N*-*n*-butylisomaleimide, and 1.6% of a low boiling unknown component. The retention time on a silicone column at 190° and 25 p.s.i. (helium) for *N*-*n*-butylmaleimide was 4.4 min.

Method B. Dehydration using acetyl chloride-triethylamine. A mixture of *N*-*n*-butylmaleamic acid (17.3 g., 0.1 mole) and triethylamine (21 g., 0.21 mole) in 200 ml. of dry ether was stirred at room temperature while acetyl chloride (7.8 g., 0.1 mole) was added dropwise with stirring. A thick precipitate of triethylamine hydrochloride began to form almost immediately. The mixture was stirred for 16 hr., filtered, and the filtrate was concentrated. The residue was dissolved in benzene, washed with dilute, aqueous sodium hydroxide, and water. The benzene was removed under reduced pressure and the residue distilled to yield 6 g. (39%) of a clear liquid, b.p. 50–55° (0.5 mm.). Vapor phase chromatographic analysis of this product showed it to be *N*-*n*-butylmaleimide uncontaminated with *N*-*n*-butylisomaleimide.

N,N'-Hexamethylenebisisomaleimide. A slurry of 62.8 g. (0.2 mole) of *N,N'*-hexamethylenebismaleamic acid in 1 l. of dichloromethane was stirred vigorously while 82.4 g. (0.4 mole) of *N,N'*-dicyclohexylcarbodiimide in dichloromethane was added dropwise over a 45-min. period. The mixture was stirred for 6 hr. and then allowed to remain unagitated for an additional 16 hr. The *N,N'*-dicyclohexylurea which precipitated was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was passed through a column of Florisil in benzene. Concentration of the benzene eluates yielded 29 g. (52%) of white crystals, m.p. 94–96°. The infrared spectrum of a Nujol mull of this product exhibited strong absorption at 1802 cm.$^{-1}$ and 1698 cm.$^{-1}$ A sample that was recrystallized to a constant-melting point from 1:1 benzene-ether melted at 95.5–97.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.58; H, 5.75; N, 10.20.

N-Phenylisomaleimide. Method A. Dehydration using ethylchloroformate-triethylamine. A slurry of 47 g. (0.25 mole) of *N*-phenylmaleamic acid in 300 ml. of dichloromethane was cooled with an ice salt bath while 25 g. (0.25 mole) of triethylamine was added dropwise with stirring. The solution was stirred and cooled to <5° followed by dropwise addition of 27.3 g. (0.25 mole) of ethyl chloroformate at a rate so as to maintain the temperature below 10°. Evolution of carbon dioxide began during the first few minutes of the addition and the solution became bright yellow. After the addition was completed, the reaction mixture was stirred an additional hour at 10° and then allowed to warm to room temperature. Triethylamine hydrochloride was removed by filtration and the filtrate was washed with water. The solvent was removed under reduced pressure and the residue was distilled to yield 27.5 g. (63%) of a pale, yellow liquid at 119–130° (1 mm.) which crystallized, m.p. 40–60°. Recrystallization from carbon tetrachloride gave 20 g. (46%) of product, m.p. 57–62°. A mixture melting point with *N*-phenylisomaleimide prepared by Method B was undepressed.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. A slurry of 15.6 g. (0.082 mole) of *N*-phenylmaleamic acid in 150 ml. of dichloromethane was treated with 16.7 g. (0.081 mole) of *N,N'*-dicyclohexylcarbodiimide in 30 ml. of dichloromethane by a dropwise addition over a 20-min. period. The mixture was stirred for 2 hr. at room temperature followed by filtration to remove the *N,N'*-dicyclohexylurea (17.9 g., 98%) that had precipitated. The solvent was removed under reduced pressure and the residue, 13.2 g. (93%) crystallized in yellow prisms, m.p. 60–62°. A sample was further purified by solution in benzene and chromatography on a Florisil column prepared with pentane. The product that was obtained was recrystallized three times from 1:1 ether-petroleum ether (b.p. 39–54°) and dried *in vacuo*, m.p. 61.5–62.5°.

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.61; H, 4.17; N, 8.27.

The infrared spectrum of a melted film possessed absorption at 1791 cm.$^{-1}$ (s) and 1680 cm.$^{-1}$

Method C. Dehydration using trifluoroacetic anhydride-triethylamine. A mixture of 10 g. (0.052 mole) of *N*-phenylmaleamic acid and 10 g. (0.1 mole) of triethylamine in 50 ml. of dichloromethane was cooled with an ice bath. Trifluoroacetic anhydride (11 g., 0.052 mole) was added dropwise with stirring over a 10-min. period. The mixture was allowed to remain at room temperature for 16 hr., washed with water, dried, and concentrated under reduced pressure. The residue was dissolved in benzene and passed through a column of Florisil. The yellow eluate was concentrated to yield 4.5 g. (50%) of yellow crystals, m.p. 58–60°. A mixture melting point with *N*-phenylisomaleimide prepared by Method B was undepressed.

Bis(4-N-phenylisomaleimido)methane. Method A. Dehydration using ethylchloroformate-triethylamine. To a slurry of 19.7 g. (0.05 mole) of bis(4-*N*-phenylmaleamic acid)methane[15] in 125 ml. of dichloromethane at 0–5°, 10.1 g. (0.1 mole) of triethylamine was added with stirring. The mixture was stirred and cooled to −5° and 11.9 g. (0.11 mole) of ethyl chloroformate was added dropwise over a 20-min. period. The temperature of the reaction mixture was maintained below 7° during the addition and for an additional 30 min. after it was completed. The reaction mixture was then stirred without external cooling for 35 min. The amine hydrochloride was removed by filtration and the filtrate was washed with water and 10% sodium bicarbonate solution. The organic solution was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crystalline residue, 8.5 g. (47%) melted at 145–150°. A mixture melting point with bis(4-*N*-phenylisomaleimido)methane prepared by Method B was undepressed.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. To a slurry of 19.7 g. (0.05 mole) of bis(4-*N*-phenylmaleamic acid)methane in 50 ml. of dichloromethane and 20 ml. of ether, a solution of 20.6 g. (0.1 mole) of *N,N'*-dicyclohexylcarbodiimide in dichloromethane was added dropwise over a 40-min. period with stirring. Stirring was continued for 3 hr. after the addition was completed, the *N,N*-dicyclohexylurea that had precipitated was removed by filtration, and the product was recovered from the filtrate by removal of the solvent under reduced pressure. The yield was 16 g. (89%) of yellow crystals, m.p. 150–151°. A mixture melting point with bis(4-*N*-phenylmaleimido)methane was depressed, m.p. 120–145°. The infrared spectrum of a Nujol mull possessed strong absorption at 1795 cm.$^{-1}$ and 1680 cm.$^{-1}$ An analytical sample prepared by passage through a column of Florisil in benzene and subsequent recrystallization from 1:1 benzene-ether melted at 155–156°.

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.81; H, 4.31; N, 7.66.

N-(o-Tolyl)isomaleimide. To a slurry of 43 g. (0.21 mole) of *N*-(*o*-tolyl)maleamic acid in 300 ml. of dichloromethane, a solution of 41.2 g. (0.2 mole) of *N,N'*-dicyclohexylcarbo-

(15) I. A. Murphy, Ph.D. thesis, Indiana University, p. 37, September 1957.

diimide in 40 ml. of dichloromethane was added dropwise over a 30-min. period. The reaction mixture was stirred at room temperature for 24 hr., followed by removal of the precipitated *N,N'*-dicyclohexylurea by filtration. The filtrate was concentrated by distillation and the residue was dissolved in benzene, and passed through a column (1" × 10") of Florisil in benzene. The product, yellow-orange crystals, m.p. 37–40°, weighed 39 g. (100%) and exhibited a carbonyl absorption at 1790 cm.$^{-1}$ in the infrared spectrum of a melted film.

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.85; H, 5.02; N, 7.54.

N-(o-Chlorophenyl)isomaleimide. To a slurry of 45 g. (0.2 mole) of *N*-(*o*-chlorophenyl)maleamic acid in 1 l. of dichloromethane, a solution of 41.2 g. (0.2 mole) of *N,N'*-dicyclohexylcarbodiimide in 40 ml. of dichloromethane was added dropwise over a 30-min. period. The mixture was stirred at room temperature for 24 hr., followed by filtration of the *N,N'*-dicyclohexylurea and distillation of the solvent under reduced pressure. The residue in benzene was passed through a column of Florisil and the eluates were concentrated to yield 40 g. (97%) of yellow crystals, m.p. 60–66°. Recrystallization of a sample from 1:1 benzene–petroleum ether (b.p. 39–54°) gave an analytical sample, m.p. 65–67°.

Anal. Calcd. for $C_{10}H_6O_2NCl$: C, 57.85; H, 2.91; N, 6.75. Found: C, 58.35; H, 2.73; N, 6.58.

The infrared spectrum of a liquid film showed strong carbonyl absorption at 1800 cm.$^{-1}$

Isomerization of N-n-butylisomaleimide to N-n-butylmaleimide. A solution of 5.0 g. (0.033 mole) of *N*-*n*-butylisomaleimide, 6.06 g. (0.06 mole) of triethylamine, and 3.6 g. (0.06 mole) of acetic acid in 100 ml. of benzene was heated at reflux for 90 min. The solution was cooled, washed with water, dilute sodium hydroxide solution, and again with water. The benzene was removed under reduced pressure and the residue was distilled to yield a clear liquid, b.p. 50–55° (0.5 mm.). Vapor phase chromatographic analysis of this material showed it to be a mixture containing 40% *N*-*n*-butylisomaleimide, 59.4% *N*-*n*-butylmaleimide and 0.6% of an unknown impurity. The recovery was 3.5 g. (70%).

Isomerization of N-phenylisomaleimide to N-phenylmaleimide. A mixture of 5.0 g. (0.029 mole) of *N*-phenylisomaleimide, 1.0 g. (0.012 mole) of anhydrous sodium acetate and 15 ml. of acetic anhydride was heated on the steam bath for 1 hr. After the mixture had cooled to 25°, it was poured into 100 ml. of water causing long, yellow needles to separate. These were collected and dried, 4.5 g. (90%) m.p. 90–91°. A mixture melting point with an authentic sample of *N*-phenylmaleimide was undepressed. When sodium acetate was absent in this reaction, the starting material was recovered.

Isomerization of N,N'-hexamethylenebisisomaleimide to N,N'-hexamethylenebismaleimide. A solution of 4 g. (0.014 mole) of *N,N'*-hexamethylenebisisomaleimide, 1.8 g. (0.03 mole) of acetic acid, and 2.6 g. (0.026 mole) of triethylamine in 200 ml. of dry benzene was heated under reflux for 16 hr., cooled, and washed with water. The benzene was removed under reduced pressure and the residue, 1.4 g. (35%) was recrystallized from isopropyl alcohol, m.p. 136–141°. A mixture melting point with authentic *N,N'*-hexamethylenebismaleimide was undepressed.

Acknowledgment. We are indebted to Miss Olive M. Garty for the vapor phase chromatographic analyses and to Mr. William Birch and Mr. J. T. Commerford for technical assistance.

BOUND BROOK, N. J.

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The Chemistry of Maleimide and Its Derivatives. II. Maleimide and *N*-Methylolmaleimide

P. O. TAWNEY, R. H. SNYDER, R. P. CONGER, K. A. LEIBBRAND, C. H. STITELER, AND A. R. WILLIAMS

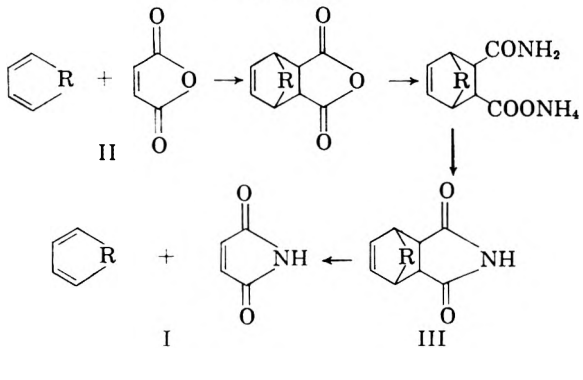
Received March 18, 1960

Maleimide was conveniently synthesized by preparation and pyrolitic decomposition of 3,6-*endo*-methylene-Δ^4-tetrahydrophthalimide. A variety of new *N*-substituted derivatives of maleimide were prepared. The olefinic bonds of maleimide and the derivatives were reactive in vinyl type polymerization under conditions of free radical or anionic initiation.

In an earlier paper,[1] a practical preparation of maleimide (I) by way of *N*-carbamylmaleimide was reported. In this paper, an alternate route for preparation for I and certain aspects of the chemistry of I are presented.

Preparation of I. The sequence of reactions shown in Chart A provides I in yields varying with the substituent R of the diene, II. Selection of cyclopentadiene (II, R = —CH_2—) was dictated by such factors as economy, convenience and ease of hydrolysis of the imide, III.

CHART A

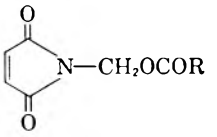


Chemistry of I. There are two reactive sites on the maleimide ring—the carboximide function and the double bond. Each exerts an influence upon

(1) P. O. Tawney, R. H. Snyder, C. E. Bryan, R. P. Conger, F. S. Dovell, R. J. Kelly, and C. H. Stiteler, *J. Org. Chem.*, **25**, 56 (1960).

TABLE I

MALEIMIDOMETHYL ESTERS (VI)



Acyl Group	M.P.	B.P.	Yield, %	Method[a]	Nitrogen, % Calcd.	Nitrogen, % Found
Acetyl	91–92°		93	A	8.28	8.12 8.12
Propionyl	43–44°		53	A	7.66	7.60 7.62
n-Butyryl		106–107.5°/ 0.6 mm.	65	A	7.11	6.90 7.06
Crotonyl	60–61°		34	C	7.18	6.93[b]
Benzoyl	120.5–121.0°		66	B	6.06	6.01
Trifluoroacetyl	68.5–69.5°		86	A	6.29	6.27
β-Carboxypropionyl	80.5–82.0°		91	A	6.18	6.31 6.25

[a] A, acid-catalyzed reaction of IV with an acid anhydride; B, reaction of IV with an acylpyridinium halide; C, reaction of IV with mixed anhydride of trifluoroacetic and crotonic acids (see ref. 2). [b] Carbon, calcd.: 55.5; found: 55.0, 55.3; hydrogen, calcd.: 4.61; found: 4.53.

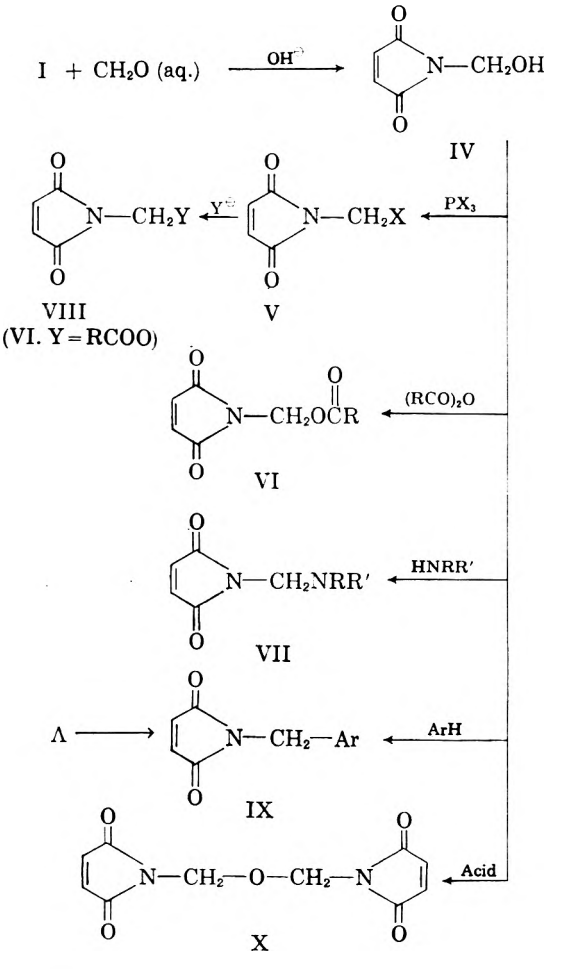
the reactivity of the other, causing I to be somewhat unlike a typical cyclic carboximide or cyclic olefin.

The imide group. Reactions of the carboximide function of I are shown in Chart B. Methylolation of I provided excellent yields of *N*-methylolmaleimide, IV, but the addition of a small amount of base was necessary. Thus, no reaction occurred in a formalin-I solution having a *p*H of about 3, but took place vigorously when the *p*H had been adjusted to about 5 by addition of a small amount of potassium hydroxide solution.

IV was the source of a series of derivatives of maleimide. Esters (Table I) resulted from acid catalyzed reaction with carboxylic acid anhydrides or from reaction with the mixed anhydride of trifluoroacetic acid and a carboxylic acid.[2] An alternate method consisted of reaction of IV with acylpyridinium halides, a variation of the Schotten-Baumann technique which avoided exposure of IV to an alkaline medium in which maleimide polymerizes.

Reaction of IV with phosphorus trichloride produced *N*-chloromethylmaleimide (V. X = Cl) in 80% yield. IV failed to react with concentrated hydrochloric acid, while alcoholic hydrogen chloride merely added hydrogen chloride across the double bond. The halogen of V was apparently no more than moderately reactive, although a complete comparison with other chloromethylimides was impossible due to the sensitivity of the maleimide nucleus to alkaline conditions. In acetone, V reacted with potassium thiocyanate to form maleimidomethyl thiocyanate (VIII. Y = —SCN); in

CHART B

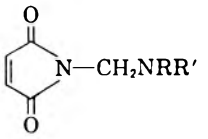


acetic acid solution, V and sodium acetate provided a rather low yield of acetoxymethylmaleimide (VI. R = CH_3). Reaction with acetic acid alone provided the same yield of ester, however, indicat-

(2) E. J. Bourne, J. E. B. Randle, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Am. Chem. Soc.*, **76**, 3206 (1954).

TABLE II

ALKYLAMINOMETHYLMALEIMIDES



R	R′	M.P.	B.P.	Yield, %	Method[b]	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5—	C_2H_5—		51–55°/0.04 mm.	73	B	15.3	15.2
n-C_4H_9	*n*-C_4H_9		68–69.2°/ 0.02 mm.[a]	74	A	11.7	11.4
				88	B		11.5
—C_5H_{10}—		103–104.5°		40	A	14.4	14.5[e]
				82.5	B		
H	C_6H_5—	127–128.5°		88	C	13.8	13.5[c]
—$C_2H_4OC_2H_4$—		143–145°		62	B	14.3	14.3[d,f]
				65	A		14.3

[a] n_D^{20} 1.4789. [b] A, azeotropic separation of water eliminated from IV and the amine; B, reaction of I with a dialkylaminomethyl ethyl ether; C, reaction of IV with the amine in refluxing dioxane. [c] Mol. wt.: calcd.: 202; found: 192. [d] Mol. wt.: calcd.: 196; found: 188. [e] Carbon, calcd.: 62.0; found: 62.1; hydrogen, calcd.: 7.25; found: 7.04. [f] Carbon, calcd.: 55.2; found, 57.7, 57.8; hydrogen, calcd.: 6.14; found: 6.32, 6.15.

ing that solvolysis may be important in reactions of V in a solvating medium.

Synthesis of a number of other compounds by displacement reactions of V was attempted. Silver nitrite apparently reacted with V but the product was too unstable to isolate. Cyanide ion in water proved too strongly basic, polymerizing the maleimide derivative, while cuprous cyanide would not react under a variety of conditions. In alcoholic hydrogen chloride, V added hydrogen chloride across the double bond, no reaction occurring at the *N*-methylene carbon. Ethoxide ion caused polymerization.

Primary and secondary amines displaced hydroxide from IV, forming the alkylaminomethylmaleimides VII (Table II). The tendency to attack the maleimide ring apparently paralleled the basicity of amines. Thus, aniline reacted solely at the methylene carbon, while piperidine was capable of reacting at both the methylene carbon and the double bond to form *N*-(1-piperidylmethyl)-α-1-piperidyl)succinimide. Piperidine was shown to add to maleimide to form α-(1-piperidyl)succinimide. As it was possible to prepare *N*-(1-piperidylmethyl)maleimide (VII. RR′ = C_5H_{10}) by slow addition of piperidine to a solution of IV with prompt removal of eliminated water from the medium, reaction at the methylene carbon was slightly more facile than reaction at the double bond. The amine derivatives were bright yellow solids or yellow oils, with the exception of the morpholine derivative which was a cream-colored solid. Two items of chemical evidence support the assignment of the maleimide structure to the yellow compounds: (1) they copolymerized with other monomers when initiated by a decomposing free radical source—evidence that the double bond still existed, and (2) the derivatives of secondary amines could be synthesized in high yield by an alternate route[3]—reaction of I with the appropriate dialkylaminomethyl ethyl ether.[4] IV in concentrated sulfuric acid or V (X = Cl), catalyzed by Lewis acids, alkylated benzene, and its derivatives, a reaction displayed by other methylolimides and their derivatives. Another acid-catalyzed reaction of IV was its self-condensation to form bismaleimidomethyl ether (X).

Comparison of the chemistry of I with that of phthalimide is restricted by the sensitivity of the nucleus of the former toward strong bases. A number of reagents, reported in the literature to react smoothly with phthalimide or *N*-methylolphthalimide derivatives, initiate anionic polymerization of maleimide derivatives. Methylolation of phthalimide proceeds rapidly under acid conditions[5] while maleimide reacts slowly or not at all at a pH below 5. Halomethylphthalimides result from reaction of *N*-methylolphthalimide with aqueous hydrohalic[6] acids and solvolyze readily with water or alcohols.[7] *N*-methylolmaleimide does not react with hydrochloric acid to yield *N*-chloromethylmaleimide, nor does the latter form *N*-ethoxymethylmaleimide by reaction with ethyl alcohol. As an explanation, it is suggested that the nitrogen atom of the maleimide nucleus is more electronegative than the nitrogen of phthalimide so that stabilization of a carbonium ion XI is less effective than for XII. This difference should make bond-forming more important in the transition state of displace-

(3) H. F. Tseou and C. T. Yang, *J. Org. Chem.*, **4**, 123 (1939).

(4) C. M. McLeod and G. M. Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

(5) S. R. Buc, *J. Am. Chem. Soc.*, **69**, 254 (1947).

(6) S. Gabriel, *Ber.*, **41**, 242 (1908).

(7) E. J. Sakellarios, *J. Am. Chem. Soc.*, **70**, 2822 (1948).

TABLE III

POLYMERIZATION[a] OF MALEIMIDE (I)

Comonomer	Monomer Ratio (I:Comonomer) Feed	Polymer	Solvent[b]	Initiator[b]	Conversion, %	$[\eta]$ (Solvent)[b]
Methyl acrylate	1:1	0.7:1	A	C	75	0.15 (A)
Vinyl acetate	1:1	1.3:1	A	C	70	0.09 (A)
Maleic anhydride	1:1	1.5:1	A	C	79	0.12 (B)
Ethyl fumarate	1:1	23.6:1	—	D	35	0.04 (B)
Ethyl maleate	1:1	4.2:1	—	D	5	0.22 (B)

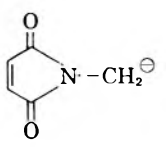
[a] I at 10% concentration in solvent; initiator 2 mole % based on I. [b] A = Dioxane, B = Dimethylformamide, C = Bisazoisobutyronitrile. D = Benzoyl peroxide.

TABLE IV

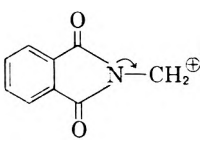
POLYMERIZATION[b] OF MALEIMIDE DERIVATIVES

Maleimide Derivative	Comonomer	Monomer Ratio (Maleimide: Comonomer) Feed	Polymer	Solvent[a]	Initiator[a]	Conversion, %	$[\eta]$ (Solvent)[a]
IV	Styrene	1:4.9	1:1.4	A	E	47	—
IV	Methyl methacrylate	1:5	1:9	B	E	33	0.7 (C)
IV	Isobutylene	1:9.2	1:1.2	B	E	28	0.52 (A)
IV	Vinyl chloride	1:8	1:6.5	B	E	69	
IV	Isopropylene acetate	1:5	1:1	B	E	19.4	0.33 (C)
IV	Maleic anhydride	1:1.32	3.21:1	B	E	13	0.22 (C)
IV	Ethyl fumarate	1.36:1	5.8:1	B	E	9	0.13 (C)
V, X = Cl	Styrene	1:13	1:2.6	B	E	27	0.60 (C)
V, X = Cl	Acrylonitrile	1:8	1:10	B	D	33	0.43 (C)
VI, R = CH_3	Styrene	1:6.5	1:2.1	B	E	45	0.67 (A)
VI, R = CH_3	Vinyl acetate	1:4.6	1:1.1	B	E	43	0.58 (A)
VI, R = CH_3	Acrylonitrile	1:13	1:19	B	E	62	1.65 (C)
VII, R_1R_2 = C_5H_{10}	Styrene	1:7.5	1:22.2	B	E	1	
VII, R_1 = R_2 = n-C_4H_9	Styrene	1:8.8	1:17	—	D	53	0.20 (C)
VII, R_1 = H, R_2 = C_6H_5	Styrene	1:7.8	1:1.7	B	E	32	
VIII, Y = —SCN	Acrylonitrile	1:12.4	1:10.4	B	E	39	1.67 (C)

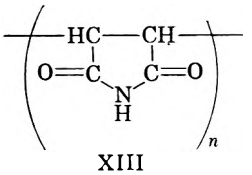
[a] A = Dioxane, B = Acetone, C = Dimethylformamide, D = Azoisobutyronitrile, E = Benzoyl peroxide. [b] Maleimide derivative at 10% concentration in solvent; initiator at 2 mole % based on maleimide derivative.



XI



XII



XIII

ment reactions of methylenemaleimides than of methylenephthalimides. Nucleophilic strength of attacking reagents should thus be more important in reactions with the maleimides than with phthalimides.

The double bond. I and all of the *N*-substituted maleimides described in this paper were reactive vinyl monomers in free-radical initiated polymerization. The reactivity was displayed in both copolymerization and, unlike maleic anhydride, homopolymerization. In fact, polymerization of I is a very vigorous reaction, yielding a white powder which softens above 400°. It was not possible to demonstrate the presence of aspartic acid among the hydrolysis products of the polymer, indicating that the polymer had a polysuccinimide structure (XIII).

Copolymerization of I and the *N*-substituted derivatives with various vinyl monomers is presented in Tables III and IV. Only the system I-styrene has been studied sufficiently to allow assignment of monomer reactivity ratios.[8] These ratios have been found to be 0.02 for I and 0.05 for styrene,[9] evidence of a marked tendency to alternate in the copolymer.

Table III presents qualitative data on the reactivity of I with monomers ranging from donor to acceptor types and varying in reactivity. The tendency to alternate is greatest with styrene and least with monomers bearing an electronegative group conjugated with the double bond. The results of

(8) F. R. Mayo and C. T. Walling, *Chem. Revs.*, **46**, 191 (1950).

(9) J. F. Petras, H. C. Tingey, D. E. Cable, unpublished results, these laboratories.

copolymerization of N-methylene derivatives of I are presented in Table IV. It may be noted that while IV, V (X = Cl), and VI (R = CH_3) exhibited a tendency to alternate with styrene, the general activity of the derivatives appears to be less than that of I.

As surprising as the radical-initiated homopolymerization of I was its base-catalyzed polymerization, a reaction which prevented the preparation of many derivatives attainable in the case of other imides. Inoculation of a solution of I with hydroxide or alkoxide ion was followed by an induction period during which the solution gradually developed a red color. Mildly exothermic polymerization then took place. The polymer was red and had a much lower molecular weight than the radical polymer. The color was essentially—but not completely—discharged by stirring in acetic acid, while the radical polymer turned red when suspended in a strongly basic medium. Either polymer in aqueous base slowly dissolved to a colorless solution. Ethyl aconitanilate, which can be considered as a model of an unsaturated group in a polymaleimide molecule similarly is deep red in alkaline medium.[10] As no difference in structure of the two polymers could be demonstrated by examination of hydrolysis products, the anionic polymerization probably proceeds by carbanion attack on olefinic carbon.

Acceptor character. The acceptor[11] character of the maleimide molecule was demonstrated by formation of a yellow 1:1 complex with resorcinol which occurred in an aqueous solution of the components or from a dry melt of the components. The complex had a maximum, congruent melting point at 126–128°. By employing differential spectroscopy, the complex was demonstrated to have a very weak absorption at 329 mμ.

EXPERIMENTAL[12]

Preparation of maleimide. 3,6-*endo*-Methylene-Δ^4-tetrahydrophthalic anhydride (1 kg.) was treated at room temperature with 930 ml. of concd. ammonium hydroxide and 600 ml. of water. After standing several hours in an ice bath, the solid was collected by filtration and the filtrate evaporated to dryness. This residue was combined with the solid from filtration and subjected without further purification to ring closure and pyrolysis.

The apparatus used for pyrolysis consisted of a heated distilling head connected to a 36-inch, 1-inch in diameter Pyrex tube fitted with a concentric thermocouple tube and packed with 4-mesh silica chips. Free volume of this tube was about 239 ml. The tube was heated by a full-length furnace constructed by winding coils of Nichrome wire on a metal pipe. An upper six-inch coil served as a preheater, while the remaining length was covered by the main heater coil. The furnace was lagged with magnesia pipe covering. At the effluent end of the furnace were two 1-l. flasks in series, cooled in ice-water, followed in order by two cold-finger traps cooled in Dry Ice, and a vacuum pump.

One kilogram of the product of reaction of the bicyclic anhydride with ammonium hydroxide was placed in a 2-l. flask and heated by means of a Glas-col mantle until the pot temperature reached 186° and the liquid charge (now the imide) ceased bubbling. The weight of crude imide was 806 g. The flask and mantle were then attached to the cracking apparatus, and the imide was distilled at 3 mm. pressure and 200° pot temperature into the cracking column which had been heated to 405–415°. The rate of distillation into the column averaged 5.56 g. per min.

High boiling products were collected in the ice-cooled receivers, and 243 g. of cyclopentadiene in the Dry Ice traps. The pot residue, presumably polymerized starting material, amounted to 165 g. Maleimide was separated from unchanged starting material by distillation through a 24-inch Vigreux column, yielding 295 g. of product, boiling at 102–105° at 4 mm., and leaving 85 g. of starting material as a higher-boiling residue. The yield of maleimide, based on unrecovered bicyclic imide, was 70%. The crude maleimide melted at 89–91°; one recrystallization from ethyl acetate raised the melting point to 92–93°.[13]

N-Methylolmaleimide. To a suspension of 98 g. (1 mole) of maleimide in 81 ml. of 37% formalin at 30° was added 3 ml. of 5% sodium hydroxide. Within 10 min. all of the maleimide had dissolved and a mildly exothermic reaction had raised the temperature to 35°. Separation of the product began promptly. After 2.5 hr. at room temperature the solution was filtered, yielding 96 g. (75%) of product melting at 99–103°. One recrystallization from ethyl acetate raised the melting point of the material to 104–106°.

Anal. Calcd. for C_5H_5OH: N, 11.05. Found: N, 11.00.

Esterification of IV. *Method A. N-Acetoxymethylmaleimide.* Sulfuric acid (2 drops) was added to a suspension of 10 g. (0.079 mole) of N-methylolmaleimide in 9.4 ml. (0.1 mole) of acetic anhydride. When the exothermic reaction had stopped, the solution was cooled and diluted with water, precipitating the ester as a white solid. The yield was 12.3 g. (93%), m.p. 91–92°, unchanged by recrystallization from alcohol.

Anal. Calcd. for $C_7H_9O_4N$: N, 8.28. Found: N, 8.12, 8.12.

Method B. N-Benzoyloxymethylmaleimide. N-Methylolmaleimide (20 g., 0.15 mole) in 30 ml. of hot acetone was added to the suspension formed by mixing 13 ml. of dry pyridine and 19 ml. of benzoyl chloride in 25 ml. of acetone. The temperature rose to 64° and held constant for some time. After cooling, precipitated pyridine hydrochloride was filtered, and the filtrate was diluted with 100 ml. of water. The product (24 g., 66%) separated as a dark oil which solidified quickly. Successive recrystallizations from acetone and aqueous ethanol provided tan crystals melting at 122–123.5°.

Anal. Calcd. for $C_{12}H_9O_4N$: N, 6.06. Found: N, 6.01, 6.02.

Method C. N-Crotonyloxymethylmaleimide. A mixture of 23 g. (0.274 mole) of crotonic acid and 38 ml. (0.274 mole) of trifluoroacetic anhydride was warmed for 10 min. in an oil bath held at 70°. To the resulting solution was added 25 g. (0.2 mole) of N-methylolmaleimide. The solid dissolved rapidly as an exothermic reaction set in. After cooling to room temperature, the solution was poured into ice cold bicarbonate solution. The partially solidified ester was taken up in chloroform, dried, and fractionated. There was obtained 13.2 g. (34%) of ester, b.p. 115,117° at less than 0.5 mm., m.p. 60–61°.

Phenylurethane of methylolmaleimide. Phenyl isocyanate (41.7 g., 0.35 mole) was added to a refluxing solution of 50 g. (0.4 mole) of methylolmaleimide in 300 ml. of dry benzene. The solution was refluxed for 1.5 hr. and then left overnight. The benzene was decanted from a precipitated

(10) C. A. Nau, E. B. Brown, and J. R. Bailey, *J. Am. Chem. Soc.*, **47**, 2599 (1925).

(11) R. S. Mulliken, *J. Phys. Chem.*, **56**, 801 (1952).

(12) All melting points are uncorrected. Analyses were performed by the Analytical Research Department of the Research Center or by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(13) P. O. Tawney, U. S. Patent **2,524,145**, October 3, 1950.

red oil and on partial evaporation yielded 17.6 g. of the urethane, m.p. 164–167°. Recrystallization from methanol raised the melting point to 167–167.5°. The red oil could not be induced to crystallize and was discarded.

Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 58.5; H, 4.07; N, 11.39. Found: C, 58.3; H, 4.32; N, 11.22.

N-Chloromethylmaleimide. Phosphorus trichloride (4.3 g., 0.03 mole) was added to a solution of 10 g. (0.08 mole) of *N*-methylolmaleimide in 50 ml. of acetone in an ice bath. The solution was stirred for a half-hour longer and then concentrated at the aspirator. Water, 50 ml., was added to the partly crystalline residue, precipitating the product. Filtration, followed by thorough washing with ice water, provided 9.2 g. (81%) of white crystals, m.p. 78–79°. Recrystallization from benzene–petroleum ether (b.p. 60–70°) did not change the melting point.

Anal. Calcd. for $C_5H_4O_2NCl$: Cl, 24.4. Found: Cl, 24.44, 24.37.

N-Bromomethylmaleimide, m.p. 82.3–83.3°, was apparently prepared in 52% yield using this technique. However, the compound proved unstable to brief storage and was not analyzed. The preparation was not repeated.

Attempted preparation of N-ethoxymethylmaleimide from IV. Saturated alcoholic hydrogen chloride (30 ml.) and 10 g. of *N*-methylolmaleimide were mixed at room temperature. Solution was complete in 6.25 hr. After standing overnight, the alcohol was evaporated, leaving a solid residue, m.p. 59–70°, insoluble in benzene and petroleum ether and soluble in alcohol and ethyl acetate. Two recrystallizations from ethyl acetate/petroleum ether (b.p. 60–70°) raised the melting point to 75.5–78°. The substance sharply depressed the melting point of *N*-chloromethylmaleimide and gave a positive Beilstein halogen test. Elemental analysis suggested that it was α-chloro-*N*-methylolsuccinimide.

Anal. Calcd. for $C_5H_6O_3NCl$: Cl, 21.7. Found: Cl, 21.4.

N-Thiocyanatomethylmaleimide. Potassium thiocyanate (35 g., 0.4 mole) was added to a stirred solution of 50 g. (0.34 mole) of *N*-chloromethylmaleimide in 150 ml. of acetone. A mildly exothermic reaction held the temperature of the resulting suspension to about 40° for over 1 hr. Stirring was continued for an additional hour at room temperature. The solid phase was filtered and extracted twice with hot benzene to yield 19.8 g. of product. The filtrate from the reaction liquors was subjected to two cycles of cooling (ice), filtration, and concentration to yield an additional 21 g. of product. The combined yield of white crystals was 72%, m.p. 106.5–107.5°. Recrystallization from aqueous acetone raised the melting point to 107–108°. The material was insoluble in water and alkanes, soluble in benzene and acetone.

Anal. Calcd. for $C_6H_4O_2N_2S$: N, 16.7; S, 19.0. Found: N, 16.5; S, 19.2.

N-Acetoxymethylmaleimide. 1. A solution of 5 g. (0.034 mole) of *N*-chloromethylmaleimide in 20 ml. of glacial acetic acid was refluxed for 2.75 hr. and then poured into 125 ml. of ice water. The crystals which precipitated melted at 89–91° and did not depress the melting point of ester prepared in esterification method A above. The yield was 2.5 g., 43%.

2. Gentle warming of a mixture of 5 g. (0.034 mole) of *N*-chloromethylmaleimide, 3 g. (0.037 mole) of sodium acetate and 20 ml. of acetic acid caused the solids to dissolve. Precipitation of sodium chloride occurred immediately. The mixture was poured into water and the crystals which precipitated were collected. The yield was about 2 g. The product did not depress the melting point of the ester prepared in method A.

Attempted preparation of N-nitromethylmaleimide. A solution of 14.5 g. (0.1 mole) of *N*-chloromethylmaleimide in 100 ml. of acetonitrile was run into a stirred suspension of 23 g. (0.15 mole) of silver nitrite in 50 ml. of acetonitrile. A mildly exothermic reaction developed, and the reaction temperature was held in the 19–26° range by a cold water bath. Stirring and cooling were continued for 1.5 hr., during which the suspension took on a yellowish color. Evolution of nitrogen oxides could not be detected at this point. The solution was filtered and concentrated at the aspirator leaving a dark residue which decomposed steadily at room temperature with evolution of nitrogen oxides.

Attempted preparation of N-cyanomethylmaleimide. A. *Sodium cyanide.* A warm solution of 10 g. (0.07 mole) of *N*-chloromethylmaleimide in 25 ml. of ethanol was added quickly to 4.3 g. (0.08 mole) of sodium cyanide in 4 ml. of water. An exothermic reaction occurred immediately and deposition of a red, gummy solid resulted. The reaction mass was discarded.

B. *Cuprous cyanide.* A mixture of 1.3 g. (0.01 mole) of *N*-chloromethylmaleimide and 1.9 g. (0.01 mole) of commercial cuprous cyanide was heated on a steam bath for a half hour. Extraction of the reaction mass with hot benzene yielded a solid melting at 77–79°, undepressed on admixture with chloromethylmaleimide.

Similarly, no reaction occurred with freshly prepared cuprous cyanide, even when inoculated by liquors of an allyl bromide–cuprous cyanide reaction.

Ethers. Attempted preparation of N-ethoxymethylmaleimide from V. *N*-Chloromethylmaleimide (10 g., 0.07 mole) and 30 ml. of saturated alcoholic hydrogen chloride were shaken together at room temperature. Solution was complete in 2.25 hr. After standing overnight, the solution was concentrated and diluted with water which precipitated a white solid, m.p. 69–72°. After recrystallization from benzene-ligroin, the product gave a positive Beilstein test. Elemental analysis suggested that this material was α-chloro-*N*-chloromethylsuccinimide.

Anal. Calcd. for $C_5H_5O_2NCl_2$: Cl, 39.0. Found: Cl, 38.2.

Preparation of maleimidomethylamines (VII). *Method A. N-Di-n-butylaminomethylmaleimide.* Di-*n*-butylamine (16.8 ml., 0.1 mole) was dripped slowly into a refluxing solution of 12.7 g. (0.1 mole) of *N*-methylolmaleimide in 75 ml. of purified dioxane in a flask equipped with a 20 cm. glass helix-packed column and total-reflux head. Water was removed as its dioxane azeotrope as elimination proceeded, 10 ml. of distillate boiling below 90° being collected. The solution was stripped and distilled. A total of 17.7 g. of yellow oil (74%) was collected in three fractions boiling in the range 66–69.2° at 0.02 mm. The last two fractions had n_D^{20} 1.4789.

This technique provided the corresponding derivatives of aniline, piperidine, and morpholine in 85, 40, and 64% yield, respectively.

Method B. N-(1-Piperidylmethyl)maleimide. Piperidylmethyl ethyl ether[4] (7.2 g., 0.05 mole) was poured over 4.7 g. (0.05 mole) of maleimide, causing a mildly exothermic reaction. The mixture was warmed gently to 80° and allowed to cool. Filtration yielded 8 g. (82.5%) of yellow needles, m.p. 103–104.5°.

This technique provided the corresponding derivatives of di-*n*-butylamine and diethylamine in 88 and 73% yield respectively.

Method C. N-Phenylaminomethylmaleimide. A solution of aniline (7.3 g., 0.08 mole) and *N*-methylolmaleimide (10.0 g., 0.08 mole) in 25 ml. of dry, peroxide-free dioxane was refluxed for 3.75 hr. Cooling and concentrating gave 14 g. (88%) of a yellow solid, m.p. 121–125°. Recrystallization from aqueous acetone gave bright yellow needles, m.p. 127.5–128.5°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.8; mol. wt., 202. Found: N, 13.5; mol. wt., 192.

N-(1-Piperidylmethyl)-α-(1-piperidyl)succinimide. Piperidene (7.9 ml., 0.08 mole) was poured over 10 g. (0.08 mole) of *N*-methylolmaleimide, causing a vigorous exothermic reaction. The red oil was cooled and diluted with 10 ml. of ethanol and 20 ml. of water, causing deposition of 5.5 g. of white needles. After recrystallization from aqueous ethanol and then from petroleum ether (b.p. 60–70°), the product melted at 123–124°.

Anal. Calcd. for $C_{15}H_{25}O_2N_3$: C, 64.5; H, 8.96; N, 15.1;

neut. equiv. 140. Found: C, 64.7; H, 8.74; N, 15.2, 15.4; neut. equiv. 146, 151.

N-Benzylmaleimide. A solution of 29 g. (0.2 mole) of *N*-chloromethylmaleimide in 90 ml. of dry benzene containing 0.5 g. of zinc chloride was refluxed for 18 hr. The reaction was allowed to cool to room temperature and filtered to remove a small amount of high-melting solid. The filtrate was chilled in ice, depositing 31 g. (83%) of white crystalline solid melting at 65–70° with a slight amount of solid residue. Five grams, recrystallized from a mixture of 15 ml. of benzene and 10 ml. of petroleum ether (b.p. 60–70°) melted at 68–69° (lit. m.p. 67.5°[14]).

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.6; H, 4.81; N, 7.49. Found: C, 70.4, 70.2; H, 5.10, 5.02; N, 7.49, 7.47.

N-(3-Nitro-4-methylbenzyl)maleimide. *N*-Methylolmaleimide (12.7 g., 0.1 mole) was added to a stirred, ice cold solution of 11.8 ml. (0.1 mole) of *o*-nitrotoluene in 36 ml. of concd. sulfuric acid. Stirring was continued for an hour at ice temperature. The solution was then allowed to warm to room temperature and let stand. The reaction was poured into 400 g. of ice and water where a semisolid mass separated and slowly solidified. This solid was recrystallized from 150 ml. of alcohol yielding 3.1 g. (12%) of material melting at 161–163°. After two successive recrystallizations from benzene, the product melted at 164–165°.

Anal. Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.5; H, 4.06; N, 11.4. Found: C, 58.7, 58.8; H, 4.06, 4.35; N, 11.03.

2,4-Bis(maleimidomethyl)phenol. A solution of 19 g. (0.2 mole) of phenol in 100 ml. of benzene was poured quickly into a stirred solution of 29 g. (0.2 mole) of *N*-chloromethylmaleimide in 100 ml. of benzene. One gram of zinc chloride was added, and the solution was heated to reflux. Hydrogen chloride evolution was initially very brisk and had practically stopped after 1.5 hr. Little change occurred in the original yellow color of the solution during this period, but solid lumps of catalyst became very dark and some brown resin formed. The solution was decanted from the resin and catalyst and concentrated to a greenish syrup. The syrup crystallized when triturated with 20 ml. of ethanol to yield 12.5 g. of crude product. Recrystallization from alcohol yielded pale yellow crystals melting, and apparently polymerizing to a clear gel, at 180.5–182°. The product did not form a colored complex with ferric chloride but was easily soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.0; H, 4.43; N, 6.90; for $C_{16}H_{12}O_5N_2$: C, 61.5; H, 3.85; N, 8.97. Found: C, 61.6, 61.3; H, 4.02, 4.10; N, 8.61, 8.49.

Bismaleimidomethyl ether. A solution of 50 g. (0.395 mole) of *N*-methylolmaleimide and 1 g. of *p*-toluenesulfonic acid in 150 ml. of toluene was refluxed for 7 hr. in an apparatus which included a Deane-Stark trap for collecting eliminated water. Only 2.9 ml. of water (theory called for 3.6 ml.) was collected. The hot solution was filtered and allowed to cool overnight. Filtration yielded 35.6 g. of product, m.p. 92–117°. One recrystallization from 500 ml. of ethanol gave 19 g. of material melting at 128–132°, 41% yield. A small sample was recrystallized again for analysis; m.p. 130–131°.

Anal. Calcd. for $C_{10}H_8N_2O_5$: C, 50.9; H, 3.41; N, 11.9; O, 33.9; mol. wt. 236. Found: C, 51.2; H, 3.61; N, 11.6; O, 34.1; mol. wt. 248.

α-(N-Piperidyl)succinimide. Piperidine (8.2 ml., 0.084 mole) was poured into a suspension of 9.7 g. (0.1 mole) of maleimide in 25 ml. of cool water. The temperature of the mixture rose quickly to 50°, and a dark pink color developed. Crystallization occurred on standing overnight at room temperature. Filtration yielded 10.5 g. (68%) of white crystals melting at 141.5–142.5°. The product was soluble in water as well as in aromatic and polar organic solvents. Recrystallization from petroleum ether did not change the melting point.

Anal. Calcd. for $C_9H_{10}O_2N_2$: N, 15.39. Found: N, 15.24, 15.32.

(14) E. Giustiniani, *Gazz. chim. ital.*, **22**, I, 169 (1892).

Polymaleimide. (A) *Free radical initiated.* Maleimide (10 g.) and 0.3 g. of benzoyl peroxide were dissolved in 190 g. of chlorobenzene and heated for 2 hr. at 80–90° and then cooled. Petroleum ether (b.p. 60–70°) (800 ml.) was added, and the white polymer (10 g.) was filtered. The material did not soften below 400° and had a dilute solution viscosity of 0.21 in dimethylformamide. It was soluble in dimethylformamide and dimethyl sulfoxide and insoluble in all other pure solvents; however, it was soluble in 3–50% aqueous acetone, aqueous methyl ethyl ketone, and aqueous dioxane and in methanolic acetone or methyl acetate. When suspended in a strongly alkaline non-aqueous medium, the polymer turned deep red, the color being discharged by acidification. In aqueous alkali, the polymer slowly hydrolyzed and dissolved to a colorless solution. A sample was prepared for analysis by 24-hr. extraction with hot acetone.

Anal.[15] Calcd. for $C_4H_3O_2N$: C, 49.5; H, 3.11; N, 14.4. Found: C, 46.7, 46.8; H, 4.56, 4.52; N, 11.5.

(B) *Base-initiated.* Ten grams of maleimide was dissolved in 15 g. of dimethylformamide, and the solution was cooled to 5° by means of an ice bath. Five milliliters of a 10% solution of sodium ethoxide in absolute ethanol was added. A pink color began to develop shortly after addition of the base so that, after 15 min., the solution was deep red. The viscosity of the solution had increased markedly at this point. After 26 hr., the solution was run into 500 ml. of methanol, precipitating 10 g. of a deep red polymer. The color could be nearly discharged by stirring the polymer in glacial acetic acid. The physical properties of this polymer were like those of the radical-initiated polymer, except that the molecular weight was lower—dilute solution viscosity in dimethylformamide, 0.08. A sample was prepared for analysis by 24-hr. extraction with hot acetone.

Anal. Calcd. for $C_4H_3O_2N$: C, 49.5; H, 3.11; N, 14.4. Found: C, 46.3, 45.6; H, 3.92, 3.76; N, 12.27.

Copolymerization of maleimide derivatives. Copolymerization of maleimide and its *N*-substituted derivatives was run in solution in organic solvents, initiated by conventional free radical sources. Details are set forth in Tables III and IV.

Maleimide-resorcinol complex. A solution of 25 g. (0.227 mole) of resorcinol and 15 g. (0.15 mole) of maleimide in 100 ml. of warm water deposited, on cooling, 26 g. of a yellow crystalline product, m.p. 126–128°. Recrystallization from water caused no change in the melting point.

Anal. Calcd. for $C_{10}H_8O_4N$: C, 58.2; H, 3.91; N, 6.79 Found: C, 57.5; H, 4.30; N, 6.66.

The ultraviolet absorption spectrum of the complex was obtained by differential spectroscopy using a Beckman DK-2 spectrophotometer. Solutions of maleimide (5.02 g./l.) and resorcinol (8.02 g./l.) in water were placed in separate 1-cm. cells in the blank beam of the instrument and a solution of maleimide (2.51 g./l.) and resorcinol (4.01 g./l.) in water in a single 2-cm. cell in the sample beam. The spectrum had an absorption maximum at 329 mμ having an optical density of 0.64.

Acknowledgment. The authors gratefully acknowledge the assistance of Drs. R. W. Amidon, S. van der Burg, H. H. Fletcher, A. A. Fournier, and E. J. Prill who participated in certain phases of this research. The authors also wish to express their gratitude to Drs. F. H. Westheimer and H. Kwart for valuable and stimulating discussions held during the course of the research and preparation of this paper.

WAYNE, N. J.

(15) Close check with the theoretical composition has proved impossible to obtain for polymaleimide due to lack of a means for completely decomposing the polymer.

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

The Synthesis of 2-Carboethoxy-Δ^2-cyclohexenone[1]

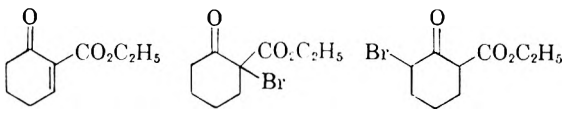
JOSEPH E. BRENNER[2]

Received April 22, 1960

The literature concerning the synthesis and properties of 2-carboethoxy-Δ^2-cyclohexenone and some related compounds is corrected, and an unequivocal synthesis from acyclic starting materials is described.

The purpose of this paper is to correct the long-standing inaccuracies in the literature concerning the preparation and properties of 2-carboethoxy-Δ^2-cyclohexenone (I) and some related compounds and to record an unequivocal synthesis of this interesting dihydrobenzene system.

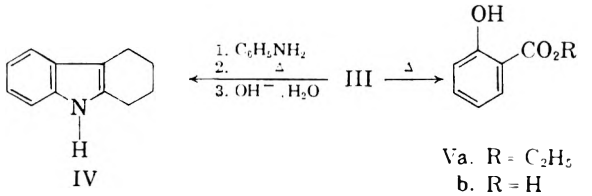
The synthesis of I was reported by Kötz,[3,4] by Ruhkopf[5] in 1939, and most recently by Mousseron[6] in 1954. These workers claim to have prepared the compound by aniline or thermal dehydrobromination of 2-bromo-2-carboethoxycyclohexanone (II). The following observations, obtained in this laboratory, strongly suggest that these claims are incorrect: 1) The bromo-2-carboethoxycyclohexanone the above authors had in hand was almost certainly the 6-bromo isomer (III); 2) au-



I II III

thentic 2-bromo-2-carboethoxycyclohexanone, first characterized adequately in the course of this work, cannot be dehydrobrominated by the listed methods or several others; 3) the properties of authentic I, prepared by an unequivocal route, are at variance with the few available in the literature for material prepared as above

Kötz[3] reported that bromination of 2-carboethoxycyclohexanone at ice salt bath temperatures with passage of an inert gas through the reaction mixture gave II. Sheehan,[7] using essentially the same conditions but then treating the reaction mixture with anhydrous hydrogen bromide, obtained what he designated as III on the basis of analogy with the bromination of acetoacetic ester.[8] We have found that bromination of I using Kötz's conditions leads to material of the *same refractive index* as that of Sheehan. More important, the bromination product displays a conjugate-chelate type of infrared spectrum (bands at 5.80, 6.08 and 6.20 μ) and possesses a strong maximum in the ultraviolet, λ_{max} 269 mμ, ϵ_{max} 10,200. Further, on treatment of III with aniline in ether, following the procedure of Kötz, no volatile material was obtained on steam distillation; however, ether extraction yielded a high-boiling, viscous liquid which possessed a characteristic indole spectrum in the ultraviolet and infrared regions. A band at 5.82 μ in the latter was indicative of a carboxylic ester; and basic treatment resulted in hydrolysis and decarboxylation to tetrahydrocarbazole (IV), readily identified by its spectral characteristics, as well as



IV Va. R = C_2H_5 b. R = H

by its melting point and mixed melting point with authentic material.

Alternatively, distillation of III at atmospheric pressure[3] followed by rectification in vacuum gave, in low yield, a liquid which from its infrared and ultraviolet spectra appeared to be ethyl salicylate (Va). This product gave a purple color with ferric chloride solution and on alkaline hydrolysis in an inert atmosphere it yielded the readily identifiable salicylic acid, m.p. 155°. Kötz reported a melting point of 128° for the acid secured in this manner which he considered to be the *dihydro* compound. It is likely, rather, that he had in hand an impure sample of Vb, his reported conversion of the acid to cyclohexenone notwithstanding.[9]

Mazza and Crapetta[10] reported a melting point

(1) Abstracted from the doctoral thesis of Joseph E. Brenner, University of Wisconsin, 1958.

(2) Allied Chemical and Dye Corp. Fellow, 1957–1958. Present address: Department of Chemistry, Massachusetts Institute of Technology.

(3) A. Kötz, *Ann.*, **358**, 183 (1908).

(4) A. Kötz, *J. prakt. Chem.*, (2), **80**, 473 (1909).

(5) H. Ruhkopf, *Ber.*, **72**, 1978 (1939).

(6) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim.*, 1246 (1954).

(7) J. C. Sheehan and C. E. Mumaw, *J. Am. Chem. Soc.*, **72**, 2127 (1950).

(8) The α-bromoacetoacetic ester initially produced in the bromination is rapidly rearranged by the hydrogen bromide formed to the γ-isomer. This change appears to be markedly inhibited by water (H. Gault and L. Klees, *Bull. Soc. Chim.*, [4], **39**, 883 (1926).

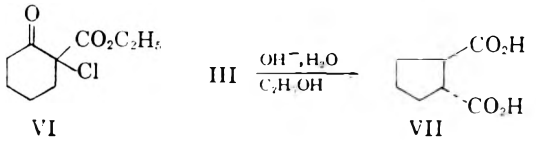
(9) P. D. Bartlett and G. F. Woods, *J. Am. Chem. Soc.*, **62**, 2933 (1940) have presented data which indicate that some of Kötz's thermometers read from 10–12° low; this circumstance is probably not involved here, since in the same paper,[3] Kötz gives the correct melting point for salicylic acid, obtained in another experiment.

(10) F. P. Mazza and C. Crapetta, *Gaz. Chim. Ital.*, **57**, 292 (1927).

of 125° for the acid they obtained by a complex sequence of manipulations of ethyl anthranilate, beginning with sodium in amyl alcohol reduction. This agreement is surprising unless the thermometer used by Mazza and Crapetta also read low or their sample was as impure. In fact, hydrolysis of authentic 2-carboethoxycyclohexenone (I), in complete disagreement with the above result, produces no "dihydrosalicylic acid," but affords cyclohexenone itself, isolated as its 2,4-dinitrophenylhydrazone.

If 2-carboethoxycyclohexanone is brominated in a cold, vigorously stirred emulsion of carbon tetrachloride, ether, and a large excess of saturated potassium bicarbonate solution, 2-bromo-2-carboethoxycyclohexanone (II) can be obtained. Presumably, the aqueous base neutralizes the hydrogen bromide formed, preventing its isomerizing activity. The low refractive index of our product, the lack of evidence of enol in the infrared, faint, or absent color with ferric chloride, and lack of selective absorption in the ultraviolet (λ_{inf} 260 mμ, ϵ_{inf} 310), support the structural assignment. Unfortunately, treatment of II with aniline, dimethylaniline, or collidine yielded no characterizable product, and thermal treatment, *sicut ante*, gave salicylic ester in low yield, contaminated with some other phenolic material.[11]

2-Chloro-2-carboethoxycyclohexanone (VI) was prepared from 2-carboethoxycyclohexanone by sulfuryl chloride chlorination[12] in the presence of potassium carbonate. VI likewise could not be dehydrochlorinated by sodium acetate in acetic acid (reported by Kötz[4]), lithium chloride in dimethylformamide, or the organic bases aniline, dimethylaniline, or collidine.



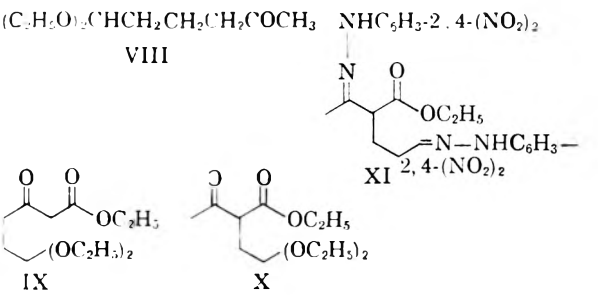
VI VII

(11) The successful bromination and dehydrobromination with quinoline of 2-methyl-2-carboethoxycyclopentanone to the corresponding cyclopentenone has been reported (P. C. Dutta, *J. Ind. Chem. Soc.*, **26**, 109 (1949). However, the starting material is not an enolizable β-ketoester, nor can aromatization take place; thus the analogy is strained. M. Yanagita, S. Inayama, and R. Kitagawa, *J. Org. Chem.*, **21**, 612 (1956) were able to obtain 2-methyl-2-carboethoxy-Δ^5-cyclohexenone in a similar manner. The only additional points of interest are that during the dehydrobromination, the carboethoxyl group was in part lost, and partial migration of the double bond occurred as well to afford a mixture of 2-methyl- and 6-methylcyclohexenones. Incidentally, this result suggests a rationalization of the appearance of phenol itself in the thermal decomposition of II and III.

(12) *Cf.* E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951). The preparation of VI was also reported by Kötz,[3] but the structure of his product is equivocal for the same reasons as above, as rearrangement of the product by the acid formed, while less likely than before, is not impossible.

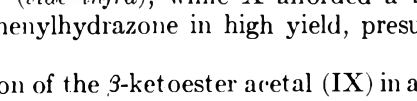
An interesting reaction takes place when 6-bromo-2-carboethoxycyclohexanone (III) is boiled with aqueous ethanolic sodium hydroxide. *trans*-Cyclopentane-1,2-dicarboxylic acid is produced in 91% yield. It was characterized by its carbon-hydrogen analysis, melting point, and mixed melting point with authentic material,[13] and conversion *via* the crystalline *cis* anhydride to *cis* diacid. Similar basic treatment of II and VI gave intractable mixtures from which no crystalline acid could be isolated.

The successful synthesis of 2-carboethoxy-Δ^2-cyclohexenone (I) was carried out as follows: the anion of acetylacetone, prepared with sodium hydride in a 1:1 mixture of benzene and dimethylformamide, was alkylated with β-chloropropion-



aldehyde diethylacetal in the presence of small amounts of potassium iodide. The resulting β-diketone was hydrolyzed without isolation to the keto-acetal, VIII, in about 45% over-all yield. In a large excess of diethyl carbonate, the action of sodium methoxide introduced a carboethoxy group on the terminal methyl,[14] yielding the β-ketoester acetal (IX, 55%). This structural assignment is in accord with the observations of Wallingford, *et al.*,[14] and it was confirmed by the alkylation of acetoacetic ester with chloropropionaldehyde diethylacetal to give, in 81% yield, the isomer X. The infrared spectra of IX and X were similar, but differed in significant detail. Further, on treatment with 2,4-dinitrophenylhydrazine reagent, IX yielded the derivative of 2-carboethoxycyclohexenone (I) (*vide infra*), while X afforded a bis-2,4-dinitrophenylhydrazone in high yield, presumably XI.

Solution of the β-ketoester acetal (IX) in acetone containing a catalytic amount of *p*-toluenesulfonic acid and stirring for twelve hours under nitrogen



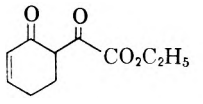
(13) Nitric acid oxidation of a sample of *trans*-1,2-bis-(hydroxymethyl)cyclopentane (A. T. Blomquist, J. Wolinsky, Y. C. Meinwald, and D. T. Longone, *J. Am. Chem. Soc.*, **78**, 6057 (1956), kindly furnished by Dr. Wolinsky, gave 78% yield of pure VII.

(14) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Am. Chem. Soc.*, **63**, 2252 (1941).

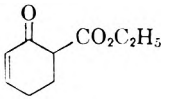
produced the desired 2-carboethoxycyclohexenone in 35–50% yield, the remainder being nonvolatile material. Apparently, *trans*-acetalization had occurred and the free aldehyde, under the influence of the acid catalyst, had undergone ring closure in this highly favorable case.

The unsaturated β-ketoester (I) was a highly enolic material with a characteristic odor resembling both ethyl salicylate and 2-carboethoxycyclohexanone; it dissolved readily in dilute base and produced a bright turquoise color with ferric chloride solution (Kötz[3,4] reported that his material gave a *brown* coloration with ferric chloride). In the infrared, I displayed bands at 5.75, 5.85, 6.10, 6.30, 13.38, and 14.42 μ among numerous others. However, it could be determined that only a trace, if any, of the fully aromatic salicylic ester could be present. 2-Carboethoxycyclohexenone had ultraviolet absorption maxima at 232 and 305 mμ, ε 7800 and 2700 respectively. Catalytic reduction with 30% palladium-on-charcoal in 95% ethanol resulted in the uptake of only about 0.15–0.20 equivalent of hydrogen; however, treatment of the reduction product with 2,4-dinitrophenylhydrazine reagent afforded a fair yield of the derivative of 2-carboethoxycyclohexanone. A probable explanation of the hydrogenation result is that I undergoes rapid disproportionation in the presence of the catalyst to yield ethyl salicylate and 2-carboethoxycyclohexanone. This supposition was confirmed by stirring a sample of I with palladium-on-charcoal in the absence of hydrogen. Hydrolysis of the reaction mixture permitted the isolation of 94% of the theoretical quantity of salicylic acid (*i.e.*, 0.47 mole per mole of I).

For purposes of comparison, we decided to prepare 6-carboethoxy-Δ^2-cyclohexenone (XIII). This was accomplished by reaction of cyclohexenone with diethyl oxalate in the presence of sodium methoxide[15] according to the published procedure.[4] The decarbonylation of the intermediate glyoxalate



XII



XIII

XII was not smooth, and the unsaturated β-ketoester obtained did not have a completely satisfactory carbon-hydrogen analysis. It gave a purple color with ferric chloride solution. Its infrared spectrum showed the expected bands at 5.73 and 5.94 μ but in the 6.0 μ–6.5 μ region, where 2-carboethoxycyclohexenone (I) and its saturated analog both absorb strongly, there was only a weak band at 6.18 μ. In this respect XIII resembles cyclohexenone itself (strong band at 5.95 μ, weak band at 6.20 μ). The ultraviolet, similarly, showed λ_{max} 225 mμ, ϵ_{max} 9700, almost identical with the spectrum of cyclohexenone.

Mousseron[6] reported a melting point of 155–156°, λ_{max} 365 mμ ϵ_{max} 26,900 for the 2,4-dinitrophenylhydrazone of XIII in poor agreement with our values for this compound. Mousseron further reported, for the 2,4-dinitrophenylhydrazone of I, a melting point of 228–230° and λ_{max} 356–357 mμ and 387–388 mμ, both ϵ_{max} 15,500 (a very low value for the 2,4-dinitrophenylhydrazone of an α,β-unsaturated ketone) in complete disagreement with our findings[16] (see Table I). In view of our inability to prepare I by Kötz's method, which Mousseron claims to have done, we are inclined to regard Mousseron's data as completely erroneous.

EXPERIMENTAL[17]

6-Bromo-2-carboethoxycyclohexanone (III). Bromine, 29.1 g., 0.182 mole, was added dropwise over a period of 1 hr. to a vigorously stirred solution of 2-carboethoxycyclohexanone,[18a] 31.0 g., 0.182 mole in 10 ml. of dry ether, cooled in an ice salt bath. The red color of the bromine was not discharged rapidly after about 75% had been added. The reaction mixture was diluted with ether and poured onto a mixture of 20 g. of sodium carbonate and ice. The product was worked up in the usual manner and gave a main fraction on distillation through a short column, 39.3 g., b.p. 104–106°/0.5 mm., n_D^{25} 1.5302, 86%. The product gave an intense purple color with ferric chloride solution. A sample was redistilled for analysis, b.p. 92–93°/0.3 mm., n_D^{25} 1.5280. Sheehan[7] reports b.p. 93–94°/0.4 mm., n_D^{25} 1.5260; infrared: 5.80 μ, 6.08 μ, 6.20 μ; ultraviolet: λ_{max} 268 mμ, ϵ_{max} 10,200.

Anal. Calcd. for $C_9H_{13}O_3Br$: C, 43.39; H, 5.26. Found: C, 43.54; H, 5.11.

An essentially identical result was obtained when the reaction mixture was flushed with nitrogen during the bromination.

Thermal decomposition of III. 6-Bromo-2-carboethoxycyclohexanone, 30.0 g., 0.12 mole, was heated at 220–240° in a current of dry nitrogen. The crude distillate, b.p. 165–190°, was collected and recycled. This distillate, *ca.* 15 g., was redistilled into two rough fractions, A, b.p. 40–60°/1 mm. and B, b.p. 80–110°/0.5 mm. The latter on saponification gave an acid, m.p. 160–161°, shown later to be *trans*-cyclopentane-1,2-dicarboxylic acid, and thus consisted largely of starting bromoketoester. The infrared spectrum of A was essentially that of ethyl salicylate (bands at 3.20 μ, 5.78 μ, 6.02 μ, 6.22 μ, 6.30 μ, 13.24 μ, 14.30 μ, and 15.07 μ); ultraviolet: λ_{max} 238 mμ, ϵ_{max} 7500; λ_{max} 306 mμ, ϵ_{max} 2800; (reported[19] for methyl salicylate λ_{max} 238 mμ, ϵ_{max} 9300;

(15) This condensation, occurring on the side of the carbonyl remote from the double bond, has proved of great value in certain recent steroid syntheses, *e.g.*, the preparation of methyl 3-oxo-1,4,17(20)-pregnatriene-21-oate from 11-oxoprogesterone *via* 2,21-diethoxalyl-11-oxoprogesterone [J. Korman and J. A. Hogg, U. S. Patent 2,774,775; *Chem. Abstr.*, 51, 6715 (1957)].

(16) S. N. Balasubrahmanyam, Indian Institute of Science, Bangalore, has reported (private communication) that he has obtained evidence for the production of XIII by the methods of Kötz for I (no experimental data).

(17) Infrared spectra of all liquids were taken on liquid films on Baird and "Infracord" spectrophotometers. Ultraviolet spectra were all measured on a Cary spectrophotometer on samples dissolved in 95% ethanol. Melting and boiling points are uncorrected.

(18) (a) M. R. Snyder, L. A. Brooks, and M. Shapiro, *Org. Syntheses*, Coll. Vol. II, 531 (1943); (b) E. J. Witzemannet, *et al.*, *Org. Syntheses*, Coll. Vol. II, 137 (1943).

(19) E. D. Bergmann, Y. Hirshberg, and S. Pinchas, *J. Chem. Soc.*, 2351 (1950).

TABLE I

ULTRAVIOLET SPECTRA OF 2,4-DINITROPHENYLHYDRAZONES

Compound	Melting Point	λ_{max}, mμ	ϵ_{max}	λ_{max}, mμ	ϵ_{max}
Cyclohexanone	162°	362	23,900	230	16,300
2-Carboethoxycyclohexanone	157–158°	358	23,500	230	14,800
Cyclohexenone	167–169°	373	29,100	251	16,900
2-Carboethoxycyclohexenone	164–165°	368	26,400	255	13,300
	228–230°[a]	356–357[a]	15,500[a]		
6-Carboethoxycyclohexenone	129–130°	367	28,600	253	14,400
	155–156°[a]	365[a]	26,900[a]		
Butylidene acetoacetic ester	131–133°	368	32,400	253	17,100

[a] Ref. 6. All other values were measured in this Laboratory and agreed satisfactorily with the literature values where available.

λ_{max} 306 mμ, ϵ_{max} 4400). Basic hydrolysis of A yielded salicylic acid in 87% yield, m.p. 155°, undepressed on admixture with an authentic sample. The hydrolysis was carried out under nitrogen.

Treatment of III *with aniline.* The bromoketoester, 30.0 g., 0.12 mole, was dissolved in 200 ml. dry ether and warmed for 10 min. on the steam bath with 45 g., 0.48 mole of freshly distilled aniline. When nearly all the ether had evaporated, a strongly exothermic reaction began. The mixture was allowed to stand overnight, then mixed with a solution of 45 g. of oxalic acid in 800 ml. of cold water. Steam distillation of this mixture[4] gave no steam volatile material. The mixture was then cooled and extracted thoroughly with ether. Removal of the ether, after drying with sodium sulfate, and distillation of the residue gave *ca.* 6 g. of a viscous liquid, b.p. *ca.* 175°/0.4 mm. The same result was obtained on omitting the steam distillation step, taking the reaction mixture up in ether, and washing with dilute hydrochloric acid. The ultraviolet spectrum of this distillate displayed bands at 225, 276, 284, and 292 mμ in a pattern indistinguishable from a normal indole. The infrared (chloroform) had a band at 5.82 μ (carboethoxyl carbonyl). Basic hydrolysis gave a good yield of material, m.p. 120–121° after recrystallization from ethanol-water, undepressed on admixture with an authentic sample of tetrahydrocarbazole.[20] The infrared spectra in chloroform were identical.

Favorski reaction of 6-bromo-2-carboethoxycyclohexanone. The bromoketoester (III), 3.0 g., 0.012 mole, was refluxed for 1 hr. with a solution of 3.0 g. of sodium hydroxide in 10 ml. water and 150 ml. of ethanol. Nitrogen was bubbled through the solution. Most of the alcohol was then evaporated and the solution acidified with concd. hydrochloric acid and saturated with ammonium chloride. Ether extraction and the usual workup gave 1.75 g. of crude acid, VII, 91% yield, m.p. 155–158°. A further recrystallization from benzene-methanol (clusters of small needles) and sublimation gave analytically pure material, m.p. 161–162° (reported[21] m.p. 160°).

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.33. Found: C, 53.09; H, 6.36. Neut. equiv.: Calcd.: 79.1. Found: 80.1, 80.3.

Oxidation of trans-1,2-bis(hydroxymethyl)cyclopentane.[13] The diol, 1.0 g., 0.0075 mole, was dissolved in 20 ml. of concd. nitric acid at room temperature in a flask fitted with an air condenser. After a few minutes of shaking, a *violent* reaction took place. The mixture was then warmed for 1 hr. at 60°, the excess nitric acid removed under reduced pressure, and the residual solid dissolved in 20 ml. of hot water from which deposited on cooling 920 mg. of crystals, m.p. 162–163°, 78% yield. This material did not depress the melting point of VII. The infrared spectra (Nujol mull and potassium bromide pellet) showed little resolution but were superimposable. Following the method of Perkin,[21] a sample of VII was heated with acetyl chloride to form the *cis* anhydride, m.p. 70–72°, which on alkaline treatment afforded *cis*-cyclopentane-1,2-dicarboxylic acid, m.p. 140–141°.

2-Bromo-2-carboethoxycyclohexanone (II). 2-Carboethoxycyclohexanone, 30.0 g., 0.176 mole, was added to 200 ml. of water, 150 g. of potassium bicarbonate, 50 ml. of ether, and 50 ml. of carbon tetrachloride. Bromine, 28.2 g., 0.176 mole was added dropwise over a period of 2 hr. to the cooled vigorously stirred emulsion. The red color which persisted on completion of the reaction was removed by shaking with a small amount of cold dilute sodium thiosulfate solution. The product was extracted with additional ether. The usual workup gave a main fraction, 30.0 g., b.p. 97–93°/0.3 mm., n_D^{25} 1.4937–1.4942, 69% yield. A sample was redistilled for analysis, b.p. 84–86°/0.1 mm., n_D^{25} 1.4932. The infrared had a strong broad band at 5.79 μ, weak traces at 6.05 and 6.20 μ; ultraviolet: λ_{inf} 260 mμ, ϵ_{inf} 310; λ 220 mμ, ϵ 810.

Anal. Calcd. for $C_9H_{13}O_3Br$: C, 43.39; H, 5.26. Found: C, 43.60; H, 5.33.

2-Chloro-2-carboethoxycyclohexanone (VI). Sulfuryl chloride, 14.8 g., 0.11 mole, in 10 ml. of carbon tetrachloride, was added to a stirred mixture of 17.1 g., 0.10 mole, of 2-carboethoxycyclohexanone and 16.7 g. of potassium carbonate in 50 ml. carbon tetrachloride with cooling in an ice salt bath. When the addition was complete, ice water and additional carbon tetrachloride were added. The organic layer was separated, dried, and distilled to yield 15.5 g. of material, b.p. 73–100°/0.4 mm. Redistillation gave 12.1 g., b.p. 85–91°/0.4 mm., n_D^{25} 1.4715–1.4728, 59%. The product gave a very faint coloration with ferric chloride. The infrared had one intense band centered at 5.77 μ and no absorption in the 6.0 μ–6.5 μ region; ultraviolet: λ_{max} *ca.* 257 mμ, ϵ_{max} 110, calculated as due to starting material.

6,6-Diethoxyhexane-2-one (VIII). Sodium hydride, 9.6 g., 0.40 mole, was placed in a thoroughly dried 1 l. round bottomed flask fitted with reflux condenser, mercury-seal stirrer, and dropping funnel and immediately covered with 50 ml. of 1:1 dry benzene–dimethylformamide under a blanket of dry nitrogen. The flask was placed in an ice bath and 40 g., 0.40 mole, acetylacetone (Eastman Kodak Co. Yellow Label, dried by azeotropic distillation with benzene using a water separator) in 50 ml. of the same solvent added dropwise with stirring over a period of 1 hr. The ice bath was replaced by a heating mantle and the flask was warmed until the sodium enolate had dissolved and the last traces of hydride had disappeared. Then 55 g., 0.32 mole, of chloropropionaldehyde diethylacetal[18b] in 50 ml. of 1:1 benzene-dimethylformamide were added rapidly, followed by 800 mg. of dry potassium iodide. The mixture was refluxed gently for 24 hr. The major portion of the solvent was removed under reduced pressure and then a solution of 20 g., 0.50

(20) This was prepared in essentially quantitative yield from cyclohexanone phenylhydrazone and Amberlite IR-120 resin in hot water (S. Yamada, I. Chibata, and R. Tsurui, *Pharm. Bull. Jap.*, 1, 14 (1953); *Chem. Abstr.*, 48, 12078 (1954).

(21) W. H. Perkin, Jr., *J. Chem. Soc.*, 572 (1894).

mole, of sodium hydroxide in 800 ml. water added with stirring. After warming to 85° over a period of 0.5 hr., an oily layer separated. The mixture was then cooled, and extracted with ether. The usual workup gave, after a short forerun, 31 g. of material, b.p. 100–105°/8 mm., 51% yield. A sample, redistilled for analysis, had the following constants: b.p. 123°/18 mm., n_D^{25} 1.4231; infrared: single sharp band in carbonyl region, 5.80 μ.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.99; H, 10.41.

Ethyl 3-keto-7,7-diethoxyheptanoate (IX). Sodium methoxide (Matheson Chemical Co.), 13.5 g., 0.25 mole, was placed in a dried three necked 500 ml. flask fitted with a mechanical stirrer, dropping funnel, and short Vigreux column with a fractional take-off head. The sodium methoxide was immediately covered with 200 ml. of diethyl carbonate (Eastman Kodak Co., White Label, dried by refluxing with and distillation from calcium hydride). The flask was evacuated and refilled with dry nitrogen several times through the take-off head. The ketoacetal (VIII), 38 g., 0.20 mole, in 50 ml. of diethyl carbonate was added in a few minutes. The mixture was then heated, with vigorous stirring, at a pressure of about 120 mm. at 100° for 2.5 hr., alcohol and diethyl carbonate being allowed to distill slowly. The pressure was then reduced further and most of the carbonate removed. After cooling, the thick dark red mixture was poured on a mixture of ice and water and washed from the flask with ice water, then acidified with 20 g. glacial acetic acid in 50 ml. ice water. Extraction with ether and the usual work-up gave 30 g. of material, b.p. 110–125°/0.3 mm. with some superheating, 58% yield; ultraviolet: λ_{max} 248 mμ, ϵ_{max} 850; infrared: bands at 5.75, 5.83, 6.08, and 6.14 mμ. A sample, redistilled for analysis twice, had the following characteristics: b.p. 114–125°/0.3 mm., n_D^{25} 1.4380.

Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.17; H, 9.35.

Ethyl 2-acetyl-5,5-diethoxypentanoate (X). Sodium hydride, 2.4 g., 0.10 mole, was suspended in 100 ml. of 1:1 benzene-dimethylformamide under a blanket of nitrogen. Acetoacetic ester, 16 g., 0.125 mole, in 20 ml. of the same solvent was added dropwise with cooling and stirring. The mixture was then warmed to 80° and when all the hydride had dissolved, 0.5 g. potassium iodide was added, followed by chloropropionaldehyde diethylacetal, 17 g., 0.10 mole, in 20 ml. of benzene-dimethylformamide over a period of 1 hr. The bath temperature was raised to 120° and the mixture refluxed 22 hr., then cooled, and ice water containing 5 ml. of glacial acetic acid added. Ether extraction and the usual workup afforded 21.2 g. of product, b.p. 103–106°/0.15 mm., n_D^{25} 1.4328, yield 81%. An analytical sample had the following properties: b.p. 103–105°/0.1 mm., n_D^{25} 1.4352; ultraviolet λ_{max} 241 mμ, ϵ_{max} 1200; infrared: bands at 5.74, 5.81, 6.10 μ, shoulder 6.15 μ.

Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.11; H, 9.29.

The bis-2,4-dinitrophenylhydrazone (XI) of X was prepared in the usual manner. It was a light yellow in color. A sample, recrystallized for analysis, separated as balls of microscopic needles from 95% ethanol-benzene, m.p. 154°.

Anal. Calcd. for $C_{21}H_{22}N_8O_{11}$: C, 46.15; H, 4.14. Found: C, 46.39; H, 4.00.

2-Carboethoxy-Δ²-cyclohexenone (I). The β-ketoester acetal (IX), 20 g., 0.077 mole, was dissolved in 250 ml. acetone; *p*-toluenesulfonic acid monohydrate, 150 mg., was added with stirring. The air in the 500 ml. flask was replaced with nitrogen and the stirring (magnetic) continued for 12 hr. The acetone was then removed under reduced pressure at 65° after the addition of 150–200 mg. sodium bicarbonate, until a volume of about 40 ml. remained. The mixture was filtered through Celite and further concentrated on the steam bath in a stream of nitrogen. The residue was distilled under nitrogen to give 7.4 g. of a mobile liquid, b.p. 74–76°/0.5 mm., 57%. The pot residue weighed 4.2 g. A sample was redistilled for analysis, b.p. 59°/0.1 mm, n_D^{25} 1.5051; ultraviolet: λ_{max} 232 mμ, ϵ_{max} 7800; λ_{max} 305 mμ, ϵ_{max} 2700; infrared: 5.75, 5.85, 6.10, 6.30, 13.38, and 14.42 μ.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.97; H, 6.98.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, separated as red-orange needles from ethanol–ethyl acetate, m.p. 164–165°.

Anal. Calcd. for $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63. Found: C, 51.86; H, 4.65.

Acid hydrolysis of I. 2-Carboethoxycyclohexenone, 427 mg., 2.54 mmoles, was refluxed for 1 hr. with 20 ml. of 1*N* sulfuric acid. Steam distillation gave four 40-ml. fractions, each of which were treated with 50 ml. 0.1% 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. After standing 3 hr., they were extracted with benzene to give 239 mg. of crude derivative, 47% on the basis of reagent taken, 1.85 mmoles. The relatively low yield is attributed to insufficient reagent for the first fractions of the distillate. After two recrystallizations from ethanol–ethyl acetate the derivative melted at 166–168°, mixed melting point with authentic cyclohexenone 2,4-dinitrophenylhydrazone (m.p. 167–169°) was 167–168°. The ultraviolet spectra were identical. Repetition of the hydrolysis of I and treatment of the steam distillate with excess 2,4-dinitrophenylhydrazine as above permitted the isolation of the derivative of cyclohexenone in 80% crude yield.

The catalytic reduction of I. 2-Carboethoxycyclohexenone, 465 mg., 2.77 mmoles, was hydrogenated in 20 ml. of 95% ethanol at room temperature and pressure in the presence of 250 mg. of 30% palladium-on-charcoal. Thirteen milliliters of hydrogen was absorbed in 5 min. (calculated 70 ml.) and uptake ceased. Butylidene acetoacetic ester, 306 mg., 1.66 mmoles, was then added and rapid uptake of the calculated amount of hydrogen (41 ml.) took place.

In another run, 432 mg., 2.57 mmoles of I was hydrogenated in the same manner. Ten of the calculated sixty-four milliliters were absorbed in 13 min. when the reaction ceased. The catalyst was removed by filtration and 2,4-dinitrophenylhydrazine reagent added. The crude derivative, 485 mg., 54% yield, separated. After three recrystallizations it melted at 148–151°, mixed melting point with the authentic 2,4-dinitrophenylhydrazone of 2-carboethoxycyclohexanone (m.p. 157–158°) was 151–153°. Purification was better effected by silica gel (Davison Chemical Co.) chromatography, which gave material, m.p. 158°, no depression on admixture with the authentic derivative. The ultraviolet spectra were identical.

The disproportionation of I *with palladium-on-charcoal.* 2-Carboethoxycyclohexenone, 2.0 g., 0.012 mole, was dissolved in 30 ml. of 95% ethanol and stirred overnight with 500 mg. of 30% palladium-on-charcoal. The catalyst was removed by filtration and the solution refluxed with 5 g. of potassium hydroxide in 5 ml. of water. The mixture was diluted with water, extracted with ether to remove neutral material, and acidified with concentrated hydrochloric acid. Reextraction with ether gave 0.77 g. of crude product, 94% of the calculated 0.006 mole of salicylic acid. After recrystallization from hot water and sublimation it melted at 158–159° and did not depress the melting point of an authentic specimen of salicylic acid.

6-Carboethoxy-Δ²-cyclohexenone (XIII). Sodium, 3.7 g., 0.161 mole, was dissolved in 45 ml. of absolute ethanol and the cooled solution added under nitrogen to a cold (−12°) stirred mixture of cyclohexenone, 15 g., 0.156 mole, and ethyl oxalate, 24 g., 0.165 mole at such a rate that the temperature did not rise above −5°. After the addition was complete, the mixture was allowed to stand at 5° for 15 hr. Ice and 1 equivalent of sulfuric acid were added, and the mixture, diluted with ice water, was subjected to the usual workup. Distillation gave 22 g. of a bright yellow liquid, b.p. 147–160°/10 mm., presumably mainly the glyoxalate XII. Two redistillations of this with 1 g. of powdered soft glass containing a trace of iron powder[18a] gave 7.2 g. of a light yellow liquid, b.p. 67–76°/0.3 mm. as well as about 4 g. of

unchanged glyoxalate and much tar. The former was distilled twice more for the preparation of a sample which had the following properties, b.p. 73–74°/0.3 mm., n_D^{25} 1.4806. This sample did not have a satisfactory carbon-hydrogen analysis, possibly because of contamination with unchanged glyoxalate XII. However, XIII formed a 2,4-dinitrophenylhydrazone (see below) which gave highly acceptable analytical data.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 62.04; H, 7.19.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, separated as orange-yellow needles from ethanol–ethyl acetate, m.p. 129–130°.

Anal. Calcd. for $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63. Found: C, 51.86; H, 4.66.

Butylidene acetoacetic ester. This compound was prepared in 76% yield by the method of Cope and Hoffman.[22] A carefully redistilled sample had the following characteristics: b.p. 56°/0.1 mm., n_D^{25} 1.4515. It gave no color with ferric chloride solution; ultraviolet: λ_{max} 220 mμ, ϵ_{max} 6800; infrared: bands at 5.80, 5.98, 6.11 μ, shoulder 6.20 μ. The compound formed a 2,4-dinitrophenylhydrazone, m.p. 131–133°, orange-yellow needles from ethanol.

Acknowledgment The author wishes to express his appreciation to Prof. E. E. van Tamelen for the suggestion of this problem and for much helpful advice.

MADISON, WIS.

(22) A. C. Cope and C. M. Hoffman, *J. Am. Chem. Soc.*, **63**, 3456 (1941).

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

Some Exploratory Syntheses of Benzosuberans and Tetrahydrobenzazepinones and Some Related Diazoöxides

PETER A. S. SMITH AND WILLIAM L. BERRY[1]

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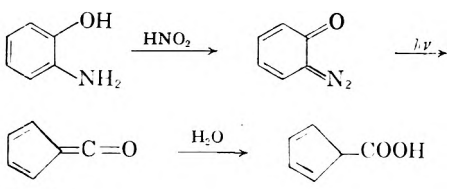
The following new diazoöxides have been investigated in exploration of the feasibility of their ring contraction as a general laboratory preparative method: benzosuberan-5-ol-2,3-diazoöxide, benzosuberan-3,2-diazoöxide, 4,5-dihydro-1-benzazepin-2(3H)-one-7,8-diazoöxide, acetophenone-3,4-diazoöxide, acetanilide-3,4-diazoöxide, benzophenone-3,4-diazoöxide, and diphenylmethane-3,4-diazoöxide. Irradiation with ultraviolet light of intensities available without unusual equipment led to mixtures of dyes presumably arising from coupling of ring-contraction products with the parent diazoöxides. Thermal rearrangement was successful for converting naphthalene-1,2-diazoöxide to indenecarboxylic acid derivatives, but similar treatment was not successful with diazoöxides derived from the benzene ring. Naphthalene-1,2-diazoöxide is reduced to β-naphthol in preparative yields by heating with benzyl alcohol or benzylamine. Several synthetic sequences leading to benzosuberan and 3,4-dihydrobenzazepinone derivatives are reported.

INTRODUCTION

In 1944 Süs reported[2] the first example of the extension to *o*-diazoöxides of the Wolff rearrangement[3] of α-diazo ketones. This process accomplishes the remarkable result of shrinking a benzene ring, as it exists in the *o*-aminophenols from which *o*-diazoöxides are prepared, to cyclopentadienecarboxylic acid derivatives. As reported by Süs and extended[4] by him and by De Jonge and Dijkstra,[5] the conversion is brought about by radiation in the near ultraviolet.



We were interested in exploring the compatibility of the benzene ring-shrinking process to compounds containing carbonyl and amide groups, particularly in cases where the benzene ring is fused to a seven-membered ring. At the same time, we were interested in adapting the reaction as a preparative procedure capable of being accomplished with ordinary equipment. As it has been reported, the reaction requires exceptionally intense ultraviolet radiation for success in synthetic applications; the lower intensities ordinarily available lead to appreciable quantities of dyes derived from coupling of yet unphotolyzed diazoöxide with the cyclopentadiene system. The work reported here consists of the synthesis and investigation of some derivatives of benzene *o*-diazoöxide, some investigations of experimental techniques for rearranging them and also naphthalene-1,2-diazoöxide, and some synthetic schemes leading to diazoöxides in the benzosuberan and 3,4-dihydrobenzazepinone series.

RESULTS AND DISCUSSION

Acetophenone-3,4-diazoöxide was prepared as a highly unstable, explosive solid by diazotizing 3-amino-4-hydroxyacetophenone and liberation of

(1) From the doctoral thesis of W.L.B., Edgar C. Britton, Fellow in Organic Chemistry, 1953–1955. Present address: American Cyanamid Co., Bound Brook, N. J.

(2) O. Süs, *Ann.*, **556**, 65 (1944).

(3) W. E. Bachmann and W. S. Struve, *Org. Reactions*, **I**, 38 (1942).

(4) O. Süs, *Ann.*, **593**, 91 (1955).

(5) J. De Jonge and R. Dijkstra, *Rec. trav. chim.*, **67**, 328 (1947).

the product with sodium carbonate. The originally extremely dark red substance exploded when heated to 96°, and showed infrared absorption characteristic of the diazoöxide structure. Deterioration was rapid, however, even on storage *in vacuo* in the dark, and a lighter red, nonexplosive substance was produced; it was not further investigated.

For the preparation of acetanilide 3,4-diazooxide, 3-nitro-4-hydroxyacetophenone was first converted to 3-nitro-4-hydroxyacetanilide by the Schmidt reaction. Reduction to 3-amino-4-hydroxyacetanilide and diazotization gave the diazoöxide as an explosive orange solid.

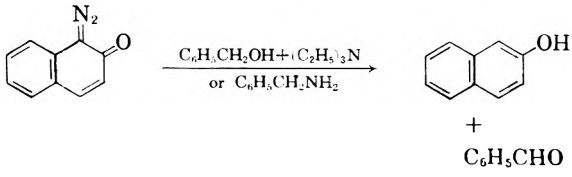
The conversion of 3-amino-4-hydroxybenzophenone to benzophenone-3,4-diazoöxide, an explosive red solid, was accomplished satisfactorily only in the presence of copper sulfate. 3-Amino-4-hydroxydiphenylmethane could not be converted to the diazoöxide in as simple a manner as the foregoing substances, but by extraction into ether as fast as the diazoöxide was liberated from the diazonium solution by the addition of sodium carbonate, it was obtained as explosive, golden flakes.

Photolyses of the foregoing diazoöxides and of naphthalene-1,2-diazoöxide were carried out near 0° in dilute, acidic aqueous solution with a lamp delivering 15.5 watts in the 380–500 mμ region, in which diazoöxide absorption bands lie.[6] These conditions are essentially those of Süs, except that our radiation source, which is near the maximum intensity obtainable with simple apparatus and compatible with cooling needs, was much less intense. Under these conditions, coupling to give dyes predominated with naphthalene-1,2-diazoöxide, and only a poor yield of indenecarboxylic acid was obtained. With the other diazoöxides, only coupling products were obtained; the addition of heavy metal salts or changing the acidity did not help. These were complex mixtures, as shown by chromatography and partial fractional crystallization, and only from benzophenone-3,4-diazoöxide could a tentatively identifiable compound be isolated.

We next turned attention to the catalytic agents effective with α-diazo ketones. The silver benzoate-triethylamine catalyst developed by Newman and Beal[7] did not cause noticeable gas evolution from naphthalene-1,2-diazoöxide, but instead converted it to a black gum. Copper powder was similarly ineffective.

There remained thermal rearrangement, for which there was the encouraging precedent of the formation of indene compounds from the pyrolysis of naphthalene-1,2-diazoöxide.[8] These substances presumably arose from the ketene formed initially, in which case it might be intercepted before undesirable reactions by pyrolyzing the diazoöxide in the presence of an amine or alcohol. Such an event was realized by dropping naphthalene-1,2-diazoöxide into aniline, *p*-toluidine, or phenol at 180°; indene-1-carboxanilide was obtained in 32% yield, the *p*-toluidide in 34%, and phenyl indene-1-carboxylate in 57% yield. Unfortunately, the analogous reaction could not be realized with the other diazoöxides studied; cyclopentadienecarboxylic acids could not be isolated, and complex mixtures of dyes similar to those resulting from photolysis were obtained. It appears that the diazo coupling reaction is a faster reaction with cyclopentadienes as contrasted to indenes, and we reluctantly conclude that the ring-shrinking rearrangement is not likely to be a useful preparative method unless exceptional facilities for high intensity radiation are available.

A potentially useful reaction was observed when thermal rearrangement of naphthalene 1,2-diazooxide was attempted in benzyl alcohol instead of phenol. Instead of an ester, β-naphthol was produced in 47% yield, accompanied by benzaldehyde. When tributylamine was also present, reaction took place spontaneously at room temperature to produce a 44% yield of β-naphthol. Benzoyl peroxide did not initiate reaction at 83°. With benzylamine alone the diazoöxide was converted to β-naphthol at either room temperature or 184° in 50–53% yields. When the benzyl alcohol reaction was tried with diphenylmethane-3,4-diazooxide or benzophenone-3,4-diazoöxide, only gums and amorphous colored solids could be isolated. It appears that the reaction might nevertheless have usefulness in the naphthalene series as an alternative when conventional deamination[9] gives unsatisfactory results.



4,5-Dihydro-1-benzazepin-2(3H)-one-7,8-diazooxide (V) was prepared from 7-hydroxy-1-tetralone (I) as outlined in Chart A, which also shows some related transformations which provide support for the assigned structures. The Schmidt reaction was used to convert I to II, followed by nitration to give III. Catalytic reduction yielded an amine (IV) with the reducing properties to be expected of an *o*-amino phenol. Diazotization was satisfactory only in strongly acidic solution, and the diazoöxide V could not be isolated from its salt without rapid decomposition.

(6) L. C. Anderson and M. Roedel, *J. Am. Chem. Soc.*, **67**, 955 (1945); J. D. C. Anderson, R. J. W. Le Fevre, and I. R. Wilson, *J. Chem. Soc.*, 2082 (1949).

(7) M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.*, **72**, 5161 (1950).

(8) L. Horner, E. Spietschka, and A. Gross, *Ann.*, **573**, 17 (1951); P. Yates and E. W. Robb, *J. Am. Chem. Soc.*, **79**, 5760 (1957).

(9) N. Kornblum, *Org. Reactions*, II, 262 (1944).

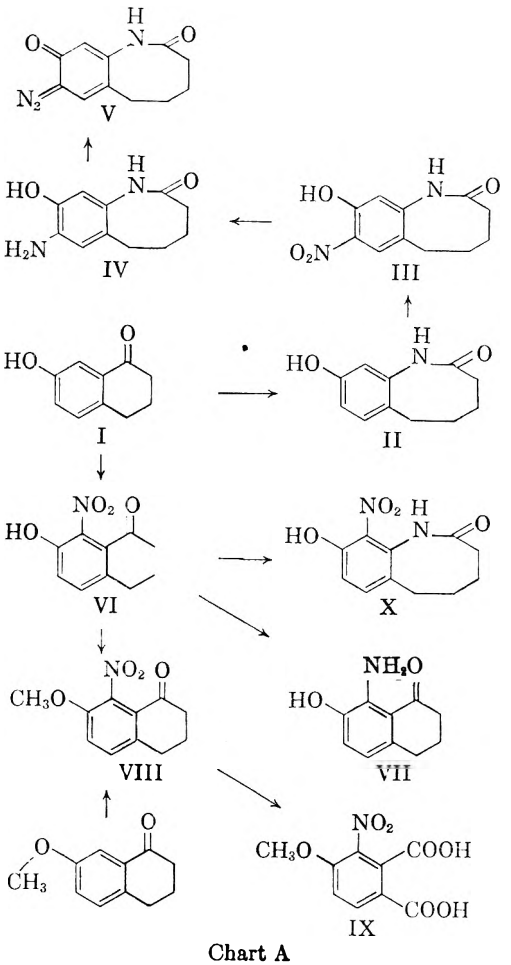


Chart A

The assignment of structure III was confirmed by the synthesis of the isomeric *o*-nitro phenol, X. Nitration of I gave a nitrophenol (VI) which was reduced to the aminophenol VII, which showed the reducing properties of an *o*-aminophenol. Methylation of VI gave the same nitromethoxytetralone (VIII) as was obtained by the direct nitration of 7-methoxy-1-tetralone; oxidation to 3-nitro-4-methoxyphthalic acid (IX) established the position of the nitro group. The Schmidt reaction converted VI into the nitrophenolic lactam X, whose melting point and infrared spectrum showed it to be distinct from its isomer, III. The methoxynitrotetralone VIII was also converted to a lactam by the Schmidt reaction; this compound is soluble without hydrolysis in 10% sodium hydroxide, as is characteristic of *o*- and *p*-nitroanilides.[10]

The phenolic lactam II was also approached from 7-nitro-1-tetralone. Although this route was abandoned in favor of that in Chart A, our initial work on it disclosed an erroneous identification in the literature. The Schmidt reaction converted 7-nitro-1-tetralone unequivocally to 8-nitro-4,5-dihydro-1-benzazepin-2-one, m.p. 220–222°. This compound had already been reported by von Braun[11] and Rawicz as the product, m.p. 225°, obtained by the direct nitration of the lactam 4,5-dihydro-1-benzazepin-2-one. We repeated this preparation and confirmed the melting point, but found that the melting point is depressed by 8-nitro-4,5-dihydro-1-benzazepin-2-one prepared from 7-nitro-1-tetralone. Accordingly, the product obtained by nitrating the lactam must be the 7-nitro isomer, not the 8-nitro as previously reported, and is thus the result of nitration *para* to the amide grouping, as is reasonable to expect as a result of normal orientation behavior.

Methanesulfonic acid was found to be the catalyst-solvent of choice for the foregoing several Schmidt reactions on phenolic acetophenones and tetralones. Trichloroacetic acid[12] in some cases gave little amide and much decomposition, perhaps as a result of the higher temperature (50°) needed. Trifluoroacetic acid, which allows operation at room temperature, gave erratic results and a product usually contaminated with polymeric material.

In view of our successful conversion of cyclic ketones to lactams by means of the Schmidt reaction, we reexamined the report by Huisgen[13] that benzosuberan-5-one gives mostly tetrazole and only 10% lactam. The experimental conditions reported were such as would favor tetrazole formation. Under the general conditions we have been using, however, benzosuberan-5-one is converted to the lactam 3,4,5,6-tetrahydro-1-benzazocin-2-one in high yield (82% as the trichloroacetic acid addition compound), and an anomaly is thus resolved.

Benzosuberan diazoöxides were first approached by a route involving the Demyanov ring expansion of appropriate tetralin derivatives, but when an alternate route proved more attractive, this one was discontinued. It was carried to the stage of 1-aminomethyl-7-methoxytetralin, prepared by the Curtius degradation of ethyl 7-methoxytetralin-1-acetate, obtained from 7-methoxy-1-tetralone by the Reformatsky reaction, dehydration, and hydrogenation. An attempt to prepare 1-aminomethyl-7-methoxy-1-tetralol for utilization in the Tiffeneau-Demyanov ring expansion failed when formation of the hydrazide from ethyl 7-methoxy-1-hydroxytetralin-1-acetate could not be accomplished without dehydration.

The successful alternative synthesis starts with benzosuberanone (XI), and is outlined in Chart B. Nitration gave 3-nitrobenzosuberan-5-one (XII), which was reduced first to the nitro alcohol (XIII) and then to the amino alcohol (XIV), which was converted to benzosuberan-3,5-diol (XV) by hy-

(10) V. Meyer and P. Jacobson, *Lehrbuch der Organischen Chemie*, Vol. II, Verlag von Veit and Co., Leipzig, 1902, p. 216; S. Kleemann, *Ber.*, 19, 334 (1886).

(11) J. von Braun and M. Rawicz, *Ber.*, 49, 799 (1916).

(12) J. R. Dice and P. A. S. Smith, *J. Org. Chem.*, 14, 179 (1949).

(13) R. Huisgen, *Ann.*, 574, 171 (1951).

drolyzing its diazonium salt. Nitration gave a nitrophenol (XVI), which was reduced to the aminophenol (XVII), diazotization of which gave the diazoöxide XVIII as an explosive, yellow-brown solid.

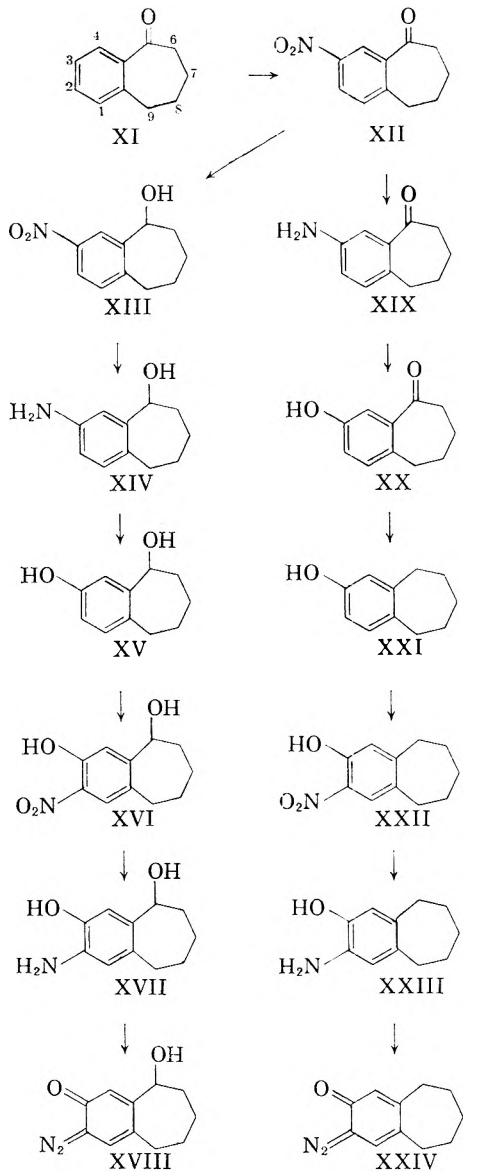


Chart B

The position of the nitro group in XII was effectively established by oxidation of XII to 4-nitrophthalic acid, which strictly shows only that the nitro group is in either the 2- or 3-position. However, the 3-position, *meta* to the carbonyl group, is the only one consistent with orientation rules, and is analogous to the positions in which α-hydrindanone[14] and α-tetralone[15] are nitrated.

The position taken by the nitro group in XVI would be either 2- or 4- according to orientation effects and the successful conversion to a diazoöxide. The vicinal position, 4-, is improbable on steric grounds; examination of scale models (Courtauld) shows that a nitro group can only be attached at the 4-position when the 5-hydroxyl group is axial, and even then crowding is sufficient to prevent the nitro group becoming coplanar with the benzene ring. The infrared spectrum of XVI in dilute solution in chloroform showed two bands in the O—H stretching region. One, at 3570 cm.$^{-1}$, is properly located for unassociated aliphatic hydroxyl. The other somewhat wider band centered on 3225 cm.$^{-1}$ is properly located for a chelated phenol and is superimposable on the band at the same position in the spectrum of *o*-nitrophenol. As effective chelation requires coplanarity of the nitro group with the benzene ring and the phenolic hydroxyl group and only the 2-position is uncrowded enough to allow this, the structural assignment of XVI follows.

The synthesis of the unsubstituted benzosuberan diazoöxide XXIV is also shown in Chart B. 3-Nitrobenzosuberanone (XII) was reduced catalytically to the amino ketone XIX, which was diazotized and hydrolyzed to obtain the phenolic ketone XX. Reduction of XX afforded an alternate route to the phenolic alcohol XV. Clemmensen reduction of XX failed, but the Huang-Minlon modification of the Wolff-Kishner reduction gave 2-hydroxybenzosuberan (XXI), which showed the same physical properties as those reported by Prelog, Ruzicka, and Metzler,[16] who prepared it by a more complex route. Nitration to XXII and reduction of XXII to the *o*-aminophenol XXIII were accomplished without complication, and diazotization of XXIII gave the benzosuberan 2,3-diazoöxide (XXIV) as an explosive light brown solid.

The position of the nitro group in XXII is inferred by analogy with 3,4-xylenol,[17] hydrindanol-5,[18] and 6-hydroxytetralin,[18,19] all of which have been shown to undergo nitration at the nonvicinal position *ortho* to the hydroxyl group. That the nitro group is *ortho* to the hydroxyl group is also shown by ultimate conversion to a diazoöxide, and by the properties of the aminophenol XXIII, which reduces Tollens' reagent instantly.

The several nitrations of phenolic compounds mentioned in the foregoing discussion were in most cases tried with conventional solvents (sulfuric or glacial acetic acids), but the results were often poor in yield and quality. With trifluoroacetic acid as the reaction medium, however, high yields of

(14) C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, **123**, 1469 (1923).

(15) G. Schroeter, *Ber.*, **63**, 1317 (1930).

(16) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1741 (1947).

(17) E. Diepolder, *Ber.*, **42**, 2916 (1909); G. D. Parks, *J. Chem. Soc.*, 2143 (1948).

(18) R. T. Arnold and R. L. Evans, *J. Am. Chem. Soc.*, **62**, 556 (1940).

(19) H. Thomas and W. Kross, *Arch. Pharm.*, **265**, 336 (1927).

clean products were uniformly obtained, and this solvent is strongly to be recommended.

The infrared spectra of Nujol mulls of the diazooxides described here are in agreement with the observations of Le Fevre, Sousa, and Werner[20]; diazo absorption was found in the region 2120–2200 cm.$^{-1}$, and that of the flanking carbonyl group at 1580–1640 cm.$^{-1}$, and was always clearly distinguishable from ketone or amide carbonyl. Splitting of the diazo absorption into two bands separated by 50 cm.$^{-1}$ was observed with benzosuberan-2,1-diazoöxide and acetanilide-3,4-diazooxide.

EXPERIMENTAL[21]

Acetophenone-3,4-diazoöxide. A solution of 1.0 g. (0.0058 mole) of 3-amino-4-hydroxyacetophenone[22] (prepared by hydrogenation of 3-nitro-4-hydroxyacetophenone[23]) in 175 ml. of 10% hydrochloric acid was diazotized at 2° with a solution of 0.42 g. (0.0061 mole) of sodium nitrite. Cold sodium carbonate solution was added until the solution was basic, and the dark brown mixture was extracted with three 100 ml. portions of chloroform. The combined dried chloroform extracts were evaporated in the dark in a stream of nitrogen, leaving 0.40 g. (62%) of reddish-black solid, m.p. 96° with explosion. The infrared spectrum obtained immediately showed absorption bands at 2150, 1700, and 1630 cm.$^{-1}$, consistent with the structure acetophenone-3,4-diazoöxide, but decomposition was rapid, even *in vacuo* in the dark. A nonexplosive red solid was formed which was not further investigated. Because of this instability, elementary analyses of this diazoöxide could not be obtained.

3-Nitro-4-hydroxyacetanilide. To a solution of 18.1 g. (0.10 mole) of 3-nitro-4-hydroxyacetophenone in 200 ml. of technical grade methanesulfonic acid at room temperature was added 11 g. (0.15 mole) of sodium azide in small portions during 4 hr. with stirring. Ten hours after the completion of the addition, the black mixture was poured on cracked ice and neutralized with sodium bicarbonate. A yellow solid, 15.0 g., m.p. 147–152°, precipitated. The filtrate was extracted with three portions of chloroform. Treatment of the extracts with charcoal and evaporation gave an additional 2.1 g.; total yield, 17.1 g. (82%). Recrystallization from aqueous alcohol gave 15.0 g., m.p. 154–156° (reported[24] m.p. 157–158°).

Acetanilide-3,4-diazoöxide. Hydrogenation of 3-nitro-4-hydroxyacetanilide in methanol solution in a Parr apparatus over Adams' Catalyst, concentration of the filtered solution and saturation with hydrogen chloride gave 3-amino-4-hydroxyacetanilide[25] as its hydrochloride, m.p. 218–221° dec., in quantitative yield. A solution of 1.5 g. (0.0074 mole) of the hydrochloride and 1.0 ml. of concd. hydrochloric acid in 100 ml. of water was diazotized at 4° with 0.75 g. (0.011 mole) of sodium nitrite, added all at once in a little water. After 15 min. the resulting dark brown solution was made basic with cold sodium carbonate solution and extracted with three 75-ml. portions of chloroform. The combined extracts were dried and evaporated to incipient crystallization, and then diluted with petroleum ether (b.p. 60–70°). On standing in a refrigerator, 0.68 g. (52%) of orange solid precipitated; m.p. 120° expl., infrared absorption at 2200, 2150, 1690, and 1640 cm.$^{-1}$

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.99; N, 23.72. Found: C, 54.35, 54.29; H, 4.20, 4.17; N, 23.47, 23.82, 23.36.

Benzophenone-3,4-diazoöxide. A suspension of 1.38 g. (0.0057 mole) of 3-nitro-4-hydroxybenzophenone[26] in 100 ml. of absolute ethanol was hydrogenated at atmospheric pressure in the presence of 0.40 g. of Adams' Catalyst. The filtered mixture was treated with charcoal and evaporated to a small volume under nitrogen and aspirator vacuum. Dilution with *ca.* 200 ml. of ether and treatment with hydrogen chloride gas precipitated a nearly colorless granular solid, 1.29 g. (91.5%), m.p. 185–196° dec. This presumed 3-amino-4-hydroxybenzophenone hydrochloride decomposed rapidly on exposure to air, and so was used at once in the next step without recrystallization or analysis.

This procedure gave the best results of the several variations tried. A solution of 0.17 g. (0.0025 mole) of sodium nitrite and 0.10 g. (0.0006 mole) of anhydrous copper sulfate in 10 ml. of water was cooled to 3° and then added all at once with shaking to a solution of 0.48 g. (0.0019 mole) of the foregoing crude amine hydrochloride in 30 ml. of water, cooled to 3°. The fluffy yellow precipitate which formed immediately was collected and dried in the dark; 0.42 g. (95%), m.p. 114° expl. Recrystallization from aqueous ethanol gave stout, lustrous red needles, m.p. 116° expl., infrared absorption at 2170, 1610, and 1580 cm.$^{-1}$

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.63; H, 3.60. Found: C, 69.56, 69.91, 69.70; H, 4.01, 3.82, 3.69.

Diphenylmethane-3,4-diazoöxide (4-Benzylbenzene-2,1-diazoöxide). 3-Nitro-4-hydroxydiphenylmethane[27] was hydrogenated at near atmospheric pressure in suspension in absolute ethanol with Adams' Catalyst. Evaporation of the filtered mixture to a small volume, dilution with ether, and treatment with hydrogen chloride precipitated the presumed 3-amino-4-hydroxydiphenylmethane hydrochloride in essentially theoretical yield. It was used at once.

The conditions used for preparing the benzophenone analog from the amine gave only tar; the following procedure was successful, however. A cold solution of 0.8 g. (0.0116 mole) of sodium nitrite in a little water was added all at once to a solution of 2.0 g. (0.0085 mole) of the foregoing crude amine hydrochloride and 4 ml. of concd. hydrochloric acid in 100 ml. of water chilled to 3°. After 15 min. the excess nitrous acid was destroyed with sulfamic acid and the solution was filtered. The cold filtrate was overlaid with *ca.* 150 ml. of ether and mechanically stirred rapidly while cold dilute sodium carbonate solution was added until the solution became basic. After 10 min. the ether layer was removed and the aqueous layer was extracted with *ca.* 100 ml. of ether. The combined ether extracts were washed once with water, dried in the dark over calcium sulfate, and treated with charcoal. The solution was then rapidly evaporated to half its volume in a stream of dry air and *ca.* 100 ml. of petroleum ether (b.p. 60–70°) was added. Further evaporation in an air stream with periodic addition of small portions of petroleum ether precipitated fragile golden flakes; 1.38 g. (72%), m.p. 72–74° dec., infrared absorption at 2200, 2130, and 1630 cm.$^{-1}$

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.72. Found: C, 74.36; H, 4.85; N, 13.33.

8-Hydroxy-4,5-dihydro-1-benzazepin-2-(3H)-one (lactam of γ-(o-amino-p-hydroxyphenyl)butyric acid) (II). To a stirred mixture of 1.0 g. (0.0057 mole) of 7-hydroxy-1-tetralone[28]

(20) R. J. W. Le Fevre, J. B. Sousa, and R. L. Werner, *J. Chem. Soc.*, 4686 (1954).

(21) Analyses by Spang Microanalytical Laboratory, Ann Arbor, or by Dr. Goji Kodama, or by Mrs. A. Griffin. Melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 instrument.

(22) M. Julia and M. Baillarge, *Bull. soc. chim. France*, 639 (1952).

(23) F. C. Brown, *J. Am. Chem. Soc.*, **68**, 872 (1946).

(24) P. Friedländer and M. Zeitlin, *Ber.*, **27**, 197 (1894).

(25) Farbwerke vorm. Meister Lucius and Bruning, D. R. P. 164,295; *Chem. Zentr.*, 1905 II, 1701.

(26) W. Blakely, W. I. Jones, and H. A. Scarborough, *J. Chem. Soc.*, 2870 (1927).

(27) E. H. Rennie, *J. Chem. Soc.*, **41**, 221 (1882).

(28) E. Mosettig and E. L. May, *J. Org. Chem.*, **5**, 533 (1940).

and 30 ml. of methanesulfonic acid cooled to 8° was added 0.55 g. (0.0085 mole) of sodium azide over 0.5 hr. with constant cooling. After an additional hour, the dark brown mixture was poured onto ice. The light brown solid which collected weighed 0.40 g., m.p. 220–225° dec. The filtrate was neutralized with sodium bicarbonate and extracted with three 20-ml. portions of ethyl acetate. Evaporation of the dried extracts left 0.41 g. of brown solid, m.p. 222–225° dec. (total yield 76%). Recrystallization from aqueous ethanol gave an analytical sample, m.p. 232–234° dec.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26. Found: C, 67.74; H, 6.32.

When the reaction was carried out in anhydrous trifluoroacetic acid at room temperature, erratic yields of up to 69% were obtained.

7-Nitro-8-hydroxy-4,5-dihydro-1-benzapin-2-(3H)-one (lactam of γ-(2-amino-3-nitro-4-hydroxyphenyl)butyric acid) (III) A solution of 0.5 g. (0.0028 mole) of II in 7 ml. of anhydrous trifluoroacetic acid was cooled to 3° and 2.0 ml. of concd. nitric acid (d. 1.42) was added drop by drop while the temperature was kept between 3 and 5°. After 30 min. standing in an ice bath, the deep red mixture was poured into 50 ml. of an ice water slurry. The light yellow solid that precipitated weighed 0.59 g. (90%); m.p. 231–237° dec. Three recrystallizations from 95% alcohol gave 0.40 g., m.p. 236–238° dec.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54. Found: C, 54.16; H, 4.80.

7-Amino-8-hydroxy-4,5-dihydro-1-benzazepin-2-(3H)-one (IV). A solution of 0.50 g. of III in 80 ml. of absolute ethanol in the presence of Adams' Catalyst absorbed the calculated amount of hydrogen in 45 min. at atmospheric pressure. Evaporation of the filtered solution in a nitrogen atmosphere and aspirator vacuum left 0.43 g. (100%) of IV, m.p. 227–228° dec. Rapid recrystallization from aqueous ethanol gave a nearly colorless, granular product, m.p. 229–230° dec., which rapidly darkened in air.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.30. Found: C, 61.98; H, 6.57.

Attempts to prepare a hydrochloride gave a solid decomposing in the range 180–210°, but it turned to gums upon attempts at further purification.

Diazotization of IV. A cold solution of 0.213 g. (0.0031 mole) of sodium nitrite and 0.13 g. (0.0008 mole) of anhydrous copper sulfate in 12 ml. of water was poured into a solution of 0.60 g. (0.0026 mole) of the crude hydrochloride of IV in 35 ml. of water. The mixture turned intense black and evolved gas vigorously. No diazoöxide could be obtained by chloroform extraction, salting out, or freezing. When the reaction was carried out at 3° in the presence of sufficient hydrochloric acid to give *p*H *ca.* 2, darkening and effervescence did not occur, and the diazoöxide (V) was presumably formed in solution; all attempts to isolate it were unsuccessful, however.

7-Hydroxy-8-nitro-1-tetralone (VI). Over a 10-min. period, 0.5 ml. (0.007 mole) of concd. nitric acid (d. 1.42) was added in 5-drop portions to a solution of 1.0 g. (0.0062 mole) of 7-hydroxy-1-tetralone in 20 ml. of trifluoroacetic acid cooled to 1°. After 30 min. the dark brown solution was poured on ice, precipitating a light tan solid, m.p. 205–210° dec., 1.18 g. (93%). An analytical sample was obtained as colorless granules by three recrystallizations from aqueous ethanol; m.p. 231° with vigorous decomposition (bath preheated to 225°).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38. Found: C, 57.88; H, 4.34.

7-Methoxy-8-nitro-1-tetralone (VIII). A. *from 7-methoxy-1-tetralone.* Over a 10-min. period, 36 drops of concd. nitric acid (d. 1.42) was added with occasional stirring to a solution of 2.5 g. of 7-methoxy-1-tetralone[28,29] in 30 ml. of trifluoroacetic acid cooled to 0°. After 0.5 hr. at 0°, the mixture was poured on ice, precipitating a fluffy, yellow solid, m.p. 110–117°, 3.0 g. (98.2%). After four recrystallizations from 95% ethanol there was obtained 1.6 g. (52%) as colorless plates, m.p. 127–128°, unchanged by further recrystallizations from benzene–petroleum ether mixture.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01. Found: C, 59.64; H, 5.12.

B. *From 7-hydroxy-8-nitro-1-tetralone* (VI). An excess of ethereal diazomethane was added to a solution of 20 mg. of VI in 40 ml. of a 1:1 mixture of ether and methanol. After 15 min. at 0–5°, the excess diazomethane was destroyed with acetic acid and the solvents were evaporated. Recrystallization of the brown residue from 95% ethanol gave colorless plates, m.p. 125–127°, undepressed when mixed with VIII prepared from 7-methoxy-1-tetralone; the infrared spectra of the two preparations were superimposable.

Oxidation of VIII *to 3-nitro-4-methoxyphthalic acid* (IX). A suspension of 3.0 g. of VIII in a solution of 19.5 g. of potassium permanganate and 3 ml. of 20% sodium hydroxide in 360 ml. of water was refluxed for 5 hr. The manganese dioxide was filtered and the yellow filtrate was acidified with hydrochloric acid and extracted with three 50-ml. portions of ethyl acetate. Evaporation of the extracts left a brown mass, *ca.* 1 g., which was dissolved in warm water. The solution was separated from some gummy material which formed on cooling; slow evaporation gave light yellow plates, m.p. 224–225° dec., after two recrystallizations from water (reported[30] m.p. 223–224° dec.).

Anal. Calcd. for $C_9H_7NO_7$: C, 44.82; H, 2.93; N, 5.81. Found: C, 44.85; H, 2.96; N, 5.79.

7-Hydroxy-8-nitro-1-benzazepin-2-(3H)-one (X). To a suspension of 0.68 g. (0.0033 mole) of VI in 50 ml. of technical grade methanesulfonic acid at room temperature was added 0.33 g. (0.005 mole) of sodium azide over a 3-hr. period. The ketone slowly dissolved and the solution had become black after 10 hr. The mixture was poured on cracked ice; small, yellow needles separated slowly on standing. The solid was collected by filtration and the mother liquors were extracted with four portions of ethyl acetate. Evaporation of the washed and dried extracts gave a further quantity of yellow solid; total wt. 0.61 g. (84%) m.p. 198–204°. Recrystallization from aqueous ethanol gave fine yellow needles, m.p. 205–207°, unaltered by further recrystallizations. It reduced Tollens' reagent in aqueous alcoholic solution instantaneously to a black precipitate of silver.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.10, 54.13; H, 4.55, 4.57; N, 12.34, 12.23.

When X was mixed with its isomer (III), the m.p. was 185–227° dec.; the infrared spectra are dissimilar.

7-Hydroxy-8-amino-1-tetralone (VII). A solution of 0.308 g. of VI in absolute alcohol was hydrogenated at 33° and 741 mm. pressure over Adams Catalyst; 116 ml. of hydrogen was absorbed in 25 min. Evaporation of the filtered solution left 0.25 g. (96%) of light brown prisms, m.p. 210–213° dec. Sublimation at reduced pressure gave a light yellow powder, m.p. 215–217°. It reduced Tollens' reagent in aqueous alcoholic solution instantaneously to a black precipitate of silver. Under the same conditions, *o*-aminophenol showed similar behavior, but *m*-aminophenol showed slow reduction only after 10 to 15 min., forming a mirror over a 3-hr. period.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.83; H, 6.38; N, 7.94.

8-Methoxy-9-nitro-4,5-dihydro-1-benzazepin-2-(3H)-one. To a solution of 1.1 g. (0.05 mole) of VIII in 65 ml. of slightly warm methanesulfonic acid was added 0.5 g. (0.075 mole) of sodium azide in portions over a 4-hr. period. After 15 hr. more at room temperature, the red-brown solution was poured into an ice water slurry, precipitating 0.9 g. of a brown powder, m.p.16 6–170°. Four recrystallizations from 95% ethanol gave pale yellow plates, m.p. 177.6–

(29) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 1951 (1934).

(30) H. King, *J. Chem. Soc.*, 1162 (1939).

178.5°, insoluble in 5% sodium bicarbonate solution, but easily soluble in 5% sodium hydroxide.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.85. Found: C, 55.85, 56.00; H, 4.94, 4.99; N, 11.89, 11.97.

Attempts to prepare the foregoing product by treating X with ethereal diazomethane led to mixtures which were not further investigated when separation proved difficult.

Schmidt reaction on benzosuberan-5-one. During a 1-hr. period, 1.0 g. (0.015 mole) of sodium azide was added in portions to a solution of 1.6 g. (0.01 mole) of benzosuberan-5-one in 15 g. of trichloroacetic acid heated to 60°. After 4.5 hr. the light yellow mixture was still evolving gas slowly. An additional 0.1 g. of sodium azide was added and the heating continued 1.5 hr. more. The pasty mass was then stirred with ice, causing the separation of a light brown oil which solidified within an hour; 2.37 g. (82%), m.p. 95–101°. Four recrystallizations from petroleum ether (b.p. 60–70°) gave fine white needles of *3,4,5,6-tetrahydro-1-benzazocin-2-one-trichloroacetic acid adduct*, m.p. 103.5–104.3°.

Anal. Calcd. for $C_{11}H_{13}NO.C_2HO_2Cl_3$: C, 46.11; H, 4.17; N, 4.14. Found: C, 46.23; H, 4.21; N, 4.21. Equivalent weight to base calcd.: 338.6. Found (phenolphthalein end point): 343.

When the adduct was shaken with dilute sodium hydroxide it liquefied and rapidly resolidified. Crystallization from benzene–petroleum ether mixture gave 3,4,5,6-tetrahydro-1-benzazocin-2-one, m.p. 153–154.5° (reported[13] m.p. 151.5–153°) with only mechanical losses.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.32; H, 7.40; N, 7.92.

8-Nitro-4,5-dihydro-1-benzazepin-2-(3H)-one. To a solution prepared from 1.4 g. (0.008 mole) of 7-nitro-1-tetralone[31] and 0.9 ml. of concd. sulfuric acid in 12 g. of molten trichloroacetic acid was added 0.8 g. (0.012 mole) of sodium azide at such a rate that the temperature was maintained at 70° without having gas evolution become stormy. After 90 min., the viscous, yellow mixture was poured on ice and then treated with 10 ml. of concd. ammonium hydroxide. The light tan solid that separated weighed 1.05 g (70%) m.p. 217–219°. It was insoluble in 10% sodium hydroxide. Two recrystallizations from ethanol (charcoal) gave an analytical sample, m.p. 220–222°. When mixed with the 7-nitro isomer obtained by nitration of 4,5-dihydro-1-benzazepin-2-(3H)-one, the melting point was strongly depressed.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89. Found: C, 58.17; H, 4.90.

When the reaction was attempted without the use of sulfuric acid, only starting material was recovered.

7-Nitro-4,5-dihydro-1-benzazepin-2-(3H)-one. To a solution of 1.5 g. of 4,5-dihydro-1-benzazepin-2-(3H)-one (homodihydrocarbostyryl[32]) in 4 ml. of concd. sulfuric acid cooled to 0° was added 1.5 ml. of concd. nitric acid (d. 1.42) over a 15-min. period while the temperature was kept below 10°. The mixture was poured onto ice, precipitating 1.81 g. (94.5%) of light tan crystals, m.p. 206–218°. Two recrystallizations from ethanol gave an analytical sample, pale yellow plates, m.p. 220–222.5° dec. (von Braun and Rawicz reported[11] m.p. 225° for the product of this reaction). The compound is slightly soluble in 10% sodium hydroxide.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89. Found: C, 58.50; H, 4.95.

7-Methoxy-3,4-dihydronaphthalene-1-acethydrazide. A solution of 2.7 g. of 7-methoxy-1-tetralone and 2.3 ml. of ethyl bromoacetate in 125 ml. of anhydrous ether was added all at once to 3.1 g. of 30-mesh granulated zinc covered with 125 ml. of benzene. A pinch of iodine was added, and the mixture was stirred and warmed; reaction became evident after 5 to 10 min. Thereafter 1.5 g. of zinc and a crystal of iodine were added after each of three 45-min. intervals. After 3 hr. further refluxing, the mixture was cooled and treated with 200 ml. of 10% hydrochloric acid. The layers were separated and the aqueous phase extracted with three 50-ml. portions of ether. The combined organic phases were washed with three 50-ml. portions of 2% ammonium hydroxide, then with water, and dried. Distillation of the solvents left a red oil, from which was distilled 2.9 g. of a light yellow oil, b.p. 150–155°/0.1 mm. This was boiled for 2-hr. with 2.0 ml. of 85% hydrazine hydrate in 30 ml. of 95% alcohol. Dilution with water and chilling gave 2.5 g. of lustrous white plates, m.p. 118–119°, unchanged by two recrystallizations from benzene–petroleum ether mixture. The same substance was obtained when the red oil was treated with hydrazine hydrate without prior distillation.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.95. Found: C, 67.11; H, 6.96.

The *N'-isopropylidene derivative* was prepared by refluxing a small portion in acetone for 30 min. The white solid produced was recrystallized from benzene–petroleum ether (b.p. 60–70°) mixture to obtain an analytical sample, m.p. 169–170°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40. Found: C, 70.16; H, 7.87.

Ethyl 7-methoxy-3,4-dihydronaphthalene-1-acetate. The Reformatsky reaction was carried out on 60 g. of 7-methoxy-1-tetralone according to the foregoing procedure, and the crude, oily product was warmed with 130 ml. of 90% formic acid for 20 min. and then allowed to stand for 8 hr. Water (200 ml.) and benzene (200 ml.) were added, the resulting layers were separated, and the aqueous phase was extracted with three 50-ml. portions of benzene. The combined organic layers were washed with dilute sodium bicarbonate solution, then water, dried, and distilled, giving 59 g. (70%) of ethyl 7-methoxy-3,4-dihydronaphthalene-1-acetate as a pale yellow oil, b.p. 140–145°/0.35–0.40 mm.; n_D^{21} 1.5557.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.23.

We were unable to obtain the undehydrated ester reported by Hoch.[33]

7-Methoxytetralin-1-acethydrazide. A solution of 22 g. of ethyl 7-methoxy-3,4-dihydronaphthalene-1-acetate in 175 ml. of 95% alcohol in the presence of 0.4 g. of Adams' Catalyst in a Parr apparatus absorbed the theoretical amount of hydrogen in 45 min. The solution was filtered and evaporated and 5.2 ml. of 99% hydrazine hydrate was added to the residue. Enough 95% alcohol was added to give a homogeneous solution, and the mixture was refluxed. After 7 days reaction was essentially complete, as indicated by the formation of a nearly clear solution when a few drops of the mixture was diluted with 5% hydrochloric acid. The entire mixture was then poured into an excess of 10% hydrochloric acid and extracted with two 100-ml. portions of ether. Neutralization of the aqueous layer with aqueous sodium acetate precipitated 12.5 g. (60%) of the hydrazide, m.p. 134–136°. Three recrystallizations from benzene–petroleum ether (b.p. 60–70°) mixture gave an analytical sample, m.p. 135.5–137.5°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.69; H, 7.78.

7-Methoxy-1-aminomethyltetrolin hydrochloride. A solution of 5.3 g. (0.023 mole) of 7-methoxytetralin-1-acethydrazide and 5 ml. of 6*N* hydrochloric acid in 40 ml. of water was covered with 150 ml. of ether, cooled to 0°, and 1.75 g. (0.025 mole) of sodium nitrite dissolved in a little water was added with stirring. After 10 min. of stirring the layers were separated and the aqueous phase was extracted with two 50-ml. portions of ether. The combined ether layers were dried (calcium chloride), and the ether was distilled off while the volume was kept roughly constant by the addition of benzene. Toluene was added until the mixture boiled at about 90°, and refluxing was continued for 3 hr.

(31) J. von Braun and H. Jungmann, *Ann.*, 451, 40 (1926).

(32) P. A. S. Smith, *J. Am. Chem. Soc.*, 70, 320 (1948).

(33) J. Hoch, *Bull. soc. chim.*, 55, 264 (1938).

To the warm solution was added all at once 30 ml. of concd. hydrochloric acid which had been saturated with hydrogen chloride at 0°. The resulting mixture was refluxed for 2 hr. (until gas evolution ceased), the layers were then separated, and the nonaqueous phase was extracted twice with water. The combined aqueous phases were decolorized with charcoal, alkalized with 10% sodium hydroxide, and extracted with three 100-ml. portions of benzene. The combined extracts were washed with water, dried (calcium sulfate) saturated with anhydrous hydrogen chloride, and diluted with 400 ml. of dry ether. Chilling overnight gave 3.35 g. off white granules, and addition of petroleum ether (b.p. 60–70°) precipitated a further 0.9 g.; total yield, 82.5%, m.p. 167–168°.

Anal. Calcd. for $C_{12}H_{18}NOCl$: C, 63.28; H, 7.97. Found: C, 63.10; H, 7.89.

3-Nitrobenzosuberan-5-one (XII). Following the procedure used by von Braun[31] for nitrating α-tetralone, 6.0 g. of benzosuberan-5-one[34] was slowly dropped into 17.5 ml. of yellow fuming nitric acid (d. 1.49) at 14° over a 10-min. period, and the mixture was then kept between −10 and −5° for 25 min. It was then poured on ice, precipitating 7.4 g. (96.2%) of a nearly white solid, m.p. 67–85°. Four recrystallizations from 95% alcohol gave 6.1 g. (82.5%) of clusters of stout colorless rods, m.p. 92–92.8°.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.19; H, 5.37.

The dinitrophenylhydrazone had m.p. 232–234°.

3-Nitrobenzosuberan-5-ol (XIII). A solution of 5.13 g. (0.025 mole) of XII in 25 ml. of anhydrous isopropyl alcohol was added to a boiling solution of 25.5 g. (0.125 mole) of aluminum isopropoxide in 100 ml. of isopropyl alcohol, following the general procedure of Truett and Moulton.[35] The light yellow suspension was refluxed for 2 hr. and then poured while warm into about 750 ml. of water and treated with 100 ml. of 10% sodium hydroxide. The precipitated solid weighed 5.0 g. (98%); m.p. 114–116°. Two recrystallizations from benzene-petroleum ether mixture gave an analytical sample, m.p. 116–116.7°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32. Found: C, 63.79; H, 6.14.

3-Aminobenzosuberan-5-ol (XIV). A solution of 3.50 g. of XIII in 100 ml. of 95% alcohol was hydrogenated at room temperature for 15 min. in the presence of 0.1 g. of Adams Catalyst. The mixture was then warmed, filtered, and diluted with *ca.* 75 ml. of water. Storage in the refrigerator precipitated slender, white needles, 2.74 g. (92%), m.p. 163–165°. Recrystallization from benzene–petroleum ether mixture gave an analytical sample, m.p. 163.7–164.4°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.79; H, 8.66.

3-Hydroxybenzosuberan-5-ol (XV). A. *From* XIV. A solution of 2.0 g. of XIV in 200 ml. of 10% sulfuric acid was cooled to 0° and diazotized with 0.03 g. of sodium nitrite dissolved in a little water. After 15 min. sulfamic acid was added to destroy excess nitrous acid, the solution was filtered, overlaid with *ca.* 150 ml. of benzene, and allowed to stand at room temperature for 18 hr. The benzene layer was then separated and the aqueous phase was extracted with three more small portions of benzene. Evaporation of the combined extracts left 1.8 g. of residue, m.p. 145–160°; recrystallization from benzene–petroleum ether mixture gave 0.66 g. (33%) of XV, m.p. 156–157°, and an insoluble residue, m.p. 250°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.20; H, 7.72.

When the diazonium solution was decomposed at 70°, the yield was only 7%; when the benzene overlay was omitted, only 17% was obtained.

B. *From 3-hydroxybenzosuberan-5-one*(XX, see below). To a solution of 2.0 g. of XX in 42 ml. of 95% alcohol and 75 ml. of water at room temperature was added 1.0 g. of sodium borohydride all at once. After 35 min., the mixture was acidified with dilute hydrochloric acid and extracted with three portions of ether. The combined extracts were washed with water, dried, treated with charcoal, and evaporated under nitrogen at the water pump to give 1.82 g. (90%) of light tan plates, m.p. 151–155°. Two recrystallizations from benzene (charcoal) gave colorless plates, m.p. 156–157°.

Anal. Found: C, 74.14; H, 7.99.

2-Nitro-3-hydroxybenzosuberan-5-ol (XVI). A solution of 0.25 ml. of concd. nitric acid in 3 ml. of glacial acetic acid was added all at once to a solution of 0.70 g. of XV in 30 ml. of glacial acetic acid cooled to 15°. After standing for 15 min. between 18 and 22°, the solution was poured on ice, precipitating 0.47 g. (53%) of light yellow needles, m.p. 140–143°. Two recrystallizations from benzene-petroleum ether mixture gave an analytical sample, m.p. 141–142.5°.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.15; H, 5.85; N, 6.31.

2-Amino-3-hydroxybenzosuberan-5-ol (XVII). A solution of 0.503 g. of XVI in 30 ml. of absolute alcohol was hydrogenated over Adams Catalyst for 20 min. at ambient pressure and temperature. The filtered solution was evaporated under nitrogen at the water pump to give 0.400 g. (92.5%) of white powder, m.p. 155–157° with evolution of water and apparent polymerization.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.26; H, 7.76.

Benzosuberan-5-ol-2,3-diazoöxide (XVIII). A solution of 252 mg. of XVII in 50 ml. of 10% hydrochloric acid was diazotized at 5° with 0.112 g. of sodium nitrite dissolved in a little water. The light yellow diazonium solution was overlaid with ether and alkalized with cold, dilute sodium carbonate solution. The ether layer was separated after shaking, and the aqueous phase was extracted with three more portions of ether. The extracts were combined, washed with water, dried in the dark, and evaporated under nitrogen at the water pump, leaving about 125 mg. of an explosive, yellow-brown solid, m.p. 92–97° dec., infrared absorption at 2120 and 1620 $cm.^{-1}$

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.70; H, 6.12.

3-Aminobenzosuberan-5-one (XIX). A suspension of 15.7 g. of 3-nitrobenzosuberan-5-one (XII) in 150 ml. of 95% alcohol was hydrogenated in a Parr apparatus at *ca.* 50 p.s.i. and 28° over 0.1 g. of Adams Catalyst. After 15 min. the resulting light yellow solution was filtered from catalyst and evaporated under nitrogen at the water pump, leaving light orange needles, m.p. 96–102°. This residue was taken up in 10% hydrochloric acid, leaving behind 220 mg. (1.2%) of bright orange material, m.p. 150–162° (*vide infra*). The solution was treated with charcoal and neutralized with sodium acetate to precipitate 14 g. of light yellow solid, m.p. 103–105°. Recrystallization from aqueous ethanol gave an analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.14; H, 7.25.

An *acetyl derivative*, prepared in the usual manner, formed colorless plates, m.p. 103–104°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 72.12; H, 6.87.

The orange by-product of the reduction kept the same long melting range in spite of recrystallizations and chromatography (alumina). Its color was destroyed by either zinc dust and acetic acid or sodium hydrosulfite. Reductive acetylation with zinc dust and acetic anhydride gave 3-acetamidobenzosuberan-5-one, m.p. 99–102°, undepressed by mixture with a sample prepared directly from the amine. The orange material is thus believed to be *3,3'-azobenzosuberan-5-one.*

(34) C. W. Muth, P. O. Steiniger, and Z. B. Papanastassion, *J. Am. Chem. Soc.*, **77**, 1008 (1955).

(35) W. L. Truett and W. N. Moulton, *J. Am. Chem. Soc.*, **73**, 5913 (1951).

Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.29, 76.34; H, 6.63; N, 7.93, 7.82.

3-Hydroxybenzosuberan-5-one (XX). A solution of 11.1 g. of XIX in 300 ml. of 10% sulfuric acid was diazotized at 8° with 4.55 g. of sodium nitrite in a little water. Sulfamic acid was added to destroy excess nitrous acid, and the mixture was filtered, poured into 800 ml. of 10% sulfuric acid, overlaid with 300 ml. of benzene, and kept at room temperature for 3 days. The layers were then separated and the aqueous phase extracted with three 150-ml. portions of benzene. The combined extracts were dried and evaporated, leaving 8.5 g. (76%) of hard, yellow needles, m.p. 96–99°. Sublimation at 97° and 0.3 mm. gave a colorless analytical sample, m.p. 99–100°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.97; H, 6.87.

2-Hydroxybenzosuberan (benzosuberan-2-ol) (XXI). A solution of 2.0 g. (0.0114 mole) of XX, 2.0 g. (0.03 mole) of potassium hydroxide and 1.2 ml. of hydrazine hydrate in 30 ml. of diethylene glycol was heated at 155° for 105 min. under a condenser equipped with an alembic take-off adapter, after which distillation was allowed to occur until the temperature had risen to 207°, and refluxing was then continued for 4 hr. The cooled solution was then poured into *ca.* 250 ml. of water, acidified with dilute hydrochloric acid, and extracted with three portions of ether. The combined extracts were washed with water, dried, treated with charcoal, and evaporated under nitrogen at the water pump, leaving an oil which solidified on standing to a light tan solid, wt. 1.70 g. (92.5%), m.p. 63–69°. Two recrystallizations from petroleum ether (b.p. 60–70°) gave 1.4 g., m.p. 70–72°, and a sample sublimed *in vacuo* had m.p. 71–72° (reported,[16] m.p. 72°).

3-Nitro-2-hydroxybenzosuberan (3-nitrobenzosuberan-2-ol) (XXII). A solution of 1.17 ml. (0.0185 mole) of concd. nitric acid. (d. 1.42) in 10 ml. of glacial acetic acid was added over 4 min. to a solution of 3.0 g. (0.0185 mole) of XXI in 30 ml. of glacial acetic acid cooled to 15° and kept below 20° during the addition and 2 min. more. The mixture was then poured into *ca.* 350 ml. of water, and the resulting suspension was extracted with three portions of ether. The combined extracts were washed with seven portions of water, dried, treated with charcoal, and evaporated under nitrogen at the water pump. The viscous, brown residue was taken up in hot 95% alcohol, from which on cooling there crystallized 1.7 g. (45%) of small, yellow plates, m.p. 83–86°. Two recrystallizations from 95% alcohol raised the m.p. to 85–87°, and vacuum sublimation gave an analytical sample, m.p. 86–86.8°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32. Found: C, 63.78; H, 6.29.

3-Amino-2-hydroxybenzosuberan (3-nitrobenzosuberan-2-ol) (XXIII). A solution of 0.50 g. of XXII in 50 ml. of ethanol was hydrogenated over Adams Catalyst at ambient temperature and pressure for 45 min. Evaporation of the filtered solution in a stream of nitrogen at the water pump left 0.414 g. (96.5%) of nearly white plates, m.p. 156–160° dec. Vacuum sublimation gave an analytical sample, m.p. 163–165° dec. It reduced Tollens' reagent instantly.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.54; H, 8.65.

Benzosuberan-3,2-diazoöxide (XXIV). A solution of 0.20 g. (1.13 mmole) of XXIII in 30 ml. of 5% hydrochloric acid was diazotized at 5° by adding all at once 0.09 g. (1.13 mmole) of sodium nitrite in 8 ml. of water. After 10 min., the solution was overlaid with 75 ml. of ether, recooled to 5°, and adjusted to *p*H 9 by the addition of dilute sodium carbonate solution. The ether layer was separated after shaking, and the aqueous phase was extracted twice more with ether. The combined extracts were washed with water, dried (calcium sulfate) in the dark, treated with charcoal, and evaporated in the dark under nitrogen at the water pump, leaving 0.107 g. (51%) of light brown solid, m.p. 96–98° with vigorous decomposition. When heated in a flame it explodes with a flash. Infrared absorption: 2150, 2100, 1625 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.89. Found: C, 70.14; H, 6.48; N, 14.81.

Irradiation experiments. The various diazoöxides were irradiated in concentrations of $5 \times 10^{-3}M$ and lower in solution in water, hydrochloric acid (concd. and dilute), water containing copper or manganese salts, aqueous acetic acid, aqueous dioxane, aqueous-alcoholic hydrochloric acid, or chloroform containing aniline. Radiation sources used were a 400-watt General Electric AH-1 mercury arc, a 250-watt General Electric RS-1 Sunlamp, a 1500-watt Sylvania tungsten lamp, a 500-watt resonance arc, and sunlight. Solutions were kept at 0–5° during irradiation. Completion was determined by a negative test for diazo coupling with aqueous-ammoniacal phloroglucinol. The time required for completion was roughly proportional to the intensity of the radiation. Deep red to black substances were invariably produced, usually containing little or nothing extractable by aqueous bicarbonate. However, in the case of naphthalene-1,2-diazoöxide we were able to extract indene-1-carboxylic acid in about 35% yields after irradiation by the AH-1 mercury arc, in qualitative confirmation of earlier reports.[2,4,5]

Irradiation of benzophenone-3,4-diazoöxide. A solution of 2.24 g. (0.01 mole) in 2 l. of 30% acetic acid was irradiated with an RS-1 Sunlamp; completion was reached in 1 hr. A black sludge, 1.9 g., m.p. 200–210°, was collected by filtration. It was dissolved in hot 5% sodium hydroxide, treated with charcoal, and reprecipitated by acid to give an apparently similar reddish-black material. Digestion of a portion with benzene gave a brilliant red solution and left only a small black residue. The extract was chromatographed on Magnesol-Celite (2:1) and eluted with 1% methanol in benzene to give five bands in various shades of red. Another portion of the material was extracted with 5% sodium bicarbonate solution, the extracts treated with charcoal, and acidified. A deep red solid, m.p. 180–184°, was obtained.

Anal. Calcd. for $C_{39}H_{28}N_2O_8$: C, 71.77; H, 4.32; N, 4.29. Found: C, 71.25, 70.64; H, 4.73, 4.86; N, 4.52, 4.43.

The portion insoluble in sodium bicarbonate was taken up in 5% sodium hydroxide solution, treated with charcoal, and reprecipitated with acid. A red solid, m.p. 210–220° dec., was obtained.

Anal. Found: C, 70.95, 70.40; H, 4.34, 4.53; N, 5.75, 6.23.

These substances were not further investigated.

Thermal rearrangement of naphthalene-1,2-diazoöxide. A. In aniline. A solution of 1.0 g. of naphthalene-1,2-diazoöxide in 10 ml. of freshly distilled aniline was plunged into an oil bath preheated to 180°. After a *ca.* 20-second induction period, gas evolution began and continued vigorously for 3 min. After 5 min. the now black mixture was cooled and poured into dilute hydrochloric acid, precipitating a red-brown amorphous mass, 1.1 g. Extraction of 0.5 g. of this for 2 hr. with hot petroleum ether (b.p. 60–70°) gave a pale red solution, which was treated with charcoal and evaporated, giving 0.2 g. (32%) of fine white needles of indene-1-carboxanilide, m.p. 158–159.5° (reported[8] m.p. 159–160°).

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.78; H, 5.43.

B. In p-toluidine. In a similar experiment with 10 ml. of molten *p*-toluidine in place of aniline, 0.95 g. of crude product was obtained, which in turn yielded 34% of *indene-1-carbox-p-toluidide*, m.p. 168–169°.

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.07. Found: C, 82.02; H, 6.16.

C. In phenol. A similar procedure was followed, with 10 ml. of molten phenol in place of aniline. The reaction mixture was poured into water, precipitating a red oil. The mixture was then extracted with three 100-ml. portions of ether, and the combined extracts were washed with 10% sodium hydroxide, then water, and dried. Evaporation of the ether at the water pump gave 0.51 g. (57%) of *phenyl indene-1-*

carboxylate as pale orange needles, m.p. 108–111°. Sublimation gave an analytical sample, m.p. 110–111°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.42; H, 5.11.

Reaction of diphenylmethane-3,4-diazoöxide with aniline and with benzyl alcohol. A solution of 0.57 g. of diphenylmethane-3,4-diazoöxide in 10 ml. of pure aniline was plunged into an oil bath preheated to 180°. When gas evolution ceased (3 min.), the reddish black mixture was poured on ice drenched with hydrochloric acid, precipitating a dark red, amorphous solid, 0.50 g., m.p. 205–215° dec. Attempted crystallization by extraction with aqueous alcohol or petroleum ether was not successful, but a benzene solution deposited a presumably purified material (deep red) when diluted with petroleum ether (b.p. 60–70°) and chilled; m.p. 220–221° dec. (bath preheated to 215°). Its identity was not apparent from its analysis, and no more was done with it.

Anal. Found: C, 77.92; H, 5.38; N, 8.39.

A similar experiment using benzyl alcohol in place of aniline gave only brown to black, intractable tars.

Reactions of benzophenone-3,4-diazoöxide with aniline, with benzyl alcohol, and with phenol. A solution of 0.7 g. of benzophenone-3,4-diazoöxide in 8 ml. of aniline was heated at 180° for 1.5 min., then cooled and poured on ice drenched with excess hydrochloric acid; a dark red solid, 0.73 g., m.p. 200–245°, was obtained. Hot petroleum ether did not dissolve this material significantly, and extraction with hot alcohol yielded only slimes from the extract. Extraction of 0.23 g. with boiling benzene for 3 hr. gave a bright red solution. Washing with dilute sodium hydroxide removed the color, but acidification then gave only 13 mg. of red solid, not further investigated. Evaporation of the benzene solution left a light solid, 0.20 g., m.p. high and indefinite.

Anal. Found: C, 74.28; H, 5.08; N, 7.57.

Similar experiments using benzyl alcohol or phenol in place of aniline gave intractable tars accompanied by lesser amounts of amorphous, red solids.

Reaction of naphthalene-1,2-diazoöxide with silver benzoate triethylamine and methanol. Following the procedure of Newman and Beal,[7] a solution of 1.0 g. of silver benzoate in 13 ml. of triethylamine was added dropwise to a solution of 0.15 g. of naphthalene-1,2-diazoöxide in 10 ml. of dry methanol. The solution darkened appreciably and a silver mirror formed; no gas evolution was observed. After 0.5 hr., the mixture was filtered and concentrated, but only viscous, black tars could be obtained.

Reaction of naphthalene-1,2-diazoöxide with benzyl alcohol. A. Alone. A solution of 1.0 g. of naphthalene-1,2-diazoöxide in 10 ml. of benzyl alcohol was plunged into an oil bath preheated to 180°. When gas evolution ceased (3 min.), the mixture was cooled, diluted with 75 ml. of ether, and extracted with three portions of 5% sodium hydroxide, then water, and dried. Acidification of the basic extracts precipitated 0.40 g. (47%) of β-naphthol, m.p. 120–121°, undepressed by mixture with an authentic sample. Treatment of the ethereal solution with 2,4-dinitrophenylhydrazine reagent gave 3.56 g. (212%) of benzaldehyde dinitrophenylhydrazone, m.p. 234–236°, undepressed by mixture with an authentic sample.

B. *In the presence of tri-n-butylamine.* A mixture of 0.5 g. of naphthalene-1,2-diazoöxide, 1 ml. of tri-*n*-butylamine and 6 ml. of benzyl alcohol began to evolve gas at room temperature within a minute of mixing. After 30 min., the mixture was worked up as described in part A, to give 0.19 g. (44%) of β-naphthol, and much benzaldehyde (as dinitrophenylhydrazone).

Reaction of naphthalene-1,2-diazoöxide with benzylamine A. With heat. A solution of 1.0 g. of naphthalene-1,2-diazoöxide in 11 ml. of dry benzylamine was placed in an oil bath preheated to 184°; gas evolution began after a short induction period and lasted for 3 min. The resulting green mixture was poured into dilute hydrochloric acid, precipitating a red oil. It was extracted with three portions of benzene, and the combined extracts were washed with water and dried. Evaporation at the water pump left a red solid, from which was obtained by three recrystallizations from benzene–petroleum ether mixture, 0.45 g. (53%) of β-naphthol, m.p. 120–122°. In another experiment, the drowned reaction mixture was treated with dinitrophenylhydrazine reagent, precipitating a large quantity of the benzaldehyde derivative (identity confirmed by mixed melting point).

B. At room temperature. A solution of 0.20 g. of naphthalene-1,2-diazoöxide in 8 ml. of benzylamine was kept at room temperature for 35 min. Work-up as before yielded 0.083 g. (50%) of β-naphthol.

Effect of benzoyl peroxide on naphthalene-1,2-diazoöxide. Two solutions were prepared, each consisting of 0.27 g. of naphthalene-1,2-diazoöxide in 7 ml. of benzyl alcohol, and to one was added *ca.* 50 mg. of benzoyl peroxide. Both solutions were then heated at 83° for 4 hr. Workup as before gave no more than traces of β-naphthol from either solution.

ANN ARBOR, MICH.

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

Reactions of Sodium Methoxide with 2-Alkyl-2,3-dichloroaldehydes. II. Methacrolein Dichloride

SCOTT SEARLES, JR., RAIMOND LIEPINS, AND HARRISON M. KASH

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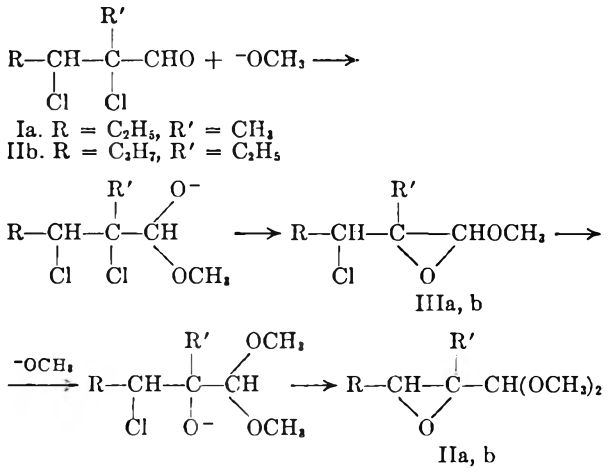
Reaction of 2,3-dichloro-2-methylpropanal (methacrolein dichloride) with sodium methoxide in methanol gave 1,1-dimethoxy-2,3-epoxy-2-methylpropane (epoxymethacrolein dimethyl acetal, IIc) in 70–80% yield, whereas in dry ether the product is 3-chloro-2-methoxy-2-methylpropanal. In methanol this aldehyde appears to form a relatively stable hemiacetal, thought to be the intermediate in the formation of IIc. The mechanism of the reaction in ether appears to be of the "borderline S_N2" type. A third type of reaction, resulting only in substitution of the β-chlorine atom, was observed when the dichloroaldehyde was treated with potassium *t*-butoxide in *t*-butyl alcohol.

It was established recently that α,β-dichloro-α-alkylaldehydes (Ia,b) reacted with two moles of methanolic sodium methoxide to form the corresponding epoxyacetals (IIa,b).[1] These products had previously been assumed to be either 2,3 di-

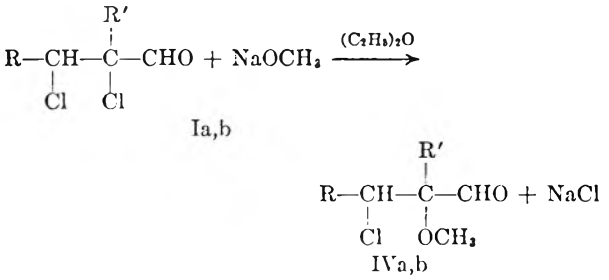
(1) S. Searles, Jr., E. K. Ives, and H. M. Kash, *J. Org. Chem.*, 22, 919 (1957).

methoxyoxetanes or 1,3-dimethoxy-1,2-epoxides.[2-4]

The isolation of a 3-chloro-1-methoxy-1,2-epoxide (IIIb) from the reaction of 2,3-dichloro-2-ethylhexanal with one mole of methanolic methoxide suggested that the reaction proceeded:



When these reactions were carried out in dry ether, instead of dry methanol, only one chlorine atom was replaced by a methoxyl group even when two to three molecular equivalents of sodium methoxide were used. The products were α-methoxy-β-chloroaldehydes (IVa,b).



These results, both in methanol and ether, were quite different from those of Stevens and coworkers on similar reactions of α-chlorocarbonyl compounds.[5-7] They had reported that in dry ether, α-chlorocarbonyl compounds reacted with sodium methoxide to form epoxyethers, while in dry methanol, α-hydroxyacetals or ketals were formed due to a further reaction with the solvent. We believe that the cause for the different course of reaction with 2,3-dichloroaldehydes is the large steric and electrical effect of the β-chlorine atom.

The simplest member of this 2,3-dichloraldehyde series, 2,3-dichloro-2-methylpropanal (Ic), has now been found to react in the same manner as the previously reported homologs, although at first, due to some experimental artifacts, an entirely different reaction was thought to have taken place. The reaction of this compound with one mole of methanolic sodium methoxide under a variety of conditions gave a product which appeared to be 3-methoxy-2-chloro-2-methylpropanal. This assignment was based on elemental and methoxyl analyses, infrared spectrum, sharp boiling point upon repeated distillations, and chemical tests for chlorine and aldehyde group.

Vapor phase chromatography of this material, however, showed it to be a mixture of two compounds. The retention time of one was identical with that of the starting compound, 2,3-dichloro-2-methylpropanal, while the retention time of the other was identical with that of the dimethoxy compound which was obtained in 70–80% yield by reaction of the dichloride with two molecular equivalents of sodium methoxide. Subsequently, these two pure compounds, boiling points only 5° apart, were isolated by fractional distillation through an efficient spinning band column, and were characterized. There was no evidence of any chloromethoxy compound.

The structure of the dimethoxy compound formed by two molecular equivalents of sodium methoxide was established by an independent synthesis as 1,1-dimethoxy-2,3-epoxy-2-methylpropane. The product of 2-methylacrolein dimethyl acetal and monoperphthalic acid reaction was identical in all physical properties, including vapor phase chromatograph, infrared spectra, and high resolution NMR spectra to that obtained in the two-mole sodium methoxide reaction. NMR spectra gave an elegant confirmation of the structure, showing the two protons of the epoxy ring to be in a different spatial environment and the two methoxyl groups also to be different, apparently because of hindered rotation.

In dry ether, 2,3-dichloro-2-methylpropanal reacted with sodium methoxide to form one product, 3-chloro-2-methoxy-2-methylpropanal (IVc), even in the presence of a large excess of sodium methoxide. The structure of this compound was established by hydrolysis, using dilute sulfuric acid to give a 78% yield of 3-chloro-2-hydroxy-2-methylpropanal (V). The chlorohydrin aldehyde (V), reacted with aqueous sodium carbonate or methanolic sodium methoxide to form impure 2,3-epoxy-2-methylpropanal. The latter was made (Payne[8]) by alkaline hydrogen peroxide epoxidation of 2-methylpropenal. Treatment of the epoxy aldehyde with dilute hydrochloric acid formed both chlorohydrin aldehydes: 3-hydroxy-2-chloro-2-methylpropanal (VI) in 11% yield and 3-chloro-2-hydroxy-2-methylpropanal (V) in 22% yield. Oxidation cleavage of V from the dilute sulfuric acid hydrolysis of the

(2) J. Lichtenberger and M. Naftali, *Bull. soc. chim.*, **4** (5), 325 (1937).

(3) A. Kirrmann and J. Lichtenberger, *Compt. rend.*, 205 1259 (1939).

(4) F. Krausz, *Ann. chim.*, **4** (12), 811 (1949).

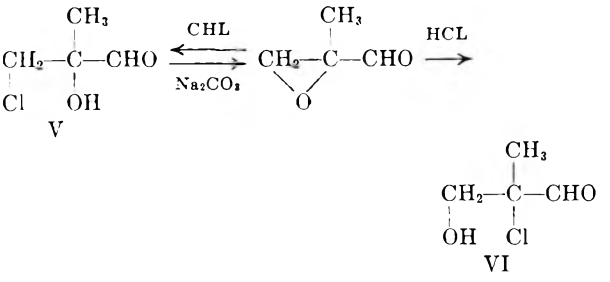
(5) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

(6) C. L. Stevens, E. Farkas, and B. Gillis, *J. Am. Chem. Soc.*, **76**, 2695 (1954).

(7) C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, **79**, 3448 (1957).

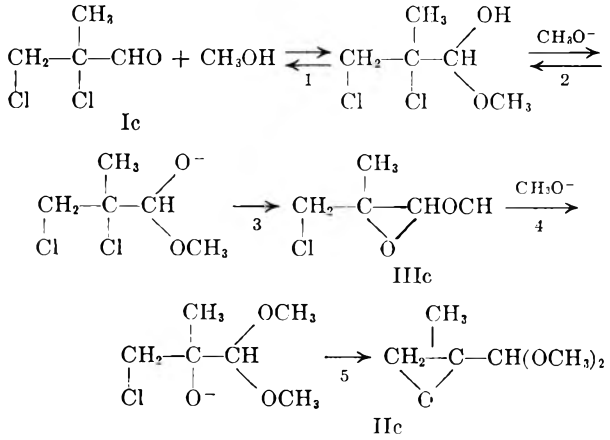
(8) G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959).

ethereal sodium methoxide reaction product with periodic acid gave chloroacetone in practically quantitative yield. The structure of VI was established by the fact it is an isomer of V with the same functional groups.



These strikingly diverse results may be due, at least in part, to reaction of the aldehyde with methanol. 2,3-Dichloro-2-methylpropanal and methanol interact rapidly without catalyst to form a relatively stable hemiacetal. This was shown by the large amount of heat evolved on mixing, the practically total loss of the carbonyl bands, the appearance of characteristic hemiacetal bands[9,10] in the infrared spectrum, and the large positive deviation in the index of refraction of the mixture,[11–13] the maximum occurring in an approximately equimolar mixture. The hemiacetal can be distilled from the mixture under reduced pressure, but on standing it dissociates to some extent. A value of 23 was determined spectrally for the equilibrium constant for formation of the hemiacetal in methanol solution at 30°.

It seems likely, therefore, that the reaction observed with methanolic sodium methoxide is actually with the hemiacetal of the dichloroaldehyde, rather than with the aldehyde directly. In this



mechanism[14] step 3, forming IIIc, must be slower than the subsequent steps, since none of IIIc could be detected in reaction with one mole of sodium methoxide in spite of the use of a variety of experimental conditions.[15] Furthermore, methanolysis of IIIc can not be occurring because the yield of IIc was less than 50% (in fact, never more than 32%) when one mole of sodium methoxide was used. If methanolysis were occurring, either the yield of IIc should have been as high with one mole of sodium methoxide as with two, or 3-chloro-2-hydroxy-2-methylpropanal dimethyl acetal should have been formed. No appreciable quantities of any materials were evident except the epoxyacetal and the starting compound.

In ether the reaction of the dichloroaldehyde itself must be observed. The lack of reaction at the carbonyl group is due, as pointed out earlier,[1] to the shielding of the latter by the β-chlorine atom, in conjunction with the α-chlorine and α-methyl group. Adjacent carbonyl groups strongly activate halogen atoms with regard to ease of substitution, apparently overcoming in this case the unfavorable tertiary nature of the α-chlorine atom. Involved here may be the so-called "borderline S_N2"[13] mechanism, in which the bond breaking is more important than bond making. The transition state in this mechanism is more polar than in the ordinary S_N2 mechanism, due to delocalization of electrons involving the carbonyl group and longer partial bonds,[16] as skillfully stated recently by Zimmerman and Ahramjian.[17] This results in the reaction's being less subject to steric hindrance at the α-carbon than is usual for S_N2 reactions.

A third possible course of reaction, substitution of the β-chlorine atom by the alkoxy group, was apparently observed in the reaction of 2,3-dichloro-2-methylpropanal with potassium *t*-butoxide in *t*-butanol. The product isolated by distillation was 3-hydroxy-2-chloro-2-methylpropanal, which could reasonably have formed from thermal pyrolysis of initially formed 3-*t*-butoxy-2-chloro-2-methylpropanal during distillation with loss of isobutylene.

The failure of this alkoxide to react at either the carbonyl group or the α-carbon atom is probably because of its bulk and the shielding about these positions. No hemiacetal formation was observed with *t*-butanol and the dichloroaldehyde. Thus, the reaction was restricted here to the relatively slow substitution process at the β-position.

(9) G. B. B. M. Sutherland, *Trans. Faraday Soc.*, **41**, 206 (1945).

(10) A. Ashdown and T. A. Kletz, *J. Chem. Soc.*, 1454 (1948).

(11) I. Lauder, *Trans. Faraday Soc.*, 44, 734 (1948).

(12) G. W. Meadows and B. deB. Darwent, *Trans. Faraday Soc.*, **48**, 1015 (1952).

(13) F. E. McKenna, H. V. Tartar, and E. C. Lingafetter, *J. Am. Chem. Soc.*, **75**, 604 (1953).

(14) A similar mechanism would apply to the homologous cases previously reported (ref. 1).

(15) Step 3 might not be the slowest one in the sequence for the reaction of homologous compounds: with 2,3-dichloro-2-ethylhexanal (Ib), the isolation of IIIb indicates that step 4 is slower. This is probably due to the bulk of the adjacent ethyl and propyl groups in that case.

(16) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

(17) H. E. Zimmerman and L. Ahramjian, Am. Chem. Soc. Meeting Abstracts, Sept. 13–18, 1959, p. 1P.

EXPERIMENTAL

2,3-Dichloro-2-methylpropanal. Dry chlorine was bubbled slowly with stirring into 250 g. of α-methylacrolein, kept at −5° to −10° and protected from light. When absorption of chlorine ceased, the material was distilled through a 6-inch glass helices-packed column to give 30 g. (12%) of recovered α-methylacrolein and 360 g. (71%) of a liquid, b.p. 72–73° (60 mm.), n_D^{20} 1.4558 (reported b.p. 147°[18]). An elemental analysis was carried out, since none was reported previously.[18]

Anal. Calcd. for $C_4H_6OCl_2$: C, 34.1; H, 4.29. Found: C, 33.9; H, 4.33.

It formed a 2,4-dinitrophenylhydrazone, m.p. 122–122.5°.

Chlorination of α-methylacrolein in chloroform solution was generally less satisfactory than without solvent because of the tendency for chlorination to proceed beyond the dichloride stage giving 2,3-dichloro-2-methylpropionyl chloride, b.p. 80–82° (60 mm.), n_D^{20} 1.4690. Treatment of the latter with methanol and distillation gave the methyl ester, b.p. 170–172°, n_D^{20} 1.4510, identical in infrared spectrum and other properties with methyl 2,3-dichloro-2-methylpropionate, b.p. 170–172°, n_D^{20} 1.4504, obtained by chlorination of authentic methyl α-methylacrylate; reported[19] for this ester b.p. 170–171° and n_D^{20} 1.4545.

Reaction of 2,3-dichloro-2-methylpropanal with one mole of methanolic sodium methoxide. 2,3-Dichloro-2-methylpropanal (254 g.) was added at a fast drop rate to a stirred solution of 39.1 g. of sodium in 1.5 l. of methanol cooled in an ice bath. The solution was warmed to room temperature and was stirred for 15 hr. The precipitated sodium chloride was removed by filtration, washed with cold methanol. Distillation gave 150 g. of a material, b.p. 61–65° (30 mm.), n_D^{20} 1.4334. This is a 65% yield of the 1:1 mixture of 2,3-dichloro-2-methylpropanal and 1,1-dimethoxy-2,3-epoxy 2-methylpropane.

Anal. Calcd. for $C_5H_9O_2Cl$: C, 43.9; H, 6.64. Found: C, 43.6; H, 6.47.

Vapor phase chromatography of this material through a 4-foot column at 100° and a flow rate of 97 ml. per min. on tricresyl phosphate produced two components, one with a retention time of 44.4 min., the other with 53.8 min. These retention times were identical with those of pure 1,1-dimethoxy-2,3-epoxy-2-methylpropane and pure 2,3-dichloro-2-methylpropanal, respectively.

Fractionation of the material through a Piros-Glover spinning band distillation column gave the first fraction as essentially pure 2,3-dichloro-2-methylpropanal, b.p. 75° (70 mm.), n_D^{20} 1.4510 and last fraction as essentially pure 1,1-dimethoxy-2,3-epoxy-2-methyl-propane, b.p. 80° (70 mm.), n_D^{20} 1.4257. The intermediate fractions appeared to be mixtures of the two components.

1,1-Dimethoxy-2,3-epoxy-2-methylpropane. To a stirred, ice-cooled solution of sodium methoxide, prepared by dissolving 13.3 g. of sodium in 500 ml. of dry methanol, was added 49 g. of 2,3-dichloro-2-methylpropanal at a slow drop rate. The solution was allowed to warm up to room temperature and was stirred for 22 hr. The precipitated sodium chloride was removed by filtration, washed with cold methanol. Distillation gave 28.5 g. (75%) of 1,1-dimethoxy-2,3-epoxy-2-methylpropane, b.p. 53–55° (20 mm.), n_D^{20} 1.4158.

Anal. Calcd. for $C_6H_{12}O_2$: C, 54.5; H, 9.15; OCH_3, 47.0. Found: C, 54.5; H, 8.73; OCH_3, 46.8.

Reaction of potassium t-butoxide with 2,3-dichloro-2-methylpropanal. A solution of potassium *t*-butoxide in butanal (6.9 g. of potassium in 500 ml. *t*-butanol) was added dropwise with stirring to a cooled solution of 2,3-dichloro-2-methylpropanal (25 g.) in 200 ml. of *t*-butanol. The solution was stirred at room temperature for 16 hr. Distillation left a semisolid residue which was extracted with chloroform and distillation of the extracts gave 4 g. (19%) of a material, b.p. 57–63° (15 mm.), n_D^{20} 1.4540. Its infrared spectrum contained absorption bands at 2.90, 5.70, 9.35, and 13.2–13.5 μ. characteristic of a primary hydroxyl, saturated aldehyde, and a carbon-chlorine bond. This material appears to be 3-hydroxy-2-chloro-2-methylpropanal, since its infrared spectrum, boiling point, and index of refraction were practically identical with those properties of the 3-hydroxy-2-chloro-2-methylpropanal obtained from the reaction of hydrochloric acid with 2,3-epoxy-2-methylpropanal, described below.

1,1-Dimethoxy-2,3-epoxy-2-methylpropane by epoxidation. α-Methylacrolein dimethyl acetal, b.p. 103–105°, n_D^{20} 1.4041 (lit.[20] b.p. 102°) was obtained in a 78% from α-methylacrolein and methyl orthoformate. Its infrared spectrum was in accord with the assigned structure, showing no carbonyl absorption but absorption bands for the terminal double bond (3.6, 6.0, and 11.3 μ). A solution of 20 g. of α-methylacrolein dimethyl acetal and approximately 0.22 mole of monoperphthalic acid[21] (as determined by titration[21] and used directly) in 450 ml. of ether was kept at 0° for 60 hr. Extraction of the etherate with 10% potassium carbonate and distillation gave 10 g. (50%) of unchanged α-methylacrolein dimethyl acetal, b.p. 100–108°, n_D^{20} 1.4087 and 2 g. (18%)[22] of 1,1-dimethoxy-2,3-epoxy-2-methylpropane, b.p. 55–57° (20 mm.), n_D^{20} 1.4140. The infrared spectrum of this material had bands at 7.50, 7.70, 11.90, and 13.0 μ, which were not present in the spectrum of the unsaturated acetal, and it was identical in all respects with that of the product from the reaction of sodium methoxide with 2,3-dichloro-2-methylpropanal.

3-Chloro-2-methoxy-2-methylpropanal. To 56 g. of anhydrous sodium methoxide in 600 ml. of anhydrous ice-cooled ether was added dropwise with stirring 66 g. of 2,3-dichloro-2-methylpropanal in 200 ml. of anhydrous ether. After being stirred at room temperature for 24 hr., the now-bright orange solution was filtered and fractionally distilled to yield 38 g. (60%) of 3-chloro-2-methoxy-2-methylpropanal, b.p. 63–64° (18 mm.), n_D^{20} 1.4323. The infrared spectrum showed a strong absorption band at 5.7 μ but no absorptions characteristic of an epoxide.

Hydrolysis of 3-chloro-2-methoxy-2-methylpropanal. 3-Chloro-2-methoxy-2-methylpropanal (20 g.) was added slowly to 100 ml. of ice-cooled 1*N* sulfuric acid solution. After being warmed on a steam bath for 3 hr. and left at room temperature for 20 hr., the light yellow solution was neutralized with a saturated solution of sodium bicarbonate, saturated with ammonium sulfate, extracted with chloroform, followed by a 55-hr. continuous ether extraction. The combined extracts were dried over magnesium sulfate and fractionally distilled giving 14 g. (78%) of 3-chloro-2-hydroxy-2-methylpropanal, b.p. 60–65° (0.8 mm.), n_D^{20} 1.4650 (immediately after distillation; a few days later it changed to n_D^{20} 1.4885 with a considerable increase in viscosity; this change may be due to dimerization, common with α-hydroxyaldehydes[23–27]).

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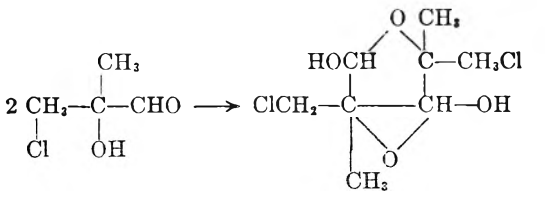

Anal. Calcd. for $C_4H_7O_2Cl$: C, 39.2; H, 5.76. Found: C, 39.6; H, 5.62.

An interesting polymorphism was observed with the *p*-nitro- and 2,3-dinitrophenylhydrazones of this compound. The 2,4-dinitrophenylhydrazone existed in two forms: m.p. 114° and 165°, while the *p*-nitrophenylhydrazone had three forms: m.p. 106°, 115°, and 129°. If the lowest melting modification is slowly heated, the other modifications may be observed in succession.

Anal. Calcd. for $C_{10}H_{11}O_5N_4Cl$: C, 39.7; H, 3.66. Found: C, 39.9; H, 3.36.

Chloroacetone. A solution of 3.2 g. of 3-chloro-2-hydroxy-2-methylpropanal in 20 ml. of hot water was cooled and added to a solution of 5.95 g. of periodic acid in 303 ml. of water, neutralized to *p*H 7.0 with sodium bicarbonate. As soon as the solutions were mixed, lacrimatory vapors were given off. After the solution was kept at room temperature for 24 hr., it was neutralized, extracted with chloroform, and the magnesium sulfate–dried extracts were fractionally distilled, giving 2.3 g. (95%) of chloroacetone, b.p. 117–119°, (lit.[28] b.p. 119°), 2,4-dinitrophenylhydrazone, m.p. 123.5–124° (lit.[29] m.p. 125°). A mixed melting point with 2,4-dinitrophenylhydrazone of acetone (both have the same melting point) gave a depression.

Alkaline hydrogen peroxide epoxidation of 2-methylpropenal. A mixture of 75.1 g. of 2-methylpropenal and 12.3 g. of 30% hydrogen peroxide was agitated and added dropwise to stirred and cooled (25–35°) aqueous sodium hydroxide, the *p*H of which was maintained at 8.0–8.5 by constant addition of 1*N* sodium hydroxide. The solution was stirred at room temperature for an additional hour, then saturated with ammonium sulfate, extracted with chloroform, and extracts were dried over magnesium sulfate and fractionally distilled to give 25 g. (27%) of anhydrous 2,3-epoxy-2-methylpropanal, b.p. 53–54° (80 mm.), n_D^{20} 1.4220 [reported[8] b.p. 52–53° (80 mm.)].

Dilute hydrochloric acid hydrolysis of 2,3-epoxy-2-methylpropanal. After adding 14.8 g. of 2,3-epoxy-2-methylpropanal to 200 ml. of 1*N* hydrochloric acid, the solution was warmed for about 3 hr. The cooled solution was neutralized with sodium bicarbonate, saturated with ammonium sulfate, and extracted with chloroform. The magnesium sulfate–dried extracts were fractionally distilled giving 2 g. (11%) of a material, b.p. 80–85° (23 mm.), n_D^{20} 1.4560 and 4 g. (22%) of 3-chloro-2-hydroxy-2-methylpropanal, b.p. 140–145° (23 mm.), n_D^{20} 1.4860, in addition to about 3 g. of a high boiling residue. The infrared spectrum of the material from the first fraction contained absorption bands at 2.90, 5.72 (strong), 7.50, 9.20, and 13.3–13.4 μ, which was very similar to that of the second fraction, bands at 2.90, 5.75 (medium), 7.25, 9.0–9.3, 9.1–10.0, and 13.3–13.4 μ, which are characteristic of a hydroxyl, a saturated carbonyl, and a carbon-chlorine bond.

The 2,4-dinitrophenylhydrazone of the material from the second fraction gave no depression with that from the ethereal sodium methoxide reaction. After several weeks of standing, this material had formed some white solid which may be the dimer mentioned earlier.

The material from the first fraction was an isomer of that from the second fraction.

Anal. Calcd. for $C_4H_7O_2Cl$: C, 39.2; H, 5.76. Found: C, 38.6; H, 5.5.

The 2,4-dinitrophenylhydrazone of the material from the first fraction had a melting point 120–121° and gave a 7–10° depression on mixture with the 2,4-dinitrophenylhydrazone of 3-chloro-2-hydroxy-2-methylpropanal obtained from the ethereal sodium methoxide reaction.

Anal. Calcd. for $C_{10}H_{11}O_5N_4O$: C, 39.7; H, 3.66; N, 18.51. Found: C, 39.8; H, 3.72; N, 18.50.

Reaction of 2,3-dichloro-2-methylpropanal with methanol. 2,3-Dichloro-2-methylpropanal (10 g.) was added to 25 g. of cooled, dry methanol. Heat was liberated as the addition was carried out. The solution was agitated at room temperature for about 2 hr. Fractional distillation gave 2.2 g. (18%) of a material, b.p. 35–38° (19 mm.). Its infrared spectrum was in accord with the assigned structure, showing no carbonyl absorption but characteristic absorption bands (9.05, 9.80, and 11.85 μ) for a hemiacetal.[9,10] Redistillation produced a material, the infrared spectrum of which contained a carbonyl absorption for a saturated aldehyde.

The refractive index of 2,3-dichloro-2-methylpropanol-methanol solutions showed maximum deviation at 45–50 mole % methanol (as shown in Table I), indicating 1:1 compound formation.

TABLE I

REFRACTIVE INDICES OF 2,3-DICHLORO-2-METHYLPROPANAL-METHANOL SOLUTIONS

Mole % CH_3OH	n_D^{20}
0.20	1.4668
0.45	1.4698
0.49	1.4697
0.55	1.4690
0.70	1.4664
0.95	1.4610

An estimation of the extent of hemiacetal formation was carried out by means of infrared spectra by measuring the area of the 5.70 μ carbonyl band and comparing with the areas in the infrared spectra of solutions of known concentration. The spectra were obtained with the double beam Perkin-Elmer Infracord, using matched cells. A solution of 50 mole % of 2,3-dichloro-2-methylpropanal in methanol had the same carbonyl absorption as a 4% solution of 2,3-dichloro-2-methylpropanal in ether, the determinations being made at 30°. This corresponds to only 4% of the free aldehyde in the former case indicating a 96% conversion to the hemiacetal. The equilibrium constant for the formation of hemiacetal, K = [hemiacetal]/[aldehyde][methanol], is 23.

Corresponding estimation of the hemiacetal formation in *t*-butyl alcohol gave 5% as the average value for the amount of aldehyde converted to hemiacetal. This might have been due to solvent effects rather than an actual hemiacetal formation.

Acknowledgment. We thank Dr. George Van Dyke Tiers and the Minnesota Mining and Manufacturing Co. for the NMR data; Dr. Robert W. Kiser for the vapor phase chromatograms; Dr. Jack Hine for a valuable discussion; and the Carbon and Carbide Chemicals Co. of South Charleston, W. Va. for a generous gift of methylacrolein.

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

Polycyclic Compounds Containing Nitrogen. III. The Diels-Alder Reaction of Nitroethylene

NATHAN L. DRAKE[1] AND CHARLOTTE M. KRAEBEL[2a,b]

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The development of a route to the morphinan and 4-dibenzo[de,g]quinoline nuclei was undertaken by way of the Diels-Alder adduct of nitroethylene with bi-1-cyclohexen-1-yl. The dodecahydro-9-nitrophenanthrene obtained was reduced catalytically to the amine, which was alkylated to give *N*-carboxymethyl-9-aminododecahydrophenanthrene. Ring closure of this amino acid should provide a convenient route to the above polycyclic compounds containing ring nitrogen.

The ozonolysis of dodecahydro-9-nitrophenanthrene gave 1-nitro-1,2-bis(2-ketocyclohexyl)ethane; the latter was partly converted to 1-keto-1,2-bis(2-ketocyclohexyl)ethane by the Nef reaction on its sodio salt. A pair of isomeric unsaturated ketones, isolated as their 2,4-dinitrophenylhydrazones, were obtained from the Nef reaction on the sodio salt of dodecahydro-9-nitrophenanthrene.

Investigation of the Diels-Alder reaction of 1-nitro-1-alkenes as dienophiles[3] has shown that the nitrocyclohexenes obtained may be converted to heterocyclic substances by way of intermediate aminocyclohexenes.

The reaction of the simplest nitro-olefin, nitroethylene, with bi-1-cyclohexen-1-yl yielded dodecahydro-9-nitrophenanthrene (Ia). This compound, as shown in Chart I, was reduced to the corresponding amine IIa. The reduction was carried out by hydrogenation with palladium on charcoal catalyst. An attempt to reduce the nitro compound using stannous chloride and hydrochloric acid gave a significantly lower yield of the amine. Similar reductions[4] are reported to fail.

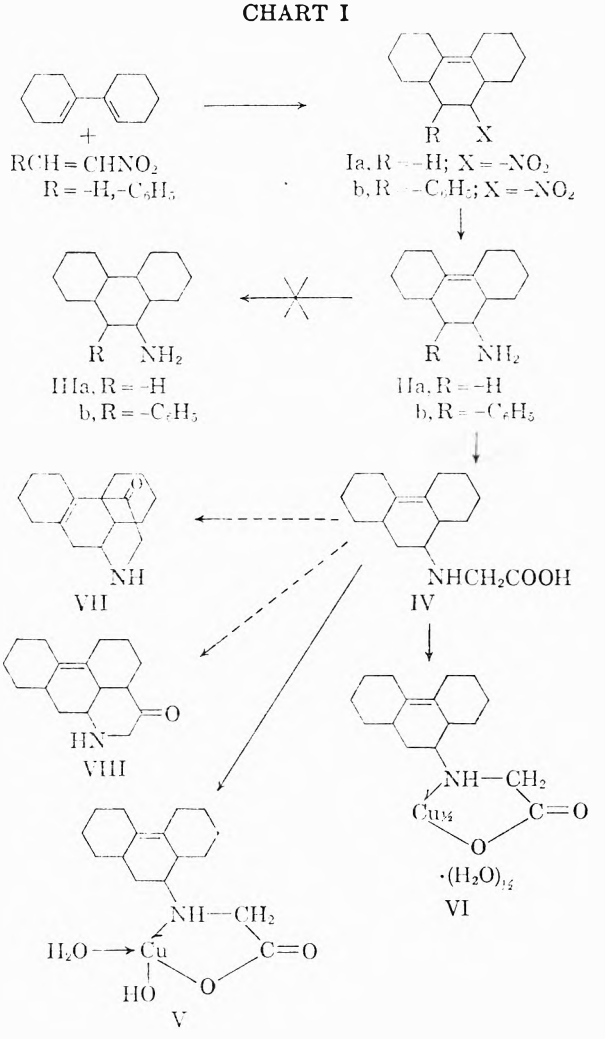
The amine IIa had an infrared spectrum characteristic of a primary amine; the spectrum had strong peaks at 3329, 3284, and 1597 cm.$^{-1}$ The amine hydrochloride showed a strong band at 1608 cm.$^{-1}$ (NH_3^- deformation, antisymmetric) and a weak band at 1300 cm.$^{-1}$ (NH_3^+ deformation, symmetric) in the infrared.[5]

An attempt to hydrogenate dodecahydro-9-aminophenanthrene (IIa) to the perhydro compound IIIa failed. The adduct Ib of β-nitrostyrene with bi-1-cyclohexen-1-yl is reported to be inert to exhaustive catalytic hydrogenation,[6] probably because of the blocking effect of the cyclohexane rings on the olefinic linkage at C_{12}–C_{13}.

The *N*-substituted amino acid IV was prepared by the reaction of dodecahydro-9-aminophenanthrene (IIa) with chloroacetic acid. Sodium hydroxide was used as the alkaline condensing agent.[7] The acid was insoluble in aqueous acids; its sodium salt was soluble.

The infrared spectrum of the compound showed

CHART I



(1) Deceased, October 13, 1959.

(2) (a) Celanese Corporation Fellow, 1958–59. From a thesis submitted by C. M. Kraebel in partial fulfillment of the requirements for the Ph.D. Degree, University of Maryland, 1959. (b) Present address: The B. F. Goodrich Company, Research Center, Brecksville, Ohio.

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no absorption above 3200 cm.$^{-1}$ and strong peaks at 1580 cm.$^{-1}$ and 1625 cm.$^{-1}$ No absorption in the region 3500–3300 cm.$^{-1}$ is shown by amino acids or their hydrochlorides; the ionic carboxyl of amino acids appears as a strong band in the region 1600–1560 cm.$^{-1}$ The probable position of the $>NH_2^+$ deformations in acids like sarcosine cannot be predicted. *dl*-Proline absorbs at 1653 cm.$^{-1}$ and sarcosine at 1625 cm.$^{-1}$, but *N*-phenylglycine does not absorb in this region.[6] It seems likely that for compound IV the peak at 1580 cm.$^{-1}$ is due to ionic carboxyl and that at 1625 cm.$^{-1}$ to the $>NH_2^+$ group.

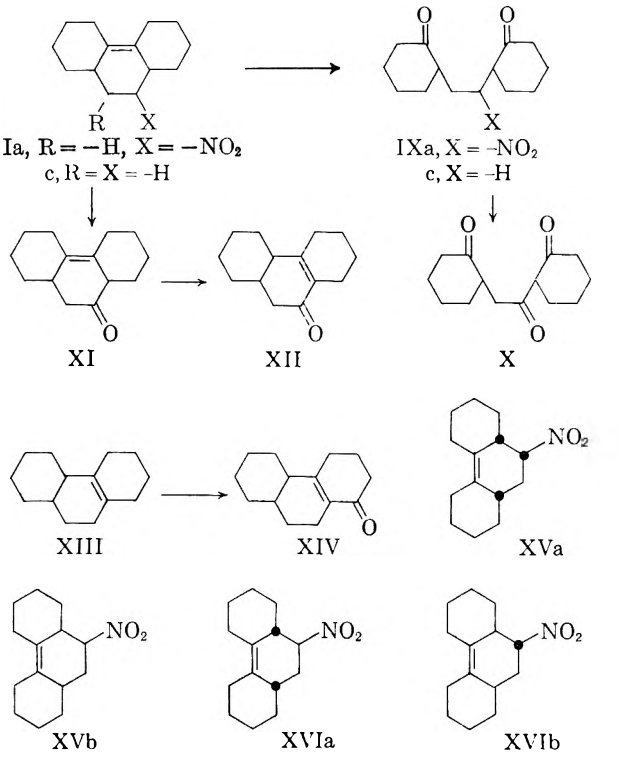
Acid IV was characterized as a copper salt,[7,8] which is thought to be the monohydrate of a basic copper salt V. A salt approaching composition VI was obtained by the reaction of the sodium salt of IV with Benedict's solution.

Conversion of acid IV to its acyl chloride, followed by a Friedel-Crafts attack on the olefinic bond[9] might provide a feasible route to the morphinan nucleus VII. Alternatively, ring closure to a hydro-4-dibenzo[de,g]quinoline VIII might be accomplished.

The position of the double bond in adduct Ia is of interest in determining the site of Friedel-Crafts reaction if compounds like VII are prepared by this route. The infrared spectrum of Ia showed a very strong peak at 1541 cm.$^{-1}$ and lesser peaks at 1379 and 1358 cm.$^{-1}$ This arrangement is found in 4-nitrocyclohexene and in nitrocyclohexane.[10] The absence of a peak in the olefinic region is probably due to molecular symmetry, since this band is weak for compounds having a symmetrically or pseudosymmetrically substituted ethylenic linkage.[5,11] The lack of olefinic band tends to exclude an α- or β-nitroolefin structure for Ia, since these compounds show enhanced olefinic absorption.[10]

The ozonolysis[12] of adduct Ia (Chart II) yielded a nitrodiketone IXa, which had strong peaks in the infrared at 1558 cm.$^{-1}$ ($-NO_2$) and 1720–30 cm.$^{-1}$ ($>C=O$). Partial conversion to triketone X was accomplished by Nef reaction on the sodio salt of IXa. The infrared spectrum of the mixture of diketone IXa and triketone X showed a strong band at 1707 cm.$^{-1}$ ($>C=O$) and weaker bands at 1542 cm.$^{-1}$ ($-NO_2$) and 1605 cm.$^{-1}$ (β-diketone).

CHART II



Diketone IXa was characterized by its bisphenylhydrazone and its bis-2,4-dinitrophenylhydrazone.

Ozonolysis of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14-dodecahydrophenanthrene (Ic) is reported to yield diketone IXc, whereas a conjugated monoketone XIV is obtained by ozonolysis of 1, 2, 3, 4, 5, 6, 7,-8, 9, 10, 11, 12-dodecahydrophenanthrene (XIII).[13]

The Nef reaction on the sodio salt of Ia yielded a pair of isomeric ketones, XI and XII, isolated as 2,4-dinitrophenylhydrazones. In each case the primary ketonic product was slightly contaminated by the other isomer. Ketone XI had a strong infrared absorption band at 1705 cm.$^{-1}$ (unconjugated $>C=O$) and weaker peaks at 1542 cm.$^{-1}$ ($-NO_2$) and 1660 cm.$^{-1}$ (conjugated $>C=O$). Its ultraviolet spectrum showed a plateau at 265–290 mμ. The yellow-orange 2,4-dinitrophenylhydrazone obtained showed a slight inflection at 260 mμ in the ultraviolet. Oil containing ketone XI was converted to the 2,4-dinitrophenylhydrazone of XII by prolonged exposure to acidic 2,4-dinitrophenylhydrazine solution.

Conjugated ketone XII was obtained by heating the Nef reaction product of Ia in an acidic medium. The infrared spectrum of XII showed a strong peak at 1660 cm.$^{-1}$ (conjugated $>C=O$) and weaker

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bands at 1545 cm.$^{-1}$ and 1707 cm.$^{-1}$ The ultraviolet spectrum showed maxima at 235 mμ (ϵ 3,880) and 280 mμ (ϵ 940). This is not inconsistent with a conjugated ketone.[14] The red 2,4-dinitrophenylhydrazone of XII had a maximum at 260 mμ (ϵ 20,400) and an inflection at 293 mμ in the ultraviolet. Conversion of 1,2-dimethyl-4-nitro-5-phenylcyclohexene to 1,6-dimethyl-4-phenylcyclohexen-3-one *via* 1,2-dimethyl-5-phenylcyclohexen-4-one has been reported.[15] For the 2,4-dinitrophenylhydrazones of certain α,β-unsaturated cyclohexenones, ultraviolet absorption maxima in the region 256–263 mμ (ϵ 15,580–16,400) are cited[15,16]; the corresponding β,γ-unsaturated cyclohexenone derivatives do not absorb in this region.

Partial regeneration of Ia from its sodio salt by addition to hydroxylamine hydrochloride solution[17] suggests inconclusively that the sodio salt of Ia does not isomerize prior to the Nef treatment.

A consideration of the stereochemistry of adduct Ia indicates that formation of two diastereoisomeric racemates (XV and XVI) is possible. Vapor-phase chromatographic analysis of the adduct indicates the presence of only one racemate. This may be explained, if both racemates were formed initially, by epimerization of the more unstable adduct *via* the aci form of the nitro group. No attempt was made to separate the racemate probably obtained.

EXPERIMENTAL

Melting points were determined in a Hershberg apparatus and are corrected; boiling points are uncorrected. The microanalyses and molecular weight determinations were performed by the Misses M. K. Gerdeman and J. Swan. Ultraviolet spectra were obtained on a Beckman DK-1 spectrophotometer with quartz cells. Infrared spectra were obtained, unless otherwise noted, in Nujol mulls on a Beckman IR-4 spectrophotometer by Mr. W. R. Feairheller, Jr. Vapor-phase chromatograms were obtained on a Model 17A Gas Chromatograph (K. and M. Scientific Glassware Co.).

2-Nitroethanol. The nitroalcohol was prepared from nitromethane and paraformaldehyde by a published method.[18]

2-Nitroethyl acetate. The acetate was prepared by sulfuric acid-catalyzed esterification with acetic anhydride.[3a] The acetate boiled at 90° (5 mm.); n_D^{27}, 1.4275.

Nitroethylene. The olefin was obtained by pyrolysis of 2-nitroethyl acetate over glass helices[19] at 350° or by the dehydration of 2-nitroethanol with phthalic anhydride.[20]

Bicyclohexyl-1,1′-diol. The bimolecular reduction of cyclohexanone with aluminum amalgam gave 28–48% yields of the desired diol.[21]

Bi-1-cyclohexen-1-yl. The diene was obtained by the dehydration of bicyclohexyl-1,1′-diol with dilute sulfuric acid,[22] potassium aluminum sulfate,[23] and phosphorus oxychloride and pyridine.[24] Only the latter procedure gave diene free of ketonic contaminants.

Dehydration of bicyclohexyl-1,1′-diol was also carried out at 350° on a column packed with 8–14 mesh activated alumina. The material obtained by this method apparently contained various isomers of the desired diene; its reactivity with β-nitrostyrene[6] and with nitroethylene was poor.

The adduct with tetracyanoethylene, described below, was made in an attempt to develop an assay method for bi-1-cyclohexen-1-yl and other dienes.

The dehydration of 10 g. of the diol with 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of benzene gave 95% of the water theoretically possible after 4 hr. of heating under reflux. The catalyst was removed by filtration and the benzene solution was washed thoroughly with cold saturated aqueous sodium carbonate. Fractional distillation of the dry benzene solution yielded no diene; the distillation residue was a viscous liquid to yellow-brown glass. Distillation over an open flame afforded two major fractions, which boiled at 340–360° ($n_D^{24.6}$, 1.5480) and 370–372° ($n_D^{24.5}$, 1.5524). Vapor-phase chromatograms run at 245–250° indicated the presence of at least seven components in each fraction.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-nitrophenanthrene (Ia). In a typical experiment, 67.5 g. (0.75 mole) of 2-nitroethanol was dehydrated with 108.1 g. (0.69 mole) of phthalic anhydride. The nitroethylene produced was collected in 15 ml. of acetic anhydride. The nitroethylene solution was added drop by drop to 38.3 g. (0.24 mole) of bi-1-cyclohexen-1-yl in a 250-ml. three-necked flask equipped with a reflux condenser, thermometer, and dropping funnel. Stirring was provided by a magnetic stirring bar; the reaction flask was purged with nitrogen before the addition of nitroethylene was begun; during the remainder of the reaction period nitrogen was swept over the condenser outlet.

During the initial stages of the olefin addition, the temperature of the reaction mixture reached 120°; the reaction was moderated by adjusting the rate of addition and by the application of external cooling. The mixture was stirred at room temperature for 24 hr. after the addition of nitroethylene was complete. The mixture, to which was added about twice its volume of 95% ethanol, was decolorized with Darco and filtered from the decolorizing charcoal. Water was added to the clear filtrate until the cloud point was reached; crystallization was induced by the addition of a seed crystal. The weight of adduct was 33.7 g. (61%). The adduct, recrystallized from aqueous ethanol, melted at 74.0–74.8°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.47; H, 9.00; N, 5.81; mol. wt., 235. Found: C, 71.40, 71.31; H, 9.07, 8.84; N, 5.81, 5.95; mol. wt. (Rast method; camphene solvent), 260, 282.

A sample sublimed at the temperature of boiling acetone under 1.5 mm. pressure showed peaks at 1541 cm.$^{-1}$, 1379 cm.$^{-1}$, and 1358 cm.$^{-1}$ in the infrared (potassium bromide pellet); no peak was present in the 1600 cm.$^{-1}$ region.

Vapor-phase chromatograms run at 260° and 280° (bromobenzene solvent) indicated that the adduct was one substance (or racemate) by the appearance of only one peak.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9,9,10,10-tetracyanophenanthrene. A solution of 0.40 g. (0.0025 mole) of bi-1-cyclohexen-1-yl and 0.32 g. (0.0025 mole) of tetracyanoethylene[25a,b] in 5 ml. of benzene was allowed to stand at room temperature for 2 days. The olefin produced a green

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complex in the presence of diene and solvent. The color faded to yellow-orange after one day; it did not change further. Removal of the solvent yielded a brown mass which was recrystallized twice from aqueous ethanol. The yield was 0.55 g. (76%) of adduct. Further recrystallizations improved the color of the pale brown solid and gave a product melting at 146.3–148.8°.

Anal. Calcd. for $C_{14}H_{18}N_4$: C, 74.44; H, 6.25. Found: C, 74.81, 74.87; H, 6.34, 6.12.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-aminophenanthrene (IIa).

(a) *Catalytic hydrogenation.* A solution of 10.0 g. of dodecahydro-9-nitrophenanthrene in 100 ml. of 95% ethanol was placed in a 500-ml. pressure bottle. To this was added 4 g. of 10% palladium on charcoal catalyst (Fisher catalyst; lot 4452). The reduction was conducted in a Parr hydrogenation apparatus with an initial hydrogen pressure of 50 p.s.i. At the end of 13 hr., 90% of the 3 moles of hydrogen needed to reduce the nitro group had been absorbed.

The suspension of amine was warmed to dissolve the amine, the solution of which was removed by filtration from the catalyst. The catalyst was washed three times with hot 95% ethanol. The amine (2.63 g.; 30%) was recovered from the combined filtrate and washings by removal of most of the solvent under reduced pressure. An additional 4.87 g. (47%) of amine hydrochloride was recovered from the amine mother liquors by the addition of concd. hydrochloric acid to them. The hydrochloride, washed once with 1:4 aqueous hydrochloric acid and four times with ether, decomposed at 271.8–272.3°.

Anal. Calcd. for $C_{14}H_{24}ClN$: C, 69.55; H, 10.00. Found: C, 69.24, 69.52; H, 9.80, 9.87.

The *benzoyl derivative*, prepared by the Schotten-Baumann procedure, melted at 218.4–219.2° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{21}H_{27}NO$: C, 81.51; H, 8.80. Found: C, 81.83, 81.68; H, 8.95, 8.82.

The infrared spectrum of the amine[26] had strong peaks at 3329 cm.$^{-1}$, 3284 cm.$^{-1}$, and 1597 cm.$^{-1}$ The amine hydrochloride showed no absorption above 3000 cm.$^{-1}$; there was absorption at 1608 cm.$^{-1}$ (strong) and 1300 cm.$^{-1}$ (weak).

(b) *Exhaustive hydrogenation.* A solution of 2.0 g. of dodecahydro-9-nitrophenanthrene in 100 ml. of 95% ethanol was shaken with 0.4 g. of 10% palladium on charcoal catalyst (Matheson catalyst; lot 311373) in the Parr apparatus for 5 hr., at the end of which the amount of hydrogen necessary to reduce the nitro group to the amine had been taken up. No further hydrogen was absorbed during 61 hr. more of shaking in the hydrogenation apparatus.

(c) *Stannous chloride reduction.* A solution of 7.5 g. (0.0322 mole) of stannous chloride dihydrate[4] in 15 ml. of concd. hydrochloric acid was warmed on a steam bath prior to the addition of a solution of 2.5 g. (0.0105 mole) of dodecahydro-9-nitrophenanthrene in 15 ml. of ethanol. The mixture was heated under reflux until all of the nitro compound had redissolved; 3 hr. of heating were required. The ethanol was removed from the solution under reduced pressure.

The precipitated double salt, after removal by filtration, was suspended in ether and washed repeatedly with 5% sodium carbonate solution. The ether extracts of the amine were washed once with potassium carbonate and three times with water, and then dried over magnesium sulfate. The oil remaining after removal of the ether from the dried extracts was suspended in 15 ml. of water; the addition of 10 ml. of concd. hydrochloric acid resulted in the precipitation of 0.26 g. (13%) of amine hydrochloride.

N-Carboxymethyl-1,2,3,4,5,6,7,8,9,10,11,14-dodecahydro-9-aminophenanthrene (IV). A suspension of 4.90 g. (0.024 mole) of dodecahydro-9-aminophenanthrene, 0.96 g. (0.024 mole) of sodium hydroxide, and 2.28 g. (0.024 mole) of chloroacetic acid in 25 ml. of water was heated on a steam bath for 18 hr. To the hot mixture was added an additional 0.96 g. of sodium hydroxide.

The cooled alkaline solution was extracted three times with ether; aqueous hydrochloric acid was added to these extracts for the recovery of 2.08 g. (36%) of the amine hydrochloride.

The alkaline solution of amino acid was heated and filtered hot; the acid was precipitated by the addition of 1:1 hydrochloric acid to the clear filtrate (to *p*H 6). The amino acid (2.05 g.; 49% based on unrecovered amine) was separated by filtration from the resulting gelatinous mass. It was reprecipitated by way of its sodium salt to give material which decomposed at 225.7–226.5°.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.57; N, 5.32. Found: C, 72.73, 72.84; H, 9.50, 9.40; N, 5.65, 5.85. Its infrared spectrum showed no band above 3200 cm.$^{-1}$; strong peaks occurred at 1625 cm.$^{-1}$ and 1580 cm.$^{-1}$

Copper salt (V). A solution of 0.25 g. (0.001 mole) of *N*-carboxymethyldodecahydro-9-aminophenanthrene in 10 ml. of 0.1*N* sodium hydroxide was added to a solution of 0.25 g. (0.001 mole) of copper sulfate pentahydrate[8] in 5 ml. of water. The resulting blue precipitate was removed by filtration and washed with 125 ml. of hot water. The solid melted at 186.7–187.7°.

About 100 mg. of this solid was suspended in 5 ml. of water containing 3 ml. of ammonium hydroxide. After digestion on a steam bath for several hours, the solid was blue-grey in color and decomposed from 187.0 to 195.0°. The analytical sample was dried under 0.4 mm. pressure at the temperature of refluxing xylene.

Anal. Calcd. for $C_{14}H_{21}NHCH_2COOCu(OH).H_2O$ = $C_{16}H_{27}CuNO_4$: C, 53.25; H, 7.54; N, 3.88; Cu, 17.61. Found: C, 53.53, 53.72; H, 7.69, 7.52; N, 3.93; Cu (as residual CuO), 18.05, 17.85.

An attempt to remove water of hydration by heating 25 mg. of the salt overnight under 0.2 mm. pressure at the temperature of refluxing cymene changed the color of the salt to grey; the sample decomposed at 190–200°.

Anal. Calcd. for $C_{16}H_{25}CuNO_3$: C, 56.07; H, 7.35; N, 4.09; Cu 18.54. Found: C, 54.12, H, 7.62; Cu, 20.56.

Copper salt (VI). A solution of 0.25 g. of the amino acid in 5 ml. of 0.24*N* sodium hydroxide was added to 5 ml. of Benedict's solution. A blue-grey salt, decomposing at 180–181°, was isolated in small yield. A blank yielded neither turbidity nor precipitate.

Anal. Calcd. for $(C_{14}H_{21}NHCH_2COO)_2Cu$=$C_{32}H_{48}CuN_2O_4$: C, 65.33; H, 8.22; Cu, 10.80. Calc. for $(C_{14}H_{21}NHCH_2COO)_2$-$Cu.H_2O$=$C_{32}H_{50}CuN_2O_5$: C, 63.37; H, 8.31; Cu, 10.49. Found: C, 63.13, 63.31; H, 8.63, 8.89; Cu, 11.49, 11.35.

1-Nitro-1,2-bis(2-ketocyclohexyl)ethane (IXa). The ozone generator employed was substantially that described in the literature.[27] A solution of 2.0 g. of dodecahydro-9-nitrophenanthrene in 100 ml. of dry ethyl acetate was exposed to a stream of oxygen containing ozone for slightly longer than the time required to complete the ozonization. The reaction vessel was immersed in an ice-salt water bath. Ozone not absorbed by the compound was allowed to pass through 2% potassium iodide solution; the liberated iodine was titrated with standard potassium thiosulfate.

The ozonide solution was transferred to a 500-ml. three-necked flask fitted with dropping funnel, reflux condenser, and mechanical stirring.[12] During the drop by drop addition of 100 ml. of water, the mixture was cooled in an ice bath. At the end of the addition, the mixture was allowed to warm to room temperature. The ethyl acetate was removed by distillation. The product, recrystallized from aqueous acetone, weighed 2.01 g. (89%) and melted at 107.5–108.1°. It was stable on storage.

(26) This spectrum was obtained on a Beckman IR-3 spectrophotometer with the assistance of Dr. H. W. Schamp, Jr., and Dr. W. G. Maisch of the Institute for Molecular Physics.

(27) L. Smith, F. Greenwood, and O. Hurdick, *Org. Syntheses*, Coll. Vol. III, 673 (1955).

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.11, 63.35: H, 8.33, 8.18; N, 4.08; 3.95 (Dumas); N, 5.64, 5.55 (Kjeldahl). The infrared spectrum showed strong peaks at 1558 cm.$^{-1}$ and 1720–30 cm.$^{-1}$; lesser peaks appeared at 1340 cm.$^{-1}$ and 1137 cm.$^{-1}$

The *bisphenylhydrazone*, prepared in the usual manner,[28] melted at 151.8–154.8° after thorough washing with 95% ethanol.

Anal. Calcd. for $C_{26}H_{33}N_5O_2$: C, 69.76; H, 7.43. Found: C, 69.41, 69.51; H, 7.37, 7.52.

The *bis-2,4-dinitrophenylhydrazone* was prepared by allowing 0.05 g. of the ketone to react with 5.4 ml. of 2,4-dinitrophenylhydrazine solution (5% sulfuric acid in ethanol; 66 ml. contain 1 g. of 2,4-dinitrophenylhydrazine) at room temperature for 18 hours. The red-orange solid, washed three times with cold 95% ethanol, melted at 117.5–119.5°.

Anal. Calcd. for $C_{26}H_{29}N_9O_{10}$: C, 49.74; H, 4.66. Found: C, 50.12. 50.20; H, 4.78, 5.06.

1-Keto-1,2-bis(2-ketocyclohexyl)ethane (X). A suspension of 1.0 g. (0.0038 mole) of 1-nitro-1,2-bis(2-ketocyclohexyl)-ethane (IXa) in 20 ml. of absolute ethanol was cooled under a nitrogen atmosphere. To the magnetically stirred suspension was added over a period of 30 min. a solution resulting from the reaction of 0.15 g. (0.0075 mole) of sodium with 15 ml. of absolute ethanol.[15] The resulting yellow sodio-salt solution was stirred for 1 hr. with cooling under the nitrogen atmosphere.

The cold sodio-salt solution was added, over a period of 30 min., to a chilled solution of 0.5 ml. (0.008 mole) of concd. hydrochloric acid in 5 ml. of water and 4 ml. of ethanol. Stirring of the yellow solution was continued for 1 hr., after which 50 ml. of water was added. The organic material was recovered by four extractions with 35-ml. portions of ether. The ether extracts were washed twice with 5% sodium carbonate solution and four times with water. The residual yellow oil obtained from the dried ether extracts could not be crystallized. The infrared spectrum of the oil showed a very strong carbonyl band at 1707 cm.$^{-1}$, a less strong band at 1542 cm.$^{-1}$, and a weak band at 1605 cm.$^{-1}$

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-ketophenanthrene (XI). The same procedure[15] used above to obtain triketone X was followed, using 2.0 g. of dodecahydro-9-nitrophenanthrene (Ia). The ether was removed from the dry extracts without heat; a stream of nitrogen aided the process. The infrared spectrum of the residual oil had strong bands at 1705 cm.$^{-1}$ and 1542 cm.$^{-1}$; there was a weak band at 1660 cm.$^{-1}$ An ultraviolet spectrum (in iso-octane) showed a plateau at 265–290 mμ (ε 147).

Reaction of some of the ethereal extracts with chilled 2,4-dinitrophenylhydrazine solution for 20 min. at 0° produced a yellow-orange precipitate which was removed by filtration and washed once with 5% potassium carbonate solution and three times with water.[16] This *yellow 2,4-dinitrophenylhydrazone* melted at 158.0–158.6° after recrystallization from ethyl acetate and ethanol.

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29. Found: C, 62.16, 62.40; H, 6.27, 6.02. The ultraviolet spectrum (in chloroform) had a slight inflection at 260 mμ.

A red 2,4-dinitrophenylhydrazone, identical with that obtained below, was isolated by allowing the ketonic oil to react with acidic 2,4-dinitrophenylhydrazine solution at room temperature for several hours.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-9-ketophenanthrene (XII). A solution of 2.5 g. (0.01 mole) of dodecahydro-9-nitrophenanthrene and 1 g. (0.025 mole) of sodium hydroxide in 40 ml. of ethanol was cooled for 30 min.[29] The yellow solution was poured rapidly into 70 ml. of cold 1:6 hydrochloric acid. The resulting mixture was stirred with cooling for 1.5 hr.; it was allowed to warm to room temperature overnight.

The organic material was extracted from the solution with ether; the ether was removed from the dry extracts by heating on a steam bath. The residual brown oil could not be crystallized; its infrared spectrum had a strong band at 1660 cm.$^{-1}$ and weak peaks at 1707 and 1545 cm.$^{-1}$ Its ultraviolet spectrum (in isooctane) showed maxima at 235 mμ (ε 3,880) and 280 mμ (ε 940).

A *brick-red 2,4-dinitrophenylhydrazone*, melting at 233.5–234.1° after recrystallization from ethyl acetate and ethanol (1:1), was isolated.

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29. Found: C, 62.37, 62.33; H, 6.17, 6.44. Its chloroform solution showed an inflection at 293 mμ and a maximum at 260 mμ (ε 20,400) in the ultraviolet.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-nitrophenanthrene (Ia) from its sodio salt. Sodio salt was prepared from 2.0 g. of dodecahydro-9-nitrophenanthrene (Ia) by reaction with ethanolic sodium ethoxide at 0° under a nitrogen atmosphere. To the sodio-salt solution was added over a period of 20 min. a chilled solution of 1.25 g. (0.018 mole) of hydroxylamine hydrochloride[17] in 25 ml. of water. The mixture was stirred with cooling.

The weight of recovered product (from aqueous ethanol) was 0.82 g. (41%); it was identical with the adduct in melting point, mixed melting point, and infrared spectrum.

COLLEGE PARK, MD.

(28) R. Shriner and R. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 1948 (3rd ed.), p. 116.

(29) A. B. Ross, Ph.D. thesis, University of Maryland, 1957.

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

A Study of the Alkylation of β,β,β-Trialkylpropionitriles

NORMAN RABJOHN AND P. R. STAPP[1]

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A study has been made of the alkylation of β,β,β-trialkylpropionitriles (I) by means of alkyl halides and sodamide. It has been found that α-alkylated nitriles (II), *N*-α-dialkyl substituted ketenimines (III) and α,α-dialkylated nitriles (IV) are formed in varying proportions depending upon conditions.

In view of the recent report[2] of the isolation of ketenimines from the alkylation of dialkylacetonitriles, we wish to describe our results on the alkylation of β,β,β-trialkylpropionitriles (I) which confirm and

(1) Phillips Petroleum Fellow, 1959–60.

(2) M. S. Newman, T. Fukunaga, and T. Miwa, *J. Am. Chem. Soc.*, 82, 873 (1960).

TABLE I

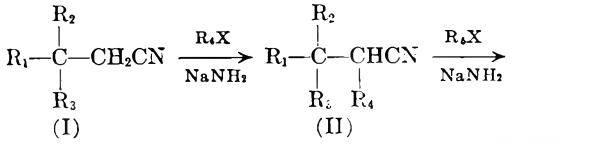
ALKYLATION OF 3,3-DIPROPYLHEPTANONITRILE WITH *n*-BUTYL BROMIDE IN VARIOUS SOLVENTS

Solvent	Moles Halide[a] /Moles Nitrile	Reflux Time, Hr.	% Yield of Alkylated Product, IIa + IIIa + IVa	Composition of Alkylated Product, Weight %		
				IIa	IIIa	IVa
Liquid ammonia	1.1	3	89	94	6.0	Trace
Benzene	3.0	48	93	70	9.6	19.9
Benzene	3.0	24	14	100	Trace	0
Benzene	1.1	48	71	98	1.6	0
Ether	1.1	48	84	96	4.3	0
Ether	1.1	24	85	96	4.2	0
Toluene	1.1	24	57	78	22[b]	0
Tetrahydrofuran	1.1	24	23	84	16[c]	0

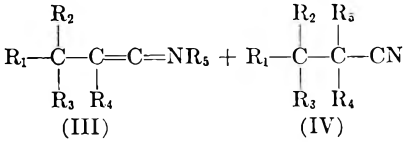
[a] Equimolar amounts of alkyl halide and sodamide were employed in each experiment. [b] Determined by titration with standard bromine solution. [c] The percentage ketenimine as determined by titration with standard bromine solution was 15%.

supplement the work of Newman and his associates.

Preliminary experiments on the alkylation of several β,β,β-trialkylpropionitriles (I), by means of alkyl halides and commercial sodamide in varying proportions and in different solvents, led to α-alkylated nitriles (II) in poor yields, and/or inseparable mixtures of II, ketenimines (III), α,α-dialkylated nitriles (IV) and unidentified by-



(I) (II)



(III) (IV)

Ia = Ib = Ic

Ia–IVa

$R_1 = R_4 = R_5 = n\text{-}C_4H_9$
$R_2 = R_3 = n\text{-}C_3H_7$

IIb–IVb

$R_1 = n\text{-}C_4H_9$
$R_2 = R_3 = n\text{-}C_3H_7$
$R_4 = R_5 = n\text{-}C_8H_{17}$

IIc–IVc

$R_1 = n\text{-}C_4H_9$
$R_2 = R_3 = n\text{-}C_3H_7$
$R_4 = R_5 = i\text{-}C_4H_9$

products with infrared absorptions at 6.2 μ, which were probably amidines.[3] The presence of ketenimines was inferred on the basis of a strong absorption band at 5.0 μ in the spectra of the reaction mixtures.[4] In addition, hydrolysis of the mixtures caused the disappearance of the band at 5.0 μ with the appearance of bands at 3.0, 6.1, and 6.5 μ, which are characteristic of *N*-alkylamides[5]; however, the amides could not be isolated in a pure state. The use of a large excess of sodamide and alkyl halide, as well as higher reaction temperatures, increased significantly the amount of the unidentified by-products. Attempts at preforming the carbanion from the nitrile by heating a mixture of the latter with sodamide in the solvent, before adding the alkyl halide, apparently resulted also in increased amidine formation with no noticeable increase in yield of alkylated materials.

In an effort to obtain higher yields of alkylated products, a systematic investigation was undertaken of the alkylation of 3,3-dipropylheptanonitrile (Ia) with *n*-butyl bromide in a number of solvents. Relatively mild conditions were employed, as compared with those in the preliminary study, and the products were analyzed by gas chromatography. Mixtures of unchanged starting material (Ia), 2-butyl-3,3-dipropylheptanonitrile (IIa), the ketenimine, 5-aza-7-butyl-8,8-dipropyl-5,6-dodecadiene (IIIa) and 2,2-dibutyl-3,3-dipropylheptanonitrile (IVa) were obtained as summarized in Table I. No amidine formation was observed under these conditions.

It appears that when dialkylation occurred, IIIa was formed almost to the exclusion of IVa in most cases. The relative ease of alkylation of Ia in ether as compared with the higher boiling solvents was of interest also. Since alkylation in liquid ammonia gave results comparable to commercial sodamide in ether, further studies were carried out with the latter system as a matter of convenience.

The structure of IIIa was determined by hydrolysis of the mixture from Run 7 and removal of IIa by distillation. The residual *N*,2-dibutyl-3,3-dipropylheptanamide was shown to be identical with a sample of the amide prepared from 2-butyl-3,3-dipropylheptanoic acid.

A series of alkylations of Ia was performed then using different alkyl halides. The mixtures of α-alkylated nitriles and ketenimines were analyzed again either by gas chromatography or by titration with standard bromine solution. The results are tabulated in Table II.

(3) N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948); C. J. Eby and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 723 (1957).

(4) C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **75**, 657 (1953).

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., J. Wiley and Sons, Inc., New York, 1958, p. 211.

TABLE II

ALKYLATION OF 3,3-DIPROPYLHEPTANONITRILE WITH VARIOUS HALIDES IN ETHER

Halide	% Yield of Alkylated Products	Composition of Alkylated Product, Weight % $C_4H_9-C(C_3H_7)_2-CHCN$	Composition of Alkylated Product, Weight % $C_4H_9-C(C_3H_7)_2-C\equiv C-NR$
C_2H_5Br	89	96.7	3.3[a,b]
n-C_4H_9Br	85	95.8	4.2[a]
i-C_4H_9Br	75	88.1	11.9[b]
i-C_4H_9Cl	38	85.6	14.4[b]
s-C_4H_9Br	30	79.6	20.4[b]
i-$C_5H_{11}Br$	73	93.6	6.4[b]
n-$C_8H_{17}Br$	93	92.4	7.6[c]
$C_6H_{11}Br$	5	87.3	12.7[b]
C_6H_5Br	10	100	0
CH_2=$CHCH_2Cl$	Trace	—	—
$C_6H_5CH_2Cl$	0	—	—
$C_6H_5CH_2Cl$	31[d]	100	0

[a] Determined by gas chromatographic analysis. [b] Determined by titration with standard bromine solution. [c] Determined by isolation. [d] Run in refluxing toluene for 24 hr.

In contrast to the findings of Goerner and Holzschuh,[6] it was observed that, with the butyl bromides, the yields of alkylated nitriles varied in the order: normal > iso > secondary. The alkylations with ethyl, isoamyl, and n-octyl bromides proceeded normally to give the expected mixtures of α-alkylated nitriles and ketenimines in essentially the same ratios as those obtained by alkylation with n-butyl bromide. Since the boiling points of 2-octyl-3,3-dipropylheptanonitrile (IIIb) and the ketenimine, 8-aza-6-octyl-5,5-dipropyl-6,7-hexadecadiene (IIIb) are fairly far apart, it was possible to separate the mixture by fractional distillation. No isolable amount of the α,α-dialkylated nitrile, 2,2-dioctyl-3,3-dipropylheptanonitrile (IVb), was present.

Phenylation of Ia by means of bromobenzene and sodamide in refluxing ether was accomplished, though in low yield, with no evidence of ketenimine formation. This is in agreement with the results of Bunnett and Brotherton[7] and Bergstrom and Agostinho[8] who found that aliphatic nitriles can be phenylated in liquid ammonia.

In view of the many successful alkylations of aliphatic nitriles with both benzyl and allyl chlorides,[9] the data for these reactions of Ia given in Table II are of interest. Attempted alkylation of Ia with benzyl chloride in refluxing ether for twenty-four hours afforded a nearly quantitative recovery of unchanged starting materials. In a similar experiment, employing allyl chloride, 89% of Ia was recovered along with a considerable amount of polymeric material (presumably from the reaction of allyl chloride with sodamide). A vapor phase analysis of the Ia indicated a purity of 99%, with only trace amounts of 2-allyl-3,3-dipropylheptanonitrile present. The alkylation of Ia with benzyl chloride was accomplished in 31% yield, however, by carrying the reaction out in refluxing toluene.

The observation that no ammonia was liberated on refluxing an ether solution of Ia with sodamide supports the view that the α-hydrogen atoms would be expected to be less acidic than those in a simple monosubstituted acetonitrile. Apparently the formation of the carbanion is an equilibrium process. Likewise, the α-alkylated nitriles (II) must afford ambident anions; otherwise, it would be difficult to account for the presence of ketenimines.

The dialkylation of Ia was undertaken then with a large excess of isobutyl bromide and sodamide in order to obtain a sufficient amount of a relatively pure ketenimine for further study. After careful fractionation, there was obtained a 63% yield of 4-aza-6-isobutyl-2-methyl-7,7-dipropyl-4,5-undecadiene (IIIc) in 88% purity (contaminated by 12% of IVc). A sample of this material was hydrolyzed to an amide which was shown to be identical with authentic N,2-diisobutyl-3,3-dipropylheptanamide. An attempt to characterize the ketenimine (IIIc) by conversion to an α-bromoamide, by treatment with bromine followed by hydrolysis with aqueous acetic acid, resulted in the formation of N,2-diisobutyl-3,3-dipropylheptanamide. The reaction was not investigated further, but it seems possible that the α-bromoimino bromide suffered loss of bromine and reverted to the ketenimine which then was hydrolyzed.

In Table III are recorded the results of alkylation studies on two 2-alkyl-3,3-dipropylheptanonitriles (II). The reactions were performed under the same conditions as were employed previously with 3,3-dipropylheptanonitrile (Ia). The mixtures of II, ketenimines (III), and 2,2-dialkyl-3,3-dipropylheptanonitriles (IV) were analyzed also by gas chromatography. The data illustrate the steric

(6) G. L. Goerner and A. A. Holzschuh, *J. Org. Chem.*, **23**, 1346 (1958).

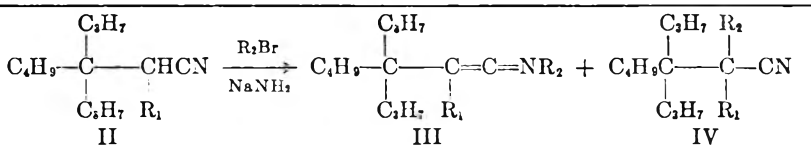
(7) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958).

(8) F. W. Bergstrom and R. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).

(9) A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 294 (1957).

TABLE III

ALKYLATION OF 2-ALKYL-3,3-DIPROPYLHEPTANONITRILES WITH VARIOUS HALIDES



R_1	R_2	Solvent	% Yield II	% Yield III	% Yield IV	Ketenimine/Dialkylated Nitrile
n-C_4H_9	n-C_4H_9	Ether	16.7	43.6	37.5	1.16
n-C_4H_9	i-C_4H_9	Ether	50.1	32.7	13.8	2.37
i-C_4H_9	i-C_4H_9	Ether	65.3	28.4	06.2	4.58
n-C_4H_9	n-C_4H_9	Tetrahydrofuran	34.0	39.0	27.2	1.44

influence of carbon *vs.* hydrogen atoms in evaluating steric hindrance by the "rule of six."[10] All of the monoalkylated nitriles (II) have a "six number" of 12, and all of the dialkylated nitriles (IV) have a "six number" of 15, yet the ratio of nitrogen to carbon alkylation (which is undoubtedly related to steric factors), approximately doubles upon increasing the number of carbon atoms in the six position from 4 to 5 (Experiments 2 and 3, Table III).

An attempt to isolate 2,2-dibutyl-3,3-dipropylheptanonitrile (IVa) from Experiment 1, Table III met with only partial success. The reaction mixture was hydrolyzed to convert the ketenimine to an amide and then distilled. Three careful fractionations finally produced a small amount of pure IVa.

EXPERIMENTAL[11]

3,3-Dipropylheptanonitrile (Ia) was prepared in 42% yield from 4-heptanone according to the method of Rabjohn, Phillips, and DeFeo[12]; b.p. 137–138° (20 mm.), n_D^{25} 1.4420.

Anal. Calcd. for $C_{13}H_{25}N$: C, 79.93; H, 12.90. Found: C, 80.36; H, 13.08.

Alkylation of Ia *with n-butyl bromide in various solvents.* A mixture of Ia, commercial sodamide, *n*-butyl bromide, and 100 ml. of the appropriate dry solvent for each 0.1 mole of nitrile was refluxed for the specified time in a 1-l. three necked flask fitted with a sealed stirrer and a reflux condenser protected with a drying tube. After cooling, the mixture was filtered with suction through a sintered glass filter, the solvent was removed, and any unchanged starting material was removed by careful fractionation through a modified Podbielniak column.[13] The resulting mixtures of 2-butyl-3,3-dipropylheptanonitrile (IIa), 5-aza-7-butyl-8,8-dipropyl-5,6-dodecadiene (IIIa), and 2,2-dibutyl-3,3-dipropylheptanonitrile (IVa) were analyzed by gas chromatography[14] or by titration with standard bromine solution[15,16] with the results shown in Table I.

Alkylation of Ia *with n-butyl bromide in liquid ammonia.* To a suspension of sodamide from 3.8 g. (0.165 g.-atom) of sodium in 200 ml. of liquid ammonia, was added 29.3 g. (0.15 mole) of Ia and the mixture was stirred for 15 min. Then 22.6 g. (0.165 mole) of *n*-butyl bromide was added dropwise over a period of 30 min., the mixture was stirred for 3 hr., 150 ml. of dry ether was added, and the ammonia was allowed to evaporate at room temperature. The mixture was filtered through a sintered glass filter, the ether was removed, and the residue was distilled under reduced pressure. There was obtained 35.1 g. of material, b.p. 140–175°/1 mm., which was analyzed by gas chromatography. The composition of the product is indicated in Table I.

Isolation of 2-butyl-3,3-dipropylheptanonitrile (IIa) *and N,2-dibutyl-3,3-dipropylheptanamide.* A mixture of 13.8 g. of IIa and IIIa (from treatment of 0.1 mole of Ia with 0.11 mole of sodamide and 0.11 mole of *n*-butyl bromide in toluene for 24 hr.) was boiled with 100 ml. of 95% ethanol, 10 ml. of water, and 1 ml. of 10% hydrochloric acid for 4 hr. The ethanol was removed by distillation, the residue was poured into 200 ml. of water, and the mixture was extracted several times with ether. The combined ether extracts were washed with water, 10% sodium bicarbonate solution again with water, and then were dried over magnesium sulfate. The solution was filtered, the ether was removed, and the residue was distilled under reduced pressure. There was obtained 9.4 g. (37.5% based on Ia) of IIa as a viscous, colorless oil, b.p. 165–167°/20 mm., n_D^{25} 1.4520.

Anal. Calcd. for $C_{17}H_{33}N$: C, 81.20; H, 13.23. Found: C, 81.33; H, 13.28.

The high boiling residue in the distillation flask solidified on cooling. This was recrystallized from acetonitrile and 2.0 g. (16% based on Ia) of *N*,2-dibutyl-3,3-dipropylheptanamide was obtained as fluffy, colorless needles, m.p. 118–122°. One additional recrystallization from acetonitrile raised the melting point to 122–124°. A mixed melting point with authentic *N*,2-dibutyl-3,3-dipropylheptanamide (see below) melted at 123–125°, and the infrared spectra were also identical.

No 2,2-dibutyl-3,3-dipropylheptanenitrile (IVa) was detected in either the distillate or the residue.

Preparation of 2-butyl-3,3-dipropylheptanoic acid. A modi-

(10) M. S. Newman, *J. Am. Chem. Soc.*, 72, 4783 (1950); M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, p. 206.

(11) All melting points are uncorrected. The carbon, hydrogen, and nitrogen analyses were performed by Drs. Weiler and Strauss of Oxford, England.

(12) N. Rabjohn, L. V. Phillips, and R. J. DeFeo, *J. Org. Chem.*, 24, 1964 (1959).

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

(14) The gas chromatographic analyses were performed on a Perkin-Elmer Model 154 Vapor Fractometer using Column C (Silicone Oil) at a temperature of 225°. Helium was used as a carrier gas with a flow rate of 40 ml./min.

(15) G. S. Hammond, O. D. Trapp, R. T. Keys, and D. L. Neff, *J. Am. Chem. Soc.*, 81, 4878 (1959).

(16) A 1–2 g. sample was dissolved in 15 ml. of carbon tetrachloride and titrated with a standard (*ca.* 0.1*M*) solution of bromine in carbon tetrachloride until the bromine color persisted. A solvent blank was titrated also with the standard bromine solution in order to determine the correction for excess titrant added. It was determined that neither Ia or IIa reacted appreciably with the bromine solution upon standing at room temperature up to 4 hr.

TABLE IV

2-ALKYL-3,3-DIPROPYLHEPTANONITRILES (II) ISOLATED FROM REACTION MIXTURES

R	B.P. (Mm.)	n_D^{25}	% Carbon		% Hydrogen	
			Calcd.	Found	Calcd.	Found
C_2H_5	151–153 (20)	1.4508	80.64	80.44	13.09	12.71
n-C_4H_9	165–167 (20)	1.4520	81.20	81.33	13.23	13.28
i-C_4H_9	160–162 (20)	1.4511	81.20	81.17	13.23	13.00
s-C_4H_9	156–158 (20)	1.4540	81.20	80.92	13.23	13.18
i-C_5H_{11}	174–175 (20)	1.4517	81.43	81.17	13.29	13.08
n-C_8H_{17}	186–188 (1)	1.4553	82.01	82.29	13.44	13.24
C_6H_5	146–148 (1)	1.5004	84.07	84.06	10.77	10.84
$C_6H_5CH_2$	230–231 (1)	1.5002	84.14	84.55	10.95	10.90

TABLE V

N,2-DIALKYL-3,3-DIPROPYLHEPTANAMIDES (IV) ISOLATED FROM REACTION MIXTURES

R	M.P.	Recrystallized Solvent	% Carbon		% Hydrogen	
			Calcd.	Found	Calcd.	Found
n-C_4H_9	125–126	Acetonitrile	77.48	77.74	13.32	13.19
i-C_4H_9	108–109	Ethyl acetate	77.48	77.57	13.32	13.16
i-C_6H_{13}	127.5–129	Acetonitrile	78.12	77.84	13.40	13.35

fication of the procedure of Sarel and Newman[17] was used. A mixture of 25.1 g. (0.10 mole) of IIa and 100 g. of 75% (by weight) sulfuric acid was heated at 100–125° for 8 hr. with vigorous stirring. After standing overnight, the dark, gummy mass was poured into 500 ml. of ice water, and extracted several times with ether. The combined ether extracts were washed with water, dried over magnesium sulfate, filtered, and the ether was evaporated. The residue was distilled under reduced pressure from a Claisen flask and 24.5 g. (91%) of 2-butyl-3,3-dipropylheptanamide was obtained as a nearly colorless, very viscous oil, b.p. 185–187°/1 mm., n_D^{25} 1.4720. The amide could not be induced to crystallize.

Anal. Calcd. for $C_{17}H_{35}NO$: C, 75.77; H, 13.09. Found: C, 75.91; H, 12.96.

A stirred suspension of 20 g. (0.074 mole) of 2-butyl-3,3-dipropylheptanamide in 125 g. of 75% sulfuric acid was prepared, and the mixture was heated to 80°. The source of heat was removed, and 34.5 g. (0.5 mole) of sodium nitrite was added in small portions so that the temperature was maintained at 80–90°. After cooling to room temperature, the mixture was poured into 500 ml. of ice water and extracted several times with ether. The combined ether extracts were washed twice with water, dried over magnesium sulfate, filtered, and the ether was removed at atmospheric pressure. The residue was distilled under reduced pressure and 17.2 g. (86%) of 2-butyl-3,3-dipropylheptanoic acid was obtained as a light yellow, viscous oil; b.p. 173–174°/1 mm., n_D^{25} 1.4570.

Anal. Calcd. for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67; neut. equiv., 270.4. Found: C, 75.74; H, 12.76; neut. equiv., 275.3.

Preparation of N,2-dibutyl-3,3-dipropylheptanamide. A mixture of 15.0 g. (0.055 mole) of 2-butyl-3,3-dipropylheptanoic acid and 17.9 g. (0.15 mole) of thionyl chloride was refluxed for 2 hr., cooled, 50 ml. of dry benzene was added, and the benzene and excess thionyl chloride were removed at reduced pressure. The crude acid chloride was added dropwise to a solution of 11.6 g. (0.165 mole) of n-butylamine in 100 ml. of dry benzene at ice-bath temperature. After standing for 2 days, the mixture was worked up in the usual fashion to give 12.2 g. (69%) of N,2-dibutyl-3,3-dipropylheptanamide as fine, white needles, m.p. 122–124°. An analytical sample was obtained after several recrystallizations from acetonitrile as fluffy, white needles, m.p. 125–126°.

(17) S. Sarel and M. S. Newman, *J. Am. Chem. Soc.*, 78, 5416 (1956).

Anal. Calcd. for $C_{21}H_{43}NO$: C, 77.48; H, 13.32. Found: C, 77.74; H, 13.19.

Alkylation of Ia *with various halides in ether.* A mixture of Ia, 0.11 mole of sodamide, 0.11 mole of the halide, and 100 ml. of dry ether for each 0.10 mole of Ia, was refluxed for 24 hr. in a three necked flask fitted with a sealed stirrer and a reflux condenser protected by a drying tube. After cooling, the mixture was filtered with suction through a sintered glass filter, and the ether was removed. Unchanged Ia was removed by fractionation through a Modified Podbielniak Column, and the remaining mixtures were distilled as long as volatile material could be obtained. The resulting mixture of monoalkylated nitrile and ketenimine was analyzed then with the results shown in Table II.

Isolation of nitriles and amides from the above alkylations. The mixtures of monoalkylated nitriles and ketenimines from 0.15 mole of Ia were refluxed with 150 ml. of 95% ethanol, 10 ml. of water, and 2 ml. of 10% hydrochloric acid for 4 hr., and the ethanol was removed by distillation. The residues were poured into 200 ml. of water and extracted several times with ether. The combined ether extracts were washed with water, 10% sodium bicarbonate solution, again with water, dried over magnesium sulfate, and filtered. The ether was removed at atmospheric pressure and the residues were distilled at reduced pressure. The nitriles obtained are listed in Table IV.

The residues from the distillations were recrystallized to constant melting point when they could be induced to crystallize. The amides obtained are recorded in Table V.

Preparation of 2-octyl-3,3-dipropylheptanonitrile (IIb) *and 8-aza-6-octyl-5,5-dipropyl-6,7-hexadecadiene* (IIIb). A mixture of 29.3 g. (0.15 mole) of Ia, 6.4 g. (0.165 mole) of sodamide, 31.8 g. (0.165 mole) of n-octyl bromide, and 150 ml. of dry ether was refluxed for 24 hr. After work-up and distillation, there were obtained 39.4 g. (85%) of 2-octyl-3,3-dipropylheptanonitrile, b.p. 186–188°/1 mm., n_D^{25} 1.4553; and 4.4 g. (7%) of crude ketenimine, b.p. 248–250°/1 mm.

Anal. Calcd. for $C_{21}H_{41}N$: C, 82.01; H, 13.44. Found: C, 82.89; H, 13.24.

The crude ketenimine was fractionated carefully through a 24-in. spinning band column, and 3.0 g. of pure material, n_D^{25} 1.4654, was obtained.

Anal. Calcd. for $C_{39}H_{67}N$: C, 82.98; H, 13.69. Found: C, 82.50; H, 13.76.

Preparation of 4-aza-6-isobutyl-2-methyl-7,7-dipropyl-4,5-undecadiene (IIIc). In a 1-l. three necked flask fitted with a sealed stirrer and a reflux condenser protected with a drying

tube were placed 29 g. (0.2 mole) of Ia, 11.7 g. (0.31 mole) of sodamide, 41.1 g. (0.31 mole) of isobutyl bromide, and 150 ml. of dry benzene, and the mixture was refluxed for 6 hr. An additional 11.7 g. (0.3 mole) of sodamide and 41.1 g. (0.3 mole) of isobutyl bromide were added, and refluxing was continued for 16 hr. Still a third portion of 11.7 g. (0.3 mole) of sodamide, and 41.1 g. (0.3 mole) of isobutyl bromide was added, and refluxing was continued for an additional 10 hr. The flask was cooled in an ice bath and the mixture was decomposed by cautiously adding 250 ml. of cold water. The layers were separated, the aqueous layer was extracted with ether, and the combined organic solutions were washed with water and dried over magnesium sulfate. After filtration, the solvents were removed at atmospheric pressure and the residue was fractionated under reduced pressure. There was obtained 38.6 g. (63%) of the ketenimine as a colorless oil, b.p. 183–185°/20 mm., n_D^{25} 1.4650, having a characteristic isocyanide odor. The purity of the product was 88% as determined by gas chromatography, with the remaining 12% being 2,2-diisobutyl-3,3-dipropylheptanonitrile (IVc).

Anal. Calcd. for $C_{21}H_{41}N$: C, 82.01; H, 13.14; N, 4.55. Found: C, 82.04; H, 13.49; N, 4.44.

Hydrolysis of 4-aza-6-isobutyl-2-methyl-7,7-dipropyl-4,5-undecadiene (IIIc). A mixture of 17.8 g. (0.058 mole) of the ketenimine, 75 ml. of glacial acetic acid, and 25 ml. of water was refluxed for 4 hr., cooled, and poured into 250 ml. of cold water. The layers were separated, the aqueous layer was extracted three times with ether, and the combined organic layers were washed with water, then with 10% sodium hydroxide solution until neutral, again with water, and dried over magnesium sulfate. The solution was filtered, the ether was removed at atmospheric pressure, and the residue was distilled at reduced pressure. There was obtained 12.2 g. (65%) of *N*,2-diisobutyl-3,3-dipropylheptanamide, b.p. 169–171°/1 mm., which crystallized in the receiver. An analytical sample was recrystallized from ethyl acetate as fine white needles, m.p. 108–109°.

Anal. Calcd. for $C_{21}H_{43}NO$: C, 77.48; H, 13.32. Found: C, 77.57; H, 13.16.

Preparation of 2-benzyl-3,3-dipropylheptanonitrile. A mixture of 17.5 g. (0.09 mole) of Ia, 3.9 g. (0.10 mole) of sodamide, 12.7 g. (0.10 mole) of benzyl chloride, and 100 ml. of dry toluene was refluxed for 24 hr. After filtration, the solvent and a trace of unchanged benzyl chloride were removed at reduced pressure. An infrared spectrum of the residue indicated the presence of amines, ammonium salts, and nitrile, but with no band at 5.0 μ characteristic of a ketenimine.[4] The residue was taken up in ether and washed several times with 10% hydrochloric acid, twice with water, dried over magnesium sulfate, and filtered. The ether was removed at atmospheric pressure and the residue was distilled under reduced pressure. There were obtained 7.7 g. (44%) of Ia, and 8.0 g. (31%) of crude 2-benzyl-3,3-dipropylheptanonitrile, b.p. 230–236°/1 mm., which was contaminated by a trace of solid material. The residue in the flask, presumably tetrabenzylammonium chloride, amounted to about 4 g. and was not investigated further. The crude 2-benzyl-3,3-dipropylheptanonitrile was filtered with suction through a sintered glass filter and fractionated carefully through a spinning band column. There was obtained 7.0 g. of a colorless, very viscous oil, b.p. 230–231°/1 mm., n_D^{25} 1.5002.

Anal. Calcd. for $C_{20}H_{31}N$: C, 84.14; H, 10.95. Found: C, 84.55; H, 10.90.

The aqueous solution and washings were combined and made alkaline with 10% sodium hydroxide solution. The mixture was extracted several times with ether, the ether solutions were combined, washed twice with water, and dried over potassium hydroxide pellets. The ether was removed and 2.0 g. of a mixture of benzylamine, dibenzylamine, and tribenzylamine (as indicated by infrared spectra) was obtained.

Preparation of N,2-diisobutyl-3,3-dipropylheptanamide. The hydrolysis of 16 g. (0.06 mole) of 2-isobutyl-3,3-dipropylheptanonitrile to 2-isobutyl-3,3-dipropylheptanoic acid was accomplished by heating with 120 g. of 96% sulfuric acid at 100–120° for 8 hr., followed by treatment with 16.6 g. (0.24 mole) of sodium nitrite. The reaction was accompanied by considerable charring and tar formation. After work-up and distillation, there was obtained 7.1 g. of material, b.p. 161–162°/1 mm., which appeared to be a mixture of amide and acid. The mixture was treated with thionyl chloride, followed by isobutylamine, to give, after purification, 2.7 g. (13%) of *N*,2-diisobutyl-3,3-dipropylheptanamide; m.p. 107–108° (from ethyl acetate). A mixed melting point with the amide from hydrolysis of IIIc was not depressed.

Anal. Calcd. for $C_{21}H_{43}NO$: C, 77.48; H, 13.32. Found: C, 77.39; H, 13.01.

Attempted preparation of 2-bromo-N,2-diisobutyl-3,3-dipropylheptanamide. A solution of 4.8 g. (0.03 mole) of bromine in 25 ml. of carbon tetrachloride was added dropwise to a solution of 8.1 g. (0.026 mole) of 4-aza-6-isobutyl-2-methyl-7,7-dipropyl-4,5-undecadiene (IIIc) in 25 ml. of carbon tetrachloride while maintaining the temperature at −5 to 0° in an ice-salt bath. The bromine color was discharged immediately. The addition of the bromine solution was discontinued as soon as the bromine color persisted (about 2 ml. of solution was unused). The contents of the flask were allowed to warm to room temperature overnight and the solvent was removed under reduced pressure. There remained an intractable oil which was mixed with 100 ml. of 50% acetic acid and refluxed for 3 hr. The resulting mixture was poured into 500 ml. of cold water and extracted several times with ether. The combined ether extracts were washed with water, then with 10% sodium hydroxide solution, again with water, dried over magnesium sulfate, and filtered. The ether was evaporated, leaving a light brown oil which crystallized on standing. This was recrystallized from acetonitrile to give 4.6 g. (54%) of slightly yellow crystals, m.p. 83–88°. Repeated recrystallizations, first from acetonitrile, then from ethyl acetate, gave an analytical sample in the form of fine, colorless needles, m.p. 108.5–109.5°. The melting point was not depressed on admixture with authentic *N*,2-diisobutyl-3,3-dipropylheptanamide, and the infrared spectra were identical. A sodium fusion gave a negative test for bromine.

Alkylation of 2-alkyl-3,3-dipropylheptanonitriles with various halides. A mixture of 0.10 mole of the appropriate 2-alkyl-3,3-dipropylheptanonitrile (II), 0.11 mole of sodamide, 0.11 mole of the halide, and 100 ml. of the solvent was refluxed for 24 hr. After filtration, removal of solvent, and distillation, the resulting mixtures of unchanged starting material (II), dialkylated nitrile (IV), and ketenimine (III), were analyzed by gas chromatography. The results are shown in Table III.

Isolation of 2,2-dibutyl-3,3-dipropylheptanonitrile (IVa). A mixture of 29.1 g. of the reaction mixture from the alkylation of 2-butyl-3,3-dipropylheptanonitrile (IIa) with *n*-butyl bromide in ether, 150 ml. of 95% ethanol, 10 ml. of water, and 2 ml. of 10% hydrochloric acid was refluxed for 4 hr. After removal of the ethanol, extraction, and distillation in the usual manner, there were obtained 3.3 g. (13%) of unchanged 2-butyl-3,3-dipropylheptanonitrile, b.p. 137–140°/1 mm., and 10.3 g. (33%) of crude 2,2-dibutyl-3,3-dipropylheptanonitrile, b.p. 176–178°/1 mm., which was contaminated by traces of amide. After fractionation twice through a spinning bond column, a sample of pure 2,2-dibutyl-3,3-dipropylheptanonitrile, b.p. 176–177°/1 mm., n_D^{25} 1.4650, was obtained.

Anal. Calcd. for $C_{21}H_{41}N$: C, 82.01; H, 13.44. Found: C, 82.29; H, 13.35.

The original distillation residue solidified on cooling. This was recrystallized from acetonitrile to give 8.3 g. (27%) of *N*,2-dibutyl-3,3-dipropylheptanamide, m.p. 123–125°.

COLUMBIA, MO.

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

Addition Reactions of Trinitromethane and α,β-Unsaturated Ethers

HAROLD SHECHTER AND HARRY L. CATES, JR.[1]

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Addition of trinitromethane to α,β-unsaturated ethers occurs in ether solvents to give α-trinitromethyl ethers. Dioxane and trinitromethane form a crystalline adduct having the molecular formula, $C_4H_8O_2.2HC(NO_2)_3$; the adduct serves as a convenient source of trinitromethane. The preparation and properties of five α-trinitromethyl ethers are described. The direction of addition of trinitromethane to isobutyl vinyl ether was determined by reduction of the adduct, isobutyl 1-methyl-2,2,2-trinitroethyl ether, with lithium aluminum hydride to 2-isobutoxypropylamine. 2-Isobutoxypropylamine was synthesized by reduction with iron and hydrochloric acid of isobutyl 1-methyl-2-nitroethyl ether prepared by base-catalyzed addition of isobutyl alcohol to 1-nitro-1-propene. Reduction of isobutyl 1-methyl-2,2,2-trinitroethyl ether with iron and hydrochloric acid yielded 2-isobutoxypropionamide.

Trinitromethane (nitroform), a strong acid ($K_{ion(H_2O)} \sim 10^{-1} - 10^{-2}$),[2] undergoes 1,4-addition with conjugatively-unsaturated aldehydes,[3a] ketones,[3a,b] acids,[3a] esters,[3a] nitriles,[3a] and nitro[3c,d] compounds to give the corresponding trinitromethyl derivatives. It is now reported that reaction of equimolar quantities of α,β-unsaturated ethers and trinitromethane (Equation 1) occurs in

$$RCH{=}CH{-}OR + HC(NO_2)_3 \longrightarrow RCH_2{-}\underset{\displaystyle C(NO_2)_3}{\underset{|}{CH}}{-}OR \quad (1)$$

satisfactory yields (> 50–81%) to give α-trinitromethyl ethers.[4] The additions take place readily at room temperature, with little polymerization, in basic solvents such as dioxane and ethyl ether. Upon mixing dioxane and trinitromethane, heat is evolved, and a white crystalline adduct containing two equivalents of trinitromethane and one of dioxane is precipitated (Equation 2).[5] The solid adduct is fairly stable and can be distilled at reduced pressures. In water the adduct decomposes quantitatively to dioxane and trinitromethane. The addition-complex is dissociated in various solvents and may be used as a convenient source of trinitromethane.[6]

$$O(CH_2{-}CH_2)_2O + 2HC(NO_2)_3 \rightleftharpoons (O_2N)_3CH{\cdot}O(CH_2{-}CH_2)_2O{\cdot}HC(NO_2)_3 \quad (2)$$

Trinitromethane has been added (Table I) to ethyl vinyl ether, isopropyl vinyl ether, isobutyl vinyl ether, 2-methoxyethyl vinyl ether, and 2,3-dihydropyran. The adducts were isolated and purified without serious hazard by use of conventional distillation techniques at reduced pressures. 2,3-Dihydro-5-methylfuran reacted readily with trinitromethane; the product could not be purified adequately however because of its thermal instability.

The structure of the adduct of isobutyl vinyl ether and trinitromethane, isobutyl 1-methyl-2,2,2-trinitroethyl ether, was determined by characterizing its reduction products. Reduction of the adduct with iron and hydrochloric acid occurred slowly to give 2-isobutoxypropionamide (Equation 2)[7a,b]; with lithium aluminum hydride, the trinitromethyl ether was reduced to 2-isobutoxypropylamine[7c] (Equation 3).

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(1) (a) Abstracted from the Ph.D. dissertation of Harry L. Cates, Jr., The Ohio State University, 1951. (b) This research was supported by the Office of Naval Research.

(2) A. Hantzsch and K. Rinckenberger, *Ber.*, **32**, 635 (1899).

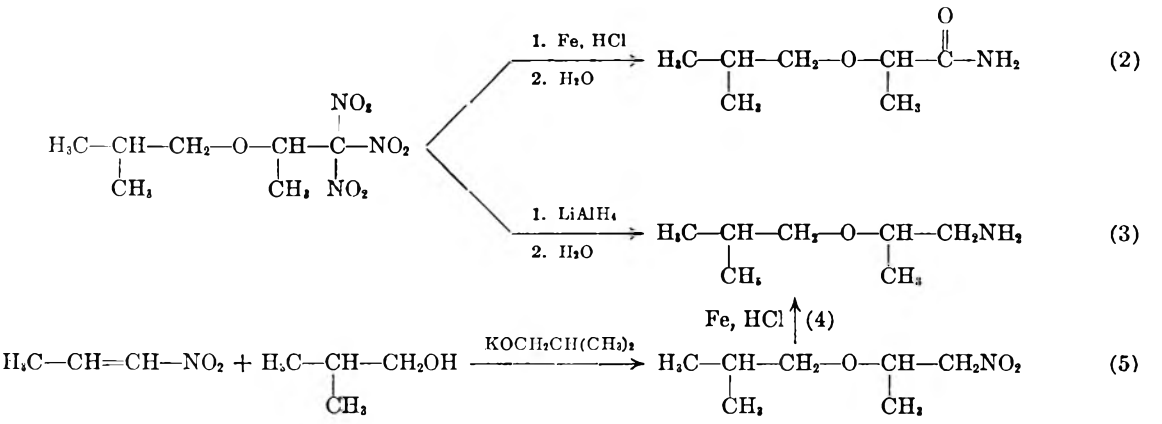
(3) (a) K. Schimmelschmidt, Ger. Patent 852,684, Oct. 16, 1952; (b) S. S. Novikov, I. S. Korsakova, and N. A. Yatskovskaya, *Doklady Akad. Nauk S.S.S.R.*, **118**, 954 (1958); (c) S. S. Novikov, I. S. Korsakova, and K. K. Babievsky, *Izzv. Acad. Nauk S.S.S.R.*, **10**, 1847 (1959); (d) S. S. Novikov, K. K. Babievsky, and I. S. Korsakova, *Doklady Akad. Nauk S.S.S.R.*, **125**, 560 (1959).

(4) Additions of trinitromethane to α,β-unsaturated compounds are acid catalyzed. Reactions of the intermediate conjugate acids with the ambident trinitromethane anion by carbon rather than oxygen-alkylation probably stem from thermodynamic factors.

(5) Heat is evolved upon mixing trinitromethane with tetrahydrofuran or dimethyl Cellosolve; however, no solid product could be isolated.

(6) The acid-base reactions of trinitromethane and dioxane and the properties of the adduct are analogous to those of dioxane and sulfur trioxide; C. M. Suter, P. B. Evans, and J. M. Kiefer, *J. Am. Chem. Soc.*, **60**, 538 (1938).

(7) (a) This is the first example of reduction of a 1,1,1-trinitro compound to an amide. The basic organic products from this reduction were not identified because of their complexity. (b) T. Henderson and A. K. Macbeth, *J. Chem. Soc.*, **121**, 892 (1922) have reported that reduction of tetranitromethane with titanous chloride yielded guanidine. V. Meyer and J. Locher, *Ann.*, **180**, 172 (1876) obtained formic acid, hydrogen cyanide, ammonium chloride, hydroxylamine, and oxides of nitrogen from reduction of tetranitromethane with zinc and hydrochloric acid. It is thus possible that reduction of isobutyl 1-methyl-2,2,2-trinitroethyl ether with iron and hydrochloric acid yielded 2-isobutoxypropionamidine which then hydrolyzed to 2-isobutoxypropionamide and ammonia. (c) Reduction of a 1,1,1-trinitro compound to its corresponding amine by lithium aluminum hydride has not been reported previously.



The amine and its derivative, 1-(2-isobutoxypropyl)-3-phenyl-2-thiourea, are identical with that prepared by reduction of isobutyl 1-methyl-2-nitroethyl ether with iron and hydrochloric acid (Equation 4) and reaction of the product with phenyl isothiocyanate. Isobutyl 1-methyl-2-nitroethyl ether was synthesized by reaction of 1-nitro-1-propene, isobutyl alcohol, and potassium isobutoxide (Equation 5). The direction of addition of trinitromethane to α,β-unsaturated ethers is thus analogous to that of vinyl ethers with hydrogen halides,[8] carboxylic acids, and alcohols,[8] respectively.

EXPERIMENTAL

Materials. Trinitromethane was prepared by slowly adding concd. sulfuric acid to a cool suspension of potassium trinitromethane in petroleum ether (b.p. 60–90°). After potassium sulfate had been removed by filtration, trinitromethane was isolated by crystallization at −60 to −80°. Repeated recrystallization of the product from petroleum ether yielded very pure trinitromethane; white needles, m.p. 26.38°[9]; lit. m.p. 15°,[2] 22–23°.[10] Trinitromethane has been stored for months in Pyrex bottles at refrigerator temperatures without extensive decomposition. Distillation of trinitromethane can be effected at reduced pressures; however, a higher melting product is obtained by crystallization. Potassium trinitromethane was prepared by reduction of tetranitromethane with alcoholic potassium ethoxide.[11]

Vinyl ethers were supplied by the Carbide and Carbon Chemicals Corporation. Dihydropyran was obtained from E. I. du Pont de Nemours and Co. 1-Nitro-1-propene was prepared by dehydration of 1-nitro-2-propanol with phthalic anhydride.[12]

Isobutyl 1-methyl-2,2,2-trinitroethyl ether. A mixture of isobutyl vinyl ether (10.7 g., 0.107 mole) and dioxane (35 ml.) was added dropwise (2.5 hr.) to a stirred solution of trinitromethane (16.5 g., 0.109 mole) and dioxane (15 ml.) at 20°. The yellow mixture, after standing at room temperature for 4 days, was distilled to give isobutyl 1-methyl-2,2,2-trinitroethyl ether as a colorless liquid; b.p. 64–65° (0.7 mm.) (Table I); yield, 18.2 g. (75%).

Trinitromethane-dioxane adduct. Dioxane (4.4 g., 0.05 mole) was added dropwise to trinitromethane (15.1 g., 0.10 mole). Heat was evolved and cooling was necessary to keep the temperature of the mixture below 20°. On completion of the addition, the mixture solidified to a white crystalline mass. The product was distilled under reduced pressure to yield the pure trinitromethane-dioxane adduct as a white solid: b.p. 61–62° (9 mm.); m.p. 44–44.5°; yield, 18.0 g. (92%).

Anal. Calcd. for $C_6H_{10}N_6O_{14}$: C, 18.47; H, 2.58; N, 21.54. Found: C, 18.06; H, 2.77; N, 21.11.

The solid adduct dissolves in water to yield an acidic yellow solution which has a neutral equivalent of 193; the calculated neutral equivalent for $C_4H_8O_2.2CH(NO_2)_3$ is 195. Reaction of the adduct with an alcoholic solution of potassium hydroxide yields potassium trinitromethane and dioxane.

Ethyl 1-methyl-2,2,2-trinitroethyl ether. A solution of ethyl vinyl ether (6.0 g., 0.083 mole) and dioxane (20 ml.) was added dropwise (1 hr.) to a stirred solution of trinitromethane-dioxane complex (16.0 g., 0.041 mole) and dioxane (25 ml.) at 23°. After standing at room temperature for 4 days, the amber solution was distilled to give ethyl 1-methyl-2,2,2-trinitroethyl ether (Table I); b.p. 59–60° (0.6 mm.); yield, 13.4 g. (73%). The product was identical with that obtained from reaction of trinitromethane and ethyl vinyl ether.

Isobutyl 1-methyl-2,2,2-trinitroethyl ether and lithium aluminum hydride. A solution of isobutyl 1-methyl-2,2,2-trinitroethyl ether (55.1 g., 0.219 mole) and anhydrous ethyl ether (750 ml.) was added dropwise (6 hr.) to a stirred mixture of lithium aluminum hydride (40.0 g., 1.054 moles) and anhydrous ethyl ether (1000 ml.). The excess hydride was decomposed with water (30 ml.); 20% potassium sodium tartrate solution (900 ml.) was then added to the mixture. The ether layer was separated and washed with potassium sodium tartrate solution, water, and saturated sodium chloride solution. Distillation of the dried solution yielded 2-isobutoxypropylamine as a colorless liquid; b.p. 40–41° (7 mm.); n_D^{20} 1.4170; yield, 5.3 g. (18%). The amine was identical with that prepared by reduction of isobutyl 1-methyl-2-nitroethyl ether.

Reduction of isobutyl 1-methyl-2,2,2-trinitroethyl ether with iron and hydrochloric acid. A solution of isobutyl 1-methyl-2,2,2-trinitroethyl ether (50.0 g., 0.199 mole) and ethyl ether (100 ml.) was added dropwise (4 hr.) to a stirred, refluxing suspension of clean iron filings (100.0 g., 1.791 moles) in water (200 ml.). Throughout the reduction, concd. hydrochloric acid (24 ml.) was added in 1-ml. portions every 10 min., and the aqueous mixture was kept refluxing by application of heat. The ethyl ether was removed by distillation and the mixture was refluxed for 9

(8) (a) W. Reppe and K. Baur, Ger. Patent 566,033, March 15, 1938.

(9) The melting point was determined by Bro. V. J. Wottle, Ph.D. dissertation, The Ohio State University, 1951.

(10) K. v. Auwers and L. Harres, *Ber.*, 62, 2296 (1929).

(11) E. Schmidt, R. Schumacher, and H. Kuhlmann, *Ber.*, 54, 1483 (1921).

(12) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).

TABLE I

ADDUCTS FROM α,β-UNSATURATED ETHERS AND TRINITROMETHANE

Compound[a,b]	Yield, %	B.P.[d]	d_{20}^{20}	n_D^{20}	MRD Calcd.	MRD Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl 1-methyl-2,2,2-trinitroethyl ether	68	63–64.5° (0.6 mm.)	1.3145	1.4386	43.8	44.6[e]	26.91	26.28	4.06	4.20	18.83	18.47
Isopropyl 1-methyl-2,2,2-trinitroethyl ether	73	65° (0.4 mm.)	1.2720	1.4390	48.4	49.0	30.38	29.90	4.68	4.48	17.72	17.55
Isobutyl 1-methyl-2,2,2-trinitroethyl ether	75	65° (0.7 mm.)	1.2227	1.4389	53.0	54.0	33.47	33.60	5.22	5.34	16.73	16.88
• 2-Methoxyethyl 1-methyl-2,2,2-trinitroethyl ether	50	102–103° (1.5 mm.)	1.3194	1.4468	50.1	51.2	28.46	28.01	4.38	4.36	16.60	16.29
2-Trinitromethyltetrahydropyran	81	103° (1.0 mm.)	1.3968	1.4708	—	—	30.64	30.92	3.86	4.02	17.87	17.09

[a] The adducts were obtained from trinitromethane and ethyl vinyl ether, isopropyl vinyl ether, isobutyl vinyl ether, 2-methoxyethyl vinyl ether, and dihydropyran, respectively. [b] The reactions were conducted at room temperature over periods ranging from 4–34 days using equimolar quantities of the unsaturated ether and trinitromethane in dioxane. [c] The products have been kept for more than three years at 10° without appreciable decomposition. [d] No attempt was made to obtain maximum yields. The residues from reaction were discarded because of their instability. [e] The lower boiling trinitroethers distill without decomposition to yield colorless liquids: 2-trinitromethyltetrahydropyran and 2-methoxyethyl 1-methyl-2,2,2-trinitroethyl ether decompose slightly during distillation.

hr. The mixture was then cooled and filtered under vacuum. The filtrate was extracted with ether. The combined ether extracts were washed with water, dried, and distilled under reduced pressure to yield 2-isobutoxypropionamide; b.p. 98° (3 mm.); yield, 4.7 g. (16%). Upon cooling the amide crystallized into a soft, white solid; m.p. *ca.* 30°. 2-Isobutoxypropionamide is insoluble in dilute hydrochloric acid and dilute sodium hydroxide; when heated with 10% sodium hydroxide solution, the amide evolved ammonia.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: 58.05; H, 10.47; N, 9.41.

No 2-isobutoxypropylamine was found in the acidic aqueous layer from the reduction mixture; the products isolated (in low yield) were high-boiling alkaline substances which were not identified; b.p. 85–102° (1 mm.); neut. equiv. 349–394.

Isobutyl 1-methyl-2-nitroethyl ether. A solution of 1-nitro-1-propene (19.8 g., 0.227 mole) and isobutyl alcohol (75 ml.) was added dropwise (2 hr.) to a stirred mixture of potassium (9.1 g., 0.233 mole) and isobutyl alcohol (100 ml.) in ethyl ether (75 ml.) at 0°. After being warmed to 25°, the mixture was diluted with water (100 ml.) and acidified with 20% acetic acid (60 ml.). The two layers were separated, and the aqueous phase was extracted with ether. The ether extracts were combined with the isobutyl alcohol layer. After the solvents had been removed by distillation at 50 mm., isobutyl 1-methyl-2-nitroethyl ether was obtained as a colorless liquid; b.p. 55–59° (2 mm.); n_D^{20} 1.4210; d_{20}^{20} 0.9747; MRD (Calcd.) 41.79; MRD (Found) 41.90; yield 16.1 g. (44%). The residue (10.4 g.) from the distillation was a polymeric black oil.

Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.22; H, 9.31; N, 8.68.

2-Isobutoxypropylamine. Concentrated hydrochloric acid (four 15-ml. portions) and isobutyl 1-methyl-2-nitroethyl ether (15.2 g., 0.094 mole) were added alternately in small portions, with stirring, to a refluxing mixture of water (35 ml.) and clean iron filings (20.0 g., 0.358 mole).[13] The mixture was stirred and refluxed for 4 hr. After having been cooled, the mixture was filtered, and solid sodium hydroxide (10.0 g.) was added to the filtrate. The addition of sodium hydroxide caused precipitation of iron hydroxides, but, after 12 hr., the basic mixture was easily separated from the solid by decantation. The alkaline solution was extracted with ether; the extracts were washed with water, dried, concentrated at atmospheric pressure and then distilled to give 2-isobutoxypropylamine as a colorless liquid; b.p. 46° (19 mm.); d_{20}^{20} 0.8311; n_D^{20} 1.4172; MRD (Calcd.) 39.72; MRD (Found) 39.72; neut. equiv. (calcd.) 131; neut. equiv. (found) 134; yield, 4.9 g. (40%).

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67. Found: C, 64.08; H, 12.80; N, 10.88.

1-(2-Isobutoxypropyl)-3-phenyl-2-thiourea. 2-Isobutoxypropylamine (0.32 g.), prepared by reduction of isobutyl 1-methyl-2-nitroethyl ether, and phenyl isothiocyanate (excess) reacted to give 1-(2-isobutoxypropyl)-3-phenyl-2-thiourea as white needles; m.p. 64–65°, recrystallized from a mixture of ethanol and water; yield, 0.65 g. (100%).

Anal. Calcd. for $C_{14}H_{22}N_2OS$: C, 63.32; H, 8.32; N, 10.52. Found: C, 62.80; H, 8.30; N, 10.39.

2-Isobutoxypropylamine (0.24 g.), prepared by the reduction of isobutyl 1-methyl-2,2,2-trinitroethyl ether with lithium aluminum hydride, and phenyl isothiocyanate reacted to yield 1-(2-isobutoxypropyl)-3-phenyl-2-thiourea; m.p. 64–65°; yield, 0.30 g. (62%). The melting point of this derivative was not depressed by the addition of the substituted thiourea prepared from 2-isobutoxypropylamine obtained from isobutyl 1-methyl-2-nitroethyl ether.

Anal. Calcd. for $C_{14}H_{22}N_2OS$: C, 63.32; H, 8.32; N, 10.52. Found: C, 63.29; H, 7.85; N, 10.60.

COLUMBUS 10, OHIO

(13) M. Senkus, *Ind. Eng. Chem.*, 40, 506 (1948).

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Spiranes. II. Spiro[3.3]heptane Derivatives

LEONARD M. RICE AND CHARLES H. GROGAN

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Derivatives of spiro[3.3]heptane have been prepared from the basic Fecht acid, *dl*-spiro[3.3]heptane-2,5-dicarboxylic acid. Spiro[3.3]heptane-2,2,5,5-tetracarboxylic acid tetraamyl ester has been isolated and shown to be a major intermediate in the preparation of Fecht acid. Improved syntheses of the corresponding diacid chloride, amide, glycol, and methyl ester have been developed. From these materials new dialkylaminoalkyl esters, alkyl and dialkylamides, a dinitrile, and the corresponding amines obtained by reduction of the alkyl and dialkylamides, and the dinitrile have been prepared. Spiro[3.3]-heptane-2,5-diacetic acid has been obtained in low yield.

Compounds possessing the spirane carbon nucleus attracted our attention several years ago because of the lack of information on pharmacological activity of compounds with this type of structure. Spiroheptanedicarboxylic acid was first obtained in small yield in 1907 by Fecht[3] by the sodium-alcohol condensation of pentaerythritol tetrabromide and dimethyl malonate. Interest in this basic structure was aroused when it was reported that weak optical activity was present even though no asymmetric carbon atom is involved. Backer and Schurink[4] succeeded in partially resolving Fecht acid, spiro[3.3]heptane-2,5-dicarboxylic acid, into its *d* and *l* isomers.

The study of the chemistry of Fecht acid (in the older literature the name 4-spiroheptane-2,6-dicarboxylic acid is used) was facilitated when in 1931 Backer and Schurink[5] improved the laborious synthesis of this acid. They used ethyl malonate instead of methyl malonate previously employed. Ester exchange takes place between the amyl alcohol and ethyl malonate in the presence of sodium but does not occur appreciably with methyl malonate; the resulting ethanol can be readily distilled.

We have improved and increased by five times the preparation of the starting material, Fecht acid (I). We have likewise improved the preparation of derivatives of Fecht acid containing functional groups suitable for further transformations. Among these are included the diacid chloride (II), previously reported by Janson and Pope[6] and Backer and Kemper,[7] the dimethyl ester (IX),[7] the diamide (XV),[6,7] and the diglycol (X).[7]

For the sake of completion of the literature at this point, it should be stated that spiro[3.3]heptane-2,5-diamine was prepared by Janson and Pope[6] and resolved into its *d* and *l* isomers. Backer and Kemper[8] studied 2,5-dibromospiro[3.3]heptane-2,5-dicarboxylic acid and prepared several derivatives involving the carboxyl group as well as the replacement of bromine by the sulfonate group.

Our studies branched out in several directions from the basic Fecht acid. First, we isolated the tetraamyl ester of the intermediate spiro[3.3]-heptane-2,2,5,5-tetracarboxylic acid (III), which proved to be a major intermediate in the preparation of Fecht acid by condensation of pentaerythritol tetrabromide with ethyl malonate. The tetracarboxylic acid had been isolated by Backer and Schurink.[7] This tetraamyl ester was reduced to the new interesting bis-*gem*-glycol (IV), which was further characterized as the dibenzal derivative (V).

The second series of synthetic transformations involved the formation of the known diamide (XV) and its efficient conversion to the new dinitrile (XVI). This dinitrile was converted by reduction to the next higher homologous diamine (XVII), which was characterized by five derivatives.

A third type of transformation involved formation of bisalkyl and bisdialkylamides (VI), and their reduction to the corresponding bisalkylaminomethyl and dialkylaminomethyl spiro[3.3]-heptanes (VII). The amine (VIIb) was converted to the bismethonium salt (VIII) which was compared with hexamethonium for hypotensive activity. Its hypotensive activity was slight and of short duration. It likewise had a weak curarimimetic activity.

A fourth series of new derivatives was obtained by preparing representative dialkylaminoalkyl esters (XVIII) from the acid chloride (II) and dialkylaminoalkanols.

(1) This project was begun at Georgetown University Medical Center several years ago. It was continued by one of us (L. M. R.) at The Celanese Corporation of America, Summit, N. J., and at the Wyeth Institute for Medical Research, Radnor, Pa.

(2) The project was brought to its present stage of completion with the support of the Geschickter Fund for Medical Research, Inc. The support of these organizations is hereby gratefully acknowledged.

(3) H. Fecht, *Ber.*, **40**, 3883 (1907).

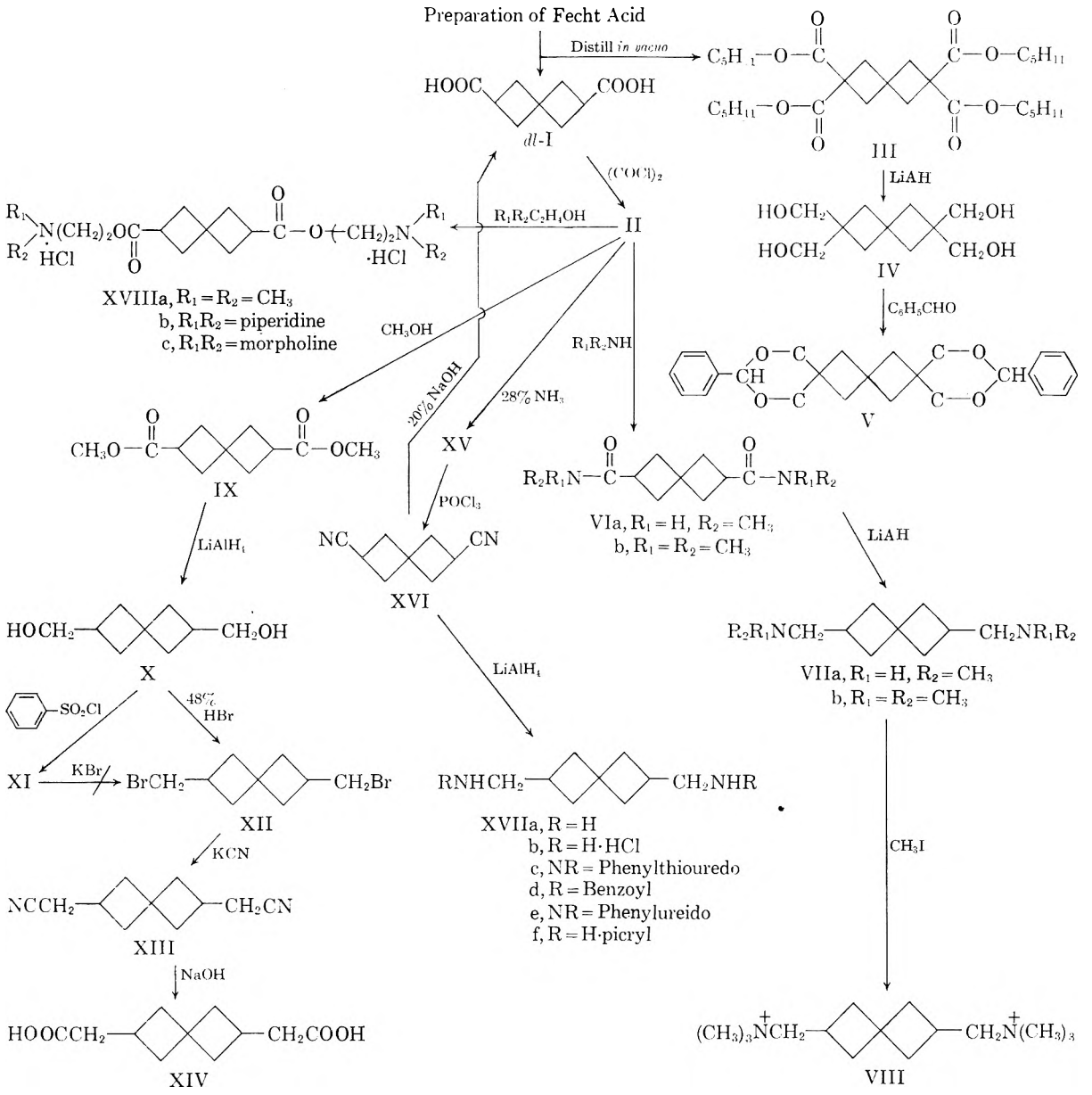
(4) H. J. Backer and H. B. J. Schurink, *Proc. Acad. Wetenschoppen (Amsterdam)*, **31**, 370, April 28 (1928).

(5) H. J. Backer and H. B. J. Schurink, *Rec. trav. chim.*, **50**, 921 (1931).

(6) S. E. Janson and Sir W. J. Pope, *Proc. Roy. Soc. (London)*, **A-154**, 53 (1936).

(7) H. J. Backer and H. G. Kemper, *Rec. trav. chim.*, **57**, 1249 (1938).

(8) H. J. Backer and H. G. Kemper, *Rec. trav. chim.*, **57**, 761 (1938).



The final type of transformation was aimed at the next higher aliphatic acid homolog, spiro[3.3]-heptane-2,5-diacetic acid. The dimethyl ester of Fecht acid (IX) was obtained in excellent yield by treating the acid chloride with absolute methanol. This was reduced in excellent yield with lithium aluminum hydride to the corresponding diglycol (X). The conversion of the diglycol to the required dibromide (XII) proved to be very difficult. The dibromide was finally obtained in low yield by direct repeated treatment of the glycol with 48% aqueous hydrobromic acid. Other methods failed entirely to give isolable amounts of the dibromide.

Two other methods that might be of value in this conversion are: (1) the use of lithium bromide instead of potassium bromide in the dibenzenesulfonate (XI) process and (2) direct esterification with anhydrous phosphoric acid and potassium bromide. We did not have sufficient quantity of the necessary glycol (X) to try these possible alternative methods. Since the dibromide (XII) is a key intermediate for the preparation of higher homologs, a practicable synthesis is still to be desired.

In view of the difficulty encountered in obtaining the dibromide (XII), a detailed study of its conversion into the dinitrile (XIII) was not possible. However, the standard conversion with potassium cyanide takes place in low yield and sufficient crude dinitrile (XIII) was obtained to prepare and characterize the spiro[3.3]heptane-2,5-diacetic acid (XIV).

It should be pointed out that no attempt was made to resolve those derivatives of the spiro nucleus which are capable of optical resolution.

EXPERIMENTAL

dl-Spiro[3.3]heptane-2,5-dicarboxylic acid (Fecht acid) (I). A modification of the improved synthesis of Backer and

Schurink[5] was used. Four separate runs were made using 0.5*M* quantities of pentaerythritol tetrabromide. One run was modified so as to isolate the tetraamyl ester of spiro-[3.3]heptane-2,2,5,5-tetracarboxylic acid. The procedure was as follows: Sodium, 2.5 moles, 57.5 g., was dissolved in 2.5 l. of absolute amyl alcohol. When solution of the sodium was complete, 400 g. (2.5 moles) of ethyl malonate was added with stirring and warming until the sodium compound was dissolved. Then 200 g. (0.5 mole) of pentaerythritol tetrabromide was added. The mixture was distilled until the vapor temperature reached 130°, near the boiling point of amyl alcohol. Most of the ethanol, formed by ester exchange between the ethyl malonate and amyl alcohol in the presence of sodium, was contained in the distillate. The reflux condenser was replaced, a volume of amyl alcohol equal to the distillate added, and the mixture refluxed for 40–50 hr.

Most of the amyl alcohol was then distilled, some water added, and the remainder of the amyl alcohol removed by distillation. The upper layer was extracted several times with ether to remove the ester salt, the ether stripped, and the ester salt saponified by adding a solution of 450 g. of potassium hydroxide (7.5 moles) in 3.75 l. of ethanol and letting the mixture stand at room temperature for 48 hr. The potassium salt was filtered, dissolved in water, decolorized with charcoal, and acidified with concd. hydrochloric acid. The acid was extracted out with ether in the Eykman continuous ether extractor.

The ether extract was dried over sodium sulfate and the ether stripped, leaving a solid residue which consisted of a mixture of spiro[3.3]heptane tetra- and dicarboxylic acids. The former is present in greater amount. The solid mixture of carboxylic acids, on being heated slowly to 200–212°, melted, lost carbon dioxide, and solidified on cooling. The resultant brown mass was dissolved in 1 l. of boiling water, decolorized with charcoal, and recrystallized from water. After a further recrystallization from water or ethyl acetate, the desired *dl*-spiro[3.3]heptane-2,5-dicarboxylic acid was obtained as colorless needles, m.p. 212°, 70–75 g., 75–80%.

Tetraamylspiro[3.3]heptane-2,2,5,5-tetracarboxylate (III). If during the preparation of Fecht acid (I), the distillation, prior to the saponification step and after removal of solvents, was continued *in vacuo*, a total of 153 g. of material boiling under 200°/0.2 mm. was obtained. There was a clean break in the temperature at this point and the pressure fell to 0.05–0.06 mm. Continued distillation yielded a 185 g. of a fraction, b.p. 218–225°/0.05–0.06 mm., which proved to be the tetraamyl ester of the intermediate tetracarboxylic acid. No attempt was made to identify components of the fraction boiling up to 200°, which was probably a mixture of esters of the di- and tetracarboxylic acids.

Anal. Calcd. for $C_{31}H_{52}O_8$: C, 67.36; H, 9.48. Found: C, 67.10; H, 9.52. n_D^{25} 1.4541.

2,2,5,5-Tetrahydroxymethylspiro[3.3]heptane (IV). This glycol was prepared in good yield from the tetraamyl ester (III) by reduction with lithium aluminum hydride in anhydrous ether. Two runs were made using 25 g. of lithium aluminum hydride and 100 g. and 76 g., respectively, of the ester. The reduction was standard procedure except that after the decomposition of the reaction mixture with water, drying the ether over anhydrous sodium sulfate and stripping the ether, *very little product was found in the ether*. The glycol is only slightly soluble in ether and most of it was found with the inorganic salt residue. The residue from the lithium aluminum hydride reduction was extracted in a Soxhlet overnight with absolute ethanol. On cooling the extract, the glycol crystallized. The solution was concentrated and the glycol crystallized from ethanol. The crude product melted at 185–187.5°. Two additional recrystallizations from ethanol gave the analytically pure material, m.p. 187.5–188.5°. The two runs gave 25.2 and 20.6 g. of glycol, respectively, for an average yield of 67%.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.30; H, 9.41.

2,2,5,5-Tetrahydromethylspiro[3.3]heptane dibenzal acetal (2,5-bis(4′-phenyldioxolane)-spiro[3.3]heptane). The glycol was further characterized by conversion into the dibenzal derivative. The glycol, 3.92 g. (0.01 mole) and 2.2 g. (0.02 mole) of chlorine-free benzaldehyde were dissolved in 50 ml. of toluene and 50 ml. of acetic acid. A crystal of *p*-toluenesulfonic acid was added and the mixture refluxed for 3 hr. while fitted with a trap to remove water vapor. The reaction mixture was evaporated to dryness on a steam bath and the crude product recrystallized from methanol, m.p. 122–124°. An additional crystallization from absolute methanol gave a constant melting product, m.p. 128–129°.

Anal. Calcd. for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.41; H, 7.50.

Spiro[3.3]heptane-2,5-dicarboxylic acid chloride (II). The acid chloride of Fecht acid has been prepared by other workers (Backer and Kemper[7] and Janson and Pope[6]) by older methods employing phosphorus chlorides and thionyl chloride. Since this was one of the key intermediates in our conversions, and in view of the laborious preparation of the Fecht acid, the more elegant reagent, oxalyl chloride, has been investigated. The conversion with oxalyl chloride was clean-cut and gave a high yield, 80–90%, of pure product, b.p. 154°/15 mm.

Spiro[3.3]heptane-2,5-dicarboxamide (XV). Fecht acid chloride, 31 g. (0.14 mole), was added dropwise with rapid stirring to 40 g. of 28% ammonia in 200 ml. of water maintained at or below 10°. The mixture was stirred for 1 hr., filtered, and the crude amide washed with cold ethanol and then water, m.p. 246–247°, 20.5 g., 80%. Recrystallization from water gave a m.p. of 247–248°, ethanol-water mixture, 248.5–249°. Janson and Pope[6] give m.p. 249–250°. The crude amide is suitable for other transformations. Recrystallization of 18 g. of the amide from 200 ml. of water resulted in recovery of 12.6 g. of product, m.p. 248.5–249°. The diamide is nearly insoluble in ethanol, ethyl acetate, and acetone at room temperature.

Dimethylspiro[3.3]heptane-2,5-dicarboxylate (IX). The known dimethyl ester of Fecht acid was prepared in 95% yield by reaction of the acid chloride with excess absolute methanol. It was isolated by vacuum distillation, b.p. 117–118°/3 mm. Backer and Kemper[7] report b.p. 141°/11 mm.

2,5-Dihydroxymethylspiro[3.3]heptane (X). The known glycol of Fecht acid was prepared by Backer and Kemper[7] by sodium-alcohol reduction of the diphenyl ester in only 46% yield. The glycol has been prepared in excellent yield and purity by reduction of the methyl ester (IX) with lithium aluminum hydride. From 87 g. (0.41 mole) of the ester and 22 g. (excess) of lithium aluminum hydride in anhydrous ether there was obtained 52 g., 81%, of the glycol, b.p. 112–113°/0.1 mm. Backer and Kemper[7] report b.p. 167°/16 mm.

2,5-Dihydroxymethylspiro[3.3]heptane dibenzenesulfonate (XI). The glycol, 15.6 g. (0.1 mole), and 20 ml. of pyridine were cooled to 0° in an ice bath and 35.2 g. (0.2 mole) of benzenesulfonyl chloride slowly added. The mixture was allowed to stand overnight. The product was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution, and copiously with water. It was dried *in vacuo* and cooled at −25° but could not be induced to crystallize.

Anal. Calcd. for $C_{21}H_{24}S_2O_6$: C, 57.78; H, 5.54. Found: C, 57.77; H, 5.80.

2,5-Dibromomethylspiro[3.3]heptane (XII). This dibromide proved most difficult to prepare. The method of Kamm and Marvel[9] was first tried. The reaction, carried out with 87.2 g. of 48% aqueous hydrobromic acid, 12.4 ml. of concd. sulfuric acid and 15.6 g. (0.1 mole) of the glycol, yielded a tarry mass from which none of the desired product could be isolated. The usual methods employing phosphorus bromides or benzenesulfonamide also yielded intractable

(9) O. Kamm and C. S. Marvel, *Org. Syntheses*, Coll. Vol. I, 25 (1941).

tarry residues. Refluxing the glycol bisbenzenesulfonate with potassium bromide in ethanol for several hours gave only traces of the dibromide. The desired dibromide was finally obtained under forcing conditions in poor yield as follows: The glycol, 40 g. (0.26 mole), was refluxed with 3 molar equivalents of 48% aqueous hydrobromic acid for 8 hr. on a steam bath. The reaction mixture was poured into a large volume of water. A blue oil separated. The water was extracted three times with ether, the ethereal solution dried over calcium chloride, the ether stripped, and the product distilled. The material boiling between 85–100°/0.4–0.5 mm. was collected. This product had a low bromine content, 45% as compared to 56.73% theory, and a correspondingly high carbon content. The entire product was recycled through the entire procedure *three* more times. The bromine content gradually increased until, on the fourth cycle, 11.50 g. (16%), of product b.p. 90–92°/0.4 mm., was collected.

Anal. Calcd. for $C_9H_{14}Br_2$: C, 38.33; H, 5.00; Br, 56.67. Found: C, 38.70; H, 5.08; Br, 56.53.

Spiro[3.3]heptane-2,6-diacetic acid (XIV). The dibromide (XII), 11.50 g. (0.041 mole), was dissolved in 50 ml. of absolute ethanol together with 7.6 g. (0.082 mole corrected to 100%) of potassium cyanide and a crystal of potassium iodide and the mixture refluxed for 8 hr. The mixture was evaporated to dryness, the oily residual solid extracted with ether, the ether extract dried over sodium sulfate, and the ether stripped. Attempted vacuum distillation of the residue showed it to be a mixture of unchanged bromide and the desired dinitrile; but the quantity of material was too small to permit isolation of the nitrile in analytical purity. The crude dinitrile was mixed with an excess of 20% aqueous sodium hydroxide and the mixture allowed to stand overnight. The mixture was strongly acidified with concd. hydrochloric acid and extracted with ether in a continuous extractor overnight. On evaporation of the ether to dryness, 3.5 g. (40% based on the dibromide), of crude material was obtained. Two recrystallizations from ethyl acetate gave the acid with constant melting point, 134–135°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.42; H, 7.61.

Molecular weight from neutralization equivalent: Calcd. 212.2. Found: 213. The same acid was obtained in poor yield by Arndt-Eistert conversion from the acyl chloride (II) with diazomethane.

2,6-Bis(N,N-dimethylamido)spiro[3.3]heptane (VIb). An excess (80 g. of a 25% aqueous solution) of dimethylamine was placed in a three necked reaction flask equipped with stirrer, reflux condenser, and dropping funnel and cooled to near 0° in an ice bath. Fecht acid chloride, 22.1 g. (0.1 mole), was added dropwise with rapid stirring keeping the temperature below 10°. The clear solution was evaporated to dryness, the residue dissolved in a minimum of water, and the water solution extracted overnight in a continuous ether extractor. The ether solution was evaporated to dryness yielding 19.5 g. (82%) of crude product, m.p. 105–110°. Recrystallization from isopropyl alcohol–petroleum ether (b.p. 30–60°) sharpened the m.p. to 111–112°. An additional recrystallization from the same system gave a m.p. of 111.5–112°.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.45; H, 9.30; N, 11.65.

2,6-Bis(N-methylamido)spiro[3.3]heptane (VIa). This compound was prepared in a manner analogous to the *N,N*-dimethylamide. From 22.1 g. (0.1 mole) of the acid chloride and an excess of 25% aqueous methylamine, 17 g. (81%) of crude product, m.p. 171–176°, was obtained. Recrystallization from isopropyl alcohol raised the m.p. to 188–190°. Further recrystallization from water gave a constant melting product, m.p. 192–193°.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.00; H, 8.63; N, 13.49.

2,6-Bis(N,N-dimethylaminomethyl)spiro[3.3]heptane (VIIb). The *N,N*-dimethylamide (VIb), 12 g. (0.05 mole), was reduced in the usual manner with an excess of lithium aluminum hydride in absolute ether and yielded 7.5 g., 71%, of the amine, b.p. 142–144°/30 mm. It was converted directly to the *dihydrochloride* by adding an excess of saturated alcoholic hydrogen chloride to the amine dissolved in isopropyl alcohol and precipitating with ether, m.p. 292°. Recrystallization from isopropyl alcohol–methanol gave the salt with m.p. 295–296° dec.

Anal. Calcd. for $C_{13}H_{28}Cl_2N_2$: C, 55.11; H, 9.96; N, 9.89; Cl, 25.05 Found: C, 55.29; H, 10.12; N, 9.82; Cl, 25.00.

The *picrate* was formed in ethanol water and melted at 209–210°.

Anal. Calcd. for $C_{25}H_{32}N_8O_{14}$: N, 16.76. Found: N, 16.47.

2,6-Bis(N-methylaminomethyl)spiro[3.3]heptane (VIIa). This amine was prepared in a similar manner by reduction of 8 g. of the amide (VIa) and obtained in 85% yield as the *dihydrochloride*, m.p. 286–287° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{11}H_{24}Cl_2N_2$: C, 51.76; H, 9.48; N, 10.98; Cl, 27.78. Found: C, 51.64; H, 9.25; N, 11.00; Cl, 27.80.

The *picrate* was prepared from 0.5 g. of the amine liberated from the hydrochloride in methanol water, and recrystallized from methanol water, m.p. 211–212°.

Anal. Calcd. for $C_{23}H_{28}N_8O_{14}$: C, 43.13; H, 4.41; N, 17.50. Found: C, 43.32; H, 4.37; N, 17.46.

2,6-Bis(trimethylaminomethyl)spiro[3.3]heptane diiodide (VIII). The bismethonium quaternary salt of the amine (VIIb) was prepared from 5 g. of the amine and a 10% excess of methyl iodide in isopropyl alcohol. On standing overnight, the product crystallized. It was washed with ethanol and ether and melted at 302°. Recrystallization from methanol–isopropyl alcohol gave white crystals, m.p. 302–303°.

Anal. Calcd. for $C_{15}H_{32}I_2N_2$: C, 36.45; H, 6.52; N, 5.67; I, 51.36. Found: C, 36.44; H, 6.78; N, 5.42; I, 51.30.

2,6-Dicyanospiro[3.3]heptane (XVI). This dicyanide proved almost as difficult to prepare as the dibromide (XII). Several trials using phosphorus pentoxide, thionyl chloride, and phosphorus pentachloride as dehydrating agents yielded little or none of the desired product. The desired dinitrile was finally prepared in good yield as follows: When 20 g. (0.11 mole) of the diamide was heated under reflux for 1 hr. in a mixture of 90 ml. of benzene and 90 ml. of phosphorus oxychloride, the amide all dissolved giving a clear solution. On cooling, the mixture was slowly poured with stirring over 1 l. of crushed ice. The benzene layer was separated and the aqueous phase extracted twice with benzene. The benzene solution was dried over anhydrous sodium sulfate, the benzene stripped, and the product distilled *in vacuo*, b.p. 122–127°/0.3 mm., yield 14.2 g. (88%). The product solidified in the receiver and melted at 45° and was not changed by recrystallization from hexane.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.93; H, 6.89; N, 19.10. Found: C, 73.79; H, 6.56; N, 19.09.

Proof that this was the desired 2,6-dinitrile was afforded by hydrolysis to Fecht acid. One gram of the nitrile was dissolved in 8 ml. of concd. sulfuric acid by swirling. After standing for 5 min., 20 ml. of water was added and the mixture refluxed for 2 hr. On cooling, crystals were deposited which were removed by filtration. The aqueous phase was extracted three times with ether. A total of 1.1 g. of material was obtained from the residue and ether extract, m.p. 205°. Recrystallization from ethyl acetate raised the m.p. to 211–211.5°. A mixed melting point with authentic Fecht acid (I) gave no depression. The infrared absorption spectra were identical.

2,6-Aminomethylspiro[3.3]heptane (XVIIa). When 11 g. of the nitrile (XVI) was reduced with lithium aluminum hydride in anhydrous ether, 7.5 g. (64%) of the desired amine was obtained, b.p. 66–72°/0.35 mm.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07· H, 11.76; N, 18.17. Found: C, 70.53; H, 12.02; N, 18.09.

The dihydrochloride was formed in the usual manner in

isopropyl alcohol, m.p. over 360°, and recrystallized from isopropyl alcohol–ether, m.p. over 360°.

Anal. Calcd. for $C_9H_{20}Cl_2N_2$: C, 47.58; H, 8.87; N, 12.33; Cl, 31.22. Found: C, 47.84; H, 8.85; N, 12.49; Cl, 31.30.

The picrate was formed in the usual manner in methanol, m.p. 236°, not changed on recrystallization.

Anal. Calcd. for $C_{21}H_{21}N_8O_{14}$: C, 41.16; H, 3.95. Found: C, 41.33; H, 4.21.

The *phenylurea* was formed from 0.5 g. of the amine and a slight excess of phenylisocyanate in benzene, m.p. 200–201°. On recrystallization from methanol, the m.p. was raised to 204°.

Anal. Calcd. for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.28. Found: C, 70.53; H, 7.44; N, 14.14.

The *phenylthiourea* was formed from 0.5 g. of the amine and phenylisothiocyanate in benzene, m.p. 185°. On recrystallization from methanol the m.p. was raised to 186°.

Anal. Calcd. for $C_{23}H_{28}N_4S_2$: C, 65.06; H, 6.65; N, 13.28. Found: C, 65.05; H, 6.90; N, 13.40.

The *dibenzamide* was formed from 0.5 g. of the amine and benzoyl chloride by the Schotten-Bauman procedure, m.p. 168–170°, increased to 170–170.5° on recrystallization from methanol.

Anal. Calcd. for $C_{32}H_{36}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.24; H, 7.20; N, 7.83.

2,5-Bismorpholinoethylspiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIc). The bismorpholinoethyl ester of Fecht acid was prepared by adding 4.42 g. (0.02 mole) of the acid chloride in 50 ml. of benzene to 5.24 g. (0.04 mole) of morpholinoethyl alcohol dissolved in 50 ml. of benzene and refluxing several hours. On cooling, the crude product crystallized. It was filtered, washed with benzene and ether, and dried, m.p. 199–201°, 8 g. (83%). Two recrystallizations from isopropyl alcohol–ether gave a constant melting product, m.p. 207–208°.

Anal. Calcd. for $C_{21}H_{36}Cl_2N_2O_6$: C, 52.17; H, 7.51; N, 5.80; Cl, 14.67. Found: C, 52.33; H, 7.66; N, 5.99; Cl, 14.70.

2,5-Bispiperidinoethylspiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIb) was prepared in an analogous manner from 4.42 g. (0.02 mole) of the acid chloride and 5.17 g. (0.04 mole) of piperidinoethyl alcohol. There was obtained 7.8 g. (81%) of product which melted after two recrystallizations from isopropyl alcohol–ether, at 228–229°.

Anal. Calcd. for $C_{23}H_{40}Cl_2N_2O_4$: C, 57.60; H, 8.41; N, 5.84; Cl, 14.79. Found: C, 57.48; H, 8.76; N, 5.90; Cl, 14.97.

2,5-Bis(2-dimethylaminoethyl)spiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIa) was prepared in an analogous manner from 6.63 g. (0.03 mole) of the acid chloride and 5.35 g. (0.06 mole) of 2-dimethylaminoethanol in 150 ml. of benzene and refluxed for 1 hr. There was obtained 11.55 g. crude product, m.p. 209–212° (94%). Recrystallization from methanol–ether raised the m.p. to 234–235° and from isopropyl alcohol–ethanol to 234.5–235°.

Anal. Calcd. for $C_{17}H_{32}Cl_2N_2O_4$: C, 51.13; H, 8.08; N, 7.02; Cl, 17.75. Found: C, 50.81; H, 8.02; N, 7.22; Cl, 17.60.

908 Lincoln Ave.
Falls Church, Va.

[Contribution from The Department of Chemistry, Kansas State College and Strosacker's Laboratory, The Dow Chemical Company]

Dichloromethylallyl Compounds. III. N-(3,3-Dichloro-2-methylallyl)amines

D. G. KUNDIGER,[1] H. PLEDGER, Jr.,[2] and R. L. SOULEN[3]

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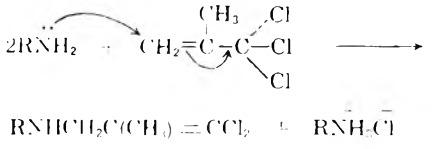
A new series of new amines were prepared by the reaction of 3,3,3-trichloro-2-methyl-1-propene and 1,1,3-trichloro-2-methyl-1-propene with *N*-substituted amines, ammonia, and hydrazine. The physical constants and the preparation of these compounds and some of their derivatives are reported.

In continuation of earlier studies[4] on the chemistry of 3,3,3-trichloro-2-methyl-1-propene (I) and 1,1,3-trichloro-2-methyl-1-propene (II) with nucleophilic reagents, this paper reports the results of a study of the reactions of these chlorides with *N*-substituted amines, ammonia, and hydrazines. Previous work[4,5] has indicated that these isomeric chlorides are highly reactive. The same compound results when either chloride reacts with the same nucleophile. For example, the reaction of aqueous sodium hydroxide with chloride I or II yields 3,3-dichloro-2-methyl-2-propen-1-ol.[6] The reactions of chlorides I and II with amino compounds has further substantiated the earlier indications. The highly exothermic reaction between amino compounds and chloride I probably proceeds by an SN2′ reaction.



The expected inductive withdrawal of electrons from nitrogen by the γ-chlorine atoms in the dichloromethylallyl group is greatly facilitated by the double bond in the allylic system. This base weakening effect leads to interesting results. This

(1) Deceased.

(2) Present address, Organic Process Development Laboratory, The Dow Chemical Company, Freeport, Tex. To whom requests for reprints should be sent.

(3) Portions of this paper represent part of a dissertation submitted by Robert L. Soulen in partial fulfillment of the requirements for the Ph.D. degree at Kansas State University.

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effect is strikingly demonstrated by *N,N*-bis(3,3-dichloro-2-methylallyl)aniline and by tris(3,3-dichloro-2-methylallyl)amine. Neither compound is soluble in concentrated hydrochloric acid but dissolves slowly in concentrated sulfuric acid. Dilution of the sulfuric acid solution yields the amine unchanged. During the reaction of *N*-(3,3-dichloro-2-methylallyl)aniline with chloride I under thermally forced conditions to produce *N,N*-bis(3,3-dichloro-2-methylallyl)aniline, gaseous hydrogen chloride was evolved. These forcing conditions illustrate the base weakening effect of one dichloromethylallyl group attached to nitrogen and the evolution of hydrogen chloride illustrates the even more pronounced effect of two such groups on nitrogen.

Whenever chloride I or II reacts with a primary amine there is a possibility of substitution of two additional groups. Again, however, because of the base weakening effect of one dichloromethylallyl group, substitution of one group predominates and is often exclusive. The predominance of substitution of one group is indicated by the reaction of aniline. Chloride I gave 52.5% monosubstituted aniline and 4.9% disubstituted aniline even though the reaction temperature exceeded 200°.

The reaction of chloride II and ammonia or hydrazine gave unstable products when only one or two dichloromethylallyl groups were substituted. Product stability increased with increase in the number of dichloromethylallyl groups attached to nitrogen. Rapid decomposition of (3,3-dichloro-2-methylallyl)amine and of bis(3,3-dichloro-2-methylallyl)hydrazine could be prevented by formation of the hydrochloride salt.

Pyridine reacted with either chloride I or II yielding the same compound in 100% yield. We have never established whether the compound is 2-(3,3-dichloro-2-methylallyl)pyridine hydrochloride or *N*-(3,3-dichloro-2-methylallyl)pyridinium chloride. We favor the latter structure, as it is the salt one would expect from the reaction scheme we have proposed.

The structure of the disubstituted hydrazine derived from hydrazine and chloride II is suspected of being *N,N'*-bis(2,2-dichloro-3-methylallyl)hydrazine, as the base weakening effect of the firstly substituted group should render the substituted nitrogen less basic than the unsubstituted nitrogen.

Table I contains physical constants of an analytical results on the various amines prepared in this work. Further evidence for their structure was obtained from their infrared absorption spectra. All showed strong absorption at 6.15–6.20 μ and at 11.10–11.22 μ typical of the $Cl_2C{=}C(CH_3)CH_2{-}$ group.

EXPERIMENTAL

General method for the synthesis of N-(3,3-dichloro-2-methylallyl)amines. Either 3,3,3-trichloro-2-methyl-1-propene (I) or 1,1,3-trichloro-2-methyl-1-propene (II) was added slowly to the amine (2 moles of amine to 1 mole of chloride I or II). In most cases the reaction was exothermic and rapid but occasionally heating was required for initiation. After addition, the reaction mixture was heated for an additional period to insure complete reaction. Ether was added to the cooled mixture and the by-product amine hydrochloride separated in near quantitative or quantitative yields. Fractionation of the ether solution gave the *N*-(3,3-dichloro-2-methylallyl)amine. Physical constants and analyses of the various dichloromethylallylamines are listed in Table I.

N,N-Bis(3,3-dichloro-2-methylallyl)aniline. *N*-(3,3-Dichloro-2-methylallyl)aniline, 266.6 g. (1.23 moles), and 196.5 g. (1.23 moles) of 3,3,3-trichloro-2-methyl-1-propene were mixed and heated between 177–183° for 30 min., evolving hydrogen chloride rapidly. After standing 3 days the mixture solidified. This solid was stirred with ether and 10% sodium hydroxide solution. The base extracted ether was dried and concentrated to a solid which was recrystallized from absolute ethanol. The crystals (305.4 g.), m.p. 67.5–68.0°, were distilled giving a center cut, 205.8 g., b.p. 134° (0.4 mm.) –155° (0.2 mm.), m.p. 78.5–82.0°. This material was crystallized from 95% ethanol yielding 160.0 g. of pure *N,N*-bis(3,3-dichloro-2-methylallyl)aniline, m.p. 84.0–85.5°. A mixture melting point of this material with by-product *N,N*-bis(3,3-dichloro-2-methylallyl)aniline obtained from reaction of chloride I and aniline gave no depression. The infrared spectrum of this compound showed bands at 13.40 and 14.43 μ (typical of *N,N*-dialkylated-aniline), 6.15 and 11.21 μ (typical of $Cl_2C{=}C(CH_3)CH_2{-}$ and no band at 2.93 μ (typical of N—H). Analyses are in Table I.

N-(3,3-Dichloro-2-methylallyl)pyridinium chloride. One mole (79.0 g.) of pyridine and 159.5 g. (1.0 mole) of 3,3,3-trichloro-2-methyl-1-propene were mixed and slowly heated to 120° with gradual separation of a red oil. Without further heating, the temperature rapidly rose to 143°. Upon cooling small amounts of ether were added that induced crystallization. The solid was broken up, added to boiling dry carbon tetrachloride, filtered, and dried *in vacuo*. The resulting brown solid (234 g., 99%), m.p. 148.5–150.0°, was used for analysis.

Anal. Calcd. for $C_9H_{10}Cl_3N$: C, 45.32; H, 4.19. Found: C, 45.62; H, 4.09.

The solid was very hygroscopic, dissolved in ethanol and water, and gave an immediate precipitate with aqueous silver nitrate.

3,3-Dichloro-2-methylallylamines. Procedure I. Ammonia was bubbled into a mixture of 478.2 g. (3.0 moles) of 1,1,3-trichloro-2-methyl-1-propene in 500 ml. of 95% ethanol for 3.5 hr. The temperature was held below 35° by a cooling bath during addition, then allowed to stand 2 hr. at room temperature. Hydrogen chloride was bubbled into the alcohol solution until acid to litmus. The solution was concentrated under reduced pressure, ether added, and the amine hydrochlorides filtered. Distillation of the ether gave 21.5 g. of unchanged starting halide and a solid residue. Recrystallization of this solid from ethanol gave 74 g. (17%) of tris(3,3-dichloro-2-methylallyl)amine, m.p. 63.5–65.0°. Analyses are in Table I.

The amine hydrochlorides were mixed into excess 10% sodium hydroxide and extracted with ether. The combined ether extracts were dried and distilled to give 6.6 g. (2.7%) of 3,3-dichloro-2-methylallylamine, b.p. 33° (0.9 mm.), n_D^{20} 1.5052 and 149.6 g. (27%) of bis(3,3-dichloro-2-methylallyl)amine, b.p. 103° (0.3 mm.), n_D^{20} 1.5245.

The primary amine was unstable and decomposed rapidly at room temperature. The hydrochloride salt, m.p. 201–202°, was stable. Analyses are in Table I.

The secondary amine hydrochloride, m.p. 157–158°, was stable and the free amine decomposed after prolonged periods. Analyses are in Table I.

Procedure II. Anhydrous methanol (200 ml.) and 209 g. (1.31 moles) of 1,1,3-trichloro-2-methyl-1-propene were added to approximately 50 ml. of liquid ammonia cooled

TABLE I

PROPERTIES OF SUBSTITUTED DICHLOROMETHYLALLYL AMINES, $Cl_2C{=}C(CH_3){-}CH_2{-}N(R)(R')$

Halide Used[a]	R	R′	B.P.	Mm.	n_D^{20}	d_4^{20}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Yield, %
I	Phenyl	H	111–112	0.9	1.5841	1.243	55.58	55.26	5.13	5.15	32.82	32.45	52.5
I	Phenyl	$Cl_2C{=}C(CH_3)CH_2{-}$	83.5–84.5[b]	—	—	—	49.7	49.1	4.46	4.37	41.82	42.15	4.9[c]
II	Phenyl	H	111–112	0.5	1.5831	—	—	—	—	—	—	—	79.9
I	Phenyl	Methyl	95	0.1	1.5768	1.208	—	—	—	—	30.8	32.1	58.8
I[c]	Phenyl	$Cl_2C{=}C(CH_3)CH_2{-}$	84.5–85.5[b]	—	—	—	—	—	—	—	—	—	48.2
II	Cyclohexyl	H	83	0.6	1.4757	1.104	54.4	53.54	7.31	8.22	—	—	69.8
II	Cyclohexyl	H	not dist.	—	1.4760	—	—	—	—	—	—	—	80.1
I	*n*-Butyl	*n*-Butyl	71–73	0.2	1.4709	0.996	57.14	57.17	9.15	8.70	—	—	72.5
II	*n*-Butyl	*n*-Butyl	not dist.	—	1.4693	—	—	—	—	—	—	—	99.0
II	*n*-Butyl	H	64	1.0	1.4756	1.053	49.0	50.3	8.05	7.72	—	—	52.0
I	1,1,3,3-Tetramethylbutyl	H	78	0.5	1.4788	1.061	57.2	57.0	9.15	8.81	28.1	28.3	59.2
I	*N*(R)(R′)=Piperidyl	—	56	0.1	1.5000	1.103	51.9	52.2	7.27	7.23	—	—	77.0
I	*N*(R)(R′)=Morpholyl	—	72.5	0.8	1.5010	1.187	45.7	45.9	6.24	6.42	—	—	76.0
II	2-Aminoethyl	H	76	1.0	1.5088	1.183	39.4	39.2	6.62	6.57	38.8	38.1	35.4
II	2-Hydroxyethyl	H	107.5	2.2	1.5110	1.225	39.2	39.4	6.03	6.28	38.5	37.9	21.9
II	2-Hydroxyethyl	$Cl_2C{=}C(CH_3)CH_2{-}$	145	0.9	1.5283	—	39.4	39.3	4.93	5.25	46.	45.6	32.7
I[e]	H	H	38	1.1	1.5048	—	—	—	7.36[d]	7.78[d]	60.25	59.98	11.2
I	$Cl_2C{=}C(CH_3)CH_2{-}$	H	96	0.2	1.5242	—	—	—	5.33[d]	5.28[d]	53.90	53.65	68.7
I	$Cl_2C{=}C(CH_3)CH_2{-}$	$Cl_2C{=}C(CH_3)CH_2{-}$	63.5–65.0[b]	—	—	—	—	—	3.64[d]	3.41[d]	55.11	55.35	17.0
I	N(R)(R′)=phthalimidyl	—	118–119[b]	—	—	—	—	—	—	—	26.28	26.47	79.0
I	$Cl_2C{=}C(CH_3)CH_2NH{-}$	$Cl_2C{=}C(CH_3)CH_2{-}$	90–91[b]	—	—	—	—	—	6.98[d]	6.64[d]	53.15	53.36	31.0
I[e]	$Cl_2C{=}C(CH_3)CH_2NH{-}$	H	112	0.2	—	—	30.55	30.75	8.91[d]	9.15[d]	56.47	56.04	37.0

[a] I is 3,3,3-trichloro-2-methyl-1-propene. II is 1,1,3-trichloro-2-methyl-1-propene. [b] Melting point. [c] Equimolar quantities of halide and *N*(3,3-dichloro-2-methylallyl)aniline. [d] Nitrogen analysis. [e] Analysis on hydrochloride salt.

by a Dry Ice bath. A slow stream of ammonia was bubbled through the mixture for 24 hr as it warmed to room temperature. The reaction mixture was concentrated under reduced pressure, poured into 300 ml. of 20% sodium hydroxide, and extracted repeatedly with ether. The ether was dried, treated with hydrogen chloride, and the amine hydrochlorides removed. The ether gave 7.5 g. of starting chloride. The amine hydrochlorides were converted to the free amines and distilled to give 19.8 g. (11%) of 3,3-dichloro-2-methylallylamine, b.p. 38° at 1.1 mm. and 114.3 g. (69%) of bis-(3,3-dichloro-2-methylallyl)amine, b.p. 97° at 0.2 mm.

The benzenesulfonamide of the primary amine was recrystallized from ethanol, m.p. 72–74°. Reported value[7] is m.p. 72–74°.

The acetamide of the secondary amide was prepared from acetic anhydride and bis(3,3-dichloro-2-methylallyl)amine and distilled at 129° (0.01 mm.), n_D^{20} 1.5344.

The dichloroacetamide of the secondary amine was prepared from dichloroacetyl chloride and bis(3,3-dichloro-2-methylallyl)amine and was recrystallized from petroleum ether (b.p. 60–70°) to give a white solid, m.p. 100.0–102.5°.

The trichloroacetamide of the secondary amine was prepared from trichloroacetyl chloride and bis(3,3-dichloro-2-methylallyl)amine and was recrystallized from ethanol to give a slightly yellow solid, m.p. 56.0–58.5°.

The benzenesulfonamide of the secondary amine was crystallized from ethanol, m.p. 131–132°.

3,3-Dichloro-2-methylallylamine via Gabriel synthesis. The Sheehan and Bolhofer modification[8] of the Gabriel synthesis was used to prepare *N*-(3,3-dichloro-2-methylallyl)-phthalimide. From 190 g. (1.02 moles) of potassium phthalimide and 159.4 g. (1.0 mole) of 1,1,3-trichloro-2-methyl-1-propene was obtained 214 g. (79%) of *N*-(3,3-dichloro-2-methylallyl)phthalimide, m.p. 118–119°. Analyses are in Table I.

The Ing and Manske modification[9] of the Gabriel synthesis was used for the hydrolysis of *N*-(3,3-dichloro-2-methylallyl)phthalimide. From 54 g. (0.2 mole) of the phthalimide was obtained 17.2 g. (61%) of 3,3-dichloro-2-methylallylamine, b.p. 85–87° (50 mm.), n_D^{25} 1.4992.

Bis and tris(3,3-dichloro-2-methylallyl)hydrazine. To 320 g. (2.0 moles) of 1,1,3-trichloro-2-methyl-1-propene in 400 ml. ethanol was added 110 g. (3.44 moles) of anhydrous hydrazine in small portions during 1 hr. The reaction was heated at 60° for an additional hour. After cooling, the solid was separated and identified as hydrazine hydrochloride, m.p. 87–89°. The alcohol solution was concentrated under reduced pressure and poured into 5% hydrochloric acid. The solid which separated was washed with 4500 ml. of hot water and was crystallized from ethanol. The solid was identified as tris(3,3-dichloro-2-methylallyl) hydrazine, m.p. 90–91°. Analyses are in Table I.

The hot water washes and the acid solution were combined, made basic with sodium hydroxide, and extracted repeatedly with ether. The ether was dried and distilled to give 101.8 g. (37%) of bis(3,3-dichloro-2-methylallyl hydrazine, b.p. 109–115° (0.2 mm.) and an undistilled solid in the distilling flask. The distillate decomposed rapidly to resinous products but was stable as the hydrochloride salt, m.p. 143–145°. Analyses are in Table I.

This compound was believed to be the symmetrical isomer (see discussion).

The undistilled portion was dissolved in boiling petroleum ether (b.p. 60–70°) and on cooling gave two crystalline forms. These crystals were hand separated: 29.0 g. of hard square plates, m.p. 88°, identical with the tris(3,3-dichloro-2-methylallyl)hydrazine isolated above; 24.0 g. of soft fine needles which were tris(3,3-dichloro-2-methylallyl)hydrazine hydrochloride, m.p. 164–165°. Total yield of the trisubstituted hydrazine was 31%.

Anal. Calcd. for $C_{12}H_{17}Cl_7N_2$: Cl^- 8.11; Cl, 56.75; N, 6.41. Found: Cl, 8.06; Cl, 56.37; N, 6.21.

Acknowledgment. We wish to express our gratitude to The Dow Chemical Company for their financial support of this research.

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

Allylic Chlorides. XXVI. The 1-Chloro-2-heptenes and 1-Chloro-4,4-dimethyl-2-pentenes

LEWIS F. HATCH, HERBERT D. WEISS,[1] AND TAO PING LI

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The 1-chloro-2-heptenes and the 1-chloro-4,4-dimethyl-2-pentenes have been synthesized, characterized, and their relative reactivities toward potassium iodide in acetone and sodium ethoxide in ethanol determined. The data indicate that the rate of reaction is influenced more by the steric requirements imposed by the nature of the group in the *gamma* position of allyl chloride than by inductive effects. Energies and entropies of activation have been calculated for the reaction of the 1-chloro-4,4-dimethyl-2-pentenes with both of these reagents.

The relative reactivities of various methyl substituted allylic chlorides toward potassium iodide in acetone and sodium ethoxide in ethanol have been reviewed by Hatch and Noyes.[2] This area of research has now been extended to include the 1-chloro-2-heptenes (γ-*n*-butylallyl chlorides) and the 1-chloro-4,4-dimethyl-2-pentenes (γ-*iert*-butylallyl chlorides) in order to evaluate further the influence of steric factors on these reactions. A similar study has been made by Bartlett and Rosen on the effect of *n*-butyl and *t*-butyl groups for the reaction between potassium iodide in ace-

(1) Present address: American Alcolac Corporation, Baltimore 26, Md.

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tone and 1-bromo-2-heptyne and 1-bromo-4,4-dimethyl-2-pentyne.[3]

cis-1-Chloro-2-heptene was prepared by the reaction between the corresponding alcohol and phosphorus trichloride.[4] The alcohol was synthesized by the catalytic hydrogenation of 2-heptyn-1-ol using palladium on barium sulfate.[5] The acetylenic alcohol was obtained by the method of Newman and Wotiz.[6] *trans*-1-Chloro-2-heptene was prepared in a similar manner from *trans*-2-hepten-1-ol by use of sodium in liquid ammonia for the reduction.[7,8,9]

The 2-hepten-1-ols have been reported[10,11] but the pure isomers were not isolated. Smets[11] obtained a mixture containing 10% *trans*-2-hepten-1-ol and 90% *cis*-2-hepten-1-ol as indicated by Raman spectra. His claim for pure *trans*-2-hepten-1-ol is based on a stereospecific allylic rearrangement to give only the *trans* isomer. The purity of this alcohol is questioned. Smets prepared the chlorides corresponding to these alcohols. He reported obtaining a mixture containing 25% of the *trans* isomer and 75% of the *cis* isomer. He also reported the preparation of pure *trans*-1-chloro-2-heptene.

The estimation of purity for all of the alcohols and chlorides prepared in the present study is based on their physical properties, infrared spectra, and the melting points of their 3,5-dinitrobenzoates and mixture melting points.

The preparation of both isomers of 1-chloro-4,4-dimethyl-2-pentene by the chlorination of *cis*- and *trans*-4,4-dimethyl-2-pentene with *tert*-butyl hypochlorite has recently been reported.[12] Apparently a mixture of isomers was obtained; detailed physical data were not given. Vernon has utilized 1-chloro-4,4-dimethyl-2-pentene in a kinetic study but neither the method of its preparation nor its geometrical configuration was given.[13]

The 1-chloro-4,4-dimethyl-2-pentenes used in the present investigations were synthesized by an extension of the procedure of Bartlett and Rosen for the production of 4,4-dimethyl-2-pentyn-1-ol. *trans*-4,4-Dimethyl-2-penten-1-ol was obtained by stereospecific reduction *via* the sodium-ammonia method. The *cis* isomer was prepared by catalytic reduction using both Raney nickel[14] and palladium on calcium carbonate.[8,9,15,16] Infrared spectra and physical properties showed the compounds obtained by either catalyst to be identical. The palladium catalyst is recommended for this stereospecific reduction, however, because of the several operational problems inherent in the use of Rancy nickel for this reaction.

The 4,4-dimethyl-2-penten-1-ols were converted to the corresponding chlorides by the use of phosphorus trichloride in the presence of a *small* amount of pyridine[4] and by the reaction between the alcohol and thionyl chloride. The infrared spectra of the chlorides prepared by both methods were essentially identical. The infrared spectrum of the *trans* chloride prepared using thionyl chloride, however, indicated the presence of both a terminal double bond (10.8 μ) and a carbon-carbon triple bond (4.59 μ). These compounds could have been formed by an initial S_Ni' reaction[17] to give 3-chloro-4,4-dimethyl-1-pentene which dehydrochlorinated to *tert*-butylallene. The allene could then rearrange to the corresponding acetylene. There was no allene absorption (5.10 μ). The phosphorus trichloride method is more applicable for the preparation of primary allylic chlorides.

The rate constants for the reaction between *cis*- and *trans*-1-chloro-2-heptene and *cis*- and *trans*-1-chloro-4,4-dimethyl-2-pentene and potassium iodide in acetone were determined at 20° for the γ-*n*-butylallyl chlorides and 10°, 20°, and 30° for the γ-*tert*-butylallyl chlorides. Similar data were obtained for their reaction with sodium ethoxide in ethanol at 50° and at 40°, 50°, and 60°, respectively. These kinetic data and relative reactivities are in Table I.

Vernon has published the results of a kinetic investigation of the reaction between a series of allylic chlorides and sodium ethoxide in ethanol at 44.6°. The relative reactivity of an uncharacterized 1-chloro-4,4-dimethyl-2-pentene obtained from these data is 1.96. From this datum it would appear that Vernon used a mixture of the geometrical isomers of 1-chloro-4,4-dimethyl-2-pentene. This conclusion is substantiated by the reported physical properties [b.p. 63.4–63.6° (58 mm.), n_D^{25}, 1.4390]. The conclusions drawn from the kinetic data of Vernon by DeWolfe and Young[17] in respect to the influence of substituents on the γ-carbon atom of allyl chloride are still valid, however. Both

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TABLE I

REACTION RATES AND RELATIVE REACTIVITIES OF CERTAIN γ-BUTYLALLYL CHLORIDES

Compound	k, l. mole^{-1} hr.$^{-1}$ 10°	20°	30°	Relative Reactivity[a] 20°
REACTION WITH POTASSIUM IODIDE IN ACETONE				
cis-1-Chloro-2-heptene		5.37 ± 0.03		10.7
trans-1-Chloro-2-heptene		1.19 ± 0.02		2.37
cis-1-Chloro-4,4-dimethyl-2-pentene	1.19 ± 0.015	2.97 ± 0.03	8.41 ± 0.16	5.92
trans-1-Chloro-4,4-dimethyl-2-pentene	0.24 ± 0.005	0.692 ± 0.007	2.00 ± 0.02	1.38
REACTION WITH SODIUM ETHOXIDE IN ETHANOL				
	40°	50°	60°	50°[b,c]
cis-1-Chloro-2-heptene		3.66 ± 0.07		3.13
trans-1-Chloro-2-heptene		3.15 ± 0.08		2.77
cis-1-Chloro-4,4-dimethyl-2-pentene	0.721 ± 0.05	1.83 ± 0.02	4.38 ± 0.13	1.55
trans-1-Chloro-4,4-dimethyl-2-pentene	1.03 ± 0.01	2.75 ± 0.03	7.15 ± 0.05	2.33

[a] Allyl chloride as 1.00 with k = 0.502. [b] Allyl chloride as 1.00 with k = 1.18. [c] Vernon [*J. Chem. Soc.*, 4462(1954)] reported a relative reactivity of 1.96 for an uncharacterized 1-chloro-4, 4-dimethyl-2-pentene with sodium ethoxide in ethanol at 44.6°.

isomers of γ-*tert*-butylallyl chloride are less reactive than either isomer of γ-methylallyl chloride (crotyl chloride). The *trans* isomer of γ-*tert*-butylallyl chloride is 1.5 times more reactive than the *cis* isomer toward sodium ethoxide but the *cis* isomer is 4.3 times more reactive than the *trans* isomer with potassium iodide. It is apparent that the difference between these isomers not only depends on the configuration of the allylic chloride but also upon the character of the entering group. This reversal was not observed with the γ-*n*-butylallyl chlorides. They show the expected greater reactivity of the *cis* isomer toward both reagents. The difference in reactivity between the *cis* and the *trans* isomers is larger for the reaction with potassium iodide than it is for the reaction with sodium ethoxide.

Bartlett and Rosen in their work with the butylpropargyl bromides indicate that there is very little difference between the *n*-butyl and the *t*-butyl group for the reaction between the substituted propargyl bromides and potassium iodide in acetone. For the corresponding allylic chlorides when the groups are either *cis* or *trans* to the allylic chlorine atom, the γ-*n*-butylallyl chloride is approximately 1.8 times more reactive than the γ-*tert*-butylallyl chloride.

With both the *n*-butyl and *t*-butyl groups the ratio between the reactivity of the *cis* isomer and the *trans* isomer is approximately 4.4. This difference in reactivity between the geometrical isomers must be steric in nature because the inductive effect is the same for each isomer. The difference between the reactivity of the *n*-butyl and the *t*-butyl groups may be steric or inductive. The large size of the butyl groups in the *cis* position may hinder free rotation of the chloromethyl groups. This is especially true with the *t*-butyl group. This hindrance should be more significant when the entering group is large. This is reflected by the fact that the *cis* derivative is less reactive than the *trans* derivative when sodium ethoxide ion is the reagent. All of these data lead to the conclusion that the electron releasing power of the group in the *gamma* position is not as important as the steric requirements of the group.

The data at three different temperatures for the 1-chloro-4,4-dimethyl-2-pentenes permitted the calculations of the energies of activation and the entropies of activation for their reactions with both reagents (Table II). The energies of activation are essentially the same. The slightly lower energy required for the *cis* isomer indicates that the *trans* form is thermodynamically more stable than the *cis*. The negative values for the entropy of activation indicate that a frequency factor is involved in these reactions. Orientation is required to permit the formation of a transition state. The size and shape of the entering group and the configuration of the allylic chloride are the main factors influencing this orientation.

Similar rate data have been obtained for *gamma* isopropyl, ethyl, and methyl groups and will be published in a subsequent paper.

EXPERIMENTAL

cis-1-Chloro-2-heptene. 2-Heptyn-1-ol. This acetylenic alcohol was prepared from 1-hexyne by the method of Newman and Wotiz.[6] A 44% yield of 2-heptyn-1-ol was obtained: b.p. 57.5° (2mm.); d_4^{20} 0.8868, d_4^{25} 0.8832, d_4^{30} 0.8794; n_D^{20} 1.4530, n_D^{25} 1.4518, n_D^{30} 1.4502; lit.[6] b.p. 98° (28 mm.); d_4^{20} 0.8854; n_D^{25} 1.4523.

cis-2-Hepten-1-ol. *cis*-2-Hepten-1-ol was prepared by the catalytic reduction of 2-heptyn-1-ol using palladium on barium sulfate.[5] The yield was only 45% because of polymerization during the distillation of the 2-hepten-1-ol. Martin, Schepartz, and Dauber also reported polymerization during the distillation of a mixture of 2-hepten-1-ols.[10] The *cis*-2-hepten-1-ol had the odor of new mown hay and the following physical properties: b.p. 59.8–60.0° (4 mm.), d_4^{20} 0.8479, d_4^{25} 0.8436; d_4^{30} 0.8403; n_D^{20} 1.4430, n_D^{25} 1.4414;

TABLE II

ENERGIES AND ENTROPIES OF ACTIVATION FOR THE 1-CHLORO-4,4-DIMETHYL-2-PENTENES

Isomer	Reagent	T°K	$k \times 10^3$ 1 mole^{-1} sec.$^{-1}$	Ea cal. mole^{-1}	$S^{\ddagger}$ cal. deg.$^{-1}$ mole^{-1}
cis	KI	283	0.305	17,130	−13.96
trans	KI	303	0.556	18,070	−13.82
cis	C_2H_5ONa	333	1.23	18,400	−12.23
trans	C_2H_5ONa	333	1.97	19,850	−11.56

n_D^{30} 1.4396; lit.[11,18] b.p. 59.8–60.0° (4 mm.); d_4^{20} 0.8481; n_D^{20} 1.44424.

cis-1-Chloro-2-heptene. *cis*-1-Chloro-2-heptene was obtained by the reaction between *cis*-2-hepten-1-ol and phosphorus trichloride plus pyridine.[4] The yield was 48% and the product had the following physical properties: b.p. 48.5–49.5° (15 mm.); d_4^{20} 0.9002, d_4^{25} 0.8963, d_4^{30} 0.8924; n_D^{20} 1.4471, n_D^{25} 1.4448, n_D^{30} 1.4422; lit.[11,19] b.p. 84.5–86.5° (70 mm); d_4^{20} 0.90142; n_D^{20} 1.44685.

trans-1-Chloro-2-heptene. *trans-2-Hepten-1-ol.* The sodium in liquid ammonia procedure of Campbell and Eby[7] and others[8,9] was used for the *trans* hydrogenation of 2-heptyn-1-ol to *trans*-2-hepten-1-ol. A 51% yield of *trans*-2-hepten-1-ol was obtained. It had the odor of new mown hay and the following physical properties: b.p. 57.9–58.1° (4 mm.); d_4^{20} 0.8516, d_4^{25} 0.8486, d_4^{30} 0.8454; n_D^{20} 1.4460, n_D^{25} 1.4442, n_D^{30} 1.4423; lit.[5] b.p. 52.6–52.8° (4 mm.); d_4^{20} 0.84255; n_D^{20} 1.44249.

trans-1-Chloro-2-heptene. The procedure of Juvalla[4] was used to convert *trans*-2-hepten-1-ol to *trans*-1-chloro-2-heptene by use of phosphorus trichloride in the presence of pyridine. The yield was 33% and the product had the following physical properties: b.p. 50.5–51.1° (15 mm.); d_4^{20} 0.8955, d_4^{25} 0.8911, d_4^{30} 0.8869; n_D^{20} 1.4467, n_D^{25} 1.4448, n_D^{30} 1.4420; lit.[11] b.p. 87–89° (70 mm.); d_4^{20} 0.90128; n_D^{20} 1.44745.

cis-1-Chloro-4,4-dimethyl-2-pentene. This allylic chloride was prepared from the corresponding alcohol which in turn was obtained by the catalytic hydrogenation of 4,4-dimethyl-2-pentyn-1-ol. The acetylenic alcohol was synthesized from pinacolone by using the general procedure of Bartlett and Rosen.[3]

Pinacolone. Pinacolone was obtained both by the dehydration of pinacol hydrate[20] (76% yield) and by the reaction between acetic anhydride and *tert*-butylmagnesium bromide[21] (50% yield).

2,2-Dichloro-3,3-dimethylbutane and 2-chloro-3,3-dimethyl-1-butene. A mixture of these two compounds was obtained when pinacolone was treated with phosphorus pentachloride at 0–5° for 12 hr. The yield of 2-chloro-3,3-dimethyl-1-butene was 15% and the yield of the dichloride was 67%. In another run the yields were 37% and 56% respectively. The melting point of the 2,2-dichloro-3,3-dimethylbutane was 151–152.5° (lit.[3,22] m.p. 151–152°). The physical properties of the 2-chloro-3,3-dimethyl-1-butene were: b.p. 97–99°; d_4^{20} 0.8843; d_4^{30} 0.8794; n_D^{20} 1.4251, n_D^{25} 1.4230, n_D^{30} 1.4203; lit.[23] b.p. 95.5° (730 mm.); d_4^{20} 0.8888; n_D^{20} 1.4247.

3,3-Dimethyl-1-butyne (tert-butylacetylene). The methods of deGraef,[24] Ivitzky,[22] and Bartlett and Rosen[3] for the dehydrochlorination of the mixture of 2-chloro-3,3-dimethyl-1-butene and 2,2-dichloro-3,3-dimethylbutane to 3,3-dimethyl-1-butyne were modified by equipping the reaction flask with a reflux condenser maintained at 50°. This permitted the removal of the acetylene without loss of reactants. A temperature of 160° was maintained for 12 hr. and of 200° for 2 hr. The yield of 3,3-dimethyl-1-butyne was 88% and the physical properties were: b.p. 37.0–37.5° (758 mm.); n_D^{20} 1.3750; lit. b.p. 36.4–37.8 (768 mm.)[3]; n_D^{20} 1.37493.[22]

A yield of 84% 3,3-dimethyl-1-butyne was obtained from the treatment of 2,2-dichloro-3,3-dimethylbutane (1.00 mole) with potassium hydroxide (9.52 moles) in a similar manner to that used for the mixture of mono- and dichlorides. Similar treatment of 2-chloro-3,3-dimethyl-1-butene with potassium hydroxide gave a 85% yield of the acetylene.

4,4-Dimethyl-2-pentyn-1-ol. 4,4-Dimethyl-2-pentyn-1-ol was synthesized by treatment of 3,3-dimethyl-1-butyne with ethylmagnesium bromide to produce the acetylenic Grignard compound and treatment of this compound with formaldehyde.[3,6,25] The yield was 74% and the alcohol had the following physical properties: b.p. 49.0–50.0° (5 mm.); d_4^{20} 0.8578, d_4^{25} 0.8542, d_4^{30} 0.8505; n_D^{20} 1.4420, n_D^{25} 1.4401, n_D^{30} 1.4380; lit.[3] b.p. 71.6° (18 mm.); d_4^{22} 0.8565; $n_D^{21.5}$ 1.4427.

cis-4,4-Dimethyl-2-penten-1-ol. 4,4-Dimethyl-2-pentyn-1-ol was reduced to *cis*-4,4-dimethyl-2-penten-1-ol by Raney nickel[14] using the procedure of Campbell and O'Conner.[26] The yield was 55%. The reduction was also carried out using a palladium on calcium carbonate catalyst[15] and standard procedure.[8,9,16] The yield was 55%. Both processes gave an allylic alcohol with the same physical properties which were: b.p. 73.5–74.0° (20 mm.); d_4^{20} 0.8418, d_4^{25} 0.8384, d_4^{30} 0.8352; n_D^{20} 1.4390, n_D^{25} 1.4370, n_D^{30} 1.4351.

Anal.[27] Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.58; H, 11.59.

cis-1-Chloro-4,4-dimethyl-2-butene. *cis*-1-Chloro-4,4-dimethyl-2-pentene was prepared by treating the corresponding alcohol with phosphorus trichloride and pyridine in a manner similar to that used for the preparation of *cis*-1-chloro-2-heptene from *cis*-2-hepten-1-ol. The yield was 50%. The chloride was also produced by the treatment of *cis*-4,4-dimethyl-2-penten-1-ol with thionyl chloride in the presence of a small amount of pyridine.[28,29] The yield was 54%. Both processes gave products with the same physical properties which were: b.p. 58–59° (50 mm.); d_4^{20} 0.8860, d_4^{25} 0.8816, d_4^{30} 0.8771; n_D^{20} 1.4422, n_D^{25} 1.4399, n_D^{30} 1.4374.

Anal. Calcd. for $C_7H_{13}Cl$: C, 63.39; H, 9.88; Cl, 26.73. Found: C, 64.27, H, 9.81; Cl, 25.76.

trans-1-Chloro-4,4-dimethyl-2-pentene. *trans*-1-Chloro-4,4-dimethyl-2-pentene was synthesized from the corresponding

(18) These data were reported for a mixture containing 10% *trans*-2-hepten-1-ol and 90% *cis*-2-hepten-1-ol.

(19) These data were reported for a mixture containing 25% *trans*-1-chloro-2-heptene and 75% *cis*-1-chloro-2-heptene.

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allylic alcohol which in turn was produced by the *trans* hydrogenation of 4,4-dimethyl-2-pentyn-1-ol.

trans-4,4-Dimethyl-2-penten-1-ol. This alcohol was obtained by the hydrogenation of 4,4-dimethyl-2-pentyn-1-ol with sodium in liquid ammonia in a process similar to that used for the production of *trans*-2-hepten-1-ol from 2-heptyn-1-ol. The yield was 80% and the physical properties were: b.p. 71.2–72.7° (20 mm.); d_4^{20} 0.8325, d_4^{25} 0.8291, d_4^{30} 0.8256; n_D^{20} 1.4380, n_D^{25} 1.4360, n_D^{30} 1.4340.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.69; H, 11.91.

trans-1-Chloro-4,4-dimethyl-2-pentene. *trans*-1-Chloro-4,4-dimethyl-2-pentene was prepared from *trans*-4,4-dimethyl-2-penten-1-ol by reaction with phosphorus trichloride and with thionyl chloride using the same procedures as used for the preparation of the *cis* isomer. The yields were 48% and 56% respectively. The infrared spectra of the compounds produced by these two methods show some small differences. The product from the thionyl chloride procedure has a peak at 4.6 μ indicating the presence of a carbon-carbon triple bond.

The following physical constants were obtained from the chloride synthesized using phosphorus trichloride: b.p. 59–59.5° (50 mm.); d_4^{20} 0.8826, d_4^{25} 0.8783, d_4^{30} 0.8737; n_D^{20} 1.4410, n_D^{25} 1.4387, n_D^{30} 1.4361.

Anal. Calcd. for $C_7H_{13}Cl$: C, 63.39; H, 9.88; Cl, 26.73. Found: C, 63.50; H, 9.51; Cl, 26.36.

3,5-Dinitrobenzoates. The 3,5-dinitrobenzoates of the alcohols were prepared by standard procedure. The 3,5-dinitrobenzoates of the chlorides were prepared by reaction with the silver salt of 3,5-dinitrobenzoic acid. All melting points are corrected.

2-Heptyn-1-ol: m.p. 61.9–62.9.

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: N, 9.14. Found: N, 8.88.

cis-2-Hepten-1-ol: m.p. 41.1°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: N, 9.08. Found: N, 9.06.

trans-2-Hepten-1-ol: m.p. 56.3–56.8.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: N, 9.08. Found: N, 8.89.

cis-1-Chloro-2-heptene: m.p. 41.0–41.3°.

trans-1-Chloro-2-heptene: m.p. 56.5–56.9°.

cis-4,4-Dimethyl-2-penten-1-ol: m.p. 68–69°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: N, 9.08. Found: N, 9.08.

trans-4,4-Dimethyl-2-penten-1-ol: m.p. 86–86.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: N, 9.08. Found: N, 9.27.

cis-1-Chloro-4,4-dimethyl-2-pentene: m.p. 68.5–69°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.75; H, 5.04; N, 8.97.

trans-1-Chloro-4,4-dimethyl-2-pentene: m.p. 86.5–87°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.27; H, 5.04; H, 9.05.

Infrared spectra. The infrared spectrum of each of the compounds prepared in this study was obtained. With each compound the spectrum confirmed the assigned structure. Photostatic copies of these spectra are available upon request.

Reaction with potassium iodide in acetone. The procedure used was the same as that described previously.[30] With the usual modified second-order rate equation, the plot of log $5\text{-}Z/(5)(1\text{-}Z)$ *vs.* time, where Z is the fraction of potassium iodide have reacted in time t, gave a straight line between 40 and 90% reacted at 20° for *cis*-1-chloro-2-heptene and between 21 and 68% reacted at 20° for *trans*-1-chloro-2-heptene. The rate data are summarized in Table I.

Rate data for *cis*- and *trans*-1-chloro-4,4-dimethyl-2-pentene were obtained at 10°, 20°, and 30°. The plot of log $b(a - x)/a(b - x)$ *vs.* time for the *cis* isomer gave a straight line between 21 and 71% reacted at 10°, between 25 and 74% at 20°, and between 49 and 70% at 30°. The *trans* isomer gave a straight line between 37 and 62% reacted at 10°, between 34 and 72% at 20°, and between 54 and 73% at 30°. Representative rate data are summarized in Table I. Thermodynamic functions calculated from these data are in Table II.

Reaction with sodium ethoxide in ethanol. The procedure used was similar to that described previously.[31] The sodium ethoxide solution was 0.05040M for the reaction of both *cis*- and *trans*-1-chloro-2-heptene. Both chlorides were 0.06345M. The data were calculated using the rate expression for a second-order reaction. A plot of log $b(a - x)/a(b - x)$ *vs.* time gave a straight line for the *cis* isomer between 11 and 56% reacted at 50° and for the *trans* isomer between 19 and 55% reacted at the same temperature. The rate data are summarized in Table I.

Rate data for *cis*- and *trans*-1-chloro-4,4-dimethyl-2-pentene were obtained at 40°, 50°, and 60°. A plot of log $b(a - x)/a(b - x)$ *vs.* time for the *cis* isomer gave a straight line between 30 and 58% reacted at 40°, between 29 and 49% at 50°, and between 50 and 69% reacted at 60°. The *trans* isomer gave a straight line between 39 and 64% reacted at 40°, between 43 and 67% at 50°, and between 53 and 67% reacted at 60°. The concentration used for the *cis* isomer were a(chloride) = 0.1046M and b(NaOH) = 0.04789M at 40°, a = 0.05289M and b = 0.04784M at 50°, and a = 0.05289M and b = 0.04789M, at 60°. The concentration for the *trans* isomer were a = 0.1034M and b = 0.04788M at 40°, a = 0.05259M and b = 0.04784M at 50°, and a = 0.05259M and b = 0.04788M at 60°. Representative rate data are given in Table I. Thermodynamic data are in Table II.

Acknowledgment. This research was supported in part by a Research Fellowship from the Research Corporation (H.D.W.) and in part by The Robert A. Welch Foundation. The authors wish to acknowledge their indebtedness to these two sources of funds for research.

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Reactions of Lactams with Diazoalkanes[2]

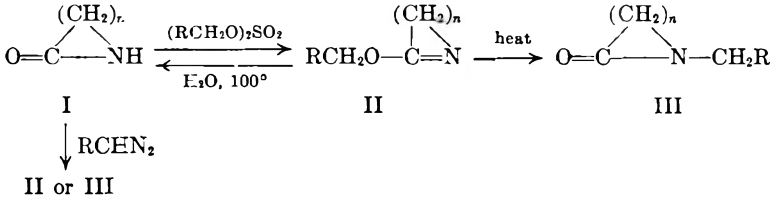
JACK W. RALLS[3]

Received April 22, 1960

Five-, six-, and seven-membered lactams react sluggishly with diazomethane and diazoethane to produce *O*-alkyllactims or *N*-alkyllactams. Only traces of products are formed from lactams and diazoalkanes in pure ether solution. The reaction is promoted by alcohols. Caprolactam and valerolactam give *O*-alkyllactims with alcoholic, ethereal diazoalkane solutions. The *N*-alkylation of butyrolactam is catalyzed by fluoboric acid.

During a study of vegetable flavor, non-volatile acids were determined by gas chromatography of their ethyl esters.[4,5] In the preparation of reference standards for this determination, an anomalous reaction was observed between 5-pyrrolidone-2-carboxylic acid and diazoethane. A second product, $C_9H_{15}O_3N$, accompanied the expected ethyl ester; it appeared to be formed by ethylation of the lactam moiety. To obtain a better understanding of this result, an investigation of the reactions of monocyclic lactams with diazoalkanes was made.

A literature search through 1956 revealed no previous description of the reactions of monocyclic, monofunctional lactams with diazoalkanes. A number of more complex lactams have been treated with diazomethane and the products identified. While oxindole does not react,[6] the methylation



of 3-hydroxymethyleneoxindole has been reported by several groups[7]; the products are 3-methoxymethyleneoxindole and 2-methoxy-3-formylindole. Benzoxazolinones produce *N*-alkylated products on treatment with diazomethane.[8] Dissolved 2-oxo-1,2-dihydrobenzo-1,3,4-triazine reacts to produce the *O*-alkylated product; treatment of the solid compound with ethereal diazomethane results in *N*-alkylation primarily.[9] The recorded information suggests that *N*-alkylation is the expected result of the reaction between lactams and diazoalkanes. *O*-alkylation would take place when the rare[10,11] lactim tautomer is favored.

The alkylation, hydrolysis, and thermal rearrangement of lactams are summarized in the following representation. The preparation of *O*-alkylcaprolactims (II. $n = 5$, R = CH_3, H) by the slow addition of an alkyl sulfate to a refluxing solution of caprolactam in benzene was described by Benson and Cairns.[12] Using the same conditions, it was found that valerolactam gave the *O*-alkyllactim (II. $n = 4$, R = H) and that butyrolactam gave only the *N*-alkyllactam (III. $n = 3$, R = CH_3). Thermal rearrangement of the *O*-alkyllactims provided the *N*-alkyllactams.[12]

Analysis of the mixtures produced by the reactions of lactams with diazoalkanes was made using gas chromatography. The retention times of the compounds used in this study are tabulated in Table I.

The results of reactions of lactams with two equivalents of diazoalkane under various solvent conditions are shown in Table II. The extent of reaction is very low with alcohol-free, ethereal, solutions of diazoalkanes.

With the six- and seven-membered ring lactams,

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Dept. of Agriculture.

(2) Presented in part before the Organic Chemistry Division, American Chemical Society, 137th National Meeting, Cleveland, Ohio, April 1960.

(3) Collaborator employed by the National Canners Association with which this work was conducted cooperatively.

(4) H. G. Walker, unpublished results, Western Regional Laboratory, 1956–57.

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(6) G. Heller, *Ber.*, **52**, 741 (1919).

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(12) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).

TABLE I

RETENTION TIMES FOR LACTAMS AND ALKYLATED LACTAMS, MINUTES

Compound	Column Substrate: LAC 446 150°	LAC 446 202°	Apiezon 150°	DEGA 202°
N-Ethylbutyrolactam	—	—	12.3	—
Butyrolactam	—	—	18.4	—
O-Methylvalerolactim	1.6	—	4.5	—
N-Methylvalerolactam	15.0	—	—	—
Valerolactam	45.2	—	—	—
O-Methylcaprolactim	2.0	—	6.6	—
O-Ethylcaprolactim	2.3	—	9.0	—
N-Ethylcaprolactam	20.6	—	29.7	—
Caprolactam	54.2	11.3	—	—
Ethyl 1-ethyl-5-pyrrolidone-2-carboxylate	12.1	2.6	—	16.8
Ethyl 5-pyrrolidone-2-carboxylate	>150.0	32.9	—	42.8

TABLE II

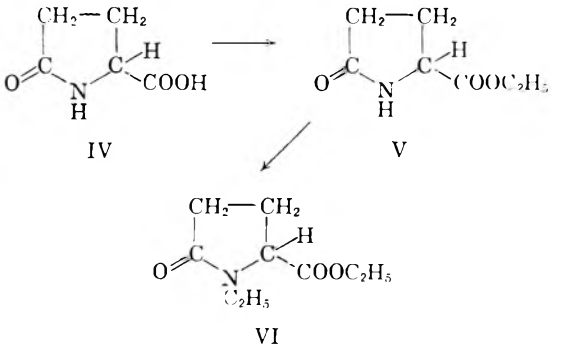
REACTIONS OF LACTAMS WITH DIAZOALKANES

Compound	Conditions[a]	Products, Ratio of GC Peak Areas: *O*-Alkyl	*N*-Alkyl	Lactam
Butyrolactam	C	0	0	98
	D	0	1	15
Valerolactam	A	1	0	63
	B	1	0	7.3
Caprolactam	A	1	0	86
	B	1	0	14
	C	1	0	10
Ethyl 5-pyrrolidone 2-carboxylate	C	0	1	29
5-Pyrrolidone-2-carboxylic acid	C	0	1	2
	E	0	1	1275

[a] A. Diazomethane in anhydrous ether. B. Diazomethane in ether-methanol. C. Diazoethane in ether-ethanol-1-propanol. D. Diazoethane in ether + 5 mole % fluoboric acid. E. Diazoethane in anhydrous ether.

the addition of alcohol promotes a slow reaction to form *O*-alkyllactims. No reaction takes place with the unsubstituted butyrolactam until the reaction is catalyzed with fluoboric acid[13,14] and the product is the *N*-alkyllactam.

The observation which motivated this study is apparently a special case of catalysis by the surface of the ether-insoluble 5-pyrrolidone-2-carboxylic acid (IV). The secondary product is ethyl 1-ethyl-5-pyrrolidone-2-carboxylate (VI); this conclusion follows from the empirical formula, infrared spectrum, and thermal and hydrolytic[12] stability. The observation that V gives about a 3% yield of VI under conditions where butyrolactam forms no *N*-ethylbutyrolactam may imply that a concerted intramolecular *trans*-ethylation is operating in the



pyrrolidonecarboxylic acid series. No further study of these reactions is planned.

The results reported here emphasize the importance of using alcohol-free diazoalkane solutions to avoid possible reaction with the lactam portion of a compound being treated. The reaction of lactams with diazoalkanes is so slow that in most uses of diazoalkanes other functional groups would react preferentially to the lactam portion. A recent example of this situation is the formation of the enol ether of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate on reaction with excess diazomethane in ether-methanol.[15]

EXPERIMENTAL

Diazoalkane solutions. A. Diazomethane in absolute ether prepared from nitrosomethylurea by distillation with ether and drying over potassium hydroxide pellets.[16] B. Above preparation containing added methanol (2% by volume). C. Diazoethane in ether containing some ethanol and 1-propanol[17] prepared from nitrosoethylurethane by distillation with ether.[18] D. Diazoethane in anhydrous ether prepared from nitrosoethylurethane and a solution of sodium in ethylene glycol with nitrogen sweeping.[19] The yield was only 25% and considerable low boiling material was formed concurrently (shown by gas chromatography). E. Diazoethane in anhydrous ether prepared as for diazomethane[20] except that *N*-ethyl-*N*-nitroso-*p*-toluenesulfonamide[21] was used in place of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; yield 35%. The content of diazoalkanes was determined by the benzoic acid assay method. The reactions of lactams with diazoalkane solutions were carried out by swirling at 0–4° for 1 hr. followed by standing at 22–26° for 16 hrs.

The gas chromatography unit was an Aerograph Model A-110 C instrument with a four filament thermal conductivity cell and a 1-mv., recorder. The 1/4 in. by 5 ft. columns used were LAC 446 (glycol-adipate polymer), Apiezon "M," or diethylene glycol–adipate polymer (DEGA) 30 parts on firebrick (30–60 mesh) 70 parts. The carrier gas was helium at a flow rate of 50 ml. per min. Temperature control was ±1°.

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(21) D. H. Hey and T. J. deBoer, *Rec. trav. chim.*, **73**, 686 (1954).

Preparation of the reference compounds followed literature directions. *O*-ethylcaprolactim[12] (infrared: 3.4, 5.95, 6.90, 7.26, 7.45, 7.98, 8.37, 9.17, 9.52 μ), *N*-ethylcaprolactam[12] (infrared: 3.42, 6.12, 6.74, 6.96, 7.25, 8.34 μ), *N*-methylvalerolactam[22] [infrared: 2.9 (hygroscopic), 3.4, 6.14, 6.64, 7.38 μ]. *O-Methylvalerolactim* was prepared using the method described for *O*-methylcaprolactim.[23] The fraction b.p. 56°/32 mm. was collected, yield 48%, n_D^{25} 1.4538. Infrared: 3.4, 5.96, 6.96, 7.35, 7.45, 8.22, 9.83 μ.

Anal. Calcd. for $C_6H_{11}ON$ (113.15): C, 63.68; H, 9.80; N, 12.38. Found: C, 63.4; H, 9.65; N, 12.3.

Attempted *O*-alkylation[23] of 2-pyrrolidone (butyrolactam) gave, as the only product, *N*-ethylbutyrolactam,[24] b.p. 90–92°/15 mm., n_D^{25} 1.4624 in 38% yield.

Treatment of ethyl D,L-5-pyrrolidone-2-carboxylate under the same conditions[23] with ethyl sulfate resulted in a partial reaction (ethyl sulfate recovered) and a poor yield of ethyl 1-ethyl 5-pyrrolidone-2-carboxylate.

The following method for preparation of the known[25] ethyl D,L-5-pyrrolidone-2-carboxylate was used: A suspension of 15 g. of D,L-5-pyrrolidone-2-carboxylic acid[26] in 150 ml. of ethanol was mixed with 1.5 g. of *p*-toluenesulfonic acid monohydrate and heated under reflux. The solution was treated with 50 ml. of benzene and slowly distilled using a Vigreux column over a period of 0.5 hr. During another 4.5 hr., addition of a mixture of 75 ml. of benzene and 19 ml. of ethanol was made to keep the volume of the reaction mixture essentially constant. The cooled reaction mixture was treated with 0.42 g. of anhydrous sodium carbonate, filtered, and the ethanol and benzene removed at reduced pressure. The residue was distilled. The fraction boiling at 136–138°/0.5 mm. was collected. The liquid product (15.9 g., 87% yield) solidified after long standing, m.p. 49–51°; infrared: 3.05, 3.32, 5.75, 5.85, 8.28 μ.

Anal. Calcd. for $C_7H_{11}O_3N$ (157.17): C, 53.49; H, 7.06; N, 8.91. Found: C, 53.4; H, 6.99; N, 8.80.

Ethyl 1-ethyl-5-pyrrolidone-2-carboxylate. The reaction of 3 g. of D,L-5-pyrrolidone-2-carboxylic acid with two equivalents of diazoethane[18] gave a liquid product. Distillation produced 0.8 g. of liquid, b.p. 83–85°/2 mm., n_D^{25} 1.4496, and 1.8 g. of ethyl 5-pyrrolidone-2-carboxylate. The first fraction was not homogenous as shown by gas chromatography. The purified sample was isolated from the effluent helium stream of the gas chromatography unit, n_D^{25} 1.4596, infrared: 3.36, 5.74, 5.88, 6.85, 7.03, 7.80, 8.34 μ.

Anal. Calcd. for $C_9H_{15}O_3N$ (185.22): C, 58.36; H, 8.16; N, 7.56. Found: C, 57.6; H, 8.15; N, 7.45.

The product was stable at 180–220° and also was recovered after heating in boiling water for 5 hr.[12,27]

Acknowledgments. The author is indebted to H. G. Walker, J. W. Corse, and L. A. Goldblatt for gifts of reagents and for discussions of the problem. The analyses were made by L. M. White and G. E. Secor. The 2-pyrrolidone was a gift from Antara Chemicals, New York.

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(27) Mention of specific products does not imply endorsement by the Department of Agriculture over others of a similar nature not mentioned.

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

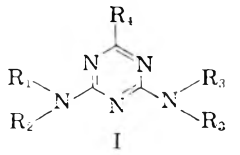
Guanamines. V. Chloromethylguanamines

SEYMOUR L. SHAPIRO, ELAINE S. ISAACS, VINCENT A. PARRINO AND LOUIS FREEDMAN

Received May 19, 1960

A series of chloromethylguanamines (I) have been prepared. The reduction of I, R_4 = $-CH_2Cl$ to I, R_4 = $-CH_3$ with acetone-sodium iodide-acetic acid has been effected in a wide variety of I, and a mechanism for this reaction proposed.

As intermediate reactants for preparation of aminomethylguanamines[1] and allied derivatives, halomethylguanimines of the type I were required.



I

R_1 = alkyl, aralkyl, aryl
R_2 = hydrogen, alkyl
R_1R_2N = heterocyclic rings
R_3 = hydrogen, methyl
R_4 = $-CH_2Cl$, $-CHCH_3Cl$

The compounds were obtained from the R_1-R_2—N^1—, R_3R_3—N^5— substituted biguanide upon reaction with the appropriate ester, $R_4COOC_2H_5$, or acid chloride, R_4COCl, as previously described[2] (Table I).

As reactions of the halogen in chloromethylguanamines have been only briefly evaluated,[3–5] it was of interest to study this in further detail.

Heating typical compounds wherein I, R_4 = $-CH_2Cl$ (or even $-CH_2I$), $-CHCH_3Cl$ in alcoholic silver nitrate gave no precipitate of silver halide. Treatment of such compounds with sodium iodide in acetone, with warming, yielded rapid precipitation of sodium chloride. Employment of acetone–sodium iodide–acetic acid reagent[3] (ASA reagent) resulted in rapid oxidation of iodide to iodine. Upon treatment of the reaction mixture with aqueous sodium bisulfite, a variety of I,

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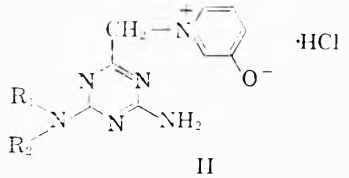
R = —CH_2Cl, were converted to I, R = —CH_3 including compounds in which R_1, R_2, and R_3 afforded mono-tetra substitution on the amino nitrogens.

The conversion was confirmed by identity of the dehalogenated compounds with authentic I, R_4 = CH_3 prepared from the biguanide and ethyl acetate or acetyl chloride, or through the corresponding picrates. In the preparation of compound 47, using acetyl chloride, 67% of *N*-carbamidoindoline was isolated, presumably from hydrolysis of the reactant biguanide.[6]

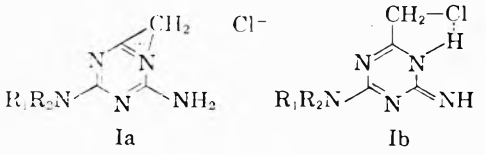
When the acetic acid was not incorporated in the ASA reagent, the reduction of the I, R_4 = —CH_2Cl to I, R_4 = CH_3 was effected, with compound 9 giving compound 39.

The chloromethylguanamines reacted readily with 3-hydroxypyridine to give betaines[7] (II).

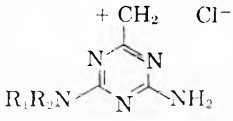


II

Consideration of the structural formula of the chloromethylguanamines in terms of such reactions indicates that forms such as Ia–Ic may be proposed in addition to the conventional formula, I.



Ia Ib



Ic

The ionic character of the halogen in formulas Ia and Ic is not consistent with the noted inactivity of the compounds with the alcoholic silver nitrate. Elimination of formula Ia, a modification of the ethyleneimonium ion, excluded consideration of these compounds as typical of adrenergic blocking agents.[8]

Form Ib, requires that at least one of the amino nitrogen substituents, R_1—R_3 be hydrogen and conversion to I, R_4 = CH_3 of the tetra-substituted compound 23 with the ASA reagent eliminates form Ib in this reaction.

In the attempt to elucidate, in particular, the "positive halogen"[9] reaction with the ASA reagent, other types of halomethyl compounds were evaluated. Benzyl halides were not reduced to toluene with the ASA reagent. However, selected benzotrichlorides[9] give this reaction in acetic acid medium on prolonged heating, with enhancement of positive halogen activity as the number of chlorine atoms on the reactant group increases. By contrast, in this work the reaction proceeded in less than one hour at 20°, and in the absence of acetic acid. It was observed as well, that as additional halogen was introduced to give I, R_4 = —$CHCl_2$,[3] —$CHBr_2$, —CCl_2F, —CF_3[2] the reaction failed. Additionally, compound 25, where I, R_4 = —$CHClI_3Cl$ was recovered unchanged suggesting a steric influence, although the excellent yield with I, R_4 = —CH-CH_3Br to I, R_4 = —C_2H_5[3] argues for greater reactivity of bromine in this reaction.[10] The mechanism proposed by the Spanish workers[9] does not therefore, apply in the ASA reaction.

The phenacyl halides were reduced to the acetophenones[11,12] under conditions more vigorous than herein employed. In this work phenacyl halides were found to react promptly in the ASA reaction to give the acetophenones.

Significant distinctions are found, however, between the phenacyl halides and I, R_4 = —CH_2Cl, in that the former react rapidly with alcoholic silver nitrate, whereas the latter do not react at all. Additionally, I, R_4 = —CH_2Cl is readily reduced to I, R_4 = —CH_3 with palladium on calcium carbonate,[3] whereas 2,4′-dibromoacetophenone is reduced to phenacyl bromide by palladium on charcoal.[13]

Paralleling some of the properties of I, R_4 = —CH_2Cl, is 1-phenyl-5-chloromethyl tetrazole[14] which is highly reactive in second order nucleophilic substitution reactions, but unreactive under first order conditions. This compound also reacts rapidly with amines.[15]

In keeping with concepts embodying the —C = N— group of the triazine ring as a carbonyl type function,[2,16] and with analogies similarly applied by Herbst[17] to the tetrazoles, the halomethylguan-

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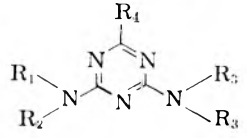
TABLE I

GUANAMINES[a]



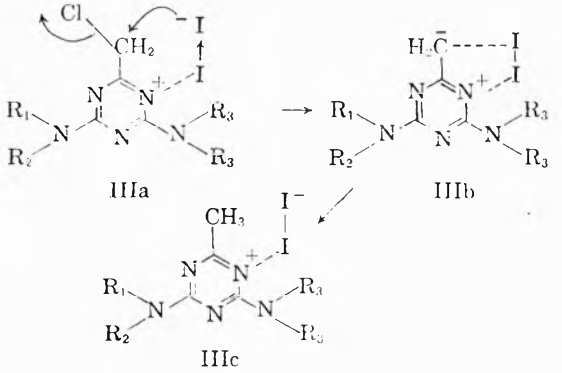
No.	R_1	R_2	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R_4 = CH_2Cl							
1	CH_3—	CH_3—	176–179	A	57	$C_6H_{10}ClN_5$	38.4	38.5	5.4	5.5	37.2	37.4
2	C_3H_5—[f]	H	125–126	A	52	$C_7H_{10}ClN_5$	42.1	41.7	5.1	4.9	35.1	35.2
3	n-C_4H_9—	H	118–120	A	32	$C_8H_{14}ClN_5$					32.5	32.4
4	n-C_5H_{11}—	H	118–119	A	39	$C_9H_{16}ClN_5$					30.5	30.2
5	HPic[g]		135–136	B		$C_{17}H_{19}ClN_8O_7$	39.3	38.8	4.2	4.2	24.4	24.4
6	i-C_5H_{11}—	H	103–105	A	37	$C_9H_{16}ClN_5$	47.7	48.1	7.0	7.3		
7	HPic[g]		142–143	B		$C_{12}H_9ClN_8O_7$	39.3	39.4	4.2	4.1	24.4	24.5
8	—$(CH_2)_5$—		160–162	A	59	$C_9H_{14}ClN_5$	47.5	48.0	6.2	6.5		
9	$C_6H_5CH_2CH_2$—	H	145–147	A	85	$C_{12}H_{14}ClN_5$	54.7	54.8	5.4	5.3	26.6	26.8
10	$C_6H_5CH_2$—	CH_3—	115–117	A	60	$C_{12}H_{14}ClN_5$	54.7	55.1	5.4	5.3	26.6	26.4
11	p-$CH_3C_6H_4$—	H	162–163	A	61	$C_{11}H_{12}ClN_5$					28.1	27.9
12	p-$CH_3OC_6H_4$—	H	185–187	A	35	$C_{11}H_{12}ClN_5O$	49.7	49.3	4.6	5.0		
13	m-ClC_6H_4—	H	129–134	C	23	$C_{10}H_9Cl_2N_5$					25.9	25.5
14	p-ClC_6H_4—	H	185–187	A	73	$C_{10}H_9Cl_2N_5$					25.9	26.2
15	3,4-di$CH_3C_6H_3$—	H	218	F	13	$C_{12}H_{14}ClN_5$					26.6	26.6
16	—$C_6H_4CH_2CH_2$—		>300	i	57	$C_{12}H_{12}ClN_5$	55.1	54.8	4.6	4.6	26.8	26.9
17	—$C_6H_4CH_2CH_2CH_2$—[k]		135–147	C	53	$C_{13}H_{14}ClN_5$[l]	56.6	56.8	5.1	5.3		
18	—$CH_2C_6H_4CH_2CH_2$—[m]		178–180	F	62	$C_{13}H_{14}ClN_5$	56.6	57.0	5.1	5.2		
19[a1]	CH_3—	CH_3—	65–67	C	30	$C_8H_{14}ClN_5$	44.5	45.0	6.5	6.4	32.5	32.2
20[a1]	C_6H_5—	H	105	D	57	$C_{12}H_{14}ClN_5$					26.6	26.1
21[a1]	2,6-di$CH_3C_6H_3$—	H	140–141	A	16	$C_{14}H_{18}ClN_5$					24.0	23.5
22[a1]	HPic[g]		165–167	E		$C_{20}H_{21}ClN_8O_7$	46.1	46.3	4.1	4.5		
23[a1]	—$C_6H_4CH_2CH_2$—[h]		135–136	C	58	$C_{14}H_{16}ClN_5$	58.0	57.8	5.6	5.6		
					R_4 = —$CHCH_2Cl$							
24	CH_3—	CH_3—	159–160	C	49	$C_7H_{12}ClN_5$	41.7	42.0	6.0	5.9	34.7	35.1
25	$C_6H_5CH_2CH_2$—	H	128–129	C	66	$C_{13}H_{16}ClN_5$	56.2	56.1	5.8	6.1	25.2	25.4
26	C_6H_5—	H	140–141	C	62	$C_{11}H_{12}ClN_5$	52.9	52.8	4.9	5.1	28.1	28.2
27	o-$CH_3C_6H_4$	H	155–157	C	49	$C_{12}H_{14}ClN_5$	54.7	54.6	5.4	5.3	26.6	26.9
28	2,6-di$CH_3C_6H_3$—	H	198–200	C	28	$C_{13}H_{16}ClN_5$	56.2	56.2	5.8	6.0	25.2	25.5
29	o-ClC_6H_4—	H	127–128	C	30	$C_{11}H_{11}Cl_2N_5$	46.5	46.2	3.9	4.0		
30	m-ClC_6H_4—	H	51–54	C	18	$C_{11}H_{11}Cl_2N_5$	46.5	46.6	3.9	4.3	24.7	24.8
31	2-CH_3-5-ClC_6H_3—	H	148–149	C	40	$C_{12}H_{13}Cl_2N_5$	48.3	48.4	4.4	4.1		
32	o-BrC_6H_4—	H	131–133	C	40	$C_{11}H_{11}BrClN_5$	40.2	40.3	3.4	3.2	21.3	20.9
33	m-X-C_6H_4—[n]	H	141–143	C	18	$C_{13}H_{16}ClN_5O$	53.2	52.9	5.5	5.7	23.8	24.0

TABLE I (*Continued*)

No.	R_1	R_2	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R_4 = CH_3—[o]							
34	CH_3—	CH_3—	192–193	A	39[p]	$C_6H_{11}N_5$	47.0	47.0	7.2	6.9		
35	C_3H_5—[f]	H	117–119	A	44	$C_7H_{11}N_5$					42.4	42.7
36	*n*-C_6H_{11}—	H	138–141	A	69	$C_9H_{17}N_5$	55.4	55.8	8.8	8.7	35.9	35.8
37	*i*-C_6H_{11}—	H	134–135	A	40	$C_9H_{17}N_5$	55.4	55.3	8.8	8.8	35.9	36.2
38	—$(CH_2)_5$—		192–193	A	73	$C_9H_{15}N_5$	55.9	55.9	7.8	7.9	36.2	36.4
39	$C_6H_5CH_2CH_2$—	H	145–147	A	67	$C_{12}H_{15}N_5$	62.9	62.6	6.6	6.6	30.6	30.6
40	HPic[q]		240–241	E		$C_{18}H_{18}N_8O_7$	47.2	47.2	4.0	3.7	24.5	24.3
41	$C_6H_5CH_2$—	CH_3—	134–136	A	56	$C_{12}H_{15}N_5$	62.9	63.0	6.6	6.6	30.6	30.5
42	HPic[q]		169–171	G		$C_{18}H_{18}N_8O_7$	47.2	47.3	4.0	3.4	24.5	24.6
43	*p*-$CH_3C_6H_4$—	H	211–213	A	21	$C_{11}H_{13}N_5$	61.4	61.1	6.1	5.9	32.5	32.9
44	*p*-$CH_3OC_6H_4$—	H	213–214	A	14	$C_{11}H_{13}N_5O$					30.3	30.3
45	*p*-ClC_6H_4—	H	194–196	A	15	$C_{10}H_{10}ClN_5$	51.0	51.1	4.3	4.4	29.7	30.0
46	HPic[q]		215–219	E		$C_{16}H_{13}ClN_8O_7$					24.1	23.9
47	—$C_6H_4CH_2CH_2$—		229–233	A	12[p]	$C_{12}H_{13}N_5$	63.4	62.8	5.8	5.8	30.8	31.3
48[a1]	C_6H_5—	H	119–120	A	37[p]	$C_{12}H_{15}N_5$	62.9	62.5	6.6	6.7		
49[a1]	2,6-di$CH_3C_6H_3$—	H	196–199	A	22[p]	$C_{14}H_{19}N_5$	65.3	65.4	7.4	7.0		
50[a1]	—$C_6H_4CH_2CH_2$—		108–109	A	63[p]	$C_{14}H_{17}N_5$	65.9	65.7	6.7	6.5	27.4	27.4

[a] R_3 = hydrogen, unless otherwise specified; [a1] R_3 = methyl. [b] Melting points are uncorrected. [c] S = recrystallizing solvent; A = isopropyl alcohol; B = acetone water; C = acetonitrile; D = methanol; E = water; F = propanol; G = ethanol. [d] Yields are reported as recrystallized product. [e] Analyses by Weiler and Strauss, Oxford, England. [f] C_3H_5— = allyl. [g] HPic = picrate of compound listed immediately above. [h] With attached nitrogen, is derived from indoline. [i] Not recrystallized. [j] Chlorine, Calcd./Found: 13.6/13.6. [k] With attached nitrogen is derived from tetrahydroquinoline. [l] Chlorine, Calcd./Found: 12.9/13.0. [m] With attached nitrogen is derived from tetrahydroisoquinoline. [n] X = *m*-CH_3CHOH—. [o] The compounds were prepared from the biguanide and ethyl acetate; [p1] prepared from acetyl chloride.

amines might be considered as analogs of the phenacyl halides. Sufficient distinction has been demonstrated to question this parallelism, and consideration of the mechanism of the ASA reaction with these chloromethyltriazines has suggested that molecular iodine may participate,[18] in a form similar to that described for pyridine,[19] as shown for IIIa followed by IIIb,[20,21] which is protonated, IIIc followed by deiodination through



the sodium bisulfite to I, $R_4 = CH_3$. This mechanism is being explored further.

EXPERIMENTAL[22]

Biguanides not previously reported are given in Table II and were prepared as described elsewhere.[2,23]

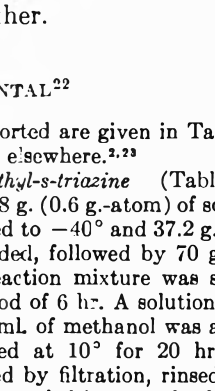
2-Amino-4-indolino-6-chloromethyl-s-triazine (Table I, Compound 16). A solution of 13.8 g. (0.6 g.-atom) of sodium in 480 ml. of methanol was chilled to −40° and 37.2 g. (0.31 mole) of ethyl chloroacetate added, followed by 70 g. (0.3 mole) of the biguanide. The reaction mixture was stirred as it warmed to 20° over a period of 6 hr. A solution of 48 ml. of hydrochloric acid in 108 ml. of methanol was added, and the reaction mixture stored at 10° for 20 hr. The formed precipitate was separated by filtration, rinsed with 500 ml. of acetone, and then suspended in 500 ml. of water which was adjusted to *p*H 6.0. The insoluble suspension of product was separated, 44.5 g. (57%), m.p. >300°.

2-Dimethylamino-4-indolino-6-chloromethyl-s-triazine (Table I, Compound 23). A mixture of 5.5 g. (0.0206 mole) of the biguanide (Table II, compound 8) was suspended in a mixture of 8 ml. of water and 12 ml. of acetonitrile. With continued stirring and cooling (10°) 7.5 ml. of 40% sodium hydroxide solution was added, followed by addition over 20 min. of 3.4 g. (0.03 mole) of chloroacetyl chloride in 10 ml. of acetonitrile. After the addition was complete, stirring was continued at 20° for 1 hr., and the product separated and recrystallized.

2-Amino-6-chloromethyl-4-(β-phenethyl)amino-s-triazine (Table I, Compound 9). A solution of 24.1 g. (0.1 mole) of β-phenethylbiguanide hydrochloride in 50 ml. of water and 75 ml. of acetonitrile was maintained at 10° during the addi-

TABLE II

*N*¹,*N*⁵-BIGUANIDES



No.	R_1	R_2	M.P.	S[b]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3—	CH_3—	227–230	A	40	$C_6H_{16}ClN_5$	37.2	36.8	8.3	8.1	36.2	36.3
2	C_6H_5—	H	257–258	B	44	$C_{10}H_{16}ClN_5$	49.7	49.8	6.7	6.9	29.0	28.6
3	*m*-ClC_6H_4	H	>250	B	56	$C_{10}H_{15}Cl_2N_5$	43.5	43.6	5.5	5.6	25.3	25.3
4	*p*-ClC_6H_4—	H	239–241	B	67	$C_{10}H_{15}Cl_2N_5$					25.4	25.5
5	*p*-$NH_2SO_2C_6H_4$—	H	162–164	B	52	$C_{10}H_{17}ClN_6O_2S$	37.4	37.1	5.3	5.4		
6	$HSO_3C_6H_4$—	H	243–245	B		$C_{10}H_{18}ClN_5(O_3S)_1$	36.1	36.6	5.9	5.7		
7	2,6-di$CH_3C_6H_3$—	H	197–199	C		$C_{12}H_{19}N_5{}^{c_2}$	61.8	61.7	8.2	8.1	30.0	29.9
8	—$C_6H_5CH_2CH_2$—		243–245	D	83	$C_{12}H_{18}ClN_5$	53.8	54.0	6.8	6.9	26.2	26.1

[a] The salt is hydrochloride unless otherwise specified; ^{c_1} hydrochloride hydrate; ^{c_2} free base. [b] S = recrystallizing solvent: A = acetonitrile; B = water; C = isopropyl alcohol; D = ethanol-hexane.

(18) K. Meyer, *Ann.*, 380, 212 (1911).

(19) R. A. Zingaro and W. E. Tolberg, *J. Am. Chem. Soc.*, 81, 1353 (1959).

(20) J. G. Carey and I. T. Millar, *Chem. & Ind.*, 97 (1960).

(21) J. G. Carey, G. Jones, and I. T. Millar, *Chem. & Ind.*, 1018 (1959).

(22) Descriptive data shown in the tables are not reproduced in the Experimental.

(23) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3725 (1959).

tion of 30 ml. (0.3 mole) of 10*N* sodium hydroxide. Stirring and cooling were continued during the addition of a solution of 16.9 g. (0.15 mole) of chloroacetyl chloride in 40 ml. of acetonitrile over 30 min. Stirring was continued over 2 hr. as the temperature was allowed to rise to 20°. The product, 24.4 g. (92%), was separated, m.p. 145–147°.

2-Amino-4-(o-bromo)anilino-6-α-chloroethyl-s-triazine (Table I, Compound 32). A suspension of 10.2 g. (0.035 mole) of *o*-bromophenylbiguanide hydrochloride in 30 ml. of methanol was treated with 11.0 ml. (0.05 mole) of 25% sodium methoxide in methanol, followed by 5.5 g. (0.04 mole) of ethyl α-chloropropionate. After 48 hr. the reaction mixture was decanted into 150 ml. of water and the product separated, 6.33 g. (55%), m.p. 120–126°.

2-Amino-4-(n-amyl)amino-6-methyl-s-triazine (Table I, Compound 36). Following the procedure described above using *n*-amylbiguanide hydrochloride, and ethyl acetate, as the reactant ester, the product was obtained in 75% crude yield, m.p. 133–136°.

2-Amino-6-ethyl-4-(β-phenethyl)amino-s-triazine. Following the procedure above and using β-phenethylbiguanide hydrochloride and ethyl propionate as the reactant ester, the product was obtained in 66% yield, m.p. 135–137°.

Anal. Calcd. for $C_{13}H_{17}N_5$: C, 64.2; H, 7.0; N, 28.8. Found: C, 64.4; H, 7.0; N, 29.0.

N-[(2-Anilino-4-dimethylamino-triazin-6-yl)methyl]-3-oxypyridyl betaine hydrochloride. A mixture of 2.6 g. (0.01 mole) of 2-anilino-4-dimethylamino-6-chloromethyl-s-triazine and 1.0 g. (0.01 mole) of 3-hydroxypyridine in 15 ml. of isopropyl alcohol was heated under reflux with stirring for 6 hr. When cool, the product was separated and recrystallized (ethanol), m.p. over 250°.

Anal. Calcd. for $C_{17}H_{19}ClN_6O$: C, 56.9; H, 5.3; N, 23.4. Found: C, 56.5; H, 5.3; N, 23.8.

In a similar manner, using compound 10 (Table I) the corresponding betaine was prepared, m.p. 206–208° (acetonitrile).

Anal. Calcd. for $C_{17}H_{19}ClN_6O$: C, 56.9; H, 5.3; N, 23.4. Found: C, 56.9; H, 5.6; N, 23.5.

In a similar manner, using compound 4 (Table I) the corresponding betaine was prepared, m.p. 244–245° (isopropyl alcohol).

Anal. Calcd. for $C_{13}H_{19}ClN_6O$: C, 50.2; H, 6.2; N, 27.1. Found: C, 50.2; H, 6.4; N, 27.4.

2-Amino-4-indolino-6-methyl-s-triazine (Table I, Compound 47). A slurry of 5.0 g. (0.02 mole) of indolinylbiguanide hydrochloride and 40 ml. of acetonitrile was treated (cooling to 10°) with a solution of 1.6 g. (0.04 mole) of sodium hydroxide in 10.0 ml. of water, followed by 2.4 g. (0.03 mole) of acetyl chloride in 15 ml. of acetonitrile added dropwise over 0.5 hr. After standing at 20° for 20 hr., the reaction mixture was decanted into 150 ml. of water, and the product, 0.53 g. (12%), m.p. 229–233°, separated.

The filtrate, treated with 6 ml. of 10*N* sodium hydroxide, yielded a solid (3.84 g.) which after solution in 100 ml. of boiling water gave, after cooling, 2.17 g. (67%) of *N*-carbamidoindoline, m.p. 159–161°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.9; H, 6.3; N, 17.1.

The melting point was not depressed on admixture with authentic *N*-carbamidoindoline, mixed m.p. 162–165°.

N-Carbamidoindoline. To a stirred warmed (30°) mixture of 17.3 g. (0.145 mole) of indoline in 30 ml. (0.177 mole) of 6*N* hydrochloric acid, was added portionwise, over 20 min., 12.5 g. (0.155 mole) of finely powdered potassium cyanate, forming a dense white precipitate of product. After dilution with 100 ml. of water, the product was separated, 21.3 g. (91%), m.p. 162–165°; recrystallized (water), m.p. 163–165°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2. Found: C, 66.6; H, 6.3.

Reduction of I, $R_4 = CH_2Cl$. In a typical procedure, compound 1 (Table I) 0.375 g. (0.002 mole) in 5 ml. of acetone was added to a solution of 3.0 g. of sodium iodide in 10 ml. of acetone and 1 ml. of acetic acid. Within 10 min. the rapidly browning (iodine) solution had reached maximum color intensity. A solution of 0.25 g. of sodium bisulfite in 10 ml. of water was added, and the reaction mixture made basic with sodium hydroxide. After standing, the precipitate was separated and recrystallized (isopropyl alcohol) 0.13 g. (40%), m.p. 192–193°, not depressing the melting point of compound 34 (Table I).

In a similar manner, the following I, $R_4 = —CH_2Cl$, compounds 4, 6, 8, 11, 12, 16, and 20 (Table I), were reduced to I, $R_3 = —CH_3$, compounds 36, 37, 38, 43, 44, 47, and 48 (Table I), as established by mixed melting point and analysis. In the following group the reduction of compounds 9, 10, and 14 produced I, $R_4 = —CH_3$ confirmed as the picrates, compounds 40, 42, and 46.

The reaction proceeded in a similar manner in the absence of acetic acid; compound 9, Table I, yielded compound 39.

Although a substantial liberation of iodine occurred, the following compounds were not reduced to the corresponding alkyl derivatives, and the reactant halo compound was isolated unchanged: Compound 25, Table I; and I, $R_1R_2N— = C_6H_5CH_2NH—$ (or $(CH_3)_2N—$), $R_3R_3N— = NH_2$, $R_4 = CHBr_2$, $—CFCl_2$, $—CF_3$.

Reduction of compound 23, Table I. This compound, reduced as described above, yielded a compound with an unsatisfactory analysis, but showed ultraviolet absorption spectra identical with compound 50.

2-Amino-6-iodomethyl-4-(β-phenethyl)amino-s-triazine. A solution of 2.64 g. (0.01 mole) of compound 9 (Table I) in 30 ml. of acetone was treated with a solution of 15 g. of sodium iodide in 50 ml. of acetone. After 2 hr., the sodium chloride was separated, rinsed with acetone, and dried, 0.52 g. (92%). The filtrate, on standing, formed a dense precipitate which on exposure to air and light colored in sequence from orange to red-brown to violet to white. (See forms III above.) The precipitate was separated and triturated with water (this immediately decolorized any colored portions of the precipitate). There was obtained 2.15 g. (61%) m.p. 138–139°, recrystallized (acetonitrile), m.p. 149–153°, not obtained analytically pure.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

No.[a]	λ_{max}, mμ	ε × 10⁻³
1	273	3.8
17	260	14.5
18	271	4.5
23	234	18.6
	266	22.2
	298	15.6
50	230	18.3
	268	20.7
	294	17.8
[b]	276	3.9

[a] Compound number in Table I. [b] Iodo analog of compound 9.

Anal. Calcd. for $C_{12}H_{14}IN_5$: C, 40.6; H, 4.0; N, 19.7. Found: C, 41.4; H, 4.4; N, 21.2.

Reduction of phenacyl halides. Employing the ASA reagent, the following were reduced: *p*-Chlorophenacyl chloride gave *p*-chloroacetophenone (64%), b.p. 46° (0.6 mm.), confirmed by its 2,4-dinitrophenylhydrazone, m.p. 231–232° (ethanol).

Anal. Calcd. for $C_{14}H_{11}ClN_4O_4$: C, 50.2; H, 3.3. Found: C, 50.3; H, 3.4.

In a similar manner, *m*-nitrophenacyl chloride gave *m*-

nitroacetophenone (55%), m.p. 79–80° (ethanol), confirmed by its 2,4-dinitrophenylhydrazone, m.p. 218–221° (ethanol).

Anal. Calcd. for $C_{14}H_{11}N_3O_6$: C, 48.7; H, 3.2; N, 20.3. Found: C, 48.4; H, 3.1; N, 20.5.

Ultraviolet absorption data. Selected spectra were established in methanol and are reported in Table III.

YONKERS 1, N. Y.

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

Guanamines. VI. Aminomethylguanamines

SEYMOUR L. SHAPIRO, ELAINE S. ISAACS, AND LOUIS FREEDMAN

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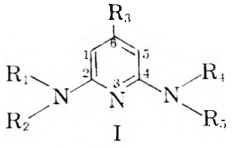
A series of guanamines of the class I, R_3 = $—CH_2NR_6R_7$ has been synthesized and examined for antiinflammatory, analgesic, and tranquilizing activity.

In continuation of our explorations of guanamines with pharmacological activity,[1] compounds of type I, R_3 = $—CH_2NR_6R_7$ have been examined for pharmacological activity. These compounds have



I

$R_1R_2N—$ = substituted amino and anilino
$R_4R_5N—$ = $—NH_2$ and $—N(CH_3)_2$

been envisioned as chlorpromazine analogs wherein the $R_1R_2N—$, as indolino, tetrahydroquinolino, and tetrahydroisoquinolino, replaces the phenothiazine ring and the trimethylene chain of chlorpromazine has been substituted by a four atom unit extending from the 2-position of the triazine ring to the amino methyl nitrogen.[2] Treatment of the halomethylguanamine[3] with an excess of the required amines under mild heat gave the aminomethylguanamine (see Table I) in good yield.

There was no evidence of *trans*-amination of the 2- and 4-amino substituents of I.[4] Further, when the reactant was a primary amine, there were no indications of formation of the tertiary amines involving reaction of two equivalents of I, R_3 = $—CH_2Cl$.[5] Monoethanolamine reacted readily[6] to give I, R_3 = $—CH_2NHCH_2CH_2OH$.

Although I, R_3 = $—CHCH_3Cl$ was not as active in other systems,[3] it reacted readily with *N*-methylpiperazine to give the required aminomethylguanamine.

The compounds were inspected, in particular, for tranquilizing,[7] antiinflammatory,[8] and analgesic[9] properties with effective compounds being found in each category. Other interesting effects were the antihistamine activity of compound 2 and the marked potentiation of adrenalin by compound 25.

EXPERIMENTAL[10]

The biguanides[1b,3,11] and halomethylguanamines[3] required as intermediates have been described.

2-Amino-4-indolino-6-[(N-ethyl)ethanolaminomethyl]-s-triazine (Compound 7). A mixture of 2.6 g. of 2-amino-4-indolino-6-chloromethyl-*s*-triazine and 6 ml. of *N*-ethylethanolamine was warmed to effect complete solution and then heated in an oil bath maintained at 100° for 5 min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of the product separated.

Unless otherwise stated the compounds were prepared by this general procedure.

2-Dimethylamino-4-indolino-6-dimethylaminomethyl-s-triazine (Compound 16). A mixture of 2.9 g. of 2-dimethylamino-4-indolino-6-chloromethyl-*s*-triazine and 10 g. of dimethylamine in a pressure bomb was heated at 100° for 30

(1) (a) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959); (c) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379 (1960); (d) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 384 (1960).

(2) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **46**, 333 (1957).

(3) S. L. Shapiro, E. Isaacs, V. A. Parrino, and L. Freedman, *Guanamines V. Chloromethylguanamines*, *J. Org. Chem.*, **26**, 68 (1961).

(4) J. T. Thurston, F. C. Schaefer, J. R. Dudley, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2992 (1951).

(5) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(6) C. B. Kremer, M. Meltsner, and H. Hindin, *J. Am. Chem. Soc.*, **64**, 1010 (1942).

(7) The procedure in S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958) gave the following: compound no./LD_{min} mg./kg. s.c. (mice)/% reduction in motor activity at a test dose of 100 mg./kg. s.c.: 4/450/53; 16/300/48; 17/400/31; 19/150/31; 20/400/52; and at 50 mg./kg. s.c.: 5/200/47; 11/200/31; 13/300/39; 24/350/47.

(8) The procedure of E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957) gave the following: compound no./LD_{min}/% protection at 50 mg./kg. s.c.: 2/400/75; 4/450/75; 5/200/69; 6/200/82; 7/300/88; 9/500/63; 11/20/94; 14/20/69; 16/300/100; 17/400/56; 19/150/90; 21/350/50; 24/350/63.

(9) The procedure of C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954) gave the following: compound no./LD_{min}/analgesic ED_{50} mg./kg. s.c.: 4/450/147; 10/1000/225; 19/150/31; 20/400/96.

(10) Descriptive data shown in Table I are not reproduced in the Experimental.

(11) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959).

TABLE I

AMINOMETHYLGUANAMINES[a] (FORMULA I)

No.	R_6	R_7	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	R_1R_2N = *m*-chloroaniline											
1	CH_3—	CH_3—	73–75	A		$C_{12}H_{15}ClN_6O$					30.2	30.0
2	$HOCH_2CH_2$—	H	146–148	A	59	$C_{12}H_{15}ClN_6O$	48.9	48.9	5.1	5.5	28.5	28.6
3	$HOCH_2CH_2$—	$HOCH_2CH_2$—	114–115	A	80	$C_{14}H_{19}ClN_6O_2$	49.6	49.6	5.7	5.8	24.8	24.7
4	—$(CH_2)_4$—		185–188	B	60	$C_{14}H_{23}Cl_3N_6O_2$[f]	40.6	41.4	5.6	5.8	20.3	19.9
5	—$(CH_2)_2NCH_3(CH_2)_2$—		211–212	C	43	$C_{12}H_{20}ClN_7$	54.0	54.1	6.0	6.2	29.4	29.3
	R_1R_2N = indolino											
6	CH_3—	CH_3—	169–170	C	24	$C_{14}H_{18}N_6$	62.2	61.8	6.7	6.8	31.1	30.8
7	$HOCH_2CH_2$—	H	165–168	D	43	$C_{14}H_{18}N_6O$	58.7	58.2	6.3	6.3	29.4	29.6
8	*n*-C_6H_{11}—	H	131–134	D	52	$C_{17}H_{24}N_6$	65.4	65.1	7.7	8.0	26.9	27.1
9	—$(CH_2)_5$—		189–191	B	64	$C_{16}H_{20}N_6$	64.8	64.8	6.8	6.6	28.4	28.2
10	—$(CH_2)_2O(CH_2)_2$—		178–180	D	47	$C_{15}H_{20}N_6O$	61.5	61.2	6.5	6.5		
11	—$(CH_2)_2NCH_3(CH_2)_2$—		216–220	C	58	$C_{17}H_{23}N_7$	62.7	62.2	7.1	7.3	30.1	27.8
12	HEP[g]		158–160	D	50	$C_{18}H_{25}N_7O$	59.6	59.8	7.4	7.2	28.6	28.8
13	$C_6H_5CH_2CH_2$—	H	145–147	D	46	$C_{20}H_{22}N_6$					24.3	24.4
14	$HOCH_2CH_2$—	C_2H_5—	125–126	D	76	$C_{16}H_{22}N_6O$	61.1	61.2	7.1	7.2	26.7	26.7
15	$(CH_3)_2N(CH_2)_3$—	H	106–119	E	22	$C_{17}H_{25}N_7$	62.4	62.1	7.7	7.6	30.0	30.3
16[a1]	CH_3—	CH_3—	119–120	A	87	$C_{16}H_{22}N_6$	64.4	63.9	7.4	7.7	28.2	27.9
17[a1]	$HOCH_2CH_2$—	H	156–157	A	61	$C_{16}H_{22}N_6O$	61.1	61.1	7.1	7.0	26.7	26.9
18[a1]	$HOCH_2CH_2$—	$HOCH_2CH_2$—	93–94	A	63	$C_{18}H_{26}N_6O_2$	60.3	60.2	7.3	7.2	23.5	23.7
19[a1]	—$(CH_2)_4$—		229–234	A	21	$C_{18}H_{24}N_6$					25.9	25.9
20[a1]	—$(CH_2)_2NCH_3(CH_2)_2$—		105–107	A	62	$C_{19}H_{27}N_7$					27.8	28.1
	R_1R_2N— = tetrahydroquinolino											
21	$HOCH_2CH_2$—	H	138–139	A	45	$C_{15}H_{20}N_6O$	60.0	60.3	6.7	6.1		
22	$HOCH_2CH_2$—	$HOCH_2CH_2$—	103–105	A	58	$C_{17}H_{24}N_6O_2$	59.3	59.7	7.0	7.3	24.4	24.2
23	—$(CH_2)_2N(CH_2)_2$—		149–151	A	47	$C_{18}H_{25}N_7$	63.7	63.6	7.4	7.3	29.0	29.1
24	$(CH_3)_2N(CH_2)_3$—	H	126–128	A	14	$C_{18}H_{27}N_7$	63.3	63.4	7.8	8.1	28.7	28.8
25[h]	—$(CH_2)_2NCH_3(CH_2)_2$—		148–150	A	16	$C_{18}H_{25}N_7$	63.7	63.9	7.4	7.4		

[a] R_1, R_5 = hydrogen unless otherwise specified; [a1] R_4, R_5 = methyl. [b] Melting points are uncorrected. [c] S = recrystallizing solvent; A = ethyl acetate; B = isopropyl alcohol; C = ethanol; D = acetonitrile; E = methanol. [d] Yields are reported as recrystallized product. [e] Analyses by Weiler and Strauss, Oxford, England. [f] Isolated as dihydrochloride dihydrate: chlorine, Calcd./Found: 25.6/25.3. The dipicrate melted 188–189°d. (water). *Anal.* Calcd. for $C_{26}H_{23}ClN_{12}O_{14}$: C, 40.9; H, 3.0; N, 22.1. Found: C, 40.7; H, 3.3; N, 21.9. [g] R_6R_7N— = *N*-hydroxyethylpiperazino. [h] R_1R_2N— = tetrahydroisoquinolino.

min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of product separated.

Compounds 1 and 6 were processed in this manner.

2-Amino-4-(β-phenethyl)amino-6-α-(4-methylpiperazino)-ethyl-s-triazine. A mixture of 2.8 g. (0.01 mole) of 2-amino-6-chloromethyl-4-β-phenethylamino-s-triazine and 6 ml. of *N*-methylpiperazine were maintained in an oil bath at 100° for 30 min. On standing 5 days the reaction mixture solidified, and after washing with water gave 3.02 g. (89%), m.p. 140–152°; recrystallized (acetonitrile), m.p. 162–163° yielded 70% of product.

Anal. Calcd. for $C_{18}H_{27}N_7$: C, 63.3; H, 8.0; N, 28.7. Found: C, 63.2; H, 8.0; N, 28.5.

Ethyl α-pyrrolidino acetate was prepared in 63% yield from pyrrolidine and ethyl bromoacetate,[12] b.p. 58–60° (3 mm.).[13]

(12) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, 56, 697 (1934).

(13) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942) report b.p. 110° (27 mm.).

2-Amino-4-m-chloroanilino-6-pyrrolidinomethyl-s-triazine (Compound 4, free base, from ester and the biguanide) was prepared from the ester above, and *m*-chlorophenylbiguanide following the general procedure previously described,[1b] in 34% yield (ethyl acetate), m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{17}ClN_6$: N, 27.6. Found: N, 27.3.

Its identity was confirmed by its dipicrate, m.p. 188–189° (water) which did not depress the melting point of the picrate prepared from compound 4, processed from pyrrolidine and 2-amino-4-*m*-chloroanilino-6-chloromethyl-*s*-triazine, mixed m.p. 187–188°.

Acknowledgment. The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds and to V. Parrino for the synthesis of several compounds.

YONKERS 1, N. Y.

[CONTRIBUTION NO. 29 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED]

Novel Condensation of Cyclohexanone with Urea

A. F. McKAY, E. J. TARLTON AND C. PODESVA

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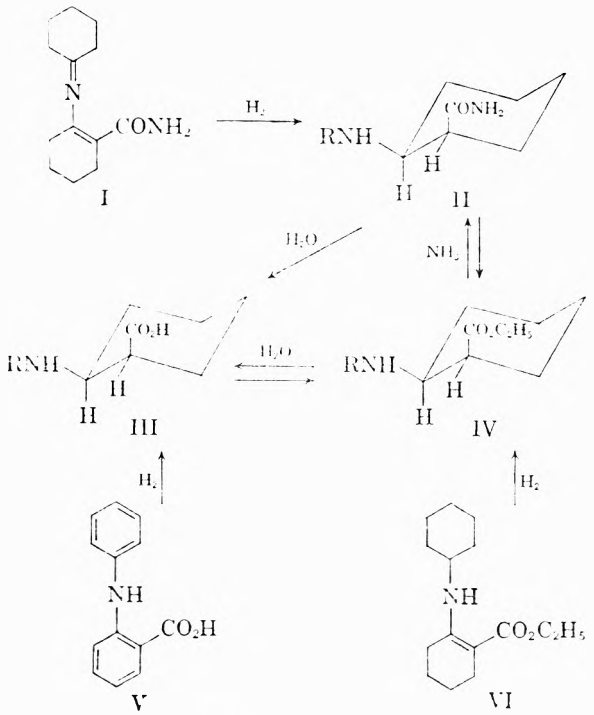
Cyclohexanone condenses with urea in an alkaline medium to give cyclohexylidene 2-carbamylcyclohex-1-enylamine. This compound on hydrogenation and acid hydrolysis gave an amino acid hydrochloride which was identical with cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared from the product of the catalytic hydrogenation of *N*-phenylanthranilic acid.

Cyclohexanone condenses with urea in an alkaline medium to give an unsaturated amino acid amide which has been identified as cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). The structure of this compound was verified by conversion to the saturated amino acid, cyclohexyl 2-carboxycyclohexylamine (III). The hydrochloride salt of this amino acid did not depress the melting point of a sample of cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared by treating the product from the catalytic hydrogenation of *N*-phenylanthranilic acid (V) with hydrochloric acid. Since hydrogenation of *N*-phenylanthranilic acid gave a low yield (11%) of cyclohexyl 2-carboxycyclohexylamine hydrochloride, the latter acid also was prepared in 55% overall yield by the hydrogenation and hydrolysis of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI).

Preparations of cyclohexyl 2-carbethoxycyclohexylamine (IV) from the catalytic hydrogenation of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI) and the esterification of cyclohexyl 2-carboxycyclohexylamine (III) were found to be identical by a comparison of their physical constants and infrared spectra.

Hünig and Kahanek[1] have shown that catalytic hydrogenation of 3,4,5,6-tetrahydroanthranilic acid yields the *cis* isomer of 2-aminocyclohexanecarboxylic acid. Since the cyclohexane compounds, II, III, and IV described in this study have been prepared by the catalytic hydrogenation of unsaturated intermediates, they have been assigned the *cis*



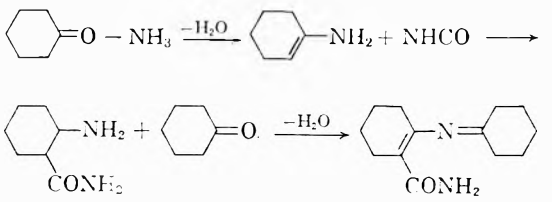
R = cyclohexyl

(1) S. Hünig and H. Kahanek, *Ber.*, **86**, 518 (1953).

configuration. Also the interconversions of these compounds shown on the chart confirm the assignment of the same configuration to these three compounds. Attempts to isomerize cyclohexyl 2-carbamylcyclohexylamine hydrochloride and cyclohexyl 2-carboxycyclohexylamine hydrochloride by heating in the presence of 37% hydrochloric acid in a sealed tube at 180° lead to decomposition. This observation also agrees with the assigned *cis* configurations for these compounds. This unstable character of the *cis* compounds would be expected because the cyclohexylamine group and the hydrogen atom of the adjacent carbon atoms are trans to each other.

An attempt to prepare *trans*-cyclohexyl 2-carboxycyclohexylamine from cyclohexylamine and cyclohex-1-enecarboxylic acid by Plieninger and Schneider's[2] procedure for the preparation of *trans*-2-amino-cyclohexanecarboxylic acid was unsuccessful. A similar experiment designed to prepare *trans*-cyclohexyl 2-cyanocyclohexylamine was also unsuccessful. In both cases high yields of the starting materials were recovered.

The condensation of cyclohexanone with urea under alkaline conditions can be considered to involve an enamine intermediate. Urea splits into ammonia and isocyanic acid which can combine with cyclohexanone as follows:



This interpretation is supported to some extent by the fact that cyclohexanone condenses with ethylurea under similar conditions to give a low yield of the same product, cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). Davis and Underwood[3] have demonstrated that monosubstituted ureas split in two ways as follows:

$$RNH_2 + HNCO \rightleftharpoons RNHCONH_2 \rightleftharpoons RNCO + NH_3$$

Thus ethylurea can supply the components for the formation of compound I.

In cyclohexylidene 2-carbamylcyclohex-1-enylamine, the conjugation of the amide group with the unsaturated system shifts the C=O stretching frequency from 1672 cm.$^{-1}$ (compound II) to 1625 cm.$^{-1}$ Similarly conjugation of the ester group with the double bond in cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI) shifts the absorption frequency of the ester group from 1735 (compound IV) to 1647 cm.$^{-1}$

(2) H. Plieninger and K. Schneider, *Ber.*, **92**, 1594 (1959).

(3) T. L. Davis and H. W. Underwood, Jr., *J. Am. Chem. Soc.*, **44**, 2595 (1922).

EXPERIMENTAL[4]

1-Cyanocyclohex-1-ene. 1-Cyanocyclohex-1-ene (b.p. 61–62°/6 mm., n_D^{25} 1.47983) was prepared in 76% yield from cyclohexanone by the method of Wheeler and Lerner.[5]

Cyclohex-1-enecarboxylic acid. 1-Cyanocyclohex-1-ene was converted into cyclohex-1-enecarboxylic acid (m.p. 36–38°) in 58% yield by the method of Wheeler and Lerner.[5]

N-(Cyclohex-1-enyl)pyrrolidine (b.p. 117–119°/19 mm) was obtained in 83% yield by the procedure of Hünig, *et al.*[6]

2-Carbethoxycyclohexanone (b.p. 117–120°/18 mm., n_D^{25} 1.47564) was prepared in 26% yield as described by Stork.[7]

Cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). *Method A.* Urea (36 g., 0.6 mole), cyclohexanone (150 g., 1.53 moles) and triethanolamine (6 g.) were refluxed together for 1.5 hr. The cooled reaction mixture was dissolved in warm ethanol (100 ml.), diluted with water (200 ml.) and allowed to cool slowly. The crystals (m.p. 224–225° evac. capil.) were recovered by filtration and washed with water, yield 33.55 g. Concentration of the mother liquors gave an additional 4.1 g. of product (m.p. 215–219° evac. capil.). The total yield was 28.5%. Crystallization of the first crop from aqueous ethanol did not alter its melting point.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.95; H, 9.16; N, 12.73. Found: C, 70.85; H, 9.11; N, 12.98.

Infrared spectrum of the solid in Nujol showed absorption bands at 3280, 3160, 1625, and 1525 cm.$^{-1}$

Method B. Ethylurea (8.8 g., 0.1 mole) and triethanolamine (1 g.) in cyclohexanone (25 g., 0.25 mole) were refluxed for 80 min. The product was separated as described above under Method A, yield 1.9 g. (8.6%). The crystals melted at 223–224° (evac. capil.) alone and on admixture with a sample of cyclohexylidene 2-carbamylcyclohex-1-enylamine prepared by Method A.

Cyclohexyl 2-carbamylcyclohexylamine (II). Cyclohexylidene 2-carbamylcyclohex-1-enylamine (5.5 g., 0.025 mole) in absolute ethanol (250 ml.) containing concd. hydrochloric acid (2.5 g., 0.025 mole) and 100 mg. of platinum oxide was hydrogenated at room temperature. Two mole equivalents of hydrogen were absorbed in about 2.5 hr. and some crystalline product separated from solution during the hydrogenation. The mixture was warmed to give a clear solution and the catalyst was removed by filtration. After the filtrate was evaporated to a small volume, crystals (m.p. 271–276°) separated, yield 5.2 g. (79.9%). Crystallization from absolute ethanol raised the melting point to a constant value of 276°.

Anal. Calcd. for $C_{13}H_{25}ClN_2O$: C, 59.86; H, 9.66; Cl, 13.59; N, 10.74. Found: C, 59.72; H, 9.82; Cl, 13.85; N, 10.37.

This hydrochloride salt (1.11 g., 0.0042 mole) was dissolved in water (25 ml.) and the *p*H was adjusted to 10 by the addition of 5% sodium hydroxide solution (4 ml.). An oil separated which crystallized within a few minutes, yield 0.79 g. (82.7%). The melting point (128°) of this free base was not changed by further crystallization.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.87; H, 10.84; N, 12.06.

Cyclohexyl 2-carboxycyclohexylamine (III). Cyclohexyl 2-carbamylcyclohexylamine (1 g., 0.0045 mole) in 18% hydrochloric acid (50 ml.) was refluxed for 2 hr. The solution was evaporated to a small volume after which crystals (m.p. 249–251°) were deposited from the solution, yield 1.15 g. (98.6%). A test portion of the crystals in water gave a positive test for the chloride ion with silver nitrate solution.

(4) All melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill.

(5) O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, **78**, 63 (1956).

(6) S. Hünig, E. Benzing, and E. Lucke, *Ber.*, **90**, 2833 (1957).

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Crystallization from methanol-dioxane solution raised the melting point to 250–251°.

Anal. Calcd. for $C_{15}H_{24}ClNO_2$: C, 59.65; H, 9.24; Cl, 13.54; N, 5.35. Found: C, 59.83; H, 9.20; Cl, 13.33; N, 5.19.

A solution of cyclohexyl 2-carbamylcyclohexylamine hydrochloride (256 mg., 0.00098 mole) in water (50 ml.) was eluted through a 7-inch column of IR 120 resin (13.5 ml.) in the hydroxyl form at a rate of 3 ml./min. The column was washed with water (100 ml.) until the eluant no longer gave a positive chloride ion test. The product was eluted from the column by washing with 10% ammonium hydroxide solution (200 ml.). The amino acid, which was obtained by evaporation of the eluant, was dissolved in ethanol and then precipitated from solution by addition of ether (100 ml.); yield 178 mg. (80.7%). The melting point was increased from 237–238° to 241–242° by recrystallizing from the same solvent pair.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 68.77; H, 10.04; N, 6.28.

N-Phenylanthranilic acid. N-Phenylanthranilic acid (m.p. 181–184°) was prepared in 83.1% yield by the procedure of Goldberg.[8]

The crude product (25.85 g.) was dissolved in a warm solution of sodium carbonate (12.5 g.) in water (500 ml.) and treated with charcoal. After the solution had been boiled for 5 min., the charcoal was removed by filtration and the filtrate was acidified with 10% hydrochloric acid. The cooled filtrate gave 22.3 g. of product melting at 183–185°. One crystallization from ethanol-water (1:5) solution (100 ml.) raised the melting point to 186.5–187.5° (lit.[9] m.p. 182–183°), yield 17 g.

Hydrogenation of N-phenylanthranilic acid. N-Phenylanthranilic acid (2.5 g., 0.0117 mole) in glacial acetic acid (125 ml.) was hydrogenated at 21° and 760 mm. pressure in the presence of 37% hydrochloric acid (1.10 ml., 0.018 mole) and platinum black which was obtained by reduction of platinum oxide (500 mg.) in glacial acetic acid (20 ml.). After 18 hr., 1800 ml. of hydrogen was absorbed. The calculated uptake of hydrogen for 6 moles at 21° and 760 mm. is 1689 ml.

The catalyst was removed by filtration and the filtrate was diluted with water (100 ml.), and then evaporated to dryness on the steam bath. The oily residue was dissolved in 37% hydrochloric acid and the solution was evaporated to a small volume on the steam bath under a stream of nitrogen until crystals appeared. The sludge was cooled and filtered to yield 600 mg. of crystals (m.p. 211–222°). Several crystallizations from methanol-ether (1:10) solution raised the melting point to 251–252°, yield 355 mg., 11.5%. The melting point varied from 246° to 257°. This variation in melting point is believed to be due to polymorphism. When a small amount of the compound (m.p. 251–252°) was pulverized it melted at 240–241° on the block.

Anal. Calcd. for $C_{15}H_{24}ClNO_2$: C, 59.65; H, 9.24; Cl, 13.54; N, 5.35. Found: C, 59.61; H, 9.15; Cl, 13.38; N, 5.34.

A mixed melting point determination with a sample of cyclohexyl 2-carboxycyclohexylamine hydrochloride (m.p. 251°), which was prepared by the hydrolysis of cyclohexyl 2-carbamylcyclohexylamine, showed no depression.

Cyclohexyl 2-carbethoxycyclohexylamine (IV) *from cyclohexyl 2-carbamylcyclohexylamine* (II). A solution of cyclohexyl 2-carbamylcyclohexylamine hydrochloride (16.14 g., 0.062 mole) in 37% hydrochloric acid (800 ml.) was refluxed for 2 hr. and then evaporated to dryness *in vacuo*. The white residue was dried *in vacuo* over potassium hydroxide pellets. This mixture of ammonium chloride and cyclohexyl 2-carboxycyclohexylamine hydrochloride was shaken overnight with 10% ethanolic hydrogen chloride. Most of the solid dissolved. The solution was evaporated *in vacuo* and the residue was dissolved in water. This solution was made alkaline with 5% sodium hydroxide solution and extracted with ether. The extract was washed with 5% sodium bicarbonate solution and water and then dried. After the ether was removed, the residue was fractionated in a spinning band column. The main fraction (b.p. 86°/0.1 mm., n_D^{25} 1.47786) weighed 6.72 g. (42.8%).

Anal. Calcd. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.26; H, 10.68; N, 5.96.

Cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI). 2-Carbethoxycyclohexanone (26.2 g., 0.154 mole), cyclohexylamine (16.7 g., 0.169 mole), *p*-toluenesulfonic acid (0.35 g.), and benzene (150 ml.) were refluxed for 8 hr. The evolved water was removed by means of a Barrett trap. The solvent was removed and the residue was distilled *in vacuo* through a spinning band column. The main fraction (b.p. 116–117°/0.15 mm.; n_D^{25} 1.53057) weighed 32.5 g., (84%).

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.73; H, 9.66; N, 5.62.

Infrared spectrum of the solid in Nujol showed absorption bands at 3280, 3165, 1647, and 1600 cm.$^{-1}$

Hydrogenation of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI). Platinum oxide (600 mg.) in glacial acetic acid (10 ml.) was reduced to platinum black by agitation in the presence of hydrogen at atmospheric pressure. A solution of cyclohexyl 2-carbethoxycyclohex-1-enylamine (12.94 g., 0.05 mole) in acetic acid (40 ml.) was added and the hydrogenation was continued at 23° and 762 mm. pressure. Over a period of 20.5 hr. 1280 ml. of hydrogen were absorbed. The calculated uptake of hydrogenation is 1248 ml. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* on a steam bath. The residue was then distilled. After a small amount of residual acetic acid had been removed crystals separated. The cooled mixture was diluted with ether (30 ml.) and the crystals were removed, yield 1.133 g. (9.8%). This product (m.p. 143–146°) was purified by sublimation at 80° and 0.5 mm. pressure. The sublimate (m.p. 146–147°) was identified as cyclohexylamine acetate by analysis and conversion to the known cyclohexylamine hydrochloride (m.p. 207–208°).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.37; H, 10.73; N, 8.62.

The filtrate from the cyclohexylamine acetate was evaporated to dryness and the residue was fractionated in a spinning band column. The main fraction (b.p. 92°/0.1 mm., n_D^{25} 1.47769) was shown by analysis and a comparison of infrared spectra to be identical with the cyclohexyl 2-carbethoxycyclohexylamine prepared from cyclohexyl 2-carbamylcyclohexylamine. The yield was 66.2%.

Anal. Calcd. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.22; H, 10.33; N, 5.52.

Hydrolysis of cyclohexyl 2-carbethoxycyclohexylamine in 37% hydrochloric acid gave an 83.6% yield of cyclohexyl 2-carboxycyclohexylamine hydrochloride (m.p. 239–240°). This product did not depress the melting points of samples of cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared by the hydrolysis of cyclohexyl 2-carbamylcyclohexylamine and by the hydrogenation of N-phenylanthranilic acid.

Ammonolysis of cyclohexyl 2-carbethoxycyclohexylamine. Cyclohexyl 2-carbethoxycyclohexylamine (2.0 g., 0.0079 mole) and a catalytic amount of sodium methoxide (70 mg.) in methanol (30 ml.) saturated with ammonia was allowed to stand at room temperature for 4 weeks. Removal of the methanol gave a liquid residue which on addition of water slowly crystallized, yield 1.32 g. (74.5%), m.p. 116–120°. One recrystallization from methanol-water gave 1.00 g. (56.5%), m.p. 126–127.5°. Further recrystallization raised the melting point to a constant value of 127–128°. A mixed melting point determination with the cyclohexyl 2-carbamylcyclohexylamine (m.p. 128°) derived from the urea-cyclohexanone condensation product showed no depression.

Isomerization experiments. An attempt to isomerize cyclo-

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hexyl 2-carbamylcyclohexylamine hydrochloride in 37% hydrochloric acid in a sealed Carius tube at 180° for 10 hr. resulted only in complete decomposition of the product. Attempts to isomerize either cyclohexyl 2-carbamylcyclohexylamine hydrochloride or cyclohexyl 2-carboxycyclohexylamine hydrochloride in 37% hydrochloric acid at 180° for 1 hr. also resulted in decomposition. When cyclohexyl 2-carboxycyclohexylamine hydrochloride (0.5 g.) in 37% hydrochloric acid was heated at 130° for 1 hr., starting material was recovered in 64.2% yield (0.32 g., m.p. 240–241°).

Attempts to prepare trans-cyclohexyl 2-substituted cyclohexylamines (a). A mixture of 1-cyanocyclohex-1-ene (5 g., 0.046 mole), cyclohexylamine (7 g., 0.07 mole) and a few crystals of hydroquinone was sealed in a Carius tube and heated at 150° for 50 hr. The mixture on distillation *in vacuo* gave 6.19 g. (88.5%) of unchanged cyclohexylamine and 4.4 g. (88.7%) of 1-cyanocyclohex-1-ene. No other products could be identified.

(b). A solution of cyclohex-1-enecarboxylic acid (2.5 g., 0.0198 mole) and cyclohexylamine (7.85 g., 0.080 mole) in water (12.5 ml.) was heated in a Carius tube at 180° for 66 hr. The solution was evaporated to dryness and the residue was dissolved in 10% hydrochloric acid. Extraction of the acid solution with ether gave 2.4 g. (96%) of unchanged acid which was identified by a mixed melting point determination.

LaSalle, Quebec

[Contribution from the Department of Chemistry of the University of Buffalo]

Reactions of Ethoxymethylenemalononitrile with Thioureas[1]

STEVE G. COTTIS[2] AND HOWARD TIECKELMANN

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Ethoxymethylenemalononitrile is hydrolyzed in alkaline aqueous solvents to hydroxymethylenemalononitrile, malononitrile, or tetracyanopropene, depending on conditions. 2-Amino-3,5-dicyano-6-alkoxypyridines are formed in alkaline aqueous alcohols. 2-Amino-3,5-dicyano-6-alkylthiopyridines are formed in solutions containing mercaptans or alkylthioureas. Ethoxymethylenemalononitrile condenses with 2-alkyl-2-thiopseudoureas to give 2-alkylthio-4-amino-5-cyanopyrimidines in alkaline aqueous solvents if the nitrile is added to the thiourea.

The condensation of ethoxymethylenemalononitrile (I) with amidines, guanidine, and thioureas in anhydrous solvents to form 2-substituted-4-amino-5-cyanopyrimidines is well known.[3,4] Aqueous solvents usually are not used in these condensations although 2-methyl-4-amino-5-cyanopyrimidine has been prepared in good yield from I in an aqueous medium.[5] Because of the observations that thioureas (II) often condense well to form 2-alkylthiopyrimidines in solvents containing water, we have investigated reactions of I with thioureas in alkaline aqueous solutions.

Preliminary experiments indicated that the yields of pyrimidines in aqueous solution sometimes were low but that pyridines were also formed and that the nature of the products depended, to some extent, on the ratio of starting materials, the solvent, and the order of addition of the reagents. For example, the addition of I in acetone to a solution of 2-methyl-2-thiopseudourea (II, R = CH_3) in aqueous acetone gave a good yield of 2-methylthio-4-amino-5-cyanopyrimidine (III, R = CH_3). However, when a mixture of I and II (R = CH_3) in aqueous acetone or alcohol was brought slowly to neutrality with ammonium hydroxide, the addition of more base after one hour gave a 47% yield of 2-amino-3,5-dicyano-6-methylthiopyridine (VIII).

It was not apparent immediately that some of our products were pyridines. However, a study of the behavior of I in the presence of bases, and in the absence of thioureas was informative. When a solution of I in alcohol was added slowly to an equivalent quantity of potassium hydroxide, the potassium salt of hydroxymethylenemalononitrile (VI) was formed (80%). If a solution containing one half an equivalent of potassium hydroxide in alcohol was added slowly to I in alcohol, the salt of 1,1,3,3-tetracyanopropene (VII) was formed and an odor of ethyl formate was detected. Intermediate procedures such as the addition of potassium hydroxide in one portion to I gave mixtures of VI and VII. An excess of potassium hydroxide in water added to I in methanol gave some 2-amino-3,5-dicyano-6-methoxypyridine (XI). This latter substance was more conveniently prepared from VII, which, in turn, was prepared in quantity from anilinomethylenemalononitrile and malononitrile by the method of Strell.[6]

The above observations can be explained by considering two competing reactions of I in base through a Claisen type intermediate IV. The intermediate can lose alcohol to give VI or undergo a reverse Claisen condensation to give ethyl formate

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(2) In part from a thesis submitted by Steve G. Cottis to the Graduate School of Arts and Sciences, the University of Buffalo, in partial fulfillment of the requirements for the degree of Master of Arts, February 1959.

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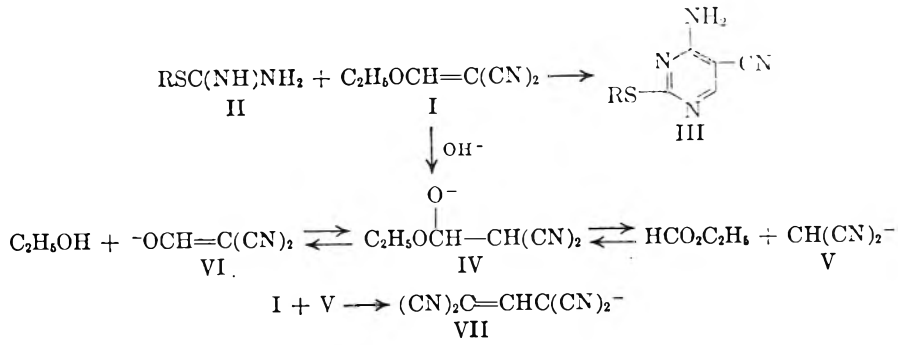
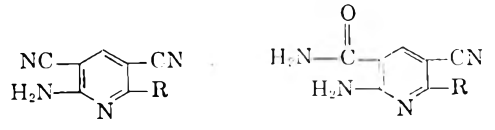


and the malononitrile anion (V). If I is present in excess it reacts readily with V to form VII.



	R		R
VIII	CH_3S—	XII	C_2H_5O—
IX	C_2H_5S—	XIII	HO—
X	$C_6H_5CH_2S$—	XIV	CH_3S—
XI	CH_3O—	XV	C_2H_5S—

The possibility was considered that VI was an intermediate in the formation of VII and of pyrimidines. Experiments indicated that under the conditions employed for the formation of these substances, the potassium salt of VI did not react with I or V to form VII or with II to form pyrimidines.

Pyrimidines were formed from I and II if an excess of I was avoided during the condensation, most easily accomplished by slow addition of a solution of I in acetone to a solution of II in aqueous acetone. An excess of base led to an only slightly lower yield. The use of alcohol as the solvent led to lower yields.

The formation of VII from I and V is well known.[7,8] Furthermore, it has been demonstrated that although VII is formed in high yield when the reaction is carried out at 0°, if the reagents are mixed without cooling, 2-amino-3,5-dicyano-6-ethoxypyridine is formed.[8] 6-Chloropyridines of this series have been formed from hydrogen chloride and VII. 6-Alkoxypyridines have been prepared from the 6-chloropyridine and by treatment of quaternary ammonium salts of VII, with alcohols in the presence of sulfuric acid.[8]

In the present work when the potassium salt of VII was heated in a basic solution of aqueous methanol, 2-amino-3,5-dicyano-6-methoxypyridine (XI) was formed but under similar conditions, when aqueous ethanol was the solvent, 2-amino-5-cyano-6-ethoxy-3-pyridinecarboxamide (XII) resulted. The structure of XII was established by conversion to 4-hydroxy-6-cyano-7-ethoxypyrido-(2,3-d)pyrimidine on treatment with formamide.

When XII was refluxed in dilute potassium hydroxide it gave a hydrate of the potassium salt of 2-amino-5-cyano-6-hydroxy-3-pyridinecarboxamide (XIII). A nitrile band in the infrared spectrum at 2220 $cm.^{-1}$ indicated this substance was a hydrated cyanocarboxamide rather than the dicarboxamide. In addition, XIII was prepared by heating VII in alkaline solution and from 2-amino-3,5-dicyano-6-chloropyridine by a similar procedure.

Although 6-alkylthiopyridines are formed by the addition of base to solution of I and II in alcohol or from VII and the corresponding mercaptan, in most cases it was more convenient to prepare members of this series from VII and 2-alkyl-2-thiopseudoureas. The structure of 2-amino-3,5-dicyano-6-ethylthiopyridine (IX) was confirmed by its synthesis from 2-amino-3,5-dicyano-6-chloropyridine.

The dicyanopyridines were readily hydrolyzed to cyanocarboxamidopyridines (XIII, XIV, XV) and under more vigorous conditions to the dicarboxylic acids (XVI, XVII). On heating with 10*N* potassium hydroxide, XIV gave 2-amino-6-hydroxy-3,5-pyridinedicarboxylic acid (XVIII).

EXPERIMENTAL[9]

Potassium 1,1,3,3-tetracyanopropene. A solution of 4.6 g. (0.082 mole) of potassium hydroxide in 50 ml. of alcohol was added slowly to 20.0 g. (0.165 mole) of ethoxymethylenemalononitrile in 20 ml. of alcohol at below 5°. After addition of 20 ml. of ether, the precipitate was collected and recrystallized from *n*-butyl alcohol–methanol to give 12.0 g. (82%) of yellow needles which decomposed at 319–320°. (Lit.: A decomposition, beginning at 250° has been reported.[6] Prepared by this method an impure material was formed which decomposed above 250°. Recrystallized several times from alcohol, long white needles were formed which decomposed sharply at 319–320°.)

Anal. Calcd. for C_7HN_4K: C, 46.65; H, 0.55; N, 31.09; K, 21.69. Found: C, 47.09; H, 0.38; N, 31.40; K, 21.67.

The potassium salt of hydroxymethylenemalononitrile. A cold solution of 5.0 g. (0.41 mole) of I in 20 ml. of alcohol was added slowly to 2.3 g. of potassium hydroxide in 5 ml. of water at below 5°. After stirring for 15 min. the precipitate was collected, washed with *n*-butyl alcohol, and

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(9) Microanalyses by Geller Laboratories, Bardonia, N. Y., and Schwartzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points are uncorrected.

recrystallized from alcohol–butyl alcohol to give 4.3 g. (79%) of yellow needles which decomposed with melting at 270–271° (lit.[10] m.p. 268°).

Anal. Calcd. for C_4N_2HOK: C, 36.35; H, 0.76; N, 21.20. Found: C, 36.08; H, 0.52; N, 21.55.

2-Amino-3,5-dicyano-6-methylthiopyridine (VIII). *Method A.* An acetone solution of 7.3 g. (0.06 mole) of I was added to a solution of 8.0 g. (0.029 mole) of 2-methyl-2-thiopseudourea sulfate in 150 ml. acetone and 20 ml. water. Concentrated ammonium hydroxide was added dropwise to neutrality. After standing for 1 hr., 200 ml. water was added. Ammonium hydroxide was again added and precipitation occurred. After standing 12 hr. the precipitate was collected, washed with water, and recrystallized from methanol to give 2.6 g. (47%) of white granules which melted to a yellow oil at 270–271°.

Method B. A solution of 9.0 g. (0.050 mole) of potassium 1,1,3,3-tetracyanopropene in 100 ml. of water was added to 10.0 g. (0.035 mole) of 2-methyl-2-thiopseudourea sulfate in 100 ml. of 1*N* potassium hydroxide. After standing overnight in a refrigerator, the precipitate was collected, washed with cold water, and recrystallized from methanol to give 8.5 g. (90%) of white granules which melted to a yellow oil at 270–271°.

Anal. Calcd. for $C_8H_6N_4S$: C, 50.51; H, 3.18; N, 29.45; S, 16.86. Found: C, 50.67; H, 3.11; N, 29.07; S, 16.90.

2-Amino-3,5-dicyano-6-ethylthiopyridine (IX). *Method A.* Ten grams (0.055 mole) of potassium 1,1,3,3-propenetetracarbonitrile in 100 ml. of 50% alcohol was added to 4.0 g. of ethyl mercaptan in 20 ml. of 4*N* potassium hydroxide. The yellow precipitate which formed on standing was collected, washed with water, and recrystallized from alcohol; yield 9.0 g. (80%), m.p. 203–205°.

Method B. One gram of ethyl mercaptan (0.016 mole), and 1.0 g. of potassium hydroxide in 5 ml. water was added to 0.5 g. (0.003 mole) of 2-amino-3,5-dicyano-6-chloropyridine[8] in 10 ml. of alcohol. After the addition of 10 ml. of water the solution was warmed to 40° and allowed to stand. The white solid, recrystallized from alcohol (0.34 g., 60%), melted at 202–204°. A mixed melting point with material from methods A and B gave no depression.

Anal. Calcd. for $C_9H_8N_4S$: C, 52.92; H, 3.95; S, 15.70. Found: C, 52.98; H, 4.01; S, 15.21.

2-Amino-3,5-dicyano-6-benzylthiopyridine (X). With method B, used for VIII, 9.0 g. of potassium 1,1,3,3-tetracyanopropene and 13.5 g. (0.067 mole) of 2-benzyl-2-thiopseudourea hydrochloride gave 6.1 g. (45%) of X, after recrystallization from benzene-methanol, m.p. 205–206°.

Anal. Calcd. for $C_{14}H_{10}N_4S$: C, 63.13; H, 3.78; S, 12.04. Found: C, 63.61; H, 3.83; S, 12.16.

2-Amino-3,5-dicyano-6-methoxypyridine (XI). *Method A.* One gram of potassium hydroxide in 15 ml. water was added to 1.0 g. (0.0055 mole) of potassium 1,1,3,3-tetracyanopropene in 50 ml. of methanol. After a 10-min. reflux the solution was cooled and 100 ml. of water was added. The precipitate was collected, washed with water, and recrystallized from methanol to give 0.81 g. (85%) of long white needles, m.p. 258–259°.

Anal. Calcd. for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.27; H, 3.72; N, 32.25.

Method B. Ten grams of potassium hydroxide in 15 ml. of water was added in one portion to 10.0 g. (0.082 mole) of I in 75 ml. of methanol. The reaction was exothermic. After cooling, the mixture was diluted with 150 ml. of water. The precipitate was recrystallized from methanol to give 2.1 g. (29%), m.p. 258–259°. A mixed melting point with material from method A gave no depression.

2-Amino-5-cyano-6-ethoxy-3-pyridinecarboxamide (XII). *Method A.* A solution of 1.6 g. of potassium hydroxide in 25 ml. of water was added to 5.0 g. of potassium 1,1,3,3-tetracyanopropene in 50 ml. of alcohol. After a 5-min. reflux the solution was cooled and diluted with 200 ml. of water. The precipitate was collected, washed with water, and recrystallized from alcohol to give 4.1 g. (69%) of long, pale green needles, m.p. 272–273°.

Method B. One gram (0.0053 mole) of 2-amino-3,5-dicyano-6-ethoxypyridine[8] in 100 ml. of 0.1*N* potassium hydroxide was refluxed 0.5 hr. and then allowed to stand at room temperature 12 hr. The precipitate was collected, washed with water, and recrystallized from alcohol to give 0.80 g. (73%), m.p. 272–273°.

Method C. A solution of 3.5 g. of XI and 3.5 g. of potassium hydroxide in 50 ml. of ethyl alcohol was heated to boiling for 3 min. After cooling and diluting with 100 ml. water the precipitate was collected, washed with water, and recrystallized from ethyl alcohol to give 3.2 g. (74%) of pale green needles, m.p. 272–274°. Mixed melting point of material from the above preparations gave no depression.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.09; H, 5.16; N, 27.25.

2-Amino-5-cyano-6-methylthio-3-pyridinecarboxamide (XIV). A mixture of 1.0 g. (0.0053 mole) of 2-amino-3,5-dicyano-6-methylthiopyridine in 50 ml. of 0.1*N* potassium hydroxide was refluxed 1.5 hr. and filtered while hot. The precipitate which formed on cooling was collected, washed with water, and recrystallized from methanol-water to give 0.31 g. (33%), white solid, m.p. 294–295°.

Anal. Calcd. for $C_9H_8N_4OS$: C, 46.14; H, 3.87; N, 26.91. Found: C, 45.80; H, 4.11; N, 26.63.

2-Amino-5-cyano-6-ethylthio-3-pyridinecarboxamide (XV). A mixture of 1.0 g. of 2-amino-3,5-dicyano-6-ethylthiopyridine (0.005 mole) and 50 ml. of 0.1*N* potassium hydroxide was refluxed 1 hr. and filtered while hot. The precipitate which formed on cooling was collected, washed with water, and recrystallized from methanol-benzene to give 0.74 g. (68%), m.p. 254–256°.

Anal. Calcd. for $C_9H_{10}N_4OS$: C, 48.63; H, 4.54; N, 25.21. Found: C, 49.10; H, 4.63; N, 25.60.

2-Amino-6-methylthio-3,5-pyridinedicarboxylic acid (XVI). A mixture of 3.0 g. (0.16 mole) of VIII in 200 ml. of 6*N* potassium hydroxide was refluxed until most of the solid had dissolved and filtered while hot. The filtrate was cooled to 5° and acidified with cold acetic acid. The precipitate was collected, washed with water, and recrystallized from water to give 2.1 g. (58%) of a white powder which decomposed at 315–316°.

Anal. Calcd. for $C_8H_8N_2O_4S$: C, 42.10; H, 3.53; N, 12.28. Found: C, 41.98; H, 3.61; N, 12.38.

2-Amino-6-ethylthio-3,5-pyridinedicarboxylic acid (XVII). With the method used for XVI, 2.0 g. (0.0098 mole) of IX in 100 ml. of 6*N* potassium hydroxide gave 1.3 g. (55%) of XVII recrystallized from aqueous acetic acid, dec. 268–270°.

Anal. Calcd. for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.57. Found: C, 44.30; H, 4.58; N, 11.50.

2-Amino-6-hydroxy-3,5-pyridinedicarboxylic acid (XVIII). A mixture of 5.0 g. (0.024 mole) of XII and 100 ml. of 10*N* potassium hydroxide was refluxed 2 hr. After filtering while hot the filtrate was cooled to 5° and acidified with acetic acid. The precipitate after recrystallization from water (2.1 g., 41%) decomposed at 218–220°.

Anal. Calcd. for $C_7H_6N_2O_5$: C, 42.43; H, 3.05; N, 14.14. Found: C, 42.03; H, 3.32; N, 14.24.

Potassium 2-amino-5-cyano-6-hydroxy-5-pyridinecarboxamide hydrate. Method A. Four grams of potassium hydroxide and 3.5 g. of VII dissolved in 75 ml. water was boiled in an open vessel until crystals formed. After cooling to 5° the precipitate was collected and recrystallized from water to give 2.4 g. (53%) of long white needles which decomposed at 327–332°.

Method B. One gram (0.005 mole) of 2-amino-5-cyano-6-ethoxy-3-pyridinecarboxamide was refluxed with 130 ml. of 1*N* potassium hydroxide until the solid dissolved (about 1.5 hr.). After cooling the solution was acidified with

(10) H. Schenk, M. Finken, Fr. Pleuger, and P. Michaelis, *Ann.*, **462**, 158 (1928).

glacial acetic acid. The precipitate was collected and treated with 10 ml. of 1*N* potassium hydroxide and the solution heated to boiling. The solid formed on cooling was recrystallized from water to give 0.53 g. (47%) of white needles which decomposed at 327–330°.

Method C. A mixture of 0.5 g. of 2-amino-3,5-dicyano-6-chloropyridine[8] in 25 ml. of 1*N* potassium hydroxide was refluxed until the solid dissolved. Method B was then followed to give 0.47 g. (71%).

Anal. Calcd. for $C_7H_7N_4O_3K$: C, 35.87; H, 3.01; N, 23.92. Found: C, 35.84; H, 2.84; N, 23.82.

7-Ethoxy-4-hydroxy-6-cyanopyrido(2,3-d)pyridine. Three grams (0.015 mole) of 2-amino-5-cyano-6-ethoxy-3-pyridinecarboxamide in 25 g. formamide was heated to 160–170° and maintained at this temperature for 2 hr. The compound slowly went into solution. Upon cooling, crystals formed which were filtered and washed with water. The filtrate was cooled to 5° in an ice bath and a second crop was obtained. Then the combined crops were shaken for a few minutes with 100 ml. of 0.1*N* potassium hydroxide and 50 ml. of water. The solution was filtered and the filtrate acidified with glacial acetic acid to yield 2.1 g. (67%) of a yellow powder which decomposed at 260–270°. An analytical sample was obtained by recrystallizing from dimethylformamide-water, m.p. 274–275°.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92; C_2H_5O, 20.85. Found: C, 55.50; H, 3.97; N, 25.93; C_2H_5O, 21.02.

2-Methylthio-4-amino-5-cyanopyrimidine. A solution of 8.0 g. of sodium hydroxide in 20 ml. of water was added to a mixture of 27.8 g. (0.100 mole) of 2-methyl-2-thiopseudourea sulfate in 100 ml. of acetone. Ethoxymethylenemalononitrile (24.4 g., 0.200 mole) in 150 ml. acetone was then added. After stirring for 2 hr. 200 ml. water was added; a precipitate formed. After standing for 12 hr. the precipitate was collected, washed with cold water, and recrystallized from alcohol-water to give 21.5 g. (65%) of fine white needles, m.p. 240–241°.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.35; H, 3.64; N, 33.71. Found: C, 43.53; H, 3.54; N, 33.67.

2-Ethylthio-4-amino-5-cyanopyrimidine. A solution of 8.0 g. of sodium hydroxide in 20 ml. water was added to a mixture of 31.0 g. (0.100 mole) of 2-ethyl-2-thiopseudourea sulfate and 100 ml. of acetone. Ethoxymethylenemalononitrile (24.4 g., 0.200 mole) in 150 ml. of acetone was then added. The mixture was allowed to stand 12 hr. The precipitate was filtered, washed with cold water, and recrystallized from alcohol-water to give 25.0 g. (70%) of fine white needles, m.p. 140° [lit. m.p. 141° (16.5%),[4] 147° (56%)].[11]

4-Amino-2-benzylthio-5-cyanopyrimidine. Ten grams (0.08 mole) of ethoxymethylenemalononitrile in 50 ml. of acetone was added slowly, with stirring, to a solution of 16.6 g. (0.080 mole) of 2-benzyl-2-thiopseudourea hydrochloride and 3.3 g. of sodium hydroxide in 50 ml. water. After all the ethoxymethylenemalononitrile solution had been added, the mixture was stirred for 0.5 hr. Then 100 ml. of water was added and the mixture cooled overnight in the refrigerator. The solid was then filtered and washed with water. Recrystallization from alcohol-water gave 15.5 g. (72%) of yellow needles, m.p. 174–176° (lit.[11] 86%, m.p. 171°).

4-Amino-2-thio-5-cyanopyrimidine. Ethoxymethylenemalononitrile (10 g., 0.080 mole) was added slowly to 7.0 g. (0.09 mole) of thiourea in a mixture of 70 ml. of water, 50 ml. of acetone, and 3.3 g. of sodium hydroxide. The solution was stirred for 0.5 hr. and 250 ml. of water added. The solution was acidified with glacial acetic acid and placed in the refrigerator overnight. A precipitate formed which was collected by filtration, washed with water, and dried. The yield of crude was 1.5 g. (12%). The infrared spectrum of this product was identical with that of 4-amino-2-thio-5-cyanopyrimidine prepared in an 85% yield by a method similar to that of Suter and Habicht.[11]

BUFFALO, N. Y.

(11) H. Suter and E. Habicht, U. S. Patent 2,698,326, December 1954.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Addition of Thiourea to 2- and 4-Vinylpyridines[1]

LUDWIG BAUER AND LIBERO A. GARDELLA, JR.

Received April 26, 1960

The acid-catalyzed addition of thiourea to 2- and 4-vinylpyridines readily afforded *S*-[2-(2- and 4-pyridinium)ethyl]-isothiuronium salts, II and IV, in excellent yields. In a cognate experiment, 2-methyl-5-vinylpyridine did not add thiourea. A mechanism is postulated to explain these phenomena. The isothiuronium salts, II and IV, were characterized by the corresponding thiols, disulfides and sulfonic acids.

Among the numerous nucleophilic reagents which have been added to the β-carbon of the side chain of 2- and 4-vinylpyridine are hydrogen cyanide,[2a] active methylene compounds (ketones,[2b] malonic esters,[2a] phenylacetonitriles,[2c] nitroalkanes[2d]), indole,[2f] imides,[2g] amides,[2c] amines[2c,2e] and phosphite esters.[2h] To establish a carbon-sulfur bond at the β-carbon of the vinyl side chain, mercaptans[3] and sodium bisulfite[2a] have been treated to form the corresponding 2-(2- and 4-pyridyl)ethyl sulfides and

(1) This work was sponsored by the Office of the Surgeon General, U. S. Army, Contract DA-49-193-MD-2047. This assistance is gratefully acknowledged.

(2) (a) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, 69, 2461 (1947); (b) V. Boekelheide and J. H. Mason, *J. Am. Chem. Soc.*, 73, 2356 (1951); R. Levine and M. H. Wilt, *J. Am. Chem. Soc.*, 74, 342 (1952) and 75, 1368 (1953); G. Magnus and R. Levine, *J. Org. Chem.*, 22, 270 (1957); (c) G. Magnus and R. Levine, *J. Am. Chem. Soc.*, 78, 4127 (1956); (d) E. Profft, *Chem. Techn.*, 8, 705 (1956); (e) A. P. Phillips, *J. Am. Chem. Soc.*, 78, 4441 (1956) and literature cited therein; E. Profft, *Chem. Ber.*, 90, 1738 (1957); 91, 958 (1958); (f) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, 79, 3554 (1957); (g) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, 79, 3805 (1957); S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, 80, 1648 (1958); (h) E. Maruszewska-Wieczorkowska and J. Michalski, *J. Org. Chem.*, 23, 1886 (1958).

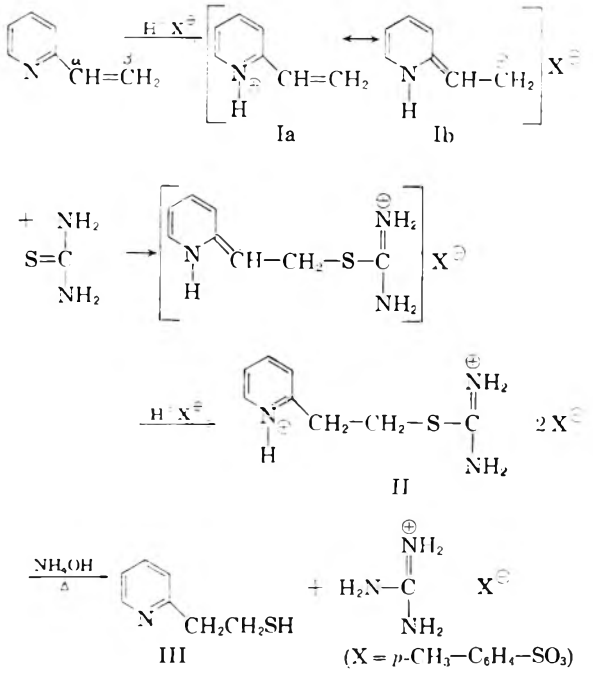
(3) W. H. Vinton, U. S. Patent 2,607,776, August 1952; *Chem. Abstr.*, 47, 6989 (1953).

2-(2- and 4-pyridyl)ethanesulfonic acids respectively.

We wish to report the facile acid catalyzed addition of thiourea to 2- and 4-vinylpyridines to afford in excellent yield *S*-[2-(2- and 4-pyridinium) ethyl]isothiuronium salts.

Experimentally, the best acid catalysts for this reaction were found to be sulfonic acids, although dry hydrogen chloride or hydrogen bromide promoted the addition very well. However, the isothiuronium chlorides and bromides were difficult to purify and for this reason sulfonic acids were used almost exclusively for this work.

Usually, nucleophilic addition to 2- and 4-vinylpyridines is base-catalyzed. Actually, in an acid medium the presence of the 2- and 4-vinylpyridinium ion should enhance nucleophilic attack at the β-carbon of the side chain because of the electron-attracting nature of the positively charged ring nitrogen atom. Furthermore, such nucleophilic attack on the 2- and 4-vinylpyridinium ion leads to favorable transition state structure in which the ring nitrogen atom is uncharged. This mechanism explains the facile acid-catalyzed addition of thiourea to 2- and 4-vinylpyridine and is illustrated for the addition of thiourea to 2-vinylpyridine, or rather, to the 2-vinylpyridinium ion, Ia, Ib:

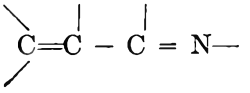


The isothiuronium salts were readily cleaved by hot concentrated ammonium hydroxide to 2-(2- and 4-pyridyl)ethanethiols. When the isothiuronium *p*-toluenesulfonates were decomposed by ammonia, guanidinium *p*-toluenesulfonate was isolated as a by-product of the reaction. In this way, *S*-[2-(2-pyridinium)ethyl]isothiuronium *p*-toluenesulfonate, II, afforded III (82%) and guanidinium *p*-toluenesulfonate (88.5% yield). The aminothiol, III, was also prepared from 2-(2-pyridyl)ethanol by the conventional synthesis.[4] This method consisted of refluxing the alcohol with 48% hydrobromic acid and thiourea for twenty-four hours to form the isothiuronium bromide, which was not isolated but immediately hydrolyzed by hot alkali to III. However, the yield was only 48% while the yields of III from the addition of thiourea to 2-vinylpyridine were consistently above 70%. Furthermore, the addition of thiourea to 2- and 4-vinylpyridines was complete after one hour reflux in ethanol. The synthesis of III is also described in the patent literature[3] and involves the addition of thiolacetic acid to 2-vinylpyridine and subsequent hydrolysis of the thiolester to III in a 23% overall yield.

Oxidation of the hydrochloride of the thiol, III, with hot concentrated nitric acid yielded the known 2-(2-pyridyl)ethanesulfonic acid.[2a] This again establishes the structure of III and hence the attachment of thiourea to the β-carbon of the side chain. Milder oxidation III with hydrogen peroxide in hydrochloric acid solution afforded 2-(2-pyridyl)-ethyl disulfide.

In contrast to the facile addition of thiourea to 2- and 4-vinylpyridine, 2-methyl-5-vinylpyridine (a typical 3-vinylpyridine derivative) failed to react with thiourea under *identical* experimental conditions used for 2- and 4-vinylpyridine. The only crystalline product isolated from the reaction mixture was thiourea *p*-toluenesulfonate in 73% yield. This substantiated the mechanism proposed above for the addition to 2- and 4-vinylpyridine. Nucleophilic attack at the β-carbon of the 3-vinyl side chain, would not be facilitated by resonance interaction with the protonated ring nitrogen atom.

It is intended to extend the acid-catalyzed addition of thiourea to systems of the type:



EXPERIMENTAL[5]

Starting materials. 2-Vinylpyridine (Reilly Coal Tar and Chemicals, Indianapolis, Ind.) was distilled, b.p. 68.5° (23 mm.), $n_D^{29°}$ 1.5455. 4-Vinylpyridine (also from Reilly) was distilled, b.p. 76° (21 mm.), $n_D^{29°}$ 1.5440. 2-Methyl-5-vinylpyridine (Monomer-Polymer Laboratories, the Borden Company, Chemical Division, Philadelphia, Pa.) was purified by vacuum distillation, b.p. 77° (13 mm.). Methanesulfonic acid was purchased from the Aldrich Chemical Co., Inc., Milwaukee, Wisc.

S-[2-(2-Pyridinium)ethyl]isothiuronium dichloride. A slow stream of hydrogen chloride gas was bubbled through a refluxing mixture of thiourea (3.8 g., 0.05 mole), and freshly distilled 2-vinylpyridine (5.25 g., 0.05 mole) in

(4) For examples of the synthesis of mercaptans from alcohols, see H. Kctod, *Org. Syntheses*, **35**, 66 (1955); Z. E. Heweihi, *Chem. Ber.*, **86**, 781 (1953).

(5) The melting points are uncorrected. The analyses were carried out by either Micro-Tech Laboratories, Skokie, Ill., Dr. Kurt Eder, Geneva, Switzerland, or by Drs. Weiler and Strauss, Oxford, England. The infrared spectra were determined with Beckman spectrophotometer, Model IR-4.

ethanol (50 ml.) for 1 hr. The reaction mixture was cooled in an ice bath and allowed to crystallize. The colorless crystals were filtered, washed with cold ethanol-ether (1:1), and dried *in vacuo* over sulfuric acid and sodium hydroxide pellets. The salt weighed 12.58 g. (99%) and melted at 208°. Recrystallization from absolute methanol-acetone did not raise the melting point.

Anal. Calcd. for $C_8H_{13}N_3SCl_2$ (254.2): C, 37.80; H, 5.15; N, 16.53. Found: C, 37.81; H, 5.25; N, 16.28.

S-[2-(2-Pyridinium)ethyl]isothiuronium bis-p-toluenesulfonate. *p*-Toluenesulfonic acid monohydrate (20.9 g., 0.11 mole) was dissolved in absolute ethanol (50 ml.) and to this solution was added thiourea (3.8 g.; 0.05 mole) and freshly distilled 2-vinylpyridine (5.25 g.; 0.05 mole). The reaction mixture was refluxed for 1 hr. on a steam bath, then half the solvent was removed *in vacuo*. Dry ether (30 ml.) was added and product allowed to crystallize. The mixture was cooled in an ice bath and the colorless crystals were filtered, washed with cold ethanol-ether (1:1), and dried. The salt weighed 24.08 g. (92%) and melted at 178°. Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{22}H_{27}N_3O_6S_3$ (525.7): C, 50.27; H, 5.18; N, 8.00. Found: C, 50.26; H, 5.45; N, 8.27.

2-(2-Pyridyl)ethanethiol. A solution of *S*-[2-(2-pyridinium)-ethyl]isothiouronium bis-*p*-toluenesulfonate (97.25 g.) was dissolved in concd. ammonium hydroxide solution (200 ml.) and water (50 ml.) and the mixture was heated on the steam bath for 0.5 hr. The solution was cooled and 50 ml. of chloroform was added. At this stage guanidinium *p*-toluenesulfonate separated. The crystals were filtered, washed with chloroform and dried. They weighed 41 g. (88.5%) and melted at 230–232°.[6] The filtrate was then extracted with chloroform (eight portions of 35 ml. each). The chloroform extract was distilled and the mercaptan obtained as a colorless oil, 21.0 g. (82.0% based on the isothiuronium salt), b.p. 137–138° (46 mm.), $n_D^{20°}$ 1.5570. It was redistilled for analysis, b.p. 57–58° (0.15 mm.), $n_D^{27°}$ 1.5581. The boiling point reported in the literature[3] is 94° (7 mm.).

Anal. Calcd. for C_7H_9NS (139.2): C, 60.39; H, 6.52; N, 10.06. Found: C, 60.31; H, 6.59; N, 10.01.

The mercaptan turned yellow within a day and after standing for a week decomposed to a brown and very viscous liquid.

The *picrate* crystallized from ethanol in yellow needles, m.p. 89°.

Anal. Calcd. for $C_{13}H_{12}N_4O_7S$ (368.3): N, 15.22. Found: N, 15.27.

The *hydrochloride*, m.p. 98–99° (in a sealed tube), was recrystallized from isopropyl alcohol. The crystals were exceedingly hygroscopic.

Anal. Calcd. for $C_7H_{10}NSCl$ (175.7): C, 47.86; H, 5.74; N, 7.97. Found: C, 47.48; H, 5.80; N, 8.29.

2-(2-Pyridinium)ethanethiol chloride from 2-(2-pyridyl)-ethanol. A solution of 2-(2-pyridyl)ethanol (12.3 g.; 0.1 mole), thiourea (7.6 g.; 0.1 mole), and 48% hydrobromic acid (37.1 g., 0.22 mole) was refluxed at 165° for 24 hr. The solution was allowed to stand for 48 hr. Half the solvent was removed *in vacuo* and acetone (20 ml.) was added to aid crystallization. The crystals which formed upon cooling were filtered and washed with cold 1:1 acetone-ethanol. These crystals were then dissolved in concd. ammonium hydroxide solution (100 ml.) and the solution heated on a steam bath for 0.5 hr. The solution was extracted with chloroform (eight 35-ml. portions). The chloroform solution was distilled and the mercaptan collected in the fraction which boiled at 120–125° (18 mm.). The aminothiol was immediately dissolved in dry ether and anhydrous hydrogen chloride was passed through this solution. The hydrochloride so formed was filtered and washed with dry ether. The crystals weighed 8.37 g. (48%), m.p. 98–99°, and were identical with the salt prepared above from 2-vinylpyridine.

2-(2-Pyridyl)ethyl disulfide. 2-(2-Pyridyl)ethanethiol (2.75 g., 0.02 mole) was dissolved in 100 ml. of 0.1*N* hydrochloric acid and treated with 3 ml. of 30% hydrogen peroxide (Superoxol) in water (20 ml.). The solution was stirred for 0.5 hr. The solvent was then evaporated *in vacuo* and the residue treated with 10% sodium carbonate solution until the solution was basic. An oil separated which was extracted with chloroform (six 35-ml. portions). The chloroform was removed by distillation. The gummy residue was extracted with hot ligroin (b.p. 60–90°). On cooling colorless needles separated, m.p. 74°, unchanged on recrystallization from the same solvent.

Anal. Calcd. for $C_{14}H_{16}N_2S_2$ (276.4): C, 60.83; H, 5.83; N, 9.95. Found: C, 60.89; H, 5.67; N, 9.80.

2-(2-Pyridyl)ethanesulfonic acid. Concentrated nitric acid (50 ml.) was added to 2-(2-pyridinium)ethanethiol chloride (3.0 g., 0.017 mole) and a vigorous reaction ensued. The reaction mixture turned deep red-brown while fumes of oxides of nitrogen were evolved. The solution was heated on the steambath until a colorless solution was obtained. Most of the solvent was removed *in vacuo* and acetone was added until the solution became opalescent. The crystals, which formed on standing were filtered, washed with cold acetone, and recrystallized from hot 90% ethanol. The sulfonic acid weighed 2.85 g. (90%) and melted at 263° with gas evolution.

The melting point, mixed melting point, and infrared spectra agreed with a sample of 2-(2-pyridyl)ethanesulfonic acid synthesized according to the method of Doering and Weil.[2a]

S-[2-(4-Pyridinium)ethyl]isothiuronium bis-p-toluenesulfonate. By a process similar to that used for 2-vinylpyridine 4-vinylpyridine gave 23.65 g. (90.1%) of the salt, m.p. 201–202°.

Anal. Calcd. for $C_{22}H_{27}N_3O_6S_3$ (525.7): C, 50.27; H, 5.18; N, 8.00. Found: C, 50.20; H, 5.43; N, 7.99.

S-[2-(4-Pyridinium)ethyl]isothiuronium bismethanesulfonate. When methanesulfonic acid was used, this salt was obtained in 84.5%, m.p. 170–171° (from methanol).

Anal. Calcd. for $C_{10}H_{19}N_3O_6S_3$ (373.5): C, 32.16; H, 5.13; N, 11.25. Found: C, 32.31; H, 5.09; N, 11.22.

2-(4-Pyridyl)ethanethiol. Using the same procedure as above, 4-vinylpyridine was treated with thiourea (both in 0.05 molar quantities) and *p*-toluenesulfonic acid monohydrate (0.11 mole) and the salt was not isolated but was converted [as described for 2-(2-pyridyl)ethanethiol] to the mercaptan which distilled as a colorless oil, b.p. 92° (0.2 mm.), $n_D^{29°}$ 1.5651. It weighed 4.5 g. and this represents a 64.8% yield based on 4-vinylpyridine. It is imperative to distil this amino mercaptan at the lowest possible pressure. Over-heating on distillation frequently caused decomposition of the mercaptan.

The mercaptan turned yellow within a day, and on standing for a week the liquid was brown and very viscous.

Anal. Calcd. for C_7H_9NS (139.2): C, 60.39; H, 6.52; N, 10.06. Found: C, 60.22; H, 6.40; N, 9.87.

The *hydrochloride* (from 2-propanol) melted at 189°, resolidified and remelted at 250° (with dec.).

Anal. Calcd. for $C_7H_{10}NSCl$ (175.7): C, 47.86; H, 5.74; N, 7.97. Found: C, 47.48; H, 5.76; N, 7.96.

2-(4-Pyridinium)ethyl disulfide dichloride. 2-(Pyridinium)-ethanethiol chloride (7.0 g.; 0.04 mole) was dissolved in 0.1*N* hydrochloric acid (100 ml.) and hydrogen peroxide (30%, 6 ml.) in water (40 ml.) was added and the solution was stirred for 2.0 hr. Half the solvent was removed *in vacuo* and 10% sodium carbonate was added until the solution was alkaline. A yellow oil separated which was extracted with pure ether (six 35-ml. portions). The ethereal solution was dried (sodium sulfate) and the most of the solvent was distilled. Dry hydrogen chloride gas was bubbled through the residual ethereal solution, and a yellowish gum

(6) This salt did not depress the melting point of an authentic sample. It also had an infrared spectra identical with that of a sample prepared from guanidine and *p*-toluene sulfonic acid.

formed which crystallized upon standing. The crystals were filtered and washed with cold dry ether. The salt weighed 3.95 g. (67.1%). Recrystallization from absolute ethanol raised the melting point to 199-200° (with dec.) with darkening at 185°.

Anal. Calcd. for $C_{14}H_{18}N_2S_2Cl_2$ (349.4): C, 48.13; H, 5.19; N, 8.02. Found: C, 48.24; H, 5.34; N, 8.11.

The *picrate* crystallized from 80% ethanol, m.p. 166° (with dec.).

Anal. Calcd. for $C_{26}H_{22}N_8O_{14}S_2$ (734.6): N, 15.25. Found: N, 15.44.

2-(4-Pyridyl)ethanesulfonic acid. Oxidation of 2-(4-pyridium)ethanethiol chloride in a manner similar to that described above for 2-(2-pyridinium)ethanethiol chloride afforded the acid (91%) which was identical with that in the literature.[2a]

Thiourea p-toluenesulfonate. A mixture of thiourea (1.52 g.; 0.02 mole) and *p*-toluenesulfonic acid monohydrate (3.8 g.; 0.02 mole) was boiled in ethanol (25 ml.) until a solution was obtained. On cooling, the crystals which formed were filtered and washed with cold ethanol. The crystals weighed 4.76 g. (96%), m.p. 173–174°. Recrystallization from ethanol did not raise the melting point. Mixedm elting point with thiourea (m.p. 180–181°) was depressed to 137–152° (with dec.).

Anal. Calcd. for $C_8H_{12}N_2O_3S_2$ (248.3): N, 11.23. Found: N, 11.22.

CHICAGO 12, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY, PIONEERING RESEARCH DIVISION, QUARTERMASTER RESEARCH AND ENGINEERING CENTER, U. S. ARMY]

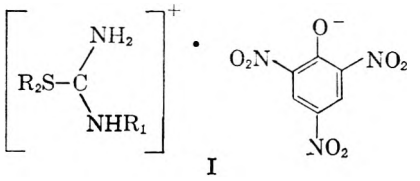
Isothiuronium, Alkylthioöxazolinium, and Alkylthiothiazolinium Picrates[1]

LOUIS LONG, JR., RICHARD C. CLAPP, FRANK H. BISSETT, AND TORSTEN HASSELSTROM

Received February 22, 1960

N-Substituted *S*-alkylisothiuronium picrates are shown to be useful derivatives in the identification of *N*-substituted thioureas derived from naturally occurring isothiocyanates, and a series of twenty-four picrates has been prepared. The procedure has been adapted to micro techniques. Conditions for the alkylation of 2-thioöxazolidones and for the preparation of a similar picrate derivative from (−)-5-vinyl-2-thioöxazolidone (goitrin) are described. The infrared spectra of the compounds are reported, and certain features are discussed.

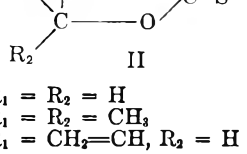
During an investigation of the naturally occurring isothiocyanates in certain plants, an attempt was made to find a derivative that would be useful in the separation and identification of substituted thioureas obtained from the isothiocyanates. The use of *S*-alkylisothiuronium picrates to identify alkyl halides has been described.[2] It is reported in the present paper that *N*-substituted *S*-alkylisothiuronium picrates (I) also constitute satisfactory



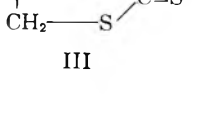
I

derivatives for *N*-substituted thioureas. The yield of picrates obtained (85–90%), their high molecular weight, their low solubility, and their crystallinity, as demonstrated in several instances by well-defined x-ray diffraction patterns,[3] favored the use of these derivatives in the isolation and identification of micro quantities.[4]

Since a derivative to assist in the identification of (—)-5-vinyl-2-thioöxazolidone (IIc), a goitrogenic compound isolated from *Brassica* seeds[5] and found to be present in micro quantities in cabbage,[6] was also desired, the preparation of a similar derivative from this compound was investigated. Hopkins[7] has reported that 5,5-dimethyl-2-thioöxazolidone (IIb) "does not combine with methyl iodide under ordinary conditions, nor does it form a picrate." However, the alkylation of 2-thiothiazolidone (III) with methyl iodide under alkaline[8] and neutral[9] conditions and the formation of a picrate from the resulting 2-methylthio-2-thiazoline have been described. Model experiments with 2-thiothiazolidone and 2-thioöxazolidone (IIa) dem-



II



III

a. $R_1 = R_2 = H$
b. $R_1 = R_2 = CH_3$
c. $R_1 = CH_2{=}CH$, $R_2 = H$

(1) Presented at the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) (a) E. L. Brown and N. Campbell, *J. Chem. Soc.*, 1699 (1937); (b) W. J. Levy and N. Campbell, *J. Chem. Soc.*, 1442 (1939); (c) L. Schotte, *Arkiv Kemi*, 5, 11 (1952).

(3) We are indebted to Dr. G. Susich and Mr. A. King of this Laboratory for the x-ray diffraction patterns.

(4) R. C. Clapp, L. Long, Jr., G. P. Dateo, F. H. Bissett, and T. Hasselstrom, *J. Am. Chem. Soc.*, 81, 6278 (1959).

(5) E. B. Astwood, M. A. Greer, and M. G. Ettlinger, *J. Biol. Chem.*, 181, 121 (1949).

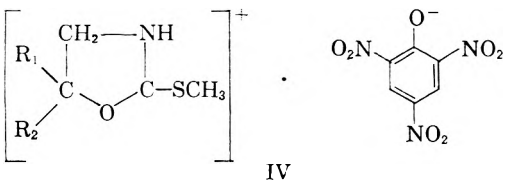
(6) (a) M. R. Altamura, L. Long, Jr., and T. Hasselstrom, *J. Biol. Chem.*, 234, 1847 (1959); (b) A. I. Virtanen, M. Kreula, and M. Kiesvaara, *Acta Chem. Scand.*, 12, 580 (1958).

(7) C. Y. Hopkins, *Can. J. Research*, 16B, 341 (1938).

(8) S. Gabriel, *Ber.*, 22, 1139 (1889).

(9) A. F. McKay, D. J. Whittingham, and M.-E. Kreling, *J. Am. Chem. Soc.*, 80, 3339 (1958).

onstrated that the alkylation could be effected most satisfactorily in absolute alcohol in the presence of sodium ethylate. 2-Methylthio-2-oxazolinium picrates (IV) could then be obtained from the 2-methylthio-2-oxazolines prepared under these conditions.



IV

a. $R_1 = R_2 = H$
b. $R_1 = R_2 = CH_3$
c. $R_1 = CH_2{=}CH$, $R_2 = H$

Infrared spectra. In the accompanying tables are shown the maxima between 3 μ and 15 μ for the *N*-substituted isothiuronium picrates. In Table I are presented those peaks which are constant for the entire group, and in Table II are listed those which vary.

TABLE I

MAJOR ABSORPTION BANDS (μ) COMMON TO *N*-SUBSTITUTED *S*-ETHYL ISOTHIURONIUM PICRATES[a]

2.91–2.94 s[b]	6.04–6.08 vs	7.88–7.91 vs
3.02 w	6.13–6.16 vs	8.61–8.65 s
3.08 w	6.28–6.30 s	9.27–9.30 s
3.18–3.19 s	6.68–6.75 s	10.99–11.02 s
3.24 m	6.99–7.02 s	12.62–12.65 s
3.34 w–m	7.30 s	13.40–13.44 s
3.40 w–m	7.50–7.52 vs	14.06–14.15 s
3.47 w–m	7.63–7.65 vs	

[a] It was not possible to distinguish between the spectra of the *S*-methyl and *S*-ethyl isothiuronium picrates. [b] vs = very strong; s = strong; m = medium; w = weak.

The spectra of all the isothiuronium picrates have strong, characteristic maxima at 6.13–6.16 μ and at 6.28–6.30 μ. Interference from picrate ion bands in this region has been eliminated by comparison with the spectrum of the corresponding iodide salt, as shown in Fig. 1 for the *N*-ethyl-*S*-methylisothiuronium salts. The maximum at 6.13–6.16 μ is probably due to an NH_2 deformation mode; in thiourea the NH_2 deformation was found to be at 6.18 μ.[10]

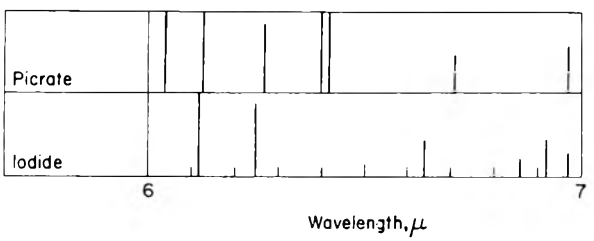


Fig. 1. Comparison of the infrared absorption bands between 6 and 7 μ of *N*-ethyl-*S*-methylisothiuronium picrate and its iodide

(10) J. E. Stewart, *J. Chem. Phys.*, **26**, 248 (1957).

The strong maximum at 6.28–6.30 μ in the isothiuronium picrates can be assigned to an N—C—N system and is analogous to the strong "thioureide"[11] band which was found to be at 6.39–6.49 μ in the corresponding substituted thioureas. The lower wave length of this band in the spectra of the isothiuronium compounds compared to that in the thioureas is the result of the alkylation of the sulfur atom, and it is indicative of the increased double bond character of the C—N bonds in the N—C—N system.

In the cyclic compounds, the effect of *S*-alkylation can be similarly observed by a quantitative shift of the "thioureide" peak at 6.60 μ in 2-thiothiazolidone[12] and in 2-thioöxazolidone,[13] which are true thiones, to a shorter wave length at 6.44 μ, due to an increase in the order of the carbon-nitrogen bond.

EXPERIMENTAL[14]

N-Substituted S-alkylisothiuronium picrates. The thioureas were obtained from isothiocyanates by treatment with ammonia in methanol. Unavailable isothiocyanates were prepared from amines by the method of Hodgkins and Ettlinger.[15]

In a typical preparation, a solution of 0.01 mole of the substituted thiourea and 0.011 mole of alkyl iodide in 10 ml. of 95% ethanol was refluxed for 10 min. A solution of 0.01 mole of picric acid in 15–20 ml. of hot 95% ethanol was added. Water was then added slowly until the crystalline picrate began to separate, and the precipitate was collected after cooling. In some instances the picrates separated without the addition of water. The compounds were purified by crystallization from ethanol, water, or aqueous ethanol.

The picrates prepared are listed in Table III. Several of the picrates have been reported in the literature but with incomplete characterization.

2-Methylthio-2-oxazolinium picrate (IVa). To a solution of 0.26 g. (0.0113 g.-atom) of sodium in 15 ml. of absolute ethanol was added 1.17 g. (0.0113 mole) of 2-thioöxazolidone.[16] A solution of 1.64 g. (0.0115 mole) of methyl iodide in 7 ml. of absolute ethanol was added in portions. After the mixture had been allowed to stand at room temperature for 1 hr., it was refluxed for 45 min. It was then concentrated under reduced pressure, and the residue was extracted with ether. Concentration of the ether afforded a liquid that was dissolved in 20 ml. of ethanol. When the solution was treated with 2.6 g. (0.011 mole) of picric acid in 50 ml. of ethanol, a precipitate (1.75 g.; 44% yield) of fine yellow crystals, m.p. 122–123.5°, resulted. Two crystallizations from acetone gave glistening yellow plates, m.p. 124.5–125.5°.

Anal. Calcd. for $C_{10}H_{10}N_4O_8S$: C, 34.68; H, 2.91; S, 9.26. Found: C, 34.78; H, 3.00; S, 9.20.

The infrared spectrum showed the following bands and intensities: 2.84(m), 3.30(m), 3.41(w), 6.06(vs), 6.16(s),

(11) *Cf.* 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. 5.

(12) Ref. 11, p. 189.

(13) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4699 (1950).

(14) We are indebted to Mr. C. DiPietro and Mr. W. Sassaman of this Laboratory for the microanalyses. Melting points were determined in capillary tubes in a Hershberg apparatus; final melting points are corrected.

(15) J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956).

(16) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950).

TABLE II

CHARACTERISTIC ABSORPTION BANDS (μ) IN *N*-SUBSTITUTED *S*-ETHYL ISOTHIURONIUM PICRATES[a]

Methyl	Ethyl	*n*-Propyl	Iso-propyl	Allyl	*n* Butyl	*sec*-Butyl	Isobutyl	3-Butenyl	3-Methylthiopropyl
6.42 vs[b]	6.39 vs	6.39 vs	6.33 vs	6.39 vs	6.33 vs	6.33 vs	6.33 vs	6.39 vs	6.33 vs
6.62 m	6.43 vs	6.43 vs	6.45 vs	6.43 vs	6.45 vs	6.45 vs	6.45 vs	6.43 vs	6.45 vs
6.81 vw	6.62 w	6.62 m	6.89 w	6.81 m	6.62 m	6.64 m	6.62 m	6.65 m	6.92 s
6.90 m	6.89 w	6.81 m	7.16 m	6.88 m	6.89 s	6.85 m	6.89 m	6.88 s	7.24 w
7.09 m	7.20 w	6.89 w	8.53 m	7.22 m	7.23 w	10.65 w	7.18 w	7.25 w	8.80 w
8.85 m	7.25 m	7.21 m	8.80 vw	8.05 vs	10.70 w	10.88 w	10.62 w	10.05 w	12.15 w
10.65 vw	8.83 m	8.80 w	10.64 w	10.11 m	12.30 w			10.65 s	12.45 w
10.75 m	10.67 vw	10.67 vw	12.50 vw	10.72 s				10.72 s	13.00 m
12.52 vw	10.80 w	10.80 m		10.79 s				12.25 m	
	12.52 w	12.50 m		12.50 w					

[a] Table I, footnote a. [b] vs = very strong; s = strong; m = medium; w = weak.

TABLE III

N-SUBSTITUTED ISOTHIURONIUM PICRATES[a] (I)

R_1	R_2	Formula	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	Methyl	$C_9H_{11}N_5O_7S$[b]	183–184.5	32.43	32.37	3.33	3.59
Methyl	Ethyl	$C_{10}H_{13}N_5O_7S$	161–162.5[c]	34.58	34.49	3.77	3.88
Ethyl	Methyl	$C_{10}H_{13}N_5O_7S$	163–164	34.58	34.37	3.77	3.65
Ethyl	Ethyl	$C_{11}H_{15}N_5O_7S$	126–127	36.56	36.49	4.18	4.19
n-Propyl	Methyl	$C_{11}H_{15}N_5O_7S$	153–154	36.56	36.49	4.18	4.15
n-Propyl	Ethyl	$C_{12}H_{17}N_5O_7S$	119–120	38.39	38.15	4.57	4.42
Isopropyl	Methyl	$C_{11}H_{15}N_5O_7S$	167–168	36.56	36.66	4.18	4.14
Isopropyl	Ethyl	$C_{12}H_{17}N_5O_7S$	154–155	38.39	38.44	4.57	4.41
Allyl	Methyl	$C_{11}H_{13}N_5O_7S$	148–149[d]	—	—	—	—
Allyl	Ethyl	$C_{12}H_{15}N_5O_7S$	124.5–125[e]	38.60	38.49	4.05	3.96
n-Butyl	Methyl	$C_{12}H_{17}N_5O_7S$	154–155	38.39	38.35	4.57	4.71
n-Butyl	Ethyl	$C_{13}H_{19}N_5O_7S$	122–123	40.10	40.11	4.92	5.07
sec-Butyl	Methyl	$C_{12}H_{17}N_5O_7S$	143–144	38.39	38.21	4.57	4.46
sec-Butyl	Ethyl	$C_{13}H_{19}N_5O_7S$	112.5–114	40.10	39.94	4.92	4.83
Isobutyl	Methyl	$C_{12}H_{17}N_5O_7S$	163.5–164.5	38.39	38.77	4.57	4.72
Isobutyl	Ethyl	$C_{13}H_{19}N_5O_7S$	151–152	40.10	39.86	4.92	4.87
3-Butenyl	Methyl	$C_{12}H_{15}N_5O_7S$	135.5–136.5	38.60	38.53	4.05	4.26
3-Butenyl	Ethyl	$C_{13}H_{17}N_5O_7S$	129–130	40.31	40.32	4.42	4.51
3-Methylthiopropyl	Methyl	$C_{12}H_{17}N_5O_7S_2$	112.5–113.5	35.37	35.16	4.21	4.28
3-Methylthiopropyl	Ethyl	$C_{13}H_{19}N_5O_7S_2$	103–104	37.05	37.25	4.54	4.56
Phenyl	Methyl	$C_{14}H_{13}N_5O_7S$	176–177.5[f]	42.53	42.18	3.31	3.25
Phenyl	Ethyl	$C_{15}H_{15}N_5O_7S$	198.5–199.5[g]	—	—	—	—
Benzyl	Methyl	$C_{15}H_{15}N_5O_7S$	173–174	44.01	44.10	3.69	3.76
Benzyl	Ethyl	$C_{16}H_{17}N_5O_7S$	143.5–144.5	45.39	45.25	4.05	4.12

[a] These compounds are indexed in *Chem. Abstr.* as picrates of, for example, 2,3-dimethyl-2-thiopseudourea. [b] J. Goerdeler, A. Huppertz, and K. Wember, *Ber.*, **87**, 68 (1954). Used in purification without characterization. [c] H. L. Wheeler and G. S. Jamieson, *J. Biol. Chem.*, **4**, 111 (1908), reported 157°. No analysis given. [d] A. E. Dixon, *J. Chem. Soc.*, 550 (1903), reported 149–150°. [e] Melted partially at 112.5–113.5° and formed complete melt at 124.5–125°. R. Douris, *Bull. sci. pharmacol.*, **15**, 629 (1908), reported sintering at 114° and melting at 123°. No analysi given. [f] Lit. (ref. *d*) 176–177°. No analysis given. [g] J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 452 (1950), reported 199.5°.

6.44(vs), 6.71(s), 6.97(m), 7.31(m), 7.52(vs), 7.86(vs), 8.17(m), 8.61(w), 9.25(w), 10.95(m), 12.61(w), 13.40(w), 14.10(w), 14.26(w), and 15.70(w) μ.

When the alkylation was carried out in aqueous ethanol in the presence of sodium hydroxide,[17] a 24% yield of picrate was obtained. When an attempt was made to alkylate 2-thioöxazolidone or 5,5-dimethyl-2-thioöxazolidone with methyl iodide in refluxing ethanol without alkali, no picrate was obtained, nor could the thioöxazolidone be recovered. Decomposition may result from the acid formed in the reaction. When solutions of the oxazolinium picrates were heated, evidence of decomposition could be observed.

2-Methylthio-5-vinyl-2-oxazolinium picrate (IVc). Alkylation of 0.5 g. of *dl*-5-vinyl-2-thioöxazolidone[16] with methyl iodide and sodium ethylate in absolute ethanol followed by treatment with picric acid yielded 0.48 g. (33%) of the picrate of the *dl*-isomer, m.p. 101–103.5°. It crystallized from chloroform-heptane (10:7) as yellow needles, m.p. 104.5–105.5°.

Anal. Calcd. for $C_{12}H_{12}N_4O_8S$: C, 38.71; H, 3.25; S, 8.61. Found: C, 38.79; H, 3.47; S, 8.65.

When 150 mg. of (−)-5-vinyl-2-thioöxazolidone, isolated from rutabaga seeds,[t] was methylated in a similar manner, 142 mg. (33% yield) of the picrate of the l-isomer, m.p.

(17) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948), preferred these conditions for the methylation of 2-thiouracil.

103–104°, was obtained. Recrystallization from chloroform-heptane afforded yellow needles, m.p. 104.5–105.5°, $[\alpha]_D^{25}$ −32.8° (*c*, 0.2 in methanol).

Anal. Calcd. for $C_{12}H_{12}N_4O_8S$: C, 38.71; H, 3.25. Found: C, 38.58; H, 3.36.

5,5-Dimethyl-2-methylthio-2-oxazolinium picrate (IVb). Methylation of 0.5 g. of 5,5-dimethyl-2-thiooxazolidone[18] in absolute ethanol, as described above, gave 0.82 g. (57% yield) of picrate, m.p. 132–134°. Yellow prismatic crystals, m.p. 133–134.5°, were obtained on recrystallization from chloroform-heptane.

Anal. Calcd. for $C_{12}H_{14}N_4O_8S$: C, 38.50; H, 3.77; S, 8.56. Found: C, 38.64; H, 3.87; S, 8.54.

Thiazolinium picrates. When 2-thiothiazolidone was refluxed in ethanol with a slight excess of methyl iodide for 45 min., 2-methylthio-2-thiazoline was isolated as the picrate in 51% yield.[19] When the reactants were refluxed for 45 min. in the presence of sodium ethylate, the picrate was obtained in 84% yield.

The preparation of 2-methylthio-2-thiazoline by the cyclization of methyl 2-hydroxyethyldithiocarbamate has been reported by Crawhall and Elliott[20] and the melting point of the picrate given as 123°. The picrate obtained in this Laboratory, however, melted at 150–151°. Since the structures of the cyclization products involved are of considerable interest,[16,21] the preparation by the method of Crawhall and Elliott was repeated. The resulting picrate melted at 150–151°, and the products from the two methods were found to be identical.

The infrared spectrum of 2-methylthio-2-thiazolinium picrate showed the following bands and intensities: 2.84(w), 6.14(s), 6.21(vs), 6.39(vs), 6.45(vs), 6.58(s), 6.74(m), 6.97(m), 7.32(s), 7.51(s), 7.61(s), 7.95(vs), 8.65(s), 9.30(m), 9.52(m), 10.88(m), 11.00(m), 12.65(m), 13.46(m), 14.25(s), and 15.12(m) μ.

2-Ethylthio-2-thiazolinium picrate, prepared by ethylation under alkaline conditions, formed prismatic crystals, m.p. 112.5–114°, from aqueous acetone.

Anal. Calcd. for $C_{11}H_{12}N_4O_7S_2$: C, 35.10; H, 3.22. Found: C, 35.24; H, 3.30.

Infrared spectra. The spectra in the 2–8 μ region were obtained employing a Perkin-Elmer model 112, single beam, double pass infrared spectrophotometer equipped with calcium fluoride optics. In the 8 μ to 16 μ region spectra were obtained from a Baird model A, double beam infrared spectrophotometer using sodium chloride optics. All samples were run as potassium bromide disks with approximately equal weights of samples.

Acknowledgments. We wish to thank Dr. M. G. Ettlinger of The Rice Institute for his valuable suggestions and advice. We thank also Dr. J. D. Margerum and his associates of the Spectroscopy Section for assistance in determining the infrared spectra.

NATICK, MASS.

(18) H. A. Bruson and J. N. Eastes, *J. Am. Chem. Soc.*, 59, 2011 (1937).

(19) The preparation of 2-methylthio-2-thiazolinium iodide from 2-thiothiazolidone and methyl iodide in 87% yield by refluxing for 2 hr. in methanol has recently been reported by McKay, *et al.*[9]

(20) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(21) A. A. Rosen, *J. Am. Chem. Soc.*, 74, 2994 (1952).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

5-Nitro-2-furyl-substituted 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, and 1,3,5-Triazines[1]

WILLIAM R. SHERMAN

Received April 13, 1960

The preparation of two new types of antibacterial nitrofurans is described. In these compounds antibacterial activity is shown for the first time to be present in 5-nitrofurans which are joined at the 2-position directly to a carbon atom in another heterocycle. Two systems of this type have been prepared. The first is one in which the atomic configuration C=N—N—C= is contained in a cyclic arrangement. This is found in the 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. In the second type of system there is no C=N—N—C= arrangement in the heterocycle, but antibacterial activity is retained. This is represented by the 1,3,5-triazines described.

In 1944 Dodd and Stillman[1a] published their finding that furans with a nitro group in the 5-position possessed antibacterial activity. In a later paper[2] the generalization was made, that, in order to be effective *in vivo*, the 2-position of the 5-nitrofuran must be substituted by a group of the general type C=N—N—C=. An example is the semicarbazone of 5-nitro-2-furaldehyde. In subsequent years, the great bulk of work carried out in this area has followed along these lines, *e.g.* nitrofurfurylidene derivatives and their vinylogs.[3]

It has now been found that the C=N—N—C= system described by Dodd *et al.*,[2] may be incorporated in a heterocycle and still retain *in vivo* activity.[3a] Such a compound is described in general terms by structure I. Two groups of such com-

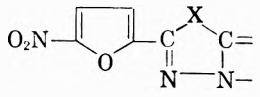
(1) Presented before the Division of Medical Chemistry, 136th Meeting, American Chemical Society, Atlantic City, N. J., September 13–18, 1959.

(1a) M. C. Dodd and W. B. Stillman, *J. Pharmacol. Exptl. Therap.*, 82, 11 (1944).

(2) M. C. Dodd, D. L. Cramer, and W. C. Ward, *J. Am. Pharm. Assoc.*, 39, 313 (1950).

(3) See, for example: K. Hayes, *J. Am. Chem. Soc.*, 77, 2333 (1955) and previous papers; H. Saikachi and H. Ogawa, *J. Am. Chem. Soc.*, 80, 3642 (1958).

(3a) Detailed information regarding the *in vitro* and *in vivo* antibacterial activity of these compounds will be published elsewhere.



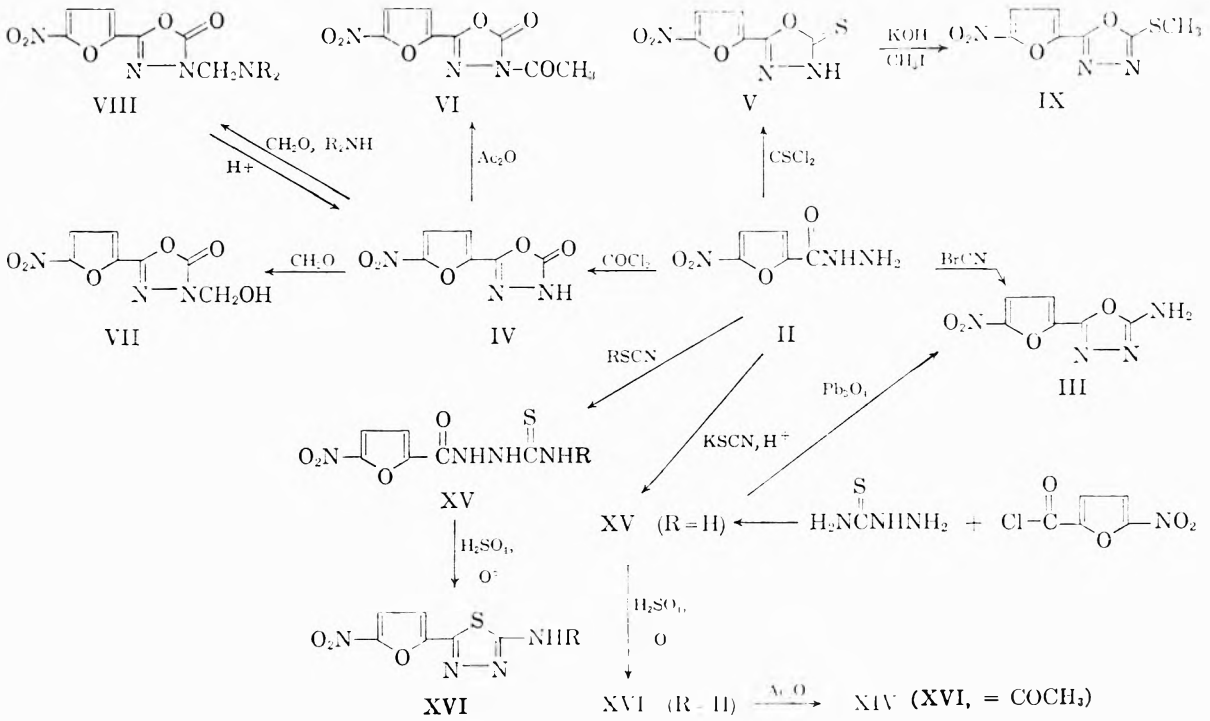
I

pounds will be described here, the 1,3,4-oxadiazoles where X = O and the 1,3,4-thiadiazoles where X = S. Perhaps more significant is the finding that certain compounds which do not contain the C=N—N—C= system at all, exhibit a high order of *in vitro* and *in vivo* activity.[3a] The nitrofuryl-1,3,5-triazines described here are examples of this type of compound.

1,3,4-Oxadiazoles. The semicarbazone of 5-nitro-2-furaldehyde was the first of the nitrofurans to have been used clinically. Although analogs and derivatives of the semicarbazone have been prepared, its structural features have never been incorporated into a heterocyclic system. This has now been done and the compound (III) found to be antibacterial both *in vitro* and in test animals. 2-Amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole (III) may be prepared by either of two routes. The preferable method is the recently described[4] reaction of cyanogen bromide with an acyl hydrazine. When 5-nitro-2-furoylhydrazine is treated with cyanogen bromide in refluxing ethanol the desired compound is formed. The aminooxadiazole may also be prepared, though in lower yield, by the general reaction[5] of an acyl thiosemicarbazide with red lead oxide in refluxing ethanol. The required 1-(5-nitro-2-furoyl)thiosemicarbazide is obtained either by the direct action of the acid chloride on thiosemicarbazide in dioxane, or by treating 5-nitro-2-furoylhydrazine with potassium thiocyanate in acidic solution.

When acyl hydrazines are treated with phosgene[6] or with thiophosgene,[7] 5-substituted 1,3,4-oxadiazole-2-ones or thiones are formed. Thus 5-nitro-2-furoylhydrazine and phosgene produce 5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (IV). In a similar way thiophosgene gives rise to the 2-thione (V). The infrared spectrum[7a] of the oxadiazolone has a strong absorption at 5.64 μ (Nujol mull) supporting the keto structure IV, at least in the solid state. The thione has medium strength absorptions at 2.92 and 3.18 μ, and strong absorption from 7.53 to 7.63 μ (1.25% in chloroform). These maxima correspond closely to values assigned to 5-methyl-1,3,4-oxadiazol-2-thione by Ainsworth[8] (2.90 N—H, monomer; 3.16 N—H dimer; 7.57 C=S dimer; 7.65 C=S monomer; all in chloroform). Ainsworth found that the methyl oxadiazolthione existed in both monomeric and dimeric states, the dimer being hydrogen-bonded thiocarbonyl to N—H. It appears that V is similar in this respect although the 7.53–7.63 region is poorly resolved due to interfering C—NO_2 absorption.

A monoacetyl derivative is obtained on treat-



(4) A. P. Swain, U. S. Patent 2,883,391 (1959).

(5) R. Stollé and K. Fehrenbach, *J. prakt. Chem.*, 122, 289 (1929).

(6) A. Dornow and K. Bruncken, *Ber.*, 82, 121 (1949).

(7) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(7a) Infrared spectra were determined by W. Washburn, of Abbott Laboratories, whose aid in the interpretation of this data is acknowledged. Spectra were measured on a Perkin-Elmer model 21 spectrophotometer.

(8) C. Ainsworth, *J. Am. Chem. Soc.*, 78, 4475 (1956).

ment of IV with hot acetic anhydride. This appears to be the *N*-acetyl compound VI for the infrared spectrum contains two carbonyl absorptions, one at 5.50μ, the other at 5.70 μ (2.3% in chloroform), eliminating the possibility of *O*-acetylation.

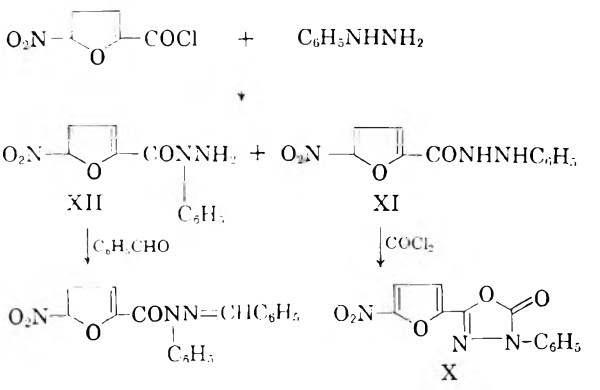
1,3,4-Oxadiazol-2-ones are known to undergo the Mannich reaction, giving rise to 3-hydroxymethyl or aminomethyl derivatives in the usual way.[9] Utilizing this reaction, the 3-hydroxymethyl (VII) and several 3-aminomethyl oxadiazolones (VIII) were obtained. The group included Mannich bases derived from dimethylamine, diethylamine piperidine, morpholine, pyrrolidine, hexamethyleneimine, and the bisnitrofuryloxadiazolylcompound from piperazine. All of these compounds were easily obtained except the hydroxymethyl derivative VII which was isolated only with difficulty, and in poor yield. The Mannich bases thus obtained were similar to those previously reported[9b] in their ready decomposition by acid to the parent compound IV.

If the thione V is treated with methyl iodide in alcohol potassium hydroxide a monomethyl derivative is formed. This is probably the methylthio compound IX since the infrared spectrum in chloroform solution does not show the presence of $N—CH_3$ and there is marked attenuation of the absorption in the 7.5 to 7.6 μ region (see above). Treatment of the thione V with mercuric oxide in either refluxing water or dioxane resulted only in the isolation of the bis salt with mercury. This procedure has been used[10] to convert oxadiazolthiones to oxadiazolones, and was expected to give rise to IV.

Another procedure which was expected to lead to the oxadiazolone IV was the treatment of the methylthio compound IX with aqueous acid. However when IX was heated with concentrated hydrochloric acid more extensive hydrolysis occurred, and only 5-nitro-2-furoic acid was isolated.

The most active member of this series in animals is the nitrofuryloxadiazolone IV. This compound and its acid-labile Mannich derivatives are effective against Gram positive and negative infections in animals by both intramuscular and oral routes. In view of the high activity of the oxadiazolone, it was surprising that the thione V had no activity either *in vitro* or *in vivo*.

Similarly inactive was 3-phenyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (X) obtained by the action of phosgene on 1-(5-nitro-2-furoyl)-2-phenylhydrazine (XI). Compound XI was obtained along with 1-(5-nitro-2-furoyl)-1-phenylhydrazine (XII) by treating phenylhydrazine with nitrofuroyl chloride in either benzene or diethyl ether. When the reaction was carried out in benzene the product ratio was 37.8% XII to 17.4% XI, while in diethyl ether the ratio was reversed, giving 16.2% XII and 58.2% XI. The structure of XII was established by conversion to its benzylidene derivative.



The reaction of nitrofuroyl chloride with phenylhydrazine to produce both XI and XII is somewhat unusual. For example treatment of phenylhydrazine with benzoyl chloride gives 1-benzoyl-2-phenylhydrazine in the cold[11] or 1,2-dibenzoylphenylhydrazine in hot benzene.[12] Only when the sodio derivative of phenylhydrazine is treated with benzoyl chloride is the 1-benzoyl-1-phenylhydrazine formed[13] and this is accompanied by 2-benzoyl and 1,2-dibenzoyl phenylhydrazine.

1,3,4-Thiadiazoles. A procedure which has been shown to be general for the preparation of 1,3,4-thiadiazoles is the cyclization of 1-acylthiosemicarbazides by cold concentrated sulfuric acid.[14] Using this method several 5-(5-nitro-2-furyl)-1,3,4-thiadiazoles were prepared. In this way 1-(5-nitro-2-furoyl)thiosemicarbazide (XV, R=H) was cyclized to 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XVI, R=H) in good yield. Similar treatment of 1-(5-nitro-2-furoyl)-4-alkyl-(or -aryl)-thiosemicarbazides gives rise to the 1-(5-nitro-2-furoyl)-4-substituted amino thiadiazoles. In this way were obtained the compounds XVI in which R is methyl, ethyl, and phenyl. The required 1-nitrofuroyl-4-substituted thiosemicarbazides (XV) were obtained by the action of isothiocyanates on nitrofuroylhydrazine (II).

The nitrofurylaminothiadiazole XVI (R=H) was the most active antibacterial of the thiadiazoles tested, being effective in animals when administered by either oral or intramuscular routes. The substituted amino derivatives showed decreasing activity in the order $R=CH_3>C_2H_5>C_6H_5$.

1,3,5-Triazines. The condensation of esters of heterocyclic acids with biguanide or substituted biguanides provides a convenient route to amino- or substituted aminotriazines.[15] Methyl 5-nitro-2-furoate reacts in this way to produce 2,4-di-

(9)(a) A. Dornow and S. Lüpfert, *Arch. Pharm.*, **288**, 311 (1955). (b) H. C. Caldwell, R. J. Seiwald, and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, **477**, 799 (1958).

(10) See for example: M. Freund and B. B. Goldsmith, *Ber.*, 21, 1240, 2456 (1888).

(11) E. Fischer, *Ann.*, **190**, 67 (1878).

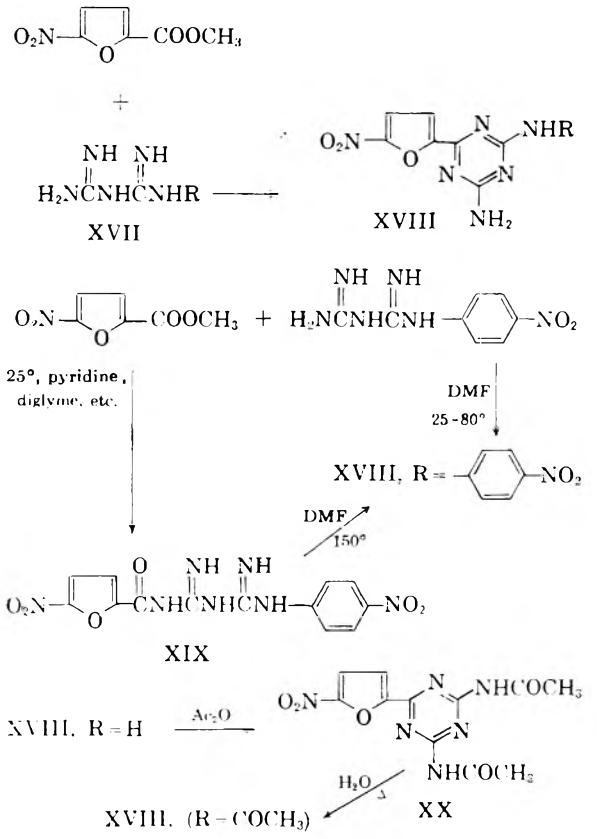
(12) H. Franzen, *Ber.*, **42**, 2465 (1909).

(13) A. Michaelis and F. Schmidt, *Ann.*, **252**, 300 (1889).

(14) E. Hoggarth, *J. Chem. Soc.*, 1163 (1949).

(15) J. T. Thurston and D. W. Kaiser, U. S. Patent 2,535,968 (1950).

amino-6-(5-nitro-2-furyl)-1,3,5-triazine[16] (XVIII, R = H). This compound was found to have a high degree of antibacterial activity in animals when administered by the intramuscular route. This is the first example of a systemically effective antibacterial which does not contain the —C=N—N—C= system felt by Dodd[2] to be requisite for *in vivo* activity. Several substituted amino derivatives of this compound have now been prepared and found to be less active in general than the parent compound (XVIII, R = H).



When methyl 5-nitro-2-furoate is allowed to react with 1-substituted biguanides (XVII, R = isopropyl, phenyl, *o*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl) the 2-amino-4-substituted amino-6-(5-nitro-2-furyl)-1,3,5-triazines (XVIII, R as above) are formed. The yields from this reaction are very low (see Experimental); however, this appears to be the most useful route to these compounds. In one attempt to prepare XVIII (R = *o*-tolyl) using nitrofuroyl chloride and *o*-tolylbiguanide no cyclized product was obtained.

A possible explanation of the low yields of the substituted aminotriazines compared with the yields obtained in the preparation of the parent compound may lie in the very slow rate of product formation when substituted biguanides are used. While XVIII (R = H) was formed in 80% yield after reacting overnight at room temperature, the substituted biguanides required from three to five days for reaction. Long standing in solution with the basic biguanides could destroy large amounts of the base-labile nitrofuran intermediates or products. The reduced rates of cyclization may result from a combination of steric and electric effects.

When *p*-nitrophenylbiguanide (XVII, R = *p*-nitrophenyl) is treated with methyl nitrofuroate at room temperature in pyridine, diethylene glycol dimethyl ether, or ethylene glycol monomethyl ether, or in refluxing ethanol, an intermediate is formed which apparently is 1-(5-nitro-2-furoyl)-5-(*p*-nitrophenyl)biguanide (XIX). The compound is isolated only as a monohydrate, and attempts to remove the molecule of water have been unsuccessful. The identity as XIX rests on the combustion analysis of the hydrate and the fact that the intermediate may be cyclized to the triazine (XVIII, R = *p*-nitrophenyl) by short boiling in dimethylformamide. If dimethylformamide is used as solvent and the reaction carried out either at room temperature or by warming on a steam bath, the triazine is obtained directly, without isolation of intermediate XIX. This appears to be due to the much greater solubility of XIX in dimethylformamide than in other solvents. When the other solvents were used, the intermediate separated and because of its low solubility did not react further. In dimethylformamide, however, the material remained in solution, facilitating cyclization.

2,4-Diamino-6-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = H) is a weakly basic compound of low solubility in most solvents. It is stable toward warm concentrated hydrochloric acid, but does not form a stable hydrochloride salt. Warm 10% sodium hydroxide decomposes the compound. When refluxed with acetic anhydride a diacetyl derivative is formed (XX), which is converted to the monoacetyl derivative (XVIII, R = $COCH_3$) by boiling for sixteen hours in water.

EXPERIMENTAL[17]

2-Amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole (III). *Procedure A.* 5-Nitro-2-furoylhydrazine[18] (68.4 g., 0.4 mole) and cyanogen bromide (48.0 g., 0.45 mole) were heated together under reflux in 2000 ml. of methanol for 1 hr. Cooling provided about 20.4 g. of crude product, m.p. 250–255°. On concentration of the mother liquor a brown oil was obtained, which, when poured into 500 ml. of water produced an additional 30 g. of crude product (m.p. 240–249°). The total yield of crude product was 50.4 g. or 64% of theory. Crystallization from dimethylformamide-ethanol gave yellow needles, m.p. 258–260° dec.

Procedure B. A mixture of 1-(5-nitro-2-furoyl)thiosemicarbazide (4.60 g., 0.02 mole) and red lead oxide (Pb_3O_4)

(16) R. U. Schock and A. Alter, unpublished results from Abbott Laboratories; R. U. Schock, U. S. Patent 2,885,400 (May 5, 1959).

(17) All melting points are uncorrected and were determined in capillary tubes.

(18) H. L. Yale, *et al.*, *J. Am. Chem. Soc.*, **75**, 1933 (1953).

(34.2 g., 0.05 mole) was heated with stirring in 250 ml. of boiling ethanol. After 24 hr. the suspension was filtered and the solid residue extracted three times with hot alcohol. On concentration of the alcoholic extracts the product separated as fine yellow needles, m.p. 260.5° dec., weighing 0.64 g. (16%). Recrystallization as above gave material, m.p. 261.5° dec.

Anal. Calcd. for $C_6H_4N_4O_4$: C, 36.74; H, 2.06. Found: C, 36.84; H, 2.12.

5-(5-Nitro-2-furyl)-1,3,4-oxadiazol-2-one (IV). A solution of 5-nitro-2-furoylhydrazine (50.15 g., 0.30 mole) in 500 ml. of dilute (10:1) hydrochloric acid was stirred with cooling while phosgene was introduced beneath the surface of the liquid. After 1 hr. the product was collected by filtration and washed with water. This gave 54 g. (92%) of light tan-colored platelets, m.p. 200–202° dec. Crystallization from acetone-water gave material melting at 201–202° dec. Repeated crystallization lowered the melting point.

Anal. Calcd. for $C_6H_3N_3O_5$: C, 36.56; H, 1.52; O, 40.59. Found: C, 36.36; H, 1.80; O, 40.36.

5-(5-Nitro-2-furyl)-1,3,4-oxadiazol-2-thione (V). To a suspension of 5-nitro-2-furoylhydrazine (17.11 g., 0.1 mole) in 375 ml. of dioxane was added thiophosgene (11.5 g., 0.1 mole) at room temperature. After the mildly exothermic reaction had ended the solution was treated with charcoal and filtered. The solution was diluted with 700 ml. of hexane, cooled, and seeded or scratched to produce 13.40 g. of yellow product, m.p. 154–155° dec. (64%). This may be crystallized from boiling water to give yellow needles, m.p. 157.5–158° dec.; however, the recovery is only 65%. This compound is soluble in chloroform, alcohols, acetone, etc., and in dilute potassium carbonate, from which it precipitates unchanged on acidification.

Anal. Calcd. for $C_6H_3N_3O_4S$: C, 33.81; H, 1.42; N, 19.72; S, 15.01. Found: C, 34.04; H, 1.59; N, 19.67; S, 15.01.

3-Acetyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VI). Compound IV (10 g., 0.51 mole) was covered with acetic anhydride and heated under reflux for 2 hr. The solution was taken to dryness *in vacuo* and the residue crystallized from acetone-water to give 10.22 g. (84%) of light yellow crystals, m.p. 143–144°. Two recrystallizations as above gave product, m.p. 144–144.5°.

Anal. Calcd. for $C_8H_5N_3O_6$: C, 40.18; H, 2.11; N, 17.57. Found: C, 39.98; H, 1.98; N, 17.41.

3-Hydroxymethyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VII). A mixture of IV (9.85 g., 0.05 mole), formalin (3.75 ml., 0.05 mole), and 40 ml. of water was heated to boiling and then warmed on a steambath for 30 min. On cooling, an oil separated which on long standing produced a few crystals of product. The crystals were collected and crystallized from ethanol-cyclohexane giving white needles, m.p. 110–111°, weighing 0.54 g. (4.7%).

Anal. Calcd. for $C_7H_5N_3O_6$: C, 37.01; H, 2.22; O, 42.27. Found: C, 37.12; H, 2.62; O, 41.95.

3-Dimethylaminomethyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIIa). To a stirred, ice cold suspension of IV (19.7 g., 0.1 mole) in 200 ml. of absolute ethanol was added formalin (7.5 ml., 0.1 mole) followed by an alcoholic solution of dimethylamine (30 ml. of 0.15 g./ml., 0.1 mole). A deep red solution formed which soon began to precipitate orange crystals. After 10 min. the material was collected by filtration. Following crystallization from alcohol, this weighed 14 g. and melted 117–147°. When this was extracted with 800 ml. of hot benzene, a residue (partly of starting material, partly of unknown composition) remained. Evaporation of the benzene filtrate to 100 ml. and cooling gave 7.1 g. (28%) of VIIIa, m.p. 118–119°.

Anal. Calcd. for $C_9H_{10}N_4O_5$: C, 42.52; H, 3.97; N, 22.04. Found: C, 42.68; H, 3.93; N, 22.02.

3-Diethylamino-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIIb). A hot solution of IV (19.71 g., 0.1 mole) in 200 ml. of absolute alcohol containing 10 ml. of dimethylformamide was cooled to 40° and formalin (7.5 ml., 0.1 mole) and diethylamine (7.31 g., 0.1 mole) added. The solution was cooled in an ice bath and crystallization induced by scratching. The yellow product obtained weighed 6.08 g. (22%) and melted at 99–99.5°. VIIIb is soluble in carbon tetrachloride, benzene, alcohols, *etc.* slightly soluble in water, and insoluble in cyclohexane, *etc.* Recrystallization from solvents or solvent pairs could not be achieved.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; O, 28.35. Found: C, 46.59; H, 5.03; O, 28.62.

3-Piperidinomethyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIIc). The general procedure outlined above for VIIIb was followed using piperidine (8.52 g., 0.1 mole). The product separated directly as flat orange needles, m.p. 134.5–135°, weighing 23.00 g. (78.2% of theory). Crystallization from ethanol gave yellow crystals, m.p. 133.5–134°.

Anal. Calcd. for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.10; H, 4.98; N, 19.25.

3-Morpholinomethyl-2-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIId). The general procedure outlined above for VIIIa was followed using morpholine (8.71 g., 0.1 mole). Cooling gave 27.4 g. (93%) of yellow crystals, m.p. 191.5–192.5°. Crystallization from dimethylformamide-alcohol lowered the melting point to 190–191°.

Anal. Calcd. for $C_{11}H_{12}O_6N_4$: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.77; H, 4.27; N, 18.85.

3-Pyrrolidinomethyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIIe). The general procedure outlined above for VIIIb was followed using pyrrolidine (7.11 g., 0.1 mole). Cooling provided 23.8 g. (85%), m.p. 137–138° (140–141° preheated). Crystallization from dimethylformamide-ethanol gave material, m.p. 138–139°.

Anal. Calcd. for $C_{11}H_{12}N_4O_6$: C, 47.14; H, 4.32; O, 28.55. Found: C, 47.20; H, 4.60; O, 28.82.

3-Hexamethyleneiminomethyl-5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-one (VIIIf). The general procedure outlined above for VIIIb was followed using hexamethyleneimine (9.92 g., 0.1 mole). Cooling gave 28.3 g. of crystalline yellow product (92%), m.p. 134–135°.

Anal. Calcd. for $C_{13}H_{16}N_4O_5$: C, 50.64; H, 5.23; N, 18.18. Found: C, 50.79; H, 5.45; N, 18.32.

1,4-Bis[5-(5-nitro-2-furyl)-2-keto-1,3,4-oxadiazolyl-3-methyl]piperazine (VIIIg). The general procedure outlined above for VIIIb was employed using piperazine (4.31 g., 0.05 mole). The product separated immediately as an orange powder, m.p. 200° dec., weighing 23.9 g. (95%).

Anal. Calcd. for $C_{18}H_{16}N_8O_{10}$: C, 42.86; H, 3.70. Found: C, 42.82; H, 3.35.

Decomposition of the Mannich bases by acid. A suspension of VIIIe (0.85 g., 0.003 mole) in 10 ml. of water was treated with concd. hydrochloric acid (0.25 ml., 0.003 mole) with stirring. Almost immediately the color of the starting material changed from orange to tan. The product was collected and found to weigh 0.60 g. (94%) and to melt at 196–198.5°. A mixture of the product and IV melted at 198–199°. The infrared spectra (Nujol mull) of the product and IV were identical. Compounds VIIId and VIIIf behaved in the same way as VIIIe.

2-Methylthio-5-(5-nitro-2-furyl)-1,3,4-oxadiazole (IX). To a solution of V (6.39 g., 0.030 mole) in 30 ml. of ethanol was added 6 ml. of methyl iodide and a solution of potassium hydroxide (1.68 g., 0.030 mole) in 75 ml. of ethanol. The product separated almost immediately, providing 5.82 g. (85%) of fine yellow needles, m.p. 164.5–165°. Crystallization from dimethylformamide-water gave material melting 165.5–166°, with 93% recovery.

Anal. Calcd. for $C_7H_5N_3O_4S$: C, 37.01; H, 2.22. Found: 36.95; H, 2.36.

Reaction of V *with mercuric oxide.* A suspension of yellow mercuric oxide (1.73 g., 0.008 mole) and V (0.852 g., 0.004 mole) in 50 ml. of pure, dry dioxane was heated under reflux for 15 hr. The suspension was then filtered and the cake extracted with hot dimethylformamide. Addition of water to the extract gave a bright yellow precipitate, m.p. 260.5° dec., weighing 0.70 g. (56%). Recrystallization from dimethylformamide-water brought the m.p. to 262° dec.

This reaction was also carried out in boiling water for a similar length of time, providing the same product.

Anal. Calcd. for $C_{12}H_4N_6O_8S_2Hg$: C, 23.06; H, 0.65; N, 13.45; S, 10.22. Found: C, 23.75; H, 0.37; N, 13.65; S, 10.02; Hg, present (qualitative, by emission spectrum).

Reaction of IX *with hydrochloric acid.* A mixture of IX (0.90 g., 0.004 mole) and 20 ml. of concd. hydrochloric acid was heated on a steam bath for 7 hr. During this time, solution occurred and the odor of methyl mercaptan was detected. On cooling 0.46 g. (74%) of light yellow crystal separated, m.p. 182–183° dec. This was shown to be 5-nitro-2-furoic acid by a mixture melting point determination (undepressed) with authentic material obtained by the acid hydrolysis[19] of methyl 5-nitro-2-furoate.[20]

1-(5-Nitro-2-furoyl)-1-phenylhydrazine (XII) *and 1-(5-Nitro-2-furoyl)-2-phenyl-hydrazine* (XI). *Procedure A.* To a stirred, ice-cold solution of phenylhydrazine (4.32 g., 0.04 mole) in 25 ml. of dry benzene was added, dropwise, a solution of 5-nitro-2-furoyl chloride[21] in 25 ml. of dry benzene. After the addition the suspension was heated under reflux for a few minutes, cooled, and the product collected by filtration. The residue was washed with water and crystallized from absolute ethanol. Cooling provided 1.87 g. (37.8%) of XII, as yellow crystals, m.p. 167–167.5°. The alcohol mother liquor was then taken to dryness and the residue extracted with warm water and then crystallized from toluene. In this way yellow-orange needles of XI were obtained, m.p. 127.5–128°, weighing 0.86 g. (17.4%).

Anal. Calcd. for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67. Found XII: C, 53.68; H, 3.71. Found XI: C, 53.35; H, 3.68.

Compounds XI *and* XII, *Procedure B.* A solution of 5-nitro-2-furoyl chloride (3.51 g., 0.02 mole) in 50 ml. of dry ether was added slowly to a stirred, ice cold solution of phenylhydrazine (4.32 g., 0.04 mole) in 50 ml. of dry ether. The resulting suspension was filtered and the filtrate saved. The cake was washed with water and the residue dissolved in ethanol. On cooling XII separated weighing 0.80 g. (16.2%), m.p. 163–164°. The ethanol mother liquor was combined with the ether filtrate and the solvents removed. The residue was crystallized as before to give 2.87 g. (58.2%) of XI, m.p. 124.5–125.5°.

5-(5-Nitro-2-furyl)-3-phenyl-1,3,4-oxadiazol-2-one (X). A solution of XI (1.80 g., 0.0073 mole) in 50 ml. of toluene was heated on a steam bath and phosgene bubbled through the solution for 1 hr. The toluene was then removed in an air stream and the residue slurried in 25 ml. of boiling ethanol to give 1.42 g. (71.2%) of X, m.p. 186–187°. An additional 0.26 g., m.p. 184–185° was obtained from the alcohol mother liquor (total yield 84%). The product was soluble in acetone, chloroform, slightly soluble in ethanol and insoluble in hexane. For analysis, X was crystallized from toluene, raising the melting point to 186.5–187.5°.

Anal. Calcd. for $C_{12}H_8N_3O_5$: C, 52.56; H, 2.94; N, 15.33. Found: C, 52.48; H, 2.74; N, 15.18.

1-Benzylidene-2-(5-nitro-2-furoyl)-2-phenylhydrazine. Freshly distilled benzaldehyde (5 ml.) and XII (0.5 g., 0.002 mole) were heated together on a steam bath for 40 min. On cooling, 0.53 g. (78%) of the benzylidine derivative separated, m.p. 207–208°. Crystallization from toluene gave bright yellow crystals of the same melting point.

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.65; H, 4.16; N, 12.24.

1-(5-Nitro-2-furoyl)thiosemicarbazide (XV, R = H) *Procedure A.* A solution of 5-nitro-2-furoyl chloride (5.27 g., 0.03 mole) in 30 ml. of pure, dry dioxane was added slowly to a stirred suspension of thiosemicarbazide (2.73 g., 0.03 mole) and 7 g. of sodium bicarbonate in 50 ml. of dry dioxane. After the addition, the mixture was stirred for 2 hr. at room temperature and then heated on a steam bath for 10 min., cooled, and filtered. The filtered solution was reduced in volume and the product precipitated by addition of ethanol. In this way was obtained 3.15 g. (46% of theory) of XV (R = H), m.p. 186° (dec.). Crystallization from ethanol raised the melting point to 192° (dec.).

Procedure B. A mixture of 5-nitro-2-furoylhydrazine (34.22 g., 0.20 mole), potassium thiocyanate (25 g., 0.26 mole), concd. hydrochloric acid (20 ml.) and 300 ml. of water was heated for 4 hr. on a steam bath. After cooling overnight a dark brown solid had precipitated which was collected by filtration and slurried in a small amount of boiling ethanol for a few minutes. This provided 22.8 g. (50% of theory) of yellow XV (R = H), m.p. 186° dec.

Anal. Calcd. for $C_6H_6N_4O_4S$: C, 31.31; H, 2.63; N, 24.35. Found: C, 31.45; H, 2.97; N, 24.32.

4-Methyl-1-(5-nitro-2-furoyl)thiosemicarbazide (XV, R = CH_3). A solution of 5-nitro-2-furoylhydrazine (17.11 g., 0.10 mole) and methylisothiocyanate (8.04 g., 0.11 mole) in 250 ml. of ethanol was heated under reflux for 2 hr. Cooling gave 24.0 g. (96%) of material, m.p. 163–164° (when heated slowly from 110°). Crystallization from ethanol gave white needles, m.p. 166.5–167° (slow heating). This appeared to be XV (R = CH_3) solvated with one molecule of ethanol. Heating *in vacuo* at 100° gave the unsolvated product although in a somewhat discolored state. When this was heated slowly from 145°, it decomposed at 190°C.

Anal. Calcd. for $C_7H_8N_4O_4S \cdot C_2H_5OH$: C, 37.24; H, 4.86. Found: C, 37.22; H, 5.03.

Anal. Calcd. for $C_7H_8N_4O_4S$: C, 34.43; H, 3.30; N, 22.95. Found: C, 34.47; H, 3.27; N, 22.72.

4-Ethyl-1-(5-nitro-2-furoyl) thiosemicarbazide (XV, R = C_2H_5). This was prepared in the same way as XV (R = CH_3) above using ethyl isothiocyanate (9.59 g., 0.11 mole). In this way 23.45 g. (88%) of XV (R = C_2H_5) was obtained, m.p. 189–190°. Crystallization from ethanol gave pale yellow needles, m.p. 193°.

Anal. Calcd. for $C_8H_{10}N_4O_4S$: C, 37.21; H, 3.90; S, 12.41. Found: C, 37.49; H, 4.10; S, 12.35.

4-Phenyl-1-(5-nitro-2-furoyl)thiosemicarbazide (XV, R = C_6H_5). This was prepared as above for XV (R = CH_3) using phenyl isothiocyanate (14.90 g., 0.11 mole) and 350 ml. of ethanol. The mixture was heated for 30 min. under reflux. Cooling gave 26 g. (81%) of XV (R = C_6H_5), m.p. 174° dec. Crystallization from acetone-water gave yellow crystals, m.p. 175° dec.

Anal. Calcd. for $C_{12}H_{10}N_4O_4S$: C, 47.06; H, 3.29; N, 18.30. Found: C, 47.13; H, 3.48; N, 18.59.

2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XVI, R = H). Concentrated sulfuric acid was cooled to 0° and stirred while XV (R = H) (11.51 g., 0.05 mole) was added portionwise. The mixture was stirred for 1 hr. in the cold and then allowed to warm to room temperature over a 1-hr. period. The solution was filtered to remove a small amount of insoluble material and then poured onto cracked ice and allowed to stand overnight in the cold. The precipitated yellow product was then crystallized from dimethylformamide-water giving 7.30 g. of olive-yellow material, m.p. 278° dec. An additional 0.76 g. was obtained by neutralizing the sulfuric acid solution. The total yield was 76%. Recrys-

(19) B. T. Freure and J. R. Johnson, *J. Am. Chem. Soc.*, **53**, 1142 (1931).

(20) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **52**, 2550, 4165 (1930).

(21) The nitrofuroyl chloride was obtained in 69% yield from nitrofuroic acid by heating under reflux with thionyl chloride for 20 hr. Under these conditions, a 24% yield of 5-nitro-2-furoic anhydride is also obtained. This compound, which has not been previously reported, is insoluble in cold thionyl chloride and thus is easily separated from the soluble acid chloride. It melts at 212–213° and crystallizes in light yellow needles from nitromethane. The infrared spectrum contains two strong absorptions at 5.59 and 5.76 μ (Nujol) which correspond well with known anhydride carbonyl absorptions. *Anal.* Calcd. for $C_{10}H_4N_2O_9$: C, 40.55; H, 1.36; N, 9.46. Found: C, 40.48; H, 1.53; N, 9.65.

If the acid and thionyl chloride were refluxed for 36 hr. only the acid chloride was obtained in 81% yield.

tallization as above for analysis gave yellow needles, m.p. 280° dec.

Anal. Calcd. for $C_6H_4N_4O_3S$: C, 33.97; H, 1.90; N, 26.42; O, 22.62. Found: C, 34.05; H, 2.20; N, 26.52; O, 22.35.

2-Methylamino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XVI, R = CH_3). Compound XV (R = CH_3) ethanolate (3.37 g., 0.012 mole) was added in one portion to 50 ml. of stirred coned. H_2SO_4 at 0°. After solution occurred, the mixture was allowed to warm to room temperature and then poured onto ice. The solution was adjusted to *p*H 5 and the precipitated product collected. This provided 1.37 g. (52% of theory) of XVI (R = CH_3), m.p. 213–214° (dec.). Crystallization from dimethylformamide-water gave yellow cubes, m.p. 214.5–215.5° dec.

Anal. Calcd. for $C_7H_6N_4O_3S$: C, 37.14; H, 2.67; N, 24.78. Found: C, 37.38; H, 2.97; N, 24.66.

2-Ethylamino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XVI, R = C_2H_5). This was prepared by the method described above for XVI (R = CH_3) only using XV (R = C_2H_5) (15.48 g., 0.06 mole). The crude orange solid obtained in this way weighed 13.74 g., m.p. 195–196° dec. Crystallization from dimethylformamide-water gave yellow felted needles, m.p. 216–216.5° dec., weighing 10.00 g. (70%).

Anal. Calcd. for $C_8H_8N_4O_3S$: C, 40.00; H, 3.36; N, 23.33. Found: C, 39.76; H, 3.40; N, 23.39.

2-Anilino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XVI, R = C_6H_5). This was prepared in the same way as XVI (R = CH_3) using XV (R = C_6H_5) (18.38 g., 0.06 mole). The product was crystallized from dimethylformamide-water to give 12.63 g. (73%) of flat yellow needles, m.p. 264° (preheated). Recrystallization raised the melting point to 267–267.5° (preheated).

Anal. Calcd. for $C_7H_6N_4O_3S$: C, 50.00; H, 2.80; S, 11.12. Found: C, 49.98; H, 3.10; S, 11.12.

2-Acetylamino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (XIV). A solution of XVI (R = H) (7.0 g., 0.033 mole) and 8 ml. of acetic anhydride in 200 ml. of pyridine was maintained at 80–90° for 2 hr. Cooling caused the product to separate. After crystallization from pyridine, it melted at 308° dec. and weighed 8 g. (95%).

Anal. Calcd. for $C_8H_6N_4O_4S$: C, 37.79; H, 2.39; N, 22.04. Found: C, 37.72; H, 2.48; N, 22.08.

4-Amino-6-isopropylamino-2-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = $CH[CH_3]_2$). Sodium metal (1.15 g., 0.05 g.-atom) was allowed to react with 50 ml. of dry ethylene glycol monomethyl ether. 1-Isopropyl biguanide hydrochloride[22] (8.98 g., 0.05 mole) was then added, the resulting sodium chloride filtered, and methyl 5-nitro-2-furoate (8.55 g., 0.05 mole) introduced. After standing for 3 days at room temperature, the product was collected by filtration and washed with ethanol, providing 2.73 g., m.p. 192.5–194°. After standing 2 weeks longer, the reaction mother liquor was taken to dryness and the residue was extracted with hot ethanol. This gave an additional 0.95 g., m.p. 198–200° (total yield 28%). Crystallization from ethanol gave fine yellow needles, m.p. 197–197.5°.

Anal. Calcd. for $C_{10}H_{12}O_3N_6$: C, 45.45; H, 4.58; N, 31.81; O, 18.16. Found: C, 45.47; H, 4.61; N, 31.96; O, 18.20.

4-Amino-6-anilino-2-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = C_6H_5). 1-Phenyl biguanide[22] (17.79 g., 0.1 mole) and methyl 5-nitro-2-furoate (17.10 g., 0.1 mole) were dissolved in 100 ml. of ethylene glycol monomethyl ether and heated on a steam bath for 3.5 hr. After standing for 3 days at room temperature, the precipitate which had separated was collected and crystallized from dimethylformamide-water. The resulting olive-green product melted at 259.5–260° and weighed 3.18 g. An additional 1.42 g., m.p. 243°, was obtained from the reaction mother liquor (total yield 15.4%). For analysis, the product was crystallized from 1-butanol without change in melting point.

(22) Supplied by the American Cyanamid Co.

Anal. Calcd. for $C_{13}H_{10}N_6O_3$: C, 52.35; H, 3.38; N, 28.18; O, 16.09. Found: C, 52.53; H, 3.50; N, 28.04; O, 16.01.

4-Amino-6-(o-toluidino)-1,3,5-triazine (XVIII, R = *o*-tolyl). A solution of 1-(*o*-tolyl)biguanide[22] (9.55 g., 0.05 mole) and methyl 5-nitro-2-furoate (8.55 g., 0.05 mole) in 30 ml. of ethylene glycol monomethyl ether was allowed to stand at room temperature for 5 days. The yellow product which separated weighed 1.50 g. (9.6%) and melted at 257° dec. Crystallization from 1-butanol did not change the melting point.

Anal. Calcd. for $C_{14}H_{12}O_3N_6$: C, 53.84; H, 3.87; N, 26.91; O, 15.37. Found: C, 53.78; H, 3.74; N, 26.71; O, 15.33.

4-Amino-2-(p-chloroanilino)-6-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = *p*-chlorophenyl). A solution of 1-*p*-chlorophenylbiguanide[23] and methyl 5-nitro-2-furoate (15.6 g., 0.0915) in 100 ml. of ethylene glycol monomethyl ether was heated on a steam bath for 2.5 hr. and then allowed to stand at room temperature for 5 days. The orange product was then collected by filtration. This weighed 2.60 g. (8.5%) and melted at 249–249.5°. Crystallization from dimethylformamide-water did not alter the melting point.

Anal. Calcd. for $C_{13}H_9ClN_6O_3$: C, 46.95; H, 2.72; Cl, 10.66. Found: C, 47.13; H, 2.72; Cl, 10.64.

1-(5-Nitro-2-furoyl)-5-(p-nitrophenyl)biguanide (XIX). A solution of methyl 5-nitro-2-furoate (8.55 g., 0.05 mole) and *p*-nitrophenylbiguanide[23] (11.10 g., 0.05 mole) in 200 ml. of ethylene glycol monomethyl ether was allowed to stand at room temperature for 14 days. The yellow solid which deposited during this time weighed 10.69 g. (56%) and melted at 252° dec. Similar results were obtained at room temperature using diethylene glycol dimethyl ether, pyridine, or with refluxing ethanol. Crystallization from acetic acid–ethanol gave material melting with decomposition at 259°. Analysis indicated this material to be a monohydrate; however, attempts to remove the water by drying only resulted in decomposition.

Anal. Calcd. for $C_{13}H_{11}O_6N_7 \cdot H_2O$: C, 41.17; H, 3.45; O, 29.53. Found: C, 41.35; H, 3.35; O, 29.55.

4-Amino-2-(p-nitrophenyl)-6-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = *p*-nitrophenyl). *Procedure A.* Compound XIX (6.75 g., 0.0178 mole) was introduced into a few milliliters of boiling dimethylformamide, and the resulting solution immediately cooled in ice. The triazine separated as an olive-green powder, m.p. 338° dec., weighing 0.72 g. Dilution of the mother liquor with water gave 4.35 g. of starting XIX melting at 245° dec. The yield of triazine based on returned starting material was 33% of theory.

Procedure B. A mixture of methyl 5-nitro-2-furoate (8.6 g., 0.05 mole) and 1-*p*-nitrophenylbiguanide (11.1 g., 0.05 mole) in 50 ml. of dimethylformamide was heated for 8.5 hr. on a steam bath. Cooling gave 2.10 g. (12%) of triazine, m.p. 340° dec. If the components were allowed to stand at room temperature for 8 days about 5% of the theoretical amount of the triazine was formed.

For analysis, this triazine was crystallized from dimethylformamide and dried at 150° *in vacuo*, giving material, m.p. 342° dec.

Anal. Calcd. for $C_{13}H_9N_7O_5$: C, 45.25; H, 2.65; N, 28.56. Found: C, 45.25; H, 2.86; N, 28.72.

2,4-Diacetylamino-6-(5-nitro-2-furyl)-1,3,5-triazine (XX). 2,4-Diamino-6-(5-nitro-2-furyl)-1,3,5-triazine[16] (2.22 g., 0.01 mole) was heated under reflux with 50 ml. of acetic anhydride for 1.5 hr. On cooling, 2.22 g. (72.5%) of the diacetyl compound separated, m.p. 269–270° dec. Crystallization from dimethylformamide gave tan colored crystals, m.p. 274.5–275° dec.

Anal. Calcd. for $C_{11}H_{10}O_5N_6$: C, 43.14; H, 3.29. Found: C, 43.06; H, 3.56.

2-Acetylamino-4-amino-6-(5-nitro-2-furyl)-1,3,5-triazine (XVIII, R = $COCH_3$). Hydrolysis of XX in boiling water was attempted; however, its solubility was so low that no

(23) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

reaction occurred. When XX (2.22 g., 0.00725 mole) was dissolved in a hot mixture of 1:1 dimethylformamide–water and heated under reflux for 16 hr., the monoacetyl compound was obtained on cooling in 1.20 g. yield (63%) of melting at 305° dec. Crystallization from dimethylformamide gave material melting at 317° dec. which was dried at 150° for analysis.

Anal. Calcd. for $C_9H_8N_6O_4$: C, 40.91; H, 3.05; N, 31.81. Found: C, 40.96; H, 3.13; N, 31.73.

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NORTH CHICAGO, ILL.

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

Synthesis of Polymers Containing Recurring Thiazole Rings

J. E. MULVANEY AND C. S. MARVEL

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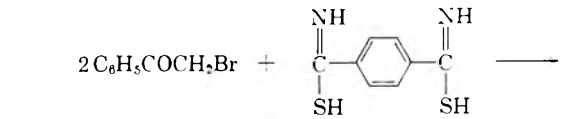
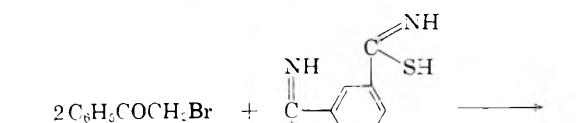
Polymers with molecular weights in the 5000 to 6000 range, one of which is a film-forming material and all of which show fair stability at 300°, have been obtained by condensing *p*-bis(bromoacetyl)benzene with dithioamides.

With the continuing[1] objective of preparing new and thermally stable high molecular weight materials containing aromatic units, a number of new polymers have been synthesized containing benzene rings and thiazole rings in a polymer chain backbone. The thiazole nucleus is more resistant to electrophilic substitutions such as sulfonation[2] than benzene itself.

A preliminary study showed that the model compounds 1,4-bis(4-phenyl-2-thiazolyl)benzene (I) and 1,3-bis(4-phenyl-2-thiazolyl)benzene (II) could be prepared as shown below in good yields by use of refluxing dimethylformamide as a solvent. The condensation of halomethylketones and thioamides has long been known[3] as a general method of preparing thiazoles. Our results encouraged us to believe that similar reactions with bis-α-bromoketones might afford the high yield[4] necessary to produce high molecular weight condensation polymers. Reactions of dithioamides and bis-α-haloketones have been carried out by Erlenmeyer[5] to yield presumably polymeric materials, other than the ones reported here, but the products were not fully characterized.



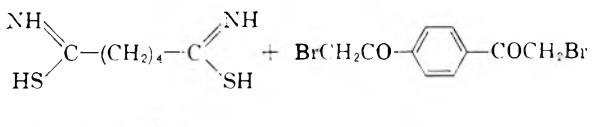
I



II

Three new thiazole polymers have been prepared and are described below. The dithioamides were made from the corresponding dinitriles by the addition of hydrogen sulfide, and the *p*-bis(bromoacetyl)benzene was prepared by treatment of *p*-diacetylbenzene with bromine in acetic acid.

A polymer (III) was synthesized by condensing dithioaldipamide and *p*-bis(bromoacetyl)benzene in acetic acid as indicated:



III

Polymer III exhibits what appears to be a polyelectrolyte effect in formic acid, displaying inherent viscosities of 3.50, 4.67, and 5.53 at concentrations of 0.239, 0.122, and 0.067 g./100 ml., respectively. However, assuming one bromine atom per chain

(1) C. S. Marvel and G. E. Hartzell, *J. Am. Chem. Soc.*, **81**, 448 (1959).

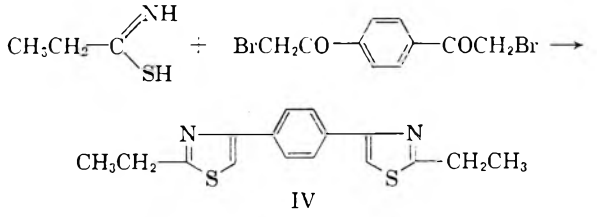
(2) R. H. Wiley, *Organic Chemistry*, ed. H. Gilman, John Wiley and Sons, Inc., New York, Vol. IV, p. 799, 1953.

(3) R. H. Wiley, D. C. England, and L. C. Behr, *Org. Reactions*, **VI**, 367 (1951).

(4) P. J. Flory, *Principles of Polymer Chemistry*, Cornell University Press, Ithaca, New York, 1953, Chapter 3.

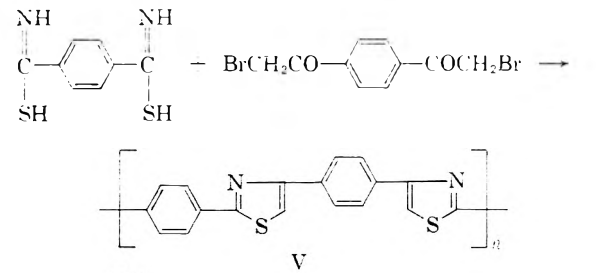
(5) (a) H. Lehr and H. Erlenmeyer, *Helv. Chim. Acta*, **27**, 489 (1944). (b) G. Bischoff, O. Weber, and H. Erlenmeyer, *Helv. Chim. Acta*, **27**, 947 (1944). (c) H. Erlenmeyer, W. Büchler, and H. Lehr, *Helv. Chim. Acta*, **27**, 969 (1944). (d) H. Erlenmeyer and M. Erne, *Helv. Chim. Acta*, **29**, 275 (1946). (e) H. Erlenmeyer and K. Degen, *Helv. Chim. Acta*, **29**, 1080 (1946). (f) H. Erlenmeyer and W. Büchler, *Helv. Chim. Acta*, **29**, 1924 (1946).

from bromoacetyl end groups, the bromine value (1.25%) indicates a number average molecular weight of about 6400 for this polymer or approximately thirty recurring units. It is insoluble in most organic solvents, but soluble in strong acids such as sulfuric, hydrochloric, or formic. A film is obtained by casting a formic acid solution. The polymer loses only 4.2% of its weight during twenty-four hours at 290–300°. In addition to the correct elemental analysis, further evidence for the structure is indicated by a comparison (Table I) of the ultraviolet spectra of Polymer III and model compound IV (prepared as shown below).

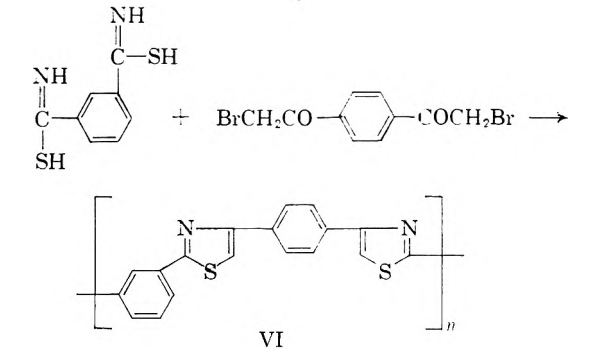


IV

The fully aromatic polymers V and VI were synthesized according to the equations:



V



VI

TABLE I

COMPARISON OF ULTRAVIOLET SPECTRA[a] OF POLYMERS III, V, AND VI WITH MODEL COMPOUNDS I, II, AND IV (IN mμ)

Compound	λ_{max1}	$(E^{1\%}_{1\ cm.})$	ϵ	$\lambda_{max2}(E^{1\%}_{1\ cm.})\ \epsilon$
Polymer III	282	(1010)		—
Model compound IV	279	(840)	25,200	—
Polymer V	282	(647)		375 (878)
Model compound I	261	(537)	23,600	377 (606) 26,700
Polymer VI	277	(790)		332 (768)
Model compound II	254	(858)	36,700	332 (512) 22,500

[a] In concentrated sulfuric acid.

The best solvent found so far for polymerization is refluxing dimethylformamide. However, even in this solvent the polymer begins to precipitate shortly after reaction commences. Both polymers V and VI are insoluble in the common organic solvents. They are soluble in sulfuric acid and slightly soluble in trifluoroacetic acid. Both polymers have been obtained as yellow powders. Polymer V has an inherent viscosity of 0.12 in sulfuric acid and polymer VI has an inherent viscosity of 0.095 in the same solvent. On the basis of the bromine content of polymer V (~1.5%) and again assuming one bromomethylketo end group per polymer chain, one arrives at a molecular weight of approximately 5300 for polymer V (about sixteen recurring units), and 5800 for polymer VI (1.38% Br). Neither V nor VI melts at 350°; both only darken slightly at this temperature. The ultraviolet spectra of polymers V and VI are compared with spectra of model compounds I and II in Table I.

EXPERIMENTAL[6]

Preparation of dithio-1,4-benzenedicarboxamide. The method used was the general procedure of Fairfull, Lowe, and Peak.[7] From a solution of 10 g. (0.077 mole) of terephthalonitrile (recrystallized from benzene, m.p. 226–227°) and 7.8 g. (0.077 mole) of redistilled triethylamine in 300 ml. of pyridine through which dried hydrogen sulfide was passed for 2.7 hr., there was obtained 15 g. (99%) of dithio-1,4-benzenedicarboxamide, m.p. 269–273° dec. One recrystallization from nitrobenzene raised the m.p. to 272–274° dec. (lit.,[8] m.p. 263°).

Anal. Calcd. for $C_8H_8N_2S_2$: C, 48.94; H, 4.11; N, 14.27. Found: C, 49.20; H, 3.69; N, 14.15.

Preparation of dithio-1,3-benzenedicarboxamide. The same procedure was used as that given for dithio-1,4-benzenedicarboxamide (above). From 4.0 g. (0.031 mole) of isophthalonitrile, there was obtained 4.3 g. (71%) of dithio-1,3-benzenedicarboxamide, m.p. 200–201° dec. (lit.,[9] m.p. 199–200 dec.), λ_{max} 230 mμ, ε 21,700; 298 mμ, ε 13,300 in ethanol.

Preparation of dithioadipamide. The general procedure[7] was again used here. From 21.6 g. (0.20 mole) of adiponitrile there was obtained 7.2 g. (20%) of dithioadipamide, m.p. 180–182° (lit.,[10] m.p. 180°), λ_{max} 265 mμ, ε 30,400, in ethanol.

Preparation of thiopropioamide. The procedure of Kindler[11] was used except that the reaction was carried out at atmospheric pressure. A 20% yield of thiopropioamide was obtained, m.p. 41–42° (lit.,[11] m.p. 42–43°).

Preparation of p-bis(bromoacetyl)benzene. The procedure was that of Ruggli and Gassenmeier.[12] From 5.0 g. (0.031 mole) of *p*-diacetylbenzene there was obtained 7.9 g. (80%)

(6) Melting points are uncorrected. Microanalyses were performed by Mr. J. Nemeth of the University of Illinois and by the Clark Laboratories and the Micro-Tech Laboratories.

(7) A. E. S. Fairfull J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, 742 (1952).

(8) G. Luckenbach, *Ber.*, **17**, 1430 (1884).

(9) G. Luckenbach, *Ber.*, **17**, 1429 (1884).

(10) H. Erlenmeyer and G. Bischoff, *Helv. Chim. Acta*, **27**, 412 (1944).

(11) K. Kindler, *Ann.*, **431**, 201 (1923).

(12) P. Ruggli and E. Gassenmeier, *Helv. Chim. Acta*, **22**, 496 (1939).

of *p*-bis(bromoacetyl)benzene, m.p. 160–165°. Recrystallization from ethanol (Darco) increased the m.p. to 176–178° (lit.,[13] m.p. 177–178°), λ_{max} 265 mμ, ε 17,800.

Preparation of 1,4-bis(2-ethyl-4-thiazolyl)benzene (IV). A solution of 1.0 g. (0.011 mole) of thiopropioamide and 1.77 g. (0.0056 mole) of *p*-bis(bromoacetyl)benzene in 40 ml. of dimethylformamide was refluxed overnight. After removal of most of the solvent under reduced pressure, there was obtained 1.1 g. of crude product, m.p. 94–97°. Two recrystallizations from dimethylformamide (Darco) gave 1.0 g. (44%) of IV, m.p. 114–116°. See Table I for ultraviolet spectra.

Anal. Calcd. for $C_{16}H_{16}N_2S_2$: C, 64.0; H, 5.33; N, 9.33. Found: C, 63.75; H, 5.29; N, 9.13.

Preparation of 1,4-bis(4-phenyl-2-thiazolyl)benzene (I). A solution of 3.270 g. (0.0166 mole) of dithio-1,4-benzenedicarboxamide and 6.637 g. (0.0333 mole) of phenacyl bromide in 150 ml. of purified dimethylformamide was heated under reflux for 18 hr. After cooling the product crystallized in the form of plates. More solid was obtained by diluting the mother liquor with 500 ml. of water. The combined solids were washed with methanol and dried in a vacuum oven at 60° to give 4.77 g. (96.9%) of I, m.p. 225–226°. One recrystallization raised the m.p. to 229–230° (lit.,[7] m.p. 225°). See Table I for ultraviolet spectra.

Anal. Calcd. for $C_{24}H_{16}N_2S_2$: C, 72.69; H, 4.04; N, 7.08. Found: C, 72.48; H, 3.86; N, 6.89.

Preparation of 1,3-bis(4-phenyl-2-thiazolyl)benzene. A solution of 1.635 g. (0.0083 mole) of dithio-1,3-benzenedicarboxamide and 3.318 g. (0.0166 mole) of *p*-bis(bromoacetyl)-benzene in 75 ml. of purified dimethylformamide was heated under reflux for 18 hr. Working up the product in the same manner as described above for compound I, there was obtained a 3.21 g. (97.5%) yield of II, m.p. 167–169°, which, after recrystallization from carbon tetrachloride, had m.p. 170°. See Table I for ultraviolet spectra.

Anal. Calcd. for $C_{24}H_{16}N_2S_2$: C, 72.69; H, 4.04; N, 7.08. Found: C, 72.55; H, 4.17; N, 6.84.

Preparation of thiazole polymer III. To a hot solution of 3.700 g. (0.0210 mole) of dithioadipamide in 425 ml. of acetic acid, there was added 6.720 g. (0.0210 mole) of *p*-bis(bromoacetyl)benzene in 250 ml. of hot acetic acid. A yellow precipitate began to form immediately. After heating with stirring at 80° for 24 hr., the solid was collected on a filter and reprecipitated twice from formic acid into a large excess of ethanol. The solid powder was ground and dried at 60° (1 mm.). Ultraviolet spectra and other properties of this polymer are mentioned in the discussion section of this paper.

Anal. Calcd. for $(C_{16}H_{14}N_2S_2)_n$: C, 64.41; H, 4.72; N, 9.38; S, 21.45. Found: C, 63.65; H, 4.75; N, 9.04; S, 20.59; Br, 1.25, 1.26.

Preparation of thiazole polymer V. A solution of 3.200 g. (0.01000 mole) of *p*-bis(bromoacetyl)benzene and 1.963 g. (0.01000 mole) of dithio-1,4-benzenedicarboxamide in 300 ml. of purified dimethylformamide was refluxed for 105 hr. with stirring. The reactants were initially soluble, but a fine yellow powder began to form within a few minutes after mixing. At the end of the reaction period, the solid was collected on a filter, washed with methanol, and dried overnight in a vacuum oven yielding 2.810 g. of fine yellow powder. The inherent viscosity was 0.12 in sulfuric acid at 25° (0.24 g./100 ml.). Ultraviolet spectra and other properties of this polymer are mentioned in the discussion section of this paper.

Anal. Calcd. for $(C_{18}H_{10}N_2S_2)_n$: C, 67.90; H, 3.17; N, 8.80. Found: C, 66.46; H, 3.92; N, 8.69; Br, 1.38, 1.65.

Preparation of thiazole polymer VI. A solution of 3.200 g. (0.0100 mole) of *p*-bis(bromoacetyl)benzene and 1.963 g. (0.0100 mole) of dithio-1,3-benzenedicarboxamide in 300 ml. of dimethylformamide was heated under reflux with stirring for 216 hr. Although the reactants were initially miscible, a fine yellow powder began to form shortly after they were mixed. At the end of the reaction period, 2.58 g. of a fine yellow powder was obtained by filtration. Addition of the mother liquor to 1 l. of methanol caused the precipitation of an additional 0.278 g. of yellow powder. This material showed the same ultraviolet maxima as the initial precipitate.

Anal. Calcd. for $(C_{18}H_{10}N_2S_2)_n$: C, 67.90; H, 3.17; N, 8.80. First precipitate: C, 64.90; H, 3.60; N, 8.44; Found: Br, 1.38. Second precipitate: C, 66.01; H, 3.68; N, 8.46; Br, 2.37.

The inherent viscosity in sulfuric acid was found to be 0.095 at 25° (0.24 g./100 ml.).

Acknowledgment. This work was carried out under the sponsorship of Contract AF-33(616)5486 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. This paper may be reproduced for any purpose of the United States Government.

It is a pleasure to acknowledge the help of Mrs. N. S. Fan, Mr. R. R. Haynes, and Mr. H. Schauble in the synthesis of intermediates.

URBANA, ILL.

(13) F. Kröhnke and I. Vogt, *Chem. Ber.*, 86, 1132 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Reactions of 2-Benzhydrylphenylacetic Acid; A New Pyrone Synthesis[1]

R. L. LETSINGER, J. D. JAMISON,[2] AND A. S. HUSSEY

Received April 20, 1960

In contrast to 8-benzhydryl-1-naphthoyl chloride, which isomerizes with 1,5-phenyl migration under Friedel-Crafts conditions, 2-benzhydrylphenylacetyl chloride cyclizes to a seven-membered cyclic ketone (IV) in the presence of aluminum or stannic chloride. When heated with a mixture of acetic acid and polyphosphoric acid both 2-benzhydrylphenylacetic acid and ketone IV afford a substituted 4-pyrone (VI) in good yield.

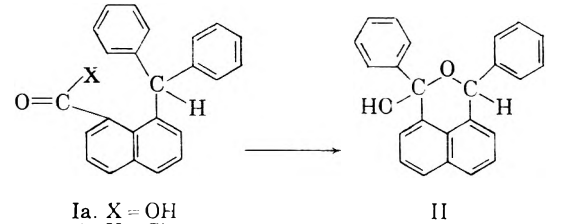
In a previous paper it was reported that 8-benzhydryl-1-naphthoyl chloride (Ib) rearranged in the presence of stannic chloride to a substance which on hydrolysis gave (>90%) 1-phenylhydroxy-

(1) Presented at the 137th Meeting of the American Chemical Society, Cleveland, April 1960.

(2) Standard Oil Co. of Indiana Fellow, 1958–59.

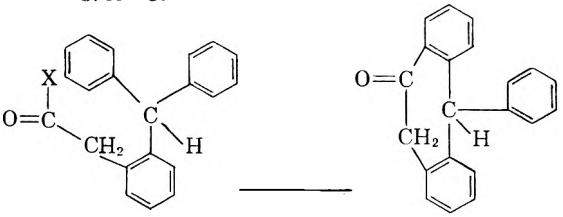
methyl-8-benzoylnaphthalene hemiketal (II).[3] A similar transformation ensued when 8-benzhydryl-1-naphthoic acid (Ia) was dissolved in concentrated sulfuric acid.

In order to extend our knowledge of systems capable of exhibiting such 1-5-aryl migrations we synthesized 2-benzhydrylphenyl-acetic acid (III) and subjected it and the corresponding acid chloride to the action of a variety of acidic reagents. Although the carboxyl and benzhydryl groups in compound III may assume a relative position very close to that obtaining in compound I, no evidence was found of products resulting from a 1,5-phenyl migration. Instead, the seven-membered cyclic ketone (IV) and substances derived from it were isolated. The reactions leading to these products were slow relative to the rearrangement of I. It therefore appears that the structural requirements for the 1,5-aryl migration are very stringent, that little deviation from the structure of I can be tolerated.



Ia. X = OH
b. X = Cl

II

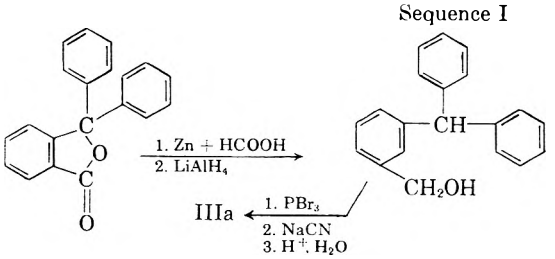


IIIa. X = OH
b. X = Cl

IV

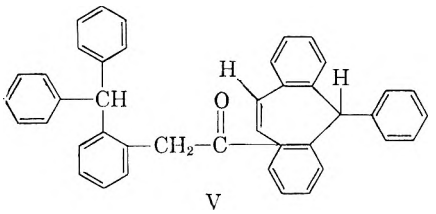
The synthesis of 2-benzhydrylphenylacetic acid is indicated by sequence 1. Yields were high throughout. Acid IIIa and its chloride (IIIb) reacted normally with alcohols (methanol and ethanol) to give the esters.

Sequence I



Ketone IV was best obtained (65% yield) by the action of aluminum chloride on 2-benzhydrylphenylacetyl chloride in carbon disulfide. It absorbed at 5.99 μ (C=O) in the infrared, gave a 2,4-dinitrophenylhydrazone derivative, and afforded an enolacetate (VIII) when treated with acetic anhydride and potassium acetate. In confirmation of the structure the NMR spectrum of IV (40 Mc./sec.) showed, in addition to the expected aromatic hydrogen bands at low field, a sharp band attributable to the tertiary hydrogen and a quartet of bands attributable to the two non-equivalent methylene hydrogens[4] ($\nu_0\delta$, 18.6 cycles/sec.; J, 17.6 cycles/sec.).[5]

With stannic chloride as a catalyst the reaction products were in general more complex. Under mild conditions (sixty hours at room temperature) ketone IV was formed (18%); however, most of the acid chloride remained unaffected and was recovered as 2-benzhydrylphenylacetic acid. A similar reaction under more strenuous conditions (fourteen hours in refluxing benzene) gave as the principal product (45%) a new, high melting, nonsublimable crystalline solid. This substance was identified as an enolacylate derivative (V) of compound IV by the analysis, the hydrolytic products (2-benzhydrylphenylacetic acid and ketone IV) and the marked similarity of the infrared and ultraviolet spectra with the spectra of the enolacetate of ketone IV. From a twenty-hour reaction of IIIb with stannic chloride in boiling carbon disulfide was obtained IIIa (45% recovery, subsequent to hydrolysis) and a neutral oil from which a small amount of V was isolated. By contrast, under similar conditions the rearrangement of Ia was essentially complete within an hour.



V

Attempts to cyclize acid IIIa directly to ketone by mineral acids were unsuccessful. Sulfuric acid either left IIIa unchanged or converted it to water-soluble products. Hydrogen fluoride proved ineffective and hot polyphosphoric acid slowly transformed it to a complex mixture of ketones from which no pure compounds could be isolated.

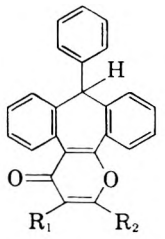
In the course of these studies a sample of 2-benzhydrylphenylacetic acid was heated with a mixture of acetic acid and polyphosphoric acid. From this mixture was obtained a good yield of a new crystalline substance, VI, the analysis of which agreed with the formula $C_{25}H_{18}O_2$. Compound VI failed to react with 2,4-dinitrophenylhydrazine in alcohol solution but did condense with hydrazine

(3) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, 78, 2649 (1956); 81, 940 (1959).

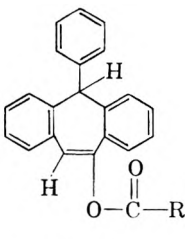
(4) See J. A. Pople, W. G. Schneider, and H. J. Berstein, *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill Co., New York (1960), p. 119.

(5) We are grateful to Mr. C. Creswell for the spectral determination and interpretation. Carbon tetrachloride was used as a solvent for these measurements.

under forcing conditions. The information described below reveals VI to be a pyrone derived from ketone IV.



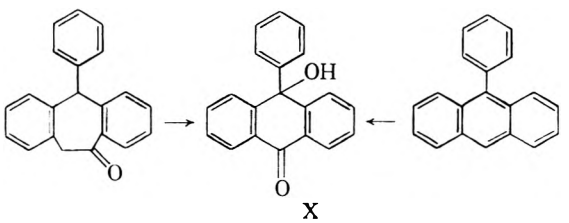
VI. $R_1 = H$; $R_2 = CH_3$
VII. $R_1 = CH_3$; $R_2 = C_2H_5$



VIII. $R = CH_3$
IX. $R = CH_2Cl$

Hydrolysis of compound VI by potassium hydroxide in refluxing ethylene glycol solution afforded a 95% yield of ketone IV, indicating that the acetic acid residues were joined at the methylene and carbonyl carbon atoms rather than to the aromatic rings. On the assumption that VI might be a pyrone, the hydrolysis was repeated under conditions that any acetone liberated would be trapped as the 2,4-dinitrophenylhydrazone. In agreement with the pyrone structure, acetone 2,4-dinitrophenylhydrazone was obtained in 60% yield (based on one mole of acetone liberated per mole of VI).

Oxidation of compound VI by alkaline permanganate yielded (84%) 10-hydroxy-10-phenylanthrone, identical with a sample of this substance prepared for comparison purposes by oxidation of 9-phenylanthracene. Since ketone IV also underwent ring contraction under similar oxidation conditions to give 10-hydroxy-10-phenylanthrone, this observation is compatible with the structure proposed for VI. Formation of the anthrone may be rationalized on the assumption that IV and VI are oxidized to a seven-membered ring vicinal diketone which subsequently undergoes a benzilic acid type rearrangement and oxidative decarboxylation. An analogous ring contraction occurs in the oxidation of phenanthrenequinone to dibenzofluorenone.[6]



X

Conclusive evidence that VI was a 4-pyrone rather than a 2-pyrone was provided by the infrared spectrum. Compound VI exhibited a triplet of bands between 6.0 and 6.3 μ which is characteristic for the 4-pyrone structure.[7,8] The 2-pyrones absorb near 5.8 μ.[8]

Propionic acid reacted with 2-benzyhydrylphenylacetic acid in polyphosphoric acid in a manner similar to acetic acid. A high melting compound was obtained which had the characteristic 4-pyrone triplet in the infrared spectrum, had an ultraviolet spectrum almost identical with that of VI, and gave an analysis consistent with the formula $C_{27}H_{22}O_2$. In view of the mode of formation this substance may be regarded as the substituted pyrone, VII. Under similar conditions chloroacetic acid reacted with 2-benzhydrylphenylacetic acid to give the enolchloroacetate (IX) as the only isolable pure compound. It was also found that pyrone VI could be obtained in good yield by heating together ketone IV, acetic acid, and polyphosphoric acid. The scope of this new pyrone synthesis will be discussed in more detail in a subsequent publication.

EXPERIMENTAL

The infrared spectra were recorded with a Baird Model AB-2 spectrophotometer with the sample in potassium bromide. Ultraviolet spectra were taken with a DK-2 Beckman ratio recording instrument. Carbon, hydrogen, and nitrogen analyses were performed by Miss Hilda Beck.

2-Benzhydrylbenzoic acid. A mixture of 19.73 g. of 3,3-diphenylphthalide, 160 g. of formic acid, 40 g. of zinc, and 40 g. of water was refluxed for 5 hr. and then poured into water. The precipitate was separated and dissolved in alcohol. After filtration to remove unchanged zinc, excess ethanol was distilled and the residue recrystallized from ethanol-water to give 7.1 g. (92%) of 2-benzhydrylbenzoic acid; m.p. 158–162°. After two further recrystallizations the sample melted at 161–162°; lit.,[9] m.p. 161°.

Anal. Calcd. for $C_{20}H_{16}O$: C, 83.33; H, 5.55. Found: C, 83.50; H, 5.50.

2-Benzylhydrylbenzyl alcohol. 2-Benzhydrylbenzoic acid (30 g., 0.104 mole) in 300 ml. of ether was added slowly with stirring to 8 g. (0.2 mole) of lithium aluminum hydride in 300 ml. of ether, the addition rate being sufficient to keep the ether refluxing. Thereafter the mixture was warmed for 2 hr., cooled with an ice bath, and hydrolyzed by additions of 15 ml. of 95% ethanol (in 80 ml. of ether) and 4 ml. of water. The ether solution was separated from the insoluble cake and washed successively with 6*M* hydrochloric acid, 10% sodium bicarbonate solution, and water. On drying and evaporation of the ether it yielded 26 g. (94%) of 2-benzhydrylbenzyl alcohol. The analytical sample (recrystallized from ligroin) melted at 108–108.5°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.62; H, 6.56. Found: C, 87.83; H, 6.58.

2-Benzhydrylbenzyl bromide was prepared by dropwise addition of 10 g. (0.037 mole) of phosphorus tribromide into a cold, stirred ether solution containing 20 g. (0.073 mole) of 2-benzhydrylbenzyl alcohol. The mixture was allowed to stand at ice temperature for 24 hr.; then it was filtered to remove the bromide which had separated. Additional product was obtained from the mother liquor by adding water, washing the ether layer with sodium bicarbonate solution, and evaporating the ether. The total yield of crystalline 2-benzhydrylbenzyl bromide was 23.7

(6) R. Anschutz and F. R. Japp, *Ber.*, **11**, 211 (1878).

(7) We are grateful to Professor C. D. Hurd for pointing out this property of 4-pyrones and for helpful discussions concerning the chemistry of these substances. A number of spectra of 4-pyrones are reproduced in the Ph.D. dissertation of S. Trofimenko, Northwestern University, 1958.

(8) R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, **78**, 2398 (1956).

(9) L. W. Jones and F. B. Root, *J. Am. Chem. Soc.*, **48**, 189 (1926).

g. (96.5%); m.p. of the analytical sample (recrystallized from ether), 123–124°.

Anal. Calcd. for $C_{20}H_{17}Br$: C, 71.23; H, 5.05. Found: C, 71.22; H, 4.90.

2-Benzhydrylphenylacetonitrile was prepared by heating 17 g. (0.050 mole) of the bromide with a solution of 4 g. of sodium cyanide, 25 ml. of water, and 100 ml. of ethanol at reflux temperature for 24 hr. On addition of water and cooling the nitrile (11.94 g., 83.5%) separated; m.p. 96–97° after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.04; H, 6.00; N, 4.95. Found: C, 88.55; H, 6.06; N, 4.89.

2-Benzhydrylphenylacetic acid (IIIa) formed quantitatively when 11 g. of the nitrile was heated for 4 hr. with a refluxing solution of 20 ml. of acetic acid, 20 ml. of water, and 20 ml. of sulfuric acid. It was collected by filtration and washed with water; m.p. 209–212°. After recrystallization from ethyl acetate a sample melted at 212–213°; infrared band, 5.9 μ.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.44; H, 5.96. Found: C, 83.25; H, 6.07.

Methyl 2-benzhydrylphenylacetate formed when a solution of 2-benzhydrylphenylacetic acid (2.0 g.) in 50 ml. of methanol and 2 ml. of sulfuric acid was refluxed for 7 hr. Concentration followed by addition of 100 ml. of water precipitated the ester. It was taken up in ether and the solution was washed with aqueous alkali, dried, and evaporated. The ester, 1.86 g. (89%), melted at 76–78°; after recrystallization from ethanol the analytical sample melted at 77–78°, infrared bands (carbon disulfide solvent) 3.30, 3.37, 5.78, 6.22, 7.5 μ.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.56; H, 6.33. Found: C, 83.93; H, 6.09.

Reactions of 2-benzhydrylphenylacetyl chloride (IIIb). In each case, unless otherwise noted, the acid chloride was prepared by heating the carboxylic acid with excess thionyl chloride, distilling the residual thionyl chloride, adding dry benzene, and then removing the benzene by vacuum distillation. The acid chloride was left as a white solid; infrared band at 5.6 μ: no absorption in hydroxyl region.

(*a*) *Ethanol.* The acid chloride, prepared from 1.45 g. of 2-benzhydrylphenylacetic acid, was warmed with 35 ml. of ethanol. The solution was then concentrated by distillation, water was added, and the oil taken up with ether. Evaporation yielded *ethyl 2-benzhydrylphenylacetate*, which crystallized from pentane as a white solid; 1.20 g. (76%); m.p. 57.5–58.5°; infrared bands (potassium bromide), 3.38, 3.45, 5.8, 6.25, and 6.70 μ.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.57; H, 6.71. Found: C, 83.77; H, 6.30.

(*b*) *Aluminum chloride in carbon disulfide.* A mixture of the acid chloride (from 3.9 g. of acid) and 5 g. of aluminum chloride in carbon disulfide was heated at reflux for 17 hr. Carbon disulfide was then removed by distillation and the residue taken up in ether, hydrolyzed, and washed with a sodium hydroxide solution (no carboxylic acid resulted on acidification). On concentration of the ether solution 2.37 g. (69%) of the cyclic ketone, *compound IV*, crystallized; m.p. 140–152°. After sublimation it melted at 151–152°.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.73; H, 5.64. Found: C, 88.94; H, 5.60.

The *2,4-dinitrophenylhydrazone* derivative melted with decomposition at 240° when heated rapidly.

Anal. Calcd. for $C_{27}H_{20}N_4O_4$: C, 69.90; H, 4.31. Found: C, 70.05; H, 4.53.

(*c*) *Stannic chloride in benzene (compound V).* The acid chloride from 3.00 g. of acid was heated with 5 ml. of stannic chloride in 40 ml. of benzene at reflux for 24 hr. The resulting mixture was hydrolyzed with 50 ml. of ice water and the products were separated by conventional extraction procedures. From an alkaline extraction was obtained 0.385 g. of 2-benzhydrylphenylacetic acid (m.p. 201–208°) and from the portion containing neutral products was isolated by crystallization from ether 1.10 g. (45% calcd. as $C_{42}H_{32}O_2$) of a white solid, m.p. 188–195°. The residual oil appeared to be a mixture of IV and VI from the infrared spectrum. Several recrystallizations of the solid from ethanol–ethyl acetate yielded the analytical sample, m.p. 201–203°. This substance, *compound V*, did not sublime when heated at reduced pressure, did not react with 2,4-dinitrophenylhydrazine, and was insoluble in cond. sulfuric acid at room temperature. It absorbed strongly at 5.7 μ in the infrared, as did the enolacetate of *III*. The ultraviolet spectra of V and the enolacetate of III were almost identical ($\lambda_{max}^{cyclohexane}$ 289 mμ in both cases).

Anal. Calcd. for $C_{42}H_{32}O_2$: C, 88.73; H, 5.67. Found: C, 88.68; H, 5.55.

Hydrolysis of the compound melting at 201–203° (0.334 g.) by boiling ethanolic potassium hydroxide (15 hr.) afforded 0.182 g. of 2-benzhydrylphenylacetic acid, m.p. 203–208°, and 0.135 g. of ketone IV (identified by the infrared spectrum), in agreement with the proposed structure.

(*d*) *Stannic chloride in benzene at room temperature.* In this case the acid chloride was prepared by heating 3.00 g. of 2-benzhydrylphenylacetic acid with 25 ml. of phosphorus trichloride for 2 hr. Excess phosphorus trichloride was removed by distillation and 5 ml. of stannic chloride in 25 ml. of benzene was added. After standing for 60 hr. at room temperature the mixture was hydrolyzed and worked up as in the previous case. Under these mild conditions relatively little reaction occurred and 2.38 g. of 2-benzhydrylphenylacetic acid (m.p. 198–205°) was recovered. None of compound V was obtained but 0.501 g. (86% calculated on the basis of the carboxylic acid not recovered) of ketone IV was isolated; m.p. 140–147°. After a recrystallization this material melted at 147–150° and the melting point was not depressed on admixture with compound IV prepared by the aluminum chloride reaction.

(*e*) *Stannic chloride in carbon disulfide.* The acid chloride (from 3.00 g. of the acid and thionyl chloride) was heated with excess stannic chloride in refluxing carbon disulfide for 20 hr. In contrast to the reaction of 8-benzhydryl-1-naphthoyl chloride,[3] which rapidly produced an insoluble complex of the rearranged product, no heterogeneous phase was formed. Hydrolysis and conventional work-up afforded 1.37 g. (45%) of recovered 2-benzhydrylphenylacetic acid, 0.32 g. of compound V, and an oil which could not be separated by chromatography or crystallization. The infrared spectrum of the oil indicated the presence of compounds IV and V and the absence of any hydroxy compounds.

Reactions of 2-benzhydrylphenylacetic acid with mineral acids. (*a*) *Hydrogen fluoride.* A suspension of IIIa (1.99 g.) in 20 g. of liquid hydrogen fluoride was stirred for an hour at 0° and an hour at room temperature. The mixture was poured onto ice and processed in a conventional manner to yield 1.71 g. of recovered acid (m.p. 208–212°) and no other isolable products.

(*b*) *Sulfuric acid.* Compound IIIa (1.0 g.) was allowed to stand an hour in 25 ml. of cond. sulfuric acid (during which time it dissolved) and then poured onto ice. No organic material separated; all products were soluble in water. Similarly, only water-soluble products were obtained when 0.375 g. of ethyl 2-benzhydrylphenylacetate was allowed to stand for an hour at room temperature in cond. sulfuric acid. Only unchanged ester was recovered when a solution of 0.5 g. of the ethyl ester in 24.5 g. of sulfuric acid and 0.5 g. of water was allowed to stand 20 min. at 0°.

(*c*) *Polyphosphoric acid.* Acid IIIa (0.5 g.) was heated for 2 hr. with 20 g. of polyphosphoric acid[10] at 120–130°. The dark green mixture was then poured into water. Ether extraction and alkaline extraction of the ether solution yielded 0.37 g. of recovered acid. The neutral oil obtained from the ether layer amounted to 0.13 g. and showed carbonyl absorption at 5.7 and 6.0 μ, but no hydroxyl absorption.

(10) The polyphosphoric acid was kindly donated by the Victor Chemical Co.

Chromatography on silica gel failed to separate any solid products.

Reaction of 2-benzhydrylphenylacetic acid with acetic acid in polyphosphoric acid. (Compound VI). 2-Benzhydrylphenylacetic acid (1.00 g.) was added to a mixture of 25 ml. of acetic acid and 20 g. of polyphosphoric acid[10] and heated rapidly to 130°. The mixture was allowed to reflux at this temperature for 10 min., then acetic acid was removed by distillation at the rate of 1 ml. every 5 min. until 15 ml. of acetic acid had been collected. During this time the pot temperature rose to 160° and the mixture acquired a brown-black appearance. After an additional 5-min. period of refluxing the mixture was cooled and poured into water.

The organic suspension was taken up in ether and the ether solution extracted three times with 10% potassium carbonate. On acidification 0.103 g. (m.p. 205–211°) of the carboxylic acid (IIIa) was recovered. From the ether layer was obtained 0.672 g. of compound VI (58%), m.p. 225–230°, and 0.235 g. of an oil. This pyrone melted at 235–236° after recrystallizations from benzene and ethanol; infrared bands to 7 μ; 3.30, 6.03, 6.17, 6.22. 6.70, and 6.90 μ. The bands near 6 μ are characteristic of 4-pyrones.[7] The ultraviolet spectrum (in cyclohexane) showed a general decrease in absorption as the wave length increased, with plateaus centered at 242 mμ (ϵ 1.4 $\times$ 10^4) and 283 mμ (ϵ 8.1 $\times$ 10^3).

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.70; H, 5.15. Found: C, 85.82; H, 4.96.

Reaction of 2-benzhydrylphenylacetic acid with propionic acid in polyphosphoric acid (VIII). A mixture containing 3.00 g. of 2-benzhydrylphenylacetic acid, 50 ml. of propionic acid, and 30 g. of polyphosphoric acid was refluxed at 145° for 10 min. Propionic acid (35 ml.) was then withdrawn over a 2-hr. period, during which the temperature rose to 170°. The mixture was cooled and poured into water. Work-up as in the previous experiment yielded 1.40 g. of base soluble material (crude recovered III, m.p. 206–211°) and 0.40 g. of neutral product, VII, m.p. 190–195°. The analytical sample of VII, recrystallized from an ethyl acetate–ethanol mixture, melted at 197–198°. The infrared spectrum was markedly similar throughout to that for compound VI, with bands (to 7 μ) at 3.28, 3.38, 3.42, 6.04, 6.18, 6.23, 6.70, and 6.90 μ (note, however, the extra bands at 3.38 and 3.42 μ due to the increased number of aliphatic C—H). Likewise the ultraviolet spectrum of VII was very close throughout to that of VI; the plateau centers for VII occurred at 243 mμ (ϵ 1.4 $\times$ 10^4) and 285 mμ (ϵ 7.4 $\times$ 10^3).

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.71; H, 5.82. Found: C, 86.03; H, 5.80.

Reaction of 2-benzhydrylphenylacetic acid with chloroacetic acid and polyphosphoric acid (IX). A mixture of 2.00 g. of 2-benzhydrylphenylacetic acid, 15 g. of chloroacetic acid, and 20 g. of polyphosphoric acid was refluxed at 190° for 20 min. and then cooled and poured into water. Conventional work-up yielded 0.64 g. (27%) of the enol-chloroacetate, m.p. 176–183°. The analytical sample melted at 189–190° (from benzene); infrared spectrum: 5.70 μ (C=O), 6.08 (C=C), 6.22 μ, 6.70 μ and 6.90 μ; ultraviolet spectrum; $\lambda_{max}^{cyclohexane}$ 288 (ϵ 1.23 $\times$ 10^4). Both the infrared and ultraviolet spectra were quite similar to the spectrum of the enol-acetate of compound IV.

Anal. Calcd. for $C_{23}H_{17}ClO_2$: C, 76.55; H, 4.72. Found: C, 76.50; H, 4.83.

Enolacetate VIII. A mixture of 0.81 g. of compound IV, 0.5 g. of potassium acetate, and 15 ml. of acetic anhydride was heated at reflux for 8 hr. It was then poured into water and the oil taken up in ether and washed with potassium hydroxide solution. From the ether layer was obtained 0.893 g. (96%) of product, m.p. 172–174°. After recrystallization from ethanol–ethyl acetate it melted at 175°; infrared bands: 5.72 (C=O), 6.10 (C=C), 6.23, 6.72, and 6.95 μ; ultraviolet spectrum; $\lambda_{max}^{cyclohexane}$ 289 mμ (ϵ 1.28 $\times$ 10^4).

Anal. Calcd. for $C_{28}H_{18}O_2$: C, 84.66; H, 5.52. Found: C, 84.27; H, 5.58.

Miscellaneous experiments in acetic acid–polyphosphoric acid. Experimental conditions and procedures were the same as in the reaction of *o*-benzhydrylphenylacetic acid with acetic acid and polyphosphoric acid. In each case 1 g. of the aromatic compound was employed.

From ketone IV was obtained 0.905 g. (76%) of VI, m.p. 225–230°. The infrared spectrum was identical with that for VI prepared directly from III.

From a similar reaction with 1 g. of triphenylmethane was obtained only slightly impure triphenylmethane, 0.99 g., m.p. 82–87°; m.p. after recrystallization from ethanol, 92–94°. This experiment shows that acylation does not occur at the aromatic rings or the tertiary hydrogen under the conditions for which 2-benzhydrylphenylacetic acid and also ketone IV were converted to VI.

Alkaline cleavage of compound VI. (a) A solution of 50 ml. of ethylene glycol, 10 g. of potassium hydroxide, and 0.65 g. of compound VI was refluxed 4 hr., cooled, and poured into water. The precipitate weighed 0.50 g. (95%) and melted at 143–149°. Recrystallization afforded a sample, m.p. 150–151.5°, identical (infrared spectrum) with compound IV.

(b) A solution of 2.00 g. of compound VI and 1.25 g. of potassium hydroxide in 25 ml. of ethanol was refluxed for 4 hr. Most of the solution was then distilled through a Vigreux column into an ethanolic solution of 2,4-dinitrophenylhydrazine (300% excess). Fresh ethanol (15 ml.) was added to the alkaline solution to replace that which had been removed and the mixture refluxed an additional 20 hr. and again partially distilled into a dinitrophenylhydrazine solution. The acetone dinitrophenylhydrazine from the two distillations weighed 0.85 g. (60% yield based on 1 mole of acetone per mole of VII and melted at 124–126°). The infrared spectrum was identical with that of an authentic sample.

In a control run, identical with the above except that compound VI was omitted, no precipitate formed in the dinitrophenylhydrazine solution.

Reaction of compound VI with hydrazine hydrate. A solution containing 0.60 g. of compound VI, 5.0 ml. of 85% hydrazine hydrate, and 35 ml. of ethylene glycol was refluxed for 5 hr., cooled, and poured into 100 ml. of water. An ether extract of this mixture was washed with dilute hydrochloric acid, dried, and evaporated to give 0.58 g. of a solid derivative; m.p. 245–257°; after recrystallization from ethanol the pale yellow product melted with decomposition (rapid heating) at 261–264°; infrared bands: 2.90, 3.30, 6.18, 6.22, 6.70, 6.91, 7.12 μ.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.45; H, 5.50; N, 7.70. Found: C, 81.96; H, 5.52; N, 8.09.

The analysis indicates that an oxygen in VI has been replaced by NNH_2. The derivative was not further characterized, however, an *N*-amino-4-pyridone structure appears plausible.

Oxidation of compound VI. Compound VI (1.00 g.) was heated with 3 g. of potassium permanganate and 5 g. of potassium hydroxide in 100 ml. of water at reflux for 5 hr. After cooling and acidification, sodium bisulfite was added to reduce excess permanganate and the organic products were extracted with ether. The ether-soluble portion gave on fractional crystallization two fractions; *A*, 0.50 g., m.p. 210–215°, and *B*, 0.3 g., m.p. 197–198°.

Substance *A* melted sharply at 215.5–216° after two recrystallizations from ethanol. The infrared spectrum showed hydroxyl (2.95 μ) and carbonyl (6.05 μ) groups. With sulfuric acid *A* gave a deep purple color, indicative of a hydroxyanthrone. Substance *A* was shown to be *10-hydroxy-10-phenylanthrone* by a mixture melting point with an authentic sample and by the identity of the infrared spectrum with the spectrum of the authentic sample.

Spectral data indicated that fraction *B* was a mixture of 10-hydroxy-10-phenylanthrone and the starting material (VI), and indeed, 0.062 g. of 10-hydroxy-10-phenylanthrone was isolated from a reaction of 0.10 g. of *B* with excess hydrazine hydrate in ethylene glycol. After the reaction

mixture had refluxed for 70 hr. it was cooled, diluted with water, and extracted with ether. Recrystallization of the residue left from evaporation of the ether afforded the anthrone. The yield of anthrone from *A* was 61%; with the added material from *B* the total yield amounted to 84%.

For comparison purposes 10-hydroxy-10-phenylanthrone was prepared by oxidation of 9-phenylanthracene by the procedure of Baeyer.[11] The purified product melted at 215–216° and gave a purple color with sulfuric acid as reported.[11] Baeyer reported a m.p. of 208°; Barnett and Cook,[12] a m.p. of 214°.

The 9-phenylanthracene was obtained by heating for 70 hr. 15 g. of 3,3-diphenylnaphthalide, 2.5 g. of red phosphorus, 50 g. of hydriodic acid, and sufficient acetic acid to give a homogeneous solution. Two recrystallizations of the organic product gave 5.0 g. (37%) of 9-phenylanthracene; m.p. 152–153°; lit. m.p. 152–153°.[11] The ultraviolet spectrum showed five peaks, as reported for 9-phenylanthracene: $\lambda_{max}^{ethanol}$ 2540 (log ϵ 5.16); 3295 (3.55); 3463 (3.90); 3638 (4.11); 3825 (4.07); reported[13]: λ_{max} 2555 (5.16); 3305 (3.56); 3465 (3.90); 3645 (4.10), and 3840 (4.08). Baeyer prepared 9-phenylanthracene by reduction of 3,3-diphenylphthalide with zinc dust in acid.[11]

Oxidation of ketone IV to anthrone X. Ketone IV (0.200 g.) was heated with a solution of 0.75 g. of potassium permanganate and 1.25 g. of potassium hydroxide in 25 ml. of water for 3.5 hr. at reflux. Dilution with water, acidification, treatment with sodium bisulfite, ether extraction, and recrystallization gave 0.10 g. (50%) of 10-hydroxy-10-phenylanthrone (identified by mixture m.p. and infrared spectrum); m.p. 213–216°.

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(11) A. Baeyer, *Ann.*, **202**, 58 (1880).

(12) E. B. Barnett and J. W. Cook, *J. Chem. Soc.*, **123**, 2638 (1923).

(13) E. Clar and D. G. Stewart, *J. Am. Chem. Soc.*, **74**, 6235 (1952).

[CONTRIBUTION FROM THE VERONA RESEARCH CENTER OF KOPPERS CO., INC.]

The Reduction of the Carbazole Nucleus. Some Derivatives of Hydrocarbazoles[1]

HANS DRESSLER AND MELVIN E. BAUM

Received May 16, 1960

Improved methods for the preparation of tetrahydrocarbazole and dodecahydrocarbazole in high yields by the catalytic hydrogenation of carbazole are described. 3-Amino-1,2,3,4-tetrahydrocarbazole and 3-amino-9-methyldodecahydrocarbazole were made by the hydrogenation of the appropriate aminocarbazoles. The reduction of carbazole with lithium in *n*-propylamine gave a 90% yield of 1,2,3,4-tetrahydrocarbazole. The latter was resistant to further reduction by this reagent, as was 1,2,3,4,10,11-*cis*-hexahydrocarbazole. 9-Methylcarbazole was reduced by lithium in *n*-propylamine to 9-methyl-1,2,3,4,-10,11-hexahydrocarbazole in 71% yield. A number of new derivatives of the hydrocarbazoles, such as the pyridylethylation products, are described.

In the past, the reduction of the carbazole nucleus by chemical agents or by catalytic hydrogenation has been difficult. Thus, compared with aromatic compounds and certain other nitrogen heterocyclics such as acridine, indole, and phenylpyrrole, carbazole is much more resistant to catalytic hydrogenation. The first report[2] of the catalytic hydrogenation of carbazole claimed the formation of 2,3-diethylindole as the main product. However, none of the subsequent investigators were able to substantiate this claim. von Braun and Ritter[3] were actually unable to hydrogenate purified carbazole in the presence of a nickel catalyst at 260° and 450 p.s.i.g., and obtained only fair yields of 9-methyl-1,2,3,4-tetrahydrocarbazole and 1,2,3,4,5,6,7,8-octahydro-9-methylcarbazole from 9-methylcarbazole. The perhydrogenation of carbazole in an organic solvent at 160–220° and 590–1200 p.s.i.g., using a nickel catalyst, was reported in a 1930 German patent[4] with little detail. The best data were obtained by Adkins and Coonradt[5] who hydrogenated carbazole in the presence of Raney nickel at 230° to obtain an 87% yield of dodecahydrocarbazole; when they used a copper chromite catalyst under these conditions, a 72% yield of 1,2,3,4-tetrahydrocarbazole was obtained. However, this procedure required rather high pressures (of 3600–4400 p.s.i.g.) and highly purified materials.

Prior work on the chemical reduction of carbazole was limited to the sodium-alcohol system. In 1907, the preparation of 1,4-dihydrocarbazole from carbazole by this reagent was reported.[6] Later it was shown that the product of this reaction is a mixture containing at least 50% of carbazole, tetrahydrocarbazole, plus unknowns.[7] Surprisingly, a 1950 publication again claimed the isolation of 1,4-dihydrocarbazole from this mixture.[8] 1,2,3,4-Tetrahydrocarbazole can indeed be prepared in fair

(1) Based upon a paper presented at the 137th National Meeting of the American Chemical Society, Cleveland, April 1960.

(2) M. Padoa and C. Chiaves, *Atti reale accad. Lincei*, 16, 762 (1908); *Gazz. chim. ital.*, 38, 236 (1903).

(3) J. v. Braun and H. Ritter, *Ber.*, 55, 3792 (1922).

(4) German pat. 514,822 (1930).

(5) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, 63, 1563 (1941).

(6) J. Schmidt and R. Schall, *Ber.*, 40, 3225 (1907).

(7) B. M. Barclay, N. Campbell, and R. S. Gow, *J. Chem. Soc.*, 997 (1946).

(8) G. Sanna, *Gazz. chim. ital.*, 80, 572 (1950).

TABLE I

CATALYTIC HYDROGENATION OF CARBAZOLE

Catalyst[a]	Medium	Total Pressure (p.s.i.g.)	Hydrogen Partial Pressure (p.s.i.g.)	Temp.	Main Product[b]
5% Ru-C	Decalin	250	250	250	53% THC
5% Ru-C	Decalin	500	500	200	81% DHC
5% Rh-C	Water (*p*H 5.5)	1000	380	200	93% DHC
U.O.P.-Ni[c]	Water	1000	380	200	88% DHC
Sponge-Ni	Water	1000	380	200	90% DHC
U.O.P.-Ni[d]	Water (*p*H 12)	1000	320	250	87% THC
U.O.P.-Ni	Water (*p*H 10)	1000	320	250	67% THC

[a] U.O.P.-Ni = Prereduced and stabilized nickel on kieselguhr (55% Ni). [b] THC = 1,2,3,4-tetrahydrocarbazole; DHC = dodecahydrocarbazole. [c] The hydrogenation was stopped at the theoretical pressure drop calculated for tetrahydrocarbazole. [d] The hydrogen uptake practically stopped at the tetrahydro stage. The *p*H of the aqueous medium was adjusted with potassium hydroxide.

yield by the reduction of carbazole with sodium and alcohol.[9]

The present paper concerns (1) a reinvestigation of the catalytic hydrogenation of carbazole, (2) a study of the chemical reduction of carbazole and derivatives with lithium metal in amine, and (3) some new *N*-substituted derivatives of carbazole and its hydrogenation products.

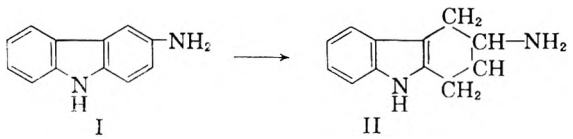
The hydrogenation of carbazole. Rhodium catalysts are effective for the hydrogenation of aromatic compounds and heterocyclics like pyrrole and pyridine at room temperature and atmospheric pressure while ruthenium catalysts are useful for the reduction of aromatic compounds at elevated temperature and pressure.[10] The use of these catalysts for the hydrogenation of condensed heterocyclic ring systems has apparently been little explored.

An investigation of the hydrogenation of carbazole revealed that 5% rhodium-carbon and 5% ruthenium-carbon were about equally effective, with reduction of the carbazole ring beginning at about 100° and 500 p.s.i.g. of hydrogen. Purification of materials was unnecessary. The use of a 5% palladium-carbon catalyst under similar conditions gave only about one fourth of the rate of hydrogenation realized with the rhodium or ruthenium catalysts. The reductions with ruthenium-carbon, rhodium-carbon, palladium-carbon, or nickel catalysts could be carried out in organic or aqueous media. The conditions for obtaining optimum yields of either tetrahydro- or dodecahydrocarbazole are summarized in Table I.

As expected, 9-alkylcarbazoles were also easily reducible. For example, 9-methylcarbazole could be hydrogenated in decalin solution at 500 p.s.i.g. of hydrogen and 150–200°, using a 5% palladium-carbon catalyst, to give an 88% yield of *N*-methyldodecahydrocarbazole.

The facile perhydrogenation of ring-substituted carbazoles was demonstrated by the example of 3-amino-9-methylcarbazole. The hydrogenation of 0.135 mole of this compound in water containing 0.27 mole of hydrochloric acid in the presence of 5% rhodium-carbon catalyst at 50–100° and 800–350 p.s.i.g. gave a 72% yield of 3-amino-9-methyldodecahydrocarbazole.

It is known that partial hydrogenation of ring-substituted carbazoles is difficult to stop at a specific stage of reduction. In addition, the ring containing the substituent and/or the unsubstituted ring may be exclusively or simultaneously hydrogenated. The only such example investigated by us was 3-aminocarbazole (I) which gave a 38% yield of unchanged starting material and an 11% yield of the hitherto unknown 3-amino-1,2,3,4-tetrahydrocarbazole (II), identified by its neutralization equivalent and ultraviolet spectrum (Table II). Compound II is structurally similar to the biologically active indole derivative tryptamine. Tests of 3-amino-1,2,3,4-tetrahydrocarbazole for its ability to inhibit (serotonin) monoamine oxidase showed it to be moderately active but not as effective as



I II

TABLE II

COMPARATIVE ULTRAVIOLET SPECTRAL DATA

	$\lambda_{max}^{C_2H_5OH}$	log ε
1,2,3,4-Tetrahydrocarbazole	227.5, 283, 291	4.5, 3.9, 3.8
9-Methyl-1,2,3,4-tetrahydrocarbazole	230, 287, 293.4	4.6, 3.8, 3.8
3-Amino-1,2,3,4-tetrahydrocarbazole	225, 283	4.5, 3.8
1,2,3,4,10,11-cis-Hexahydrocarbazole	241, 292	3.9, 3.4
9-Methyl-1,2,3,4,10,11-hexahydrocarbazole	244, 294–5	3.8, 3.3

(9) C. U. Zanetti, *Ber.*, 26, 2006 (1893).

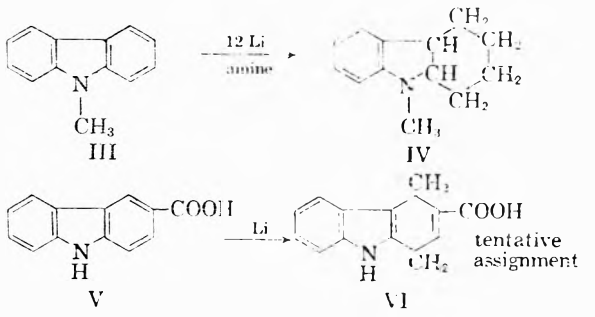
(10) G. Gilman and G. Cohn, *Advances in Catalysis*, Vol. IX, A. Farkas, ed., Academic Press, Inc., New York, N. Y., 1957, p. 733.

other compounds such as Marsilid and harmine for this purpose.[11]

The reduction of carbazole compounds with lithium in amine. The chemical reduction of benzenoid rings to the tetrahydro (cyclohexene) and hexahydro (cyclohexane) stage by means of the lithium in amine reagent has been reported recently.[12,13] The reduction of carbazole compounds with this reagent was investigated. It was hoped that 1,4-dihydrocarbazole might be obtained by 1,4-addition of lithium to one of the benzenoid rings of carbazole. However, when carbazole dissolved in *n*-propylamine was treated with two moles of lithium per mole of carbazole, a product, m.p. 137–45°, was obtained which could not be purified. When four moles of lithium per mole of carbazole were employed for the reduction, a 90% yield of 1,2,3,4-tetrahydrocarbazole was obtained. The latter was resistant to further reduction by lithium in amine. *cis*-Hexahydrocarbazole was also resistant to reduction by lithium in amine yielding an 82% recovery of starting material.[14]

Surprisingly, in view of the carbazole reduction stopping at the tetrahydro stage, the reduction of 9-methylcarbazole (III) with twelve moles of lithium per mole of carbazole derivative in *n*-propylamine proceeded to give 9-methyl-1,2,3,4,10,11-hexahydrocarbazole (IV) in good yield.[15]

The reduction of ring-substituted carbazoles was briefly investigated and proved to be more complex. Thus, the reduction of 3-aminocarbazole with lithium metal in ethylene diamine gave a 27% recovery of starting material as the only identified product. A similar reduction of carbazole-3-carboxylic acid (V) gave a 24% yield of a product tentatively identified as 1,4-dihydrocarbazole-3-carboxylic acid (VI) plus a 35% yield of an unidentified nonacidic product.



Some new N-substituted carbazole derivatives. The noncatalytic reaction of 2- and 4-vinylpyridines with nucleophilic reagents such as sodiomalonic ester, piperidine, diethylamine, and sodium bisulfite was first recognized by Doering and Weil.[16] Subsequently, this reaction, using alkali metal or acid catalysts, was applied to aromatic amines such as *N*-methylaniline,[17] and nitrogen heterocyclics such as pyrrole[17] and indole.[18] The literature mentions that diphenylamine and dicyclohexylamine, which are structurally related to carbazole and dodecahydrocarbazole, respectively, could not be pyridylethylated.[17]

Carbazole and the hydrocarbazoles, which had not been pyridylethylated before, have now been allowed to react with 2- and/or 4-vinylpyridine to give excellent to fair yields of the corresponding *N*-pyridylethylation products as listed in Table III. Carbazole itself and 1,2,3,4-tetrahydrocarbazole, which are very weak bases, were allowed to react in pyridine solution with vinylpyridine in the presence of alkali metal catalysts. 1,2,3,4,10,11-*cis*-Hexahydrocarbazole and dodecahydrocarbazole, which are relatively strong bases, were pyridylethylated using acid catalysts. Pyridylethylated carbazole has fungicidal properties which will be reported in detail elsewhere.

Although dodecahydrocarbazole has been known for more than thirty years, only a few derivatives have been prepared from it. A survey of the reactions of dodecahydrocarbazole revealed that it undergoes, as expected, all the usual transformations of a secondary cycloaliphatic amine. The melting points of the solid derivatives were not too sharp which was not surprising since the dodecahydrocarbazole was a mixture of stereoisomers.[5] The new derivatives of dodecahydrocarbazole are tabulated in Table IV.

EXPERIMENTAL

All melting and boiling points are uncorrected.

Dodecahydrocarbazole. A 1-gal. stainless steel autoclave (stirring-type) was charged with 167 g. (1.0 mole) of 97% carbazole, 85 g. of a prereduced, stabilized nickel-on-kieselguhr catalyst (55% nickel), and 1000 ml. of water. The autoclave was sealed, the mixture was stirred and heated to 200°, at which temperature the autogeneous pressure was 630 p.s.i.g. The autoclave was pressured to 1000 p.s.i.g. with hydrogen, and repressured to 1000 p.s.i.g., whenever the pressure fell to 700 p.s.i.g. After 6 hr., no further pressure drop occurred. The catalyzate was filtered.

(11) Private communication from Dr. Bernard Witkop, Chief, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases.

(12) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955).

(13) L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).

(14) This result was unexpected since R. A. Benkeser, R. F. Lambert, P. W. Ryan, and D. G. Stoffey, *J. Am. Chem. Soc.*, **80**, 6573 (1958), report that *N*-methylaniline is reduced by this reagent. However, R. A. Benkeser, J. J. Hazdra, R. F. Lambert, and P. W. Ryan, *J. Org. Chem.*, **24**, 854 (1959), indicate that large substituents may have an unfavorable effect on the ease of reduction.

(15) The overall results are not easily accommodated by Benkeser's proposed mechanisms (references in footnote 14). However, no definitive work has been reported on the lithium reduction of more closely related compounds such as pyrrole or indole.

(16) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(17) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955).

(18) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).

TABLE III

PYRIDYLETHYLATION OF CARBAZOLE AND HYDROCARBAZOLES

Nucleophile[a]	Vinylpyridine (VP)	Catalyst	Solvent	% Yield of Adduct	M.P. or B.P.
Carbazole[b]	2-VP	K	Pyridine	98	m. 77–78
Carbazole[b]	4-VP	Na	Pyridine	97	m. 173–174
THC	2-VP	Na	Pyridine	29	b. 194–201/3 mm.
THC	4-VP	Na	Pyridine	55	m. 83–84
HHC	2-VP	Acetic acid	Methanol	80	b. 175–180/1 mm.
DHC	4-VP	Acetic acid	None	65	b. 174–182/2 mm.

[a] THC = 1,2,3,4-tetrahydrocarbazole; HHC = 1,2,3,4,10,11-*cis*-hexahydrocarbazole; DHC = dodecahydrocarbazole. [b] An alternate and unequivocal synthesis of two pyridylethylated carbazoles is described in Brit. pat. 822,592 [*Chem. Abstr.*, **54**, 4628 (1960)]. The reaction of carbazole with sodium amide in xylene, followed by reaction with the appropriate haloalkylpyridine gave 9-[2-(2-pyridyl)ethyl]carbazole, m.p. 77°, and 9-[2-(4-pyridyl)ethyl]carbazole, m.p. 171–173°.

TABLE IV

DERIVATIVES OF DODECAHYDROCARBAZOLE

Dodecahydrocarbazole Treated with	Product[a] (% Yield)	Physical Properties
Lauroyl chloride	9-Dodecoyl DHC (87)	Pale yellow oil, b.p. 247–252°/3 mm.
KCNO	DHC-9-carboxamide (74)	Colorless crystals; m.p. 167–170° (benzene), 178–180° (ethanol)
Urea	DHC-9-carboxamide (88)	M.p. 180–182° (dil. ethanol)
CS_2	*N,N*-(Perhydro-*o,o'*-biphenylene) dithiocarbamate (100)	Almost colorless solid; m.p. 184–191° (ethanol)
$HCOOCH_3$	9-Formyldodecahydrocarbazole (90)	Colorless liquid, b.p. 157–159°/4 mm.
$CH_2{=}CH_2CN$	9-(2-Cyanoethyl) DHC (89)	Colorless oil, b.p. 157–161°/2 mm.
Cyclohexanone	9-(1-Cyclohexenyl) DHC (62)	Pale yellow oil, b.p. 155–160°/1 mm.
Succinic anhydride	9-(3-Carboxypropionyl) DHC (68)	Colorless solid, m.p. 111–115°
Phthalic anhydride	9-(2-Carboxybenzoyl) DHC (74)	Colorless solid, m.p. 182–187°
Maleic anhydride	9-(ω-Carboxyacrylyl) DHC (65)	Colorless solid, m.p. 124–129°
HNO_2	Nitrous salt of DHC (68)	Colorless solid, m.p. 150–155°
BF_3	BF_3 adduct of DHC (89)	Colorless solid, m.p. 212–214°

[a] DHC = dodecahydrocarbazole.

The insoluble material was extracted with 500 ml. of benzene. The benzene extract was then used to extract the filtrate. The organic phase was distilled through a 4-in. Vigreux column to give 157 g. (88% yield) of dodecahydrocarbazole, b.p. 124–125°/10 mm.[19]

The other perhydrogenations of carbazole were carried out similarly. The amount of catalyst used in the case of 5% rhodium-on-carbon or 5% ruthenium-on-carbon was 2–5% by wt. of the carbazole charge.

1,2,3,4-Tetrahydrocarbazole by the hydrogenation of carbazole. A 1-gal. autoclave, charged with 167 g. (1.0 mole) of carbazole, 1000 ml. of water adjusted to pH 12 with dilute potassium hydroxide, and 85 g. of a prereduced nickel-on-kieselguhr catalyst, was stirred and heated to 250°. A pressure of 680 p.s.i.g. was reached. The autoclave was then pressured to 1000 p.s.i.g. with hydrogen. A fast reaction ensued. The autoclave was repressured to 1000 p.s.i.g. with hydrogen when the pressure fell to 800 p.s.i.g. In 60 min., the hydrogen absorption had practically stopped. The mixture was allowed to cool, the autoclave was vented, and the catalyzate was filtered. The insoluble material was extracted with a 500-ml. and a 200-ml. portion of benzene. The combined benzene extract was shaken with three 200-ml. portions of 30% hydrochloric acid, in which carbazole is insoluble. Dilution of the combined acid extracts with water to give a 15% hydrochloric acid concentration precipitated tetrahydrocarbazole. The precipitate was filtered, washed with water, a little ammonia, and again with water, then dried to give 134 g. (87% yield) of 1,2,3,4-tetrahydrocarbazole, m.p. 115–118°; after one recrystallization from 95% ethanol, m.p. 118–119°.[19]

3-Amino-9-methyldodecahydrocarbazole. A 1-gal. stirring autoclave was charged with 26.0 g. (0.135 mole) of 3-amino-9-methylcarbazole, 1.0 l. of water, 23.8 g. (0.27 mole) of concd. hydrochloric acid, and 4.0 g. of 5% rhodium-on-carbon catalyst. The mixture was hydrogenated at 50–100° and 800–350 p.s.i.g. of hydrogen pressure during 4 hr. after which time no further pressure drop was observed. The catalyzate was filtered through a Celite filter. The clear filtrate was boiled for a short time and filtered again to remove solids which had formed. The filtrate was concentrated to 160 ml. volume, made alkaline with 28% ammonium hydroxide, and extracted with two 100-ml. portions of ether. The extract was dried over anhydrous sodium sulfate, concentrated, and the residual oil was distilled through a 4-in. Vigreux column to give 20.0 g. (72% yield) of a colorless mobile liquid, b.p. 115–125°/3 mm. Redistillation gave a center cut of b.p. 115–119°/3.5 mm.

Anal. Calcd. for $C_{13}H_{24}N_2$: Neut. equiv., 104; N, 13.4. Found: Neut. equiv., 108; N, 12.8.

1,2,3,4-Tetrahydrocarbazole by reduction of carbazole with the lithium in amine reagent. To a solution of 8.35 g. (0.05 mole) of carbazole in 100 ml. of *n*-propylamine was added 1.46 g. (0.21 mole) of lithium ribbon in small pieces during 5 hr. The mixture was stirred at room temperature overnight. Thereafter, 17 g. (0.32 mole) of ammonium chloride was added to the solution, the mixture was evaporated to dryness under vacuum, and the solid residue was taken up in 100 ml. of water. The resultant slurry was extracted with two 100-ml. portions of ether. The extract was washed with

(19) Adkins and Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941), reported b.p. 124–125°/10 mm. for dodecahydrocarbazole and m.p. 115–115.5° for 1,2,3,4-tetrahydrocarbazole.

water and dried over anhydrous sodium sulfate. Evaporation of the ethereal filtrate to dryness gave 8.6 g. (100% yield) of solids, m.p. 115–119°. One gram of this product was recrystallized from 5 ml. of cyclohexane to give 0.9 g. (90% yield) of tetrahydrocarbazole, m.p. 119–120°.

A similar reduction of carbazole in ethylenediamine at 85–100° with lithium gave a 87% yield of tetrahydrocarbazole.

3-Aminо-1,2,3,4-tetrahydrocarbazole. A solution of 36.4 g. (0.2 mole) of 3-aminocarbazole in 200 ml. (0.2 mole) of 1*N* hydrochloric acid and 800 ml. of water was hydrogenated in a 1-gal. stirring autoclave in the presence of 3.0 g. of 5% ruthenium-on-carbon catalyst at 100° and 820 p.s.i.g. of hydrogen for 12 hr. The catalyzate was then filtered to remove 17 g. of insoluble material, *i.e.* a 38% recovery of 3-aminocarbazole (corrected for catalyst weight). Extraction of the insoluble material with ethanol and concentration of the extract gave 3-aminocarbazole, m.p. 238–241°. The aqueous filtrate was alkaline (*p*H 8) due to the formation of higher hydrogenated carbazoles. It was concentrated to 200 ml. volume, made strongly alkaline with ammonium hydroxide, and extracted with ether. The extract was evaporated to dryness to give 4.2 g. (11% yield) of solids, m.p. 116–170°. After recrystallization from ethanol, m.p. 170–172°. A sample was titrated in acetic acid with perchloric acid. The calculated neutralization equivalent for the title compound is based on the fact that tetrahydrocarbazole was found to be too weakly basic to be titratable.

Anal. Calcd. for $C_{12}H_{14}N_2$: Neut. equiv. 186. Found: Neut. equiv. 184.

Since hexahydrocarbazole was titratable, the alternate structure, 3-aminohexahydrocarbazole $C_{12}H_{16}N_2$, would have a neutralization equivalent of 94. 6-Aminotetrahydrocarbazole is eliminated on the basis of its m.p. 152°. The ultraviolet spectrum of the product was similar to that of tetrahydrocarbazole but different from that of hexahydrocarbazole (Table II).

9-Methyl-1,2,3,4,10,11-hexahydrocarbazole. A solution of 9.1 g. (0.05 mole) of 9-methylcarbazole in 200 ml. of *n*-propylamine was treated with 4.3 g. (0.62 g.-atom) of lithium ribbon in small pieces during 5 hr. at 25°. After stirring for an additional 1.5 hr., some unchanged lithium pieces were removed with forceps. Finally, 33.2 g. (0.62 mole) of ammonium chloride was added to the solution. The solvent was evaporated. The residue was taken up in water and extracted with two 100-ml. portions of ether. The extract was dried over Drierite, filtered, and the filtrate was evaporated to give 9.8 g. of residue. This crude product was distilled through a semimicro Vigreux column to give 6.5 g. (71% yield) of 9-methylhexahydrocarbazole, b.p. 125–135°/1 mm., analyzed by nonaqueous titration with perchloric acid in acetic acid. An authentic sample of 9-methyl-1,2,3,4-tetrahydrocarbazole was too weakly basic to be titrated by this method.

Anal. Calcd. for $C_{13}H_{17}N$: Neut. equiv., 187. Found: Neut. equiv., 190.

The ultraviolet spectrum of the product was similar to that of 1,2,3,4,10,11-*cis*-hexahydrocarbazole itself except that the absorption maxima were shifted to slightly higher wave lengths (Table II). The crystalline picrate reported for 9-methyl-1,2,3,4-cis-hexahydrocarbazole[3] could not be obtained from our product. The neutralization equivalent, ultraviolet spectrum, and the formulation of a noncrystalline picrate indicate that our product was a mixture of *cis*- and *trans*-hexahydrocarbazole isomers.

Reduction of carbazole-3-carboxylic acid with lithium in amine. To a solution of 3.4 g. (0.016 mole) of carbazole-3-carboxylic acid in 100 g. of ethylamine was added at 25° during 40 min. 0.78 g. (0.112 g.-atom) of lithium ribbon in small pieces. After stirring for 2 additional hr. at 25°, 5.95 g. (0.112 mole) of ammonium chloride was added. The mixture was evaporated to dryness under vacuum. The residue was digested in water and the mixture was extracted with ether. The extract was evaporated to dryness to give 1.8 g. of a nonacidic solid. This solid was distilled through a Bantamware column to give 1.2 g. (35 wt. % yield) of low-melting yellow solids, b.p. 220–270° (bath)/2 mm., which were not further investigated. The alkaline aqueous solution obtained above was acidified and extracted with ether. The ether extract was evaporated to dryness to give 0.8 g. (24 wt. % yield) of solid, m.p. 215–219°; after vacuum sublimation, m.p. 220–221°, colorless crystals. While carbazole-3-carboxylic acid has a —CO absorption peak at 1660 cm.$^{-1}$, the product showed —CO absorption at 1685 cm.$^{-1}$ This indicated that the carboxyl group of the product was in conjugation with a double bond[20] and that the product was probably 1,4-dihydrocarbazole-3-carboxylic acid.

Pyridylethylation of carbazole and 1,2,3,4-tetrahydrocarbazole. A stirred mixture of 167 g. (1.0 mole) of carbazole, 115 g. (1.1 moles) of 2-vinylpyridine, 2.0 g. (0.05 g.-atom) of small pieces of metallic potassium, and 1000 ml. of pyridine was refluxed for 3 hr., then cooled to 60°, and stirred for 0.5 hr. with 15 ml. of absolute ethanol. The solution was concentrated to *ca.* 250 ml. volume and poured into 2 l. of ice-water. An oil separated which solidified quickly. The solid was filtered, washed with water, and air-dried to give 265 g. (98% yield) of crude product, m.p. 73–75°. After recrystallization from 95% ethanol, 9-[2-(2-pyridyl)-ethyl]carbazole, m.p. 77–78°, was obtained; it was analyzed by nonaqueous titration with perchloric acid in acetic acid (only the pyridine nitrogen is basic enough to be picked up by this method).

Anal. Calcd. for $C_{19}H_{16}N_2$: Neut. equiv., 272. Found: Neut. equiv., 275.

The infrared spectrum of the product showed no NH absorption peak, indicating the formation of a 9-substituted carbazole.

The reactions of carbazole with 4-vinyl pyridine and of 1,2,3,4-tetrahydrocarbazole with 2- and 4-vinylpyridine were carried out in similar fashion.

Pyridylethylation of 1,2,3,4,10,11-cis-hexahydro- and dodecahydrocarbazole. A mixture of 17.3 g. (0.1 mole) of *cis*-hexahydrocarbazole,[21] 10.5 g. (0.1 mole) of 2-vinylpyridine, 6.0 ml. (0.1 mole) of glacial acetic acid, and 50 ml. of methanol was stirred and refluxed for 8 hr. The alcohol was then stripped and the concentrate was poured over 500 g. of crushed ice. A sticky gum formed. The mixture was made alkaline by the addition of 100 ml. of 10% sodium hydroxide and extracted with two 250-ml. portions of ether. The combined extracts were dried over Drierite, filtered, and concentrated. The residue (27.0 g., 97% yield) was distilled through a 4-in. Vigreux column to give 22.4 g. (80% yield) of a fraction, b.p. 175–180°/1 mm., 9-[2-(2-pyridyl)ethyl]-1,2,3,4,10,11-*cis*-hexahydrocarbazole; it was analyzed by nonaqueous titration with perchloric acid in acetic acid (both nitrogen atoms are sufficiently basic to be picked up by this method).

Anal. Calcd. for $C_{19}H_{22}N_2$: Neut. equiv., 139.5. Found: Neut. equiv., 142.4.

Dodecahydrocarbazole was allowed to react with 4-vinylpyridine in the same manner, except that no solvent methanol was used.

9-Dodecoyldodecahydrocarbazole. A mixture of 251 g. (1.4 moles) of dodecahydrocarbazole, 1600 ml. of xylene, and 154 g. (0.7 moles) of lauroyl chloride was stirred and refluxed for 4 hr. After cooling to 25°, the mixture was filtered. The solid was washed with 300 ml. of xylene and dried to give 99.2 g. (69% yield) of dodecahydrocarbazole hydrochloride. The filtrate was concentrated to 1 l. volume, cooled to 20°, and filtered to give an additional 55.5 g. (39% yield) of crude dodecahydrocarbazole hydrochloride.

(20) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, New York, 1958, p. 168.

(21) J. Gurney, W. H. Perkin, and S. G. P. Plant, *J. Chem. Soc.*, 2678 (1927).

The filtrate was stripped of xylene and the residue was distilled through a 4-in. Vigreux column to give 220 g. (87% yield) of a pale yellow oil, b.p. 247–252°/3 mm.

Anal. Calcd. for $C_{24}H_{43}NO$: N, 3.88. Found: N, 3.84.

Dodecahydrocarbazole-9-carboxamide. The hydrochloride of dodecahydrocarbazole was formed by adding 25 ml. of 2*N* hydrochloric acid (0.05 mole) to 9.0 g. (0.05 mole) of dodecahydrocarbazole. The mixture was cooled to 25° and mixed with 4.1 g. (0.05 mole) of potassium cyanate. After standing for 2 hr. with occasional stirring, the oil which had formed initially solidified. The crystals were filtered, washed with 50 ml. of water and 25 ml. of ether, then dried to give 8.1 g. (74% yield) of crude product, m.p. 144–147°. Crystallization from benzene raised the m.p. to 167–170°, while crystallization from dilute ethanol gave a product, m.p. 178–180°. The product, m.p. 167–170° (from benzene) was analyzed by nitrogen analysis.

Anal. Calcd. for $C_{13}H_{22}N_2O$: N, 12.6. Found: N, 12.2.

As an alternate preparation, a melt of 18 g. (0.1 mole) of dodecahydrocarbazole and 12.0 g. (0.2 mole) of urea was stirred at 160° for 5 hr. (ammonia was evolved). The mix was then poured onto 100 g. of crushed ice, filtered, and the solid was washed with water to remove excess urea. The gummy insoluble material was ground under ether and filtered to give 19.6 g. (88% yield) of the crude *N*-carboxamide of dodecahydrocarbazole, m.p. 134–136°; after three recrystallizations from aqueous ethanol it melted at 180–182°. Mixture melting point with the corresponding products from the reaction of dodecahydrocarbazole with potassium cyanate was undepressed.

N,N-(Perhydro-o,o'-biphenylene)dithiocarbamate. Into a solution of 8.95 g. (0.05 mole) of dodecahydrocarbazole in 20 ml. of ether was stirred a solution of 3.8 g. (0.05 mole) of carbon disulfide in 10 ml. of ether at 20°. The solvent was evaporated to leave a pale yellow residue, 11.0 g. (102% yield) of crude dithiocarbamate of dodecahydrocarbazole, m.p. 180–190°; after recrystallization from 95% ethanol, m.p. 184–191°.

Anal. Calcd. for $C_{25}H_{42}N_2S_2$: N, 6.45; S, 14.75. Found: N, 6.20; S, 13.6.

9-Formyldodecahydrocarbazole. A mixture of 36 g. (0.20 mole) of dodecahydrocarbazole and 15 g. (0.25 mole) of methyl formate was refluxed on the steam bath for 1 hr. The methanol and the excess methyl formate were then distilled to give 46 g. of a clear yellow residue. This concentrate was distilled through a 4-in. Vigreux column to give 37.3 g. (90% yield) of crude product, b.p. 112–142°/2 mm. Redistillation of this fraction gave 21.8 g. (53% yield) of a center cut, b.p. 157–159°/4 mm.

Anal. Calcd. for $C_{13}H_{21}NO$: N, 6.77. Found: N, 6.51.

9-(2-Cyanoethyl)dodecahydrocarbazole. A mixture of 270 g. (1.5 moles) of dodecahydrocarbazole, 89 g. (1.7 moles) of acrylonitrile, and 8.0 ml. (0.13 mole) of glacial acetic acid was stirred and refluxed for 6 hr. The product was then distilled through a 4-in. Vigreux column to give 310 g. (89% yield) of a colorless oil, b.p. 157–161°/2 mm.

Anal. Calcd. for $C_{15}H_{24}N_2$: Neut. equiv., 232. Found: Neut. equiv., 243.

9-(1-Cyclohexenyl)dodecahydrocarbazole. A mixture of 17.1 g. (0.1 mole) of dodecahydrocarbazole, 9.8 g. (0.1 mole) of cyclohexanone, and 50 ml. of benzene was refluxed for 6 hr. During this time, 1.25 ml. (70%) of water was removed *via* a Dean-Stark trap. The mixture was then concentrated to remove the benzene and the residue was distilled through a 4-in. Vigreux column to give 16 g. (62% yield) of a pale yellow mobile oil, b.p. 155–160°/1 mm.

Anal. Calcd. for $C_{18}H_{29}N$: Neut. equiv., 259.5; N, 5.40. Found: Neut. equiv., 260; N, 5.25.

Reaction of dodecahydrocarbazole with acid anhydrides. A solution of 18 g. (0.1 mole) of dodecahydrocarbazole, 10 g. (0.1 mole) of succinic anhydride, and 25 ml. of ethyl acetate was refluxed for 1 hr., then kept at 5° overnight. The product was filtered to give 19 g. (68% yield) of colorless crystals, m.p. 109–114°. After recrystallization from ethyl acetate, it melted at 111–115°.

Anal. Calcd. for $C_{16}H_{25}NO_3$: Neut. equiv., 279. Found: Neut. equiv., 271.

A similar reaction of dodecahydrocarbazole with an equimolar amount of phthalic anhydride gave a 74% yield of crude 9-(2-carboxybenzoyl)dodecahydrocarbazole, m.p. 182–187°; after recrystallization from 50% aqueous ethanol, it melted at 207–209°.

Anal. Calcd. for $C_{20}H_{25}NO_3$: Neut. equiv., 327. Found: Neut. equiv., 337.

Similarly, the reaction of equimolar quantities of dodecahydrocarbazole and maleic anhydride gave a 50% yield of crude 9-(ω-carboxyacrylyl)dodecahydrocarbazole, m.p. 122–126°; after recrystallization from ethyl acetate it melted at 124–129°.

Anal. Calcd. for $C_{16}H_{23}NO_3$: Neut. equiv., 277. Found: Neut. equiv., 270.

The product showed a strong absorption band at 6.15 μ believed to be due to a conjugated *cis* CH=CH group. Apparently, no isomerization took place during the reaction.

Nitrous salt of dodecahydrocarbazole. A solution of 18 g. (0.1 mole) of dodecahydrocarbazole in 400 ml. of water and 20 ml. (0.25 mole) of concd. hydrochloric acid was neutralized with ammonium hydroxide to *p*H 8.0. To this solution was added 69 g. (1.0 mole) of sodium nitrate, the mixture was heated to 60°, filtered, and the filtrate was cooled to 5–10° for 1 hr. After filtration, there were obtained 11.3 g. (50% yield) of a colorless solid, m.p. 150–155° dec.; after recrystallization from *n*-butyl alcohol it melted at 157–158° dec. The product was characterized by nitrogen analysis and by titration for nitrite with an excess of a standard permanganate solution, followed by back titration with standard ferrous ammonium sulfate.

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: N, 12.38; HNO_2, 8.87 meq./g. Found: N, 12.08; HNO_2, 9.04 meq./g.

To the final filtrate was added another 69 g. (1.0 mole) of sodium nitrite and the mixture was stirred for 1 hr., then filtered to give an additional 4.0 g. (18% yield) of product, m.p. 145–155° dec.

Boron trifluoride adduct of dodecahydrocarbazole. To a stirred solution of 10 g. (0.056 mole) of dodecahydrocarbazole in 50 ml. of ether was added dropwise 10 ml. of boron trifluoride etherate during 15 min. The exothermic reaction brought the ether to boil and a solid precipitated. The mixture was cooled to 5° and filtered. After washing the solid with 50 ml. of ether there were obtained 12.2 g. (89% yield) of a colorless material, m.p. 212–214°.

Anal. Calcd. for $C_{12}H_{21}BF_3N$: N, 5.67. Found: N, 5.15.

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VERONA, PA.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Synthesis of Some 9-[2-(Diethylamino)ethyl]-6-substituted Purines as Potential Antimetabolites[1]

HSI HU LIN AND CHARLES C. PRICE

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Several 9-[2-(diethylamino)ethyl]-6-substituted purines were synthesized from 9-[2-(diethylamino)ethyl]-6-chloropurine (VII). This compound (VII) was prepared by direct chlorination of the corresponding 9-substituted hypoxanthine (IX) which was, in turn, obtained by cyclization of 4-[2-(diethylamino)ethylamino]-5-amino-6-chloropyrimidine (VI) in formic acid. The diaminochloropyrimidine (VI) was prepared by treatment of 4,6-dichloro-5-aminopyrimidine with *N,N*-diethylethylenediamine.

In the synthesis of various potential antagonists of the natural purines, Robins and Lin[2] reported that 9-methyl-6-chloropurine has shown the same order of activity against Adenocarcinoma 755 in C-57 black mice as 6-chloropurine,[3,4] while two other 9-methyl-6-substituted purines have shown less activity against this tumor. 9-Ethyl-6-chloropurines[5] and 9-propyl-6-chloropurine,[6] synthesized by Montgomery and Temple, have also shown the same kind of activity.

The results make the investigation of other 9,6-disubstituted purines of great interest. There were two reasons for synthesizing 9-[2-(diethylamino)-ethyl]-6-substituted purines. The first was to see how the antitumor activity of the 6-chloropurine and 6-mercaptopurine would be affected by attaching a basic 2-(diethylamino)ethyl radical on the 9-position of the purine antimetabolites. The second was for preliminary studies of possible procedures for synthesizing 9-substituted-purine nitrogen mustards as cytotoxic agents.[7]

In this investigation, treatment of 4,6-dichloro-5-nitropyrimidine (I) with an aqueous solution of excess *N,N*-diethylethylene diamine at *p*H 8 did not give the expected monosubstituted derivative but the disubstituted derivative. This was under conditions similar to those employed by Robins and Lin[2] for the synthesis of 4-methylamino-5-nitro-6-chloropyrimidine. Several other conditions were also explored by changing solvent, *p*H, reaction temperature and ratio of the two reactants. In spite of these trials, only the disubstituted product and the starting material were isolated. Failure to obtain the monosubstituted compound could arise from too small a difference between the rates for the first and second nucleophilic substitution.

In view of the above reasoning, the nitro group of the dichloronitropyrimidine was reduced to the amino group in order to deactivate the pyrimidine ring against nucleophilic attack and hopefully to enlarge the difference between the first and second nucleophilic substitution rates. When a mixture of one equivalent of the dichloroaminopyrimidine (II) and two equivalents of *N,N*-diethylethylene diamine in water was refluxed, a quantitative yield of 4-[2-(diethylamino)ethylamino]-5-amino-6-chloropyrimidine was obtained.[8] In 1954 Brown prepared 4-methylamino-5-amino-6-chloropyrimidine by heating aqueous methylamine and the pyrimidine II at 130° in a sealed tube. Montgomery and Temple,[5] using conditions similar to Brown's, succeeded in synthesizing 4-ethylamino-5-amino-6-chloropyrimidine in good yield.

When 4-[2-(diethylamino)ethylamino]-5-amino-6-chloropyrimidine (VI) was refluxed with formic acid, cyclization took place to give 9-[2-(diethylamino)ethyl]-hypoxanthine (IX) in good yield.

As the loss of a chlorine atom of various chloro-substituted 4,5-diaminopyrimidines upon formylation and cyclization with formic acid,[9,2,5] or with formamide,[10] has been reported previously, this behavior is not unexpected.

Montgomery[11] reported the synthesis of 2-chloropurine, 6-chloropurine and 2,6-dichloropurine by cyclization of the appropriate chloro-4,5-diaminopyrimidine in ethyl orthoformate and acetic anhydride combination. 9-Methyl-6-chloropurine[2] was prepared in the same manner. Temple and Montgomery[5] claimed that diethoxymethyl acetate was a better cyclizing agent than the ethyl orthoformate–acetic anhydride combination in the synthesis of 9-ethyl-6-chloropurine. The parent com-

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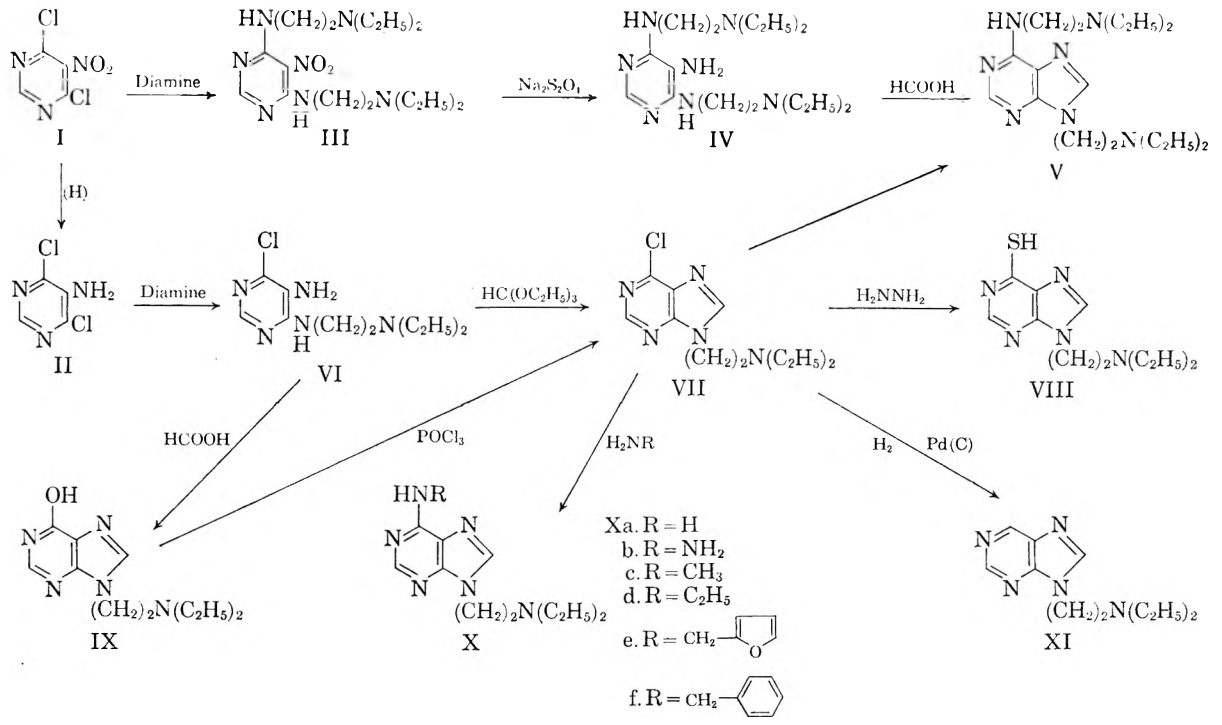
REACTION SCHEME



pound 9-[2-(diethylamino)ethyl]-6-chloropurine (VII) was prepared in low yield by cyclization in ethyl orthoformate–acetic anhydride combination. This compound (VII) was also prepared in excellent yield by direct chlorination of the corresponding hypoxanthine (IX) with phosphorus oxychloride.

The parent compound (VII) and thiourea in boiling 2-ethoxyethanol (b.p. 138°) gave 9-[2-(diethylamino)ethyl]-6-mercaptopurine (VIII). Most of the starting material was recovered when compound VII and thiourea were refluxed in absolute ethanol whereas 6-mercaptopurine,[4] 9-methyl-6-mercaptopurine,[2] and 9-ethyl-6-mercaptopurine[5] were prepared by refluxing the corresponding chloropurine with thiourea in ethanol. Montgomery and Temple[6] also reported that the condensation between thiourea and 9-propyl or 9-butyl-6-chloropurine required a solvent which has a higher boiling point than that of absolute ethanol.

9-[2-(Diethylamino)ethyl]purine (XI) was prepared[5] by hydrogenolysis of compound VII, using 10% palladium-on-charcoal as catalyst. Treatment of compound VII with concentrated ammonium hydroxide in an autoclave at 125° gave 9-[2-(diethylamino)ethyl]adenine (X*a*), which showed that replacement of the 6-chlorine atom with ammonia can be carried out using water as solvent and at a temperature lower than that used by Bendich, Russell, and Fox[4] or by Robins and Lin.[2]

9-[2-(Diethylamino)ethyl]-6-methylaminopurine (Xc) and 9-[2-(diethylamino)ethyl]-6-ethylaminopurine (Xd) were obtained by heating compound VII with the corresponding aqueous amine in a pressure bottle at 100°. 9-[2-(Diethylamino)ethyl]-6-hydrazinopurine (Xb) was prepared by merely refluxing compound VII in aqueous hydrazine. When compound VII was refluxed with furfurylamine in 1-butanol, benzylamine in 2-ethoxyethanol and with *N*,*N*-diethylethylene diamine in 2-ethoxyethanol, the corresponding 6-substituted aminopurines (Xe; Xf; V) were obtained. 9-[2-(Diethylamino)ethyl] - 6 - [2 - (diethylamino)ethylamino]-purine (V) was also prepared by another route. Treatment of 4,6-dichloro-5-nitropyrimidine (I) with *N*,*N*-diethylethylene diamine gave 4,6-bis[2-(diethylamino)ethylamino]-5-nitropyrimidine (III). Catalytic reduction of III with sodium hydrosulfite gave 4,6-bis[2-(diethylamino)ethylamino]-5-aminopyrimidine (IV) which was cyclized successfully with formic acid to give the corresponding purine (V). The product was judged to be identical with the product from the amination of compound VII on the basis of mixture melting point and identical ultraviolet absorption spectra.

In general, the condensation of compound VII with nucleophilic reagents required more vigorous reaction conditions, namely higher temperature and more polar medium than the condensation of 9-unsubstituted, 9-methyl- and 9-ethyl-6-chloropurine with the same nucleophilic reagents. This could be attributed to greater basicity of the 9-nitrogen, permitting greater electron release to the pyrimidine ring thus decreasing the ease of nucleophilic displacement of chlorine.

The ultraviolet absorption maxima in the spectra of 9-[2-(diethylamino)ethyl]-6-substituted purines are listed in Table I and II. As was expected, the ultraviolet absorption spectra of 9-[2-(diethyl-

TABLE I

THE ULTRAVIOLET ABSORPTION MAXIMA OF SEVERAL 9-[2-(DIETHYLAMINO)ETHYL]-6-SUBSTITUTED PURINES

6-R	0.1N HCl, λ_{max}, mμ	ε	0.1N NaOH, λ_{max}, mμ	ε
OH	249	10.4×10^3	255	12.7×10^3
SH	322	22.7×10^3	309	26.5×10^3
Cl	264.6	6.7×10^3		
H	263	5.8×10^3	260	7.6×10^3

TABLE II

THE ULTRAVIOLET ABSORPTION MAXIMA OF SOME 9-[2-(DIETHYLAMINO)ETHYL]-6-SUBSTITUTED AMINOPURINES

6-NHR,R =	0.1N HCl, λ_{max}, mμ	ε	0.1N NaOH, λ_{max}, mμ	ε
—H	260	15.2×10^3		
—NH_2	262	17.7×10^3		
—CH_3	263	18.6×10^3	266	18.1×10^3
—CH_2CH_3	264	11.7×10^3	268	13.7×10^3
—$CH_2C_4H_3O$	266	17.6×10^3	269	12.8×10^3
—$CH_2C_6H_5$	265	16.7×10^3	269.5	17.5×10^3
—$CH_2CH_2NEt_2$	266	22.6×10^3	269	30.1×10^3

amino)ethyl]-6-substituted purines are very similar to those of the 9-unsubstituted, 9-methyl-[2] and 9-ethyl-6-substituted purines.

EXPERIMENTAL[12]

4,6-Bis[2-(diethylamino)ethylamino]-5-nitropyrimidine (III). 4,6-Dichloro-5-nitropyrimidine (5.8 g.) was dissolved in 70 ml. of absolute ethanol. To the solution, 7 g. of *N,N*-diethylethylenediamine in 50 ml. of absolute ethanol was added slowly. The solution was refluxed for 2 hr. and distilled to half its original volume. Yellowish crystals of 4,6-bis-2-(diethylamino)ethylamino-5-nitropyrimidine dihydrochloride separated on cooling. After being filtered, washed with ethanol, and dried at 110°, they yielded 11.7 g. The dihydrochloride was dissolved in 110 ml. of cold water and made alkaline with 5% sodium hydroxide. A yellow oil separated instantly. On cooling in the refrigerator overnight, the oil crystallized as needles, which were filtered, washed with cold water, and dried at room temperature in a vacuum desiccator; yield, 9.3 g. (87%), m.p. 54–55°. The crude product was recrystallized from a mixture of acetone and water and vacuum dried at room temperature, m.p. 55°.

Anal. Calcd. for $C_{16}H_{31}N_7O_2$: C, 54.36; H, 8.84; N, 27.74. Found: C, 54.73; H, 8.77; N, 27.14.

4,6-Bis[2-(diethylamino)ethylamino]-5-aminopyrimidine (IV). 4,6-Bis[2-(diethylamino)ethylamino]-5-nitropyrimidine (5.8 g.) was suspended in 200 ml. of water (90°) and 32 g. of sodium hydrosulfite (90%) was added slowly. The yellow oily diaminonitropyrimidine dissolved at the end of the addition. The solution was heated to boiling for 5 min., filtered and cooled to room temperature. Sodium hydroxide (10%) was added slowly to the solution until it reached *p*H 10. The white oil which separated was extracted with about 200 ml. of ether. The ether layer was dried over anhydrous magnesium sulfate for 1 hr. and filtered. The filtrate was distilled under reduced pressure to a volume of 30 ml. Colorless prisms which crystallized out of the ether solution were filtered and dried in a vacuum desiccator; yield, 4.1 g. (80%), m.p. 107–108°. A portion was recrystallized from anhydrous ether and dried at 56° to give colorless prisms, m.p. 108°.

Anal. Calcd. for $C_{16}H_{33}N_7$: C, 59.40; H, 10.28; N, 30.31. Found: C, 59.13; H, 10.34; N, 30.57.

9-[2-(Diethylamino)ethyl]-6-[2-(diethylamino)ethylamino]-purine trihydrochloride (V). *Method A.* 4,6-Bis[2-(diethylamino)ethylamino]-5-aminopyrimidine (3.3 g.) dissolved in 150 ml. of formic acid (98–100%), was refluxed for 3 hr. and distilled under reduced pressure to dryness. The yellow oily residue was heated under reduced pressure on a steam bath for 0.5 hr. and 50 ml. of alcoholic ammonia was added. The separated crystals of ammonium formate were removed by filtration. The filtrate was evaporated to dryness on a steam bath and then extracted with chloroform with vigorous stirring. The chloroform solution was filtered and hydrogen chloride gas was passed through. White crystals of 9,6-disubstituted aminopurine trihydrochloride which separated were filtered at once and dried in a vacuum desiccator; yield, 3.1 g. (50%), m.p. 247–251°. The crude product was recrystallized from absolute ethanol to give white crystals, m.p. 251–252° (vacuum dried at 78°).

Anal. Calcd. for $C_{17}H_{34}N_7Cl_3$: C, 46.10; H, 7.74; N, 22.14; Cl, 24.02. Found: C, 46.40; H, 7.64; N, 22.10; Cl, 23.83.

Method B. *N,N*-Diethylethylenediamine (470 mg.) and 9-[2-(diethylamino)ethyl]-6-chloropurine (510 mg.) dissolved in 20 ml. of 2-ethoxyethanol were refluxed for 1 hr. and distilled under reduced pressure to dryness. The residue was extracted with 60 ml. of chloroform and the chloroform solution was filtered. Hydrogen chloride gas was passed through the filtrate. White crystalline solid which separated was filtered, washed with chloroform and then with absolute ethanol, and dried; yield, 350 mg. (52%); m.p. 244–250°. The crude product was recrystallized from absolute ethanol, m.p. 250–252°. No depression was found on the mixture melting point of the product from method (A) and (B). The ultraviolet absorption spectra were identical in 0.1 *N* hydrochloric acid.

4-[2-(Diethylamino)ethylamino]-5-amino-6-chloropyrimidine (VI). 4,6-Dichloro-5-aminopyrimidine (4.92 g.) was suspended in a solution which was made by dissolving 7.10 g. of *N,N*-diethylethylenediamine in 110 ml. of water. The suspension was refluxed for 5 hr. Yellowish brown oil of 4-[2-(diethylamino)ethylamino]-5-amino-6-chloropyrimidine separated out of the aqueous solution. The mixture was kept in the refrigerator overnight. Yellowish needles crystallized out from the solution and the oil. The crystals were filtered and dried; yield, 8.1 g. (90%), m.p. 76–81°. A small amount of the crude product was recrystallized from water to give light yellowish needles, m.p. 74–80°.

Anal. Calcd. for $C_{10}H_{18}N_5Cl.2H_2O$: C, 42.93; H, 7.92; N, 25.04; Cl, 12.68. Found: C, 43.27; H, 7.86; N, 25.30; Cl, 13.08.

9-[2-(Diethylamino)ethyl]hypoxanthine (IX). Dehydrated 4-[2-(diethylamino)ethylamino]-5-amino-6-chloropyrimidine (9.4 g.), dissolved in 160 ml. of formic acid (98–100%), was refluxed for 6 hr. and distilled under reduced pressure to dryness. The brown viscous residue was heated on a steam bath under reduced pressure for another hour. To the viscous residue, 25 ml. of concd. ammonium hydroxide and 10 ml. of water were added successively. White crystalline solid separated. The crude product was recrystallized from water to give tan prisms, m.p. 181°, yield, 7.63 g. (84%).

Anal. Calcd. for $C_{11}H_{17}N_5O$: C, 56.14; H, 7.28; N, 29.77. Found: C, 56.97; H, 7.28; N, 29.49.

9-[2-(Diethylamino)ethyl]-6-chloropurine (VIII). *Method A.* 9-[2-(Diethylamino)ethyl]hypoxanthine (6.5 g.), suspended in 260 ml. of phosphorus oxychloride, was refluxed for 6 hr. The dark brown solution was distilled under reduced pressure nearly to dryness. The viscous residue was poured into about 500 g. of crushed ice with frequent stirring. Ammonia gas was passed through the ice cold acidic solution until it reached *p*H 11. The cloudy basic solution was extracted with four 200-ml. portions of chloroform. The combined ex-

(12) All melting points are uncorrected and were taken on a Fisher-Johns melting point block and copper block.

tract was distilled under reduced pressure to dryness after being dried over anhydrous magnesium sulfate overnight. The viscous brown residue, after being vacuum dried at room temperature for 2 hr., was recrystallized from petroleum ether (b.p. 30–60°) in a Dry Ice–acetone bath to give white prisms which, on standing at room temperature, changed to light yellow liquid, yield 6.3 g. (90%). A small amount of this was recrystallized again under the same conditions and vacuum dried at 78°.

Anal. Calcd. for $C_{11}H_{16}N_5Cl$: C, 52.06; H, 6.36; N, 27.60; Cl, 13.97. Found: C, 52.38; H, 6.39; N, 27.75; Cl, 12.84.

Method B. 4-[2-(Diethylamino)ethylamino]-5-amino-6-chloropyrimidine (0.88 g.) was suspended in a mixture of 25 ml. of ethyl orthoformate and 25 ml. of acetic anhydride. The solution was refluxed for 5 hr. and distilled to dryness under reduced pressure. The brown viscous residue was further dried over a steam bath at 2 mm. pressure for 1 hr. and about 10–15 g. of crushed ice was then added along with cold concd. ammonium hydroxide to *p*H 11. The cold basic solution was extracted with four 50-ml. portions of chloroform. The combined extract, after being dried over anhydrous magnesium sulfate overnight, was distilled under reduced pressure to dryness. The brown viscous residue after being dried at room temperature (2 mm.) for 1 hr. was recrystallized from petroleum ether (b.p. 30–60°) in a Dry Ice–acetone bath to give white prism-like crystals which, on standing at room temperature, liquified. The light-yellowish liquid was dried at 78° (3 mm.) for 5 hr.; yield, 0.46 g. (52%). The ultraviolet absorption spectra is identical with that of the product from method (A).

9-[2-(Diethylamino)ethyl]adenine (Xa). Concentrated ammonium hydroxide (25 ml., 80%) was added to 0.8 g. of 9-[2-(diethylamino)ethyl]-6-chloropurine. The mixture was sealed in an autoclave and heated at 125° for 5 hr. The autocalve was cooled to room temperature overnight. Colorless prisms separated and were filtered and dried; yield, 0.51 g. (69%); m.p. 180–181.5°. A portion of the product was recrystallized from water to give colorless prisms, m.p. 181–182°.

Anal. Calcd. for $C_{11}H_{18}N_6$: C, 56.38; H, 7.74; N, 35.87. Found: C, 56.35; H, 7.69; N, 35.89.

9-[2-(Diethylamino)ethyl]-6-mercaptopurine (VIII). 9-[2-(Diethylamino)ethyl]-6-chloropurine (0.6 g.) and 0.2 g. of thiourea dissolved in 2-ethoxyethanol (20 ml.) were refluxed for 2 hr. and distilled under reduced pressure nearly to dryness. To the dark brown residue, 0.25 g. of sodium hydroxide in 15 ml. of water was added. The basic solution was then heated on a steam bath for 0.5 hr., boiled gently for a few minutes with charcoal and filtered. The alkaline solution was adjusted to *p*H 6–7 with concd. hydrochloric acid and evaporated to dryness. The dry residue was extracted with hot absolute ethanol. The undissolved sodium chloride was removed by filtration. As the filtrate became turbid upon evaporation, colorless needles separated. The crystals were filtered and dried; yield, 0.3 g. (44%), m.p. 247–251°. The crude product was recrystallized from absolute ethanol twice to give colorless needles, m.p. 249–251°.

Anal. Calcd. for $C_{11}H_{17}N_5S.HCl$: C, 45.90; H, 6.30; N, 24.34; S, 11.14; Cl, 12.32. Found: C, 45.77; H, 6.34; N, 24.24; S, 10.81; Cl, 12.09.

9-[2-(Diethylamino)ethyl]-6-hydrazinopurine (Xb). A solution of aqueous hydrazine (0.26 g., 60%) and 9-[2-(diethylamino)ethyl]-6-chloropurine (0.5 g.) dissolved in 20 ml. of water was refluxed for 2 hr. The solution was evaporated to dryness on a steam bath. The crystalline residue was extracted with two 40-ml. portions of chloroform. The extract after being dried over anhydrous magnesium sulfate for 1 hr. was evaporated to dryness. Light brown needles crystallized from the viscous residue on cooling, yield, 0.4 g. (81%), m.p. 126–131°. The crude product was recrystallized from benzene with activated charcoal to give colorless needles, yield, 0.31 g. (63%), m.p. 133–134°.

Anal. Calcd. for $C_{11}H_{19}N_7$: C, 53.00; H, 7.68; N, 39.32. Found: C, 52.61; H, 7.60; N, 39.96.

9-[2-(Diethylamino)ethyl]-6-methylaminopurine (Xc). A glass pressure bottle which contained 30 ml. of aqueous methylamine (40%) and 0.5 g. of 9-[2-(diethylamino)ethyl]-6-chloropurine was heated in a steam bath for 3 hr. and the solution was evaporated to dryness. On cooling the viscous residue, light yellow needles separated. The solid mixture was extracted with chloroform (60 ml.) and the extract was evaporated to dryness. The residue was recrystallized with activated charcoal from absolute ethanol to give colorless needles, yield, 0.23 g. (47%), m.p. 134–135°.

Anal. Calcd. for $C_{12}H_{20}N_6$: C, 58.04; H, 8.12; N, 33.84. Found: C, 58.50; H, 8.08; N, 33.96.

9-[2-(Diethylamino)ethyl]-6-ethylaminopurine dihydrochloride (Xd). A mixture of aqueous ethylamine (70%) and 1.6 g. of 9-[2-(diethylamino)ethyl]-6-chloropurine in a glass pressure bottle was heated on a steam bath overnight (about 20 hr.). The reaction mixture was evaporated to dryness on a steam bath. The light yellow residue was extracted with 100 ml. of chloroform. The chloroform extract after being dried over anhydrous magnesium sulfate for 1 hr. was distilled to dryness. To the viscous residue, 70 ml. of absolute ethanol was added. Hydrogen chloride gas was passed through the solution and a large amount of white crystalline solid separated. The crude product was filtered and dried, yield, 1.32 g. (66%), m.p. 260–268°. A portion of the crude product was recrystallized from 85% aqueous ethanol to give white needles, m.p. 267–270°.

Anal. Calcd. for $C_{13}H_{22}N_6.2HCl$: C, 46.56; H, 7.22; N, 25.07; Cl, 21.15. Found: C, 46.61; H, 7.07; N, 25.22; Cl, 20.81.

9-[2-(Diethylamino)ethyl]-6-furfurylaminopurine dihydrochloride (Xe). Furfurylamine (0.4 g.) and 9-[2-(diethylamino)ethyl]-6-chloropurine (0.52 g.) in 30 ml. of 1-butanol were refluxed for 6 hr. and distilled to dryness under reduced pressure. The residue was extracted with 60 ml. of anhydrous ether with constant scratching and stirring. The granular solid furfurylamine hydrochloride which was suspended in the ether extract was removed by filtration. The filtrate was distilled to dryness. The viscous residue was dissolved in 30 ml. of absolute ethanol and hydrogen chloride gas was passed through for a few minutes. Tan needles separated as the ethanolic solution was kept overnight in a refrigerator. The crude product was filtered and dried in a desiccator; yield, 0.28 g. (35%), m.p. 208–220°. The crude product was recrystallized three more times from absolute ethanol to give white needles, m.p. 241°, yield, 0.2 g. (25%).

Anal. Calcd. for $C_{16}H_{22}N_6O.2HCl$: C, 49.61; H, 6.25; N, 21.70; Cl, 18.31. Found: C, 48.71; H, 6.64; N, 21.80; Cl, 17.97.

9-[2-(Diethylamino)ethyl]-6-benzylaminopurine dihydrochloride (Xf). Benzylamine (0.36 g.) and 9-[2-(diethylamino)-ethyl]-6-chloropurine (0.42 g.) dissolved in 20 ml. of 2-ethoxyethanol, were refluxed for 1 hr. and distilled under reduced pressure to dryness. To the residue, 20 ml. of water was added. The resultant aqueous solution was extracted with 60 ml. of benzene. The benzene solution, after being dried over anhydrous magnesium sulfate for an hour, was distilled to dryness under reduced pressure. To the residue, 20 ml. of absolute ethanol was added and the alcoholic solution was made acidic by passing in hydrogen chloride gas for a few minutes. Upon standing overnight in the refrigerator, the white crystalline needles which separated out of the dark brown solution were filtered and dried; yield, 0.19 g. (30%), m.p. 220–223°. The crude product was recrystallized from absolute ethanol to give white needles, m.p. 223–224°.

Anal. Calcd. for $C_{18}H_{24}N_6.2HCl$: C, 54.41; H, 6.59; N, 21.15; Cl, 17.85. Found: C, 54.40; H, 6.58; N, 21.10; Cl, 17.85.

9-[2-(Diethylamino)ethyl]purine dihydrochloride (XI). A solution of 0.3 g. of 9-[2-(diethylamino)ethyl]-6-chloropurine in a 1:1 mixture of ethanol-water (40 ml.) containing 10% palladium on charcoal catalyst (0.2 g.) and 0.2 g. of magnesium oxide was hydrogenated at 40 lb./in.^{2} for 2 hr.

The hydrogenation was complete within 2 hr. and the catalyst was removed by filtration. The filtrate was evaporated to dryness and the residue was redissolved in 40 ml. of water and made alkaline with concd. ammonium hydroxide. The aqueous solution was then extracted with chloroform. The chloroform solution, after being dried over anhydrous magnesium sulfate, was filtered and distilled to dryness. The residue was dissolved in 25 ml. of absolute ethanol. Hydrogen chloride gas was passed through the alcoholic solution for a few minutes. Light brown needles separated upon cooling the solution in the refrigerator; yield, 0.16 g. (46.5%), m.p. 178–182°. The crude product was recrystallized from absolute ethanol to give tan needles, m.p. 179–182°.

Anal. Calcd. for $C_{11}H_{17}N_6.2HCl$: C, 45.21; H, 6.55; N, 23.97; Cl, 24.27. Found: C, 44.59; H, 6.38; N, 24.42; Cl, 24.00.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Phenazine Syntheses. X.[1a] 2,8-Disubstituted Phenazines Made as Intermediates for New Vital Stains, Together with Two New Vital Stains Related to Neutral Red

DONALD L. VIVIAN,[1b] RICHARD M. HOGART, AND MORRIS BELKIN

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The synthesis and some of the properties of a homologous series of 2-alkylamino-8-chlorophenazines are described, together with the preparation of 2,8-dibromophenazine and two new vital stains related to neutral red: 2-methylamino-8-*n*-propylaminophenazine, and 2,8-bis(methylamino)-3-methylphenazine.

Earlier work[2,3] had shown that 2,8-diaminophenazines, when converted to their hydrochlorides or other salts, possessed the property of "localized" or "particulate" staining of living cells,[4] such as is exhibited by Neutral Red, which is the hydrochloride of 2-amino-8-dimethylamino-3-methylphenazine. It was likewise shown that this ability to act as a vital stain was peculiar to these 2,8-disubstituted phenazines, and was not possessed by their 2,7-disubstituted analogs. (In the report which follows, the free bases alone will be described, with the understanding that it is the hydrochloride or similar salt that actually produces the vital staining.)

It was originally proposed, therefore, to prepare a series of 2,8-bis(alkylamino)phenazines, in order to study their vital staining ability, as well as their other properties. The planned method of preparation involved replacement of both halogens of 2,8-dihalophenazines by amino or alkylamino groups, using the same method of relatively high-temperature sealed-tube reactions as was earlier found feasible with monohalogenated phenazines.[3] When primary alkylamines were used in this procedure, however, it was found that the results were not completely satisfactory with 2,8-dichlorophenazine, for a mixture of difficultly separable compounds always resulted. The chief reasons for the multiplicity of products are probably the following: (1) The greater activity of the secondary amines which result from replacement of the first chlorine. (2) Instability of some of the reaction products at the relatively high temperatures necessary for replacement of the second chlorine. (3) The tenacity with which a small portion of the chlorine is retained, possibly due to complex formation.

Because of these complex mixtures resulting from the higher temperature reactions necessary with the dichloro compounds, complete purification has been achieved only with two 2,8-bis(alkylamino) phenazines. This paper, therefore, deals chiefly with products in which only one of the two chlorines has been replaced. These are readily obtained from the 2,8-dichlorophenazine by lower-temperature reactions than those which yield the mixtures already referred to, for it has been found that the first chlorine atom can be replaced at a much lower temperature than is required to replace the second one. Thus, replacement of the first chlorine by the more reactive amines, such as methylamine, can be effected by long reaction at as low a temperature as 100°.

In later work it is planned to proceed with the original idea of making a series of both symmetrically and unsymmetrically substituted 2,8-bis-(alkylamino) phenazines, attempting to overcome some of the difficulties encountered with 2,8-dichlorophenazine by taking advantage of the greater reactivity of the bromine atoms in the 2,8-dibromophenazine described below, as well as by determining whether long-continued reaction will ultimately result in complete replacement of all of the chlorine in 2,8-dichlorophenazine. It is also planned to study the action of secondary amines on 2,8-dihalophenazines.

(1)(a) Paper IX. *J. Org. Chem.*, 21, 1188 (1956).

(1)(b) Present address: College of Pharmacy, University of Arizona, Tucson, Ariz.

(2) D. L. Vivian and M. Belkin, *Nature*, 178, 154 (1956).

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TABLE I

PREPARATION OF CRUDE 2-ALKYLAMINO-8-CHLOROPHENAZINES

	From		Temp. of Bomb Furnace	Duration of Heating	Yield of Crude, %
	2,8-Dichlorophenazine,	1.5 g.			
A	Sodium acetate, anhydrous	1.5 g.	98–105°	160 hr.	25 (0.25 g.)
	Methylamine, 40% aqueous solution	15 cc.			
	2,8-Dichlorophenazine,	1.5 g.			
A	Sodium acetate, anhydrous	1.5 g.	98–105°	300 hr.	40 (0.40 g.)
	Methylamine, 40% aqueous solution	15 cc.			
	2,8-Dichlorophenazine,	10 g.			
A	Sodium acetate, anhydrous	10 g.	98–105°	300 hr.	50 (4.87 g.)
	Methylamine, 40% aqueous solution	100 cc.			
	2,8-Dichlorophenazine,	2.5 g.			
B	Sodium acetate, anhydrous	2.5 g.	98–105°	320 hr.	35 (0.91 g.)
	Ethylamine, 66% aqueous solution	25 cc.			
	2,8-Dichlorophenazine	2.5 g.			
C	Sodium acetate, anhydrous	2.5 g.	180°	22 hr.	56 (1.54 g.)
	n-Propylamine, aqueous solution, approximately 30%	25 cc.			
	2,8-Dichlorophenazine	2.5 g.			
C	Sodium acetate, anhydrous	2.5 g.	195°	24 hr.	43 (1.16 g.)
	n-Propylamine	10 cc.			
	2,8-Dichlorophenazine	2.5 g.			
D	Sodium acetate, anhydrous	2.5 g.	180°	22 hr.	67 (1.82 g.)
	Isopropylamine, aqueous solution, approximately 30%	25 cc.			
	2,8-Dichlorophenazine	2.5 g.			
E	Sodium acetate, anhydrous	2.5 g.	167–170°	40 hr.	10 (0.29 g.)
	n-Amylamine	12.5 cc.			
	2,8-Dichlorophenazine	2.5 g.			
E	Sodium acetate, anhydrous	2.5 g.	195–199°	24 hr.	42 (1.27 g.)
	n-Amylamine	12.5 cc.			
	2,8-Dichlorophenazine	2.5 g.			
F	Sodium acetate, anhydrous	2.5 g.	195–198°	24 hr.	42 (1.32 g.)
	n-Hexylamine	6 cc.			
	2,8-Dichlorophenazine	2.5 g.			
G	Sodium acetate, anhydrous	2.5 g.	198–205°	24 hr.	54 (1.77 g.)
	n-Heptylamine	9 cc.			

TABLE II

PROPERTIES AND ANALYSES OF PURE 2-ALKYLAMINO-8-CHLOROPHENAZINES[a]

	Compound	Crystalline Form and Color	M.P.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
A	2-Chloro-8-methylaminophenazine	Dull red microcrystals	254–255	$C_{13}H_{10}ClN_3$[c]	64.1	64.0	4.13	4.26
B	2-Chloro-8-ethylaminophenazine	Brownish red microcrystals	210–211	$C_{14}H_{12}ClN_3$	65.3	65.1	4.69	4.86
C	2-Chloro-8-*n*-propylaminophenazine	Orange-red microcrystals	190–191	$C_{15}H_{14}ClN_3$	66.4	66.5	5.16	5.42
D	2-Chloro-8-isopropylaminophenazine	Brownish red plates	170–171	$C_{15}H_{14}ClN_3$	66.4	66.7	5.16	5.40
E	2-*n*-Amyl-8-chlorophenazine	Dull red microcrystals	140–142	$C_{17}H_{18}ClN_3$	68.1	67.8	6.05	6.24
F	2-Chloro-8-*n*-hexylaminophenazine	Dark red prisms	161–162[d]	$C_{18}H_{20}ClN_3$	68.9	69.1	6.42	6.75
G	2-Chloro-8-*n*-heptylaminophenazine	Aggregates of orange microcrystals	108–109	$C_{19}H_{22}ClN_3$	69.6	69.9	6.76	6.74

[a] All were recrystallized from *n*-heptane. [b] Corrected. [c] Additional analysis: Cl, Calcd.: 14.54; Found: 14.52. [d] Verified by melting point repetition.

The preparation of all the dihalophenazines described herein was effected by the usual ring-closure through the nitro group.[5] It was originally planned to synthesize 2,8-bis(alkylamino)phenazines with two different alkylamino groups by taking advantage of the greater lability of an iodo-group, and 2-chloro-8-iodophenazine was hence prepared, as described below. Use of this compound proved to be unnecessary when it was found

(5) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, 14, 289 (1949).

that the two chlorine atoms of 2,8-dichlorophenazine differed greatly in reactivity, as already mentioned. Another compound described below, 5,5′-dichloro-2′-methoxy-2-nitrodiphenylamine was also found to be superfluous. It was prepared as a proposed intermediate for 2,8-dichlorophenazine because it had been found that when halogen was *ortho* or *para* to the imino group of 2-nitrodiphenylamine, as in 4′-chloro-2-nitrodiphenylamine, for example, a portion of the halogen was lost on ring closure, and the resulting mixture of unsubstituted phenazine with monohalophenazine was extremely difficult to purify.[6] Such a mixture has now been found not to form when 4,4′-dichloro-2-nitrodiphenylamine is subjected to ring closure; in this instance no chlorine is lost in the ring closure.

EXPERIMENTAL

2-Chloro-8-iodophenazine. (a) *5′-Chloro-5-iodo-2′-methoxy-2-nitrodiphenylamine.* A mixture of 14.7 g. of 1,2-dinitro-4-iodobenzene[7] and 31.5 g. of 5-chloro-2-anisidine was melted, with stirring, and heating and stirring were continued for about 40 hr. at 55–60°. The mixture resulting was then steam-distilled until no more product passed over, leaving a semi-solid residue weighing 25.5 g. after drying. Repeated recrystallization from 70% alcohol (Norit), gave reddish-orange microcrystals, melting at 152–154°.[8]

Anal.[9] Calcd. for $C_{13}H_{10}ClIN_2O_3$: C, 38.6; H, 2.49. Found: C, 38.6; H, 2.74.

(b) *2-Chloro-8-iodophenazine.* There was heated in an open flask immersed in an oil-bath at 260–265°, an intimate mixture of 1.5 g. once-recrystallized 5′-chloro-5-iodo-2′-methoxy-2-nitrodiphenylamine, 2.2 g. of ferrous oxalate dihydrate, and 22.5 g. of granulated lead. The internal temperature rose to a maximum of 273° within 12 min., then after 1 min. the temperature began to drop, and the flask was withdrawn from the bath. Sublimation from the entire reaction mixture at 0.01 mm., from a bath at 265–275°, gave 0.2 g. of product. Recrystallized from benzene, this gave pale yellow needles, melting at 157–159°.

Anal. Calcd. for $C_{12}H_6ClIN_2$: C, 42.3; H, 1.76. Found: C, 42.2; H, 1.78.

Elimination of the methoxy group follows the usual course of the general reaction, in which 2′-alkoxy groups are always eliminated in preference to hydrogen.[10]

5,5′-Dichloro-2′-methoxy-2-nitrodiphenylamine. A solution of 40.6 g. of 4-chloro-1,2-dinitrobenzene[11] and 94.6 g. of 5-chloro-2-anisidine in 500 cc. of alcohol was refluxed for 66 hr., and then distilled with steam until no more material passed over. There remained a residue of about 60 g. of nearly black, somewhat soft material. Recrystallization from alcohol gave about 25 g. of brick-red product. Two more recrystallizations from alcohol gave small orange rods, melting at 148–149°.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_3$: C, 49.9; H, 3.22. Found: C, 49.9; H, 3.39.

2,8-Dichlorophenazine. The intermediate 4,4′-dichloro-2-nitrodiphenylamine was prepared by Blom[12] using amyl alcohol as solvent. In the present work, a mixture of 3000 g. of *p*-chloroaniline, 4500 g. of 2,5-dichloronitrobenzene, and 4700 g. of sodium acetate was heated for 18 hr. in an oil bath at 200–220°. After steam distillation of all volatile material, the product on air-drying weighed 5300 g., and was used without further purification. When 100 g. of this crude material was intimately mixed with 1000 g. of granulated lead, and the mixture stirred by hand while being heated in an open beaker immersed in an oil bath at 250–260°, strong fumes were emitted. (Condensation of these fumes proved not worthwhile, as relatively little product was recovered.) Vacuum sublimation from the whole reaction mixture at about 0.01 mm. from an oil bath at 250–260° gave 20 g. of crude 2,8-dichlorophenazine.

When 160 g. of this crude was recrystallized from benzene, there was obtained 60 g. of pure 2,8-dichlorophenazine,[13] melting at 232–234°.

Anal. Calcd. for $C_{12}H_6Cl_2N_2$: C, 57.9; H, 2.43; Cl, 28.4. Found: C, 57.8; H, 2.54; Cl, 28.3.

Recrystallizing the intermediate before closing the ring, as well as using a mixture of ferrous oxalate dihydrate and lead, instead of lead alone, did not give a yield sufficiently larger to compensate for the additional time and material required.

2,8-Dibromophenazine. The intermediate 4,4′-dibromo-2-nitrodiphenylamine[14] was synthesized by heating a mixture of 50 g. of 2,5-dibromonitrobenzene, 60 g. of *p*-bromoaniline, and 50 g. of anhydrous sodium acetate for 18 hr. in an oil bath at 175–180°. The residue after exhaustive steam distillation and washing with water weighed about 60 g., and melted at 140–145°. This crude material was used for the preparation of the phenazine without further purification. A mixture of 16.0 g. of the crude material, 20.8 g. of ferrous oxalate dihydrate, and 240 g. of granulated lead was heated for 9.5 min. in an oil bath at 260–265°, during which the internal temperature rose to a maximum of 266°. Sublimation from the entire reaction mixture at about 0.01 mm., with the oil bath at about 250–260°, gave 4.2 g. of crude product. This, when recrystallized from 75 cc. of benzene gave 2.6 g. of lemon-yellow platelets, melting at 226–228°.

Anal. Calcd. for $C_{12}H_6Br_2N_2$: C, 42.6; H, 1.79. Found: C, 42.5; H, 1.92.

Unlike the 2,8-dichlorophenazine, this 2,8-dibromophenazine could not be prepared satisfactorily by the use of lead alone, for when the ferrous oxalate was omitted the internal temperature rose to a maximum of 360° (external bath at 250°), and only 0.41 g. of very crude material was obtained from 5.0 g. of intermediate and 50 g. of granulated lead.

2,8-Bis(methylamino)-3-methylphenazine. a. *4-Bromo-4′-chloro-5-methyl-2-nitrodiphenylamine.* A mixture of 40 g. each of 2,5-dibromo-4-nitrotoluene[15] *p*-chloroaniline, and anhydrous sodium acetate was heated for 18 hr. in an oil bath at 210–220°. Complete steam distillation and washing with water gave 43 g. of brownish-red product. Twice recrystallized from alcohol, this formed small orange needles, melting at 160–161°.

Anal. Calcd. for $C_{13}H_{10}BrClN_2O_2$: C, 45.2; H, 3.14. Found: C, 45.8; H, 3.18.

b. *2-Bromo-8-chloro-3-methylphenazine.* A mixture of 2.0 g. of the crude, unrecrystallized 4-bromo-4′-chloro-5-methyl-2-nitrodiphenylamine, 2.6 g. of ferrous oxalate dihydrate and 30 g. of granulated lead was heated in an oil bath at 260–270° until the internal temperature reached a maximum of 255°. This required 10 min. Sublimation at about 0.01 mm. from the same oil bath gave 0.49 g. of product.

(6) D. L. Vivian and J. L. Hartwell, *J. Org. Chem.*, **18**, 1065 (1954).

(7) F. Ullmann, *Ber.*, **34**, 2179 (1902).

(8) All melting points given by the authors are corrected.

(9) Microanalyses by the Microanalytical Laboratories of the National Institutes of Health, under the direction of Dr. W. C. Alford.

(10) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 291 (1949).

(11) H. F. J. Lorang, *Rec. trav. chim.*, **47**, 187 (1928).

(12) A. V. Blom, *Helv. Chim. Acta*, **4**, 1038 (1921).

(13) P. V. Chernetskii and A. I. Kiprianov, *Zhur Obscheĭ Khim.*, **23**, 1743 (1953); H. Otomasu, *Pharm. Bull Japan*, **3**, 365 (1955).

(14) British patent **738,013** (1955).

(15) J. B. Cohen and H. D. Dakin, *J. Chem. Soc.*, **79**, 1130 (1901).

Recrystallized from benzene, this gave yellow needles melting at 223–225°.

Anal. Calcd. for $C_{13}H_8BrClN_2$: C, 50.8; H, 2.62. Found: C, 50.9; H, 2.83.

c. *2,8-Bis(methylamino)-3-methylphenazine.* In a bomb tube was put a mixture of 0.88 g. recrystallized 2-bromo-8-chloro-3-methylphenazine, 4 cc. of a 40% aqueous solution of methylamine, and about 0.1 g. of cuprous chloride. The tube was sealed and heated about 20 hr. in a bomb oven at 170°. A very dark red solid resulted, which was extracted in a Soxhlet apparatus with a minimum of benzene, and the resulting solution put through a column of basic alumina 14 mm. in diameter by 140 mm. in length. Three zones resulted: a black layer on top, a dark red zone in the middle, and a lighter red zone on the bottom. The black portion was removed by spatula, and the bottom zone eluted with benzene. Soxhlet extraction of the middle dark red zone with ether, followed by evaporation of the latter, gave 0.1 g. of reddish-brown microcrystals. These melted, with gradual decomposition, at 205–210°. Because no good solvent for recrystallization was found, the product was analyzed directly.

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.4; H, 6.39. Found: C, 71.6; H, 6.36.

This compound was dissolved in dilute hydrochloric acid, and the solution diluted to a concentration of 1 to 40,000 with Hank's basal salt solution, to provide a properly buffered saline medium for living cells. When the *p*H was adjusted to 7.2 by the addition of sodium hydroxide, the resultant solution stained Sarcoma 37 ascites tumor cells very well, in the same manner as is shown by neutral red, and with little indication of toxicity.

2-Methylamino-8-n-propylaminophenazine. (a) *2-Chloro-8-n-propylaminophenazine.* A mixture of 2.5 g. of 2,8-dichlorophenazine (recrystallized, and ground to pass an 80-mesh sieve), 2.5 g. of anhydrous sodium acetate, and 10 cc. of *n*-propylamine was heated for 24 hr. in a sealed tube, in a bomb oven at 195°. The contents of the tube were dried on the steam bath, and then put into benzene solution by Soxhlet extraction. Passage through a column of basic alumina 37 mm. in diameter by 165 mm. long gave three zones, plus a small black layer at the top. The product desired was in the middle zone, dark purple in color. This zone was mechanically separated, and exhausted by Soxhlet extraction with ether. Evaporation of the ether gave 1.16 g. of dark red product. When this was recrystallized from 75% methanol it formed orange-red microcrystals, melting at 190–191°.

Anal. Calcd. for $C_{15}H_{14}ClN_3$: C, 66.4; H, 5.16. Found: C, 66.5; H, 5.42.

(b) *2-Methylamino-8-n-propylaminophenazine.* An intimate mixture was made of 0.45 g. of recrystallized and finely ground 2-chloro-8-*n*-propylaminophenazine and 0.45 g. of anhydrous sodium acetate, and to this was added 10 cc. of a 40% solution of aqueous methylamine. The whole was sealed in a bomb tube, and heated for 16 hr. in a bomb furnace 174–178°. The same procedure as above gave three zones on basic alumina, plus a small dark upper band. Mechanical separation of the bottom, nearly black zone, followed by extraction of it with ether, and evaporation of the solvent, gave 0.12 g. of deep-red microcrystals, melting at 155–160°, with decomposition. This material resisted all attempts at recrystallization, and was hence analyzed directly.

Anal. Calcd. for $C_{15}H_{18}N_4$: C, 72.7; H, 6.80. Found: C, 72.3; H, 6.93.

This compound, when treated in the same manner as already detailed for 2,8-bis(methylamino)-3-methylphenazine, stained ascites tumor cells similarly.

2-Alkylamino-8-chlorophenazines. In general, these compounds were prepared by bomb tube reactions carried out as with the 2-chloro-8-*n*-propylaminophenazine already described, starting in all instances with 2,8-dichlorophenazine, recrystallized and ground to pass an 80-mesh screen. It was found, though, that the methyl- and ethylamines were so much more reactive than their higher homologs that replacement of the first chlorine of the 2,8-dichlorophenazine could be carried out at 100°, while the amines from propyl on up required a considerably higher temperature. The time required was not carefully determined, but was judged roughly by the appearance of the bomb tube contents as time went on. Elimination of the unused portion of the amine after the reaction's completion was carried out by washing with water for the amines up to *n*-amylamine, and by steam distillation for higher homologs. All separations were carried out by extracting the whole reaction mixture with benzene in a Soxhlet apparatus, chromatographing the resulting solutions on basic alumina, separating the darkest red zone mechanically, and isolating the product by extraction of this zone with ether. The crude 2-alkylamino-8-chlorophenazines were then recrystallized from *n*-heptane. It was found that sodium acetate gave better results than did ammonium acetate, cupric acetate, or no catalyst at all, and so a weight of sodium acetate equal to that of the 2,8-dichlorophenazine was arbitrarily taken when the dichloro compound was heated with the various primary amines. The following tables summarize the results. The first table gives the yields of crude products, and shows some variations in yield obtained by such changes in reactions conditions as different temperatures, different lengths of heating, and use of anhydrous or aqueous amine. All reactions with the same amine were marked by the same letter. The second table deals with the properties and analyses of the pure monoalkylamines.

BETHESDA 14, MD.

[COMMUNICATION NO. 2092 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

The Structure of Certain Polyazaindenes. VII. 4-Amino-6-methyl-1,3,3a,7-tetrazaindene and Its Derivatives[1a]

G. A. REYNOLDS AND J. A. VANALLAN

Received June 2, 1960

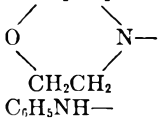
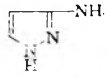
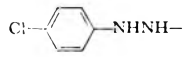
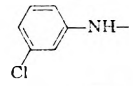
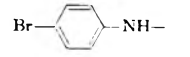
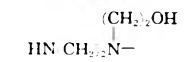
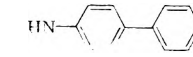
The synthesis of a number of new amino tetrazaindenes is described.

In connection with the determination of structure of some tetrazaindenes,[1b] we had occasion to synthesize a number of 4-aminotetrazaindenes. These amines were synthesized by reaction of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene (I) and the

(1a) The name of J. A. VanAllan as co-author of Part V in this series [*J. Org. Chem.*, 25 361 (1960)] was inadvertently omitted.

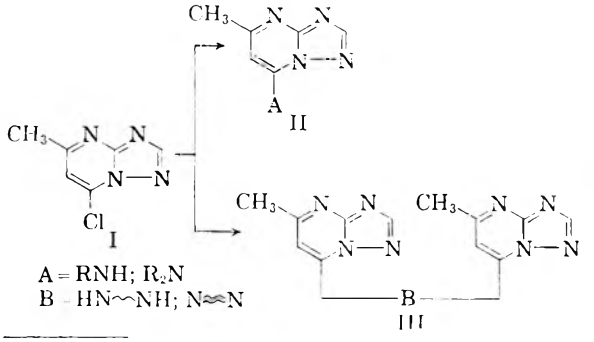
TABLE I

4-AMINO-1,3,3a,7-TETRAZAINDENES

	A;B	M.P.	Method of Preparation	Solvent for Recrystallization	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %
IIa	C_2H_5NH—	147	B	Ethanol	54.2	6.2	39.6	54.6	6.1	39.6	94
IIb		162	A	Benzene-ligroin	54.8	5.9	31.9	55.2	6.2	31.7	96
IIc	C_6H_5NH—	188	C	Benzene	64.1	4.9	31.1	64.0	4.8	30.7	65
IId	$HClNH_2(CH_2)_2NH$—[a]	196–198	C	Benzene-ethanol	42.1	5.7		41.8	5.9		20
IIe	H_2NNH—	276–278	A	Ethanol	43.8	4.9	51.2	43.9	4.8	51.3	55
IIf	$CH_3C_6H_4SO_2NHNH$—	240	D	Ethanol	49.2	4.4		49.4	4.4		82
IIg		315	E	Dimethylformamide			51.8			51.5	61
IIh		265	C	Ethoxyethanol	55.5	3.9	27.0	55.1	4.2	27.1	93
IIi[b]		228	C	Ethanol	55.5	3.9	27.0	55.6	4.1	27.0	65
IIj		211	C	Ethanol	61.2	5.1	27.4	61.0	5.2	27.7	60
IIk		265	C	Ethanol	47.4	3.2	23.0	47.9	3.5	23.3	89
III	$C_{12}H_{25}NH$—	65	C	Benzene-ligroin	68.2	9.8	22.1	68.2	9.8	22.1	64
IIIa	$HN(CH_2)_2NH$[a]	330	C	Dimethylformamide	51.8	4.9		51.3	5.2		91
IIIb	$HN(CH_2)_6NH$	242	C	Ethanol	56.8	6.3		56.8	6.8		63
IIIc		325	C		54.8	5.1	40.1	54.5	5.5	40.2	91
IIId		236–238	C	Dimethylformamide	52.2	5.4	38.0	52.6	5.8	38.2	86
IIIe		305	C	Dimethylformamide	64.3	4.5	31.3	64.0	4.8	31.3	57

[a] IIIa separated from the reaction mixture on cooling and IId was obtained by evaporation of the reaction solvent. [b] *o*-Choroaniline failed to react by this procedure.

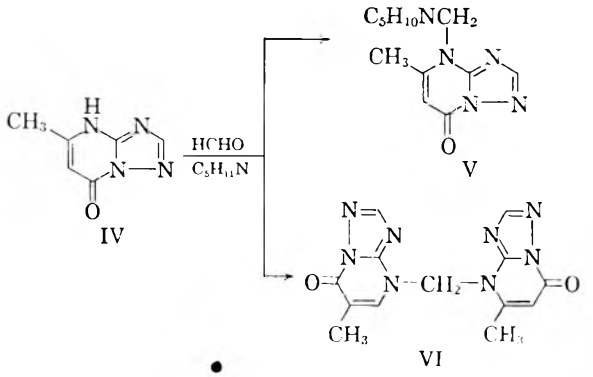
appropriate amine, as indicated below. The only anomaly was the reaction of asymmetrical dimethylhydrazine with I; this gave a product that had an analysis corresponding to 4-methylhydrazino-6-methyl-1,3,3a,7-tetrazaindene. The initial reaction was probably the quaternization of the dimethylhydrazine, followed by the elimination of methyl chloride.



(1b) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, 24, 792 (1959).

The physical properties, method of preparation, yield, and analytical data for these derivatives are collected in Table I.

With a view to obtaining amino derivatives of the tetraazaindene series in which the amino group is not directly attached to the ring, 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (IV) was treated with formaldehyde and piperidine. The two products of this reaction were assumed to be 6-methyl-7-



piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene (V), and bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)-methane (VI). The reaction was not investigated further.

EXPERIMENTAL

Method A. A mixture of 1 equivalent of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene[1b] (I), 3 equivalents of the amine, and ten parts by volume of ethanol was refluxed for 2 hr., and then cooled. The solid was either collected or the reaction mixture evaporated to dryness, depending on the solubility of the product in ethanol.

Method B. It was carried out in the same manner as Method A except that the reactants were allowed to stand at room temperature for 2 hr., rather than being refluxed.

Method C. A mixture of 1 equivalent of I, 1 equivalent of the amine, and 1.5 equivalents of triethylamine in ten parts by volume of ethanol was refluxed 2 hr. and then evaporated to dryness.

Method D. Acetonitrile was employed in place of ethanol in Method A.

Method E. Equivalent amounts of I, amine, and sodium bicarbonate in seven parts by volume of nitrobenzene were refluxed 2 hr. and the solid was collected and washed with water and ether.

6-Methyl-7-piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene. Piperidine (2.8 g.) was dissolved in 2.5 ml. of 40% formalin. After the exothermic reaction had subsided, 4.5 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (IV) was added, followed by the addition of 25 ml. of ethanol. After a 1-min. reflux, solution was complete; in 10 min., a white precipitate settled out. Reflux was continued for 30 min. more. After cooling, the product was collected and then crystallized from alcohol to give 4 g. of V, m.p. 230°.

Anal. Calcd. for $C_{12}H_{17}ON_5$: C, 58.2; H, 6.9. Found: C, 58.7; H, 6.9.

In one run, an insufficient quantity of piperidine was used and a product which had an analysis corresponding to bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)methane (VI), m.p. 310°, was obtained.

Anal. Calcd. for $C_{13}H_{12}O_2N_8$: C, 50.0; H, 3.9; N, 35.9. Found: C, 50.5; H, 4.0; N, 35.7.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DYSON-PERRINS LABORATORY]

Synthetic Furocoumarins. I. A New Synthesis of Methyl-substituted Psoralenes and Isopsoralenes

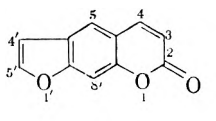
KURT D. KAUFMAN[1,2]

Received May 13, 1960

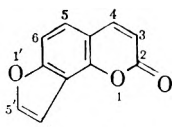
Three methyl-substituted psoralenes and two methyl-substituted isopsoralenes have been synthesized by a new method from *o*-allyl-7-hydroxycoumarins by acetylation, bromination, and cyclization in a basic medium. 7-Allyloxycoumarins undergo Claisen rearrangement to 8-allyl-7-hydroxycoumarins, which lead to methylated isopsoralenes. 7-Allyloxy-8-methylcoumarins rearrange to 6-allyl-7-hydroxy-8-methylcoumarins, which produce methylated psoralenes. 3-Allyloxyphenyl acetate gives a mixture of 2-allylresorcinol and 4-allylresorcinol on Claisen rearrangement followed by hydrolysis. The latter compound was converted to a dimethylpsoralene.

Naturally occurring furocoumarins have recently attracted attention because several of them alter the response of human skin to ultraviolet radiation.[3] In particular, xanthotoxin (8-methoxypsoralene) has been used clinically to prevent sun burning, to encourage sun tanning, and in the treatment of vitiligo.[3] Its effect on ultraviolet carcinogenesis has also been studied.[3,4] The erythema inducing activity of several synthetic furocoumarins has been studied in an effort to understand their biological mechanism of action.[5] The photosensitization of bacteria by a variety of furocoumarins (including some synthetic compounds) has also been reported.[6]

Several furocoumarin nomenclatures are currently in use and this has occasionally led to confusion.[7] Throughout this and later papers, structure I shall be designated psoralene and shall be numbered as shown, which is in accordance with the recommendation of the Food and Drug Administration.[7] Structure II shall be designated isopsoralene with a similar numbering system.[8]



I



II

(1) Present address: Department of Chemistry, Kalamazoo College, Kalamazoo, Mich.

(2) This investigation was made possible by the interest and advice of Sir Robert Robinson and by the support provided by a Fulbright Grant administered by the United States Educational Commission in the United Kingdom.

(3) Psoralenes and radiant energy, proceedings of a symposium. *J. Invest. Dermatol.*, **32**, 131-391 (1959).

(4) M. A. O'Neal and A. C. Griffin, *Cancer Research*, **17**, 911 (1957).

(5) (a) M. A. Pathak and T. B. Fitzpatrick, *J. Invest. Dermatol.*, **32**, 255 and 509 (1959); M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *ibid.*, **35**, 165 (1960); (b) L. Musajo, *Farmaco (Pavia) Ed. sci.*, **10**, 3 (1955); L. Musajo, G. Rodighiero, G. Caporale, and C. Antonello, *Farmaco (Pavia) Ed. sci.*, **13**, 355 (1958).

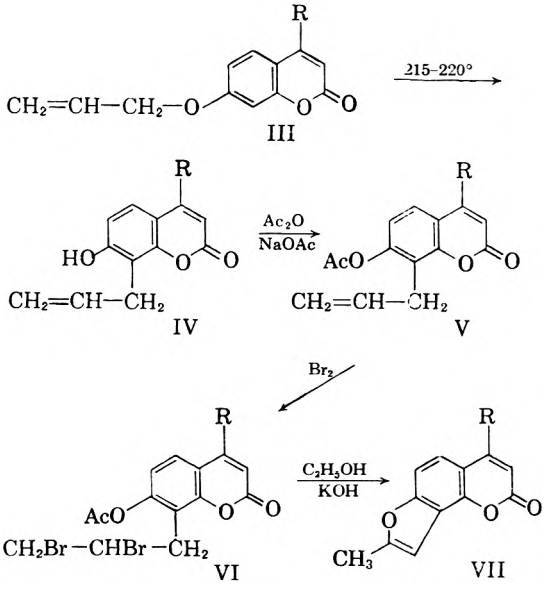
(6) W. L. Fowlks, D. G. Griffith, and E. L. Oginsky, *Nature*, **181**, 571 (1958).

(7) A. C. Curtis, *J. Invest. Dermatol.*, **32**, 133 (1959).

(8) *Chemical Abstracts* prefers δ-lactone of 6-hydroxy-5-benzofuranacrylic acid for I and δ-lactone of 4-hydroxy-5-benzofuranacrylic acid for II, but these names are not in common usage.

With a few exceptions, reported syntheses of furocoumarins have followed two general patterns. Most isopsoralenes and some psoralenes have been prepared from *o*-formyl- or *o*-acyl-7-hydroxycoumarins in three or four steps.[9] Although the latter steps usually run smoothly and give high yields, the *o*-formyl-7-hydroxycoumarins cannot be prepared in good yield and the *o*-acyl-7-hydroxycoumarins are produced by Fries rearrangements, which frequently give mixtures of isomeric products. The other general method is that of Spath,[10a] which has been modified for the synthesis of several psoralenes.[10b] It involves the preparation of dihydropsoralenes from 6-hydroxycoumarans, followed by dehydrogenation. An important disadvantage of this method is the final dehydrogenation step, which frequently gives poor yields.

This paper describes a new synthesis, involving *o*-allyl-7-hydroxycoumarins as intermediates, which has produced methyl-substituted psoralenes and isopsoralenes in quantities sufficient for biological evaluation[5a,6] and even clinical testing. The method is based on the known[11] conversion of *o*-(β,γ-dibromopropyl)phenyl acetate to 2-methylbenzofuran. Its application to the synthesis of isopsoralenes is illustrated by structures III through VII.



Two compounds, 5′-methylisopsoralene (VII, R = H) and 4,5′-dimethylisopsoralene (VII, R = CH_3), were prepared in this way. The 8-allyl-7-hydroxycoumarins (IV, R = H or CH_3) were obtained by heating 7-allyloxycoumarins (III, R = H or CH_3) at 215° to cause the Claisen rearrangement as described by earlier workers.[12]

In each case, the 7-hydroxy group of IV was acetylated to minimize the possibility of ring bromination during the addition of one equivalent of bromine to the allyl double bond. Finally, the dibromo intermediates (VI, R = H or CH_3) were refluxed for two hours with alcoholic potassium hydroxide to give yields of methylated isopsoralenes (VII, R = H or CH_3) in excess of 50%. Although extensive studies were not carried out, the two-hour reflux period is optimal in the sense that one-hour and three-hour reflux periods resulted in reduced yields.

This method was applied to the synthesis of psoralenes by the use of 7-allyloxycoumarins with a methyl group blocking the reactive 8- position. Rangaswami and Seshadri[13] have already shown that 7-allyloxy-4,8-dimethylcoumarin (X, R = CH_3) rearranges to give 6-allyl-4,8-dimethyl-7-hydroxycoumarin (XI, R = CH_3) in good yield. It was found that 7-allyloxy-8-methylcoumarin (X, R = H) also rearranges smoothly to a 6-allyl derivative (XI, R = H). Both 6-allyl compounds were acetylated, brominated, and cyclized (as in the preparation of isopsoralenes) to give 4,5′,8-trimethylpsoralene (XII, R = CH_3) and 5′,8-dimethylpsoralene (XII, R = H). In the trimethylpsoralene case, the final cyclization step was conducted with sodium ethoxide instead of potassium hydroxide in ethyl alcohol. That modification gave a product which did not require decolorization with charcoal. The reflux time was reduced to one and three quarter hours, with fifteen minutes allowed for cooling, prior to the work-up.

One of the starting materials, 7-hydroxy-8-methylcoumarin (IX, R = H),[14] was prepared by an improved method, which involved condensation of malonic acid with 4-formyl-2-methylresorcinol (VIII)[15] under the conditions described by Vorsatz.[16] The resultant 7-hydroxy-8-methylcoumarin-3-carboxylic acid (IX, R = COOH) lost carbon dioxide to give an over-all 70% yield of 7-hydroxy-8-methylcoumarin, which had m.p. 258–259° instead of the reported[14] 231–232°. As in the preparation of the other 7-allyloxycoumarins,

(9) E. Spath and M. Pailer, *Ber.*, **68B**, 940 (1935); D. B. Limaye and D. D. Gangal, *Rasayanam*, **1**, 15 (1936) and D. B. Limaye, *Rasayanam*, **1**, 187 (1939); D. N. Shah and N. M. Shah, *J. Org. Chem.*, **19**, 1938 (1954); G. Rodighiero and C. Antonello, *Ann. chim. (Rome)*, **46**, 960 (1956); C. Antonello, *Gazz. chim. ital.*, **88**, 415–433 (1958).

(10) (a) E. Spath, B. L. Manjunath, M. Pailer, and H. S. Jois, *Ber.*, **69B**, 1087 (1936). (b) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948) and **72**, 1514 (1950); C. Lagercrantz, *Acta Chem. Scand.*, **10**, 647 (1956); G. Caporale, *Farmaco (Pavia) Ed. sci.*, **13**, 784 (1958).

(11) L. Claisen, *Ann.*, **418**, 69 (1919) and *Ber.*, **53**, 322 (1920).

(12) (a) W. Baker and O. M. Lothian, *J. Chem. Soc.*, 628 (1935). (b) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **13A**, 43–8 (1941).

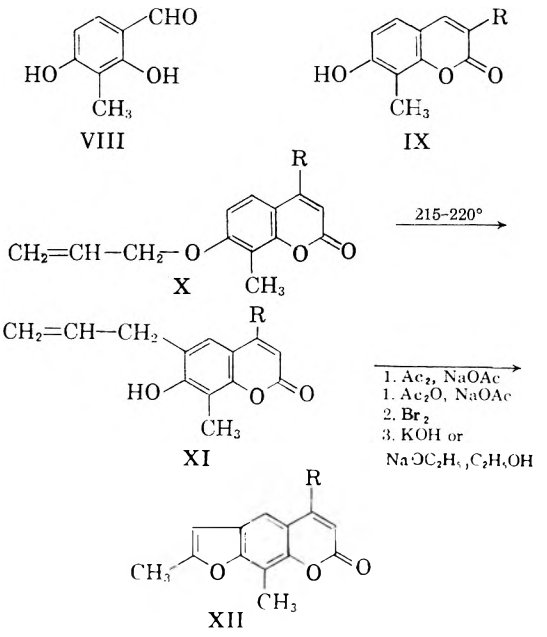
(13) S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **7A**, 8–12 (1938).

(14) T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.*, **14A**, 297 (1941).

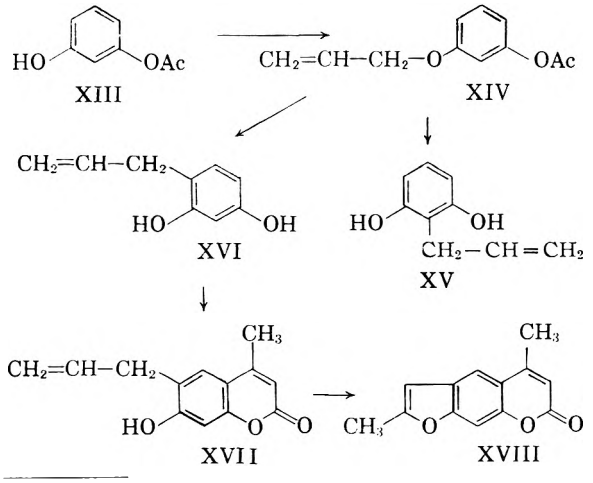
(15) W. Baker, H. F. Bondy, J. F. W. McOmie, and H. R. Tunnicliff, *J. Chem. Soc.*, 2835 (1949).

(16) F. Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936).

which were already known, 7-hydroxy-8-methylcoumarin was treated with allyl bromide and potassium carbonate in acetone to give the unknown compound 7-allyloxy-8-methylcoumarin (X, R = H).



An important disadvantage of the new method, as applied to the synthesis of linear furocoumarins (psoralenes), is the necessity of having 7-allyloxycoumarins with a blocking group to prevent migration of the allyl group to the 8 position during Claisen rearrangement. With partial success, this difficulty has been eliminated by effecting the Claisen rearrangement before forming the coumarin ring system. Resorcinyl monoacetate (XIII) was converted to 3-allyloxyphenyl acetate (XIV) which underwent Claisen rearrangement on refluxing in diethylaniline[17] and, after alkaline hydrolysis, gave an oil, expected to be 4-allylresorcinol (XVI).[18] The oil reacted with ethyl acetoacetate in a Pechmann type condensation to give a mixture of the known[12a] 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3) and its isomer, which must be 6-allyl-7-hydroxy-4-methylcoumarin (XVII). The two isomers were separated, with difficulty, by chromatography on an acid-washed alumina column. It is obvious that the oil is actually a mixture of 2-allylresorcinol (XV) and 4-allylresorcinol (XVI). Further study on the preparation of pure 4-allylresorcinol is in progress. The small quantity of 6-allyl-7-hydroxy-4-methylcoumarin (XVII) actually isolated, was enough to convert to 4,5′-dimethylpsoralene (XVIII) by the method already described.



While the present work was in progress, there was reported[19] the synthesis of a small quantity of isopsoralene by a method involving ozonolysis of 8-allyl-7-hydroxycoumarin (IV, R = H) which further emphasizes the value of *o*-allyhydroxycoumarins as intermediates in the synthesis of furocoumarins.

EXPERIMENTAL

Full details of the four step process of converting a 7-allyloxycoumarin to a furocoumarin are given only once, using the synthesis of 4,5′-dimethylisopsoralene as an example. Other compounds listed were prepared by similar methods, with the exceptions noted.

All melting points in this section are corrected. Microanalyses and spectra analyses were carried out by Drs. Weiler and Strauss, Oxford University, England. Because Pathak and Fellman have demonstrated[20] a relationship between the wave length of light absorption and photosensitizing ability, the ultraviolet maximas and minimas of each furocoumarin are given.

Claisen rearrangement. 8Allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3). Forty-eight g. (0.22 mole) of 7-allyloxy-4-methylcoumarin (III, R = CH_3)[12a] were heated at 215–220° (temperature of reaction mixture) for 2 hr. in a closed vessel. The dark brown mass was dissolved in boiling ethanol, and decolorizing charcoal (*ca.* 5 g.) was added. The hot, filtered ethanol solution was diluted with excess water and a pale yellow precipitate of crude 8-allyl-7-hydroxy-4-methylcoumarin was collected. It weighed, after drying, 45.10 g. (94% yield, m.p. 172–186°) and was suitable for use in the next step, but filtration of an acetone solution through an activated charcoal column, followed by crystallization from ethanol, gave colorless needles, m.p. 198–199° (reported,[12a] m.p. 193–194°). This compound showed a blue fluorescence in aqueous alkali or in concd. sulfuric acid, but a warm ethanol solution gave no color with ferric chloride.

Acetylation. 7-Acetoxy-8-allyl-4-methylcoumarin (V, R = CH_3). A mixture of 45.10 g. (0.175 mole) of crude 8-allyl-7-hydroxy-4-methylcoumarin and a few crystals of fused sodium acetate in 350 ml. of acetic anhydride was heated under reflux for 5 hr. and stirred with water until excess acetic anhydride had decomposed. An insoluble solid was collected by filtration and, after two recrystallizations from methanol, 40.00 g. (74% yield) of colorless needles, m.p. 87–87.5°, were obtained.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.8; H, 5.5.

Bromination. 7-Acetoxy-8-(2′,3′-dibromopropyl)-4-methylcoumarin (VI, R = CH_3). A solution of 16.00 g. (0.1 mole)

(17) L. Claisen, *Ann.*, **418**, 72 (1918).

(18) C. D. Hurd, H. Greengard, and F. D. Pilgrim, *J. Am. Chem. Soc.*, **52**, 1700 (1930).

(19) R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron*, **4**, 256 (1958).

(20) M. A. Pathak and J. H. Fellman, *Nature*, **185**, 382 (1960).

of bromine in 100 ml. of glacial acetic acid was added dropwise to a well stirred solution of 25.80 g. (0.1 mole) of 7-acetoxy-8-allyl-4-methylcoumarin in 200 ml. glacial acetic acid kept at room temperature. The reaction mixture was diluted with water (*ca.* 1 l.) and the yellow tar, which appeared initially, solidified after standing for an hour. A solid (39.50 g., 95% yield, m.p. 148–152°) was collected by filtration and was satisfactory for use in the next step. Three crystallizations from ethanol gave pale yellow prisms, m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.1; H, 3.4; Br, 37.9.

Cyclization. 4,5'-Dimethylisopsoralene (VII, R = CH_3). A solution of 30.00 g. (0.0718 mole) of crude 7-acetoxy-8-(2',3'-dibromopropyl)-4-methylcoumarin and 40.30 g. (0.718 mole) of potassium hydroxide in 1 l. of 95% ethanol was heated under reflux for 2 hr. and concentrated to about one third of its original volume. Water (1.5 l.) was added and the solution was immediately acidified with dilute hydrochloric acid. The next day, a light brown solid was collected by filtration and washed with 5% aqueous ammonia (400 ml.). A chloroform solution of the dried solid was filtered through an activated charcoal column and evaporated to leave a residue which crystallized from 95% ethanol as 9.20 g. (60% yield) of colorless prisms, m.p. 182–183°. Light absorption in methanol: λ_{max} 2500, 2975, log ϵ 4.27, 3.93; λ_{min} 2300, 2750, log ϵ 3.95, 3.66.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.7; H, 4.8.

8-Allyl-7-hydroxycoumarin (IV, R = H). Seven g. (78% yield) of crude product, m.p. 144–155° and suitable for use in the next step, was obtained by Claisen rearrangement of 9.00 g. of 7-allyloxycoumarin (III, R = H)[12b] under the conditions described above. Recrystallization from ethanol gave colorless prisms, m.p. 165–166° (reported,[12b] 162–163°).

7-Acetoxy-8-allylcoumarin (V, R = H). Acetylation of 6.00 g. of crude 8-allyl-7-hydroxycoumarin gave, after crystallization from ligroin (b.p. 60–80°), 5.80 g. (80% yield) of colorless prisms, m.p. 93–93.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 5.0. Found: C, 69.2; H, 5.1.

7-Acetoxy-8-(2',3'-dibromopropyl)coumarin (VI, R = H). 7-Acetoxy-8-allylcoumarin (2.55 g., 0.0104 mole) and 1.67 g. (0.0104 mole) of bromine, under the conditions described above, gave 4.22 g. (quantitative yield) of crude dibromide, suitable for use in the next step. Colorless, felted needles crystallized from methanol, m.p. 123–123.5°.

Anal. Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.6; H, 3.0; Br, 39.5. Found: C, 41.7; H, 3.2; Br, 39.5.

5'-Methylisopsoralene (VII, R = H). Cyclization of 2.65 g. of crude 7-acetoxy-8-(2',3'-dibromopropyl)coumarin proceeded as described above, except that filtration through a charcoal column was unnecessary. Colorless needles (0.67 g., 51% yield) crystallized from methanol, m.p. 153–154°. Light absorption in methanol: λ_{max} 2500, 3000, log ϵ 4.36, 4.09; λ_{min} 2300, 2700, log ϵ 4.07, 3.71.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.0; H, 4.0. Found: C, 72.0; H, 3.9.

7-Hydroxy-8-methylcoumarin-3-carboxylic acid (IX, R = COOH). A mixture of 15.20 g. of 4-formyl-2-methylresorcinol (VIII),[15] 20.80 g. of malonic acid, and 2 ml. of aniline (distilled from zinc dust) in 80 ml. of pyridine was kept at 40–45° for 48 hr., acidified with 5% hydrochloric acid, and diluted with an excess of water. After dissolving the resultant precipitate in 5% aqueous sodium hydroxide and reprecipitating with hydrochloric acid, 20.14 g. (92% yield) of crude product, m.p. 254–255°, were obtained. Although the crude material was suitable for use in the next step, a small portion crystallized from glacial acetic acid, m.p. 258–259° dec.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.7. Found: C, 59.9; H, 3.9.

7-Hydroxy-8-methylcoumarin (IX, R = H). A solution of 9.60 g. of crude 7-hydroxy-8-methylcoumarin-3-carboxylic acid in 100 ml. of freshly distilled glycerin was heated under reflux for 1 hr. and poured into 1 l. of water. The crude product (6.55 g., 85% yield) precipitated and was suitable for use in the next step. A small portion crystallized from ethanol as colorless needles, m.p. 258–259° (reported,[14] m.p. 231–232°). A mixture of this substance with the starting material had m.p. 237–253°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.6. Found: C, 68.4; H, 4.7.

7-Allyloxy-8-methylcoumarin (X, R = H). A mixture of 6.55 g. of crude 7-hydroxy-8-methylcoumarin, 23.50 g. of anhydrous potassium carbonate, 16.8 ml. of allyl bromide, and 500 ml. of acetone was heated under reflux for 16 hr. and was then concentrated to dryness on a steam bath. Extraction of the powdered residue with 500 ml. of 5% aqueous ammonia, followed by crystallization from aqueous ethanol, gave 6.95 g. (87% yield) of off-white needles, m.p. 125–125.5°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.5; H, 5.8.

6-Allyl-7-hydroxy-8-methylcoumarin (XI, R = H). Claisen rearrangement of 5.58 g. of 7-allyloxy-8-methylcoumarin, heated for 75 min. instead of 2 hr., gave 4.46 g. (80% yield) of crude product, suitable for use in the next step. Two recrystallizations from ethanol gave microcrystalline needles, m.p. 153–154°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 71.9; H, 5.7.

7-Acetoxy-6-allyl-8-methylcoumarin. Acetylation of 3.70 g. of 6-allyl-7-hydroxy-8-methylcoumarin gave 3.53 g. (80% yield) of off-white prisms, m.p. 119–119.5° after crystallization from ethanol (charcoal).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 70.1; H, 5.5.

7-Acetoxy-6-(2',3'-dibromopropyl)-8-methylcoumarin. Bromination of 3.53 g. (0.0137 mole) of 7-acetoxy-6-allyl-8-methylcoumarin with 2.20 g. (0.0137 mole) of bromine gave 5.74 g. (quantitative yield) of crude dibromide, suitable for use in the next step. Pale yellow prisms, m.p. 129–130°, were obtained by two recrystallizations from ethanol.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.4; H, 3.2; Br, 37.9.

5',8-Dimethylpsoralene (XII, R = H). Cyclization of 4.53 g. of crude 7-acetoxy-6-(2',3'-dibromopropyl)-8-methylcoumarin was achieved in a manner analogous to the procedure described above. Crystallization from methanol gave 1.13 g. (49% yield) of colorless prisms, m.p. 176–177°. Light absorption in methanol: λ_{max} 2500, 3000, 3350, log ϵ 4.39, 4.12, 3.83; λ_{min} 2300, 2700, 3300, log ϵ 4.20, 3.77, 3.82.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.8; H, 4.9.

7-Acetoxy-6-allyl-4,8-dimethylcoumarin. 7-Allyloxy-4,8-dimethylcoumarin[13] (195.0 g.) underwent Claisen rearrangement under the conditions described above, except that the crude 6-allyl-7-hydroxy-4,8-dimethylcoumarin obtained was only partially dry after heating at 70° for 6 hr. The moist solid was acetylated (915 ml. of acetic anhydride) to give 145.4 g. (64% yield for the two steps) of colorless needles, m.p. 144.5–145.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.6; H, 5.9.

7-Acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin. Because of the larger quantities involved, bromination was carried out in chloroform rather than acetic acid. A solution of 85.2 g. (0.534 mole) of bromine in 200 ml. of chloroform was added to a chilled (ice bath) solution of 145.4 g. (0.534 mole) of 7-acetoxy-6-allyl-4,8-dimethylcoumarin in 800 ml. of chloroform at such a rate as to keep the temperature below 25°. Evaporation of chloroform on the steam bath left an off-white residue weighing 230.6 g. (quantitative yield) which was suitable for use in the next step. Crystal-

lization of a small portion from ethanol gave colorless prisms, m.p. 141.5–142.5°.

Anal. Calcd. for $C_{15}H_{16}O_4Br_2$: C, 44.5; H, 3.7; Br, 37.0. Found: C, 44.7; H, 4.1; Br, 36.9.

4,5',8-Trimethylpsoralene (XII, R = CH_3). Crude 7-acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin (245.7 g., 0.57 mole) was heated under reflux for 1.75 hr. in a solution of 65.4 g. (2.85 mole) of sodium in 2.1 l. of absolute ethanol (magnesium dried). After cooling for 15 min., the reaction mixture was poured into a mixture of 8 kg. of ice and 8 l. of 3.5% hydrochloric acid. The precipitate obtained was washed with 5% aqueous sodium hydroxide followed by water, and dried in a vacuum desiccator. Fractional crystallization from chloroform–petroleum ether (b.p. 30–60°) using Norit and finally from chloroform alone gave 61.8 g. (48% yield) of colorless prisms, m.p. 234.5–235°. Light absorption in methanol: λ_{max} 2500, 2950, 3350, log ϵ 4.35, 3.99, 3.80; λ_{min} 2250, 2700, 3200, log ϵ 4.09, 3.68, 3.79.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.4; H, 5.4.

3-Allyloxyphenyl acetate (XIV). A mixture of 101.3 g. of resorcinyl monoacetate, 138.2 g. of anhydrous potassium carbonate, and 181.5 g. of allyl bromide in 300 ml. of acetone was heated under reflux for 24 hr. and concentrated to dryness on a steam bath. Water (1.5 l.) was added and an ethereal extract of the aqueous solution was washed with 5% aqueous ammonia, dried (magnesium sulfate), and concentrated to an oil which gave, on distillation, 105.5 g. (82% yield) of a colorless oil, b.p. 82°/0.05 mm. This sample gave a faint red-brown ferric chloride color in ethanol.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.4; active H, 0.0. Found: C, 69.1; H, 6.4; active H, 0.13.

Mixture of 2-allyl- and 4-allylresorcinol (XV and XVI). A solution of 60.2 g. of 3-allyloxyphenyl acetate in 100 ml. of diethylaniline was heated under reflux (nitrogen atmosphere) for 50 min., dissolved in ether, and thoroughly washed with 5% hydrochloric acid. Extraction with 5% aqueous sodium hydroxide gave an oil, on acidification of the alkaline extract, which was isolated with ether and distilled through a short Vigreux column. A pale yellow oil (34.2 g., 73% yield), b.p. 98°/0.1 mm.; n_D^{17} 1.5630, was obtained and a small sample gave an intense red-brown color with ferric chloride in ethanol.

Anal. Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.7; active H, 1.34. Found: C, 71.9; H, 7.0; active H, 1.30.

Condensation of mixed allylresorcinols with ethyl acetoacetate. A solution of 5.00 g. of the mixture (described above) in 50 ml. of glacial acetic acid containing 4.33 g. of ethyl acetoacetate was saturated with dry hydrogen chloride. The next day, the reaction mixture was poured into water and the oil, which separated initially, solidified after several days. An ether solution of the solid was extracted with 5% aqueous ammonia and acidification of the ammonia extract gave a solid which crystallized from aqueous ethanol as 4.07 g. of colorless prisms, m.p. 137–160°. Repeated crystallizations from ethanol gave 0.035 g. of colorless needles of 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3), m.p. 198–199° alone or mixed with the specimen prepared by Claisen rearrangement. The infrared spectra of the two specimens were identical. The recrystallization mother liquors were diluted with water and 4.01 g. of a white solid were obtained.

7-Acetoxy-6-allyl-4-methylcoumarin. Acetylation of 1.151 g. of the above white solid, with sodium acetate and acetic anhydride, gave 1.125 g. of colorless needles, m.p. 85–110°, after crystallization from ethanol. This material (0.70 g.) in benzene, was adsorbed on a column of acid-washed alumina. A small portion of a 50% chloroform-benzene mixture eluted 0.050 g. of a white solid, which crystallized from ethanol as colorless needles, m.p. 135–136°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.6; H, 5.1.

6-Allyl-7-hydroxy-4-methylcoumarin (XVII). Further elution of the above alumina column with 50% chloroform-benzene gave 0.25 g. of 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3). Finally, chloroform eluted from the column 0.23 g. of a solid, which crystallized from ethanol as colorless needles, m.p. 174–175°, of 6-allyl-7-hydroxy-4-methylcoumarin (XVII).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.2; H, 5.6.

Acetylation with sodium acetate and acetic anhydride gave a sample of 7-acetoxy-6-allyl-4-methylcoumarin, which was identical (mixed melting point) with the sample described above.

7-Acetoxy-6-(2',3'-dibromopropyl)-4-methylcoumarin. Bromination of 0.119 g. of 7-acetoxy-6-allyl-4-methylcoumarin in glacial acetic acid gave 0.191 g. (quantitative yield) of crude dibromide, suitable for use in the next step. A small portion crystallized from ethanol as pale yellow prisms, m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.5; H, 3.4; Br, 38.1.

4,5'-Dimethylpsoralene (XVIII). Cyclization of 0.155 g. of crude 7-acetoxy-6-(2',3'-dibromopropyl)-4-methylcoumarin was accomplished by the use of ethanolic potassium hydroxide. The product crystallized from ethanol as 0.044 g. (55% yield) of colorless needles, m.p. 161–162°. Light absorption in methanol: λ_{max} 2450, 2900, 3400, log ϵ 4.28, 3.82, 3.68; λ_{min} 2700, 3200, log ϵ 3.56, 3.61.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 73.0; H, 4.7.

OXFORD, ENGLAND

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

Pyrrolopyridines. IV. Synthesis of Possible Intermediates[1,2]

WERNER HERZ AND D. R. K. MURTY[3]

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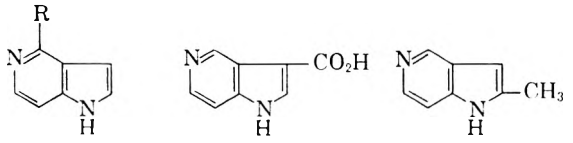
Possible routes to pyrrolo(3,2-c)pyridines from pyridine intermediates were studied. Efficient syntheses were developed for a number of pyridine derivatives, but none of them could be used for the desired purpose. 4-Nitro-3-nicotinic acid 1-oxide undergoes nucleophilic displacement by aniline.

A general synthesis of pyrrolo(3,2-c)pyridines (I,5-azaindoles) through the Bischler-Napieralski reaction of acyl derivatives of 2-(2-pyrrole)ethylamine was described in an earlier paper.[4] However, the method failed when attempts were made to prepare the parent compound (I, R = H). More recently Möller and Süs[5] obtained I (R = H) from 3-diazo-1,6-naphthyridin-4-(3H)-one by a photochemical ring contraction followed by decarboxylation of the resulting 3-carboxypyrrolo(3,2-c)pyridine (II), but in view of the large number of steps their method seemed unattractive for the synthesis of I in quantity. This paper describes our efforts to develop more convenient routes to pyrrolo(3,2-c)-pyridine.



I II III

Although Clemo and Swan[6] were unsuccessful in their attempts to prepare I (R = H) by the Madelung cyclization of 4-formamido-3-picoline (IV) and obtained only a 1% yield of 6-methylpyrrolo(3,2-c)-pyridine (III) from 4-acetamido-3-picoline, a reinvestigation of the Madelung reaction was considered advisable on two counts. First, the requisite starting material—4-amino-3-picoline (V)—is now readily available.[7] Secondly, the work of Tyson[8] on the Madelung cyclization leading to indole resulted in greatly enhanced yields due to the introduction of new bases such as sodium *t*-butoxide and sodium anilide and the use of dry sodium formate to repress an undesirable side reaction. Robison and Robison[9] utilized these findings and obtained a 51% yield of 7-azaindole, a substance which had been prepared in only 3% yield by the older technique.[10] Thus, it was reasonable to expect a similar improvement in the cyclization of IV, especially since the samples of IV prepared in the course of this work were of greater purity than the material used by the English workers.[6]

Unfortunately these expectations were not realized. In spite of many attempts under different reaction conditions, the only substance isolated in all experiments was the decomposition product 4-amino-3-picoline.[11]

Alternate methods for the synthesis of I were therefore sought. Adaptations of other standard indole syntheses[12] were considered, although the most generally useful method, the Fischer indole ring closure, was ruled out because of the report[13] that the cyclization of pyridylhydrazones proceeds only with the greatest of difficulties. This had recently been confirmed by other workers.[14]

Most of the proposed syntheses required an adequate supply of 4-nitro-3-picoline (VI). Herz and Tsai[7] reported the small-scale preparation of VI

(1) Supported in part by research grant CY-3034 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Previous paper, W. Herz and D. R. K. Murty, *J. Org. Chem.*, **25**, 2242 (1960).

(3) Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, June 1960.

(4) W. Herz and S. Tocker, *J. Am. Chem. Soc.*, **77**, 6353 (1955).

(5) K. Möller and O. Süs, *Ann.*, **612**, 153 (1958).

(6) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 198 (1948).

(7) W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **76**, 4184 (1954).

(8) F. T. Tyson, *J. Am. Chem. Soc.*, **72**, 2801 (1950).

(9) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).

(10) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).

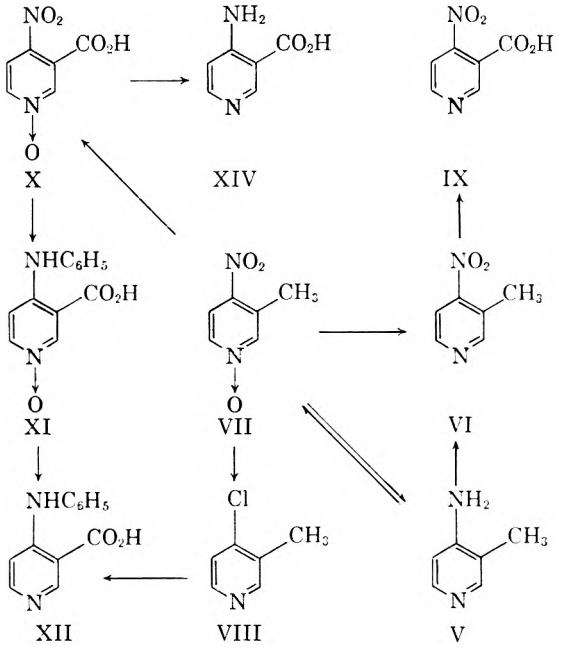
(11) After all experiments described in this paper were completed, we were informed by Dr. M. M. Robison that work in his laboratory had led to the successful preparation of I (R = H) from 4-formamido-3-picoline. This has since been published, S. Okuda and M. M. Robison, *J. Org. Chem.*, **24**, 1003 (1959). We are very grateful to Dr. Robison for communicating details of this work prior to publication. Several attempts to duplicate the cyclization under the exact conditions recommended by Okuda resulted in failure. The only substance isolated was 4-amino-3-picoline (20–25% yield). Although the melting points of 4-amino-3-picoline and pyrrolo(3,2-c)pyridine are very close, Okuda and Robison were able to establish the nature of their product by comparison with an authentic sample. We are unable to account for the discrepancy in their results and ours.

(12) P. L. Julian, E. W. Meyer, and H. C. Printy in R. C. Elderfield, *Heterocyclic Compounds*, Vol. III, Chap. 1 (1952).

(13) G. R. Clemo and R. J. W. Holt, *J. Chem. Soc.*, 1313 (1953).

(14) S. Okuda and M. M. Robison, *J. Am. Chem. Soc.*, **81**, 740 (1959). F. G. Mann, A. F. Prior, and T. J. Wilcox, *J. Chem. Soc.*, 3830 (1959).

from the corresponding *N*-oxide (VII) by the action of phosphorus trichloride, but it has now been found that the reduction is accompanied by the formation of 4-chloro-3-picoline (VIII) through nucleophilic displacement at C_4. Since the formation of VIII is favored at higher temperatures and proceeds in excellent yield at steam bath temperature, this is probably the best method for the preparation of 4-chloro-3-picoline. Large-scale runs at lower temperatures resulted in extensive recovery of VII and little VI.



Attempts were then made to obtain VI by persulfuric acid oxidation of 4-amino-3-picoline (V). The reaction was found to be very exothermic. Carefully controlled experiments gave rise to a mixture of VI and 4-nitro-3-picoline-1-oxide (VII), the latter predominating in large scale runs.

Several attempts were made to oxidize 4-nitro-3-picoline to 4-nitro-3-nicotinaldehyde which was envisioned as an intermediate in several of the proposed syntheses. Oxidations with selenium dioxide, chromic acid, and chromyl chloride failed. Potassium permanganate oxidation gave a 40% yield of 4-nitronicotinic acid (IX), but no further work was done with this substance in view of the low over-all yield from VII. Photobromination or treatment with *N*-bromosuccinimide resulted in the formation of unstable tarry products which could not be utilized. Base-catalyzed condensation of VI with ethyl oxalate, intended as the first step in a synthesis modeled on the Reissert method, was also unsuccessful. This is rather surprising since *o*-nitrotoluene easily undergoes this reaction.[15]

Attention was then focused on the use of 4-nitro-3-picoline-1-oxide (VII), whose methyl group was expected to be somewhat more reactive.[16] However, the condensation with ethyl oxalate was again a failure nor was it possible to convert it to the corresponding aldehyde. Reaction with chromyl chloride and *p*-nitroso-*N*,*N*-dimethylaniline gave intractable resinous material. No reaction took place when VII was heated with selenium dioxide in various solvents. Chromic acid oxidation gave an improved yield (80%) of X.[18] Attempts to convert this to an acid chloride failed because of conversion to 4-chloro-3-nicotinic acid-1-oxide which is very unstable.[18] Direct esterification of X was also unsuccessful. Although the methyl ester was finally prepared by the action of methyl iodide on the silver salt of X, further work directed toward a synthesis of 4-nitro-3-nicotinaldehyde or its *N*-oxide from X was abandoned because of the poor yields and the sparing solubility of the ester in common organic solvents. Ozonolysis of 4-nitro-3-styrylpyridine-1-oxide[17] followed by reductive work-up gave benzoic acid, but no aldehyde.

It has already been mentioned that further work with 4-nitronicotinic acid (IX) was not undertaken because of the poor yields encountered in the synthesis of its precursor (VI). An alternate route to the acid (IX) seemed to be deoxygenation of the corresponding *N*-oxide (X). Phosphorus trichloride, which is commonly employed for this purpose, could not be used because of the insolubility of X in suitable organic solvents. Triphenyl phosphite[19] and triphenylphosphine[20] are not suitable for the deoxygenation of nitro-pyridine-1-oxides and Meisenheimer's method[21] also seemed inapplicable. Pachter and Kloetzel[22] accidentally observed deoxygenation of a phenazine-*N*-oxide by means of aniline, but we are not aware of any systematic study of the use of this reagent.

On heating X with aniline on the steam bath, there was obtained not the expected 4-nitronicotinic acid, but a substance of formula $C_{12}H_{10}N_2O_3$ (A) which could be reduced catalytically to another substance $C_{12}H_{10}N_2O_2$ (B). Infrared spectra and chemical behavior revealed the presence of the carboxyl and the absence of a nitro group in both compounds. A logical explanation for these observations is that the reaction of X with aniline involves nucleophilic displacement of the nitro group by aniline to yield 4-anilino-3-nicotinic acid-1-oxide (XI) which is deoxygenated to XII upon catalytic reduction. This

(15) F. Mayer and G. Balle, *Ann.*, **403**, 167 (1914).

(16) The facile condensation of VII with benzaldehyde[17] is an example of this activation due to the presence of the *N*-oxide function.

(17) D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958).

(18) E. C. Taylor, Jr., and A. J. Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).

(19) M. Hamana, *J. Pharm. Soc. Japan*, **75**, 139 (1953).

(20) F. Schmitz, *Ber.*, **91**, 1488 (1958); L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956).

(21) J. Meisenheimer, *Ann.*, **397**, 273 (1913); A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

(22) I. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 971 (1952).

conclusion finds its support in the general behavior of 4-nitropyridine-1-oxides,[23] the nitro group being susceptible to displacement by strong nucleophiles such as alkoxides, phenoxides, and thiophenoxides.

Because, to our knowledge, this is the first instance of a displacement by as weak a nucleophile as aniline, because it is known that nucleophilic substitution can occur at the 2- as well as at the 4-position and because there are examples of the elimination of a nitro group on the pyridine ring,[23] it was deemed desirable to establish the structure of B more securely by comparison with authentic samples of 4-anilino-(XII) and 6-anilinonicotinic acid (XIII). The properties of the third possible isomer, 2-anilinonicotinic acid, were already recorded and differed from those of B.[24]

The synthesis of XII was accomplished as follows. 4-Chloro-3-picoline, prepared as described earlier, was oxidized with potassium permanganate to 4-chloronicotinic acid[25] which in turn on heating with aniline gave a 60% yield of XII.

XIII was prepared as shown below. 2-Amino-5-methylpyridine was converted to 2-hydroxy-5-methylpyridine. Treatment of the latter with phosphorus pentachloride gave 2-chloro-5-methylpyridine. This was oxidized with potassium permanganate to the known 6-chloronicotinic acid[26] which on heating with aniline gave XIII. Compound B was identical with XII by mixed melting point and comparison of the infrared spectra.

The facile displacement of the nitro group in X by the weak nucleophile aniline is undoubtedly due to the combined effect of the *N*-oxide function and the carboxylic acid group. In order to test this assumption, 4-nitropyridine-1-oxide and 4-nitronicotinic acid were separately treated with aniline. As anticipated, no reaction took place and the starting materials were recovered.

Miescher and Kägi[27] reported that a diazoketone prepared from 2-amino-3-nicotinoyl chloride could be cyclized to 7-azaindoxyl. It was hoped that a similar reaction sequence starting with 4-aminonicotinic acid (XIV) would lead to 5-azaindoxyl. Known methods for the preparation of XIV are laborious and proceed in low yields,[29] but the route VII → X → XIV, the last step involving a catalytic reduction in ammoniacal solution, proved to be convenient and economical. Treatment of XIV with thionyl chloride produced a highly unstable acid chloride whose formation was indicated by conversion to the methyl ester. However, the action of diazomethane produced only intractable resinous material.

Another possible route to 5-azaindoxyl involved the cyclization of 4-amino-3-acetic acid. Attempts to prepare the latter by nitration of 3-carboxymethylpyridine-1-oxide or 3-cyanomethylpyridine-1-oxide resulted in extensive decomposition whereas nitration of 3-hydroxymethylpyridine-1-oxide was accompanied by oxidation to X.

EXPERIMENTAL[28]

4-Formamido-3-picoline (IV). 4-Amino-3-picoline was prepared by catalytic reduction of 4-nitro-3-picoline-1-oxide,[7] formylated by the procedure of Clemo and Swan[6] and distilled at reduced pressure. The distillate solidified, but melted over a wide range. Prior to cyclization it was recrystallized twice from acetone, m.p. 141°. The picrate melted at 198° (lit.[6] m.p. 199–200°).

The methods used for the attempted cyclization were the same as those described previously.[2] Method A, with or without addition of dry sodium formate, gave 4-amino-3-picoline. Method B gave 4-amino-3-picoline in 25–40% yield. No other substance was isolated.

4-Nitro-3-picoline and 4-chloro-3-picoline. A solution of 25 g. of 4-nitro-3-picoline-1-oxide in 500 ml. of dry chloroform was cooled in an ice bath to 3°. Phosphorus trichloride, 100 ml., was added dropwise at such a rate that the temperature of the mixture did not rise above 10°. Stirring was continued at 5° for 40 min., and the mixture was poured over crushed ice and cautiously made basic with dilute sodium hydroxide solution. The aqueous layer was separated and extracted several times with chloroform. The combined chloroform extracts were dried, and distilled. The first fraction, 11 g., b.p. 54–64° (1.5 mm.), was colorless. Redistillation at 36° (0.5 mm.) gave an oil which was unstable at room temperature and was converted to a picrate, m.p. 151–152°. The picrate of 4-chloro-3-picoline, prepared recently by a more circuitous route, melts at 152–153°.[29]

Anal. Calcd. for $C_{12}H_9N_4O_7Cl$: C, 40.40; H, 2.54; N, 15.71. Found: C, 40.75; H, 2.16; N, 15.74.

Catalytic reduction of 4-chloro-3-picoline with palladium charcoal gave a colorless oil which was identified as 3-picoline through its picrate.

Fraction 2, b.p. 64–74° (1.5 mm.), 10 g., was redistilled. The yellow oil, b.p. 67–69° (1.5 mm.), solidified on cooling, m.p. 30°, picrate m.p. 127–128° [lit.[7] for 4-nitro-3-picoline, b.p. 57–59° (0.5 mm.), m.p. 27–29°, picrate m.p. 128–129°].

The yields of 4-chloro-3-picoline increased when the temperature of the reaction mixture was raised after the addition of phosphorus trichloride. When the mixture was refluxed for a few minutes, 4-chloro-3-picoline was isolated in 65% yield and no 4-nitro-3-picoline was obtained.

4-Nitro-3-picoline from 4-amino-3-picoline. A solution of 30 g. of 4-amino-3-picoline in 150 ml. of concd. sulfuric acid was added at 10–20° to a cold solution consisting of 525 ml. of 15% fuming sulfuric acid and 263 ml. of 30% hydrogen peroxide. Stirring was continued at 10–20° for 1 hr. A few minutes after cooling was discontinued a vigorous reaction ensued which was difficult to control. After the reaction subsided, the mixture was allowed to cool, poured over crushed ice, neutralized with dilute sodium hydroxide solution, and extracted thoroughly with chloroform. Removal of the dried chloroform at reduced pressure gave a yellow solid mixed with some oil which was filtered and recrystallized from acetone, yield 15 g. of 4-nitro-3-picoline-1-oxide. Distillation of the oily filtrate afforded a pale yellow

(23) E. Ochiai, *J. Org. Chem.*, 18, 534 (1953); A. R. Katritzky, *Quart. Revs.*, 10, 395 (1956).

(24) W. O. Kermack and A. P. Weatherhead, *J. Chem. Soc.*, 726 (1942).

(25) E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.*, 19, 1633 (1954).

(26) H. V. Pechmann and W. Welsch, *Ber.*, 17, 2384 (1884).

(27) K. Miescher and H. Kägi, *Helv. Chim. Acta*, 24, 1471 (1941).

(28) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England.

(29) Y. Suzuki, *Pharm. Bull. (Tokyo)*, 5, 78 (1957).

oil, 4.3 g., b.p. 70° (1 mm.), picrate m.p. 128°, undepressed on admixture of the picrate of authentic 4-nitro-3-picoline.

When the reaction mixture was stirred below 20° for an extended period and the product worked up without allowing to warm up to room temperature, no reaction took place and starting material was discovered. Brown[30] reported an 80% yield of crude 4-nitro-3-picoline from this reaction.

4-Nitronicotinic acid. Potassium permanganate oxidation of 7 g. of 4-nitro-3-picoline in 100 ml. of water at steam bath temperature followed by extraction with benzene gave 4 g. of starting material. The aqueous layer was concentrated and acidified, yield 1.5 g. of 4-nitronicotinic acid, m.p. 120° (lit.[30] m.p. 120°).

4-Nitronicotinic acid-1-oxide. A solution of 7.5 g. of 4-nitro-3-picoline-1-oxide in 60 ml. of concd. sulfuric acid was oxidized with 27 g. of sodium dichromate at 45–55°. After 4 hr., the viscous mixture was poured over crushed ice, filtered, and washed; yield 6.1 g. The green color[18] was removed by solution in dilute base, filtration, and reprecipitation. Two crystallizations from ethanol water gave an analytical sample, m.p. 171°.

Anal. Calcd. for $C_6H_4N_2O_5$: C, 39.14; H, 2.19; N, 15.22. Found: C, 39.50; H, 2.12; N, 15.30.

Methyl-4-nitronicotinate-1-oxide. 4-Nitronicotinic acid-1-oxide, 4 g., was dissolved in the calculated amount of dilute ammonium hydroxide solution and mixed with an equivalent quantity of silver nitrate solution. The yellow silver salt was filtered, washed, and dried, 6 g., suspended in 300 ml. of absolute methanol and refluxed with excess methyl iodide under an efficient reflux condenser with stirring overnight. Excess methyl iodide was distilled and the unchanged silver salt filtered and washed with hot methanol. The combined filtrate and washings were combined and concentrated at reduced pressure. The yellow product was recrystallized from water–dimethyl formamide, yield 0.9 g., m.p. 158–159° dec.

Anal. Calcd. for $C_7H_6N_2O_5$: C, 42.43; H, 3.05; N, 14.14. Found: C, 42.80; H, 3.20; N, 13.60.

4-Anilinonicotinic acid-1-oxide. A mixture of 25 ml. of aniline and 4 g. of 4-nitronicotinic acid-1-oxide was heated on a steam bath for 4 hr., cooled, and mixed with dilute sodium hydroxide solution. The aqueous layer was washed and acidified. The pale yellow precipitate was filtered and washed with cold water, yield 2.5 g., m.p. 242–244°. It was almost insoluble in most organic solvents and only slightly soluble in hot water and dimethyl formamide. One reprecipitation and recrystallization from water–dimethyl formamide gave the analytical sample, m.p. 244–245°.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.46; H, 4.14; N, 11.90.

4-Anilinonicotinic acid. (A) A solution of 0.45 g. of the *N*-oxide in 200 ml. of hot methanol was hydrogenated with 0.2 g. of 10% palladium charcoal. The catalyst was filtered and washed with hot methanol. The combined filtrate and washings were concentrated to small volume, yield 0.2 g. of a colorless solid, which was recrystallized from methanol, m.p. 267–269° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.04; H, 4.81; N, 12.80.

(B) A mixture of 6.3 g. of 4-chloro-3-picoline, 18.6 g. of potassium permanganate, and 200 ml. of water was refluxed for 6 hr. with stirring. The apparatus was adjusted for steam distillation and the mixture steam distilled until 100 ml. of distillate had been collected. Extraction of the distillate gave 1.1 g. of starting material. The hot reaction mixture was filtered through Filtercel and the manganese dioxide washed with hot water. The combined filtrate and washings were concentrated to 60 ml. and acidified. The pale yellow precipitate was filtered, washed with a little cold water, and dried, 4.1 g. (64%, based on 4-chloro-3-picoline actually consumed). Vacuum sublimation gave a colorless solid, m.p. 162–163°. This substance has previously been synthesized in 5% yield from nicotinic acid-1-oxide.[25]

A mixture of 1 g. of the above and 2 g. of aniline was heated at 150° for 1.5 hr., poured into a small flask while still hot, and mixed with a few milliliters of acetone. A colorless solid separated on standing and scratching. It was filtered, washed with a little acetone, and recrystallized from water-dimethylformamide, m.p. 268–269°, mixed melting point with material prepared by method A undepressed.

2-Hydroxy-5-methylpyridine. A solution of 125 g. of 2-amino-5-methylpyridine in 3 l. of 5% sulfuric acid was cooled to 5° and a solution of 150 g. of sodium nitrite in 400 ml. of water was added with stirring during a period of 40 min. The ice bath was removed, stirring continued for 1 hr., and the mixture was heated to 60°, cooled, neutralized with dilute sodium hydroxide solution, concentrated to 1.5 l., and allowed to stand overnight. The solid was filtered and washed with a small amount of acetone which removed a yellow coloration, yield 95 g. (75%). Two recrystallizations from methanol raised the m.p. to 185–187°. This compound has since been reported elsewhere,[29] m.p. 181–182°.

Anal. Calcd. for C_6H_7NO: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.81; H, 6.41; N, 12.71.

2-Chloro-5-methylpyridine. A mixture of 28 g. of 2-hydroxy-5-methylpyridine, 100 ml. of phosphorus oxychloride, and 20 g. of phosphorus pentachloride was heated for 2 hr. at 115°, cooled, poured over crushed ice, neutralized with dilute sodium hydroxide, and extracted with ether. The ether extracts were dried, concentrated, and the residue was distilled, b.p. 56° (2.5 mm.).

Anal. Calcd. for C_6H_6NCl: C, 56.46; H, 4.74; N, 11.00. Found: C, 55.90; H, 4.95; N, 11.50.

6-Chloronicotinic acid. Oxidation of 9.4 g. of 2-chloro-5-methylpyridine with potassium permanganate in a manner similar to that described for 2-chloro-3-picoline described earlier gave 1.7 g. of starting material and 6.8 g. of 6-chloronicotinic acid (71%), m.p. 198–199° (lit.[26] m.p. 199°).

6-Anilinonicotinic acid. Treatment of 1 g. of 6-chloronicotinic acid with aniline in the manner described earlier gave a quantitative yield of XIII which was recrystallized from acetone, m.p. 260–262°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.30; H, 4.73; N, 12.80.

4-Aminonicotinic acid. A solution of 1 g. of 4-nitronicotinic acid-1-oxide in the calculated amount of ammonium hydroxide was diluted with 40 ml. of water and hydrogenated with palladium charcoal. The catalyst was filtered and washed with dilute ammonium hydroxide solution. The combined filtrate and washings were concentrated to 15 ml. and neutralized. The precipitate was washed with cold water and recrystallized from ethanol water, yield 2.2 g., m.p. 330°, undepressed on admixture of a sample prepared by heating 4-chloronicotinic acid and ammonia in a sealed tube.[25]

4-Aminonicotinoyl chloride. A mixture of 0.7 g. of 4-aminonicotinic acid and 6 ml. of thionyl chloride was warmed gently and stirred for 1 hr. in an apparatus protected from the atmosphere. Excess thionyl chloride was removed *in vacuo*. The residue was very unstable. Treatment with diazomethane in methylene chloride and working up in the usual fashion gave intractable resinous material. The acid chloride was converted to the methyl ester as follows. Excess methanol was added to the residue obtained from a similar run. The mixture was heated to reflux, cooled, treated with ice, and made basic with sodium carbonate solution. Extraction with ether, drying of the ether extracts, and evaporation gave a yellow residue which solidified on cooling and was washed with a small amount of acetone, yield 0.5 g. (46%). Crystallization from acetone gave yellow plates, m.p. 170°.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.13; H, 5.16; N, 18.36.

(30) E. V. Brown, *J. Am. Chem. Soc.*, 76, 3167 (1954).

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE LABORATORY SERVICE, VETERANS ADMINISTRATION HOSPITAL]

Pyrazines. II. The Rearrangement of Pyrazine-N-Oxides[1]

BERNARD KLEIN, JUDITH BERKOWITZ, AND NATALIE E. HETMAN

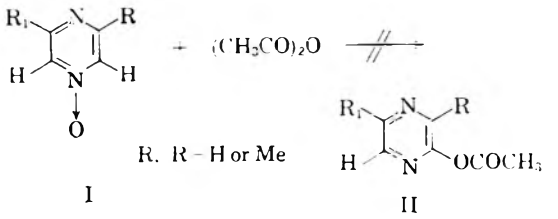
Received April 14, 1960

The action of acetic anhydride on pyrazine-*N*-oxides is reported. Pyrazine-1-oxide, 3-methylpyrazine-1-oxide, and 3,5-dimethylpyrazine-1-oxide do not rearrange to form the corresponding 2-acetoxy compounds. On the other hand, 2,5-dimethylpyrazine-1-oxide, 2,6-dimethylpyrazine-1-oxide, and 2,3,5,6-tetramethylpyrazine-1-oxide rearrange to form the 2-acetoxymethyl derivatives. Presumably, the reaction will occur when an adjacent methyl group is available. Pyrazine-1,4-dioxide does not rearrange with boiling acetic anhydride. 2-Methylpyrazine-1,4-dioxide reacts smoothly to form 3-acetoxymethylpyrazine-1-oxide. 2,5-Dimethylpyrazine-1,4-dioxide gives a reaction product from which 2,5-dimethylpyrazine-1-oxide and 2-acetoxymethyl-5-methylpyrazine-4-oxide are isolated. On prolonged heating a small amount of 2,5-diacetoxymethylpyrazine is produced. 2,6-Dimethylpyrazine-1,4-dioxide gives 2-acetoxymethyl-6-methylpyrazine and 2,6-dimethylpyrazine-4-oxide. The acetoxymethylpyrazines are smoothly converted to the corresponding pyrazylmethanols (hydroxymethylpyrazines). The ultraviolet and infrared absorption spectra are presented. The mechanism of the rearrangement is discussed in terms of a two-step, cyclic intermediate pathway.

The rearrangement of heterocyclic *N*-oxides with acetic anhydride to form acetoxy derivatives is now a well known reaction.[2,3] When this reaction is applied to 2- and 4-alkylpyridine-*N*-oxides, an alternate course is followed, leading to the formation of 2- and 4-acetoxyalkylpyridines.[4–9] Similar reactions have been described in other heterocyclic series as well, *e.g.*, quinoline,[10a–c] benzimidazole,[11] and isoquinoline.[12]

Koelsch and Gumprecht[13] reported the action of acetic anhydride on 3-methylpyrazine-1-oxide, 2,5-dimethylpyrazine-1-oxide, and 2,5-dimethylpyrazine-1,4-dioxide. The present authors have extended the reaction of pyrazine and methyl-substituted pyrazine mono- and di-*N*-oxides with acetic anhydride. This report presents the results of these studies.

Pyrazine mono-N-oxides. It has been found that pyrazine-1-oxide, 3-methylpyrazine-1-oxide, and 3,5-dimethylpyrazine-1-oxide, in contrast to the reaction with pyridine-*N*-oxide,[2] did not react with acetic anhydride to give the corresponding 2-acetoxypyrazines.[14] In each case starting material



was recovered. At the same time a good deal of dark resinous material was formed indicating that some reaction had taken place. It is suspected that this reaction is a counterpart of the reaction in the pyridine series with the formation of free radical intermediates.[15–16]

On the other hand, 2,5-dimethylpyrazine-1-oxide (VI), 2,6-dimethylpyrazine-1-oxide, and 2,3,5,6-tetramethylpyrazine-1-oxide, rearranged to form the corresponding 2-acetoxymethylpyrazine derivatives. Presumably, the reaction will proceed when an adjacent methyl group is available.[4,6]

(1) Presented in part at the 136th meeting, American Chemical Society, Atlantic City, September 1959.

(2) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947); *Chem. Abstr.*, **45**, 9337c (1951).

(3) See E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953) for leading references.

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

(5) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953), *Chem. Abstr.*, **49**, 10948e (1955).

(6) O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

(7) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).

(8) G. Kobayashi, S. Furukawa, and T. Kawada, *J. Pharm. Soc. Japan*, **74**, 790 (1954); *Chem. Abstr.*, **49**, 1164c (1955); S. Furukawa, *Pharm. Bull. Japan*, **3**, 413 (1955); *Chem. Abstr.*, **50**, 13926a (1956).

(9) F. Cislak, U. S. Patent 2,748,141, May 29, 1956.

(10) (a) K. Oda, *J. Pharm. Soc. Japan*, **64**, No. 8A, 6 (1944); *Chem. Abstr.*, **45**, 9523i (1951); (b) T. Itai, *J. Pharm. Soc. Japan*, **65**, 70 (1945); *Chem. Abstr.*, **45**, 8525h (1951); (c) I. J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).

(11) F. Montanari and A. Risaliti, *Gazz. chim. ital.*, **83**, 278 (1953), *Chem. Abstr.*, **47**, 12388f (1953).

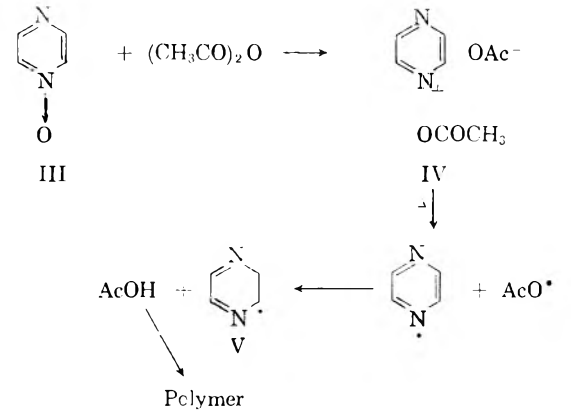
(12) M. M. Robison and B. L. Robison, *J. Org. Chem.*, 21, 1337 (1957); *J. Am. Chem. Soc.*, **80**, 3443 (1958).

(13) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **3**, 1603 (1958).

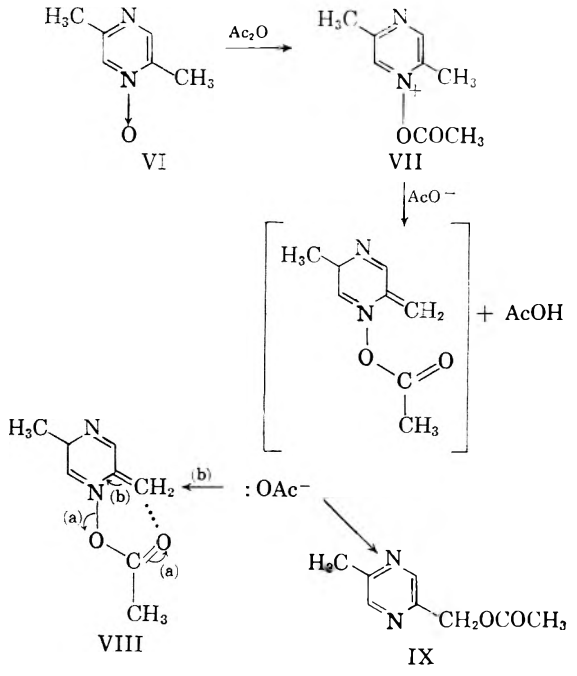
(14) Koelsch and Gumprecht (ref. 13) claimed that 3-methylpyrazine-1-oxide with acetic anhydride gave an acetate, which on saponification produced the 2-hydroxypyrazine. The ultraviolet absorption spectrum of the latter, however, closely resembled that of a pyrazine mono-*N*-oxide, rather than a hydroxypyrazine or pyrazinone (see ref. 17). After our work was completed, an exchange of letters with Dr. Hideyo Shindo, Sankyo Co., Ltd., Tokyo, Japan, brought to our attention the work of Dr. M. Asai [*Yakugaku Zasshi*, **79**, 1273 (1959)] who also found that 3-methylpyrazine-1-oxide did not rearrange on heating with acetic anhydride. He was able to obtain 2-acetoxypyrazine in only 3% yield by prolonged heating of pyrazine-1-oxide in acetic anhydride.

(15) V. Boekelheide and D. L. Harrington, *Chem. & Ind. (London)*, 1423 (1955).

(16) V. J. Traynelis and R. F. Martello, *J. Am Chem. Soc.*, **80**, 6590 (1958).



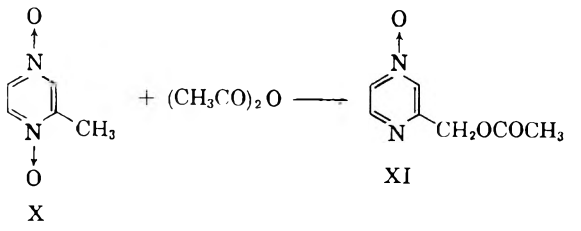
This would lend some additional support to a rearrangement mechanism involving an intramolecular cyclic intermediate.[7,10c,16] Thus, in the case of VI:



The course of the reaction was readily followed by measuring the disappearance of the *N*-oxide absorption peak at about 260 mμ and the appearance of an absorption peak at about 275 mμ, which is characteristic of the parent heterocycle.[17]

Pyrazine di-N-oxides. The action of acetic anhydride on pyrazine and methyl substituted pyrazine di-*N*-oxides was also investigated. As expected, pyrazine-1,4-dioxide was unaffected. 2-Methylpyrazine-1,4-dioxide reacted smoothly to form 2-acetoxymethylpyrazine-4-oxide. The course of this reaction was followed by measuring the decline and eventual disappearance of the absorption maxima at 235 and 295 mμ and the formation of absorption peaks at approximately 220 and 260 mμ, characteristic of pyrazine mono-*N*-oxides.[17]

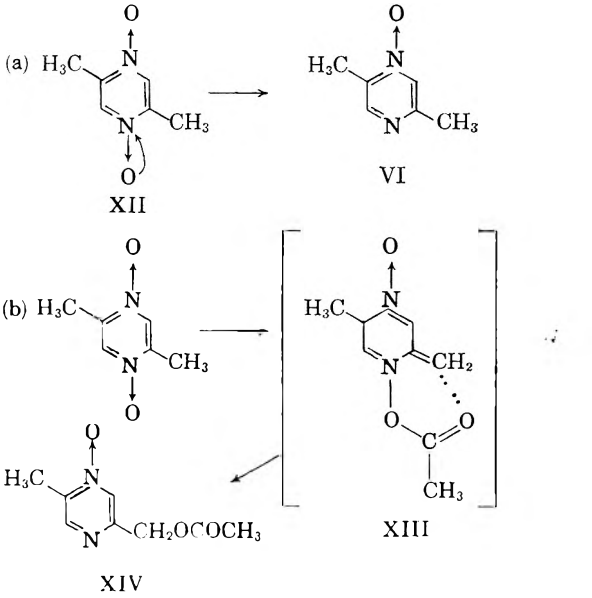
(17) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, 81, 5160 (1959).



When 2,5-dimethylpyrazine-1,4-dioxide, (XII), was heated in acetic anhydride, two principal products were obtained. They were 2,5-dimethylpyrazine-1-oxide and 2-acetoxymethyl-5-methylpyrazine-4-oxide, m.p. 73–74.5°. Prolonged heating of XII in acetic anhydride produced small amounts of 2,5-diacetoxymethylpyrazine (XV).

Koelsch and Gumprecht[13] in their study of this reaction isolated a mixture of 2-acetoxymethyl-5-methylpyrazine (IX) and 2,5-diacetoxymethylpyrazine (XV). The difference in products can be explained, in part, by procedural differences. In this laboratory the course of the reaction was followed spectrophotometrically, and terminated at the mono-*N*-oxide stage. Koelsch and Gumprecht, following the heating period, permitted the reaction mixture to stand for a prolonged period before workup.[18]

The formation of the four compounds thus produced as a result of the action of acetic anhydride on 2,5-dimethylpyrazine-1,4-dioxide can be explained by: (a) the ability of acetic anhydride to deoxygenate the $-C=\overset{+}{N}-\overset{-}{O}$ system. This has been observed in other heterocyclic series[19–21]

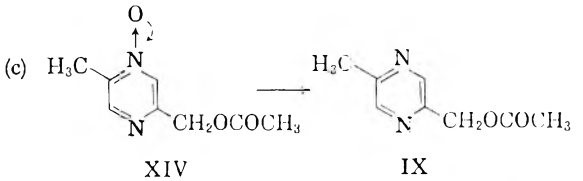


(18) This is not apparent from the published paper but is given in Dr. Gumprecht's thesis [Univ. of Minnesota (1957)].

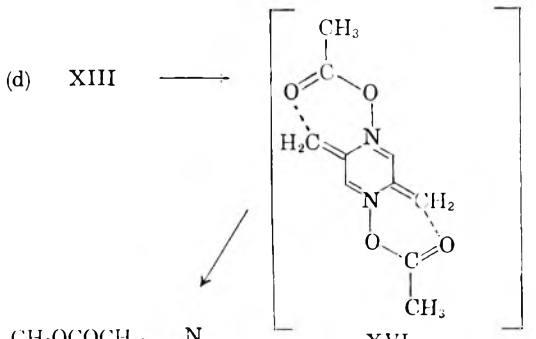
(19) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).

(20) I. Yoshiaka, *J. Pharm. Soc. Japan*, **72**, 1128 (1952); *Pharm. Bull. (Tokyo)*, **2**, 25 (1954); *J. Pharm. Soc. Japan*, **73**, 23 (1953).

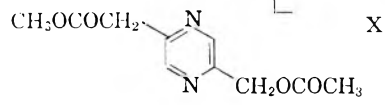
and discussed by Katritzky.[22] In this manner 2,5-dimethylpyrazine-1-oxide (VI) is formed; (b) nucleophilic attack of the acetoxy ion on the alkyl carbon of the coordinated intermediate (XIII) with subsequent rearrangement *via* a cyclic transition[10c,16] to form 2-acetoxymethyl-5-methylpyrazine-4-oxide (XIV); (c) deoxygenation of XIV by acetic anhydride, which would give 2-acetoxymethyl-5-methylpyrazine (IX); (d) nucleophilic attack of an acetoxy anion on both alkyl carbons of a doubly coordinated intermediate (XVI), arising in turn, from XIII and rearrangement at both ends of the cyclic transition to give XV. The possibility that the rearrangement may take a stepwise course: XII → XIV → XV must also be considered.



XIV IX



XVI



XV

Support for a two-stage reaction may be derived from an experiment during which XII was heated with one equivalent of acetic anhydride in glacial acetic acid. No reaction occurred over one hour, as the ultraviolet absorption spectrum remained unchanged. Upon addition of another equivalent of acetic anhydride, the reaction proceeded in the described manner. A second equivalent of reagent is evidently required to cause the intermediate to react. In this laboratory conversion of XIV to XV took place only after six hours, as demonstrated by the disappearance of the absorption maximum at 260 mμ and formation of a peak at 272 mμ. Additional time is probably necessary to form the intermediate XVI and cause its conversion to XV.

In every instance, considerable amounts of polymeric material formed. This would indicate again the formation or the existence of free radical intermediates, either accompanying or operating parallel with the ionic ones.[16]

In an attempt to establish the structure of XIV, both XIV and IX were treated with 30% hydrogen peroxide in glacial acetic acid hoping to form the known 2-acetoxymethyl-5-methylpyrazine-1,4-dioxide.[13] In each case 2-hydroxymethyl-5-methylpyrazine-1,4-dioxide was obtained. Further treatment with acetic anhydride in pyridine afforded 2-acetoxymethyl-5-methylpyrazine-1,4-dioxide.

This reaction is not a limited one, for 2-acetoxymethyl-3,5,6-trimethylpyrazine similarly treated gave a mixture of a mono- and di-*N*-oxide of 2-hydroxymethyl-3,5,6-trimethylpyrazine. Neither Koelsch and Gumprecht,[13] nor Boekelheide and Linn[4] observed this type of oxidative deacetylation in their studies. This reaction will be studied further.

Treatment of 2,6-dimethylpyrazine-1,4-dioxide with boiling acetic anhydride yielded a mixture of 2-acetoxymethyl-6-methylpyrazine and 3,5-dimethylpyrazine-1-oxide. These were identified by comparison with authentic material. Here, too, the products obtained can be accounted for by the mechanisms discussed above; that is, a coordinated intermediate undergoing attack by acetoxy ion. 3,5-Dimethylpyrazine-1-oxide, as demonstrated earlier, does not undergo further reaction with acetic anhydride and is therefore found in the reaction mixture.

Saponification of the 2-acetoxymethylpyrazine derivatives with alkali takes place readily to give the corresponding 2-hydroxymethyl derivatives (pyrazylmethanols). 2-Hydroxymethyl-5-methylpyrazine was similarly prepared and characterized by Koelsch and Gumprecht.[13] Thus a convenient, fairly general method is now available for the introduction of a functional group into the pyrazine side chain.

The physical properties and other data relating to the compounds reported in this study are given in Tables I and II.

EXPERIMENTAL[23,24]

Materials. The preparation of the pyrazine mono- and di-*N*-oxides used in this study was reported in the first paper of this series.[17,25]

(21) D. L. Vivian, *J. Org. Chem.*, 21, 1034 (1956).

(22) A. R. Katritzky, *Quart. Revs. (London)*, 10, 395 (1956).

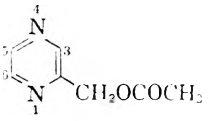
(23) All melting points were taken on a heated block and are uncorrected. Boiling points are also uncorrected.

(24) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, 77, N. Y.

(25) The melting points of some of the compounds reported in the first paper were taken on a heated block with a faulty thermometer and are incorrect. These have been redetermined: pyrazine-1-oxide, m.p. 113–114°; 3-methylpyrazine-1-oxide, m.p. 89–90°; 3,5-dimethylpyrazine-1-oxide, m.p. 130–132°; 2,3,5,6-tetramethylpyrazine-1-oxide, m.p. 100–101.5°. The melting points of the first two compounds are in closer agreement with those reported by Koelsch and Gumprecht.[13]

TABLE I

2-ACETOXYMETHYLPYRAZINES

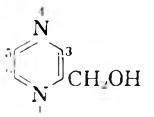


Compound	Yield, %	M.P., B.P.	mm.	t n_D	Empirical Formula	C, %	H, %	N, %
5-Methyl[a]	33	123–125	10	1.5113[17]	$C_8H_{10}N_2O_2$			
6-Methyl	60	127–130	14	1.5025[23]	$C_8H_{10}N_2O_2$	[b]		
3,5,6-Trimethyl	57	145–147	17	1.5053[24]	$C_{10}H_{14}N_2O_2$	[c]		
4-Oxide	36	104–105			$C_9H_8N_2O_3$	Calcd.: 50.00	4.79	16.66
						Found: 50.25	4.79	16.81
5-Methyl-4-oxide	30	73–74.5			$C_8H_{10}N_2O_3$	Calcd.: 52.70	5.53	15.38
						Found: 52.86	5.54	15.30
5-Methyl-1,4-dioxide	33	239–240[d]			$C_8H_{10}N_2O_4$	Calcd.: 48.48	5.09	14.14
						Found: 48.45	5.12	13.95
5-Acetoxymethyl	6	68–70[e]			$C_{10}H_{12}N_2O_4$	Calcd.: 53.56	5.40	
						Found: 53.44	5.34	

[a] Reference 13 gives the b.p. as 70–71° (0.4 mm.); $n_D^{25°}$ 1.5057. [b] Analyzed as the *picrate*, m.p. 201–202°. Calcd: for $C_{14}H_{13}N_5O_9$: C, 42.53; H, 3.31. Found: C, 42.6, H, 3.6. [c] Analyzed as the *picrate*, m.p. 96–97°. Calcd.: for $C_{16}H_{17}N_5O_9$: C, 45.39; H, 4.05; N, 16.55. Found: C, 45.61; H, 4.08; N, 16.81. [d] Reference 13 gives the m.p. as 241–242°. [e] Reference 13 gives the m.p. as 80–81°.

TABLE II

2-PYRAZINEMETHANOLS



Compound	Yield, %	M.P.	Empirical Formula	C, %	H, %	N, %
5-Methyl	85	36–39[a]	$C_6H_8N_2O$			
6-Methyl	46	43–45	$C_6H_8N_2O$	Calcd.: 58.05	6.49	22.57
				Found: 58.17	6.51	22.57
3,5,6-Trimethyl	60	65–66	$C_8H_{12}N_2O$	Calcd.: 63.13	7.95	18.41
				Found: 63.13	7.93	18.54
5-Methyl-1,4-dioxide		226–228[b]	$C_6H_8N_2O_3$	Calcd.: 46.20	5.10	17.95
				Found: 45.40	5.20	17.82
3,5,6-Trimethyl-*N*-oxide[c]	78[d]	83–85.5	$C_8H_{12}N_2O_2$	Calcd.: 57.12	7.19	16.66
				Found: 57.30	7.31	16.64
3,5,6-Trimethyl-1,4-dioxide	[d]	152.5–154.5	$C_8H_{12}N_2O_3$	Calcd.: 52.16	6.57	15.21
				Found: 52.41	6.71	15.11

[a] B.p. 137–138° (21 mm.); ref. 13 gives m.p. 36–39°. [b] Ref. 13 gives the m.p. 226–228°. [c] The position of the *N*-oxide is as yet undetermined, pending further investigation. [d] Combined yield, see Experimental.

Reaction of pyrazine-1-oxide with acetic anhydride. Solutions of 1.9 g. (0.02 mole) pyrazine-1-oxide in 5 ml. acetic anhydride were refluxed for varying periods up to 6 hr. The pale yellow solution turned dark at the end of 1 hr. but the ultraviolet absorption spectrum of samples taken at 15 min. (first 2 hr.), and then at half-hour intervals remained unchanged. From the reaction mixture, 0.6 to 1.1 g. material, m.p. 110–111°, was recovered. This material exhibited both the infrared and ultraviolet absorption spectrum of pyrazine-1-oxide.[17] The sublimed material did not depress the melting point of authentic material.

Similar experiments with *3-methylpyrazine-1-oxide, 3,5-dimethylpyrazine-1-oxide,* or *pyrazine-1,4-dioxide* and acetic anhydride, in each case, failed to demonstrate any reaction as evidenced by unchanged ultraviolet absorption spectrum,[17] and recovery of starting material.

2-Acetoxymethyl-5-methylpyrazine (IX). A solution of 24.0 g. (0.2 mole) 2,5-dimethylpyrazine-1-oxide in 60 ml. acetic anhydride was heated under reflux. During the course of the reaction, the absorption peak at 260 mμ gradually declined while an absorption peak at 274 mμ developed. At the end of 3 hr., the 260 mμ peak disappeared. The solvent was removed under reduced pressure and the oily black residue was distilled collecting 12.0 g. product, b.p. 127–130° (12 mm.). This was redistilled to give 11.0 g. material, b.p. 123–125° (10 mm.), $n_D^{17°}$ 1.5113; λ_{max}^{liquid} 5.80 μ(—C═O); 8.15 μ[—C—O— stretch, (acetate)].

2-Hydroxymethyl-5-methylpyrazine. A solution of 10.0 g. (0.06 mole) IX in 48 ml. 10% sodium hydroxide was allowed to stand 72 hr. at room temperature. The yellow solution was saturated with salt and continuously extracted with ether for 24 hr. The dried extract was concentrated and chilled to give 6.3 g. product, m.p. 25–28°. This was distilled collecting the portion b.p. 137–138° (21 mm.). This was recrystallized from ether–petroleum ether (b.p. 30–60°), m.p. 36–39°; $\lambda_{max}^{CHCl_3}$ 2.95 μ (OH); 9.70 μ (C—OH).

2-Acetoxymethyl-6-methylpyrazine. A solution of 9.0 g. (0.072 mole) 2,6-dimethylpyrazine-1-oxide (m.p. 50°) in 45

ml. acetic anhydride was heated under reflux for 1.5 hr. at which time the absorption peak at 260 mμ disappeared. The solvent was removed *in vacuo*, the residue was taken up in hot absolute ethanol, decolorized with charcoal, and concentrated *in vacuo*. The residual oil was distilled collecting a total of 7.0 g. of product in two fractions, b.p. 127–130° (14 mm.), $n_D^{22°}$ 1.5017–1.5068. A portion was redistilled, b.p. 98–99° (0.1 mm.), $n_D^{23°}$ 1.5025; $\lambda_{max}^{CHCl_3}$ 5.65 μ; 5.72 μ (—C=O).

2-Hydroxymethyl-6-methylpyrazine. A solution of 7.3 g. (0.04 mole) 2-acetoxymethyl-6-methylpyrazine in 35 ml. 10% sodium hydroxide was allowed to stand 96 hr. The dark red solution was saturated with salt and extracted with ether. The dried extract was concentrated and the residual oil, weighing 2.3 g., solidified on standing in a desiccator under vacuum. Upon recrystallization from ether–petroleum ether (b.p. 30–60°) the colorless crystals melted at 35°. For analysis the material was sublimed *in vacuo* 100–110°, (10 mm.), m.p. 45°. $\lambda_{max}^{CHCl_3}$ 3.0 μ (OH); 9.55 μ (C—OH).

2-Acetoxymethyl-3,5,6-trimethylpyrazine. A solution of 15.2 g. (0.1 mole) 2,3,5,6-tetramethylpyrazine-1-oxide in 51 ml. acetic anhydride was refluxed for 2 hr., although the absorption maximum had shifted from 259 mμ to 285 mμ in 0.5 hr. The solution was concentrated under reduced pressure. Colorless needles, 0.7 g. which appeared in the residue on cooling, were collected and washed with ether. This material melted 320–322°, left an ash on ignition, and was transparent in the ultraviolet. It was not investigated further.

The mother liquor and ether washings were combined, reconcentrated *in vacuo* and distilled giving (a) 1.2 g. of liquid, b.p. 50–75° (14 mm.), m.p. 74°, identified as tetramethylpyrazine; (b) 10.8 g. of product, b.p. 132–135° (9 mm.). This was redistilled, b.p. 145–147° (17 mm.), $n_D^{24.5°}$ 1.5053. $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O).

2-Hydroxymethyl-3,5,6-trimethylpyrazine. A mixture of 5.0 g. (0.025 mole) 2-acetoxymethyl-3,5,6-trimethylpyrazine and 25 ml. 10% sodium hydroxide was allowed to stand 2 days during which time the immiscible layers slowly disappeared and the solution turned yellow. The solution was saturated with salt, and continuously extracted with ether for 24 hr. The dried extract was concentrated leaving 2.2 g. light yellow solid, m.p. 60°. Two recrystallizations from ether–petroleum ether (b.p. 30–60°) raised the m.p. to 63–65°. For analysis, a portion was sublimed *in vacuo*, m.p. 65°. $\lambda_{max}^{CHCl_3}$ 2.92 μ (OH); 9.45 μ (—C—OH).

3-Acetoxymethylpyrazine-1-oxide. (XI). A solution of 6.3 g. (0.005 mole) 2-methylpyrazine-1,4-dioxide in 30 ml. acetic anhydride was refluxed for 2.5 hr. During this time the absorption maxima at 235 mμ and 295 mμ decreased and disappeared, while new maxima arose at about 220 mμ and 260 mμ, indicating the formation of a mono-*N*-oxide.[17]

The excess solvent was removed under reduced pressure and the black residue was extracted with three 50-ml. portions of boiling ethanol. The combined extracts were decolorized with charcoal and reduced to dryness, leaving 3.0 g. of a greasy, yellow solid. This was recrystallized several times from absolute alcohol (charcoal) to give colorless platelets, m.p. 104–105°. $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O); 7.52 μ (N → O)[17]; 11.50 μ (N → O).

2-Acetoxymethyl-5-methylpyrazine-4-oxide (XIV).[26] A solution of 28.0 g. (0.2 mole) XII in 102 ml. acetic anhydride was heated under reflux until the absorption maxima at 230 mμ and 295 mμ of samples taken at 15-min. intervals disappeared and the extinction of a newly formed peak at 260 mμ reached a maximum. In several runs this required about 2 hr. The solvent was removed under reduced pressure and the residual black oil was distilled collecting 7.45 g. amber liquid, b.p. 120–134° at 0.5–1.5 mm., $n_D^{23.5°}$ 1.5279, which crystallized completely on cooling. This was identified as 2,5-dimethylpyrazine-1-oxide, by comparison of its infrared absorption spectrum with that of the pure compound,[17] mixed melting point, and mixed melting point of the picrates, m.p. 148–149°.[27]

Anal. Calcd. for $C_{12}H_{11}N_5O_8$: C, 40.7; H, 3.1. Found: C, 40.55; H, 3.29.

The residue, 11.0 g., solidified on cooling. This was extracted with boiling benzene and the yellow extract, after decolorization with charcoal, was concentrated to a yellow, low-melting solid that liquefied at room temperature. This was distilled, collecting 5.5 g., b.p. 155–160° (0.5 mm.) which solidified in the receiver, m.p. 50–52°. Several recrystallizations from ether (charcoal) raised the m.p. to 73–74.5°; $\lambda_{max}^{CHCl_3}$ 5.77 μ (—C=O); 7.65 μ (N → O); 11.80 μ (N → O).

2-Hydroxymethyl-5-methylpyrazine-1,4-dioxide. (A) *From 2-acetoxymethyl-5-methylpyrazine* (IX). A solution of 4.0 g. (0.025 mole) (IX) in 8 ml. glacial acetic acid was heated with 11.5 ml. 30% hydrogen peroxide for 24 hr. on a steam bath. The solution was concentrated *in vacuo* until colorless crystals began to form. This was diluted with water and taken to dryness, *in vacuo*. The colorless residue, m.p. 195°, weighed 4.0 g. Two recrystallizations from 95% ethanol and one from absolute alcohol gave 2.0 g. material, m.p. 229–230°.

(B) *From 2-acetoxymethyl-5-methylpyrazine-4-oxide* (XIV). A solution of 3.7 g. (0.02 mole) (XIV) in 9.2 ml. glacial acetic acid, heated 18 hr. on a steam bath with 6.0 ml. 30% hydrogen peroxide and worked up as in (A) gave 1.3 g. material, m.p. 229–230°. Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 226–228°; λ_{max}^{KBr} 3.05 μ (OH); 3.25 μ (associated OH); 7.75 μ, 7.85 μ, 7.95 μ, 11.35 μ (N → O).

2-Acetoxymethyl-5-methylpyrazine-1,4-dioxide. A mixture of 0.4 g. 2-hydroxymethyl-5-methylpyrazine-1,4-dioxide, 5 ml. acetic anhydride, and 10 ml. pyridine was allowed to stand at room temperature for 18 hr. It was heated for 10 min. on a steam cone and poured into 100 ml. cold water. The solution was acidified to *p*H 2.5 and extracted with chloroform. The dried extract was evaporated to dryness and the yellow residual solid, 0.20 g., melted at 235°. Several recrystallizations from absolute ethanol gave colorless crystals, m.p. 239–240°. Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 242–243°; $\lambda_{max}^{CHCl_3}$ 5.65 μ (—C=O); 7.90 μ, 11.83 μ (N → O).

2,5-Diacetoxymethylpyrazine (XV). A solution of 4.2 g. (0.03 mole) XII in 15 ml. acetic anhydride was heated under reflux until a sample withdrawn for analysis showed only a single absorption peak at about 270 mμ. This took about 6 hr. Following removal of solvent under reduced pressure, the black tarry residue was extracted with ether. The combined extracts were decolorized and evaporated to dryness, leaving 0.7 g. yellow needles, m.p. 65–67°. For analysis, a small amount was sublimed *in vacuo*, giving colorless needles, m.p. 68–70°; $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O). Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 80–81°.

2-Hydroxymethyl-3,5,6-trimethylpyrazine-N-oxide. To a solution of 3.4 g. 2-acetoxymethyl-3,5,6-trimethylpyrazine in 5.1 ml. acetic acid, 4.5 ml. 35% hydrogen peroxide was added in two portions, half at the beginning of the reaction, and the remainder midway during the 7-hr. heating period (70°). Half the solvent was removed under reduced pressure, the solution was diluted with an equal volume of cold water, brought to *p*H 8 with cold 10% sodium hydroxide, and extracted with chloroform. The combined extracts were dried and evaporated to dryness leaving 2.5 g. of product, the bulk of which melted 63–66°, but which also contained higher melting material. Extraction of the solid with boiling

(26) The preparation of a 2-acetoxymethyl-5-methylpyrazine-*N*-oxide, m.p. 96–97°, by peroxidation of IX, and treatment of the dioxide with acetic anhydride is reported by Koelsch and Gumprecht.[13] It is believed their compound is the 1-oxide.

(27) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε
2-Acetoxymethylpyrazine				
5-Methyl	271[b]			
	274	3.99		
6-Methyl	273	3.99		
3,5,6-Trimethyl	279	4.36		
4-Oxide	219	4.23	260	4.18
5-Methyl-4-oxide	215	4.03	264	4.00
5-Methyl-1,4-dioxide	232	4.11	300	4.04
5-Acetoxymethyl	269	3.84		
2-Hydroxymethylpyrazine				
5-Methyl	274	3.87		
6-Methyl	274	3.83		
3,5,6-Trimethyl	280	3.90		
5-Methyl-1,4-dioxide	232	4.10	300	4.00
3,5,6-Trimethyl-*N*-oxide	216	4.31	259	3.03
			296	3.77
3,5,6-Trimethyl-1,4-dioxide	238	4.52	299	4.34

[a] All spectra taken in distilled water. [b] 95% ethanol.

petroleum ether (b.p. 30–60°) gave 0.9 g. colorless needles, which after several recrystallizations from petroleum ether (b.p. 30–60°) melted 83–85.5°; λ_{max}^{KBr} 2.95 μ (OH); 7.57 μ, 11.65 μ, 11.90 μ (N → O).

The residue from the petroleum ether extractions was recrystallized several times from methanol, to give 0.09 g. colorless crystals, m.p. 152.5–154.5°. This gave the ultraviolet absorption spectrum of a dioxide and is 2-hydroxymethyl-3,5,6-trimethylpyrazine-1,4-dioxide; λ_{max}^{KBr} 3.05 μ (OH); 7.62, 11.72 μ (N → O).

Absorption spectra. The ultraviolet absorption spectra of compounds reported in this paper were obtained with a Beckman DU spectrophotometer, with 1.0-cm. cuvets. These are given in Table III.

Infrared absorption spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer either as potassium bromide disks or in chloroform solution.[28]

(28) The authors are indebted to Dr. Oscar Auerbach and the Research Committee, Veterans Administration Hospital, East Orange, N. J., for continued loan of this instrument.

BRONX 68, N. Y.

[CONTRIBUTION FROM THE DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY, DIVISION OF UNION CARBIDE CORPORATION]

A Novel Synthesis of Homopiperazine and Its Monomethyl Derivatives

F. POPPELSDORF AND R. C. MYERLY

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Homopiperazine has been synthesized in a yield of about 32% by a new method involving the catalytic reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine. 1-, 2-, 5-, and 6-methylhomopiperazine, the four possible monomethylhomopiperazines, were prepared analogously. *N*-(2′-Aminoethyl)-1,3-propanediamine and its monomethyl derivatives were formed as co-products in 28 to 50% yields.

The intermediate cyano compounds were made by the interaction of the appropriate diamines and unsaturated nitriles.

Several derivatives of homopiperazine (1,4-diazacycloheptane) (I) have already been shown to have marked and desirable physiological activity.[1,2,3] Progress in finding new active compounds based on homopiperazine has, however, undoubtedly been hampered because of the relative inaccessibility of the base and its simple derivatives. Until very recently, the only methods published[4,5] for the preparation of homopiperazine involved the alkylation of the disodium salt of a *N*,*N*′-diarylsulfonylethylenediamine with a 1,3-dihalogenopropane followed by acid hydrolysis of the *N*,*N*′-diarylsulfonylhomopiperazine formed to homopiperazine. These syntheses are tedious and expensive and are, therefore, ill-suited for commercial production. A publication[6] which appeared last year after the work reported in this paper had been completed described the preparation of the cyclic amine (I) by the cyclodehydration of *N*-(2′-hydroxyethyl)-1,3-propanediamine by catalytic means or by pyrolysis of its hydrohalides. Over-all yields based on ethanolamine, the starting material, varied from 7.7 to 10.5% and from 7.4 to 19.2%, respectively.

Of the possible monomethylhomopiperazines, only the 1- and 2-methyl compounds have been reported in the literature. 1-Methylhomopiperazine has been made (a) by the ring enlargement of 1-methyl-4-piperidone by a Schmidt-type rearrangement followed by lithium aluminum hydride reduction of the resulting homopiperazinone,[1,7,8] and (b) in poor yield by the catalytic cyclodehydration

(1) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *J. Am. Chem. Soc.*, **76**, 5805 (1954).

(2) J. W. Reinertson and P. E. Thompson, *Antibiotics and Chemotherapy*, **5**, 566 (1955).

(3) P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).

(4) L. Bleier, *Ber.*, **32**, 1825 (1899).

(5) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2038 (1899).

(6) Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, **78**, 153 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

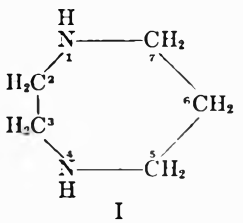
(7) J. G. Scruggs, Ph.D. dissertation, University of Michigan, 1956.

(8) P. S. Wadia and N. Anand, *J. Sci. Ind. Research (India)*, **17B**, 31 (1958); *Chem. Abstr.*, **52**, 15549 (1958).

of *N*-(2′-hydroxyethyl)-*N*-methyl-1,3-propanediamine.[6] 2-Methylhomopiperazine has recently been prepared by the catalytic cyclodehydration of *N*-(2′-hydroxypropyl)-1,3-propanediamine.[9]

We wish to report a novel and simple synthesis of homopiperazine and the four possible monomethylhomopiperazines, *i.e.*, the 1-, 2-, 5-, and 6-methyl compounds, based on the reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine (II) and its methyl derivatives. The cyano compounds required were made by the interaction of the appropriate diamines and unsaturated nitriles most of which are cheap and readily available.

In the case of homopiperazine, the synthesis involves first the addition of acrylonitrile to ethylenediamine to form the cyanoethylated diamine (II) and then reductive cyclization of this compound with hydrogen and a nickel catalyst. Under optimum conditions for the cyclization, which include a hydrogenating pressure of 650 to 950 p.s.i.g. and a reaction temperature of 130°, homopiperazine was produced in a yield of about 32% based on acrylonitrile. The four monomethylhomopiperazines were prepared analogously.



I

$H_2NCH_2CH_2NHCH_2CH_2CN$
II

$H_2NCH_2CH_2NHCH_2CH_2CH_2NH_2$
III

$H_2NCH_2CH_2N(CH_3)CH_2CH_2CN$
IV

$CH_3NHCH_2CH_2NHCH_2CH_2CN$
V

N-(2′-Aminoethyl)-1,3-propanediamine (III) and its monomethyl derivatives were formed as coproducts in over-all yields of 28 to 50% based on the unsaturated nitriles.

Because of their thermal instability, the intermediate cyanoethylated diamine (II) and its monomethyl derivatives were prepared as residue products and converted into the corresponding homopiperazines without further purification.

Cyanoethylation of *N*-methylethylenediamine yielded a product which analyses specific for aliphatic primary[10] and tertiary[11] amino groups showed to be a mixture of the isomers (IV) and (V) in the respective proportions of 73 and 27%. The isomer (IV) was separated in an almost pure state by distillation. Predominant formation of the tertiary amine (IV) may be a result of the secondary amino group of *N*-methylethylenediamine being more basic than the primary amino group.

The effectiveness of the following catalysts for the reductive cyclization was examined: commercial Raney nickel, Raney cobalt, copper chromite, Girdler G-49A catalyst,[12] and 5% palladium on carbon. Of these, only Girdler G-49A catalyst and Raney nickel proved capable of bringing about the desired cyclization. The former catalyst was much superior to the latter. Under identical reaction conditions, Girdler G-49A catalyst produced a 32% yield of homopiperazine; the yield with Raney nickel was but 4.8%.

An inert diluent was advantageous for the reductive cyclization, probably because dilution increases the likelihood of the intramolecular reaction which leads to the desired homopiperazine. Thus, catalytic reduction of the nitrile (II) without a diluent gave homopiperazine and coproduct triamine (III) in yields of 69 and 75%, respectively, of those obtained under comparable conditions when an amount of diluent (*t*-butyl alcohol) equal in weight to the cyano-compound (II) was employed. Furthermore, the weight of high-boiling nitrogeneous residue, which presumably consisted of high molecular weight amines, increased by 21%. *tert*-Butyl alcohol was the most satisfactory diluent examined. 2-Propanol and tetrahydrofuran gave inferior results.

Early reductive cyclization experiments were done by mixing the nitrile (II) with an equal weight of *t*-butyl alcohol, adding catalyst, and then hydrogenating the mixture. Later, it was discovered that gradual addition of the cyano compound (II) to a mixture of solvent and catalyst maintained at the desired temperature and pressure in the autoclave produced superior yields. Thus, when the nitrile (II) was fed to the autoclave over 3.3 hours the yield of homopiperazine was increased by about 33% over that secured by the earlier procedure.

A reaction temperature of 130° (with a Girdler G-49A catalyst concentration of 5% and a hydrogenating pressure of 650 to 950 p.s.i.g.) has been found to give the best yields of homopiperazine. The cyclization also proceeded at 115° but then the reaction was slow and unsatisfactory. Reaction

TABLE I

VARIATION OF THE YIELD OF HOMOPIPERAZINE WITH HYDROGENATING PRESSURE[a]

Hydrogenating Pressure, p.s.i.g.	Hydrogenation Time, Min.	Yield of Homopiperazine, %[b]
130–150	655	14.0
250–300	240	25.2
400–450	195	26.0
650–950	156	32.4

[a] Experiments listed were done by continuously feeding *N*-(2-cyanoethyl)ethylenediamine (200.0 g.) over 3.3 hours into a mixture of anhydrous *tert*-butyl alcohol (200.0 g.) and Girdler G-49A catalyst (20.0 g.) kept in a 3 l. stirred autoclave at 130° under the hydrogenating pressure quoted. [b] Based on acrylonitrile.

(9) Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, 79, 302 (1959); *Chem. Abstr.*, 53, 16147 (1959).

(10) F. E. Critchfield and J. B. Johnson, *Anal. Chem.*, 29, 1174 (1957).

(11) F. E. Critchfield, G. L. Funk, and J. B. Johnson, *Anal. Chem.*, 28, 76 (1956).

(12) Consists of reduced and stabilized nickel on a kieselguhr support and contains about 65% of nickel. It is sold by Girdler Catalysts, Chemical Products Division, Chemetron Corporation, Louisville, Ky.

TABLE II

METHYL-SUBSTITUTED *N*-(2-CYANOETHYL)ETHYLENEDIAMINES

Formula	B.P., Mm. and n_D^{20} or M.P.	Calcd., %			Found, %		
		C	H	N	C	H	N
$H_2NCH_2CH_2N(CH_3)CH_2CH_2CN$[a]	72/0.3; 1.4628	56.7	10.3	33.0	57.0	10.6	32.8[d]
$H_2NCH_2CH_2NHCH(CH_3)CH_2CN$	96.5/0.77; 1.4705	56.7	10.3	33.0	57.0	10.6	32.2
Dipicrate ($C_{18}H_{19}N_9O_{14}$)[b]	179–180			21.5			21.5
$H_2NCH_2CH_2NHCH_2CH(CH_3)CN$	77/0.2; 1.4635	56.7	10.3	33.0	56.5	10.6	33.4
Dipicrate ($C_{18}H_{19}N_9O_{14}$)[b]	187–188			21.5			21.7
$H_2NCH(CH_3)CH_2NHCH_2CH_2CN$ / $H_2NCH_2CH(CH_3)NHCH_2CH_2CN$ [c]	80.5/0.2; 1.4635	56.7	10.3	33.0	56.8	10.8	33.2

[a] Contained about 5% of the isomer $CH_3NHCH_2CH_2NHCH_2CH_2CN$. [b] Prepared in, and recrystallized from, ethanol. [c] Mixture of isomers. [d] Calcd.: NH_2, 12.6. Found: NH_2 [by the method of Critchfield and Johnson (ref. 10)], 11.9.

temperatures from 130 to 200° led to reduced yields of the cyclic amine (I).

The yield of homopiperazine depended on the hydrogenating pressure during the cyclization. This effect is summarized in Table I.

No attempt was made to find the best conditions for the reductive cyclization of the appropriate nitriles to the corresponding methylhomopiperazines. With one exception (the preparation of 1-methylhomopiperazine), the conditions used were those found optimum for the reductive cyclization of the cyano compound (II).

One possible way in which the reductive cyclization could take place is by cyclic deamination of the triamine (III). A nickel-catalyzed cyclic deamination of this type is, however, unlikely at a reaction temperature below 150°.[13] Positive proof that the reductive cyclization does not follow this path was provided by substituting the triamine (III) for the nitrile (II) in a reaction where conditions were otherwise optimum for the preparation of homopiperazine. Only unchanged triamine (III) could be isolated at the end of the reaction.

EXPERIMENTAL

N-(2-Cyanoethyl)ethylenediamine. Acrylonitrile (93.8 g., 1.77 moles) was gradually added with stirring and cooling to anhydrous ethylenediamine (425.0 g., 7.07 moles) kept under an atmosphere of dry nitrogen, the temperature of the mixture being maintained between 20° and 30° throughout the addition.

After being stirred for 15 min., the mixture was evaporated at a temperature below 70° under reduced pressure (30 to 5 mm.) in a current of dry nitrogen. This operation was continued until the residue no longer lost weight. Unchanged ethylenediamine (318.0 g.) was recovered and there remained *N*-(2-cyanoethyl)ethylenediamine (200.0 g., 99.8% yield) as a straw-colored oil, b.p. 106–108°/1.0 mm.

Anal. Calcd. for $C_5H_{11}N_3$: NH_2, 14.2; neut. equiv., 56.6. Found: NH_2 (by the method of Critchfield and Johnson[10]), 14.3; neut. equiv.,[14] 56.8.

This residual product was employed without further purification for the preparation of homopiperazine.

Methyl-substituted N-(2-cyanoethyl)ethylenediamines. The intermediate cyano compounds for the preparation of the monomethylhomopiperazines were made in a similar way from the appropriate diamine and unsaturated nitrile. Condensation of crotononitrile and ethylenediamine was effected at 50 to 60°. Methacrylonitrile and ethylenediamine were caused to react by adding the nitrile to the diamine over 3.75 hr. while the temperature of the reaction mixture was gradually raised from 10 to 86°; subsequently, the mixture was stirred at 100° for 0.5 hr. then refluxed for 3 hr. The methyl-substituted cyanoethylethylenediamines are listed in Table II.

Homopiperazine. Anhydrous *t*-butyl alcohol (200.0 g.) and Girdler G-49A catalyst[12] (20.0 g.) were added to a 3-l., stainless steel, autoclave fitted with a stirrer. The air was replaced by hydrogen and then the pressure in the autoclave was increased to 700 p.s.i.g. by the addition of hydrogen. The autoclave and its contents were heated to 130° whereupon *N*-(2-cyanoethyl)ethylenediamine (200.0 g., 203 cc.) was introduced therein by a proportioning pump at the rate of 1 cc. per min. (29.6% per hour), this rate being maintained throughout the addition. Absorption of hydrogen took place smoothly and regularly and was complete at the end of the feed period. During the reaction the temperature was kept at 130° and the hydrogenating pressure at 650 to 950 p.s.i.g. These conditions were maintained for 1.5 hr. after all the cyano compound had been added.

The reaction product was filtered through a kieselguhr-coated filter, the residue washed with *t*-butyl alcohol (2 × 50 g.), and the washings combined with the filtrate. Distillation of the mixture at atmospheric pressure (750 mm.) at a reflux ratio of 3:1 through a column having an efficiency of about 10 theoretical plates afforded homopiperazine (57.3 g., 32.4% yield based on acrylonitrile) as a fraction of b.p. 169° which on cooling formed colorless platelets, m.p. 43° (lit. b.p. 168–170°,[4,6] 167°/764 mm.[5]; m.p. 42°[5,6]). The homopiperazine had the following boiling points at reduced pressures: 92°/50 mm. and 60°/10 mm.

Anal. Calcd. for $C_5H_{12}N_2$: neut. equiv., 50.1. Found: neut. equiv.,[14] 50.5.

N-(2'-Aminoethyl)-1,3-propanediamine. Distillation at reduced pressure of the residue from the foregoing preparation of homopiperazine gave the triamine (86.8 g., 41.9% yield based on acrylonitrile). Properties of this amine are given in Table IV.

Monomethylhomopiperazines. With the exception of 1-methylhomopiperazine, the methylhomopiperazines were prepared in the same way as that described for homopiperazine. The 1-methyl compound was made as follows.

Anhydrous *t*-butyl alcohol (125.0 g.), *N*-(2-cyanoethyl)-*N*-methylethylenediamine (125.0 g.), and Girdler G-49A catalyst[12] (12.5 g.) were added to a 3-l., stainless steel, autoclave fitted with a stirrer. The air was replaced by hydrogen and then the pressure in the autoclave was increased to 700 p.s.i.g. by the addition of hydrogen. The

(13) H. Adkins, *The Reaction of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, Wis., 1937, p. 55.

(14) Determined by titration with perchloric acid in acetic acid.

TABLE III

THE MONOMETHYLHOMOPIPERAZINES AND THEIR PICRATES[a]

Position of Methyl Group	Yield, %[b]	B.P./Mm. and n_D^{20} or M.P.	Formula	Analyses					
				Calcd., %			Found, %		
				C	H	N	C	H	N
1	16.8	164/754; 1.4769	$C_6H_{14}N_2$			24.5			24.4[g]
Dipicrate		245 dec.[c,d]	$C_{18}H_{20}N_8O_{14}$			19.7			19.3
2	8.3	175–175.5/752[e]; 1.4802[f]	$C_6H_{14}N_2$	63.1	12.4	24.5	62.7	12.7	24.2
Dipicrate		278 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.9
5	38.7	175–175.4/745; 1.4843	$C_6H_{14}N_2$	63.1	12.4	24.5	63.2	12.2	24.5
Dipicrate		256 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.9
6	20.6	181–181.3/755; 1.4869	$C_6H_{14}N_2$	63.1	12.4	24.5	62.9	12.4	24.5
Dipicrate		255–256 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.5

[a] The picrates were prepared in, and recrystallized from, water. [b] Over-all, based on the unsaturated nitriles. [c] Ref. 6, m.p. 242–243° dec. [d] Ref. 7, m.p. 233–234°. [e] M.p. 28°. [f] Value determined at 30°. [g] Calcd.: tertiary-amino N, 12.3. Found: tertiary-amino N [by the method of Critchfield, Funk, and Johnson (ref. 11)], 12.3.

TABLE IV

N-(2′-AMINOETHYL)-1,3-PROPANEDIAMINE AND MONOMETHYL DERIVATIVES

Formula	Yield, %[a]	B.P./Mm. and n_D^{20} or M.P.	Analyses					
			Calcd., %			Found, %		
			C	H	N	C	H	N
$H_2NCH_2CH_2NHCH_2CH_2CH_2NH_2$	41.9	72/1.0; 1.4805	51.2	12.9	35.9	51.6	13.5	35.0
Tripicrate ($C_{23}H_{24}N_{12}O_{21}$)[b]		228–229 dec.			20.9			21.0
$H_2NCK_2CH_2NHCH(CH_3)CH_2CH_2NH_2$	27.9	69.3–69.4/1.0; 1.4777	54.9	13.1	32.0	54.7	13.1	32.1
Tripicrate ($C_{24}H_{26}N_{12}O_{21}$)[b]		182–183			20.5			20.1
$H_2NCH_2CH_2NHCH_2CH(CH_3)CH_2NH_2$	47.1	75–76/1.0; 1.4880	54.9	13.1	32.0	55.0	12.7	31.9
Tripicrate ($C_{24}H_{26}N_{12}O_{21}$)[b]		184–185			20.5			20.9
$CH_3NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ / $H_2NCH_2CH_2N(CH_3)CH_2CH_2CH_2NH_2$ [c]	40.5	62–65.5/1.1	54.9	13.1	32.0	54.8	13.5	31.8
$H_2NCH(CH_3)CH_2NHCH_2CH_2CH_2NH_2$ / $H_2NCH_2CH(CH_3)NHCH_2CH_2CH_2NH_2$ [c]	48.2	73–75/1.0; 1.4737	54.9	13.1	32.0	54.6	13.3	31.9

[a] Over-all, based on the unsaturated nitriles. [b] Prepared in, and recrystallized from, ethanol. [c] Mixtures of isomers.

autoclave and its contents were heated to 130° and kept at this temperature at a hydrogenating pressure of 600 to 950 p.s.i.g. until uptake of hydrogen had ceased and thereafter for 3 hours. Working up of the product by the method given for homopiperazine afforded 1-methylhomopiperazine.

The monomethylhomopiperazines and their picrates are listed in Table III.

Methyl-substituted N-(2′-aminoethyl)-1,3-propanediamines. These triamines (see Table IV) were isolated by distillation at reduced pressures of the residues from the foregoing syntheses of the monomethylhomopiperazines.

Attempted cyclic deamination of N-(2′-aminoethyl)-1,3-propanediamine. This experiment was done in the same way as that described for the reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine in the presence of Girdler G-49A catalyst excepting that an equal weight of *N*-(2′-aminoethyl)-1,3-propanediamine (200.0 g.) was substituted for the cyanoethylethylenediamine. Uptake of hydrogen was negligible during the reaction.

Distillation of the product afforded only unchanged *N*-(2′-aminoethyl)-1,3-propanediamine (191.5 g.), b.p. 70–74°/1.0 mm.

Anal. Calcd. for $C_5H_{15}N_3$: neut. equiv., 39.1. Found: neut. equiv.,[14] 39.7.

SOUTH CHARLESTON, W. VA.

[JOINT CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, SMITH KLINE AND FRENCH LABORATORIES AND THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

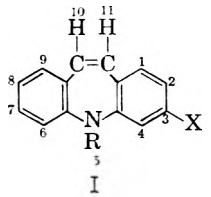
Analogs of Phenothiazines. I. 5H-Dibenz[b,f]azepine and Derivatives. A New Isostere of Phenothiazine[1]

PAUL N. CRAIG, BRUCE M. LESTER, ANDREW J. SAGGIOMO,[2] CARL KAISER, AND CHARLES L. ZIRKLE

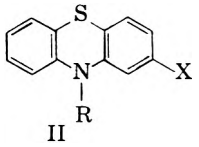
Received March 31, 1960

5H-Dibenz[b,f]azepine was prepared by catalytic dehydrogenation of "iminobibenzyl," and also by the ring expansion which accompanies the dehydration of 9-acridanylmethanol. 3-Chloro-5H-dibenz[b,f]azepine was also prepared by the latter route, and was hydrogenated to form 3-chloro-9,10-dihydro-5H-dibenz[b,f]azepine. Several 5-dialkylaminoalkyl derivatives of these new dibenzazepines were prepared and initial pharmacological test results are reported.

In view of renewed interest in 10-aminoalkylphenothiazine derivatives stemming from the discovery of their tranquilizing properties,[3] we prepared derivatives I-c and I-d of 5H-dibenz[b,f]azepines (I-a and I-b) for biological comparison with the isosteric phenothiazine compounds, II-c (promazine) and II-d (chlorpromazine).



I

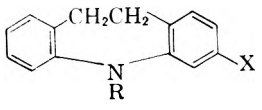


II

a. X = H, R = H
b. X = Cl, R = H
c. X = H, R = $(CH_2)_3N(CH_3)_2$
d. X = Cl, R = $(CH_2)_3N(CH_3)_2$
e. X = H, R = $COCH_3$

According to the concept of isosterism,[4] I-a bears a relationship to phenothiazine analogous to that existing between benzene and thiophene.

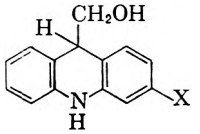
Preliminary attempts to dehydrogenate 10,11-dihydro-5H-dibenz[b,f]azepine (III-a "iminodibenzyl"), using sulfur, selenium, or palladium-charcoal under the usual conditions gave poor results. However, sublimation *in vacuo* of III-a through a hot glass tube packed with palladium-charcoal sprinkled on glass wool[5] gave 20–50% conversions to I-a, obtained as intensely colored orange-yellow platelets. Acetylation of this compound by acetic anhydride gave the colorless acetyl derivative, I-e, which was also obtained by dehydrogenation of III-b by the method of Baxter, Ramage, and Timson.[5]



III

a. X = H, R = H
b. X = H, R = $COCH_3$
c. X = Cl, R = H
d. X = Cl, R = $(CH_2)_3N(CH_3)_2$
e. X = H, R = $(CH_2)_3N$⟨⟩$N-CH_3$

A second route to I-a was found in the ring-enlargement of 9-acridane-methanol (IV-a). This reaction is analogous to the rearrangement of 9,10-dihydroanthracene-9-methanol to dibenzocycloheptatriene as reported by Rigaudy and Tardieu.[6] This method was also successfully applied to the preparation of 3-chloro-5H-dibenz[b,f]azepine (I-b) from 3-chloro-9-acridanemethanol (IV-b). The ring-enlargement of IV was found to be erratic and several methods were studied before those reported in the experimental section were found. The reagents tried included phosphorus oxychloride, 47% hydrobromic acid, thionyl chloride in pyridine, aqueous hydrogen fluoride, zinc chloride, trifluoracetic acid and anhydride, polyphosphoric acid, and phosphorus pentoxide in dimethylformamide or xylene.



IV

a. X = H
b. X = Cl

Acridinemethanol, IV (X = H), was reported recently.[7] The preparation of 3-chloro-9-acridanemethanol was carried out by the sequence employed for the unsubstituted analog, starting with the known compound, 3,9-dichloroacridine.[8]

(1) Presented in part before the Second Delaware Valley Regional Meeting, ACS, in Philadelphia, February 5, 1958.

(2) Research Institute of Temple University.

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Alkylation of I-a and I-b with 3-dimethylaminopropyl chloride in toluene in the presence of sodamide gave the aminopropyl derivatives I-c and I-d.

Although dialkylaminoalkyl derivatives of "iminodibenzyl" (III-a) and symmetrically disubstituted analogs thereof have been prepared[9,10] no compounds monosubstituted in the benzenoid ring have been reported. In the course of this work we prepared 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine (III-c) and its dimethylaminopropyl derivative III-d.

Catalytic hydrogenation of I-b gave the corresponding dihydro compound III-c in 68% yield, as well as a small amount of III-a, resulting from reductive dechlorination of either I-b or III-c. Alkylation of III-c with β-dimethylaminopropylchloride gave 3-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (III-d).

Also prepared was the 5-[3-(4-methylpiperazinylpropyl)] derivative III-e, obtained from the reaction of "iminodibenzyl" (III-a) with 4-(3-chloropropyl)-1-methylpiperazine.

Spectral data for several of these compounds are listed in Tables I & II.

TABLE I

Ultraviolet Spectral Data

Compound	Wave Length, mμ	Molecular Ext. Coeff.
III-a	290	1.15×10^4
III-b	270	7.5×10^2
	233 (shoulder)	9.3×10^3
I-a	292	3.5×10^3
	258	4.4×10^4
I-e	285	1.1×10^4
I-c (maleate)	284	4.4×10^3
	255	3.1×10^4
I-b	295	2.9×10^3
	262	5.0×10^4

Compound Ic was found to be one seventh as active as IId (chlorpromazine) as an antiemetic agent in dogs,[11] and was essentially inactive in the rat conditioned escape response test.[12] The authors are indebted to Drs. C. A. Leonard and D. H. Tedeschi for this preliminary information.

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TABLE II

Infrared Spectral Data

Compound	Peaks, μ[a]
I-a	2.98 (m), 3.30 (w), 6.20 (m), 6.32 (m), 6.65 (w), 6.80 (vs), 6.95 (s), 7.65 (m), 7.75 (m), 7.93 (m), 8.23 (m), 8.67 (m), 9.00 (s), 9.56 (w), 10.73 (s), 10.94 (m), 11.64 (m), 12.46 (vs), 13.07 (w), 13.26 (s), 13.70 (s)
I-b	3.00 (m), 6.20 (m), 6.33 (s), 6.65 (w), 6.80 (vs), 6.94 (w), 7.04 (m), 7.28 (m), 7.67 (w), 7.78 (w), 7.96 (w), 8.06 (m), 8.27 (m), 8.71 (w), 8.99 (m), 9.16 (m), 9.55 (w), 10.67 (s), 11.47 (w), 11.65 (m), 11.97 (m), 12.20 (vs), 12.70 (s), 13.39 (vs)
III-a	2.96 (m), 3.32 (w), 3.40 (w), 3.47 (w), 3.53 (w), 5.20 (w), 5.28 (m), 5.62 (m), 5.92 (w), 6.20 (m), 6.30 (vs), 6.57 (m), 6.73 (vs), 6.90 (m), 7.35 (w), 7.53 (vs), 7.72 (m), 7.83 (m), 8.00 (m), 8.15 (w), 8.29 (m), 8.45 (w), 8.62 (m), 9.00 (s), 9.50 (w), 10.35 (w), 10.50 (w), 10.68 (s), 11.54 (w), 11.65 (m), 11.86 (m), 13.10 (w), 13.37 (vs), 14.20 (w)
III-c	3.00 (w), 3.33 (w), 3.45 (w), 3.48 (w), 3.55 (w), 5.22 (w), 5.54 (w), 5.90 (w), 6.20 (m), 6.32 (vs), 6.57 (s), 6.76 (vs), 6.95 (vs), 7.20 (m), 7.42 (w), 7.52 (m), 7.83 (w), 7.90 (w), 8.08 (m), 8.30 (m), 8.42 (w), 8.53 (w), 8.70 (w), 8.98 (m), 9.02 (m), 9.17 (s), 9.50 (w), 9.58 (m), 10.53 (vs), 10.60 (vs), 10.69 (s), 11.30 (w), 11.85 (vs), 12.50 (vs), 12.64 (vs), 13.45 (vs), 13.66 (m), 13.95 (w), 14.20 (w)

[a] (w) = weak, (m) = medium, (s) = strong, (vs) = very strong.

EXPERIMENTAL[13]

Preparation of 5H-dibenz[b,f]azepine (I-a). *Method A.* An upright 35 mm. dia. glass column 14½ inches long, heated by an asbestos-covered electric tape, was packed tightly with glass wool upon which was sprinkled 2 g. of 30% palladium-on-charcoal. The colorless solid, 10,11-dihydro-5H-dibenz[b,f]azepine (2.5 g.), was placed in a flask mounted below the column and a slow stream of nitrogen was passed through the system, which was evacuated and kept between 0.3–0.5 mm. during the distillation. The column was heated first to about 160–170° and the distilling flask was heated between 120–130°. The material was distilled slowly so that a run of 2.5 g. of 10,11-dihydro-5H-dibenz[b,f]azepine required about 2 hr. to be distilled. The products condensed at the top of the column above the heated zone, and were easily removed by scraping.

The crude orange material was dissolved in benzene and chromatographed through a 25 mm. dia. column packed to a depth of about 25 cm. with activated alumina. The products were separated into fractions melting at 195–198°, 155–190°, and 101–154°. The material melting above 155° was twice recrystallized from ethanol and then was essentially pure. The predominantly unchanged material (melting below 155°) was redistilled through palladium-on-charcoal and then rechromatographed. This procedure was repeated until all of the material melted above 150°.

In this manner 13.0 g. of 10,11-dihydro-5H-dibenz[b,f]-azepine was converted to 6.4 g. of 5H-dibenz[b,f]azepine; m.p. 195–198° (I-a). The purest sample of 5H-dibenz[b,f]-azepine obtained had a melting point of 196.5–198°. The overall yield was 50%; the other 50% was lost in the repeated handling required by this procedure.

(13) Melting points uncorrected.

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.75; H, 5.94; N, 7.35.

Refluxing I-a with excess acetic anhydride in benzene for 0.5 hr. afforded the colorless *N*-acetyl derivative, I-c; m.p. 99–101°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.33; H, 5.53.

This same derivative was prepared from III (R = CH_3CO, X = H) by the experimental method A above.

Hydrolysis of the *N*-acetyl derivative by refluxing in a mixture of ethanol and 10% hydrochloric acid for 2 hr. gave back I (R = X = H).

Method B. A stirred mixture of phosphorus pentoxide (5 g.), 125 ml. of xylene, and glass beads under nitrogen was heated to reflux. To this mixture was added 2 g. of 9-acridanemethanol[7] *via* the Soxhlet extractor method. After 2 hr. the extraction was completed and the reaction was cooled and quenched with water. The aqueous layer was shaken with hot xylene, and the combined xylene layers were dried and concentrated by distillation. The residue was recrystallized from carbon tetrachloride, using decolorizing charcoal, to give 1.1 g. (58%) of 5H-dibenz[b,f]-azepine (I, R = X = H); m.p. 192–194°. One recrystallization from benzene–petroleum ether (b.p. 30–60°) raised the m.p. to 195.5–196.5°; no depression was observed on mixing with compound prepared by route A. Infrared spectral curves for samples prepared by both routes A and B were identical.

Preparation of 3-chloro-5H-dibenz[b,f]azepine. (Ib) *9-Cyano-3-chloroacridane.* Into a stainless steel pressure reactor was placed a mixture of 3,9-dichloroacridane (53.5 g., 0.216 mole), sodium cyanide (12 g., 0.24 mole), and anhydrous methanol (375 ml.). Pre-purified nitrogen was introduced (1 atm.) and the reactor was heated at 130–140° for 4.5 hr. with continuous rocking. The reactor was cooled, vented, and the product was removed with acetone. The insoluble yellow needles were filtered and washed well with water. There was obtained 9-cyano-3-chloroacridine as yellow needles (42 g., 84%); m.p. 197–199.5°. After several recrystallizations from methanol the compound melted at 202.5°.

Anal. Calcd. for $C_{14}H_7ClN_2$: C, 70.45; H, 2.96. Found: C, 70.60; H, 3.15.

Ethyl 3-chloro-9-acridinecarboxylate. A mixture of 3-chloro-9-cyanoacridine (135 g., 0.565 mole) and 90% sulfuric acid (700 ml.) was heated in a 4-l. beaker in a boiling water bath for 3 hr. with mechanical stirring. The reaction mixture was cooled to 0° and sodium nitrite (210 g.) was added in small portions. The yellow suspension was allowed to remain 1 hr. at 0–5° and 1 hr. at room temperature. The reaction beaker was gradually heated by a water bath to 55–60°, when a vigorous evolution of gas occurred. When the latter subsided, the reaction was heated 2 hr. on a boiling water bath, cooled to 0° and was diluted with ice water, dissolved in dilute sodium hydroxide, and the solution was treated with decolorizing charcoal. Acidification of the filtrate gave 3-chloro-9-acridinecarboxylic acid as a yellow solid (135 g., 86%); m.p. 268° dec.

A mixture of the above acid (128 g., 0.5 mole) and thionyl chloride (405 g.) was refluxed with stirring until all the acid dissolved (usually 3 to 4 hr.). The dark red solution was cooled and diluted with dry benzene. The yellow solid that precipitated upon scratching was collected and washed well with benzene. It was then added in portions to 800 ml. of ethanol. The mixture was gradually heated and refluxed for 2 hr. The cold dark brown solution was diluted with water and made alkaline with a cold solution of sodium carbonate. The product that formed was washed with water in a Waring Blendor. Recrystallization from hexane, with treatment by decolorizing charcoal, gave the ester as pale yellow needles, m.p. 96–96.5°. Evaporation of the mother liquors, with a subsequent recrystallization of the residue from hexane, gave a second crop of same melting point; total yield 140 g. (73%).

Anal. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.25; H, 4.23. Found: C, 67.25; H, 4.31.

3-Chloro-9-acridanemethanol. (IVb) This reaction was conducted in a carefully dried system under an atmosphere of purified nitrogen. To 300 ml. of anhydrous ether was added in portions 28 g. (0.7 mole) of lithium aluminum hydride, and the mixture was refluxed for 30 min. To this stirred suspension at room temperature was added dropwise a solution of 100 g. (0.35 mole) of ethyl 3-chloro-9-acridinecarboxylate in 1500 ml. of anhydrous ether at a rate which produced moderate refluxing of the ether. After two thirds of the addition was completed, an additional 10 g. of lithium aluminum hydride was added to the reaction to ensure its completion. Refluxing was then continued for 3 hr. The dark brown mixture was cooled to 0° in an ice-salt bath and was decomposed slowly with wet ether, followed by an excess of water. The ether layer was decanted; the milky-white aqueous layer was acidified with dilute hydrochloric acid, and was extracted with ether. The combined ether portions were dried over Drierite and the solvent was removed either *in vacuo* or in an atmosphere of pre-purified nitrogen. The brown residue, after a recrystallization from benzene–petroleum ether (b.p. 30–60°) with decolorizing charcoal, gave 3-chloro-9-acridanemethanol as white needles (65 g., 75%); m.p. 139–140°.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.22; H, 4.63; N, 5.72. Found: C, 68.17; H, 4.52; N, 5.73.

3-Chloro-5H-dibenz[b,f]azepine. (Ib) A mixture of 3-chloro-9-acridanemethanol (1 g., 0.004 mole) and 10 g. of reagent sea sand was stirred in 30 ml. of refluxing pre-dried xylene under purified nitrogen. To this was added in four portions over a 2-hr. period 4 g. (0.028 mole) of phosphorus pentoxide. The yellowish-orange reaction mixture was refluxed for an additional 90 min. It was then cooled and cautiously treated with a large excess of water. The sand was removed by filtration and the two layers separated. The aqueous layer and sand were separately extracted with hot benzene. The benzene extracts and xylene layers were combined, dried, and the solvents were removed *in vacuo*. The solid orange residue (m.p. 180–186°) was recrystallized twice from benzene with decolorizing charcoal to give 3-chloro-5H-dibenz-[b,f]azepine (0.45 g., 49%) as yellow-orange platelets, m.p. 208–209°.

Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15. Found: C, 73.85; H, 4.62; N, 6.10.

5-[3-Dimethylaminopropyl]-5H-dibenz[b,f]azepine (I-c). A solution of 5.5 g. (0.029 mole) of 5H-dibenz[b,f]azepine in 200 ml. of hot toluene was added to a suspension of freshly prepared sodamide (0.047 mole) in 100 ml. of dry toluene. After refluxing the stirred mixture 2 hr., a solution of 5.5 g. of 3-dimethylaminopropyl chloride in 50 ml. of dry toluene was added, and the mixture was refluxed and stirred for 17 hr. After cooling the mixture, 125 ml. of water was added and stirring continued for 20 min. The layers were separated and the toluene layer was extracted seven times with a 1:1 hydrochloric acid–water solution. The combined acid extracts were treated with 40% sodium hydroxide solution and the alkaline solution was extracted four times with benzene. The benzene was evaporated, leaving 8.5 g. of a dark brown oil. This oil was dissolved in benzene and chromatographed through a 25 cm. dia. column packed to a depth of 20 cm. with activated alumina. The 6.0 g. of orange-red oil obtained from the chromatogram (representing a 75% yield of free base) was dissolved in 40 ml. of ethyl acetate and added to a solution of 2.55 g. of maleic acid in 50 ml. of ethyl acetate. The maleate salt was twice recrystallized from alcohol–ether with Darco to give 7.0 g., m.p. 148–149.5° (62% overall).

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.88; H, 6.62; N, 7.11.

3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepine. (Ib) A mixture of 2.28 g. (0.01 mole) of 3-chloro-5H-dibenz[b,f]azepine, (IIIc) 100 mg. of platinum oxide, and 100 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature.

Hydrogenation was continued until the originally dark orange mixture became a pale yellow solution. At this point 120–130% of the calculated amount of hydrogen had been absorbed. The catalyst was filtered and the ethanolic filtrate was evaporated *in vacuo*. The yellow residual solid was dissolved in 10 ml. of benzene and the solution was placed on a $^3/_4'' \times 18''$ alumina column. The column was eluted with petroleum ether (b.p. 30–60°) (100 ml.), 100 ml. of 20% benzene in petroleum ether (b.p. 30–60°), and finally with 100 ml. of 50% benzene in petroleum ether (b.p. 30–60°). The first fraction was cut at the first sign of yellow coloration in the eluate. A strongly yellow colored second fraction was obtained by further elution with benzene. The second fraction was concentrated *in vacuo* to give a yellow solid, which was recrystallized from ethanol to give 0.3 g. of yellow plates; m.p. 186–195°. An infrared spectrum indicated this material was mostly recovered I-b.

The first fraction was concentrated *in vacuo* to give 1.7 g. of an almost colorless residue, m.p. 80–83° after recrystallization from aqueous ethanol. The colorless crystals were sublimed at 78° and 0.3 mm. to give a small amount of sublimate, m.p. 97–100°. The melting point of this sample was not depressed by mixture with 10,11-dihydro-5H-dibenz[b,f]azepine. The material which did not sublime was recrystallized from aqueous ethanol to give 1.55 g. of colorless crystals, m.p. 84.5–86°. (III–c.)

Anal. Calcd. for $C_{14}H_{12}NCl$: C, 73.20; H, 5.27. Found: C, 72.73, 72.62; H, 5.39, 5.28.

3-Chloro-10,11-dihydro-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (III-d). Alkylation was accomplished essentially as described above for the preparation of 5-(3-dimethylaminopropyl)dibenz[b,f]azepine. Toluene was used as the solvent, and the crude free base was not chromatographed, but was distilled; b.p. 160–170° at 0.3 mm. The hydrochloride was recrystallized from acetone-ether and then from methanol-ether to give a 75% yield of colorless crystals; m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{23}ClN\cdot HCl$: C, 64.93; H, 6.89. Found: C, 64.66; H, 6.96.

3-Chloro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (I-d). Alkylation of 3-chloro-5H-dibenz[b,f]azepine was carried out as described above for the alkylation of 5H-dibenz[b,f]azepine. Toluene was used as the solvent, and instead of chromatography, distillation was used to purify the free base of the product; b.p. 168–176° at 0.4–0.5 mm. The maleate was formed in ethyl acetate and was recrystallized three times from acetone-ether to give a 45% yield of yellow crystals; m.p. 124.5–125.5°.

Anal. Calcd. for $C_{19}H_{22}ClN_2\cdot C_4H_4O_4$: C, 64.40; H, 5.88. Found: C, 64.01; H, 6.01.

10,11-Dihydro-5-[3-(4-methyl-1-piperazinyl)propyl]-5H-dibenz[b,f]azepine (IIIe). The alkylation differed from that described above for the alkylation of 5H-dibenz[b,f]azepine as follows. Toluene was used as the solvent, and the alkylation required 12 hr. The free base was purified by distillation; b.p. 199–212° at 0.2–0.3 mm. The dihydrochloride was recrystallized from methanol-ether three times to give a 63% yield of colorless crystals; m.p. 245–246.5°. The infrared spectrum indicated that a trace of water was present.

Anal. Calcd. for $C_{22}H_{29}N_3\cdot 2HCl$: C, 64.70; H, 7.16. Found: C, 62.90; H, 7.82.

Anal. Calcd. for hemihydrate: C, 63.30; H, 7.73.

Addendum. Subsequent to the original preparation of this paper, two papers have appeared in which the preparation of Ia is reported.[14,15]

PHILADELPHIA, PA.

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

Synthesis of Potential Anticancer Agents. V. Azetidines[1,2]

WYMAN R. VAUGHAN, ROBERT S. KLONOWSKI,[3] R. STANLEY McELHINNEY, AND BRIAN B. MILLWARD

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The problem of azetidine synthesis is reviewed, several unsuccessful approaches are described, and a relatively convenient method for the preparation of certain azetidines is reported. Cyclization to the azetidine system is considered as a conformational problem.

Although azetidine (I) and its derivatives have been known since the latter part of the nineteenth century,[4] comparatively little work has been done on methods of preparation, which in general appears to be inherently difficult, azetidine or an azetidine derivative often being but a minor constituent of the reaction products.

The present work was undertaken because of the potential relationship between azetidine and ethylenimine as regards "alkylating action," which in the latter has generally been credited with its effectiveness in certain anticancer agents.[5] To this end it was proposed to prepare azetidine analogs of various ethylenimine derivatives of known clinical use in the control of neoplastic disease.

It rapidly became apparent that the major barrier to such a program was the lack of convenient syntheses affording a good yield of azetidine itself or of its carbon-substituted derivatives. Potential approaches are from 2-azetidinones (*e. g.*, β-lactams) by reduction or from acyclic 3-functionally substituted (*e. g.*, halogen, *O*-sulfonate) amines.

(1) Previous paper in this series, R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **25**, 1583 (1960).

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Reduction of 2-azetidinones. In spite of the report in 1954[6] that 1,4-diphenyl-2-azetidinone undergoes lithium aluminum hydride reduction to give 3-anilinodihydrocinnamyl alcohol, this reaction was reinvestigated, but with substantially the same results under a variety of conditions. The results are of use only as a potential source of 3-aminoalcohols for cyclization studies. Hydride reductions of 1,4-diphenyl-3,3-dimethyl-2-azetidinone[7] also afforded only the analogous acyclic alcohol, while high pressure hydrogenation over Raney nickel afforded 2,2-dimethyl-3,*N*-dicyclohexylpropionamide, which could be recovered unchanged after fifteen hours refluxing with 25% sodium hydroxide.

Our experience with 1,4-substituted 2-azetidinones has been confirmed recently by others.[8a,b] However, it is of considerable interest to note that successful reduction of 2-azetidinones to azetidines by lithium aluminum hydride is possible, providing there is no substituent on nitrogen.[8a]

Cyclization procedures. Four general methods purporting to yield azetidines by cyclization have been reported: (1) dehydrohalogenation of 3-haloalkylamines[9–13]; (2) reaction of 1,3-dihaloalkanes with amides[14–18]; (3) reaction of 3-aminoalkyl hydrogen sulfates with base[19–21]; (4) pyrolysis of diamines and related compounds.[22]

We have attempted to adapt the dehydrohalogenation of 3-haloalkylamines to the preparation of azetidine itself by way of *N*-benzylazetidine, which proved to be readily debenzylated. The necessary starting material, 3-*N*-benzylaminopropanol (II) is readily available by catalytic reduction of the Schiff base of commercially available 3-aminopropanol. Subsequent conversion of II to the *O*-tosylate (III) was realized by the procedure of Cope and Burg[23] for the mesylation of amino alcohols, but the product was difficultly separable from accompanying pyridine hydrochloride. The hydrochloride of III was cyclized using two equivalents of sodium hydroxide in the general manner for this method, and a 26% yield of *N*-benzylazetidine (V), isolated as the picrate, was obtained. This represents a reasonable yield for an otherwise unsubstituted *N*-alkylazetidine. Hydrogenolysis afforded azetidine.

We have also applied the cyclization of 3-aminoalkyl hydrogen sulfates to the synthesis of *N*-benzylazetidine (V) and obtained but a 5% yield. Almost twice the yield was obtained when 3-*N*-benzylaminopropanol was treated with concentrated sulfuric acid followed by alkali, but variations in concentrations did not improve the yield.

In view of the previous results it appeared to us that the most favorable conditions for constructing the azetidine ring system involved either cyclization of a suitable 3-substituted amine (secondary) or reaction of a 1,3-dihaloalkane with a sulfonamide in the presence of base. Consequently, we turned attention to a combination of the best features of both procedures. Thus 3-(*p*-toluenesulfonamido)-propyl *p*-toluenesulfonate (VI) provides an ideal starting point. This substance can be prepared in 95% yield from commercially available 3-aminopropanol, and the analogous 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate (VII) can be prepared in 66% yield from the corresponding aminoalcohol. Under appropriate conditions VI and VII were cyclized to IV (*p*-toluenesulfonazetidide)[15] and *p*-toluenesulfon-2-methylazetidide (VIII) in yields of 80–93% and 68% respectively. In addition *N*-(3-chloropropyl)methanesulfonamide (IX) was cyclized to methanesulfonazetidide (X) in 67% yield. This is appreciably better than the 55% yield of IV from *N*-(3-chloropropyl)-*p*-toluenesulfonamide reported by Searles.[15]

The chief problems in cyclization are competing

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eliminations and dimerization to bisazacyclo-octane sulfonamides. The former was negligible in the case of the primary tosylates, although recovery of the theoretical quantity of sodium chloride from the reaction of IX suggested that appreciable dehydrohalogenation may have occurred. Dimerization during the cyclization of VII became appreciable when the concentration of VII was increased above 0.097*M*; and with VIII appreciable dimerization occurred at lower concentrations, best yields being obtained using high dilution addition technique.

Having in hand acceptable syntheses of sulfonazetidides, we turned our attention to the previously discouraging problem of converting them to azetidines. Basic cleavage was found ineffective (*e. g.*, potassium ethoxide in toluene[24] as was high pressure hydrogenolysis (Raney nickel). With lithium aluminum hydride IV afforded a 10% yield of I, but X failed to react. Accordingly, we determined to reinvestigate the early report of almost quantitative conversion by sodium and amyl alcohol[16] in spite of later failures to duplicate this result.[10,17]

In the initial report[16] no special precautions were noted, and subsequent investigators gave no explicit details. However, since azetidine boils at 62° and amyl alcohol at 140°, and since a stream of hydrogen gas is constantly escaping, it seemed only prudent to trap any azetidine which might be carried out of the reaction. To this end the exit gases were passed through dilute sulfuric acid; and whether or not this acid was subsequently used to extract the free base from the amyl alcohol, I and 2-methylazetidine (XI) were obtained in excellent yield, while X afforded I in 42% yield. Thus the problem seems to have been largely mechanical; the free flow of hydrogen entrained the volatile azetidine, while forcing the gas through a trap served to mitigate such loss.

DISCUSSION

The substance of this investigation is the emergence of a comparatively convenient route from 3-aminopropanols to *N*-unsubstituted azetidines which is in principle limited only by the character of the hydroxyl: *i.e.*, with a tertiary alcohol, solvolysis would be expected and the resultant carbonium ion will then stabilize *via* solvent capture, deprotonation or "fragmentation" as with the analogous 3-aminopropyl halides.[25] It is perhaps surprising, though gratifying, that the anions derived from the 3-sulfonamidopropyl sulfonates do not fragment, since the gross conformation appropriate for cyclization, as well as conformations derived from it by rotation about the C_3–C_4 bond, are all sterically ideal for such a reaction. Failure to observe fragmentation with primary tosylates is in large part attributable to the greater energy requirement for heterolytic cleavage of a primary carbon-oxygen bond, but failure to observe it where this bond is secondary (VI) must be attributed to a stereoelectronic situation arising from the great bulk of the sulfonyl group which tends to place it conformationally staggered with respect to the substituents on C_3 (Fig. 1). Thus it occupies the position required of an electron pair if the latter is to participate effectively in the fragmentation process, which is the dominant if not exclusive reaction when stereoelectronic conditions are fulfilled.[25]

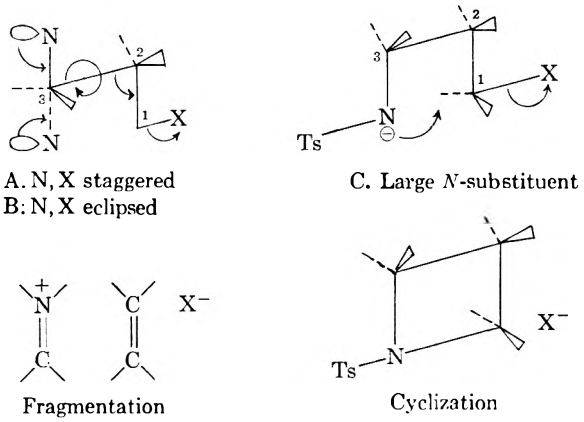

Fig. 1. Conformations during cyclization and fragmentation

By applying Grob's stereoelectronic requirements for fragmentation, one may account for previous failures to obtain satisfactory yields of azetidines from *N*-unsubstituted 3-halo- or 3-*O*-sulfonoylpropylamines and for the improvement in yield when the nitrogen is substituted. When the nitrogen is unsubstituted the conformations A and B (Fig. 1), with the π-electrons of nitrogen directed as indicated, are comparatively readily realized, and fragmentation is to be expected as a serious competitor to cyclization. When the nitrogen is substituted, the extent to which the substituent suffers non-bonded interaction with other substituents will be reflected in a stereoelectronic situation which is progressively less favorable to fragmentation with increasing substituent bulk; and while the rate of cyclization may be unfavorably affected, the rate of fragmentation will be more seriously depressed owing to its great sensitivity to stereoelectronic factors.[25]

The most favorable situation for effective cyclization to the azetidine system, then, will be found in a 3-aminopropyl system in which there are no substituents on any of the carbons and a (large) substituent on nitrogen. Symmetrical *gem*-substitution on C_2 (provided the groups are not too large) with no substituents on C_1 and C_3, or on C_3 with none on C_1 and C_2 should be approximately as good, and *threo*-substituents on C_1 and C_2 or C_2 and C_3 (or on

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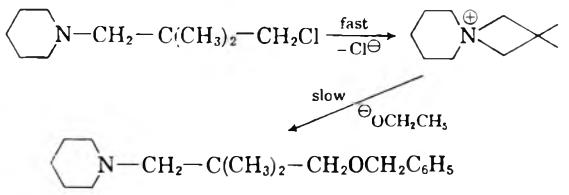
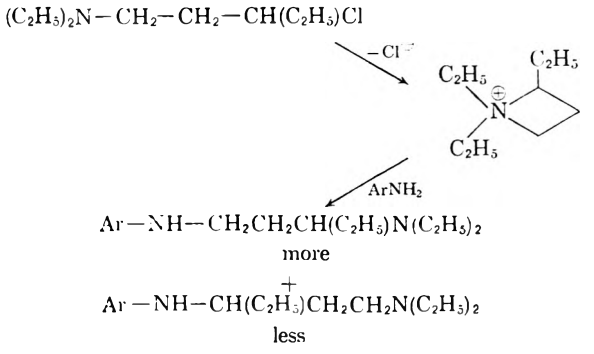
all three carbons) should not interfere with cyclization.

The effectiveness of *N*-substitution as a means of promoting cyclization is to be seen not only in the data of Table I but also in the following. It has been reported that 3-*N*-piperidyl-2,2-dimethylpropyl chloride undergoes a displacement reaction with sodium benzyloxide at a much faster rate than expected for a neopentyl-type chloride.[26] The authors explain this in terms of a fast conversion to an azetidinium ion which is then cleaved by benzyloxide ion in a slower step:



The reaction of 6-methoxy-8-aminoquinoline with 1-diethylamino-3-chloropentane to give both 6-methoxy-8-(1-diethylamino-3-pentylamino)quinoline and 6-methoxy-8-(3-diethylamino-1-pentylamino)quinoline (more) would appear to involve an azetidinium ion also.[27]



One is now in a position to predict in any given case whether cyclization will be a reasonably satisfactory reaction. Neither fragmentation nor E_2 elimination may be expected to interfere if the "leaving group" on C_1 is primary; only dimerization, which can be controlled by appropriate dilution, need be considered. When the leaving group is secondary, conditions should be selected which favor Sn_2 reactions over Sn_1; and the nitrogen should be substituted by a bulky group to inhibit fragmentation. Again suitable dilution should control the relative rates of E_2 or dimerization and cyclization. The data of Table I support these generalizations.

Strain factors arising from the size of the four-membered ring assuredly need not interfere with cyclization *per se*, although they just as assuredly do contribute to ring instability, though to a lesser extent than in the ethyleneimine system. Their chief deleterious effects are to be seen in the relatively slow rate at which cyclization occurs (slowest of the series of 3-, 4-, 5- and 6-membered nitrogen heterocycles[28]), which gives competing reactions a better chance. More serious, and also contributory to slow cyclization, are conformational effects due to substituents on the carbons of the propyl chain. The transition state for cyclization, requires that substituents on carbons 2 and 3 be eclipsed; thus large substituents *erythro* to each other (Fig. 2) will both diminish the rate of cyclization and decrease the stability of the ring once it is formed. The same may be said of large, *erythro* substituents on carbons 1 and 2, but eclipsing here is serious only in the transition state (and product) whereas on C_2 and C_3 the substituents must be eclipsed in the conformation leading to the transition state, thus materially decreasing the probability of cyclization which must proceed from an energetically unfavorable ground state.

TABLE I

EFFECT OF SUBSTITUTION ON CYCLIZATION

3-Halopropylamines	Azetidine, %	Reference
$Br(CH_2)_3NH_2$	6–26	10
$X(CH_2)_3NH_2$	poor	11
3-Bromo-*N*-methylpropylamines		
$BrCH_2C(CH_3)_2CH_2NHCH_3$	80	11
$BrCH(CH_3)CH_2CH(CH_2CH(CH_3)_2)$-$NHCH_3$	79	12a
$BrCH(CH_3)CH_2CH(CH(CH_3)_2)$-$NHCH_3$	50	12b
N-Alkyl-3-propylsulfonate ions		
$[^-OSO_3(CH_2)_3NH_2]$	[1.7]	21
$^-OSO_3(CH_2)_3NHCH_3$	8	15
$^-OSO_3(CH_2)_3NHC_2H_5$	13	22
$^-OSO_3(CH_2)_3NHCH_2C_6H_5$	9[a]	
$^-OSO_3(CH_2)_3NH$-*n*-C_4H_9	30	19
$^-OSO_3(CH_2)_3NH$-*t*-C_4H_9	47	20
3-Chloropropyl-*N*-sulfonamide ions		
$Cl(CH_2)_3N^-SO_2$-*p*-$C_6H_4CH_3$	55[b]	15
$Cl(CH_2)_3N^-SO_2CH_3$	67	
3-(4-Toluenesulfonoxy)-propyl-*N*-sulfonamide ions	55[b]	15
p-$CH_3C_6H_4SO_3(CH_2)_3N^-SO_2$-*p*-$C_6H_4CH_3$	80–93	
p-$CH_3C_6H_4SO_3CH(CH_3)(CH_2)_2N^-SO_2$-*p*-$C_6H_4CH_3$	68	

[a] This appears to be out of line. The 26% yield from 3-*N*-benzylpropyl *p*-toluenesulfonate suggests the proper value. [b] This value is probably not high enough as the intermediate shown was formed *in situ* from trimethylene chlorobromide and sodium *p*-toluenesulfonamide.

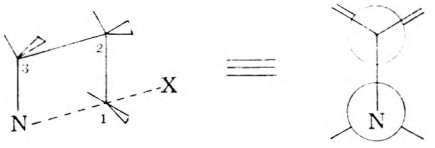


Fig. 2. Conformational effects due to substituents on the propyl chain

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(27) R. C. Elderfield and C. Ressler, *J. Am. Chem. Soc.*, **72**, 4059 (1950).

(28) H. Freundlich and G. Salomon, *Ber.*, **66**, 355 (1933).

EXPERIMENTAL[29]

3-Anilino-3-phenyl-1-propanol. To a stirred solution of 0.30 g. (7.9 mmoles) of lithium aluminum hydride in 10 ml. of dry ether was added, dropwise, a solution of 2.2 g. (10 mmoles) of 1,4-diphenyl-2-azetidinone[30] in 15 ml. of dry ether. No evolution of heat was noticed during the addition. The solution was refluxed for 0.5 hr. after which 30 ml. of a 25% sodium hydroxide solution was added. After stirring for 0.5 hr. the layers were separated and the ether layer was dried with anhydrous magnesium sulfate. Removal of the ether in a stream of air precipitated a light-yellow solid which was recrystallized from a methanol/petroleum ether (b.p. 90–100°) mixture. The yield of 3-amino-3-phenyl-1-propanol was 1.7 g. (74%), m.p. 89–90° (reported[6] m.p. 87–88°). The use of tetrahydrofuran as a solvent gave 1.9 g. (82%) of product.

1,4-Diphenyl-3,3-dimethyl-2-azetidinone. This substance was prepared by the method of Gilman and Specter[30] from ethyl α-bromoisobutyrate, benzylideneaniline, and zinc in 38.6% yield: m.p. 149–150°, reported 148–149°.[7]

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol. Reduction of 5.0 g. (20 mmoles) of 3,3-dimethyl-1,4-diphenyl-2-azetidinone by lithium aluminum hydride (0.60 g., 15.8 mmoles) in tetrahydrofuran afforded 4.7 g. of product, 1.8 g. of which was dissolved in a mixture of 25 ml. of petroleum ether (b.p. 60–75°) and 35 ml. of benzene and chromatographed on a neutral alumina[31] column. Elution with benzene gave 1.5 g. of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol (corresponds to a 93.2% reduction of the β-lactam), m.p. 105.0–105.5°.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.94; H, 8.29; N, 5.48. Found: C, 79.99; H, 8.09; N, 5.58.

The same procedure, with a recrystallization from alcohol substituted for the chromatographic procedure, was used for the reduction of the β-lactam with other metal hydrides under various conditions: (sodium borohydride, lithium borohydride, sodium borohydride–aluminum chloride, and lithium borohydride–aluminum chloride) without improvement.

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol hydrochloride. The hydrochloride was made by passing dry hydrogen chloride through a dry ethereal solution of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol. The salt precipitated quantitatively, m.p. 168.0–169.0°.

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; Cl, 12.15; N, 4.81. Found: C, 69.78; H, 7.60; Cl, 11.62; N, 4.84.

2,2-Dimethyl-N,3-dicyclohexylpropionamide. 3,3-Dimethyl-1,4-diphenyl-2-azetidinone (2.5 g., 0.01 mole) was dissolved in 70 ml. of absolute alcohol and 0.3 g. of Raney nickel catalyst (W-2) was added.

The mixture was charged with hydrogen to a pressure of 1300 p.s.i. and shaken for 11 hr. at 250°.

The catalyst was filtered and the solvent distilled from a warm water bath at reduced pressure (water-aspirator). Recrystallization of the residue from dilute alcohol gave 2.6 g. (100%) of the amide, m.p. 92.0–92.5°.

Anal. Calcd. for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.93; H, 11.64; N, 5.29.

The infrared spectrum possessed bands at 3340 and 1635 cm.$^{-1}$ but no absorption at 1600 or 1500 cm.$^{-1}$ The compound failed to hydrolyze when refluxed with 25% sodium hydroxide for 15 hr.

Attempted preparation of 3-aminopropyl methanesulfonate hydrochloride. An attempt to prepare this substance involved conversion of 3-aminopropanol to the hydrochloride in chloroform followed by addition of 1 equivalent each of pyridine and methanesulfonyl chloride at ~0°. However, only 38% of pyridinium methanesulfonate was obtained, m.p. 178–180°.

Anal. Calcd. for $C_4H_9NO_3S$: C, 41.14; H, 5.18; N, 8.00. Found: C, 41.08; H, 5.11; N, 8.11.

3-N-Benzylaminopropanol (II). One mole of benzaldehyde (106 g.) and one mole of 3-hydroxypropylamine (75 g.) were dissolved in 200 ml. of absolute ethanol and hydrogenated at 3 atm. over Adams' catalyst (0.5 g.). The absorption of hydrogen stopped after about 7 hr. Filtration through Celite and distillation afforded 138.2 g. (85%) of 3-benzylaminopropanol, b.p. 125–130° (2 mm.).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.80; H, 9.15; N, 8.54.

3-Benzylaminopropanol hydrochloride. A quantitative yield of 3-benzylaminopropanol hydrochloride was formed by bubbling dry hydrogen chloride through a dry ether solution of 3-benzylaminopropanol. Two recrystallizations from absolute alcohol–ether gave the analytical sample, m.p. 83.5–85.0°.

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.54; H, 8.00; Cl, 17.58; N, 6.94. Found: C, 59.02; H, 7.77; Cl, 18.09; N, 6.75.

N-(3-Benzoyloxypropyl)-N-benzylbenzamide. A pyridine solution of 3-benzylaminopropanol was benzoylated with a slight excess of benzoyl chloride. Three recrystallizations from an acetone-water mixture gave the analytical sample, m.p. 80.0–81.5°.

Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 76.89; H, 6.42; N, 3.73. Found: C, 77.19; H, 6.21; N, 3.75.

3-Benzylaminopropyl-p-toluenesulfonate hydrochloride. (III; *hydrochloride*). Four grams (0.02 mole) of 3-benzylaminopropanol hydrochloride was dissolved in a mixture of 6.8 g. (0.08 mole) of pyridine and 15 ml. of chloroform. The solution was cooled to −3° and 4.7 g. (0.025 mole) of *p*-toluenesulfonyl chloride was added in small portions, keeping the temperature below 3°. The solution was refrigerated (0°) for 6 days and the solvent was removed under reduced pressure. Trituration of the gummy residue with anhydrous ether gave 11.9 g. of yellow solid. Several recrystallizations from absolute ethanol–ether gave 2.0 g. (22.5%) of 3-benzylaminopropanol *p*-toluenesulfonate hydrochloride, m.p. 182–183°.

Anal. Calcd. for $C_{17}H_{22}ClNO_3S$: C, 57.36; H, 6.23; N, 3.93; S, 9.01. Found: C, 57.60; H, 6.10; N, 3.70; S, 8.65.

N-Benzylazetidine (V). *Procedure A.* Twenty-nine grams (0.25 mole) of freshly distilled chlorosulfonic acid was added dropwise to 36 g. (0.18 mole) of 3-hydroxypropylbenzylamine hydrochloride. After the initial reaction subsided, the mixture was heated on the steam bath for 30 min. and then under vacuum (water-aspirator) in an oil bath, first at 80° for 0.5 hr., then at 140° for 0.5 hr.

After cooling, the viscous oil was dissolved in 75 ml. of water and slowly added to a solution of 60 g. of potassium hydroxide in 75 ml. of water. The alkaline solution was then steam-distilled with the product coming over in the first 125 ml. of distillate.

Twenty grams of potassium hydroxide was added to the distillate, and the solution was extracted with ether. After drying and removal of solvent the product was distilled: 1.3 g. (5%) of 1-benzylazetidine, b.p. 71–75° (5 mm.). Two distillations gave the analytical sample, b.p. 78° (5.5 mm.).

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.54. Found: C, 81.48; H, 9.04; N, 9.56.

The *picrate* melted at 89–90°.

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.05; H, 4.28; N, 14.90. Found: C, 51.18; H, 4.28; N, 14.91.

(29) All melting and boiling points are uncorrected.

Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

The infrared spectra of solids were recorded from Nujol mulls on a Perkin-Elmer Model 21 Infrared Spectrophotometer; liquids were recorded as thin films by the same instrument.

(30) H. Gilman and M. E. Specter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

(31) The alumina used in this and subsequent experiments was prepared from acid-washed alumina (Merck) by shaking with ethyl acetate for 12 hr. After decanting the ethyl acetate, the alumina was washed with methanol and acetone and dried in an oven (60°).

Procedure B. A solution of 33 g. of 3-hydroxypropylbenzylamine in 15 ml. of water was cooled in an ice bath and a cold solution of 25 ml. of concd. sulfuric acid in 12 ml. of water was added. The resulting solution was maintained at 50–60° while the water was removed by distillation at reduced pressure (water-aspirator). The solution was next cooled to room temperature, and 88 g. of a 40% sodium hydroxide solution was added in 10-ml. portions. A violent reaction occurred after the first few additions, and after all the base was added the solution was steam-distilled. About 250 ml. of distillate was collected, treated with 50 g. of potassium hydroxide, and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and distilled to give 2.5 g. (9%) of 1-benzylazetidine, b.p. 71–75° (5 mm.). The infrared spectrum of this compound and *N*-benzylazetidine obtained by Procedure A were superimposable.

N-Benzylazetidine (V) (*by cyclization of 3-benzylaminopropyl p-toluenesulfonate hydrochloride* (III. *hydrochloride*). A solution of 1.9 g. (5.3 mmoles) of 3-benzylaminopropyl *p*-toluenesulfonate hydrochloride in 10 ml. of water was treated with 0.42 g. (10.6 mmoles) of sodium hydroxide. The solution was refluxed for 1 hr. An oil separated during this time. The solution was extracted with ether and the ethereal solution was washed with water and dried with magnesium sulfate. Picric acid in ether (1.2 g. (5.3 mmoles)) was added to the ether solution. A small amount of oil separated and solidified on refrigeration (0°): 0.53 g. (26%), m.p. 84–89°. A mixed melting point with a sample of *N*-benzylazetidine picrate obtained from the cyclization of 3-benzylaminopropanol showed no depression.

3-(p-Toluenesulfonamido)propyl p-toluenesulfonate (VI). A solution of 19.0 g. (0.25 mole) of 3-aminopropanol in 300 ml. of dry pyridine was cooled to −6° in an ice-salt bath. *p*-Toluenesulfonyl chloride (110 g., 0.59 mole) was added in portions, keeping the temperature below 5°. After stirring for 4 hr., the white solid was filtered (28.7 g., corresponding to a 52.5% yield of pyridine hydrochloride). The filtrate was diluted with 2 l. of ice and water, whereupon a red oil precipitated. The oil slowly crystallized to an orange solid which upon recrystallization from ethanol-water yielded 90.6 g. (95%) of 3-(*p*-toluenesulfonamido)propyl *p*-toluenesulfonate, m.p. 116–119°. Recrystallization of a 16.5-g. sample from methanol afforded 15.5 g. of pure VI: m.p. 120–121° (corr.).

Anal. Calcd. for $C_{17}H_{21}NO_5S_2$: C, 53.26; H, 5.52; N, 3.65. Found: C, 53.52, 53.47; H, 5.69, 5.58; N, 3.84, 3.77.

4-(p-Toluenesulfonamido)-2-butyl p-toluenesulfonate (VII). A solution of 8.8 g. (0.10 mole) of 4-amino-2-butanol in 150 ml. of pyridine was cooled to −6° and 38.2 g. (0.20 mole) of *p*-toluenesulfonyl chloride was added slowly, keeping the temperature below 5°. After the addition the solution was refrigerated (0°) for 3 days during which time pyridine hydrochloride precipitated and the solution turned deep red. The mixture was poured into 600 ml. of ice water. A red oil separated and solidified slowly. After standing at 0° for 1 hr. the solid was filtered and washed with cold, dilute hydrochloric acid. The adsorbed water and color were removed by dissolving the solid in chloroform, separating the water layer and filtering through Norit. The chloroform solution was then dried with magnesium sulfate and diluted with petroleum ether (b.p. 30–60°) to precipitate 26.2 g. (66%) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate, m.p. 91.0–93.5°. Two recrystallizations from the same solvent pair gave the analytical sample, m.p. 94.0–95.0°.

Anal. Calcd. for $C_{18}H_{23}NO_5S_2$: C, 54.39; H, 5.83; N, 3.52. Found: C, 54.47; H, 5.81; N, 3.40.

N-(3-Chloropropyl)methanesulfonamide (IX). A solution of 75.1 g. (1.0 mole) of 3-hydroxypropylamine and 158 g. (2 moles) of pyridine in 300 ml. of chloroform was cooled to −10°. Methanesulfonyl chloride (229.2 g., 2 moles) was added dropwise, keeping the temperature below 0°. After the addition, the solution was stirred for 3 hr. at 0°. The solvent was removed by distillation at reduced pressure and the residue, after extraction with cold water, was distilled *in vacuo* to give *N*-(3-chloropropyl)methanesulfonate [77.2 g., b.p. 150–153° (0.3 mm.); 45% yield]. The compound gave no precipitate with aqueous silver nitrate.

Anal. Calcd. for $C_4H_{10}ClNO_2S$: C, 27.99; H, 5.90; Cl, 20.65; N, 8.16; S, 18.69. Found: C, 27.80; H, 5.56; Cl, 20.74; N, 8.48; S, 18.77.

p-Toluenesulfonazetidide (IV) (A). To a solution of 5.1 g. (0.0146 mole) of 3-(*p*-toluenesulfonamido)propyl-*p*-toluenesulfonate (VI) in 425 ml. of absolute ethanol was added a solution of 0.36 g. (0.0146 g.-atom) of sodium in 75 ml. of absolute ethanol. After refluxing for 16 hr. the solvent was distilled until the remainder amounted to about 100 ml. The latter was then diluted to 1 l. with water and on standing for a few hours *p*-toluenesulfonazetidide precipitated in short needles; yield, 2.25 g. (75.5%), m.p. 119.0–121.5° (reported[16] m.p. 120°).

(B). Cyclization of 10.2 g. (0.0292 mole) of VI using 0.72 g. (0.0292 g.-atom) of sodium in a total volume of 570 ml. of absolute ethanol gave 5.0 g. (80.7%) of *p*-toluenesulfonazetidide, m.p. 118–120°.

(C). Cyclization of 10.2 g. (0.0292 mole) of VI using 0.72 g. (0.0292 g.-atom) of sodium in a total volume of 300 ml. absolute ethanol gave 4.2 g. of a white solid, m.p. 116–150°. The solid was dissolved in benzene and chromatographed on a neutral alumina[28] column. Benzene eluted 3.5 g. (56.4%) of *p*-toluenesulfonazetidide, m.p. 119–122°. Ether eluted 0.4 g. of a white solid, m.p. 210–213° (reported[14a] for 1,5-di(*p*-toluenesulfonyl)-1,5-diazacyclooctane, 215°).

(D). To a solution of 5.1 g. (0.013 mole) of VI in 500 ml. of *t*-butyl alcohol was added 14 ml. of 1.04*M* potassium *t*-butoxide, and the mixture was refluxed for 10 hr., with stirring. The fine precipitate of potassium *p*-toluenesulfonate (2.6 g., 85%) was filtered off while hot, and the solvent was removed *in vacuo* from the filtrate. The residue was taken up in hot methanol, filtered and diluted with water, whereupon there was obtained 2.6 g. (93%) of IV, m.p. 116–120°.

2-Methyl-p-toluenesulfonazetidide (VIII). *Procedure A.* To a solution of 5.92 g. (14.6 mmoles) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate in 425 ml. of absolute ethanol was added, in one portion, a solution of 0.36 g. (14.6 mg.-atoms) of sodium in 75 ml. of absolute ethanol. After refluxing for 19 hr. the solvent was distilled until the remainder amounted to about 75 ml. The latter was then diluted to 1 l. with water to precipitate 1.32 g. (35.5%) of 2-methyl-*p*-toluenesulfonazetidide, m.p. 97–99°. Two recrystallizations from a chloroform/petroleum ether (b.p. 30–60°) mixture gave the analytical sample, m.p. 99–100°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.63; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.59; H, 6.67; N, 5.98; S, 14.19.

Procedure B. A solution of 19.8 g. (50.0 mmoles) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate in 300 ml. of absolute ethanol was added in high dilution;[32] over a period of 48 hr. to a refluxing solution of 1.2 g. (50 mg.-atoms) of sodium in 350 ml. of absolute ethanol. When the addition was completed the solvent was distilled until the remainder amounted to about 150 ml. (removal of more solvent resulted in a brown product). The remainder was diluted to 1 l. with water to precipitate 8.2 g. (67.7%) of the product, m.p. 97–99°.

Methanesulfonazetidide (X). A solution of 0.5 g. (21 mg.-atoms) of sodium in 100 ml. of absolute ethanol was added in one portion to a refluxing solution of 3.4 g. (20 mmoles) of *N*-(3-chloropropyl)methanesulfonamide in 75 ml. of absolute ethanol. The resulting solution was refluxed for 48 hr. during which time sodium chloride precipitated (1.2 g., 100% yield). The solvent was distilled at atmospheric pressure and the residue was dissolved in chloroform. Concentration of the chloroform solution gave 1.8 g. of methanesulfonazetidide (66.6% yield), m.p. 81–82°.

(32) A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, 72, 985 (1950).

Anal. Calcd. for $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36; S, 23.74. Found: C, 35.64; H, 6.77; N, 10.19; S, 23.92.

Azetidine (I) (*by reduction of sulfonazetidides.*) (A) A three-necked flask (with its side-necks stoppered) was fitted with a 400-mm. reflux condenser. To the top of the condenser was attached a glass tube which extended 1 cm. into a dilute sulfuric acid solution.

A solution of 11.4 g. (0.0845 mole) of methanesulfonazetidide in 350 ml. of *n*-amyl alcohol was refluxed in the three-necked flask. Through one of the side necks was added 20 g. (0.87 g.-atom) of sodium in 1-g. pieces. The sodium was added after the preceding piece had completely reacted with the solvent. After all of the sodium had reacted the solution was cooled to room temperature and 150 ml. of water was added. The layers were separated and the aqueous layer was distilled up to 100°. This distillate was combined with the amyl alcohol and the mixture was extracted with the dilute sulfuric acid which was used as a trap. Extraction with dilute sulfuric acid was continued until the extracts were strongly acidic. The combined acid extracts were cooled and made strongly alkaline with potassium hydroxide pellets and distilled up to 100°. The distillate was made strongly alkaline with potassium hydroxide pellets and extracted with ether. After drying with potassium hydroxide pellets, the ether solution was distilled to give 2.0 g. (42.5%) of azetidine, b.p. 61–66° (750 mm.) [reported[9] b.p. 62° (730 mm.)]. The picrate melted at 161–165° (reported[4] m.p. 166–167°).

(B). A 73.0-g. (0.35 mole) sample of IV was dissolved in 2 l. of boiling *n*-amyl alcohol, and 146.4 g. of sodium was added in portions over 3 hr., waiting for most of the effervescence to cease before each subsequent addition. The condenser was connected to a sulfuric acid trap as in the preceding experiment. The mixture was allowed to cool overnight, and 900 ml. of water was added. The lower layer was separated and distilled (about 100 ml.) until no more amyl alcohol came over. The distillate was added to the alcohol layer remaining in the separatory funnel, which was then chilled and extracted with enough of 2*N* sulfuric acid (including that from the trap) to ensure complete acidity.

The resulting acidic extract was itself ether-extracted and then freed of ether by an air stream, after which it was added to the original strongly alkaline solution. Aqueous I was distilled out and the distillate was saturated with potassium hydroxide. The dried azetidine, which separated, weighed 16.9 g. [84.7%: n_D^{22} 1.4110 (reported n_D^{20} 1.4229[15])].

Azetidine (I) (*by hydrogenolysis of 1-benzylazetidine*). To 30 ml. of absolute ethanol was added 163.2 mg. (1 mmole) of 1-benzylazetidine. Twenty milligrams of 10% palladium-on-charcoal were added and the mixture was hydrogenated under 1 atm. hydrogen pressure. One millimole of hydrogen was taken up in 3 days. The catalyst was filtered off and a solution of 229 mg. (1 mmole) of picric acid in a minimum amount of absolute ethanol was added to the filtrate. The solution was diluted with dry ether and refrigerated (0°) for 2 days. Azetidine picrate, m.p. 166–169° (reported[4] m.p. 166–167°), precipitated during this time.

2-Methylazetidine (XI). To a refluxing solution of 8.2 g. (0.036 mole) of 2-methyl-*p*-toluenesulfonazetidide in 300 ml. of *n*-amyl alcohol was added 16 g. (0.70 g.-atom) of sodium in 1-g. portions. The portions of sodium were added after the preceding portion had completely reacted with the solvent. After the addition the solution was cooled and 150 ml. of water was added. The aqueous layer was distilled up to 100° and the distillate added to the amyl alcohol layer. The mixture was extracted with dilute sulfuric acid. The acid extracts were cooled and made strongly basic with potassium hydroxide pellets. The mixture was distilled up to 100° and the distillate made strongly alkaline with potassium hydroxide pellets.

The oil, which separated, was dried with potassium hydroxide pellets and distilled to give 2.0 g. [(78.2%) of 2-methylazetidine, b.p. 72–76° (755 mm.) reported[13a] b.p. 75°]. Treatment of a pyridine solution of 2-methylazetidine with *p*-toluenesulfonyl chloride followed by dilution with water gave 2-methyl-*p*-toluenesulfonazetidide, m.p. 96–99°. A mixed melting point with an authentic sample showed no depression.

The *p*-nitrobenzamide of 2-methylazetidine melted at 42.0–43.0°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.80; H, 5.42; N, 12.64.

Attempted hydrogenolysis of p-toluenesulfonylazetidide. Two grams (9.5 mmoles) of *p*-toluenesulfonazetidide was dissolved in 25 ml. of dry ether. One gram of Raney nickel (W-2) was added, and the mixture was shaken at 500 p.s.i. hydrogen pressure at 100° for 11 hr. Only starting material was recovered.

Attempted reduction of 1-methanesulfonazetidide with lithium aluminohydride. To a refluxing solution of 1.28 g. (9.50 mmoles) of 1-methanesulfonazetidide in 80 ml. of dry ether was added dropwise a solution of 1.72 g. (45.2 mmol.) of lithium aluminum hydride in 100 ml. of dry ether. The solution was refluxed for 22 hr. No azetidine was obtained on alkaline work-up.

ANN ARBOR, MICH.

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

Synthesis of Potential Anticancer Agents. VI. *N*-(3-Hydroxypropyl)-benzaldimine and Related Compounds[1,2]

WYMAN R. VAUGHAN AND ROBERT S. KLONOWSKI[3]

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The condensation product of benzaldehyde with 3-aminopropanol is identified as the Schiff base rather than 2-phenyltetrahydro-1,3-oxazine as previously reported. Its behavior with acid chlorides is described, and its use as an intermediate in the preparation of 3-*N*-benzylaminopropyl tosylate is considered. This substance was desired as an intermediate in the synthesis of *N*-benzylazetidine, for which two other potential routes involving 3-aminopropanol derivatives are described.

In connection with studies directed toward the preparation of *N*-benzylazetidine,[2] it was desired to develop a satisfactory method for preparing 3-benzylaminopropyl 4-toluenesulfonate for cyclization to the desired azetidine. The reductive alkylation of 3-aminopropanol with benzaldehyde and tosylation of the product proved unsatisfactory since the tosylation reaction afforded a difficultly separable mixture of hydrochlorides of the desired ester and pyridine. Isolation by neutralization was not feasible since the ester cyclizes to *N*-benzylazetidine, a reaction best carried out as a discrete step[3] to avoid serious competition from polymerization. The present paper describes our experience with other routes which were explored.

Since the Schiff base from benzaldehyde and 3-aminopropanol, *N*-(3-hydroxypropyl)benzaldimine (I), is readily accessible and in principle should be readily esterified, the condensation was carried out in benzene by azeotropic distillation of the water produced (Chart I). Such a condensation had been reported earlier to yield 2-phenyl-1,3-tetrahydrooxazine (II) on the grounds that the product afforded a benzoyl derivative which did not undergo the facile hydrolysis expected of an ester.[4] The derivative (III) thus was assigned the structure of II-*N*-benzamide. We obtained the same condensation product as reported earlier,[4] but though it reacted as reported with benzoyl chloride[4] to give III, an examination of the infrared and ultraviolet absorption spectra support structure I as against structure II: thus there is a band at 1650 cm.$^{-1}$, characteristic of Schiff bases; and there is an absorption maximum at 246.7 mμ (ϵ 15,400) also characteristic of Schiff bases[5a] of the benzaldimine type. The benzoyl derivative, III, shows no absorption in the region 220–260 mμ, and therefore it is evident that cyclization occurred during treatment with benzoyl chloride and not during the original condensation.

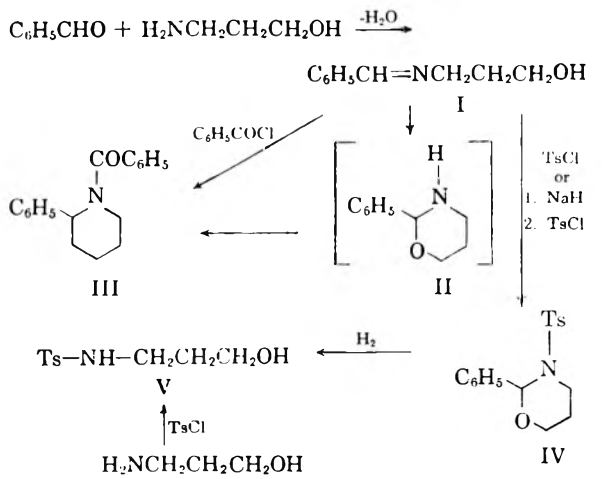

Chart I. Preparation and reactions of *N*-(3-hydroxypropyl)-benzaldimine

When I was treated with 4-toluenesulfonyl chloride a tosyl derivative (IV) was obtained. Likewise when I was converted to the sodium alkoxide with sodium hydride and the alkoxide treated with tosyl chloride, the same substance, IV, was obtained.

The structure of IV as *N*-4-toluenesulfonyl-2-phenyl-1,3-tetrahydrooxazine was demonstrated by hydrogenolysis of IV to *N*-(3-hydroxypropyl)-4-toluenesulfonamide (V) which was also prepared from 3-aminopropanol and one equivalent of tosyl chloride. Thus 3-amino- or 3-benzylaminopropyl tosylate derivatives are not accessible by this route. The present observations, supported by the work of others,[5b] who have shown that Schiff bases instead of oxazolines are produced from aldehydes and 1,2-aminoalcohols, lead us to suggest that the tetrahydro-1,3-oxazines reported to result from the reaction of 1,3-aminoalcohols, are, in fact, Schiff bases.

Another potential route to *N*-benzylazetidine is base-induced cyclization of *N*-3-benzamidopropyl benzoate (VI) or tosylate (VII), followed by re-

(1) Work supported by a Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(2) Previous paper in this series, W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

(3) Abstracted from a portion of the Ph.D. dissertation of Robert Stephen Klonowski, University of Michigan, 1959.

(4) A. I. Kiprianov and B. A. Raschkovan, *J. Gen. Chem. U.S.S.R.*, **7**, 1026 (1937) [*Chem. Abstr.*, **31**, 5356 (1937)].

(5a) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951).

(5b) L. W. Daasch and U. E. Hanninen, *J. Am. Chem. Soc.*, **72**, 3673 (1950).

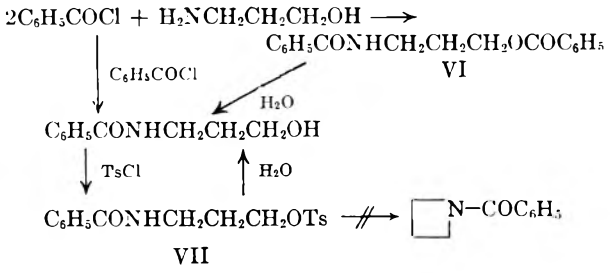

Chart II. Attempted preparation of *N*-benzoylazetidine

duction of benzoylazetidide (Chart II). To this end both compounds were prepared: VI by dibenzoylation of 3-aminopropanol; VII by tosylation of *N*-3-benzamidopropanol, prepared either by monobenzoylation of 3-aminopropanol or more satisfactorily by saponification of the ester group in VI. Upon hydrolysis of the tosyl group of VII followed by benzoylation VI was obtained, showing that no rearrangement takes place during tosylation, such as was encountered by Gabriel and Elfeldt.[6] Both VI and VII were subjected to treatment with sodium ethoxide in refluxing ethanol, which cyclizes *N*-3-(4-toluenesulfonamido)propyl tosylate,[3] but no reaction was detected with VI, while an oil (uncharacterized but showing characteristic benzamide absorption in the infrared) was obtained from VII. The considerably less acidic character of the *N*-benzamido as compared with the *N*-4-toluenesulfonamido group as well as the lesser lability of benzoate compared with tosylate group is accountable for these results. Lithium aluminum hydride reduction of VII was not attempted, since it was to be expected that the anion of *N*-3-benzylaminopropyl 4-toluenesulfonate would undergo further reactions, among which cyclization to *N*-benzylazetidine would be but one of several.

One further route to *N*-3-benzylaminopropyl tosylate was tentatively investigated. Ethylene cyanohydrin was treated with tosyl chloride and pyridine in chloroform at 0° to give a 72.5% yield of 3-(4-toluenesulfonoxy)propionitrile (*β*-cyanoethyl *p*-toluenesulfonate, VIII). It was our intention to reduce this substance to the corresponding amine and allow the amine to react with benzaldehyde. The reduction over Adams' catalyst in absolute ethanol at an initial hydrogen pressure of 53 p.s.i. was complete in seven hours, and a water soluble product was precipitated by the addition of dry ether to the evaporated solution. The solid was not allylamine 4-toluenesulfonate whose melting point it substantially depressed. Allylamine could not be extracted by ether from the aqueous solution of the solid after addition of alkali. However, upon distillation of the alkaline solution, allylamine was extracted from the distillate and isolated in the form of its picrate. From the original ether solution, from which the water soluble solid had been removed by filtration, there was isolated a very small quantity of ethylene di-4-toluenesulfonate, probably arising from traces of ethylene glycol in the ethylene cyanohydrin.

(6) S. Gabriel and P. Elfeldt, *Ber.*, 24, 3213 (1891).

EXPERIMENTAL[7]

N-(3-Hydroxypropyl)benzaldimine (I). A solution of 37.6 g. (0.5 mole) of 3-aminopropanol and 53.1 g. (0.5 mole) of benzaldehyde in 150 ml. of dry benzene was refluxed until 9.5 ml. of water was collected in a water separator. The benzene was then distilled at atmospheric pressure, and the yellow oil was vacuum distilled. After a small forerun the product distilled at 118° (0.5 mm.): yield 73.5 g. (90%).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.68; H, 8.06; N, 8.64.

The infrared spectrum possessed bands at 3360 cm.$^{-1}$ and 1650 cm.$^{-1}$ The ultraviolet spectrum showed an absorption maximum at 2467 Å with a molar extinction coefficient of 15,400.

N-Benzoyl-2-phenyl-1,3-tetrahydrooxazine (III). To a solution of 3.2 g. (0.02 mole) of *N*-(3-hydroxypropyl)benzaldimine in 15 ml. of pyridine (reagent grade) was added 2.8 g. (0.02 mole) of benzoyl chloride. Almost immediately a precipitate of pyridine hydrochloride appeared. The mixture was allowed to stand at room temperature for 15 min. and then poured into cold water to precipitate 2.4 g. of *N*-benzoyl-2-phenyl-1,3-tetrahydrooxazine, m.p. 125.0–127.5°. Three recrystallizations from an acetone-water mixture gave the analytical sample, m.p. 127–128° (reported[4] m.p. 127°).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.41; N, 5.24. Found: C, 76.97; H, 6.59; N, 5.20.

N-(p-Toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine (IV). *Procedure A.* *N*-(3-Hydroxypropyl)benzaldimine (16.3 g., 0.1 mole) was dissolved in 70 ml. of pyridine (reagent grade), and the solution was cooled to −10° in an ice-salt bath. *p*-Toluenesulfonyl chloride (21.1 g., 0.11 mole) was added in portions keeping the temperature below 0°. After the addition the yellow solution was refrigerated (0°) for 2 hr. A precipitate of pyridine hydrochloride appeared either during the addition of *p*-toluenesulfonyl chloride or during the refrigeration period, after which the mixture was poured into 500 ml. of cold water.

The precipitated product was filtered, washed with cold 5% hydrochloric acid, followed by cold water, and then was air dried. The solid, 33.2 g., contained a large amount of adsorbed water which was removed by dissolving the solid in dry chloroform, separating the water layer, and drying the chloroform solution with anhydrous magnesium sulfate. Addition of petroleum ether (b.p. 30–60°) to the warm chloroform solution precipitated 22.8 g. (72%) of *N*-(*p*-toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine, m.p. 141–143°. Two recrystallizations from dry ether gave the analytical sample, m.p. 145.5–146.0°.

Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.32; H, 6.03; N, 4.41. Found: C, 64.32; H, 6.04; N, 4.27.

Procedure B. A solution of 16.3 g. (0.100 mole) of *N*-(3-hydroxypropyl)benzaldimine in 150 ml. of dry ether was stirred for 16 hr. with 2.4 g. (0.10 mole) of sodium hydride. A solution of 19.1 g. (0.100 mole) of *p*-toluenesulfonyl chloride in 75 ml. of dry ether was added dropwise and the solution was refluxed for 1 hr. Forty milliliters of water was added and the layers were separated. The ether layer was dried with magnesium sulfate and distilled at atmospheric pressure to give a brown oil. The latter was dissolved in hot acetone and, on cooling, *N*-(*p*-toluenesulfonyl)-2-

(7) All melting and boiling points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. The infrared spectra of solids were recorded from Nujol mulls on a Perkin-Elmer Model 21 infrared spectrophotometer: liquids were recorded as thin films by the same instrument.

phenyl-1,3-tetrahydrooxazine crystallized: yield, 25.2 g. (80.5%), m.p. 143–145° which was unchanged on admixture with the compound prepared by Procedure A.

N-(3-Hydroxypropyl)-p-toluenesulfonamide (V). *Procedure A.* N-(*p*-toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine (IV) (1.58 g., 5 mmoles) was dissolved in 75 ml. of absolute ethanol which had been saturated with dry hydrogen chloride. A mixture of 0.1 g. of Adams' catalyst and 2 ml. of ethanol was added and the mixture hydrogenated at 1 atm. of hydrogen pressure. The absorption of hydrogen stopped after 4 hr. The catalyst was removed by filtration and the solution was evaporated to dryness under reduced pressure (water-aspirator). The solid was recrystallized from ether giving 1 g. (87%) of *N*-(3-hydroxypropyl)-*p*-toluenesulfonamide, m.p. 55–57°. Two recrystallizations from a mixture of dry chloroform and petroleum ether (b.p. 30–60°) gave the analytical sample, m.p. 55–56°.

Anal. Calcd. for $C_{10}H_{15}NO_3S$: C, 52.39; H, 6.59; N, 6.11; S, 13.97. Found: C, 52.07; H, 6.41; N, 5.88; S, 13.88.

Procedure B. *p*-Toluenesulfonyl chloride (19.1 g., 0.100 mole) was added in small portions to a cold solution of 7.5 g. (0.10 mole) of 3-aminopropanol in 15 ml. of pyridine. The temperature was kept below 3° during the addition. After refrigeration (0°) for 1 hr. the mixture was poured into 100 ml. of ice-water. The oil that separated was dissolved in chloroform and this was washed with cold, dilute hydrochloric acid and water. After drying with magnesium sulfate, the solution was cooled and diluted with petroleum ether (b.p. 30–60°). The product, 20.5 g. (83.7%), crystallized slowly, m.p. 52–55°. A mixed melting point with the product prepared by Procedure A showed no depression.

N-(3-Hydroxypropyl)benzamide. Procedure A. To 75.1 g. (1.0 mole) of 3-hydroxypropylamine 70.3 g. (0.5 mole) of benzoyl chloride was slowly added. The mixture was then warmed on a steam bath for 0.5 hr. and, after cooling to room temperature, was extracted with chloroform. The chloroform solution was distilled at atmospheric pressure to remove the solvent and then was vacuum distilled to give 45 g. (50%) of product, b.p. 198° (1.5 mm.), n_D^{21} 1.5590. The phenylurethan melts at 118–120°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.46; H, 6.08; N, 9.39. Found: C, 68.55; H, 6.00; N, 9.20.

Procedure B. A solution of 56 g. (0.2 mole) of 3-benzamidopropyl benzoate and 8 g. (0.2 mole) of sodium hydroxide in 500 ml. of water was refluxed for 1.5 hr., after which the homogeneous solution was continuously extracted with chloroform for 8 hr. The chloroform solution was dried with magnesium sulfate and distilled, first at atmospheric pressure to remove the solvent, and then *in vacuo*. After a very small forerun, the product distilled at 196–200° (mostly at 198°) (1.5 mm.): yield, 20 g. (57.2%). The infrared spectrum was superimposable with the spectrum of *N*-(3-hydroxypropyl)benzamide prepared by Procedure A. During the distillation the compound crystallized to a solid, m.p. 60–61° [reported[8] for *N*-(3-hydroxypropyl)benzamide, m.p. 60.0–60.5°].

3-Benzamidopropyl benzoate (VI). *Procedure A.* A solution of 75.1 g. (1.0 mole) of 3-hydroxypropylamine in 200 g. of pyridine was cooled to 0° and 285 g. (2 moles) of benzoyl chloride was added in portions. The temperature was allowed to fluctuate between 0° and 80°. After the addition the solution was heated on a steam bath for 0.5 hr. and allowed to stand at room temperature for 2 hr. Dilution with ice and 5% hydrochloric acid gave the product, m.p. 83–84°, after recrystallization from aqueous ethanol: yield, 255.7 g. (90%).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.90; H, 6.02; N, 5.08.

Procedure B. To a solution of 1.8 g. (10 mmoles) of *N*-(3-hydroxypropyl)benzamide in 5 ml. of pyridine (reagent grade) was added 1.4 g. (10 mmoles) of benzoyl chloride. During the exothermic reaction that followed pyridine hydrochloride precipitated. The mixture was poured onto ice when it cooled to room temperature, and the oil which separated solidified on standing. After filtering, the solid was washed with water, dilute hydrochloric acid, and again with water. Recrystallization from a chloroform–petroleum ether (b.p. 30–60°) mixture gave 1.7 g. (60.5%) of 3-benzamidopropyl benzoate, m.p. 83–85°. No depression of the melting point was observed on admixture with an authentic sample from Procedure A.

3-Benzamidopropyl p-toluenesulfonate (VII). *Procedure A.* A solution of 16.5 g. (0.093 mole) of 3-benzamidopropanol in 15 ml. of pyridine was cooled to 0° and 18.0 g. (0.093 mole) of *p*-toluenesulfonyl chloride was added in portions, keeping the temperature below 3°. The yellow solution was refrigerated (0°) for 2 hr. during which time white crystals of pyridine hydrochloride appeared. To this mixture was slowly added 100 ml. of ice-water. The product, which crystallized immediately, was filtered and washed with cold, dilute hydrochloric acid. The adsorbed water was removed by recrystallization from chloroform: yield, after recrystallization, 18.7 g. (60.5%), m.p. 156.5–157.0°.

Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 61.24; H, 5.74; N, 4.20; S, 9.62. Found: C, 61.31; H, 5.78; N, 4.29; S, 9.71.

Procedure B. Benzoyl chloride (14.0 g., 0.1 mole) was added to 15.0 g. (0.2 mole) of 3-hydroxypropylamine. The resulting solution was heated on the steam bath for 1 hr. and then was extracted with dry chloroform. To the chloroform solution was added 8 g. (0.1 mole) of pyridine and, after cooling to 0°, 19.1 g. (0.1 mole) of *p*-toluenesulfonyl chloride in small portions. After keeping the solution at 0° for 2 hr. it was extracted with ice-water. The chloroform solution was dried with magnesium sulfate and the solvent removed at reduced pressure. The resulting oil was dissolved in a small amount of absolute ethanol and the solution was diluted with petroleum ether (b.p. 60–75°) to give 13.5 g. (40.5%) of product, m.p. 143–147°. Recrystallization from chloroform gave a product which melted at 154–156°. A mixed melting point with the product obtained in Procedure A showed no depression.

Attempted cyclization of 3-benzamidopropyl benzoate. A solution of 0.23 g. (0.01 g.-atom) of sodium in 100 ml. of absolute ethanol was added to a solution of 2.8 g. (0.01 mole) of 3-benzamidopropyl benzoate (VI) in 100 ml. of absolute ethanol. The solution was refluxed for 4 hr. after which the solvent was removed under reduced pressure. The residue was extracted with ether. The solid remaining after the extraction was dissolved in water and acidified with dilute hydrochloric acid. No precipitation occurred.

The ethereal solution was concentrated and, on cooling, 2.3 g. of 3-benzamidopropyl benzoate precipitated, m.p. 80–82°. A mixed melting point with the starting material showed no depression.

Attempted cyclization of 3-(p-toluenesulfonamido)propyl benzoate. The above procedure was followed substituting 3.3 g. (0.01 mole) of 3-(*p*-toluenesulfonamido)propyl benzoate (VII) for 3-benzamidopropyl benzoate (VI). The ethereal extract of the solid remaining after the solvent had been removed contained an oil whose infrared spectrum showed absorption bands similar to those of the starting material. Crystallization did not occur on seeding with the starting material.

β-Cyanoethyl p-toluenesulfonate (VIII). A solution of 14.2 g. (0.2 mole) of ethylene cyanohydrin and 40 g. of pyridine in 75 ml. of chloroform was stirred and cooled in an ice-bath, and a solution of 36.0 g. (0.2 mole) of *p*-toluenesulfonyl chloride in 100 ml. of chloroform was added dropwise. The solution was stirred for 2 hr. and diluted with dilute hydrochloric acid. The chloroform layer was separated and evaporated in a stream of air to a white semisolid. Recrystallization from ethanol-water yielded 32.6 g. (72.5%) of β-cyanoethyl *p*-toluenesulfonate, m.p. 64–65°.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.30; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.58; H, 4.99; N, 6.04; S, 14.23.

(8) S. Gabriel, *Ann.*, 409, 326 (1915).

Reduction of VIII. A warm solution of 13 g. (0.05 mole) of VIII in 200 ml. of absolute ethanol containing 0.5 g. of Adams' catalyst was hydrogenated on a Parr shaker. The initial hydrogen pressure was 53 p.s.i. The solution absorbed 9.5 lb. of hydrogen in 7 hr. There was no additional absorption in the next 15 hr. The catalyst was filtered and the solvent was removed from the filtrate under reduced pressure. The addition of dry ether to the residue precipitated 12.0 g. of white solid, m.p. 350–352° dec.

Anal. C, 45.06; H, 6.01; N, 7.72; S, 18.29. The solid was soluble in water and when the aqueous solution was made basic an ammoniacal odor was detected. No amine, however, was extracted with ether. An aqueous solution was made strongly alkaline with potassium hydroxide and the solution distilled up to 100°. The distillate was saturated with potassium hydroxide and extracted with ether. To the ether solution, after drying with magnesium sulfate, was added a saturated ether solution of picric acid. Allylamine picrate, m.p. 135–140°, precipitated immediately. A mixed melting point with an authentic sample of allylamine picrate showed no depression.

From the ether solution there was obtained 0.33 g. of ethylene glycol di-*p*-toluenesulfonate, m.p. 120–121° (reported[9] m.p. 125–126°). A sample of ethylene glycol di-*p*-toluenesulfonate was prepared by the reaction of *p*-toluenesulfonyl chloride with ethylene glycol in pyridine solution. The melting point was 123–125°. A mixture of the two solids melted at 123–125°.

ANN ARBOR, MICH.

(9) C. L. Butler, W. L. Nelson, A. G. Renfrew, and L. H. Cretcher, *J. Am. Chem. Soc.*, **57**, 575 (1935).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLIII. Analogs of Chlorambucil. IV.[2] Synthesis of Isochlorambucil and Related Benzylic Type Alkylating Agents

W. A. SKINNER, ABELARDO P. MARTINEZ, HELEN F. GRAM, LEON GOODMAN, AND B. R. BAKER

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p-[Bis(2-chlorcethyl)aminomethyl]hydrocinnamic acid (XIII) (isochlorambucil), an isomer of chlorambucil containing the more chemically reactive benzylic type alkylating group, has been synthesized for evaluation as an anticancer agent. Several related monofunctional alkylating agents have also been synthesized for test evaluation, namely *p*-(2-chloroethylthiomethyl)-hydrocinnamic acid (II), *p*-[(2-chloroethyl)ethylaminomethyl]hydrocinnamic acid (IVb), methyl *p*-(1-aziridinylmethyl) hydrocinnamate (VIII), and *p*-[(2-chloroethyl)aminomethyl]hydrocinnamic acid (XIVb).

Chlorambucil,[3] 4-*p*-[bis(2-chloroethyl)amino]phenylbutyric acid, is one of the most useful alkylating agents in the clinic.[4] Although chlorambucil is highly effective against the Walker rat Sarcoma 256, it shows little activity against Sarcoma 180, Adenocarcinoma 755, or Leukemia L-1210 in the mouse. As part of the continuing search for analogs of chlorambucil[2,5,6] that may have a different tumor spectrum[4,7] or may be more efficacious in man, this paper describes a series of chlorambucil analogs wherein the alkylating function is separated from the benzene ring by a methylene group such as in Compound XIII. Since aliphatic mustards are chemically more reactive than the corresponding aryl mustards, a change in tumor spectrum or efficiency or both might be anticipated. In addition, some of the monofunctional alkylating agents of this more reactive benzylic type (such as II, IVb or XIVb) described in this paper might be irreversible enzyme inhibitors.[8,9]

Chloromethylation of hydrocinnamic acid with aqueous formaldehyde and hydrochloric acid by the method of Bogdanov[10] afforded *p*-(chloromethyl)-hydrocinnamic acid (VI) in 50% yield. Milder conditions of chloromethylation, namely chloromethyl methyl ether and stannic chloride, were without effect on hydrocinnamic acid since the latter was recovered unchanged. Fisher esterification of VI with methanolic hydrogen chloride

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(2) For paper III on Chlorambucil analogs see W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 953 (1960), paper XXXIII of this series.

(3) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

(4) R. W. Rundles, J. Grizzle, W. N. Bell, C. C. Corley, W. B. Frommeyer, B. G. Greenberg, C. M. Huguley, G. W. James III, R. Jones, Jr., W. E. Larsen, V. Loeb, L. A. Leone, J. G. Palmer, W. H. Riser, Jr., and S. J. Wilson, *Am. J. Med.*, **27**, 424 (1959).

(5) W. A. Skinner, H. F. Gram, C. W. Mosher, and B. R. Baker, paper XX of this series, *J. Am. Chem. Soc.*, **81**, 4639 (1959).

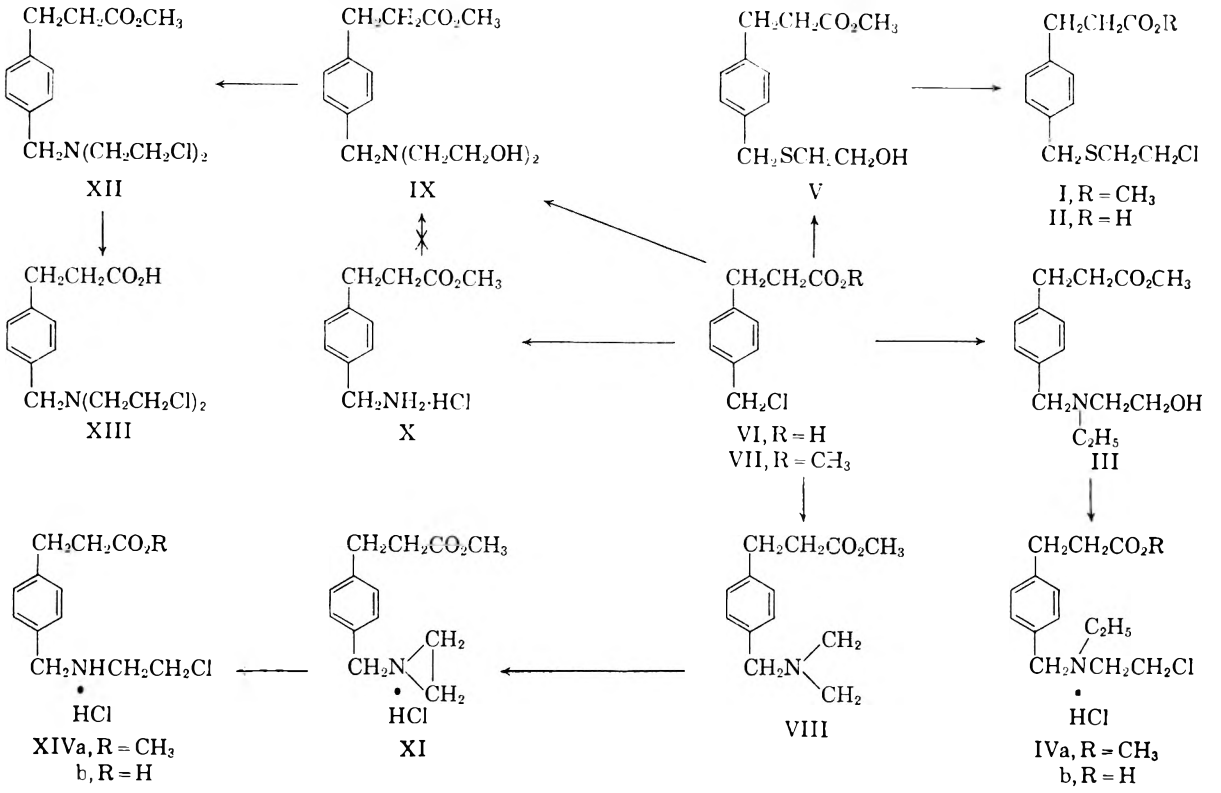
(6) W. A. Skinner, H. F. Gram, and B. R. Baker, paper XXXII of this series, *J. Org. Chem.*, **25**, 777 (1960).

(7) J. Scholler, E. Tholen, and L. H. Schmidt, *Proc. Am. Assoc. Cancer Research*, **3**, 60 (1959); L. F. Larionov, *Akad. Med. Nauk. Vestnik*, **14**, No. 6, 25 (1959).

(8) H. F. Gram, C. W. Mosher, and B. R. Baker, paper XVIII of this series, *J. Am. Chem. Soc.*, **81**, 3103 (1959).

(9) B. R. Baker, *Cancer Chemotherapy Reports*, No. 4, p. 1 (1959), published by the Cancer Chemotherapy National Service Center, National Cancer Institute.

(10) M. N. Bogdanov, *J. Gen. Chem. U.S.S.R.*, **28**, 1621 (1958), has recorded a yield of 27%.



afforded the crystalline methyl ester (VII) in 93% yield.

The benzylic chloride of methyl *p*-(chloromethyl) hydrocinnamate (VII) was readily replaced when refluxed with sodium 2-mercaptoethanol in ethanol for fifteen minutes. The resultant oil (V) was readily purified by distillation in 60% yield and was uniform (R_f 0.72) on paper chromatography[11] with solvent A when detected both by its ultraviolet absorption and by its color with iodoplatinate spray. Treatment of methyl *p*-(2-hydroxyethylthiomethyl)hydrocinnamate (V) with thionyl chloride in boiling dichloromethane afforded I as a nearly analytically pure oil in 74% yield, which was uniform (R_f 0.63) on paper chromatography[11] in solvent A. Hydrolysis of the ester group of I proceeded smoothly at 50° with 1:2 12*N*–hydrochloric acid-glacial acetic acid. After a fifteen-minute hydrolysis period, crystalline 3-(*p*-chloroethylthiomethyl)hydrocinnamic acid (II) was isolated in 72% yield. A higher temperature (b.p.) and longer reaction time (two hours) for the hydrolysis led to an unidentified, high-melting solid which contained practically no chlorine and was not further investigated.

The chlorine of methyl *p*-(chloromethyl)hydrocinnamate (VII) was also readily replaced by 2-ethylaminoethanol in boiling ethanol to form methyl *p*-[ethyl-(2-hydroxyethyl)aminomethyl]hydrocinnamate (III). Although the latter could be distilled, analysis indicated that it was slightly contaminated with VII; that it had no amine impurity was shown by its homogeneity on paper in solvent B[11] when detected by iodoplatinate spray. Nevertheless, when VII was treated with thionyl chloride in boiling chloroform for fifteen minutes, it was smoothly converted to crystalline, nearly pure methyl *p*-[(2-chloroethyl)ethylaminomethyl]-hydrocinnamate hydrochloride (IVa) in 92% yield, which was readily obtained analytically pure. Hydrolysis of the ester group of XIVa proceeded readily with hot concentrated hydrochloric acid to give an 84% yield of crystalline *p* - [ethyl - (2 - choroethyl)aminoethyl] - hydrocinnamic acid hydrochloride (IVb).

Methyl *p*-(chloromethyl)hydrocinnamate (VII) could also be converted with ethyleneimine to the aziridine, VIII. Considerable difficulty was encountered in finding proper conditions for this reaction since no suitable solvent for paper chromatography of crude VIII could be found and crude VIII was not considered distillable in the presence of unchanged VII. Eventually it was found that a seventy-hour reaction at room temperature between VII and ethyleneimine in methanol in the presence of potassium carbonate as an acid acceptor gave a 69% yield of VIII as a nearly analytically pure oil. The latter could be converted to a crystalline aziridine hydrochloride (XI) in methanol. When

(11) Paper chromatograms were run by the descending technique on Schleicher and Schuell acetylated paper No. 2495 in benzene-methanol-water (2:6:1) (solvent A) or on Whatman No. 1 paper with 1-butanol–acetic acid–water (5:3:2) (solvent B). The compounds were detected by their ultraviolet absorption or by the use of iodoplatinate spray.[12]

(12) L. R. Goldbaum and L. Kazyak, *Anal. Chem.*, 28, 1289 (1956).

VIII was treated with hydrogen chloride in ether, a quantitative yield of pure crystalline methyl *p*-[(2-chloroethyl)aminomethyl)hydrocinnamate hydrochloride (XIVa) was obtained. This conversion of VIII to crystalline XIVa could also be done with impure VIII and was the best method for determining how much VIII was present in a given crude product resulting from interaction of VII and ethyleneimine during the search for proper reaction conditions. Hydrolysis of the ester linkage of XIVa with hot concentrated hydrochloric acid gave a 95% yield of crystalline *p*-[(2-chloroethyl) aminomethyl]hydrocinnamic acid hydrochloride (XIVb).

It is surprising that a crystalline hydrochloride (XI) of methyl *p*-(1-aziridinylmethyl)hydrocinnamate (VIII) could be prepared in view of the ease with which the aziridine group is attacked by hydrogen chloride.[2,13] However, under the conditions employed, the yield of recovered hydrochloride (XI) is only 34% and can be recovered only by the fortuitous circumstance that XI is less soluble and higher melting than the ring opened product (XIVa). Nevertheless, the actual preparation of a crystalline aziridine hydrochloride, fortuitous or not, is of more than theoretical interest.

Methyl *p*-(chloromethyl)hydrocinnamate (VII) was allowed to react with excess 2,2′-iminodiethanol in boiling chloroform for six hours, then the amine was removed by thorough washing with water. The crude oil was isolated as the pure crystalline hydrochloride (IX) in 70% yield. Treatment of IX with thionyl chloride in boiling dichloromethane smoothly afforded crystalline methyl *p*-[bis(2-chloroethyl)aminomethyl]hydrocinnamate hydrochloride (XII) in quantitative yield. Removal of the ester group of XII with hot concentrated hydrochloric acid resulted in an 81% yield of *p*-[bis(2-chloroethyl)aminomethyl]hydrocinnamic acid hydrochloric (XIII) (isochlorambucil), which crystallized directly from the hydrolysis solution.

An alternate synthesis of XIII was also investigated. When methyl *p*-(chloromethyl)hydrocinnamate (VII) was treated with hexamethylenetetramine in boiling 95% methanol, an intermediate adduct was obtained which was treated with methanolic hydrogen chloride[14] to give crystalline methyl *p*-(aminomethyl)hydrocinnamate hydrochloride (X). However, this compound did not react with ethylene oxide in dilute acetic acid containing sodium acetate to give IX, but was recovered unchanged.

EXPERIMENTAL[15]

Methyl p-(chloromethyl)hydrocinnamate (VII). *p*-(Chloromethyl)hydrocinnamic acid (VI) was prepared in 50% yield by the chloromethylation of hydrocinnamic acid.[10] A solution of 6.6 g. (0.030 mole) of VI in 75 ml. of methanol saturated with hydrogen chloride at about 25° was refluxed for 1 hr., then evaporated *in vacuo* to a sirup. A solution of this sirup in 30 ml. of chloroform was washed successively with 30 ml. of water, 30 ml. of 5% sodium bicarbonate, and 30 ml. of water. The dried organic solution was evaporated to dryness *in vacuo* leaving 6.6 g. of a sirup that crystallized on cooling. Recrystallization from petroleum ether (b.p. 62–70°) gave 4.8 g. (67%) of product, m.p. 35–42°. For analysis a sample was distilled at 145° (4 mm.), then recrystallized from petroleum ether (b.p. 62–70°) to give white crystals, m.p. 48–49°: $\lambda_{max\,\mu}^{Nujol}$ 5.75 (ester C=O); 6.15, 6.57 (aryl); 8.35 (ester C—O—C); 11.80 (*p*-disubstituted benzene). No suitable reagent could be found for detection of this compound on paper chromatograms.

Anal. Calcd. for $C_{11}H_{13}ClO_2$: C, 62.1; H, 6.11; Cl, 16.7; Found: C, 62.3; H, 6.44; Cl, 16.7.

On a larger scale using pure VI the yield was 93% (120 g.) and the m.p. was 47–48° without recrystallization.

Methyl p-(hydroxyethylthiomethyl)hydrocinnamate (V). To a solution of 8.0 g. (0.10 mole) of 2-mercaptoethanol and 4.0 g. (0.10 mole) of sodium hydroxide in 300 ml. of absolute ethanol was added 21.3 g. (0.10 mole) of methyl *p*-(chloromethyl)hydrocinnamate (VII). After being refluxed for 15 min., during which time sodium chloride separated, the mixture was spin evaporated *in vacuo* to a sirup. The sirup was partitioned between 50 ml. of chloroform and 50 ml. of water. The separated chloroform layer was washed with two 50-ml. portions of water, then dried with magnesium sulfate and evaporated to dryness *in vacuo*. The resultant sirup, after a forerun with b.p. 180–218° (8 mm.), distilled at 220–222° (7 mm.); yield 15.3 g. (60%) of a colorless oil; $\lambda_{max\,\mu}^{Nujol}$ 2.90 (OH); 5.72 (ester C=O); 8.32, 8.60 (ester C—O—C); 9.55 (C—OH); 11.80 (*p*-disubstituted benzene). The compound traveled as a single spot (R_f 0.72) in solvent A[11] when detected by its ultraviolet absorption and by its color (gray white) with iodoplatinate spray.

Anal. Calcd. for $C_{13}H_{18}O_3S$: C, 61.4; H, 7.10; S, 12.6. Found: C, 61.2; H, 7.27; S, 12.2.

Methyl p-(2-chloroethylthiomethyl)hydrocinnamate (I). To a solution of 2.54 g. (10 mmoles) of methyl *p*-(2-hydroxyethylthiomethyl)hydrocinnamate (V) in 5 ml. of dichloromethane cooled in an ice bath was added 10 ml. of a cold 50% solution of thionyl chloride in dichloromethane. After being refluxed for 90 min., the solution was evaporated to dryness *in vacuo*. A solution of the residual oil in 50 ml. of dichloromethane was washed with water, then dried with anhydrous sodium sulfate and evaporated to dryness *in vacuo*; yield, 2.0 g. (74%) of a light yellow oil with $\lambda_{max\,\mu}^{Nujol}$ 5.72 (ester C=O); 8.30, 8.60 (ester C—O—C); 12.10 (*p*-disubstituted benzene); no COH near 3.0 or 9.5. The oil traveled as a single spot (R_f 0.63) in solvent A[11] when detected by its ultraviolet absorption or by iodoplatinate spray, but was not quite analytically pure.

Anal. Calcd. for $C_{13}H_{17}ClO_2S$: C, 57.2; H, 6.23; Cl, 13.0; S, 11.7. Found: C, 57.6; H, 6.46; Cl, 12.9; S, 11.2.

p-(2-Chloroethylthiomethyl)hydrocinnamic acid (II). A solution of 0.56 g. (1.8 mmoles) of methyl *p*-(chloroethylthiomethyl)hydrocinnamate (I) in 7.5 ml. of 12*N* hydrochloric acid and 15 ml. of glacial acetic acid was heated at 50° for 15 min., then diluted with three volumes of water, and cooled to 0°. The product was collected and washed well with water; yield 0.35 g. (72%), m.p. 75–78°. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave white crystals, m.p. 78–79°; $\lambda_{max\,\mu}^{Nujol}$ 3.60–4.10 (acidic OH); 5.85 (carboxyl C=O); 7.05, 8.35, 10.6 (COOH); 12.00 (*p*-disubstituted phenyl); 13.9 (C—Cl).

(13) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, 24, 1827 (1959).

(14) A. Galat and G. Elion, *J. Am. Chem. Soc.*, 61, 3585 (1939).

(15) Melting points were determined on a Fischer-Johns block and are uncorrected.

Anal. Calcd. for $C_{12}H_{15}ClO_2S$: C, 55.6: H, 5.80: Cl, 13.7: S, 12.4. Found; C, 55.9: H, 6.00: Cl, 13.8: S, 12.0.

Methyl p-[ethyl-(2-hydroxyethyl)aminomethyl]hydrocinnamate (III). A solution of 25.5 g. (0.12 mole) of methyl *p*-(chloromethyl)hydrocinnamate and 22 g. of 2-ethylaminoethanol in 55 ml. of chloroform was refluxed for 2 hr. The cooled reaction mixture was washed three times with water, then dried with magnesium sulfate, and evaporated *in vacuo* to a sirup (30.6 g.). Distillation gave 22.4 g. (70%) of product as a colorless oil, b.p. 140–180° (3 mm.): $\lambda_{max\ \mu}^{Nujol}$ 2.91 (OH); 5.75 (ester C=O); 8.55 (ester C—O—C); 9.58 (C—OH); 11.80 (*p*-disubstituted benzene). The oil traveled as a single spot (R_f 0.76) in solvent B[11] when detected with iodoplatinate spray (gray color). Since the starting material is not detectable by this spray, the paper chromatographic results, the analytical data, and the results of the next experiment are in agreement with about 5% contamination with starting material (VII).

Anal. Calcd. for $C_{15}H_{23}NO_3$: C, 67.9: H, 8.74; N, 5.28. Found: C, 67.4; H, 8.79; N, 4.80.

Methyl p-[(2-chloroethyl)ethylaminomethyl]hydrocinnamate hydrochloride (IVa). To a solution of 0.54 g. (2.0 mmoles) of methyl *p*-[ethyl-(2-hydroxyethyl)aminomethyl]hydrocinnamate (III) in 5 ml. of chloroform was added 0.22 ml. (3 mmoles) of thionyl chloride. The solution was refluxed for 15 min., then evaporated to a sirup *in vacuo*. The evaporation was repeated three times with fresh 5-ml. portions of chloroform. The residue crystallized after the last evaporation. Recrystallization from absolute ethanol-ether gave 0.59 g. (92%) of product, m.p. 131–133°. A second recrystallization afforded white crystals m.p. 132–133°; $\lambda_{max\ \mu}^{Nujol}$ 3.95 (R_3NH^+); 5.71 (ester C=O); 8.58 (ester C—O—C); 12.2 (*p*-disubstituted benzene); 13.4 (C—Cl); no COH near 3.0 or 9.5. This compound traveled as a single spot (R_f 0.82) in solvent B[11] when detected by iodoplatinate spray (gray color).

Anal. Calcd. for $C_{15}H_{22}ClNO_2.HCl$: C, 56.2; H, 7.20; Cl, 22.2; N, 4.37. Found: C, 56.4: H, 7.39; Cl, 22.3; N, 4.38.

p-[(Chloroethyl)ethylaminomethyl]hydrocinnamic acid hydrochloride (IVb). A solution of 0.50 g. (1.56 mmoles) of methyl *p*-[(2-chloroethyl)ethylaminomethyl]hydrocinnamate hydrochloride (IVa) in 15 ml. of 12*N* hydrochloric acid was refluxed for 45 min., then evaporated to residue *in vacuo*. Benzene (50 ml.) was added to the residue and benzene (20 ml.) distilled until no more water was removed. Evaporation to residue *in vacuo* left white crystals which were triturated with reagent ether; yield, 0.40 g. (84%), m.p. 141–143°; $\lambda_{max\ \mu}^{Nujol}$ 5.80 (carboxyl C=O); 8.45, 10.55 (COOH); 12.0 (*p*-disubstituted benzene); no ester bands at 5.71 or 8.58. Neither suitable solvents for recrystallization nor suitable detection agents for paper chromatography could be found. The infrared spectrum clearly showed that the ester group had hydrolyzed and no ester (R_f 0.82) could be detected when the product was chromatographed on paper with solvent B[11] and sprayed with iodoplatinate.

Anal. Calcd. for $C_{14}H_{20}ClNO_2.HCl$: C, 54.9; H, 6.87; Cl, 23.2; N, 4.58. Found: C, 54.7; H, 6.90; Cl, 23.2; N, 4.70.

Methyl p-(1-aziridinylmethyl)hydrocinnamate (VIII). To a mixture of 10.8 g. (0.050 mole) of methyl *p*-(chloromethyl)-hydrocinnamate (VII), 200 ml. of reagent methanol and 10 g. of anhydrous potassium carbonate was added 27 ml. of ethyleneimine. The mixture was stirred for 70 hr. at room temperature. After the addition of 3 g. of Celite,[16] the mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ether; the solution, clarified by filtration, was evaporated to a sirup *in vacuo;* yield, 7.6 g. (69%) of a colorless nearly pure oil with $\lambda_{max\mu}^{film}$ 3.37, 3.40 (CH); 5.72 (ester C=O); 12.10 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.82; N, 6.39. Found: C, 70.7; H, 7.74; N, 5.99.

(16) Johns-Manville Co. diatomaceous earth.

No suitable solvent system for paper chromatography could be found for this compound even though it could be detected on paper by bromocresol green.

The hydrochloride (XI) of VIII was prepared by saturating a solution of 1.5 g. of VIII in methanol with hydrogen chloride without cooling. The solution was evaporated *in vacuo* and the residue triturated thoroughly with ether. The residue (1.8 g.) was dissolved in 20 ml. of methanol and kept at 3° for 2 weeks, during which time crystals of XI separated; yield, 0.60 g. (34%), m.p. 220–225°; $\lambda_{max\ \mu}^{Nujol}$ 4.25, (R_2NH^+); 5.76 (ester C=O), 11.70 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{13}H_{17}NO_2.HCl$: C, 61.1; H, 7.05; Cl, 13.9; N, 5.48. Found: C, 60.8; H, 7.25; Cl, 13.8; N, 5.66.

Methyl p-[(2-chloroethyl)aminomethyl]hydrocinnamate hydrochloride (XIVa). Through a solution of 2.0 g. (9.1 mmoles) of methyl *p*-(1-aziridinylmethyl)hydrocinnamate (VIII) in 25 ml. of ether under a reflux condenser was passed hydrogen chloride until the solution was saturated. Evaporation to residue *in vacuo* (bath 30°) gave 2.6 g. (98%) of white crystals, m.p. 197–198°. Recrystallization from hot ethyl acetate containing the minimum amount of methanol to cause solution gave white crystals, m.p. 197–198°; $\lambda_{max\ \mu}^{Nujol}$ 3.65, 3.80, 4.15 (NH_2^+); 5.75 (ester C=O); 8.32, 8.51 (ester C—O—C); 12.1 (*p*-disubstituted benzene); 13.8 (C—Cl).

Anal. Calcd. for $C_{13}H_{17}ClNO_2.HCl$: C, 53.6; H, 6.23; Cl, 24.4; N, 4.79. Found: C, 53.2; H, 6.86; Cl, 24.6; N, 4.97.

p-[(2-Chloroethyl)aminomethyl]hydrocinnamic acid hydrochloride (XIVb). A solution of 1.65 g. (5.64 mmoles) of methyl *p*-[(2-chloroethyl)aminomethyl]hydrocinnamate (XIVa) in 10 ml. of 12*N* hydrochloric acid was heated on a steam bath for 30 min., then evaporated to dryness *in vacuo;* yield, 1.50 g. (95%) of white crystals, m.p. 173–176°. Trituration with boiling ethyl acetate raised the m.p. to 178–179°; $\lambda_{max\ \mu}^{Nujol}$ 3.20–3.90, 4.10 ($R_2NH_2^+$, acidic OH); 5.79 (carboxyl C=O); 6.29 ($R_2NH_2^+$); 6.15, 6.55 (aryl); 12.00 (*p*-disubstituted benzene); 13.2, 13.8 (C—Cl).

Anal. Calcd. for $C_{12}H_{15}ClNO_2.HCl$: C, 52.0; H, 5.77; Cl, 25.6; N, 5.05. Found: C, 51.9; H, 5.91; Cl, 25.3; N, 5.14.

Methyl p-[bis(2-hydroxyethyl)aminomethyl]hydrocinnamate hydrochloride (IX). To a solution of 2.1 g. (10 mmoles) of methyl *p*-(chloromethyl)hydrocinnamate (VII) in 25 ml. of chloroform was added 4.2 g. (40 mmoles) of 2,2′-iminodiethanol. After being refluxed for 6 hr., the solution was cooled and washed thoroughly with water (4 × 25 ml.). The organic solution, dried with magnesium sulfate, was chloroform was added 4.2 g. (40 mmoles) of 2,2′-iminodiethanol. After being refluxed for 6 hr., the solution was cooled and washed thoroughly with water (4 × 25 ml.). The organic solution, dried with magnesium sulfate, was evaporated to dryness *in vacuo*. A solution of the residue in 30 ml. of benzene was saturated with hydrogen chloride, then evaporated *in vacuo*. Crystallization from dichloromethane ether gave 2.2 g. (70%) of white crystals, m.p. 82–85°; $\lambda_{max\ \mu}^{Nujol}$ 3.02 (OH); 3.65, 3.75 (NH^+); 5.72 (ester C=O); 8.32, 8.49 (ester C—O—C); 9.32 (C—OH); 12.10 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{15}H_{23}NO_4.HCl$: C, 56.7; H, 7.56; Cl, 10.7; N, 4.42. Found: C, 56.9; H, 7.71; Cl, 10.4; N, 4.11.

Methyl p-[bis(2-chloroethyl)aminomethyl]hydrocinnamate hydrochloride (XII). To a solution of 0.40 g. (1.3 mmoles) of methyl *p*-[bis(2-hydroxyethyl)aminomethyl]hydrocinnamate hydrochloride (IX) in 5 ml. of dichloromethane was added 3 ml. of thionyl chloride. After being refluxed for 90 min., the solution was evaporated to residue *in vacuo*. The evaporation was repeated with four fresh 10-ml. portions of chloroform, then the residue crystallized on cooling; yield, 0.45 g. (100%) of white crystals, m.p. 105–110°. Recrystallization from dichloromethane-petroleum ether (b.p. 30–60°) raised the m.p. to 113–114°; $\lambda_{max\ \mu}^{Nujol}$ 4.08 (NH^+); 5.72 (ester C=O); 8.32, 8.45, 8.60 (ester C—O—C); 12.2 (*p*-disubstituted benzene); 13.4 (C—Cl).

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_2.HCl$: C, 50.7; H, 6.20; Cl, 30.2; N, 3.95. Found: C, 50.7; H, 6.12; Cl, 30.7; N, 4.02.

p-[Bis(2-chloroethyl)aminomethyl]hydrocinnamic acid hydrochloride (XII). A solution of 0.90 g. (2.5 mmoles) of methyl *p*-[bis(2-chloroethyl)aminomethyl]cinnamate hydrochloride (XII) in 10 ml. of 12*N* hydrochloric acid was refluxed for 30 min., then concentrated to about one-half volume *in vacuo* and cooled in an ice bath. The product was collected on a glass filter; yield, 0.70 g. (81%), m.p. 171–175°. A sample was recrystallized by solution in hot water, then addition of five volumes of 12*N* hydrochloric acid to give white crystals, m.p. 176–177°; $\lambda_{max\ \mu}^{Nujol}$ 3.75, 3.87 (NH^+ and acidic OH); 5.80 (carboxyl C=O); 12.0 (*p*-disubstituted benzene); 13.4 (C—Cl).

Anal. Calcd. for $C_{14}H_{19}Cl_2N_2O_2.HCl$: C, 49.3; H, 5.87; Cl, 31.3; N, 4.12. Found: C, 49.2; H, 5.95; Cl, 31.1; N, 4.15.

Methyl p-(aminomethyl)hydrocinnamate hydrochloride (X). To a stirred solution of 7.0 g. (0.050 mole) of hexamethylenetetramine[14] in 100 ml. of 95% methanol was added 8.5 g. (0.050 mole) of potassium iodide followed by 10.6 g. (0.050 mole) of methyl *p*-(chloromethyl)hydrocinnamate (VII). The reaction mixture was refluxed with stirring for 40 min., then filtered hot to remove potassium chloride. The filtrate was cooled to 0° and deposited 20.0 g. (75%) of the hexamine complex that was contaminated with some salts.

A suspension of 20 g. of the hexamine complex in 150 ml. of methanol was saturated with hydrogen chloride,[14] refluxed for 30 min., then evaporated to dryness *in vacuo*. The residue was dissolved in hot dichloromethane and filtered from some inorganic material. Evaporation of the combined filtrate and washings to dryness *in vacuo* afforded 8.8 g. (77%) of an amorphous solid, m.p. 150–155°, that gave a paper chromatogram and infrared absorption spectrum identical with the analytical sample. Crystallization of a sample from methanol ether afforded white crystals, m.p. 208–217°; $\lambda_{max\ \mu}^{Nujol}$ 3.50, 4.20, 4.85 (NH^+); 5.72 (ester C=O); 8.50 (ester C—O—C); 12.1 (*p*-disubstituted benzene). The compound traveled as a single spot (R_f 0.76) in solvent B[11] when detected by iodoplatinate spray (gray color).

This compound (X), when allowed to react in the usual manner[8] with ethylene oxide in dilute acetic acid containing an equivalent of sodium acetate, was not converted to IX as expected, but was recovered unchanged. It appears that hydroxyethylation in dilute acetic acid fails to take place because of the stronger protonation of aliphatic amines, such as X, compared to the arylamines usually employed under these conditions.[8]

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MENLO PARK, CALIF

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLVI. Analogs of Chlorambucil. V.[2] Alkylating Agents Derived from ω-Phenoxyalkanoic Acids

W. A. SKINNER, ABELARDO P. MARTINEZ, AND B. R. BAKER

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Several analogs of the chlorambucil isostere 3-*p*-{[bis(2-chloroethyl)amino]phenoxy}propionic acid (I, $n = 2$) have been synthesized for evaluation as potential anticancer agents and as potential irreversible inhibitors of lactic dehydrogenase.

A series of ω-{*p*-[bis(2-chloroethyl)amino]phenoxy}alkanoic acids (I) have been synthesized[3] and evaluated as anticancer agents against Walker rat Sarcoma 256. All four of these acids showed inhibitory action. The maximum effect was shown by the propionic acid derivative (I, $n = 2$), which was considered[3] to be an isostere of chlorambucil, 4-{*p*-[bis(2-chloroethyl)amino]phenyl}butyric acid.[4] As *m*-phenylalanine mustard[5] appears to be more effective against some tumors[6] than *p*-phenylalanine mustard,[7,8] the synthesis of the *o*- and *m*-isomers of I ($n = 1,2$) was deemed advisable in order to determine whether or not these changes would cause a change in tumor spectrum.[9,10] These

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center of the 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 not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper of this series, *cf.* A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) For paper IV on chlorambucil analogs, see W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, 25, 148 (1960), Paper XLIII of this series.

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(5) H. F. Gram, C. W. Mosher, and B. R. Baker, Paper XVII of this Series, *J. Am. Chem. Soc.*, 81, 3103 (1959).

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(7) F. Bergel, V. C. E. Burnop, and J. A. Stock, *J. Chem. Soc.*, 1223 (1955); F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954). These authors use the synonym of Merphalan for the racemate of *p*-phenylalanine mustard and Melphalan for the L-isomer.

(8) L. F. Larionov, A. S. Khokhlov, E. N. Shkodinskaia, O. S. Vasina, V. I. Trusheikina, and A. M. Novikova, *Lancet*, 269, 169 (1955). These authors use the synonym of sarcolysin for the racemate of *p*-phenylalanine mustard.

compounds are also of interest as potential irreversible inhibitors of lactic dehydrogenase.[11]

The synthesis of [*m*-[bis(2-chloroethyl)amino]-phenoxy]acetic acid (VI) and 3-{*m*-[bis(2-chloroethyl)amino]phenoxy}propionic acid (VII) was similar to the route used earlier for the synthesis of the *para* series (I).[3]

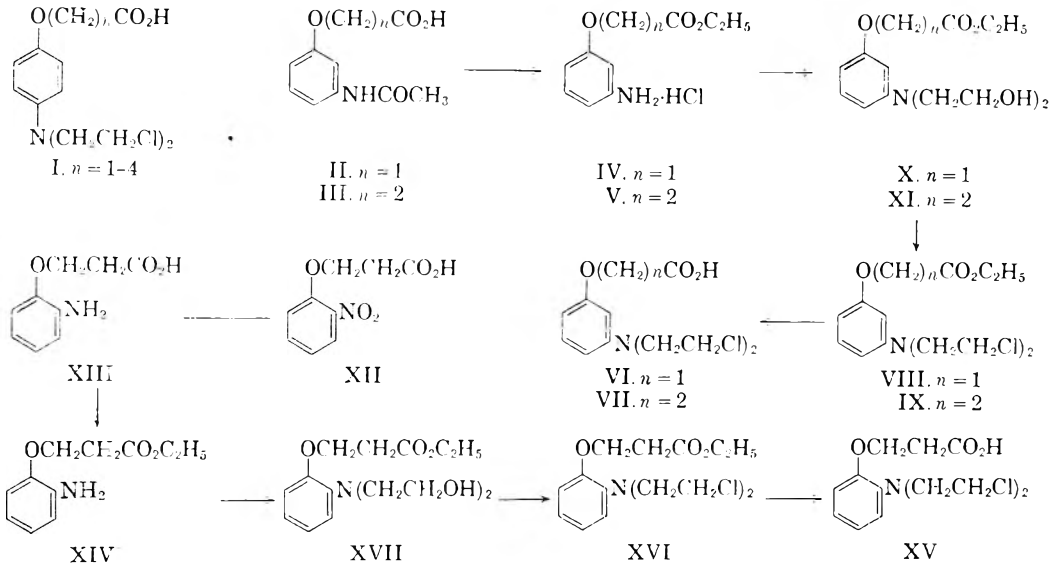
(*m*-Acetamidophenoxy)acetic acid (II) was prepared from *m*-hydroxyacetanilide in 72% yield by the method of Howard.[12] Simultaneous alcoholysis of the acetamido group and esterification with ethanolic hydrogen chloride gave crystalline ethyl (*m*-aminophenoxy)acetate hydrochloride (IV) in 62% yield. Hydroxyethylation using ethylene oxide in aqueous acetic acid afforded ethyl {*m*-[bis(2-hydroxyethyl)amino]phenoxy}acetate (X) as a nearly analytically pure oil in 92% yield that was uniform when chromatographed on paper in System A,[13] showing a single spot (R_f 0.61).

Chlorination of X by refluxing in phosphorus oxychloride for fifteen minutes gave ethyl {*m*-[bis(2-chloroethyl)amino]phenoxy}acetate (VIII) in 88% yield as a low-melting solid, m.p. 38–39°, R_f 0.52 in System A.[13] Hydrolysis of VIII with hot concentrated hydrochloric acid gave the desired *m*-phenoxyacetic acid mustard (VI) in 87% yield as an analytically pure solid.

Ethyl 3-(*m*-aminophenoxy)propionate hydrochloride (V) was prepared in 82% yield by simultaneous alcoholysis and esterification of 3-(*m*-acetamidophenoxy)propionic acid (III) with alcoholic hydrogen chloride. Hydroxyethylation of V with ethylene oxide in aqueous acetic acid proceeded smoothly to give a quantitative yield of ethyl 3-{*m*-[bis (2-hydroxyethyl) amino] phenoxy} propionate (XI) obtained as an analytically pure solid, m.p. 53–54°, R_f 0.61 (System A[13]). Treatment of XI for thirty minutes in hot phosphorus oxychloride gave a 96% yield of ethyl 3-{*m*-[bis(2-chloroethyl)amino] phenoxy}propionate (IX), m.p. 31–32°, R_f 0.61 (System A[13]).

Hydrolysis of IX with hot concentrated hydrochloric acid yielded the desired *m*-phenoxypropionic acid mustard (VII) in 88% yield, m.p. 138–139°. The analytical sample traveled as a single spot (R_f 0.70) on paper in System A.[13]

Attempts to react *o*-hydroxyacetanilide with 3-bromopropionic acid in aqueous sodium hydroxide resulted in low yields (8%) of 3-(*o*-acetamidophenoxy)propionic acid. By the method of Chakravarti and Dutta,[14] *o*-nitrophenol and 3-bromopropionic acid were allowed to react in aqueous sodium hydroxide to give a 30% yield of 3-(*o*-nitrophenoxy)propionic acid (XII). Hydrogenation of XII with palladium-on-charcoal at room temperature and atmospheric pressure afforded crystalline 3-(*o*-aminophenoxy)propionic acid (XIII) in 82% yield, readily esterified to XIV with ethanolic hydrogen



The reaction of *m*-hydroxyacetanilide with 3-bromopropionic acid in alkaline solution gave 3-(*m*-acetamidophenoxy)propionic acid (III) as an analytically pure hydrated solid in 17% yield. Substitution of lithium hydroxide for sodium hydroxide or ethyl 3-bromopropionate for 3-bromopropionic acid resulted in none of the desired product (III). A 6% yield of III was obtained when the reaction was carried out in absolute ethanol using sodium ethoxide in place of sodium hydroxide.

(9) J. Scholler, E. Tholen, and L. H. Schmidt, *Proc. Am. Assoc. Cancer Research*, **3**, 60 (1959).

(10) L. F. Larionov, *Akad. Med. Nauk. Vestnik*, **14**, No. 6, 25 (1959).

(11) B. R. Baker, *Cancer Chemotherapy Reports*, **4**, 1 (1959), published by the National Cancer Institute.

(12) C. C. Howard, *Ber.*, **30**, 546 (1897).

(13) Paper chromatograms were run by the descending technique with benzene–methanol–water (2/6/1) on Schleicher and Schuell No. 2495 acetylated paper (System A) or on Whatman No. 1 paper (System B). Spots were detected by visual examination under ultraviolet light.

(14) D. Chakravarti, and J. Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939).

chloride in 88% yield. Hydroxyethylation of the free base of XIV with ethylene oxide in aqueous acetic acid gave ethyl 3-{*o*-[bis(2-hydroxyethyl)-amino]phenoxy}propionate (XVII) as a nearly analytically pure viscous oil in 81% yield, which was homogeneous on paper in System A[13] (R_f 0.74). As in all of the hydroxyethylation reactions, thorough washing of a dichloromethane solution of the bishydroxyethyl compound (XVII) with water was necessary to remove polymeric glycol by-products. Chlorination of XVII in the usual manner with phosphorus oxychloride resulted in 82% yield of XVI as an amber oil, which melted below 20° and had R_1 0.71 in System A.[13]

Hydrolysis of XVI with concentrated hydrochloric acid gave 3-{*o*-[bis(2-chloroethyl)amino]-phenoxy}propionic acid (XV) as a pure solid, m.p. 71.5–73°, in 87% yield.[15] In common with the other phenoxyalkanoic acid mustards, this compound (XV) is light-sensitive, giving a green coloration upon exposure.

Attempts to chlorinate the various bis(hydroxyethyl)amines with thionyl chloride in methylene chloride or chloroform resulted in low yields of the mustards and led to difficulties in purification of the final compounds. Phosphorus oxychloride was found to give a much cleaner chlorination in this series.

EXPERIMENTAL[16]

3-(m-Acetamidophenoxy)propionic acid (III). To a hot solution of 1.51 g. (10 mmoles) of *m*-hydroxyacetanilide in 10 ml. of 4% aqueous sodium hydroxide was added a solution of 1.53 g. (10 mmoles) of 3-bromopropionic acid in 20 ml. of water containing 0.40 g. of sodium hydroxide. The solution was placed on a steam-bath and allowed to evaporate overnight. The residue was dissolved in 10 ml. of water, acidified to *p*H 5 and cooled in an ice bath. The unchanged phenol was removed by filtration, then the combined filtrate and washings were acidified to *p*H 1; yield, 0.41 g. (17%) of product m.p. 70–100°, resolidifies and remelts at 130–131°; $\lambda_{max(\mu)}^{Nujol}$ 2.97 (NH and H_2O); 325–4.00 (acidic OH); 5.83 (carboxyl C=O); 6.05, 6.35 (amide); 13.00 (*m*-disubstituted benzene).

Anal. Calcd. for $C_{11}H_{13}NO_4.H_2O$: C, 54.8; H, 6.27. Found: C, 54.4; H, 6.48.

Ethyl 3-(m-aminophenoxy)propionate hydrochloride (V). A solution of 18.6 g. (0.084 mole) of 3-(*m*-acetamidophenoxy)-propionic acid (III) in 240 ml. of absolute ethanol saturated with hydrogen chloride was refluxed for 1 hr., cooled, and concentrated to dryness *in vacuo* leaving 21.6 g. (105%) of solid, m.p. 95–99°. Recrystallization from ethyl acetate gave 16.8 g. (82%) of crystals, m.p. 112–113°; $\lambda_{max(\mu)}^{Nujol}$ 3.85, 4.85 (NH_3^+); 5.75 (ester C=O); 8.40, 8.52 (ester C—O—C); 12.90 (*m*-disubstituted benzene); no amide band near 6.0. The compound traveled as a single spot (R_f 0.57) in System A[13] on paper.

Anal. Calcd. for $C_{11}H_{15}NO_3.HCl$: C, 53.8; H, 6.52; Cl, 14.1. Found: C, 53.7; H, 6.62; Cl, 14.1.

Similarly, 15.0 g. of (*m*-acetamidophenoxy)acetic acid (II)[12] gave, after recrystallization from ethyl acetate, 10.3 g. (62%) of *ethyl (m-aminophenoxy)acetate hydrochloride* (IV), m.p. 129–130°; $\lambda_{max(\mu)}^{Nujol}$ 3.35, 4.97 (NH_3^+); 5.72 (ester C=O); 8.45, 8.65 (ester C—O—C); 12.95 (*m*-disubstituted benzene). The compound traveled as a single spot (R_f 0.45) in System A.[13]

Anal. Calcd. for $C_{10}H_{13}NO_3.HCl$: C, 51.9; H, 6.05. Found: C, 52.3; H, 6.22.

3-(o-Aminophenoxy)propionic acid (XIII). A mixture of 1.00 g. (4.7 mmoles) of 3-(*o*-nitrophenoxy)propionic acid (XII),[14] 75 mg. of 5% palladium-on-charcoal moistened with 2-methoxyethanol and 50 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure for 15 min. when reduction was complete. The catalyst was removed by filtration and the combined filtrate and washings were evaporated to dryness *in vacuo* leaving 0.70 g. (82%) of tan needles, m.p. 105–106°; $\lambda_{max(\mu)}^{Nujol}$ 3.60–4.00 (acidic OH); 5.95 (acid C=O); 13.17 (*o*-disubstituted benzene).

Anal. Calcd. for $C_9H_{11}No_3$: C, 59.7; H, 6.12. Found: C, 59.3; H, 5.97.

Ethyl 3-(o-aminophenoxy)propionate hydrochloride (XIV). A solution of 2.68 g. (0.015 mole) of 3-(*o*-aminophenoxy)-propionic acid (XII) in 30 ml. of absolute ethanol saturated with hydrogen chloride was refluxed for 1 hr. The solution was evaporated to dryness *in vacuo* and the residue triturated with ether; yield 3.20 g. (88%), m.p. 172–173°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.50 (NH^+); 5.79 (ester C=O); 8.25, 8.41, 8.54 (ester C—O—C); 13.20 (*o*-disubstituted benzene). The compound traveled as a single spot (R_f 0.46) in System A.[13]

Anal. Calcd. for $C_{11}H_{15}NO_3.HCl$: C, 53.9; H, 6.53. Found: C, 53.8; H, 6.71.

Ethyl m-[bis(2-hydroxyethyl)amino]phenoxyacetate (X). To a solution of 12.1 g. (0.052 mole) of ethyl (*m*-aminophenoxy)acetate hydrochloride (IV) in 150 ml. of water was added 5.0 g. of sodium bicarbonate, 82 ml. of glacial acetic acid, and 10 ml. of ethanol. The stirred solution was cooled to −5° in an ice bath and 30 ml. of ethylene oxide was added slowly. The reaction flask was stoppered and the mixture stirred for 24 hr. at room temperature. The solution was neutralized with solid sodium bicarbonate and extracted with dichloromethane (3 × 125 ml.). The combined extracts were washed with water (4 × 125 ml.) to remove glycol polymers and then dried over anhydrous magnesium sulfate. The solution was evaporated *in vacuo* to yield 15.0 g. (100%) of a light reddish oil. The oil was dissolved in hot ether, the ether solution was filtered, the concentrated *in vacuo* to yield 14.0 g. (92%) of a light red oil; $\lambda_{max(\mu)}^{film}$ 3.00 (OH); 5.78 (ester); 8.50 (ester C—O—C); 9.0 10.0 (C—OH); 13.3 (*m*-disubstituted benzene). The compound traveled as a single spot (R_f 0.61) in System A[13] and was essentially pure.

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.4; H, 7.47. Found: C, 58.9; H, 7.57.

Ethyl 3-{m-[bis(2-hydroxyethyl)amino]phenoxy}propionate (XI). Hydroxyethylation of ethyl 3-(*m*-aminophenoxy)-propionate hydrochloride (V), as described for the preparation of X, gave a quantitative yield of product that crystallized on standing and was suitable for the next step. Recrystallization of a sample from ether gave crystals with m.p. 53–54° and $\lambda_{max(\mu)}^{Nujol}$ 2.95, 9.49, 9.68 (C—OH); 5.82, 8.30, 8.36, 8.50 (ester); 13.50 (*m*-disubstituted benzene). The compound traveled in System A[13] as a single spot with R_f 0.65.

Anal. Calcd. for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.80. Found: C, 60.9; N, 7.96.

Similarly, ethyl 3-{*o*-[bis(2-hydroxyethyl)amino]phenoxy}-propionate (XVII) was obtained in 81% yield as an essentially pure oil with R_f 0.74 in System A[13] and $\lambda_{max(\mu)}^{film}$ 2.95, 9.30–9.80 (C—OH); 5.75, 8.40 (ester); 13.30 (*o*-disubstituted benzene).

Anal. Calcd. for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.80; N, 4.71. Found: C, 60.0; H, 8.17; N, 4.33.

(15) This route was not considered feasible for synthesis of *o*-phenoxyacetic acid mustard, because of the ease of lactam formation of (*o*-aminophenoxy)acetic acid and its derivatives.

(16) Melting points were taken on a Fisher-Johns block and are uncorrected.

Ethyl m-[bis(2-chloroethyl)amino]phenoxy acetate (VIII). A mixture of 1.0 g. (3.5 mmoles) of ethyl *m*-[bis(2-hydroxyethyl)amino]phenoxy acetate (X) and 7.5 ml. of freshly distilled phosphorus oxychloride was refluxed for 15 min. The green-colored solution was poured into 100 ml. of ice and stirred well for 10 min. The mixture was neutralized with sodium acetate to *p*H 5 and extracted with 100 ml. of dichloromethane. The extract was washed with 50 ml. of water, dried over anhydrous magnesium sulfate, then concentrated *in vacuo* to yield a yellow-green oil. This oil was dissolved in 10 ml. of dichloromethane and 50 ml. of toluene and evaporated to dryness (bath 50°) *in vacuo* to remove acetic acid. The residue oil crystallized upon standing; yield, 1.0 g. (88%), m.p. 38–39°; $\lambda_{max(\mu)}^{film}$ 5.63 (ester C=O); 8.30, 8.56 (ester C—O—C); 13.30 (*m*-disubstituted benzene); free of COH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.52) in System A.[13]

Anal. Calcd. for $C_{14}H_{19}Cl_2NO_3$: C, 52.5; H, 5.95; Cl, 22.2. Found: C, 52.3; H, 6.29; Cl, 22.1.

Ethyl 3-{m-[bis(2-chloroethyl)amino]phenoxy}propionate (IX). The chlorination of 1.0 g. (3.0 mmoles) of ethyl 3-{*m*-[bis(2-hydroxyethyl)amino]phenoxy}propionate (XI) was performed in essentially the same manner as described for X except that XI was heated for 30 min. with phosphorus oxychloride on a steam bath, rather than refluxed for 15 min. The product (IX), after crystallization from ether-petroleum ether (b.p. 30–60°), was obtained in 96% yield, m.p. 31–32°; $\lambda_{max(\mu)}^{Nujol}$ 5.78 (ester C=O); 8.40, 8.60 (ester C—O—C); 13.32 (*m*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.61) in System A.[13]

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_3$: C, 53.9; H, 6.29; Cl, 21.3. Found: C, 54.1; H, 6.49; Cl, 21.5.

Ethyl 3-{o-[bis(2-chloroethyl)amino]phenoxy}propionate (XVI). Treatment of 1.0 g. (3.0 mmoles) of ethyl 3-{*o*-[bis-(2-chloroethyl)amino]phenoxy}propionate (XVIII) with phosphorus oxychloride in the same manner as for X yielded 0.95 g. (82%) of a light amber oil which crystallized to fine needles melting below 20°; $\lambda_{max(\mu)}^{film}$ 5.72 (ester C=O); 8.42 (ester C—O—C); 13.30 (*o*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0 and 9.5. The compound traveled as a single spot (R_f 0.71) in System A,[13] and analysis showed it was nearly pure.

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_3$: C, 53.9; H, 6.29; Cl, 21.3; N, 4.19. Found: C, 54.7; H, 6.53; Cl, 20.7; N, 4.34.

{m-[Bis(2-chloroethyl)amino]phenoxy}acetic acid (VI). A solution of 0.10 g. (0.30 mmole) of ethyl {*m*-[bis(2-chloroethyl)amino]phenoxy}acetate (VIII) in 2 ml. of concd. hydrochloric acid was refluxed for 10 min., cooled, and neutralized with sodium acetate to *p*H 5. The product was extracted with 25 ml. of dichloromethane; the extract was washed with 10 ml. of water, dried over anhydrous magnesium sulfate, then concentrated to dryness *in vacuo*. The white solid was dissolved in toluene and again concentrated *in vacuo* to yield 0.080 g. (87%) of white crystals m.p. 127–128°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.00 (acidic OH); 5.72 (carboxyl C=O); 13.28 (*m*-disubstituted benzene); 13.45 (C—Cl). The compound traveled as a single spot (R_f 0.87) in System B.[13]

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_3$: C, 49.3; H, 5.14; Cl, 24.3. Found: C, 49.6; H, 5.43; Cl, 24.4.

3-{m-[Bis(2-chloroethyl)amino]phenoxy}propionic acid (VII). The hydrolysis of 0.90 g. (3.0 mmoles) of ethyl 3-{*m*-[bis(2-chloroethyl)amino]phenoxy}propionate (IX) was carried out in the same manner as was that of VIII except that the time of reflux was lengthened to 30 min. An 88% yield of product, m.p. 134–136°, was obtained. Recrystallization from petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 138–139°; $\lambda_{max(\mu)}^{Nujol}$ 3.50–4.00 (acidic OH); 5.83 (carboxy C=O); 13.30 (*m*-disubstituted benzene); 13.90 (C—Cl); absence of OH near 3.0. The compound traveled as a single spot (R_f 0.70) on paper in System A.[13]

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 51.0; H, 5.55; Cl, 23.2; N, 4.57. Found: C, 51.1; H, 5.62; Cl, 23.1; N, 4.75.

3-{o-[Bis(2-chloroethyl)amino]phenoxy}propionic acid (XV). Hydrolysis of 0.50 g. (1.5 mmoles) of ethyl 3-{*o*-[bis-(2-chloroethyl)amino]phenoxy}propionate (XVI) with concd. hydrochloric acid in the same manner as described for VIII yielded 0.40 g. (87%) of crystalline product, m.p. 65–67°. Recrystallization from petroleum ether (b.p. 30–60°) yielded an analytical sample, m.p. 71.5–73°; $\lambda_{max(\mu)}^{Nujol}$ 3.80–4.20 (acidic OH); 5.80 (carboxyl C=O); 13.00 (*o*-disubstituted benzene); 13.89 (C—Cl). The compound traveled as a single spot (R_f 0.77) in System A.[13]

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 51.0; H, 5.56; Cl, 23.2; N, 4.57. Found: C, 50.9; H, 5.60; Cl, 22.9; N, 4.61.

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Chiapagenin and Isochiapagenin. Two New Steroidal Sapogenins from *Dioscorea chiapasensis*[1]

I. T. HARRISON, M. VELASCO,[2] AND CARL DJERASSI

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Dioscorea chiapasensis Matuda was found to contain diosgenin, yamogenin, correlogenin (neobotogenin), and two new dihydroxy sapogenins, now named chiapagenin and isochiapagenin. Chiapagenin was shown to be 12β-hydroxyyamogenin by appropriate interconversions with correlogenin and with sisalagenin. Isochiapagerin has been identified as 12β-hydroxydiosgenin.

During the past few years relatively few new steroidal sapogenins have been isolated, most of them being C-1 hydroxylated steroids (*e.g.*, ruscogenin, rhodeasapogenin, tokorogenin, kogagenin).[3] Of particular interest is the recent report by

(1) Supported by a research grant from The Rockefeller Foundation.

(2) Research Laboratories, Syntex, S.A., Mexico, D. F.

(3) For detailed review and references on these and other steroidal sapogenins see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, chap. 21.

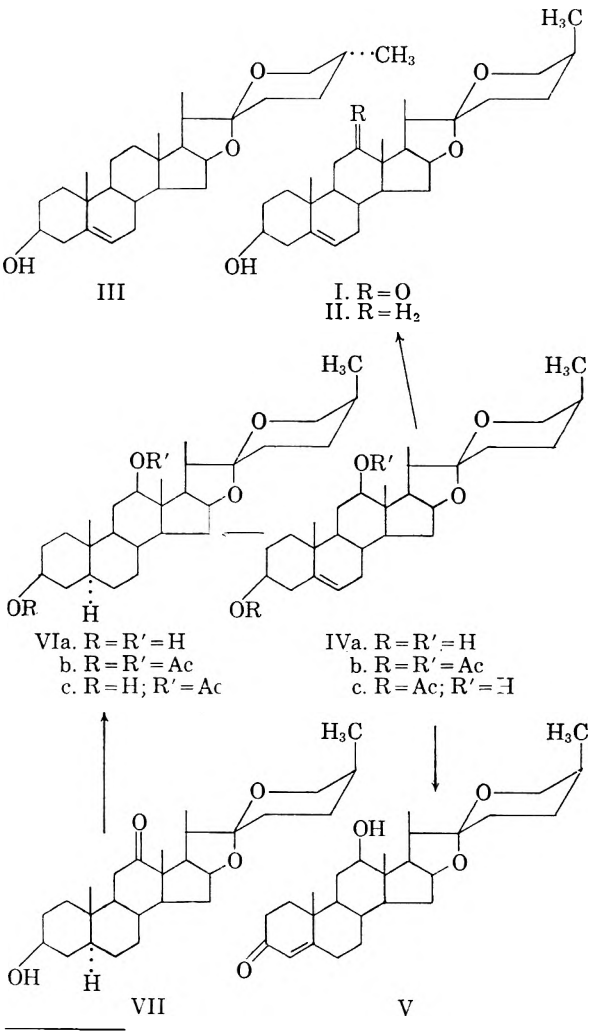
Takeda and Hamamoto[4] that metagenin represents an 11-hydroxylated sapogenin, thus demonstrating for the first time that sapogenins oxygenated at the important 11 position may be encountered in nature. This encouraged us to examine in detail *Dioscorea chiapasensis* Matuda, since this species has not been included among the 5000 plants covered in the U.S.D.A. sapogenin survey[5] and since preliminary work had indicated the presence of several sapogenins.[6]

The crude sapogenin mixture obtained on acid hydrolysis of the alcoholic extract of *D. chiapasensis* was first subjected to treatment with Girard's reagent T, since infrared examination of the crude mixture indicated the presence of some ketonic material. Chromatography of the ketonic fraction from the Girard fractionation led to a small amount of pure correlogenin (neobotogenin) (I).[7]

Most of the material appeared in the "nonketonic" fraction and since this did not exhibit any carbonyl absorption in the infrared, it could not contain any 11-ketosapogenin, which presumably would have appeared in the "nonketonic" portion. Chromatography effected separation into two principal components, which on the basis of their order of elution were judged to contain, respectively, mono and dihydroxylated sapogenins. The monohydroxy sapogenins were acetylated and rechromatographed, whereupon it could be demonstrated that they consisted of a mixture of yamogenin (II) and diosgenin (III).

The single largest component of the steroidal sapogenin mixture was represented by the dihydroxy fraction, which crystallized readily to afford a pure sapogenin $C_{27}H_{42}O_4$, m.p. 257–259°, $[\alpha]_D$ −130°, characterized further by its diacetate m.p. 194–196°, $[\alpha]_D$ −128°. Inspection of the literature[3] showed that this was a new sapogenin and we have, therefore, named it "chiapagenin" in accordance with its botanical origin.

The infrared spectrum of chiapagenin exhibited bands characteristic[8] of the "neo" series and since its optical rotation was typical[3] of Δ^5-steroidal sapogenins, one could conclude tentatively that chiapagenin is x-hydroxyyamogenin. The second hydroxyl group could not be located at positions 2 or 4, because chiapagenin did not consume any lead tetraacetate under conditions where such dihydroxy sapogenins react readily.[9] Positions 1 (*i.e.*, neoruscogenin)[10] and 7 were excluded by the course of the Oppenauer oxidation, which led to a monohydroxy Δ^4-3-ketone (V), without elimination of the second hydroxyl function, as might be expected if the latter were situated at C-1 or C-7. The formation of V confirmed the presence of a Δ^5-3-hydroxy system and this left only C-11, C-12, or C-15 as possible nuclear points of attachment for the other alcoholic function, tertiary positions being excluded by formation of chiapagenin diacetate; this problem seemed, therefore, most readily resolvable by selective oxidation of this second hydroxyl group. If the resulting ketone were not identical with correlogenin (I), then the



(4) K. Takeda and K. Hamamoto, *Tetrahedron Letters*, *No.* 3, 1 (1960).

(5)(a) M. E. Wall, C. S. Fenske, J. W. Garvin, J. J. Willaman, Q. Jones, B. G. Schubert, and H. S. Gentry, *J. Am. Pharm. Assoc.*, 48, 695 (1959) and earlier references there cited. (b) During the preparation of the present manuscript we were informed by Dr. Wall that recently he and his collaborators have also investigated *D. chiapasensis* and that they have isolated chiapagenin. Their structural conclusions coincide with ours.

(6) We are indebted to Dr. D. K. Cox of the Botanical Research Department, Syntex, S.A., Mexico, D. F. for this information and for a supply of the crude sapogenins.

(7) H. A. Walens, S. Serota, and M. E. Wall, *J. Org. Chem.*, 22, 182 (1957).

(8) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, 24, 1337 (1952); R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.*, 75, 158 (1953); A. L. Hayden, P. B. Smeltzer, and I. Scheer, *J. Am. Chem. Soc.*, 26, 550 (1954).

(9) C. Djerassi and R. Ehrlich, *J. Org. Chem.*, 19, 1351 (1954).

(10) C. Sannié and H. Lapin, *Bull. Soc. Chim. France*, 1237 (1957). The physical constants of neoruscogenin and its diacetate are quite different from those of chiapagenin and IVb.

remaining possibilities could be differentiated readily by infrared spectroscopy[11] and rotatory dispersion measurements.[12]

Selective acetylation of the homoallylic 3β-hydroxyl group was effected at room temperature and the resulting chiapagenin 3-monoacetate (IVc) was oxidized with chromium trioxide to afford in good yield correlogenin (I) acetate. This established the location of the unknown hydroxyl group at C-12, the only remaining uncertainty being its configuration. To settle this point, sisalagenin (VII)[13] was reduced with sodium borohydride to the corresponding diol (VIa), the equatorial β-orientation being assigned to the predominant isomer,[14] which was further characterized as the 3,12-diacetate (VIb) and the 12-monoacetate (VIc). The same substances were also obtained upon catalytic hydrogenation of chiapagenin diacetate (IVb) followed by partial or complete saponification, thus defining chiapagenin rigorously as 12β-hydroxyyamogenin (IVa).

EXPERIMENTAL[15]

Isolation of sapogenins. The collection of *Dioscorea chiapasensis* Matuda was carried out by Dr. D. K. Cox on the road between Santiago Atitlan and Chicacao, Suchitepequez (Guatemala). The dried and powdered roots (1 kg.) were heated under reflux for 2 hr. with 10 l. of denatured alcohol, the solvent was filtered, and the extraction repeated twice with fresh solvent. The combined extracts were concentrated to a volume of 5 l., 1.5 l. of concd. hydrochloric acid was added, and the mixture was heated under reflux for 4 hr. After diluting with 30 l. of ice water, the precipitate was filtered, washed with water, and finally dried *in vacuo* at 80° yielding 52 g. of crude material.

A suspension of 25 g. of crude sapogenins and 4.0 g. of Girard's reagent T in 150 cc. of absolute ethanol and 15 cc. of acetic acid was heated under reflux for 1 hr. The cooled solution was added to an excess of saturated sodium bicarbonate solution and unchanged sapogenins were removed by three successive extractions with ether. The aqueous layer was acidified to *p*H 1 with concd. hydrochloric acid and then heated on the steam bath for 1 hr. Extraction with ether and chromatography of the residue after evaporation of the ether on 30 g. of alumina (activity III) afforded a semisolid in the benzene eluates. After one crystallization from aqueous alcohol followed by acetylation and recrystallization from ether hexane, there was isolated 13 mg. of *correlogenin* (neobotogenin) (I) *acetate*,[7] m.p. 211–212° Identity was established by mixture melting point determination and infrared comparison with an authentic sample of the acetate of correlogenin, isolated from *Dioscorea spiculiflora* Hemsl and which was kindly supplied by Dr. A. Bowers of Syntex, S.A., Mexico, D. F.

A portion (8.8 g.) of the nonketonic sapogenins (23.5 g.) was chromatographed on 350 g. of alumina (activity III) with the following results. Elution with 500 cc. of benzene afforded, after crystallization from ethanol, 0.46 g. of a colorless substance m.p. 194–195°, $[\alpha]_D$ −188° (*c*, 1.1), whose ultraviolet absorption maxima at 227, 235, and 242 mμ indicated that it was the $\Delta^{3,5}$-diene of chiapagenin produced by dehydration[16] during the acid hydrolysis and it was not further investigated.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.70; H, 9.81.

Further elution with benzene-ether (8:2) gave 1.78 g. of crystals, m.p. 180–187°, which were found to be a difficultly separable mixture of *yamogenin* (II) and *diosgenin* (III). Chromatography of 2.1 g. of the acetylated mixture on 80 g. of alumina (activity II) provided 110 mg. of impure diosgenin acetate (m.p. 179–184°) as the first fraction eluted by hexane-benzene (1:1) and 370 mg. of impure yamogenin acetate (m.p. 174–176°) as the last fraction. Rechromatography and crystallization of the crude diosgenin acetate gave 21 mg. of the pure substance, m.p. 196–197°, $[\alpha]_D$ −126°, whose identity was established by mixture melting and infrared comparison with an authentic sample.

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71; O, 14.02. Found: C, 76.11; H, 9.95; O, 14.18.

Recrystallization of the crude yamogenin acetate from ethanol led to 219 mg. of the pure product, m.p. 177–178°, $[\alpha]_D$ −126°.

Anal. Found: C, 76.34; H, 9.69; O, 14.05.

Hydrolysis gave yamogenin, m.p. 195–196°, undepressed upon admixture with a sample kindly furnished by Dr. M. E. Wall, U.S.D.A. Plant Products Laboratory (Philadelphia, Pa.). The infrared spectra of the two specimens in carbon disulfide solution were identical.

When the column was washed with benzene-ether (6:4), there was obtained 4.03 g. of solid, which after one recrystallization from ethanol led to 3.8 g. of crude *chiapagenin* (IVa), m.p. 240–245°. The *diacetate* (IVb) was prepared by heating under reflux for 1 hr. a sample of the sapogenin with acetic anhydride and recrystallizing from ethanol, m.p. 194–196°, $[\alpha]_D$ −128° (c, 1.9).

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01; O, 18.65. Found: C, 72.51; H, 9.09; O, 18.40.

Pure chiapagenin (IVa) was regenerated from the acetate and recrystallized from ethanol, m.p. 257–259°, $[\alpha]_D$ −130° (*c*, 1.2). The infrared spectrum in carbon disulfide solution had a strong band at 922 cm.$^{-1}$ and a weak one at 895 cm.$^{-1}$ as well as one at 853 cm.$^{-1}$ indicative[8] of the "neo" (*e.g.*, II) rather than "iso" (*e.g.*, III) side chain configuration.

Anal. Calcd. for $C_{27}H_{42}O$: C, 75.28; H, 9.83; O, 14.88. Found: C, 74.96; H, 9.68; C, 15.47.

Oppenauer oxidation of chiapagenin. The oxidation was performed in the customary manner[17] by distilling some solvent from a mixture of 450 mg. of chiapagenin (IVa) and 3.1 cc. of cyclohexanone in 20 cc. of toluene, followed by the addition of 315 mg. of aluminum isopropoxide in 2 cc. of toluene and gentle refluxing for 4 hr. Water was added and the product was extracted with ether and dried. The ketone (V) crystallized from hexane-benzene as needles (190 mg.), m.p. 200–210°. The analytical sample was obtained from the same solvent pair and exhibited, m.p. 214–217°, $[\alpha]_D$ −13° (*c*, 1.0), $\lambda_{max}^{C_2H_5OH}$ 240 mμ, ε 16,800.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41; O, 14.93. Found: C, 75.12; H, 9.16; O, 15.36.

Conversion of chiapagenin (IVa) *to correlogenin* (I). Chiapagenin (IVa) (480 mg.) was acetylated with acetic anhydride (4 cc.) and pyridine (25 cc.) for 2 hr. at room temperature, and the product was extracted in the usual way. The crude monoacetate was dissolved in 5 cc. of ether

(11) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

(12) C. Djerassi and R. Ehrlich, *J. Am. Chem. Soc.*, 78, 440 (1956).

(13) R. K. Callow and V. H. T. James, *J. Chem. Soc.*, 1671 (1955). We are grateful to Dr. R. K. Callow of the National Institute for Medical Research, London, for a gift of sisalagenin.

(14) For similar reaction in the hecogenin series, see W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955).

(15) All melting points are corrected and were determined in capillaries inserted into the bath about 10° below the melting point. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol.

(16) See W. J. Peal, *Chem. & Ind.* (*London*) 1451 (1957).

(17) C. Djerassi, *Org. Reactions*, 207–72 (1951).

and unchanged chiapagenin (140 mg.) was filtered. Chromatography of the ether-soluble fraction on 20 g. of alumina (activity I), elution with benzene-ether (8:2), and recrystallization from aqueous methanol yielded 325 mg. of chiapagenin 3-monoacetate (IVc), m.p. 176–177°, $[\alpha]_D$ −119° (*c*, 0.4).

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.68; H, 9.38; O, 16.94. Found: C, 73.77; H, 9.18; O, 17.20.

To a solution of the monoacetate (IVc) (213 mg.) in 10 cc. of acetic acid was added at 10° a solution of 53 mg. of chromium trioxide in 25 cc. of acetic acid. After 30 min., water and ether were added, the organic phase was washed with water, then sodium bicarbonate, again with water, dried, and evaporated. Crystallization of the residue from aqueous methanol provided 151 mg. of correlogenin (I) acetate, m.p. 210–212°, undepressed upon admixture with an authentic sample, $[\alpha]_D$ −73° (*c*, 0.6). Identity was confirmed by infrared comparison.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00; O, 17.00. Found: C, 73.96; H, 8.97; O, 17.10.

Dihydrochiapagenin (VI). (a) *From chiapagenin* (IVa). Chiapagenin diacetate (IVb) (2.17 g.) was hydrogenated at atmospheric pressure in 50 cc. of acetic acid in the presence of 100 mg. of platinum oxide catalyst. The reaction was stopped after 2 hr. when 1.05 equivalents of hydrogen had been consumed. Chromatography of the reduction product on 100 g. of alumina and crystallization from methanol led to *dihydrochiapagenin diacetate* (VIb), m.p. 204–205°, $[\alpha]_D$ −76° (c, 0.6), while saponification with boiling 5% methanolic potassium hydroxide afforded *dihydrochiapagenin* (VIa), m.p. 202–204° (from aqueous methanol), $[\alpha]_D$ −79° (*c*, 1.1). Both substances were shown to be identical by mixture melting point determination and infrared comparison with the corresponding specimens prepared from sisalagenin [see (b) below].

Dihydrochiapagenin 12-monoacetate (VIc) was formed when 33 mg. of the diacetate (VIb) and 11.5 mg. of lithium hydroxide monohydrate[18] in 40 cc. of 80% ethanol was kept at 21° for 22 hr. The solution was diluted with water, extracted with ether, and the product was crystallized from hexane-benzene, m.p. 213–214°, $[\alpha]_D$ −84° (*c*, 0.3).

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.37; H, 9.77; O, 16.86. Found: C, 73.57; H, 9.92; O, 16.59.

(b) *From sisalagenin* (VII). Sodium borohydride (13 mg.) was added to a solution of 109 mg. of sisalagenin (VII) acetate[13] in absolute ethanol, and the mixture was heated under reflux for 2 hr. Sodium hydroxide (100 mg.) was then added and heating continued for a further 1 hr. After dilution with water, the product (VIa) was extracted with ether and crystallized from aqueous methanol, m.p. 204–205°, $[\alpha]_D$ −73° (*c*, 0.7). A polymorphic form with m.p. 194–196° was also encountered.

Anal. Calcd. for $C_{27}H_{44}O_4.CH_3OH$: C, 72.37; H, 10.41; O, 17.22. Found: C, 72.58; H, 10.32; O, 16.72.

Acetylation followed by recrystallization from methanol gave the diacetate VIb, m.p. 204–205°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.07; H, 9.37.

Selective saponification of the diacetate (VIb) with lithium hydroxide as described under (a) yielded the 12-monoacetate (VIc), m.p. 213–214°, $[\alpha]_D$ −80° (*c*, 0.7), which proved to be identical in all respects with the corresponding specimen derived from chiapagenin.

Addendum (*June 28, 1960*): A new and larger batch of *Dioscorea chiapasensis* was worked up recently and in addition to chiapagenin (IVa), yamogenin (II), and diosgenin (III) there was isolated a new sapogenin, which proved to be isochiapagenin (12β-hydroxydiosgenin). Its structure was established by monoacetylation at C-3 followed by oxidation to botogenin acetate[7] (12-ketodiosgenin acetate) as well as by partial synthesis involving sodium borohydride reduction of botogenin acetate.

EXPERIMENTAL

A 7-kg. lot of *D. chiapasensis* was worked up as above to yield 67 g. of crystalline and 63 g. of oily sapogenin mixture. Chromatography of the crystalline fraction afforded 13 g. of diosgenin mixed with yamogenin and 22 g. of chiapagenin. Similar chromatography of the oily material (63 g.) produced 20 g. of crude $\Delta^{3,5}$-diene, 14 g. of diosgenin-yamogenin mixture and (after acetylation) 0.535 g. of *isochiapagenin (12β-hydroxydiosgenin) 3,12-diacetate*, m.p. 206–207° (recrystallized from hexane), $[\alpha]_D$ −120° (*c*, 1.3).

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01; O, 18.65. Found: C, 72.11; H, 9.11; O, 19.15.

Saponification with boiling 5% ethanolic sodium hydroxide solution and recrystallization from methanol provided *isochiapagenin*, m.p. 236–237°, $[\alpha]_D^{23}$ −121° (*c*, 0.8).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83; O, 14.86. Found: C, 74.95; H, 10.25; O, 14.79.

Monoacetylation of 101 mg. of isochiapagenin as described above for chiapagenin and recrystallization from hexane led to 60 mg. of the 3-monoacetate, m.p. 208–210°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.68; H, 9.38; O, 16.94. Found: C, 73.44; H, 9.27; O, 17.17.

Oxidation of 50 mg. of the monoacetate with 15 mg. of chromium trioxide afforded 31 mg. of botogenin acetate,[7] m.p. 226–227°, $[\alpha]_D$ −56° (*c*, 0.8), whose identity was established by mixture melting point determination and infrared comparison with an authentic sample.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.75; H, 8.71.

Reduction of 97 mg. of botogenin acetate in 10 cc. of absolute ethanol with 13 mg. of sodium borohydride (2 hr. refluxing) followed by acetylation and one recrystallization from methanol gave isochiapagenin acetate, m.p. 206–207°, identical in all respects with a specimen derived from the naturally occurring material.

STANFORD, CALIF.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. LXV. Hydrogenation Products of 3β,20-Diacetoxy-5α,Δ$^{16,20(21)}$-pregnadien-12-one[2]

MONROE E. WALL, THEODORE PERLSTEIN, AND SAMUEL G. LEVINE

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Reaction of the 12-keto-16-dehydropregnene, I, with isopropenyl acetate gave the conjugated 12-keto-20-enol acetate, II. Hydrogenation of II in the presence of a palladium catalyst yielded the monounsaturated steroid, III. Hydrogenation of III in the presence of a platinum oxide catalyst under acid conditions gave a mixture which was shown to consist of the 12,20-desoxypregnane, IV, and 12-keto-20-desoxypregnane, V, and the 12-keto-20-acetate, VI.

During studies on reactions of 16-dehydro-12,20-diketopregnenes, we found it necessary to investigate the hydrogenation of 3β,20-diacetoxy-5α,Δ$^{16,20(21)}$ pregnadiene-12-one, II. The 12-keto-enol acetate, II, could be prepared in 75% yield by refluxing 3β-acetoxy-5α,16-pregnene-12,20-dione,[3] I, with isopropenyl acetate in the presence of catalytic quantities of concentrated sulfuric acid.[4a,b] Under our experimental conditions, the 12-ketone did not form an enol acetate. The inertness of the 12-ketone toward enolization has been noted in the bile acid series.[5] The structure proof of the enol acetate, II, was obtained from the following data. The carbon and hydrogen analysis was in agreement with the indicated structure. The ultraviolet spectrum of II showed a maximum at 237 mμ, ε = 12,680 and a general shape similar to that observed by Moffett and Weisblat[4a] for 3β,20-diacetoxy-5α,Δ$^{16,20(21)}$-pregnadiene. The infrared spectrum of II (*cf.* Experimental) exhibited three strong bands in the carbonyl region which were observed at the correct wave numbers for enol acetate, 3β-acetate, and 12-ketone, respectively. Catalytic hydrogenation of II with 5% palladium-carbon catalyst indicated uptake of only one mole of hydrogen to give 3β-20-diacetoxy-5α,Δ^{16}-pregnene-12-one, III. The fact that the Δ$^{20(21)}$ double bond had been preferentially hydrogenated rather than the Δ^{16}-group was proved by the disappearance of the characteristic enol acetate band[4b] and bands attributable to C = C stretching vibrations of an enol acetate with a terminal ethylenic group.[4b] Although the Δ^{16}-double bond in III was resistant toward hydrogenation under neutral conditions, it could be reduced by use of platinum oxide in the presence of 5% acetic acid. Under these conditions the 12-ketone was also reduced. Treatment of the noncrystalline reduction product with chromium trioxide in acetic acid oxidized the 12-hydroxyl group formed during the hydrogenation of III. The infrared spectrum of the glassy oxidation product showed absence of hydroxyl. However, the intensity of the band at 1710 cm.$^{-1}$ attributed to the 12-carbonyl group was considerably weaker than anticipated, thus indicating that we might be dealing with a mixture of ketonic and nonketonic steroids. This hypothesis was confirmed by a Girard T separation which gave ketonic and nonketonic fractions in a 2:1 ratio, respectively. After acetylation the nonketonic fraction was identified as 3β-acetoxy-5α-pregnane,[6a,b] IV. The infrared spectrum of IV was identical with that published by R. N. Jones and coworkers.[7]

Alkaline hydrolysis of the ketonic fraction followed by chromatography on Florisil[8] separated this fraction into mono- and dihydroxy components in 1:1 ratio. Wolff-Kishner reduction of the monohydroxy compound followed by acetylation gave the known 3β-acetoxy-5α-pregnane,[6] IV. Hence, the structure of the ketone from which IV was derived must be 3β-acetoxy-5α-pregnan-12-one, V. The carbon and hydrogen analysis, infrared spectrum, and optical rotation data[9] observed for V were all in accord with the assigned structure.[10]

Wolff-Kishner reduction of the dihydroxy component of the ketonic fraction followed by acetylation gave the known 3β,20α-diacetoxy-5α-preg-

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Previous paper in this series, Steroidal Sapogenins. LXIV. ....., Edward S. Rothman, Theodore Perlstein, and Monroe E. Wall, *J. Org. Chem.*, in press.

(3) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).

(4) (a) R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952). (b) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2810 (1952).

(5) R. Hirschmann, M. Brown, and N. L. Wendler, *J. Am. Chem. Soc.*, **73**, 5373 (1951).

(6) (a) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949). (b) A. Petit and J. P. Mathieu, *Constantes Selectionées Pouvoir Rotatoire Naturel I. Steroides*, Masson et cie, Paris, 1956.

(7) G. Roberts, B. S. Gallagher, and R. N. Jones, *Infrared Absorption Spectra of Steroids. An Atlas.* Vol. II, chart 337, 338. Interscience Publishers, Inc., New York, 1958.

(8) Mention of trade names does not imply preference over any equivalent product.

(9) According to Barton and Klyne, *Chem. and Ind.*, 755 (1948), the average molecular rotation contribution of a 12 ketone is +270. M_D of V − M_D IV = +321.

(10) The remote possibility that V might have the structure 3β-acetoxy-5α-pregnane-20-one, a known compound, was ruled out by direct comparison of the infrared spectra which showed nonidentity, particularly throughout the "fingerprint" region.

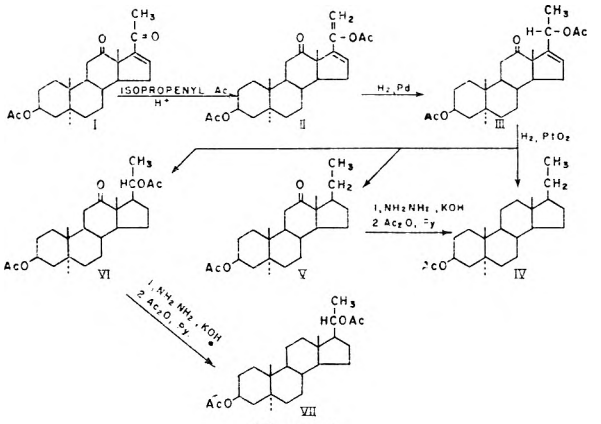

Figure 1

nane, VII,[11] with an infrared spectrum identical with that of a published spectrum.[12] Hence, the ketone from which VII was derived must be 3β,20α-diacetoxy-5α-pregnan-12-one, VI. The corresponding 20β-isomer was not isolated. However, the yield of crystalline VII from the sequence II → III → VI → VII was low. Thus the possibility that the 20β-isomer was also formed during the reduction of II to III cannot be rigidly excluded.

The saturated 12-keto diacetate, VI, was the expected reduction product. However, the Δ^{16}-double bond in III exhibited sluggish hydrogenation properties. For example, hydrogenation of III with platinum oxide as a catalyst and in the presence of 0.2% acetic acid resulted in reduction of the 12-ketone to hydroxyl with no attack on the double bond.[13] Reduction of the double bond occurred only after prolonged hydrogenation in the presence of platinum oxide and with use of 5% acetic acid. The hydrogenolysis of the allylic 20-acetate group resulting in formation of the 12-keto monoacetate, V, is analogous to the hydrogenolysis of 12-substituents (hydroxyl, methoxyl, acetate) allylic to the sluggishly reducible $\Delta^{9(11)}$ double bond.[14] We have been unable to find any precedent for the hydrogenolysis of the 12-ketone resulting in formation of IV during the reduction of III.[15]

EXPERIMENTAL[16]

3β,20-Diacetoxy-5α,$\Delta^{16,20(21)}$-pregnadiene-12-one, II. A solution of 3.43 g. of 3β-acetoxy-5α,Δ^{16}-pregnene-12,20-dione, I, (m.p. 177–180°) in 20 ml. of isopropenyl acetate containing 0.02 ml. of concd. sulfuric acid was heated under reflux for 3 hr. The solution was cooled, diluted with 30 ml. of toluene, and washed with dilute aqueous sodium bicarbonate solution followed by washing with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. On concentration of the solvent, 3.8 g. of a crude, solid residue was obtained. This was taken up in 25 ml. of benzene, filtered through 4 g. of Florisil,[8] and the concentrated eluate crystallized from freshly distilled petroleum ether (b.p. 88–98°) giving 2.92 g. of II, m.p. 166–170° (yield 75%). The analytical sample was recrystallized from methanol, needles m.p. 167.5–168.5°, $[\alpha]_D^{25}$ +201°, λ_{max} (methanol) 237 mμ, ϵ = 12,680 log ϵ = 4.1, infrared spectrum shows three strong bands of approximately equal intensity at 1758, 1733, and 1712 cm.$^{-1}$ attributed to the enol acetate,[4b] 3β-acetate, and 12-ketone, respectively, and strong bands at 1240–1245 and 1205 cm.$^{-1}$ due to C—O stretching vibrations of the 3β- and 20-acetoxy moieties respectively.[17] In addition bands were noted at 3030 and 1640 cm.$^{-1}$ due respectively to CH stretching and C=C stretching vibrations.[17]

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.64; H, 8.23.

3β,20-Diacetoxy-5α,Δ^{16}-pregnen-12-one, III. A solution of 0.212 g. of the enol acetate II in 10 ml. of ethyl acetate was hydrogenated at 1 atm. in the presence of 0.05 g. of 5% palladium on carbon. The sample took up 14.4 ml. of hydrogen in 16 min. (114%). The sample was filtered and the filtrate concentrated. The residue was crystallized from methanol to give 0.067 g. of needles, m.p. 184–188°. The analytical sample melted at 195–196°, $[\alpha]_D^{25}$ +120°, ultraviolet spectrum showed only end absorption; the infrared absorption spectrum shows a strong broad band at 1740–1735 and a somewhat weaker band at 1712 cm.$^{-1}$, the former attributed to the 3β- and the 20-acetoxy groups and the latter to the 12-ketone; and three strong bands at 1245, 1220, and 1165 cm.$^{-1}$, the first being attributed to the C—O stretching vibration of the 3β-acetate and the last two bands to C—O stretching vibrations associated with the Δ^{16}-20-acetate moiety.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.04; H, 8.64.

(11) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).

(12) K. Dobriner, E. R. Katzenellenbogen, and R. N. Jones, *Infrared Absorption Spectra of Steroids. An Atlas.* Vol. 1, chart 75. Interscience Publishers, Inc., New York, 1953.

(13) The presence of the Δ^{16}-20-acetoxy moiety in the 12-keto diacetate, III and its 12-hydroxy analogue can be readily determined by examination of the infrared spectra in the region 1250–1150 cm.$^{-1}$ In this region steroids with the Δ^{16}-20-acetate grouping show three strong bands at 1245, 1220, and 1165 cm.$^{-1}$, the band at 1245 being attributable to the C—O—C stretching vibrations of the 3β-acetate. Saturation of the Δ^{16}-double bond of III or the 12-hydroxy analogue results in disappearance of the 1220 and 1165 cm.$^{-1}$ bands, and one strong broad band between 1250–1240 cm.$^{-1}$ is observed.

(14) B. McKenzie, V. Mattox, and E. Kendall, *J. Biol. Chem.*, **175**, 249 (1948).

(15) The intermediate in the hydrogenolysis of the 12-ketone may be the 12β-hydroxyl group as the ketone is reduced much more rapidly than the Δ^{16}-double bond (*cf.* experimental on hydrogenation of III, part (a)). Because of the unprecedented nature of the hydrogenolysis at C_{12} and because of the fact that of necessity "working grade" products rather than analytically pure substances were used for the reaction sequences, the 16-dehydro pregnene, I, the enol acetate II, and the partially hydrogenated steroid III were carefully examined for 12-desoxy-contaminants which could account for the 12-desoxy pregnane, IV. In all cases the infrared spectra of the working grade products I, II and III showed the same ratio of the intensities of the 12-carbonyl to the acetate band as did the analytical samples. Only after catalytic reduction of III was there observed a marked decrease in the intensity of the 12-carbonyl band of the crude reduction product.

(16) All infrared spectra were obtained in carbon bisulfide solution, concentration 10.0 g./l.; ultraviolet spectra in methanol, 0.04 g./l., and optical rotation data in chloroform. We wish to thank S. Serota for the optical rotation data and R. Kelley for the carbon and hydrogen determinations.

(17) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York (1954), pp. 31 et seq.

Catalytic hydrogenation of III. (a) *With platinum oxide in 0.2% acetic acid.* A solution of 0.5 g. of III in 25 ml. of ethyl acetate containing 0.05 ml. of acetic acid was hydrogenated at 3 atm. in presence of 0.5 g. of platinum oxide for 3 hr. After the usual workup the crude product was isolated. The infrared spectrum showed presence of hydroxyl (3600 cm.$^{-1}$); acetate (1735 cm.$^{-1}$); absence of 12-ketone and presence of the same three strong bands in the 1250–1165 cm.$^{-1}$ discussed under III.

(b) *With platinum oxide in the presence of 5% acetic acid.* A solution of 5.0 g. of III in 240 ml. of ethyl acetate containing 5% acetic acid was hydrogenated at 3 atm. for 18 hr. in the presence of 5.0 g. of platinum oxide. The solvent was evaporated and the glassy product was oxidized with chromium trioxide in acetic acid at room temperature in the usual manner. The product, weighing 4.77 g., was examined by infrared spectroscopy and showed absence of hydroxyl, a strong band at 1735 cm.$^{-1}$ and a considerably weaker band at 1710 cm.$^{-1}$ Only one strong band at 1245 cm.$^{-1}$ was present in the 1250–1165 region.

3β-Acetoxy-5α-pregnane, IV. The total crude product obtained by method (b) above (4.77 g.) was treated with Girard T reagent. The noncarbonyl fraction, 1.5 g., was crystallized from acetone to give 0.8 g. of IV, m.p. 114–116°, $[\alpha]_D^{25}$ +3.9° (lit.,[6a,b] gives m.p. 115–116°, $[\alpha]_D^{19}$ +6°), infrared spectrum shows 1735 cm.$^{-1}$ and 1245 cm.$^{-1}$ bands.

3β-Acetoxy-5α-pregnan-12-one, V. The carbonyl fraction from the Girard T separation (3.0 g.) was deacetylated by hydrolysis with refluxing 5% potassium hydroxide in methanol. The residue after standard work-up was dissolved in benzene and chromatographed on Florisil. Elution with 20% methylene chloride in benzene and 100% methylene chloride gave 1.2 g. of a monohydroxy product. Acetylation of this compound followed by crystallization from ethanol-water gave V, m.p. 139–140°, $[\alpha]_D^{25}$ +95°; infrared spectrum shows two strong bands at 1735 and 1706 cm.$^{-1}$, one band at 1243 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.84; H, 10.33.

Conversion of V *to* IV. Wolff-Kishner reduction of 0.3 g. of V by the Huang-Minlon procedure[6] yielded, after workup and acetylation, 0.15 g. IV, m.p. 113–115°, infrared spectrum identical with that of IV isolated from hydrogenation of III.

3β,20α-Diacetoxy-5α-pregnan-12-one, VI. After removal of the monohydroxy fraction described under V, elution with 5% ethanol in benzene gave 1.3 g. of a dihydroxy compound. Acetylation yielded 0.9 g. of VI, m.p. 181–183°, $[\alpha]_D^{25}$ +69°; infrared spectrum shows strong broad band at 1735–1730 cm.$^{-1}$ and a strong but less broad band at 1706 cm.$^{-1}$, and one strong broad band at 1250–1240 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.54; H, 9.04.

3β,20α-Diacetoxy-5α-pregnane, VII. A 0.36-g. sample of the 12-ketone VI was reduced by the Huang-Minlon modification[6] of the Wolff-Kishner procedure. After acetylation, 0.2 g. of VII was obtained, m.p. 163–165° (lit.,[11] gives m.p. 165–167°), with an infrared spectrum showing one strong band at 1735 cm.$^{-1}$ and one broad band at 1250–1240 cm.$^{-1}$ The entire infrared spectrum was identical with that of VII given in reference 12.

PHILADELPHIA 18, PA.

[CONTRIBUTION FROM THE UNIT OF NATURAL PRODUCTS, NATIONAL RESEARCH CENTRE]

Natural Coumarins. I. Marmesin and Marmesinin, Further Products from the Fruits of *Ammi majus* L.

EFFAT A. ABU-MUSTAFA AND M. B. E. FAYEZ

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The isolation of marmesinin and its synthesis are described. Several reactions with marmesin and its derivatives establish that bromination and nitration occur at the six position and the same is suggested to happen with nodakenetin and analogous dihydrofurocoumarins. A correlation has been made between marmesin and products derived from peucedanin.

In a preliminary communication,[1] we reported the isolation of marmesin[2] (I, R = H), in 0.25% yield, from the alcoholic extract of defatted *A. majus* fruits, after mineral acid hydrolysis, and its presence in the fruits as a glycoside has been alluded to. In a more recent publication[3] the isolation of this glycoside, in fact a glucoside, from the same source has been described and the name "ammajin" was given to it. With the unfortunate[4] names ammoidin, ammidin, and majudin given,[5] on the basis of the botanical name of the source, to the constituents of *Ammi majus* L. before they were realized[6] to be the already well known xanthotoxin, imperatorin, and bergapten respectively having led to nomenclatural confusion—the choice of "ammajin" to denote the natural glycoside of marmesin is in our view an unjustifiable carry on of an erroneous system of names for the products of one plant source. The apparently relevant "marmesinin" would conform more closely to the conventional system of generic derivation of aglycone-glycoside names. The name is therefore proposed by the present authors to denote the natural marmesin glucoside.

(1) E. A. Abu-Mustafa, N. Badran, M. B. E. Fayez, and N. A. Starkowsky, *Nature*, 182, 54 (1958).

(2) A. Chatterjee and S. S. Mitra, *J. Am. Chem. Soc.*, 71, 606 (1949).

(3) N. A. Starkowsky and N. Badran, *J. Org. Chem.*, 23, 1818 (1958).

(4) T. B. Fitzpatrick and M. A. Pathak, *J. Invest. Dermat.*, 32, 229 (1959).

(5) I. R. Fahmy, H. Abu-Shady, A. Schönberg, and A. Sina, *Nature*, 160, 468 (1947); I. R. Fahmy and H. Abu-Shady, *Quart. J. Pharm. and Pharmacol.*, 20, 281 (1947).

(6) A. Schönberg and A. Sina, *Nature*, 161, 481 (1948); A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, 72, 4826 (1950); I. R. Fahmy and H. Abu-Shady, *Quart. J. Pharm. and Pharmacol.*, 21, 499 (1948).

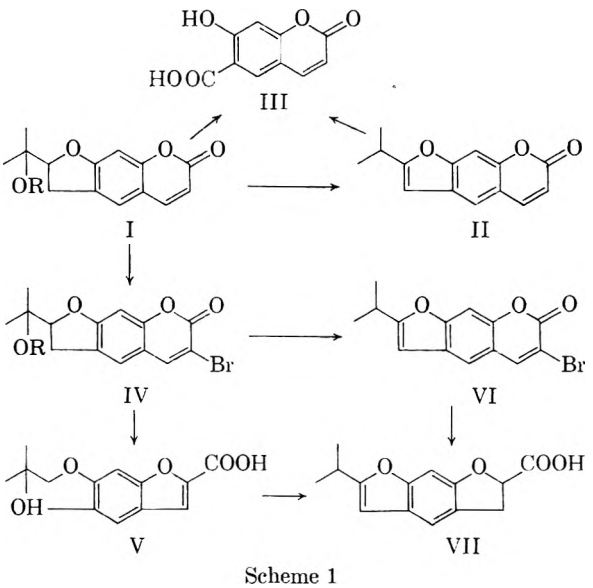
Marmesinin has been isolated in a pure crystalline state by chromatography of the acetylated glycosidic fraction of the alcoholic extract. The synthesis of marmesinin (I, R = $C_6H_{11}O_5$) has been accomplished in good yield (61%) (*cf.* ref. 3) by treating marmesin with α-acetobromoglucose in benzene solution in presence of silver carbonate under azeotropic distillation conditions. The synthesis, incidentally, precludes the possibility that the sugar moiety is attached to the phenolic hydroxyl group of the open coumarinic acid which is known[7,8] to occur with some furocoumarins.

Our work with marmesin leads us to support its constitution, as 2-(β-hydroxyisopropyl)-2′,3′-dihydro-6,7-furanocoumarin (I, R = H), proposed by Chatterjee and Mitra.[2] The presence, suspected[9] at one time, of a 2,2-dimethyl-3,4-unsaturated pyran in place of the isopropylfuran in anhydromarmesin (II) was disproved[7] by treatment with a 20% sodium hydroxide solution[10] whereby no acetone was produced and the anhydromarmesin was essentially unchanged. In addition, anhydromarmesin, like marmesin[2,3] gave unbelliferone-6-carboxylic acid (III) upon oxidation with potassium dichromate.

The optical relation between marmesin and its epimer, nodakenetin,[11,12] evident from their equal but opposite rotations,[2] has been more fully demonstrated by a comparison of their optical rotatory dispersion curves.[13] The ultraviolet absorption curve of marmesin (see Table I) was also found to be almost identical with that determined for nodakenetin. The apparent similarity of the chemical properties of these epimers has induced us to examine marmesin with the hope that its reactions might explain those described[11] for nodakenetin which remained hitherto unexplained. Our experiments with marmesin, a typical natural dihydrofurocoumarin, would also serve as examples of some general reactions in the dihydrofurocoumarin field which, as will be apparent in the sequel, are different from those known for furocoumarins.

Arima[11] reported that bromination of nodakenetin gave a monobromo derivative which upon treatment with hot alcoholic potassium hydroxide gave a "coumaric" acid containing no bromine. A similar treatment of marmesin, using two moles of bromine and also using *N*-bromosuccinimide, gave us a monobromo derivative[14] which was resistant to treatment with organic base, thus precluding the possibility of presence of the bromine atom in the dihydrofuran ring. The hydroxyl group was also not involved, as a bromoacetate derivative was obtained upon acetylation. The compound, however, was converted to marmesin by treatment with activated zinc dust in ethanol or by hydrogenation on platinum. The compound, which resisted all attempts to nitration, very readily gave, upon treatment with aqueous or alcoholic alkali, a product containing no bromine and shown to be an acid which gave a methyl ester; marmesin is unaffected by diazomethane or methyl iodide. The same acid was also obtained by alkaline hydrolysis of the bromoacetate mentioned before.

It appears therefore that the behavior of marmesin towards bromination is analogous to that of unsubstituted coumarin[15] and 6,7-disubstituted coumarins[16] in that the first bromine atom enters at the 3-position (of the coumarin nucleus) and that a coumarilic acid results from alkali treatment of a 3-bromo derivative. The marmesin bromo compound is, therefore, represented by (IV, R = H) and the product of alkali fission must be 2′-(β-hydroxyisopropyl)-2′,3′-dihydro-5,6-furanocoumarilic acid (V), or "marmesilic" acid. While sufficient nodakenetin was not available to us—the only known natural source, *Peucedanum decursivum*, is unknown in Egypt—to repeat Arima's[11] experiments, we feel that the bromination product and the acid resulting therefrom are (IV, R = H)



Scheme 1

(7) F. M. Dean, *Fortschr. Chem. org. Naturstoffe*, 9, 228 (1952).

(8) A. Stoll, A. Pereira, and J. Renz, *Helv. Chim. Acta*, **33**, 1637 (1960); H. N. Khastgir, P. C. Duttagupta, and P. Sengupta, *Indian J. Appl. Chem.*, **22**, 82 (1959).

(9) From the related *A. visnaga* was isolated a 2,2-dimethylchromeno α-pyrone, provismine: N. Badran and N. A. Starkowsky, *Proc. Pharm. Soc. Egypt* (*Sci. Ed.*), **38**, 93 (1956).

(10) J. C. Bell and A. Robertson, *J. Chem. Soc.*, 1828 (1936).

(11) J. Arima, *Bull. Chem. Soc. Japan*, **4**, 113 (1929).

(12) E. Späth and P. Kainrath, *Ber.*, **69**, 2062 (1936).

(13) These have been determined for us through the courtesy of Professor G. Ourisson, Strasbourg University, to whom we are indebted. We also thank Dr. M. Pailer, Vienna, for a gift of nodakenetin.

(14) Also reported by N. A. Starkowsky and N. Badran (ref. 3), but no structure was assigned to it.

(15) W. H. Perkin, *Ann.*, **157**, 115 (1871).

(16) V. J. Dalvi and S. Sethna, *J. Indian Chem. Soc.*, **26**, 359 (1949).

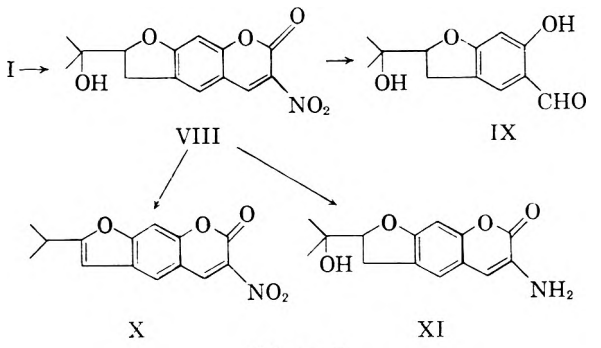
and (V) respectively but only different in the orientation of the side chain at C-2.

Additional experiments in this direction include the dehydration of 6-bromomarmesin (IV, R = H) with phosphorus pentoxide to 6-bromo-2-isopropylpsoralene (VI) which upon fission with alkali furnished an acid to be formulated as 2′-isopropyl-5,6-furanocoumarilic acid (VII). The latter compound was also obtained, in a different form with different melting point, by the direct dehydration of "marmesilic" acid (V) and by dehydration of the methyl ester of V followed by ester hydrolysis. The two forms of VII gave the same methyl ester. That the size of the isopropylfuran ring in the dehydration products (II, VI, and VII) remains the same was evident from the stability of anhydromarmesin (II) towards strong alkali. These reactions are outlined in Scheme 1.

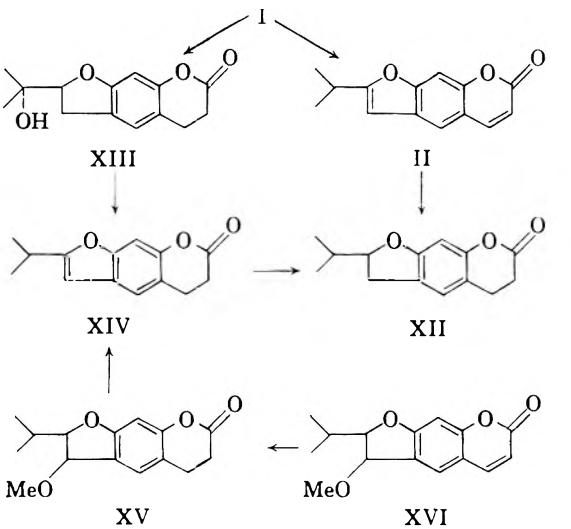
Nitration of marmesin gave a nitro derivative (VIII) in which the nitro group was shown to be attached to the 6-position by the action of mild alkali. This reaction led to an *o*-hydroxyaldehyde which is believed to be 5-formyl-6-hydroxy-2-(β-hydroxyisopropyl)-2,3-dihydrobenzofuran (IX) and from which a 2,4-dinitrophenylhydrazone derivative was prepared. It is known[17] that 3-nitrocoumarins undergo this type of reaction when warmed with aqueous alkali or concentrated ammonia solution and furnish salicylaldehydes. 6-Nitromarmesin (VIII), which was recovered unchanged after several attempts for bromination, gave an anhydro compound, 2-isopropyl-6-nitropsoralene (X), which behaved similarly towards the action of alkali. Reduction of VIII with activated zinc dust in ethanol or catalytically with hydrogen gave 6-aminomarmesin (XI); the reduction was not as effective using stannous chloride or tin and hydrochloric acid. It is noteworthy that the catalytic reduction did not affect the lactonic double bond as evidenced in the ultraviolet spectrum of the amino-compound in which the maximal absorption above 300 mμ (357 mμ) was retained (see Scheme 2).

It is known[18] that the lactone ring in a coumarin system can be opened with dimethyl sulfate to give a methoxy coumarinic acid, a reaction which was recently[19] successfully applied to xanthotoxin. Analogous to coumarins,[20] xanthotoxin[19] has also been reduced with lithium aluminum hydride to 6-hydroxy-7-methoxy-5-(3-hydroxy-1-propenyl)-benzofuran. Aluminum chloride in benzene cleaves[19,21] the furan ether–linkage in certain furocoumarins to yield 6-(1,2-diphenylethyl)-7-hydroxycoumarins. In our hands, however, the use of these reagents in similar fashion with marmesin led to no definite products.

The constitution of marmesin as 2-(β-hydroxyisopropyl)-2,3-dihydropsoralene suggests a close relationship to or even a possible common biogenetic origin[22] with some natural 2-isopropylfuracoumarins such as oreoselone and peucedanin.[23] Dehydration of dihydromarmesin (XIII), a hydrogenation product of marmesin,[2] gave a product to be formulated as 2-isopropyl-5,6-dihydropsoralene (XIV). A compound possessing the same constitution and believed to be identical with XIV has been previously prepared by Späth[23] by distillation of tetrahydropeucedanin (XV) resulting from the hydrogenation of peucedanin (XVI). The ultraviolet data, *vide infra*, seem also to support the proposed constitution. Catalytic hydrogenation of XIV gave desoxydihydrooreoselone (XII), previously prepared[2] by hydrogenation of anhydromarmesin (II) and by a similar sequence from nodakenetin[12] (Scheme 3).



Scheme 2



Scheme 3

(17) S. M. Sethna and N. M. Shah, *Chem. Revs.*, **36**, 27 (1945); A. Clayton, *J. Chem. Soc.*, 1397 (1910).

(18) H. Thoms, *Ber.*, **44**, 3325 (1911); N. M. Shah and R. C. Shah, *J. Univ. Bombay*, **7**, Pt. 3, 213 (1938); *Chem. Abstr.*, **33**, 3779 (1939).

(19) E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958).

(20) P. Karrer and P. Banerjee, *Helv. Chim. Acta*, **32**, 1692 (1949).

(21) B. Krishnawamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **16A**, 151 (1942).

(22) R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron*, **4**, 256 (1958).

(23) E. Späth, K. Klager, and C. Schlösser, *Ber.*, **64**, 2203 (1931).

TABLE I

ULTRAVIOLET ABSORPTION DATA OF MARMESIN AND ITS DERIVATIVES

Compound	Name	λ_{max} (log ϵ)			
I (R = H)	Marmesin	212[a] (3.89)	248[b] (3.50)	—	335 (4.09)
II	2-Isopropylpsoralene	211 (4.30)	251 (4.50)	294 (4.05)	334 (3.84)
IV (R = II)	Bromomarmesin	208 (4.49)	254[c] (3.71)	—	348 (4.31)
VI	6-Bromo-2-isopropylpsoralene	212 (4.32)	254 (4.34)	308 (4.07)	345 (3.87)
V	2′-(β-Hydroxyisopropyl)-2′,3′-dihydro-5,6-furocoumarilic acid	212 (4.29)	250 (3.85)	274[d] (4.04)	312[e] (4.19)
VII	2′-Isopropyl-5,6-furocoumarilic acid	—	242 (4.44)	285 (4.03)	312 (3.97)
VIII	Nitromarmesin	208 (4.20)	267 (3.82)	—	370 (4.10)
X	2′-Isopropyl-6-nitropsoralene	210 (4.38)	252 (4.32)	—	330 (3.92)
XIII	2-(β-Hydroxyisopropyl)-2,3,5,6-tetrahydropsoralene	210 (4.35)	—	292 (3.36)	—
XIV	2-Isopropyl-5,6-dihydropsoralene	211 (4.36)	255 (4.16)	288[f] (3.72)	—
XII	Desoxydihydro-oreoselone	208 (4.22)	—	294 (3.73)	—
IX[g]	5-Formyl-6-hydroxy-2-(β-hydroxyisopropyl)-2,3-dihydrobenzofuran	214 (4.14)	242 (4.07)	284 (4.06)	329 (3.84)

The following companion peaks with near extinction coefficients are also present: [a] 225; [b] 259; [c] 230, 264; [d] 266; [e] 307, 319; [f] 296 mμ. The following shoulders are also present: I (R = H), 302; V, 242, VII, 276, 306, 320; VIII, 226, 258. [g] The spectrum of this compound resembles that reported[26] for 2,4-dihydroxybenzaldehyde but with a general bathochromic shift.

In the hydrogenation products XII, XIII, and XIV, the saturation of the lactone double bond was evidenced in the ultraviolet spectra, *cf.* Table I, where no peaks above 300 mμ were present. It has recently[19] been pointed out by Brokke and Christensen that peaks above 300 mμ in the furocoumarins arise from the conjugation of the lactone carbonyl with the aromatic nucleus.[24] This important remark has been found to hold perfectly true with all our 2,3-dihydro compounds including marmesin. Moreover, the data presented in Table I indicate a remarkable association of the intense absorption in the 240–270 mμ region with the extension of the benzenoid conjugation to the furan ring in furocoumarins. The saturation of the furan ring results in a reduction of the intensity of absorption in this region or its disappearance. This observation, also evident from the spectral data given by Brokke and Christensen[19] for some psoralenes and 2,3-dihydropsoralenes and from those reported[25] for benzofuran and 2,3-dihydrobenzofuran, appears to be independent from the association of adsorption above 300 mμ with the continuity of conjugation in the coumarin portion of the molecule.

Professor A. C. Griffin of the M. D. Anderson Hospital and Tumor Institute, Houston, Tex., has kindly examined marmesin for us and reported that "as far as its photodynamic properties are concerned, it is only about one tenth as effective as xanthotoxin and is somewhat more effective following topical application rather than parental injections." Dr. M. A. Pathak, University of Oregon Medical School—through the courtesy of Professor T. B. Fitzpatrick—has also kindly examined products I (R = H), II, and V for photo-sensitizing activity on guinea pig's skin and found that II was most active although the three were considerably less so than psoralene or xanthotoxin.

(24) This observation has earlier [R. Goodwin and B. Pollock, *Arch. Biochem. Biophys.*, **49**, 1 (1954)] been made on a number of coumarin compounds.

(25) J. Jones and A. Lindsey, *J. Chem. Soc.*, 1836 (1950).

(26) H. W. Lemon, *J. Am. Chem. Soc.*, **69**, 2998 (1947).

EXPERIMENTAL[27]

Isolation of marmesinin (I, R = $C_6H_{11}O_5$). Exhaustive defatting of powdered *Ammi majus* L. fruits (300 g.) with benzene in a Soxhlet apparatus was followed by extraction with ethanol and the extract evaporated to dryness. The residue (80 g.) was taken up in hot water (1.5 l.) and after cooling it was extracted with chloroform. The aqueous layer was concentrated under vacuum to about 200 ml., excess acetone was added and the mixture left to stand overnight. The acetone layer was decanted leaving a dark brown gum (60 g.). This, after being repeatedly washed with acetone, was dried, then acetylated using pyridine and acetic anhydride. Three grams of the acetylated product were chromatographed on alumina. Prolonged benzene elution removed a small amount of an orange oil. Elution with 1% methanol in benzene gave a light orange gum which was crystallized from aqueous methanol. Pale creamish solid (30 mg.) resulted; m.p. 210–213° undepressed by a sample of marmesinin acetate prepared by the method of Starkowsky and Badran[3] who report m.p. 227°.

Synthesis of marmesinin. A solution of marmesin (0.5 g.) in benzene (dry, 75 ml.) was boiled with silver carbonate (freshly prepared, 1 g.) then treated with a solution of acetobromoglucose (dry, 2 g.) in dry benzene (75 ml.) added dropwise following exactly the rate of distillation of benzene during 1.5 hr. A further addition of dry benzene (75 ml.) was made in the same manner and the mixture then refluxed for 2 hr. Fresh silver carbonate (1 g.) was added followed by a solution of acetobromoglucose (2 g.) in benzene (75 ml.) while distilling benzene in the same way during 2 hr. The mixture was then refluxed for 0.5 hr. After cooling, the silver salts were filtered, washed with hot benzene, and the combined benzene solution evaporated on a steam bath under vacuum. Crystallization of the residue from chloroform-ethanol gave a mass of felted needles (710 mg.) which was recrystallized from ethanol to give a pure product;

(27) The melting points were taken on a Kofler block and are uncorrected, the optical rotations were measured in 1 dm. tube and the ultraviolet spectra were determined in ethanol.

m.p. 215–216° undepressed by the acetate of natural marmesinin, $[\alpha]_D$ −29° (chloroform).

Marmesin (I, R = H). The finely powdered fruits of *Ammi majus* (750 g.) were first extracted with benzene in a Soxhlet apparatus then exhausted with ethanol, (5 l.). The alcoholic solution was then concentrated to a small volume and hydrolyzed by refluxing with concd. hydrochloric acid (23 ml.) for 2 hr. Excess water was added and the mixture extracted with chloroform. After working up in usual manner, the dark brown residue (23.5 g.) was crystallized from 95% ethanol to give 1.89 g. of crude marmesin. This was recrystallized from chloroform-ethanol to give colorless prisms, m.p. 189–190° undepressed by an authentic sample,[28] $[\alpha]_D$ +25° (chloroform); reported[2] m.p. 189.5°, $[\alpha]_D$ +26.8°. The infrared spectra[29] in Nujol, of the two samples were identical in every detail. Marmesin was also obtained by mineral acid hydrolysis of marmesinin acetate.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.26; H, 5.73. Found: C, 68.12; H, 5.75.

The acetate was prepared in the usual manner[2]; m.p. 130–132°, $[\alpha]_D$ +25° (chloroform); reported[2] m.p. 130°.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.40; H, 5.54.

Alkaline hydrolysis of the acetate (100 mg.), using mild conditions, gave marmesin (70 mg.).

Umbelliferone-6-carboxylic acid (III). Anhydromarmesin (0.5 g.) was dissolved in acetic acid (stabilized, 15 ml.) and a solution of 1 g. of potassium dichromate in 10% sulfuric acid (10 ml.) was added dropwise while maintaining the temperature of the solution at 70–80°. The mixture was then left at room temperature for about 6 hr. A yellow crystalline substance deposited which was filtered and recrystallized from aqueous ethanol to give fine creamish needles, m.p. 253–257° dec. undepressed by the material prepared[2] by a similar oxidation of marmesin; reported m.p. 260°[2] and 258–262°.[3]

Bromomarmesin (IV, R = H). A. Marmesin (1 g.) was dissolved in chloroform (25 ml.), treated with a solution of bromine (2 moles) in chloroform (5 ml.) and the mixture was left at room temperature for 5 min. The solution was evaporated on a water bath and the residue, creamish fine needles, was repeatedly crystallized from chloroform-ethanol to give colorless plates (720 mg.); m.p. 231–233° dec., $[\alpha]_D$ +97° (chloroform); reported[3] m.p. 230–231°.

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.38; H, 4.00; Br, 24.61. Found: C, 51.79; H, 4.07; Br, 24.84.

B. Marmesin (1.23 g.) and *N*-bromosuccinimide (0.9 g.) were refluxed in carbon tetrachloride (100 ml.) for 2 hr. Filtration of the hot solution to remove suspended matter and cooling gave colorless plates of bromomarmesin; yield 550 mg., m.p., 230–232° dec., was undepressed by product from the previous experiment.

Bromomarmesin acetate (IV, R = Ac) was prepared by refluxing a mixture of bromomarmesin (250 mg.) and anhydrous sodium acetate (500 mg.) in acetic anhydride (5 ml.) for 5 hr. Working up the product gave 260 mg. of a material which melted at 187–189° after crystallization from chloroform-ethanol.

Anal. Calcd. for $C_{16}H_{15}O_5Br$: C, 52.31; H, 4.08; Br, 21.80. Found: C, 52.50; H, 4.23; Br, 21.72.

Elimination of bromine from bromomarmesin. A. Bromomarmesin (250 mg.) was refluxed with zinc dust (2.5 g.), which had been previously treated with 8*N* hydrochloric acid, in ethanol (70 ml.) for 24 hr. After filtration, the solution was reduced to a small volume and treated with few drops of water. A crop of flat needles (0.12 g.), m.p. 232–235°, undepressed by bromomarmesin, was first obtained. From the mother liquor there was isolated another crop (40 mg.) which proved to be marmesin by mixed melting point.

B. Bromomarmesin (500 mg.) together with palladium-charcoal (10%, 250 mg.) in pyridine (15 ml.) were shaken for 3 hr. with hydrogen until about 1 mole was absorbed. After filtration, the solution was concentrated to a small volume then a few drops of water were added. Colorless needles (160 mg.) were obtained which, after crystallization from ethanol, melted at 178–180° alone or mixed with a sample of marmesin.

2′-(β-Hydroxyisopropyl)-2′,3′-dihydro-5,6-furocoumarilic acid (V). Bromomarmesin (0.25 g.) was refluxed with 6*N* aqueous sodium hydroxide solution (12.5 ml.) for 30 min. The yellow solution was then acidified with 6*N* sulfuric acid solution. The flocculant precipitate (0.21 g.) formed was repeatedly crystallized from ethanol-water to give colorless plates; m.p. 215–217° dec., $[\alpha]_D$ +25.3°. The substance gave negative Beilstein reaction for halogen and readily dissolved in a solution of sodium bicarbonate with effervescence from which it was recovered upon acidification.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 63.93; H, 5.34.

One-half gram of bromomarmesin acetate was treated as above to give 300 mg. of a material which proved to be identical with V.

The *methyl ester* of the coumarilic acid was prepared by refluxing a mixture of 200 mg. of V, 2 ml. of methyl iodide, and 3 g. of potassium carbonate in 50 ml. of acetone for 24 hr. Filtration of the solution while hot and evaporation to dryness gave a residue which yielded 180 mg. of the methyl ester, after crystallization from aqueous alcohol, in the form of shining plates; m.p. 135–136°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.63; H, 5.83.

This substance was also prepared by treating a solution of V (250 mg.) in chloroform (20 ml.) with a solution of diazomethane in ether (8 ml.) and processed in the usual manner. The product was crystallized from aqueous ethanol to yield 230 mg. of the methyl ester; m.p. and mixed m.p. 133–134°.

In similar experiments, it was demonstrated that marmesin was unchanged by treatment with both of the above methylating agents.

6-Bromo-2-isopropylpsoralene (VI). A solution of bromomarmesin (0.25 g.) in dry benzene (40 ml.) was refluxed with phosphorus pentoxide (2.5 g.) for 5 hr. After decantation, the residue was repeatedly washed with hot benzene. The combined benzene solutions were evaporated nearly to dryness and alcohol added. Pale yellow needles (0.15 g.) deposited and were crystallized from aqueous ethanol to purity; m.p. 159–161° dec.

Anal. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.72; H, 3.58; Br, 26.05. Found: C, 55.06; H, 3.90; Br, 26.31.

2′-Isopropyl-5,6-furocoumarilic acid (VII). A. A solution of 6-bromo-2-isopropylpsoralene (100 mg.) in hot ethanol (4 ml.) was treated with an alcoholic solution of potassium hydroxide (3 g. in 18 ml. ethanol) and the mixture refluxed for 0.5 hr. Excess water was added followed by dilute hydrochloric acid till slightly acidic; a flocculant precipitate was formed at once. Filtration and crystallization from aqueous acetone gave fine colorless needles (60 mg.) which have no definite melting point but sublime at 220–230°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.7; H, 5.13.

This substance, with acid properties was methylated as described under V, and the product was crystallized from aqueous acetone to give plates; m.p. 127–128°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.46; H, 5.59.

B. 2′-(β-Hydroxyisopropyl)-2′,3′-dihydro-5,6-furocoumarilic acid (V) was dehydrated as described under VI and the product was crystallized from chloroform-methanol to give colorless felted needles; m.p. 232–233°. Methylation of this product (methyl iodide–potassium carbonate) gave

(28) We thank Dr. A. Chatterjee, Calcutta, for a sample of marmesin.

(29) We thank Dr. F. Johnson, The Dow Chemical Company, Framingham, Mass., for the infrared measurements.

the methyl ester as shining plates; m.p. 127–128°, was undepressed by a sample of the coumarilic acid methyl ester prepared under A.

C. The methyl ester of V (200 mg.) was dehydrated with phosphorus pentoxide as in the previous experiment. The product (140 mg.) was shown to be identical with the methyl ester of 2′-isopropyl-5,6-furocoumarilic acid obtained under A; m.p. and mixed m.p. 126–128°. A sample of this material (100 mg.) was treated with a mixture of concd. hydrochloric acid (3 ml.) and glacial acetic acid (13 ml.) under reflux for 2 hr. Water was added and the fluffy substance which deposited (85 mg.) was crystallized from aqueous ethanol to give colorless felted needles subliming at 220–230°. This was also obtained by alkaline hydrolysis of the methyl ester of 2′-isopropyl-5,6-furocoumarilic acid by refluxing 200 mg. of the substance in 6*N* aqueous sodium hydroxide solution (10 ml.) for 0.5 hr. After cooling the mixture was acidified and the white substance which resulted (150 mg.) was crystallized from aqueous ethanol to sublime at 220–230° like 2′-isopropyl-5,6-furocoumarilic acid obtained under A.

Nitromarmesin (VIII). One-half gram of marmesin was dissolved in glacial acetic acid (5 ml.), then treated with a solution of nitric acid (sp. gr. 1.4, 2 ml.) in acetic acid (5 ml.) and the mixture heated for 1 5 hr. on a boiling water bath. Water was added, whereby a voluminous bright yellow precipitate was formed which was filtered and crystallized from methanol to give 400 mg. of canary yellow needles; m.p. 202–204°, $[\alpha]_D$ +87° (chloroform).

Anal. Calcd. for $C_{14}H_{13}O_6N$: C, 57.73; H, 4.46; N, 4.81. Found: C, 57.98; H, 4.45; N, 4.91.

5-Formyl-6-hydroxy-2-(β-hydroxyisopropyl)-2,3-dihydrobenzofuran (IX). Nitromarmesin (100 mg.) was shaken with a 5% solution of potassium hydroxide (5 ml.) and left at room temperature for 15 min. A red color gradually developed and the solid dissolved. The solution was then acidified with dilute hydrochloric acid and chilled, whereby grayish platey needles were formed; yield 55 mg. Repeated crystallization of the product from water-ethanol gave lustrous plates; m.p. 83–85°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.44; H, 6.27.

When the reaction was carried out as prescribed by Clayton[17] for 3-nitrocoumarins, where 1 g. of the nitro compound (VIII) was warmed with concentrated ammonia solution, a much lower yield (150 mg.) of the hydroxyaldehyde (IX) was obtained.

The 2,4-dinitrophenylhydrazone derivative, m.p. 242–244°, was prepared.

Anal. Calcd. for $C_{18}H_{18}O_7N_4$: N, 13.93. Found: N, 13.87.

2′-Isopropyl-6-nitropsoralene (X). One gram of 6-nitromarmesin was dehydrated with phosphorus pentoxide in benzene as described before and the product, orange prismatic needles (600 mg.), was crystallized from ethanol; m.p. 209–211°.

Anal. Calcd. for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.29; H, 4.03; N, 4.98.

6-Aminomarmesin (XI). A. A solution of 6-nitromarmesin (250 mg.) in ethyl alcohol (50 ml.) was refluxed for 25 hr. with zinc dust (1.5 g.) which was previously treated with 8*N* hydrochloric acid. The zinc deposit was then filtered off, and the filtrate concentrated to a small volume and treated with some water. The pale yellowish flat needles (0.1 g.) formed were recrystallized several times from aqueous ethanol; m.p. 248–250° dec.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.17; H, 5.97; N, 5.43.

B. Nitromarmesin (250 mg.) was dissolved in glacial acetic acid (15 ml.) and 85 mg. of platinum oxide were added. The mixture was shaken for 1 hr. with hydrogen under atmospheric pressure. The catalyst was filtered off and the solution evaporated to dryness. The residue, after treatment with charcoal, was crystallized from aqueous ethanol to give 150 mg. of pale yellow plates; m.p. 248–250°, was undepressed by a sample of 6-aminomarmesin prepared in the previous experiment.

2-Isopropylpsoralene (II). Marmesin (1.0 g.) was refluxed with benzoyl chloride (10 ml.) for 2 hr. Water was added and the oil deposited was taken up in chloroform. The product, isolated in the usual manner, was crystallized from methanol to give colorless flat needles (0.4 g.); m.p. 135–136°, was undepressed by a sample of anhydromarmesin prepared as described in the literature[2,3]; reported m.p. 138–140°[2] and 138–138.5°.[3]

2-Isopropyl-5,6-dihydropsoralene (XIV). The starting material, 2-(β-hydroxyisopropyl)-2,3,5,6-tetrahydropsoralene or dihydromarmesin (XIII), was prepared as described by Chatterjee and Mitra[2] by hydrogenation of marmesin. This material (440 mg., m.p. 131°; reported[2] m.p. 135°) was dissolved in benzene (75 ml.) and refluxed with phosphorus pentoxide (4.5 g.) for 5 hr. The decanted benzene solution was then concentrated to a small volume and petroleum ether (b.p. 70–80°) was added until slightly turbid and left to cool. Colorless heavy prisms (280 mg.) were deposited; m.p. 134–135°. The substance was optically inactive. For the product from the distillation of tetrahydropeucedanin, reported[23] m.p. 126°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.19; H, 6.24.

Desoxydihydro-oreoselone (XII). A solution of 2-isopropyl-5,6-dihydropsoralene (185 mg.) in glacial acetic acid (15 ml.) was shaken with 10% palladium on charcoal (185 mg.) in the presence of hydrogen for 60 hr. The catalyst was removed and water added to the clear solution whereby colorless plates (90 mg.) deposited; m.p. 113–115°, undepressed by the material prepared[2] by a similar hydrogenation of 2-isopropylpsoralene (II), $[\alpha]_D$ +25.5°; reported m.p. 116–117°[2] and 115–117°.[12]

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.54; H, 7.08.

DOKKI, CAIRO
EGYPT, U.A.R.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF STANFORD UNIVERSITY AND WAYNE STATE UNIVERSITY]

Terpenoids. XLVI.[1] Copalic Acid[2]

T. NAKANO[3] AND CARL DJERASSI

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The acidic fraction of "Brazil Copal" consists largely of a diterpene acid which has now been named copalic acid. Dehydrogenation and other degradation studies have shown that copalic acid has the skeleton of agathanedicarboxylic acid and related diterpene acids. On the basis of NMR and mass spectrographic evidence, copalic acid appears to consist of several double bond isomers; in terms of absolute configuration copalic acid corresponds essentially to dehydroeperuic acid.

The Brazilian "jutaicica (or jutahycica)" resin[4]—elsewhere known as "Brazil Copal" or "Brazil Dammar"—represents the exudate of the stem and roots of a huge tropical tree, *Hymenaea Courbaril L.*, which grows in northern Brazil, especially in the state of Pará. The name "Brazil Dammar" is definitely a misnomer since Dammar resin—a rich source of triterpenes[5]—comes from trees of the *Dipterocarpaceae* family, while the genus *Hymenaea* belong to the family *Leguminosae*, subfamily *Caesalpinoideae*. Earlier studies,[6] though of an inconclusive nature, indicated the presence of terpene acids in this resin, which is still employed industrially for varnishes in northern Brazil. Through the kind cooperation of Dr. Walter B. Mors of the Instituto de Quimica Agricola (Rio de Janeiro), a commercial sample of "Brazil Copal" was made available to us and the present report is concerned with the acidic terpene fraction of this resin.

The isolation scheme involved extraction of the powdered resin with ether containing some methanol, precipitation of insoluble polymers with methanol, and extraction of the ether phase with dilute alkali. Acidification yielded an oily acid, which was methylated with diazomethane and chromatographed thus affording up to 13% of a methyl ester, named methyl copalate. The distilled analytical sample was optically active ($[\alpha]_D$ −11° to −13°) and its analysis corresponded to $C_{21}H_{34}O_2$, whereupon it can be concluded that the parent acid, copalic acid, is a diterpene. Microhydrogenation resulted in the uptake of two equivalents of hydrogen, indicating that copalic acid is bicyclic and possesses two double bonds. One of these appeared to be present as an exocyclic methylene function, as methyl copalate exhibited infrared bands at 6.05 and 11.20 μ, and this was confirmed subsequently by ozonolysis and isolation of formaldehyde. The second double bond appeared to be conjugated with the ester function, as some samples of methyl copalate exhibited an ultraviolet absorption maximum at 225 mμ (log ϵ 4.06). As pointed out below, this was not reproducible from batch to batch and some specimens had a lower extinction or at times showed only terminal absorption. The presence of two double bonds was also confirmed by perbenzoic acid titration.

Saponification of methyl copalate proceeded readily—in marked contrast to the behavior of members of the abietic acid class of diterpenes—to furnish copalic acid ($C_{20}H_{32}O_2$). Important structural information was gained from its selenium dehydrogenation which provided 1,2,5-trimethylnaphthalene and 1,1,4,7-tetramethylphenalan (I).[7] The latter represents an extremely characteristic degradation product, which has so far only been obtained from agathanedicarboxylic acid (II)[8] and very close relatives such as cativic acid (III).[9] Consequently, on the basis of these results and the spectral data mentioned above, it appeared reasonable to assign structure VIa (without stereochemical implications) to copalic acid. Aside from agathanedicarboxylic acid (II)[8] and cativic acid (III),[9] only two other diterpene acids, eperuic acid (IV)[10,11] and labdanolic acid (V)[12] possess this same skeleton and it is pertinent to note that of these, cativic (III), and eperuic (IV) acids are

(1) Paper XLV. R. A. Finnegan and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 4342 (1960).

(2) Part of the experimental work was performed at Wayne State University. We are indebted to the Division of Research Grants of the National Institute of Health (grant No. RG-3863 at Wayne State University and grant No. RG-6840 at Stanford University) and to the Rockefeller Foundation for financial support.

(3) Recipient of a Fulbright travel grant while on leave from the University of Kyoto.

(4) J. L. Rangel and H. S. Schneider, *Copaes do Brasil*, Instituto Nacional de Technologia, Rio de Janeiro, 1936.

(5) J. S. Mills and A. E. A. Werner, *J. Chem. Soc.*, 3132 (1955).

(6) For a complete review see A. Tschirch and E. Stock, *Die Harze*, Verlag Borntraeger, Berlin, 1936, Vol. II, second half, second part, pp. 1344–1357.

(7) G. Büchi and J. J. Pappas, *J. Am. Chem. Soc.*, **76**, 2963 (1954). We are grateful to Prof. Büchi for an authentic sample of tetramethylphenalan picrate.

(8) L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, **13**, 1402 (1930); L. Ruzicka, R. Zwicky, and O. Jeger, *Helv. Chim. Acta*, **31**, 2143 (1948).

(9) H. H. Zeiss and F. W. Grant, *J. Am. Chem. Soc.*, **79**, 1201 (1957).

(10) F. E. King and G. Jones, *J. Chem. Soc.*, 658 (1955).

(11) For discussion of absolute configuration see ref. 12a and C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957).

(12) (a) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 4262 (1956); (b) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 4401 (1957); (c) for discussion of configuration at C-13 see ref. 17 as well as J. A. Barltrop and D. B. Bigley, *Chemistry and Industry*, 1447 (1959).

derived from plant sources (*Prioria copaifera* Griseb., respectively *Eperua* species) which belong to the same subfamily (*Caesalpinioideae*) as does "Brazil Copal" (*Hymenaea Courbaril*). If expression VIa is correct, then depending upon the absolute configuration of copalic acid, an interconversion should be possible with either eperuic (IV) or labdanolic (V) acids and subsequent experiments were designed with this purpose in mind.

The simplest correlation appeared to be *via* methyl tetrahydrocopalate (VIIb), since this might be identical with methyl dihydrocativate (VIII) (m.p. 43–44°, $[\alpha]_D$ +23°), which has been obtained from cativic acid (III)[9] as well as from labdanolic acid (V).[12a] However, all attempts to crystallize methyl tetrahydrocopalate (VIIb) or tetrahydrocopalic acid (VIIa) failed, possibly because of the formation of a mixture of isomers at C-8 and C-13. Nevertheless, it is noteworthy that the rotation of methyl tetrahydrocopalate (VIIb) ($[\alpha]_D$ −20.5°) was nearly identical with but opposite in sign to that of methyl dihydrocativate (VIII) and, as will be shown in the sequel, this is in agreement with our stereochemical assignment.

We then turned to the sodium-butanol reduction of copalic acid (VIa), which should only result in the reduction of the double bond in the side chain. Such reduction would simplify the stereochemical problem, as only one new asymmetric center is generated, and might lead to either eperuic acid (IV)[10] or $\Delta^{8(20)}$-labden-15-oic acid(IX).[12a] While neither one of these acids is crystalline, crystalline degradation products of them are known.

In accordance with expectation, the reduction product dihydrocopalic acid (Xa) was not crystalline and as was noted subsequently from the ozonization experiments, it represented a mixture of isomers. Nevertheless, it was possible to separate from this mixture in fair yield a crystalline cyclohexylamine salt, whose infrared spectrum was identical with that of the crystalline $\Delta^{8(20)}$-labden-15-oic acid (IX) cyclohexylamine salt.[12a,13] Furthermore, the respective specific rotations were exactly opposite in sign (salt of Xa: $[\alpha]_D$ −21.7°; salt of IX, $[\alpha]_D$ +22°), so that we are justified in concluding that copalic acid must contain a substantial amount of Δ^{13}-eperuic acid (VIa). Decomposition of the salt afforded dihydrocopalic acid (Xa) and thence methyl dihydrocopalate (Xb). While neither sample was crystalline, their specific rotations were similar in magnitude but opposite in sign to those of syrupy $\Delta^{8(20)}$-labden-15-oic acid (IX)[12a] and its methyl ester.

Further evidence for the antipodal stereochemistry of the A/B ring juncture of copalic acid was adduced by ozonolysis of methyl dihydrocopalate (Xb) (derived from its crystalline cyclohexylamine salt), which led to formaldehyde and an oily 20-nor keto ester whose optical rotatory dispersion curve[14] was characterized by a strong positive Cotton effect (peak at $[\alpha]_{317.5}$ +1228°). For comparison there were already available the rotatory dispersion curves[11] of the keto esters XI (trough at $[\alpha]_{317.5}$ −1440°) derived from labdanolic acid (V) and of XIII (peak at $[\alpha]_{317.5}$ +1585°) derived from eperuic acid (IV); the qualitative agreement between the positive Cotton effect curves of the keto esters from methyl dihydrocopalate (Xb) and methyl eperuate (IV methyl ester) establish the coincidence in terms of absolute configuration of their A/B ring fusions.

The authentic keto esters XI[12a] and XIII[10] are oily, but they have been converted into the crystalline oximes of their keto acids. The oxime of the keto acid XII of the labdanolic acid series (V) exhibits[12a] m.p. 188–190°, $[\alpha]_D$ +74.5°, while the keto acid oxime XIV from eperuic acid (IV) is reported[10] to show m.p. 223°, $[\alpha]_D$ −79.4°. This discrepancy in the melting points has been confirmed[11] and it has been suggested[11] that the two substances may perhaps not be antipodal at every asymmetric center.

When the keto ester from methyl dihydrocopalate (Xb) was converted into the keto acid oxime, its melting points (178–180°) resembled that of XII, but there was a substantial difference in rotations ($[\alpha]_D$ −33.4° *vs.* $[\alpha]_D$ +74.5°). When the reaction sequence was repeated with methyl dihydrocopalate, which was derived from the mother liquors of the crystalline cyclohexylamine salt of dihydrocopalic acid, there was obtained a crude keto ester, which showed only a very weak positive Cotton effect, yet conversion to the keto acid oxime gave in very poor yield a crystalline product, m.p. 214–216°, $[\alpha]_D$ −82°, which proved to be completely identical (including infrared spectral comparison) with the keto acid oxime XIV of eperuic acid. We believe that in both cases, the keto ester of methyl dihydrocopalate represented a mixture of stereoisomers and that partial separation was effected by crystallization of the oxime.

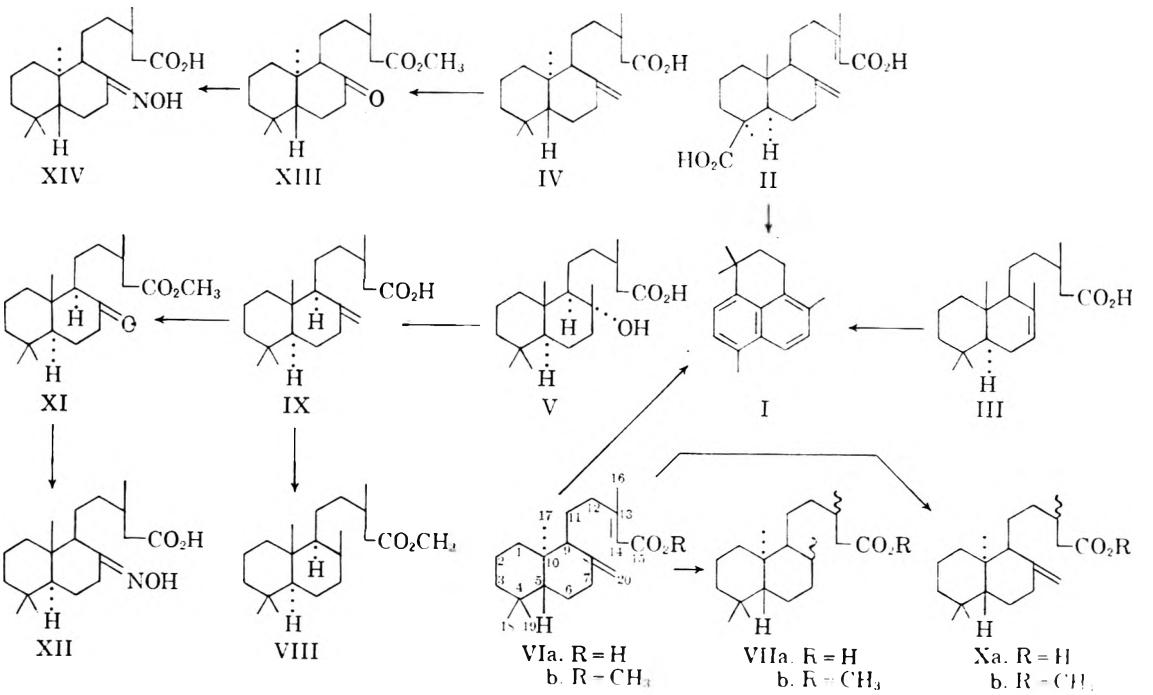
The above described transformations establish the gross structure of copalic acid in terms of stereoformula VIa, but they also indicate that copalic acid is not necessarily optically or stereochemically pure. Indeed, the ultraviolet evidence to which reference was made in the beginning of this article suggests the possibility of double bond isomerism as well. A characteristic feature of copalic acid in particular and indeed of this class of diterpene acids in general is the great difficulty of obtaining crystalline derivatives. As we were unsuccessful in securing a single crystalline salt or derivative of copalic acid (VIa), which might serve as a criterion

(13) We are indebted to Dr. T. G. Halsall (Oxford University) for this specimen.

(14) See C. Djerassi, *Optical Rotatory Dispersion. Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1960.

of homogeneity, it was decided to synthesize copalic acid in the form of its antipode. It was hoped that the synthesis would also settle the question of possible geometrical isomerism around the 13–14 double bond.

A similar behavior was observed with some specimens of methyl copalate and it should be noted that the infrared spectra of methyl copalate (VIb) and copalic acid (VIa) were essentially identical with those of the synthetic methyl ester



The starting material was sclareol (XV)[15] whose relative and absolute configuration is completely settled.[16] This alcohol has been transformed by Bory and Lederer[17] *via* the aldehyde XVI[18] into two crystalline unsaturated esters (XVII), representing the two geometric isomers in the side chain. It is noteworthy, however, that their respective ultraviolet spectra show practically no differences, as might be expected by analogy to angelic and tiglic acid derivatives.[19] Each of the pure crystalline hydroxy esters (XVII) was dehydrated separately under exactly the same conditions employed by Cocker and Halsall[12a] for the conversion of methyl labdanolate (V methyl ester) into the methyl ester of IX.

The higher melting hydroxy ester XVIIa (m.p. 130–131°)[17] afforded an oily methyl ester XVIIIa ($[\alpha]_D$ +9.7°; $\lambda_{max}^{C_2H_5OH}$ 218 mμ), which upon saponification led to the free acid, $[\alpha]_D$ +19.5°, which, however, showed only a slight inflection rather than a maximum in the 220 mμ region. XVIIIa and its derived acid. Furthermore, the rotations of the methyl esters were of the same order of magnitude, but of opposite sign in accordance with their antipodal character.

The lower melting hydroxy ester XVIIb (m.p. 98–99°)[17] on similar dehydration afforded an unsaturated ester XVIIIb[20] ($\lambda_{max}^{C_2H_5OH}$ 219 mμ), whose rotation ($[\alpha]_D$ +48.1°) served to distinguish it from isomer XVIIIa or methyl copalate (VIb). Furthermore, saponification afforded an acid, whose infrared spectrum exhibited some differences in the 8–9 μ region when compared to copalic acid (VIa).

These results again confirm the earlier conclusion that copalic acid should be represented largely by structure VIa. Nevertheless, the absence of solid derivatives for purposes of characterization and comparison, the peculiar ultraviolet absorption spectra of some specimens, and the similarity but not complete coincidence of the rotations (in terms of magnitude, but not in sign) of methyl copalate when compared with those of transformation products of labdanolic acid (V) and sclareol (XV) led us to doubt the homogeneity of the substance. In fact, when methyl copalate was subjected to gas phase

(15) We would like to acknowledge a very generous gift of sclareol on the part of Dr. M. Stoll (Firmenich and Co., Geneva).

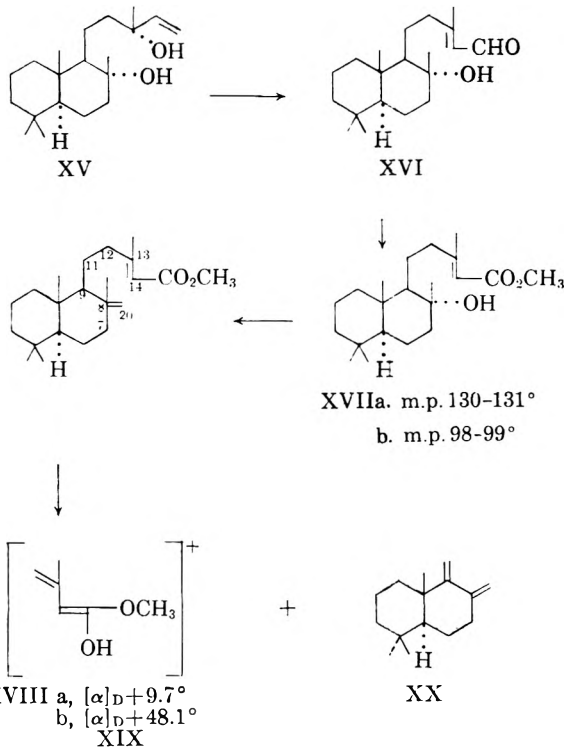
(16) For pertinent references see G. Büchi and K. Biemann, *Croat. Chem. Acta*, 29, 163 (1957).

(17) S. Bory and E. Lederer, *Croat. Chem. Acta*, 29, 157 (1957).

(18) Similar to the procedure of M. Stoll and A. Commarmont, *Helv. Chim. Acta*, 32, 1354, 1356 (1949) for the oxidation of linalool and nerolidol.

(19) See A. J. Nielsen, *J. Org. Chem.*, 22, 1539 (1957).

(20) After completion of our experiments there appeared an article by G. Ohloff, *Ann.*, 617, 134 (1958) in which an alternate synthesis of an unsaturated ester XVIII from sclareol (XV) and manool is reported. The rotation of this ester ($[\alpha]_D$ +26.5°) indicates that it represents a mixture of XVIIIa and b.



XV XVI

XVIIa. m.p. 130–131°
b. m.p. 98–99°

XVIII a, $[\alpha]_D$+9.7°
b, $[\alpha]_D$+48.1°

XIX XX

chromatography under conditions[21] which have proved very satisfactory for the separation of higher terpenoids, it appeared to consist of about three major components (*ca.* 50%, 30%, and 20%). A similar examination of the unsaturated ester XVIIIa indicated about 80% of one component with admixture of 20% of two others, while XVIIIb was essentially homogeneous. It should be noted that two of the three peaks of methyl copalate (VIb) coincided with the major peaks of XVIIIa and XVIIIb.

As it was conceivable that some decomposition or double bond isomerization may have occurred during the gas phase chromatography (191°), several of the compounds were examined in a mass spectrometer.[22] Such an examination appeared pertinent on two grounds. It would indicate whether this inhomogeneity might be due to contaminants of different molecular weight and it might give some indication of stereochemical differences as has been observed in the mass spectrographic fragmentation patterns of some isomeric diterpene acids.[23] The mass spectrum of the higher melting hydroxy acid XVIIa was identical with that of its derived unsaturated ester XVIIIa and a similar coincidence was observed in the isomeric pair XVIIb, XVIIIb. This result shows that the thermal cracking in the mass spectrometer proceeds in the same direction as the chemical dehydration (phosphorus oxychloride and pyridine). The mass spectra of the two isomeric unsaturated esters XVIIIa and XVIIIb from sclareol (XV) are essentially identical. The first important peak after the molecule ion (mass 318) is at 303 corresponding to the loss of a methyl group. There follow a series of minor peaks until mass 204 and 205, which are both intense in XVIIIb, followed by a multiplicity of peaks in the mass range 15–200. This entire region is completely identical in the mass spectra of the two esters; in fact, the only noticeable difference between them is that XVIIIb possesses two large peaks at masses 204 and 205, while in XVIIIa, the former is much smaller. Particularly noteworthy is the observation that the most intense peak in their spectra corresponds to mass 114 and it seems very likely[22] that the peaks at 114 and 204 represent the two portions from scission of the molecule ion (m/e 318) between carbon atoms 11 and 12 to yield the ion XIX (m/e 114) and the diene XX (m/e 204), the hydrogen atom of C-9 having been transferred to the carbonyl oxygen.

Turning now to the mass spectrum of methyl copalate, the peaks at m/e 318, 303 (due to loss of methyl group) and the very characteristic region between m/e 15 to 200 are very similar to what was observed with the isomeric esters XVIIIa and XVIIIb, the most striking difference being that the typical peaks at m/e 204 and 114 (due to rupture of XVIII to XIX + XX) are much smaller. This could only be ascribed to some difference in the side chain or possibly in the stereochemistry of C-9 and because the above described chemical transformations of methyl copalate would only permit a difference in stereochemistry or location of double bonds, but not in terms of structure, the nuclear magnetic resonance spectra were examined[24] in order to shed some light on this last point.

As reference compound, there was studied first the NMR spectrum of the unsaturated ester XVIIIa, which showed definitely that the compound was homogeneous insofar as the 13–14 double bond is concerned, but that in regard to the nuclear unsaturation the substance consisted of *ca.* 66% of the $\Delta^{8(20)}$ and 23% of the $\Delta^{7(8)}$ isomers, the remainder presumably being due to $\Delta^{8(9)}$-isomer, which could not be determined directly. The presence of the exocyclic double bond in XVIII had been demonstrated qualitatively by the infrared spectrum, but this, of course, did not eliminate contamination by the other isomers. It would appear almost certain that the same situa-

(21) G. Eglinton, R. J. Hamilton, R. Hodges and R. A. Raphael, *Chemistry and Industry*, 955 (1959). We are indebted to Dr. R. Hodges (University of Glasgow) for performing these determinations.

(22) We should like to express our indebtedness to Prof. Einar Stenhagen (University of Göteborg, Sweden) for his very generous help in securing the mass spectra of our samples and for many valuable comments.

(23) H. H. Bruun, R. Ryhage, and E. Stenhagen, *Acta Chem. Scand.*, 12, 789, 1355 (1958).

(24) We should like to acknowledge the valuable help of Dr. J. N. Shoolery (Varian Associates, Palo Alto, Calif.) in securing the spectra and in their interpretation.

tion also applies to the dehydration[12a] in the labdanolic acid series and such NMR examination of partially synthetic (*e.g.*, IX) or naturally occurring (*e.g.* III, IV) olefins might prove to be very instructive.

A similar NMR study[24] with methyl copalate indicated a somewhat more complex mixture in agreement with the above cited gas phase chromatographic results. All that can be stated from this spectrum is that methyl copalate (VIb) contains at least 35% of an exocyclic methylene component admixed with 15–30% of the $\Delta^{7(8)}$-isomer. Most importantly, this particular sample[25] of methyl copalate which was also used for the mass spectrographic analysis, appeared by NMR analysis to contain only about 30% of conjugated ($\Delta^{13(14)}$) double bond and this readily explains the low m/e peaks in the mass spectrum associated with the cleavage of the 11–12 bond. As the mass spectrographically determined molecular weight corresponds to 318, the other component of this methyl copalate specimen must be a nonconjugated isomer of VIb. The exocyclic $\Delta^{13(16)}$ position is excluded from the NMR results, thus leaving the $\Delta^{12(13)}$-isomer as the most likely possibility, which of course is also most compatible with the mass spectrographic data. It is interesting to note that the only other naturally occurring diterpene with this type of unsaturated acid side chain, agathanedicarboxylic acid (II), also appears to be contaminated by some of the nonconjugated Δ^{12}-isomer.[26]

In conclusion, copalic acid can be considered to be a mixture consisting of structure VIa and its double bond isomers. As far as its absolute configuration is concerned, the optical rotatory dispersion results of the ketone derived from methyl dihydrocopalate (Xb) leave no doubt that C-5 and C-10 correspond to eperuic acid (IV) rather than cativic (III) and labdanolic (V) acids.[27] Our studies with copalic acid offer an instructive example of the use to which physical methods such as mass spectrography and NMR spectrometry can be put. Indeed, in this particular series of diterpenoids where homogeneity cannot be established readily by classical criteria, these methods, possibly coupled with gas phase chromatography, represent the most straightforward approach to the solution of structural problems.

EXPERIMENTAL[28]

Isolation of copalic acid. A commercial sample of the resin of *Hymenaea Courbaril* L. furnished by Dr. Walter B. Mors (Rio de Janeiro) was powdered and 673 g. of it was extracted with 1.5 l. of ether and 0.5 l. of methanol by stirring at room temperature overnight. Methanol (1 l.) was added to precipitate insoluble material, the supernatant liquid was decanted and the residue was extracted as before. After three such operations, the combined extracts were evaporated to dryness *in vacuo* at 55°, the residue was dissolved in ether and extracted with 2% aqueous sodium hydroxide. The ether solution was washed with water, dried, and evaporated to leave 70 g. of *neutral fraction*, the composition of which will form the subject of another paper.

The alkaline solution was acidified with hydrochloric acid, extracted with ether, washed with water, dried, and evaporated yielding 206 g. of *acidic fraction*. A 20-g. sample was methylated for 15 min. at room temperature with an ethereal diazomethane solution and the resulting methyl ester (17 g.) was chromatographed on 900 g. of alumina which had been deactivated with 9 cc. of 10% aqueous acetic acid. The benzene-ether (9 : 1) eluted fractions were shown to be identical by infrared spectroscopy and these were combined (5.84 g.) and rechromatographed on 250 g. of deactivated alumina. Distillation of the pooled benzene-ether (9 : 1) eluted fractions (3.68 g.) at a bath temperature of 160°/0.2 mm. provided 2.43 g. of *methyl copalate* (VIb) as a colorless oil, $[\alpha]_D$ −11.4° (*c*, 1.06), $\lambda_{max}^{C_2H_5OH}$ 225 mμ, log ε 4.06, $\lambda_{max}^{CHCl_3}$ 5.80, 6.05, 11.20, and 11.56 μ; yellow color with tetranitromethane. Perbenzoic acid titration resulted in the uptake of 1.6 equivalents after 1 day (5°) and 1.9 equivalents within 1 week.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05; methoxyl, 9.74. Found: C, 78.72; H, 10.62; O, 10.69; methoxyl, 9.90.

The methyl ester (0.93 g.) was heated under reflux for 2 hr. with 15 cc. of 10% methanolic sodium hydroxide solution, diluted with water, extracted with ether (discarded), acidified, and extracted with ether. Washing, drying, and evaporation left 0.68 g. of *copalic acid* which was distilled at a bath temperature of 160°/0.005 mm., $[\alpha]_D$ −6.9° (*c*, 1.15), $\lambda_{max}^{C_2H_5OH}$ 220 mμ, log ε 3.80, $\lambda_{max}^{CHCl_3}$ 5.89, 6.09, 11.20 μ. The infrared spectrum was identical with that of the acid obtained on saponification of the unsaturated ester XVIIIa described below.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.27; H, 10.01; O, 10.53.

Copalic acid and its methyl ester from the same batch of starting material were employed for the subsequently reported chemical transformations. For the mass spectrographic, NMR and gas phase chromatographic determinations of methyl copalate mentioned in the discussion section, a new batch of resin was employed which was processed as follows:

The powdered resin (1 kg.) was extracted as described above furnishing after methylation of the acidic fraction 375 g. of crude methyl ester, which upon chromatography led to 133.7 g. of purified methyl ester. This was saponified by heating under reflux for 1.5 hr. with 2 l. of 5% *t*-butanolic

(25) This sample of methyl copalate was analytically pure and had been obtained from copalic acid by methylation, saponification, methylation, repeated chromatography, saponification and finally remethylation. It exhibited essentially no ultraviolet absorption maximum in the 220 mμ region but only terminal absorption.

(26) L. Ruzicka, F. Bernold, and A. Tallichet, *Helv. Chim. Acta*, **24**, 223 (1941).

(27) At least one of the components of the copalic acid mixture possesses a 9β-oriented hydrogen atom as the cyclohexylamine salt of dihydrocopalic acid (Xa) was the only crystalline derivative where a completely antipodal relationship to a member of the labdanolic acid group could be proved. Cocker and Halsall (ref. 12b) have established a 9,10-*anti* relationship in labdanolic acid.

(28) Unless noted otherwise, rotations were measured in chloroform solution. We are indebted to Miss B. Bach for the infrared spectra and to Dr. J. Vandenbelt (Parke, Davis and Co., Detroit) for many of the ultraviolet spectral determinations. The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. The distillations were conducted in an electrically heated airbath under conditions where the bath temperature is practically identical with the boiling point.

potassium hydroxide giving 84.6 g. of acid and 39.1 g. of nonsaponified ester. The 84.6 g. of acid was again methylated, the resulting ester (83.6 g.) was chromatographed on 1.8 kg. of Merck acid-washed alumina and the apparently homogeneous (identical infrared spectra) methyl ester (49.2 g.) thus obtained was saponified again with *t*-butanolic potassium hydroxide. This treatment provided 34.7 g. of acid and 4.1 g. of ester. Methylation of this acid and distillation of the methyl ester at a bath temperature of 180°/0.05 mm. afforded *methyl copalate* (VIb) with $[\alpha]_D$ −12.7° (*c*, 1.05), $\lambda_{max}^{CHCl_3}$ 5.80, 6.09, 11.21, and 11.56 μ. The ultraviolet absorption spectrum exhibited no pronounced maximum at 220 mμ but only high terminal absorption to 200 mμ. R.D. (*c*, 0.391) in methanol): $[\alpha]_{589}$ −13°, $[\alpha]_{500}$ −25°, $[\alpha]_{400}$ −39°, $[\alpha]_{350}$ −55°, $[\alpha]_{300}$ −89°, $[\alpha]_{290}$ −99°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05; methoxyl, 9.74; mol. wt., 318.5. Found: C, 78.80; H, 10.75; O, 10.52; methoxyl, 9.91; mol. wt. (mass spectrographic[22]), 318.

Tetrahydrocopalic acid (VIIa). Methyl copalate (0.131 g.) in 5 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 30 mg. of platinum oxide catalyst. Hydrogen consumption corresponding to 2 molar equivalents was complete within 10 min., after which time no more gas uptake was observed. Filtration of the catalyst, evaporation of the acetic acid *in vacuo*, and distillation at a bath temperature of 150°/0.2 mm. yielded 0.109 g. of methyl tetrahydrocopalate (VIIb), $[\alpha]_D$ −20.5° (*c*, 1.02), $\lambda_{max}^{CHCl_3}$ 5.80 μ, no high ultraviolet absorption, negative tetranitromethane test.

Anal. Calcd. for $C_{21}H_{38}O_2$: C, 78.20; H, 11.88; O, 9.92. Found: C, 78.83; H, 11.35; O, 10.19.

Saponification of the above methyl ester was accomplished by heating under reflux for 2 hr. with 10% methanolic sodium hydroxide solution. Distillation at a bath temperature of 150°/0.1 mm. gave tetrahydrocopalic acid (VIIa), $[\alpha]_D$ −17° (c, 1.00), $\lambda_{max}^{CHCl_3}$ 5.82 μ.

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76; O, 10.37. Found: C, 77.32; H, 11.59; O, 10.77.

Selenium dehydrogenation of copalic acid (VIa). Copalic acid (2.71 g.) and 3.0 g. of selenium were heated in a metal bath at 300° for 30 hr. The cooled residue was ether extracted and the combined extracts were filtered and evaporated. The dark residue (1.68 g.) was distilled to afford two fractions, b.p. 130–140°/0.5 mm. and b.p. 135–155°/0.2 mm.

The lower boiling fraction was transformed into a picrate and recrystallized from 95% ethanol; yield, 0.56 g., m.p. 135–136.5°; reported[9] for 1,2,5-trimethylnaphthalene picrate, m.p. 135–137°.

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.14; H, 4.29; N, 10.52; O, 28.05. Found: C, 57.70; H, 4.27; N, 10.73; O, 27.52.

The second fraction afforded 0.26 g. of picrate which exhibited m.p. 135–136° after recrystallization from ethanol. Identity with 1,1,4,7-tetramethylphenalan (I) picrate was established by mixture melting point determination and infrared spectral comparison with an authentic specimen.[7]

Anal. Calcd. for $C_{23}H_{23}N_3O_7$: C, 60.92; H, 5.11; N, 9.27. Found: C, 60.95; H, 5.42; N, 9.36.

Dihydrocopalic acid (Xa). To a refluxing and stirred solution of 5.52 g. of copalic acid in 600 cc. of *n*-butyl alcohol was added as rapidly as possible 22 g. of sodium metal. After 40 min., all of the sodium had dissolved, whereupon the solution was cooled, diluted with water, and concentrated *in vacuo* to remove most of the butyl alcohol. Acidification, extraction with ether, washing, drying, and evaporation afforded 4.74 g. of a viscous residue which was distilled at a bath temperature of 170°/0.08 mm., leading to 4.37 g. of dihydrocopalic acid. The acid was treated in hot ethyl acetate with 1.5 g. of cyclohexylamine to yield 2.2 g. of the *cyclohexylamine salt* (m.p. 112–126°). Recrystallization from ethyl acetate–chloroform provided 1.95 g. of the salt with m.p. 123–126°,[29] $[\alpha]_D$ −21.7° (*c*, 0.76). The infrared spectrum was identical with that of $\Delta^{8(20)}$-labden-15-oic acid (IX) cyclohexylamine salt[13] (lit.,[12a] m.p. 123–136°, $[\alpha]_D$ +22°).

Anal. Calcd. for $C_{26}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 76.60; H, 11.75; N, 3.55.

The cyclohexylamine salt (1.23 g., m.p. 123–136°) was dissolved in chloroform and shaken twice with 5% hydrochloric acid. After washing with water, drying and evaporating, there was obtained 0.98 g. of *dihydrocopalic acid* (Xa) which was distilled at 150°/0.03 mm., $[\alpha]_D$ −19.9° (*c*, 1.44).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.01; H, 10.97; O, 10.03.

Methylation with diazomethane and distillation at 130°/0.01 mm. afforded *methyl dihydrocopalate* (Xb), $[\alpha]_D$ −19.1° (*c*, 1.34), whose infrared spectrum was essentially identical with that of the methyl esters of eperuic acid (IV)[10,30] (lit.,[10] $[\alpha]_D$ −28.2° for methyl ester) and of $\Delta^{8(20)}$-labden-15-oic acid (X)[12a,13] (lit.,[12a] $[\alpha]_D$ +27° for methyl ester).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 9.98. Found: C, 78.21; H, 11.03; O, 10.23.

The divergence in the rotations may be due to one or both of the following factors: (a) mixture of stereoisomers at C-13; (b) admixture of Δ^7 or Δ^8 isomers (see discussion of NMR spectral data).

Ozonolysis of methyl dihydrocopalate (Xb). The above methyl ester Xb (0.87 g.) derived from the crystalline cyclohexylamine salt of dihydrocopalic acid (Xa) was ozonized at −70° in ethyl acetate (100 cc.) solution until a blue color persisted. Nitrogen was then passed through the solution for 10 min. followed by stirring at room temperature with 3.5 g. of zinc dust and 18 cc. of acetic acid until no starch-iodide reaction was obtained. The reaction mixture was filtered, the filtrate washed with water, and the aqueous washings treated with Brady's reagent affording 40 mg. of formaldehyde 2,4-dinitrophenylhydrazone (m.p. and mixture m.p. 162–164°). Evaporation of the dried organic phase to dryness left 0.80 g. of the 20-nor 8-keto methyl ester (*cf.* XIII), whose rotatory dispersion curve (*c*, 0.076 in dioxane) exhibited a strong positive Cotton effect: $[\alpha]_{589}$ +26°, $[\alpha]_{317.5}$ +1228°, $[\alpha]_{287.5}$ −858°, $\lambda_{max}^{liquid\ film}$ 5.76, 5.85 μ (identical with the infrared spectrum of XIII).

The keto ester (0.7 g.) was heated under reflux for 2 hr. with 50 cc. of 10% methanolic potassium hydroxide giving 0.68 g. of keto acid, which could not be crystallized. The acid was transformed into its oxime (*cf.* XIV) by heating under reflux for 30 min. in 5 cc. of ethanol and 1.5 g. of hydroxylamine hydrochloride dissolved in 9 cc. of water, which had been made barely alkaline by the addition of a 10% solution of sodium hydroxide. Acidification, extraction with ether, washing, drying, evaporation, and crystallization from ethyl acetate afforded 0.32 g. of crystals, m.p. 170–176°, raised to 178–180° upon recrystallization from ethanol; $[\alpha]_D$ −33.4° (dioxane), infrared spectrum identical with that of the keto acid oxime XII[12a,13] (m.p. 184–188°, $[\alpha]_D$ +74.5° in dioxane) derived from labdanolic acid. Comment on the discrepancy in the magnitudes of these rotations is made in the Discussion section.

Anal. Calcd. for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.31; H, 10.06; N, 4.39.

The mother liquors from the separation of 2.2 g. of dihydrocopalic acid cyclohexylamine salt (*vide supra*) were decomposed as described for the crystalline salt to give 1.94 g. of acid ($[\alpha]_D$ −2.1°) and thence the methyl ester ($[\alpha]_D$ −1.5°). Ozonolysis of 1.3 g. of this ester led to 0.2 g. of formaldehyde 2,4-dinitrophenylhydrazone (the improved yield being due to steam distillation of the formaldehyde from the reaction mixture) and 0.825 g. of 20-norketo ester,

(29) This melting point is very much dependent upon the rate of heating as has already been noted[12a] for the corresponding salt in the labdanolic acid series.

(30) We are indebted to Dr. Gurnos Jones (University College of North Staffordshire) for this specimen.

which exhibited only a very small positive Cotton effect (peak at $[\alpha]_{310}$ +140°). Saponification to the keto acid, conversion to the oxime, and crystallization from ethyl acetate afforded a small amount (20 mg.) of pure oxime, m.p. 214–216°, $[\alpha]_D$ −82° (*c*, 0.81 in dioxane), whose infrared spectrum proved to be superimposable upon that of the keto acid oxime XIV[10,30] (lit.,[10] m.p. 223°, $[\alpha]_D$ −79.4° in dioxane).

Conversion of sclareol (XV) *to isomeric methyl* $\Delta^{8(10),13}$-*labdadien-15-oates* (XVIIIa, XVIIIb). Following the procedure of Bory and Lederer,[17] 50 g. of sclareol (XV)[15] was transformed to 21.3 g. of the crude aldehyde XVI and thence by oxidation with silver oxide and methylation to 19.5 g. of crude ester. Chromatography on 500 g. of Merck acid-washed alumina provided in order of ease of elution: (a) 2.0 g. of oxido ester[17] (resulting from addition of the C-8 hydroxyl group to the Δ^{13} double bond), m.p. 105–106°; (b) 1.7 g. of the hydroxy ester XVIIa, m.p. 130–131° after recrystallization from acetone-hexane (lit.,[17] m.p. 132–134°), $\lambda_{max}^{C_2H_5OH}$ 222 mμ, log ε 4.11, $\lambda_{max}^{CHCl_3}$ 2.87 (very sharp), 5.85, 6.07, 11.69 μ, whose mass spectrum[22] was identical with that of XVIIIa; (c) 1.4 g. of hydroxy ester XVIIb, m.p. 98–99° (lit.,[17] m.p. 99–101°), $\lambda_{max}^{C_2H_5OH}$ 220 mμ, log ε 4.17, $\lambda_{max}^{CHCl_3}$ 2.79 (weak and broad), 5.83, 6.06, 11.60 μ, the mass spectrum[22] being identical with that of XVIIIb.

An interesting distinction between the two hydroxy esters was noted in terms of their rotatory dispersion curves, a difference which persisted also in their respective dehydration products (XVIIIa,b). The higher melting hydroxy ester XVIIa (m.p. 130–131°) exhibited a plain[14] dispersion curve (*c*, 0.090 in methanol) which changed sign below 400 mμ: $[\alpha]_{589}$ +7°, $[\alpha]_{500}$ +7°, $[\alpha]_{400}$ +7°, $[\alpha]_{370}$ −7°, $[\alpha]_{350}$ −24°, $[\alpha]_{300}$ −42°, while the lower melting isomer XVIIb (m.p. 98–99°) possessed a plain dispersion curve (*c*, 0.098 in methanol) which remained positive: $[\alpha]_{589}$ +23°, $[\alpha]_{500}$ +23°, $[\alpha]_{400}$ +39°, $[\alpha]_{370}$ +55°, $[\alpha]_{350}$ +67°, $[\alpha]_{300}$ +120°.

A 2.0-g. sample of the higher melting hydroxy ester XVIIa in 40 cc. of pyridine was kept at room temperature for 15 hr. with 7 cc. of phosphorus oxychloride and the solution was then added cautiously to ice water. Ether extraction afforded 1.87 g. of material lacking an infrared hydroxyl band and chromatography on Merck acid-washed alumina provided in the petroleum ether eluates, 1.76 g. of colorless oil, which was distilled at a bath temperature of 140°/0.01 mm. The resulting unsaturated ester XVIIIa exhibited $\lambda_{max}^{C_2H_5OH}$ 218 mμ, log ε 4.14, $\lambda_{max}^{CHCl_3}$ 5.83, 6.07, 11.23, 11.63 μ, $[\alpha]_D$ +9.7° (*c*, 1.73), whose plain rotatory dispersion curve (*c*, 0.378 in methanol) behaved just like that of its precursor (XVIIa) in changing sign below 400 mμ: $[\alpha]_{589}$ +6°, $[\alpha]_{500}$ +8°, $[\alpha]_{400}$ +6°, $[\alpha]_{370}$ −2°, $[\alpha]_{350}$ −12°, $[\alpha]_{300}$ −72°, $[\alpha]_{285}$ −117°. The mass spectrographic, gas phase chromatographic, and NMR results have already been summarized in the Discussion.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05; methoxyl, 9.74. Found: C, 78.91; H, 10.45; O, 10.35; methoxyl, 9.74.

Saponification of 0.18 g. of this ester XVIIIa was accomplished by heating under reflux for 1.5 hr. with 20 cc. of 3% methanolic potassium hydroxide. The oily acid (0.165 g.) was distilled at 160°/0.03 mm. and did not exhibit an ultraviolet absorption maximum, only a shoulder at 217 mμ, log ε 3.89 being observed, $[\alpha]_D$ +19.5° (*c*, 1.03), $\lambda_{max}^{CHCl_3}$ 5.89, 6.09, 11.20, 11.60 μ. The infrared spectrum was identical with that of copalic acid (VIa).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.99; H, 9.97.

The dehydration of 2.0 g. of the lower melting hydroxy ester XVIIb (m.p. 98–99°) was performed exactly as described for XVIIa and proceeded in identical yield to afford an unsaturated ester (XVIIIb) with the following constants (see Discussion for mass spectrographic and gas phase chromatographic results): $\lambda_{max}^{C_2H_5OH}$ 219 mμ, log ε 4.14, $\lambda_{max}^{CHCl_3}$ 5.83, 6.06, 11.20, 11.56 μ,[31] $[\alpha]_D$ +48.1° (*c*, 1.18), the plain optical rotatory dispersion curve (*c*, 0.426 in methanol), remaining positive as had already been noted with its precursor XVIIb: $[\alpha]_{589}$ +50°, $[\alpha]_{500}$ +64°, $[\alpha]_{400}$ +119°, $[\alpha]_{370}$ +148°, $[\alpha]_{350}$ +174°, $[\alpha]_{300}$ +277°, $[\alpha]_{285}$ +353°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05; methoxyl, 9.74. Found: C, 79.19; H, 10.44; O, 10.34; methoxyl, 9.68.

Saponification led to the free acid, which after distillation at 160°/0.01 mm. exhibited $[\alpha]_D$ +38.2° (*c*, 1.16), $\lambda_{max}^{CHCl_3}$ 5.88, 6.10, 11.20, 11.50 μ, the infrared spectrum differing in the 8–9 μ region from that of copalic acid (VIa). The ultraviolet absorption spectrum showed an inflection at 217 mμ, log ε 3.95.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.86; H, 10.76; O, 10.72.

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(31) The principal difference between this spectrum and those of its isomer XVIIIa and methyl copalate (VIb) resided in the 8–9 μ region.

[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA SCHOOL OF FORESTRY]

On the Occurrence of α-Thujaplicinol in the Heartwood of *Cupressus pygmaea* (Lemm.) Sarg.

EUGENE ZAVARIN, ARTHUR B. ANDERSON, AND ROSALIND M. SMITH

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A new tropolone, α-thujaplicinol, and nootkatin, have been isolated from the heartwood of *Cupressus pygmaea* (Lemm.) Sarg. On the basis of spectroscopic data and degradative experiments, the structure of the first is deduced to be that of 6-isopropyl-7-hydroxytropolone.

In the course of paper-chromatographic investigation of the tropolonic fractions from heartwood of species mainly of the genera *Cupressus* and *Juniperus*, a number of spots that could not be related to any of the known tropolones appeared on the paper in several instances.[1] The heartwood of *Cupressus pygmaea*, a species growing in Mendocino County, California, seemed particularly rich in these materials. This report deals with the

(1) E. Zavarin, R. M. Smith, and A. B. Anderson, *J. Org. Chem.*, 24, 1318 (1959).

determination of the structure of α-thujaplicinol, a tropolone type compound isolated from the heartwood of *Cupressus pygmaea* and designated previously as T-11.

Steam distillation of the acetone extract of the *Cupressus pygmaea* heartwood sawdust gave a 2% yield[2] of volatile oil, a small part of which crystallized. The crystals were purified to yield 0.004% of nootkatin. The remaining oil was separated by the usual methods to give 8% neutral materials, 14.8% phenols, 69% tropolones, and 8.2% acids. During the separation it was noticed that part of the tropolones formed with dilute sodium hydroxide a salt of very low solubility; paper chromatography indicated that this was composed essentially of pygmaein.[1] The sodium hydroxide soluble part of the tropolonic substances on fractional crystallization of its dicyclohexylamine adduct gave crystals, m.p. 130.0–130.5°, which, when chromatographed, gave a spot corresponding to the T-11 compound. Liberation of the parent substance by means of dilute sulfuric acid and distillation gave a colorless oil, which could not be induced to crystallize.

The isolated material gave positive ferric chloride and copper acetate tests for tropolones. The molecular formula was $C_{10}H_{12}O_3$, as determined by elementary analysis and Rast molecular weight determination (192 ± 20%). It was characterized in addition to the mentioned dicyclohexylamine adduct by the preparation of the benzylamine adduct, m.p. 110–111°, and the copper chelate, m.p. 303.5–304.5°. The latter formed in 1:1 molecular ratio and did not show any hydroxyl bands in infrared[3] indicating that the tropolonic nucleus should carry a second hydroxyl.

The ultraviolet and infrared spectra of the isolated substance (Figs. 1 and 2) as well as of its copper complex were characteristically tropolonic[4] and very similar to those of β-thujaplicinol.[3] Run in various concentrations in carbon tetrachloride, the infrared 3230 cm.$^{-1}$ hydroxyl peak of the obtained material appeared as a singlet and did not change essentially its position or shape. This,[3] as well as the fine structure around 360 mμ in ultraviolet,[5] suggests the *ortho* placement of the second hydroxyl. The NMR spectrum exhibited *inter alia* a doublet at +8.70 and +8.82 p.p.m.[6] (J of 7 c.p.s.[7]) assigned to the isopropyl methyl protons and a multiplet at +6.26 p.p.m. assigned to the isopropyl tertiary hydrogen.

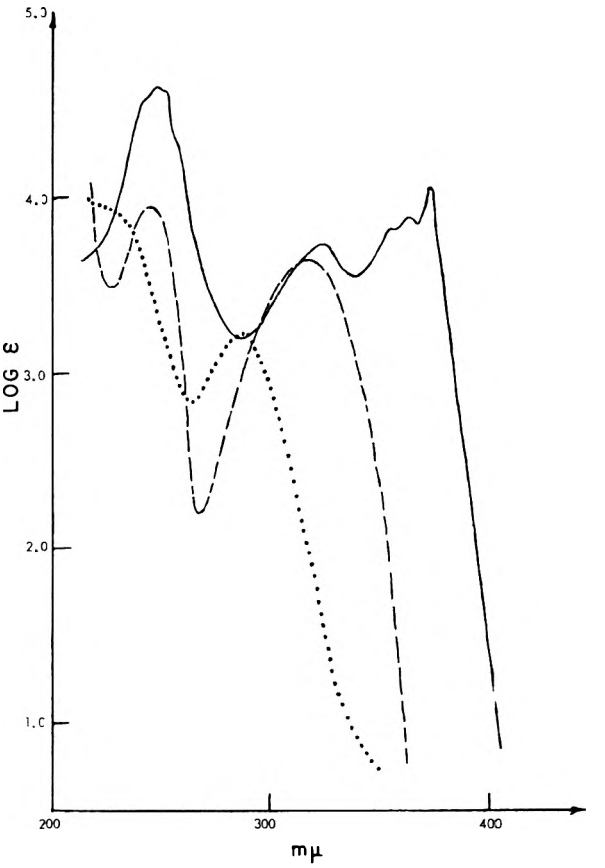


Fig. 1. Ultraviolet absorption spectra of α-thujaplicinol (——), 2-methoxy-3-isopropylbenzoic acid (.....), and 3-isopropylsalicylic acid (------)

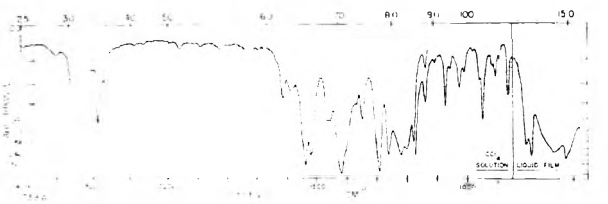


Fig. 2. Infrared spectrum of α-thujaplicinol

The determination of the isopropyl nature of the side chain by NMR methods, and the suggestion from infrared and ultraviolet data, that the additional hydroxyl is *ortho* positioned, reduce the number of the possible structural isomers to two, one of which corresponds to β-thujaplicinol. The isolated substance accordingly should possess the structure of 6-isopropyl-7-hydroxytropolone or of α-thujaplicinol (I), if named in conformity to the β-isomer.[8]

Treatment of the isolated compound with an excess of diazomethane in ethyl ether, followed by refluxing of the resulting methyl ethers with methanolic sodium methoxide, gave an aromatic acid, $C_{11}H_{14}O_3$, m.p. 66–67° (II), containing one methoxyl. Cleavage of the methoxyl with hydriodic/acetic acid mixture produced a corresponding

(2) All yields referring to wood substance are calculated on dry wood basis.

(3) J. A. F. Gardner, G. M. Barton, and H. McLean, *Can. J. Chem.*, **35**, 1039 (1957).

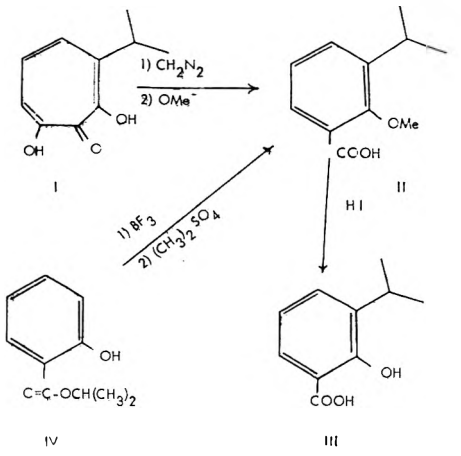
(4) P. L. Pauson, *Chem. Revs.*, **55**, 19 (1955).

(5) T. Nozoe, S. Seto, S. Ito, M. Sato, and T. Katono, *Sci. Rep. Tôhoku Univ., Ser. 1*, **37**, 191 (1953).

(6) The chemical shifts in parts per million were calculated in relation to tetramethylsilane peak as +10.

(7) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 53.

(8) J. A. F. Gardner and G. M. Barton, *Can. J. Chem.*, **36**, 1612 (1958).



hydroxy acid, $C_{10}H_{12}O_3$, m.p. 68–69°, (III). Contrary to II, III gave a violet color with aqueous ferric chloride, in the ultraviolet the benzenoid B-band moved from 287 to 317 mμ,[9] and in the infrared the carboxylic carbonyl peak shifted from 1695 to 1632 cm.$^{-1}$, [10] indicating a salicylic acid structure. The identity of the acid (III) was finally established by comparison with the 3-isopropylsalicylic acid synthesized by rearrangement of isopropyl salicylate (IV) with boron trifluoride.[11,12] This seems to determine unequivocally the structure of tropolone (I) as well as of its rearrangement product.

As far as is known, α-thujaplicinol has neither been isolated from any natural source nor synthetically prepared. It has been postulated as an intermediary product in alkaline peroxide oxidation of α- and β-thujaplicins.[13] Attempts to prepare it through diazotization of 3-amino-4-isopropyltropolone gave only 6-isopropylsalicylic acid.[14] Persulfate oxidation of α-thujaplicin resulted in formation of only 5-hydroxy-α-thujaplicin.[15] It has been chromatographically identified in *Cupressus pygmaea*, *abramsiana*, and *goveniana*.[1] Investigation is planned for its possible fungistatic activity toward wood destroying fungi.

(9) According to P. Grammaticakis, [*Bull. soc. chim. France*, 821 (1953)], methylation of phenolic hydroxyl of salicylic acid causes hypsochromic shift of both benzenoid and K-ultraviolet absorption bands.

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., London, 1954, 145.

(11) All isopropylsalicylic acids are known; (a) 3-isopropylsalicylic acid, m.p. 71–72°, M. Fileti, *Gazz. chim. ital.*, **16**, 113 (1886); (b) 4-isopropylsalicylic acid, m.p. 95–96° and 6-isopropylsalicylic acid, m.p. 122–123°, T. Nozoe, Y. Kitahara, and K. Doi, *J. Am. Chem. Soc.*, **73**, 1895 (1951); (c) 5-isopropylsalicylic acid, m.p. 116°, H. Meyer and K. Bernhauer, *Monatsh.*, **53** and **54**, 721 (1929).

(12) W. J. Croxall, F. J. Sowa, and J. A. Nieuland, *J. Am. Chem. Soc.*, **56**, 2054 (1934).

(13) T. Nozoe, *Festschr. Arthur Stoll*, Birkhauser, A. G. Basel, 1957, p. 765.

(14) T. Nozoe, Y. Kitahara, and K. Doi, *Proc. Japan Acad.*, **27**, 282 (1951).

(15) T. Nozoe, S. Seto, S. Ito, M. Sato, and T. Katono, *Proc. Japan Acad.*, **28**, 488 (1952).

EXPERIMENTAL[16]

Preparation of volatile oil. The sample of *Cupressus pygmaea* wood was collected in the Pygmy Forest, east of Fort Bragg, California. A 3022-g. heartwood sawdust portion, containing about 10% moisture, was extracted with acetone and the extract steam distilled using 39 l. of water. The oil contained in the final 16 l. of distillate solidified upon standing. It was filtered and recrystallized three times from 10 ml. of iso-octane to give 115 mg. of material, m.p. 95–96° (0.004% yield), found to be identical with nootkatin according to the mixed melting point and infrared techniques, using the compounds themselves and their copper chelates.

The remaining steam distillate was repeatedly extracted with a total of 7 l. of chloroform under addition of an excess of copper acetate during the later stages of extraction. The chloroform extracts were treated with an excess of hydrogen sulfide, evaporated to about 300 ml., filtered and evaporated to dryness to give 54.8 g. of an oil (1.97% yield).

Segregation of the volatile oil. The total amount of extract was dissolved in 130 ml. of *n*-hexane, treated with 100 ml. of 10% sodium hydroxide and cooled to +5°. The heavy, yellow precipitate of tropolone salts was filtered and washed with water and *n*-hexane to give 21.40 g. of sodium tropolonates. Chromatography indicated that this fraction was composed essentially of pygmaein.

The aqueous phase was separated from the filtrates, and the *n*-hexane solutions were extracted with 100 ml. of 10% sodium hydroxide in two portions. The separated organic layer gave 4.40 g. of neutral materials (8.0% in oil; 0.16% wood basis).

The *p*H of the aqueous extract was adjusted to 8.0 with carbon dioxide, the resulting liquid was extracted with 300 ml. of ethyl ether in four portions, and the extracts were washed with 300 ml. of water. The aqueous extracts were combined, acidified with an excess of hydrochloric acid, and extracted with 250 ml. of ethyl ether in four portions. The ether extracts gave 4.50 g. of acidic materials (8.2% in oil 0.16% wood basis). The material gave negative cupric acetate test for tropolones.

The ether extracts from the solution of *p*H 8.0 were combined and evaporated to dryness. The residue gave strong cupric acetate test for tropolones. It was dissolved in 400 ml. of *n*-hexane, and shaken with 400 ml. of 85% phosphoric acid in four portions.[17] The organic phase was separated to give 8.15 g. of phenolic oil (14.8% in oil; 0.29% wood basis).

The phosphoric acid solution was diluted with 2.5 l. of water containing 200 ml. of concd. ammonia, and extracted with 450 ml. of chloroform in five portions. The organic extract gave 18.55 g. of tropolonic oil. Thus, the amount of tropolones isolated from the volatile oil, together with pygmaein, isolated before as sodium salt, could be estimated as 37.75 g. (69% in oil; 1.36% wood basis).

Isolation and characterization of α-thujaplicinol. The total amount of tropolonic mixture separated by means of phosphoric acid was dissolved in 75 ml. of *n*-hexane, treated with 20 g. of dicyclohexylamine (1:1.07 molar ratio) and the separated precipitate washed with *n*-hexane to give 28.5 g. of yellow powder. Repeated crystallization of one half of this material from iso-octane/chloroform gave 5.5 g. of crystals, m.p. 129.2–130.7° (10% yield from the oil). Chromatograms showed composition essentially of T-11 tropolone.

(16) All melting points are corrected; microanalysis by Microchemical Laboratory, University of California, Berkeley. Ultraviolet and infrared spectra were run on Beckman DK II and Perkin-Elmer Model 21 recording spectrophotometers, respectively, and NMR spectra on Varian Associates spectrometers.

(17) Y. T. Lin, T. B. Lo, and K. T. Wang, *J. Chinese Chem. Soc.* (Taiwan) **5**, 54 (1958).

From a 1.01-g. portion of this salt, the parent tropolone was regenerated by the procedure already described[18] and evaporatively distilled at 2 mm. pressure to give 448 mg. of a colorless oil (89% yield), n_D^{25} 1.6323, d_4^{22} 1.184.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.81; H, 6.59; mol. wt. (Rast): Calcd.: 180. Found: 192 ±10%.

An analytical sample *of dicyclohexylamine salt* was prepared by crystallization from acetone to give rhomboidal crystals, m.p. 130.0–130.5°.

Anal. Calcd. for $C_{22}H_{35}O_3N$: C, 73.09; H, 9.76. Found: C, 73.01; H, 9.53.

A *benzylamine adduct* was prepared in the usual way,[18] and purified by recrystallization from iso-octane to give fine yellow needles, m.p. 110.2–110.8°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37. Found: C, 71.43; H, 7.35.

The *copper complex* was prepared by the usual procedure, and recrystallized from benzene/iso-octane to give a fine powder, m.p. 303.5–304.5° with previous darkening.

Anal. Calcd. for $C_{10}H_{10}O_3Cu$: C, 49.69; H, 4.17; Cu, 26.29. Found: C, 49.92; H, 4.45; Cu, 25.93.

Spectral characteristics of α-thujaplicinol (*I*). Ultraviolet: λ max 247.5 mμ (log ε 4.63); 324 mμ (log ε 3.73); 356 (log ε 3.82); 364 mμ (log ε 3.88); 372.5 mμ (log ε 4.05)—(iso-octane).

Infrared: 3230m, 2950m, 2860w, 1615w, 1585w, 1538s, 1520s, 1455–1470m, 1420s, 1350m, 1292s, 1262s, 1220s, 1200s, 1180s, 1140w, 1110w, 1075w, 1060w, 1027w, 1010w, 938w, 962, 950, 920, 910, 895, 866 (all weak)—carbon tetrachloride; 805m, 790m, 710m, 675m—(liquid film).

The influence of concentration on the hydroxyl singlet was determined by running the infrared spectra of the compound as liquid film (6.57*M*), and as 0.524, 0.262, and 0.040*M* carbontetrachloride solutions. The position of the hydroxyl peak shifted from 3260 to 3200 cm.$^{-1}$ when going toward more concentrated solutions. The shape of the peak remained the same; the ratio of the intensity of the hydroxyl peak to that of the strongest carbon-hydrogen stretching peak changed from 0.835 to 1.21, 1.35, and 2.20 going toward the more concentrated solutions.

NMR: (25% in carbon tetrachloride; 60 mc; tetramethylsilane as internal standard).[6] A singlet at +0.73 p.p.m. due to the two hydroxyls, an asymmetric multiplet with a main peak at +2.88 p.p.m. due to aromatic protons, a symmetric multiplet corresponding to isopropyl heptuplet with five peaks discernable and with a middle peak at +6.26 p.p.m. (J = 7.0), and the isopropyl doublet at +8.70 and +8.82 p.p.m. (J = 7.0) were observed; intensities of the above groups of peaks were roughly in the expected order of 2:3:1:6.

Special characteristics of α-thujaplicinol copper complex. Ultraviolet: λ_{max} 660 mμ (log ε 1.59); 397 mμ (log ε 3.62); 327 mμ (log ε 3.78); 270 mμ (log ε 4.42)—(ethanol).

Infrared: No OH stretching bands–carbon tetrachloride; carbonyl at 1615 cm.$^{-1}$—potassium bromide.

Ultraviolet of β-thujaplicinol copper complex: λ_{max} 670 mμ (log ε 1.50); 398 mμ (log ε 3.67); 326 (log ε 3.96); 266 mμ (log ε 4.38); 228 mμ (log ε 3.70)–(ethanol).

Rearrangement of the methylated α-thujaplicinol. The free α-thujaplicinol was obtained from 513 mg. of its dicyclohexylamine complex, m.p. 129.0–130.5°, and methylated with diazomethane using the known procedures. The resulting mixture was refluxed for 45 min. with a solution of 0.5 g. of sodium in 10 ml. of absolute methanol, acidified with dilute hydrochloric acid, treated with an excess of ammoniacal copper acetate solution and the separated copper tropolonates filtered off. The acidified filtrate was extracted with chloroform and the extract dried, filtered, and evaporated to dryness. The residue was dissolved in 5 ml. of iso-octane, filtered from small amount of impurities, and treated with 0.25 g. of dicyclohexylamine. The resulting precipitate was filtered and recrystallized from iso-octane to give 20 mg. of material, m.p. 153–154° (4% yield).

When the same experiment was conducted using pygmaein, a monomethyl ether of α-thujaplicinol,[19] in the diazomethane methylation, a 31% yield of the above material was obtained.

An analytical sample of this salt was prepared by recrystallization from iso-octane/benzene to give clusters of small platelets, m.p. 155.5–156.5°.

Anal. Calcd. for $C_{23}H_{37}O_3N$: C, 73.56; H, 9.93. Found: C, 73.76; H, 10.00.

The parent acid was regenerated from 185 mg. of the dicyclohexylamine salt, m.p. 154.5–156.0°, with dilute sulfuric acid and evaporatively distilled at 2 mm. pressure to give 73.5 mg. of distillate which solidified to crystals, m.p. 65.8–66.8° (77% yield).

An analytical sample was prepared by recrystallization from *n*-hexane, to give small crystals, m.p. 67.5–68.5°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; OCH_3, 15.98. Found: C, 67.94; H, 6.91; OCH_3, 15.75.

Ultraviolet: λ_{max} 287 mμ (log ε 3.23)—(iso-octane). Infrared: Carboxylic carbonyl at 1695 cm.$^{-1}$–potassium bromide.

Preparation of 3-isopropylsalicylic acid (III). A 408-mg. portion of the acid (II), m.p. 65–67°, was refluxed for 2 hr. with a mixture of 8 ml. of 47% hydriodic acid and enough acetic acid to form a homogeneous solution and then diluted with water. The precipitate was filtered to give 328 mg., m.p. 65–67°; crystallization from *n*-hexane gave rhomboidal plates, m.p. 69–70°. The material was found to be identical with the synthetic compound by mixed melting point and infrared techniques.

Ultraviolet: λ_{max} 317 mμ (log ε 3.64); 245 mμ (log ε 3.95)–(isooctane). Infrared: Carboxylic carbonyl at 1632 cm.$^{-1}$–(potassium bromide).

Synthesis of 2-methoxy-3-isopropylbenzoic acid. The rearrangement was conducted using 21 g. of commercial isopropyl salicylate[20] according to the procedure of Croxall, *et al.*[12] The mixture of rearrangement products obtained was methylated four times using 80-ml. portions of 80% sodium hydroxide and 25-g. portions of dimethyl sulfate. The resulting liquid was made basic with an excess of sodium hydroxide, heated until clear, acidified with hydrochloric acid and extracted with *n*-hexane. The extract obtained was treated with 15.5 g. of dicyclohexylamine, the resulting precipitate filtered and recrystallized from *n*-hexane/benzene to give 3.7 g. of material, m.p. 155–156° (8.5% yield).

This salt as well as the free acid regenerated from it, m.p. 68–69°, were found to be identical by mixed melting point and infrared techniques with the corresponding dicyclohexylamine salt and the free acid obtained by rearrangement of the α-thujaplicinol methyl ethers.

Acknowledgments. The authors are indebted to Mr. William Dost of the California Redwood Association for the *Cupressus pygmaea* wood, to Mr. Alvin J. Berlin for NMR spectra and to Mr. G. M. Barton for a sample of β-thujaplicinol.

RICHMOND, CALIF.

(18) E. Zavarin, R. M. Smith, and A. B. Anderson, *J. Org. Chem.*, 24, 1534 (1959).

(19) To be published.

(20) Eastman Kodak, b.p. 120–122°/18 mm.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF CARLO ERBA S.p.A.]

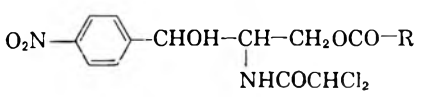
Monoesters of Chloramphenicol, Esterified on the Secondary Hydroxyl Group in the Presence of Trifluoroacetic Anhydride and Methanesulfonic Anhydride

LUIGI ALMIRANTE AND GIAMPAOLO TOSOLINI

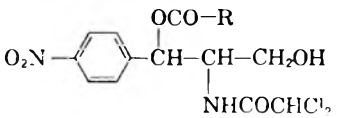
Received May 9, 1960

Chloramphenicol esters, esterified on the secondary hydroxyl group, have been prepared by condensing chloramphenicol with weak organic acids in the presence of trifluoroacetic and methanesulfonic anhydrides. The mechanism of the reaction and the infrared spectra of the compounds obtained are discussed.

During the last ten years, chloramphenicol esters have been greatly used in medicine for the parenteral administration[1] of the antibiotic and for obtaining tasteless derivatives[2] mainly for pediatric use. Chloramphenicol monoesters, synthesized for the above purposes, are esters on the primary hydroxyl group; their general formula is as follows:

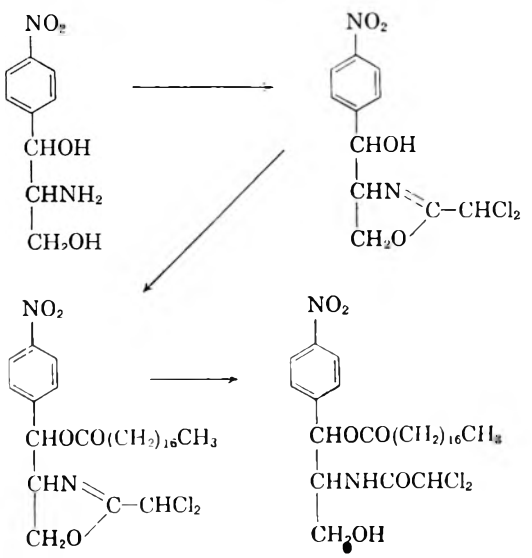


In order to study the difference in behavior between chloramphenicol esters on the primary hydroxyl group and the corresponding esters on the secondary hydroxyl group of general formula



with regard to the enzymatic hydrolysis, we considered the possibilities of synthesis of the latter class of compounds.

In a previous article, one of us[3] had already reported obtaining the stearic ester of chloramphenicol on the secondary hydroxyl group according to the following scheme of reaction:



However, the total yield was low. Later, Edgerton, *et al.*[4] prepared D(−)threo-2-dichloroacetamido-1-(*p* - nitrophenyl) - 1 - palmitoyl - 1,3 - propanediol through N → O[1] migration of the palmitoyl group of the corresponding 2-palmitoylamidopropanediol and successive dichloroacetylation at the nitrogen. However, the total yield was only 2–3%. Continuing the studies in this field we followed the possibilities of direct esterification; in particular, our attention was drawn to the use of trifluoroacetic anhydride as a condensing agent. As is known,[5] an alcohol reacts with an acid, in the presence of trifluoroacetic anhydride, according to the following scheme:

$$R{-}OH + R'{-}COOH + (CF_3CO)_2O \longrightarrow R'{-}COOR + 2CF_3{-}COOH$$

This is therefore a method of esterification under very mild conditions which is of great interest, particularly in carbohydrate chemistry.

Specifically on studying the applications of this reaction to polyvalent alcohols, our attention was drawn to a work by Schmidt and Staab[6] regarding the synthesis of 3,5-diphenoylglucose in which is described the intermolecular closure of the diphenic 3-monoester of 1,2-acetoneglucofuranose to 1,2-acetone-3,5-diphenoylglucofuranose, occurring in benzol, in the presence of trifluoroacetic anhydride. Closure involved a secondary and not a primary hydroxyl group. The investigators attribute this particular reaction to trifluoroacetylation in position 6, subsequent esterification in position 5, and splitting of the trifluoroacetic radical by treating the reaction mixture with alkali.

In the case of chloramphenicol, where the primary hydroxyl group is much more active than the

(1) G. Ceriotti, A. Defranceschi, I. de Carneri, and V. Zamboni, *Farmaco, Ed. sci.*, **9**, 21 (1954).

(2) G. Pauletta, *Farmaco, Ed. sci.*, **7**, 3 (1952); A. J. Glazko, W. H. Edgerton, W. A. Dill, and W. R. Lenz, *Antibiotics and Chemotherapy*, **2**, 234 (1952).

(3) L. Almirante and L. Caprio, Ist. "Carlo Erba," Ricerche terap., Raccolta pubbl. chim. biol. e med., **2**, 1-9 (1956); *Chem. Abstr.*, **53**, 12278d (1959).

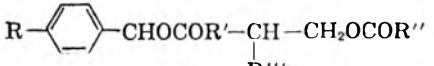
(4) W. H. Edgerton, V. H. Maddox, and J. Contreulis, *J. Am. Chem. Soc.*, **77**, 27 (1955).

(5) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).

(6) O. T. Schmidt and W. Staab, *Chem. Ber.*, **87**, 388 (1954).

TABLE I

1-PHENYLACYLPROPANDIOLS (1,3)

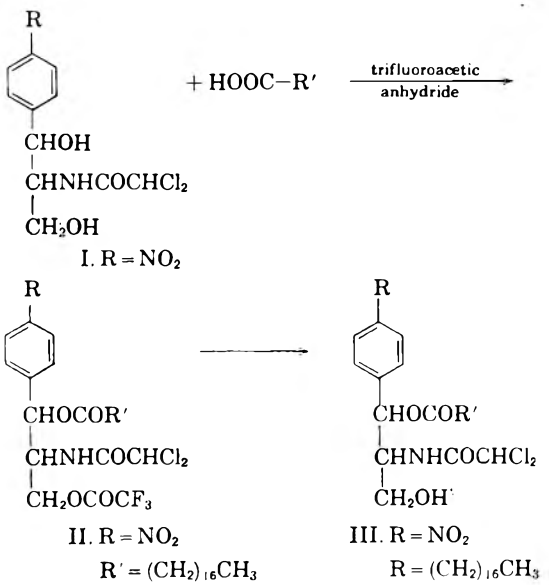


No.	R	R′	R″	R‴	M.P.	Recr. Solv.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
I	NO_2	H	H	$NHCOCHCl_2$	[a]								
II	NO_2	$(CH_2)_{16}CH_3$	CF_3	$NHCOCHCl_2$	[b]		$C_{31}H_{46}Cl_2F_3N_2O_7$						
III	NO_2	$(CH_2)_{16}CH_3$	H	$NHCOCHCl_2$	103–104	Trichloroethylene	$C_{29}H_{46}Cl_2N_2O_6$	59.08	58.93	7.86	7.77	12.03	11.98
IV	NO_2	H	$(CH_2)_{16}CH_3$	$NHCOCHCl_2$	91–92[c]	Trichloroethylene	$C_{29}H_{46}Cl_2N_2O_6$						
V	NO_2	C_6H_5	H	$NHCOCHCl_2$	154–155	Ethanol, dil.	$C_{18}H_{16}Cl_2N_2O_6$	50.60	50.30	3.77	3.83	16.60	16.48
VI	NO_2	H	C_6H_5	$NHCOCHCl_2$	196–197[c]	Ethanol	$C_{18}H_{16}Cl_2N_2O_6$						
VII	NO_2	CH_3	H	$NHCOCHCl_2$	134–135	Isopropyl alcohol	$C_{13}H_{14}Cl_2N_2O_6$	42.76	42.92	3.86	3.74	19.42	19.31
VIII	NO_2	H	CH_3	$NHCOCHCl_2$	82–84[c]	Ethanol	$C_{13}H_{14}Cl_2N_2O_6$						
IX	NO_2	CF_3	CF_3	$NHCOCHCl_2$	140–141	Ethanol	$C_{15}H_{10}Cl_2F_6N_2O_7$	34.97	34.80	1.95	2.14	13.77	13.28
X	NO_2	CF_3	H	$NHCOCHCl_2$	120–121	Benzene	$C_{13}H_{11}Cl_2F_3N_2O_6$	37.25	37.18	2.64	2.80	16.92	17.01
XI	H	H	H	$NHCOCHCl_2$	100–101	1,2-dichlorooctane	$C_{11}H_{13}Cl_2NO_3$	47.50	47.70	4.71	4.74	25.49	25.41
XII	H	C_6H_5	H	$NHCOCHCl_2$	141–142	Ethanol	$C_{18}H_{17}Cl_2NO_4$	56.56	56.40	4.48	4.21	18.56	18.48
XIII	H	H	C_6H_5	$NHCOCHCl_2$	139–140	Benzene	$C_{18}H_{17}Cl_2NO_4$	56.56	56.32	4.48	4.40	18.56	18.36
XIV	H	H	H	H	[d]								
XV	H	$(CH_2)_{16}CH_3$	$(CH_2)_{16}CH_3$	H	60–61	Ethanol	$C_{34}H_{68}O_4$	78.89	78.75	11.77	11.64		
XVI	H	H	$(CH_2)_{16}CH_3$	H	41–42	Ethanol, dil.	$C_{27}H_{46}O_3$	77.46	78.35	11.07	11.00		
XVII	H	H	C_6H_5	H	150/0.5 mm.		$C_{16}H_{16}O_3$	62.36	62.31	5.23	5.20		
XVIII	H	$C_6H_3(NO_2)_2$	$C_6H_3(NO_2)_2$	H	96–97	Ethanol	$C_{24}H_{16}N_4O_{12}$	51.11	51.30	2.98	3.00		

[a] M. C. Rebstock, H. M. Crooks, J. Controulis, and G. R. Bartz, *J. Am. Chem. Soc.*, **71**, 2458 (1949). [b] Not crystallized. Calcd.: F, 8.31. Found: F, 7.98. [c] Ref. 2. [d] M. G. J. Beets, *Rec. Trav. Chim.*, **70**, 24 (1951).

secondary one, there was a good probability of obtaining esters at the secondary hydroxyl group using trifluoroacetic anhydride as a condensing agent. In fact, the reaction between one mole of stearic acid, one mole of chloramphenicol and an excess of trifluoroacetic anhydride gave an excellent yield of a product identical with that already obtained by one of us[3] by the above-mentioned way. The identity was determined by mixed-melting point and by infrared spectrum.

Using infrared spectra we were able to demonstrate the mechanism of reaction. After allowing one mole of stearic acid to react with one mole of chloramphenicol (I) in an excess of trifluoroacetic anhydride, we evaporated the mixture to dryness, removing traces of stearic acid with petroleum ether. The crude solid obtained was examined by elementary fluorine analysis and infrared spectrum. The product is 1-*p*-nitrophenyl-1-stearoyl-3-trifluoroacetyl-1,3-propanediol (II). On suspending this ester in water made acid with hydrochloric acid over night, the trifluoroacetic acid radical is split and the stearic ester of chloramphenicol on the secondary hydroxyl group is obtained (III):



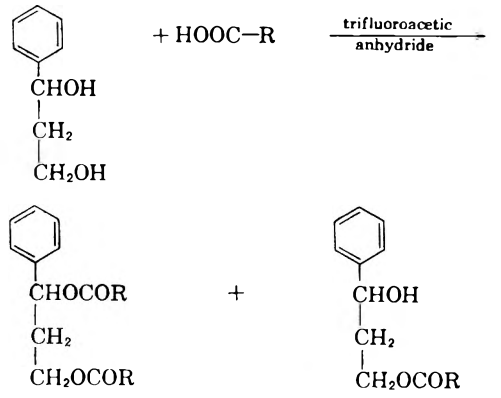
The same method was used to synthesize the benzoic ester (V) and the acetic ester (VII) of the secondary hydroxyl group. 1-Phenyl-2-dichloroacetamido-1,3-propanediol (XI) reacting with benzoic acid in the presence of trifluoroacetic anhydride has also given 1-phenyl-1-benzoyl-2-dichloroacetamido-1,3-propanediol (XII).

The melting point and the infrared spectra of these compounds differ from the corresponding esters at the primary hydroxyl group. The stearic ester (IV), benzoic esters (VI and XIII), and the acetic ester (VIII) were prepared from one mole of the corresponding dichloroacetamido-propanediols and one mole of the acid chloride in anhydrous pyridine.[2]

The infrared spectra of 1-acyl derivatives showed the presence of bands due to C—O stretching vibration of the free primary hydroxyl group. In compound (III) the band was at 1066 cm.$^{-1}$ in (V) at 1072 cm.^{1}, in (VII) at 1070 cm.$^{-1}$, in (X) at 1071 cm.$^{-1}$ and in (XII) at 1063 cm.$^{-1}$

In the case of the benzoic esters (V) and (XII) the band was split for an absorption due to C—H in plane deformation vibration of the monosubstituted benzene ring[7]). The ditrifluoroacetyl ester (IX) does not show bands in the 1020–1100 cm.$^{-1}$ zone; but it does a very intense band at 1792 cm.$^{-1}$, thus confirming its structure. The attempt to esterify chloramphenicol with strong acids such as formic, monochloroacetic, or dichloroacetic acids, using trifluoroacetic anhydride as condensing agent, did not succeed as was to be expected.[5] In these cases, apart from chloramphenicol ditrifluoroacetate (IX), we also isolated a monotrifluoroacetic ester (X) to which, by the aid of the infrared spectrum, we attribute a structure similar to the above-mentioned esters of the secondary hydroxyl group.

1-Phenyl-1,3-propanediol (XIV) with stearic acid and trifluoroacetic anhydride formed almost equal quantities of 1-phenyl-1,3-distearoylpropanediol (XV) and 1-phenyl-3-stearoyl-1,3-propanediol (XVI) according to the reaction:



Benzoic acid gave only 1-phenyl-3-benzoyl-1,3-propanediol (XVII) and 3,5-dinitrobenzoic acid only 1-phenyl-1,3-dinitrobenzoyl-propanediol (XVIII), besides other products containing fluorine which we did not purify. In the reaction for obtaining product III with trifluoroacetic anhydride as the condensing agent and as the main product using the methanesulphonic anhydride, we obtained a second compound of identical elementary formula and spectrum (in carbon tetrachloride solution) which melted at 40° but did not crystallize from trichloroethylene. The product, purified from dilute alcohol, is probably amorphous. Thus, also in this case, the stearic ester of chloramphenicol (III) is present in two forms, one crystalline and the other amorphous, as we recently showed with a roentgenographic study for the stearic ester of chloram-

(7) A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, 4155 (1958).

phenicol at the primary hydroxyl group (IV).[8] In the latter case, the biological activity is closely linked to the amorphous form of the ester and to the size of the particles[9]: the crystalline product does not undergo enzyme hydrolysis and therefore does not produce detectable blood levels of chloramphenicol, but is eliminated unaltered in the feces. In contrast, the amorphous product is completely absorbed from the gastrointestinal tract and is therefore therapeutically efficacious. In the case of esters of the secondary hydroxyl group, enzyme hydrolysis occurs only to a minimum extent and there is no appreciable difference between the crystalline and amorphous forms of the stearic ester (III).

EXPERIMENTAL

D(−)-*threo*-1-(*p*-*Nitrophenyl*)-1-*stearoyl*-2-*dichloroacetamido*-1,3-*propanediol* (III). Stearic acid (8.3 g., 0.0294 mole) was suspended in 12 ml. (0.086 mole) of trifluoroacetic anhydride. After 30 min. shaking at 25°, 10 g. (0.031 mole) of D(−)-*threo*-1-(*p*-nitrophenyl)-2-dichloracetamido-1,3-propanediol (CAF; I) was added a little at a time. Complete solution occurred at the end of the addition. The solution was allowed to stand at 25° for 45 min., and then at 50° for 5 min. It was then poured into ice and neutralized with sodium bicarbonate after a few minutes. The mixture was filtered and the crystals so obtained were purified by dissolving in methanol and precipitating with water. Crude product (14.2 g.) was obtained, melting at 80–86°; yield, 82.5%. The product contained 2% of stearic acid and was recrystallized twice from trichloroethylene. Pure product, 6 g., was obtained, melting at 103–104°. On evaporation of the trichlorethylene and trituration with petroleum ether (b.p. 60–70°) 7 g. of a product melting at 40–42° was obtained.

Anal. Calcd. for $C_{29}H_{46}Cl_2N_2O_6$: C, 59.08; H, 7.86; Cl, 12.03. Found: C, 60.12; H, 8.01; Cl, 11.57.

The infrared spectrum confirmed the chloramphenicol monostearic ester structure at the secondary hydroxyl group. The product (III) was therefore in two forms, one crystalline and the other probably amorphous. However, unlike what occurred in the case of D(−)-*threo*-1-(*p*-nitrophenyl)-3-stearoyl-2-dichloroacetamido-1,3-propanediol, the two forms have not been transformed into each other by crystallization.

Using *methanesulfonic anhydride* as the condensing agent, the reaction proceeded in the same way, always giving the ester (III); but the total yield of the product was lower and the form melting at 40° was almost exclusively obtained.

In the same way, using trifluoroacetic anhydride as condensing agent, D(−)-*threo*-1-(*p*-nitrophenyl)-1-benzoyl-2-dichloroacetamido-1,3-propanediol (V) and D(−)-*threo*-1-(*p*-nitrophenyl)-1-acetyl-2-dichloroacetamido-1,3-propanediol (VIII) and DL-*threo*-1-phenyl-1-benzoyl-2-dichloroacetamido-1,3-propanediol (XII) were obtained. The later was produced starting from DL-*threo*-1-phenyl-2-dichloroacetamido-1,3-propanediol (XI), already mentioned in literature,[10] with a melting point of 95–97° after crystallization from water.

1-Phenyl-1,3-distearoyl-1,3-propanediol (XV) *and 1-phenyl-3-stearoyl-1,3-propanediol* (XVI). Stearic acid (9.4 g., 0.033 mole) was added to 10 ml. (0.071 mole) of trifluoroacetic anhydride and the whole shaken for an hour, heating gently until complete solution was obtained. The mass solidified immediately afterwards. 1-Phenyl-1,3-propanediol (XIV) (5 g., 0.033 mole) was added, cooling with ice. On bringing to room temperature, an exothermic reaction occurred and the whole mass went into solution. After 45 min. the liquid was poured on ice and neutralized with sodium bicarbonate. It was filtered after being allowed to stand for 2 days, and the solid crystallized from 95% ethanol. The product (XV) melting at 60–61° was obtained. Evaporation of the ethanol gave a waxy product which was crystallized from a mixture of ethanol and water and filtered after cooling. This product (XVI) was dried in a dessicator and melted at 41–42°. It did not depress the melting point of a sample of 3-stearoyl ester obtained from 1-phenyl-1,3-propanediol with stoichiometric quantities of stearoyl chloride in pyridine. The infrared spectrum was also identical.

1-Phenyl-3-benzoyl-1,3-propanediol (XVII) and *1-phenyl-1,3-(3,5-dinitro)benzoyl-1,3-propanediol* (XVIII) were prepared in the same way.

Acknowledgment. The authors acknowledge the technical assistance of S. Colombo and G. Salvadori and wish to thank Dr. E. Pella for microanalyses.

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(8) L. Almirante, I. de Carneri, and G. Coppi, *Farmaco, Ed. pract.*, 15, 671 (1960).

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Alkaloids of the Amaryllidaceae. XIX. On the Structures of Crinamidine, Flexinine, and Nerbowdine[1]

H. M. FALES AND W. C. WILDMAN

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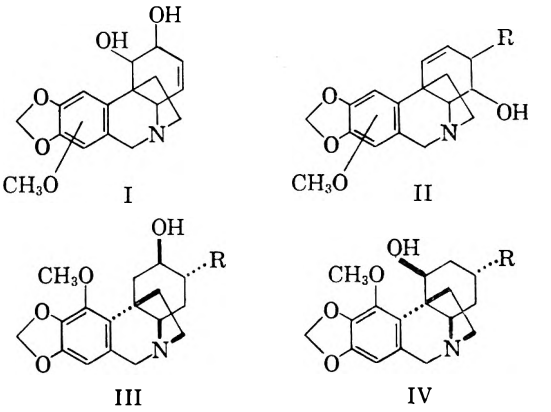
From degradative evidence and partial syntheses, crinamidine and flexinine have been assigned structures Va and Va (no OCH_3), respectively. A key intermediate (XVIa) in the proof of these structures has been identified as the naturally occurring alkaloid nerbowdine.

Crinamidine, a relatively rare alkaloid of the Amaryllidaceae, occurs in small amounts in *Crinum moorei* Hook. f.,[2,3] *Nerine bowdenii* W. Wats.,[2,4] *N. corusca* Herb.[5] and *N. flexuosa* Herb.[5] It was characterized by the German workers as a tertiary base, $C_{17}H_{19}NO_5$, which contains one methylenedioxy and one methoxyl group but no *N*-methyl function.[3–5] The two remaining oxygen atoms were considered to be present in hydroxyl groups because crinamidine was reported to form both a mono- and a di-*O*-acetyl derivative. As the infrared spectrum of crinamidine is nearly identical with that of powelline, these authors proposed that the alkaloid was a hydroxypowelline. Based on the structure of powelline considered most likely at that time,[6] crinamidine was formulated as I.[5] With the determination of the correct structure of powelline (XIV),[7,8] Boit and Döpke[9] amended the structure of crinamidine to IIa. Additional support for this structure was claimed in the observation that crinamidine gave a positive test for vicinal glycol with periodic acid.[9]

In previous papers of this series the structure of undulatine has been elucidated to the complete stereostructure Vb.[8,10] Conformational assignments cited for the substituents of ring C of Vb are valid when this ring is in the half-chair form. As *O*-methylation of crinamidine afforded undulatine,[8] and it has been demonstrated that this methylation takes place with retention of configuration at C_3, we consider Va the only tenable structure for



Series a. R = OH
b. R = OCH_3
c. R = 2-tetrahydropyranyloxy

crinamidine. The additional degradations described below provide complete substantiation for this structure.

In agreement with structure Va, crinamidine was found to contain only one active hydrogen and was not reduced by catalytic methods in neutral solution. It gave no test for a 1,2-glycol with periodic acid[11] in the cold but gave a positive test when the crinamidine, periodic acid, and dilute nitric acid solution were warmed briefly. This behavior is consistent with a hydrolytic cleavage of the epoxide group in the warm, acidic reaction mixture. Acetylation of crinamidine in the presence of acetic anhydride and pyridine at room temperature gave, in our hands, a single, crystalline mono-*O*-acetyl derivative in good yield. The infrared spectrum of the product, either in chloroform solution or as a Nujol mull, showed no hydroxyl absorption from 5000–3000 cm.$^{-1}$ It could be converted to an *O*-acetylcrinamidine hydroperchlorate which proved to be dimorphic. The two melting points of this salt, 157–160° and 200–206°, agree well with those reported by Boit and Ehmke[5] for "diacetylcrinamidine perchlorate" (m.p. 160–161°) and "monoacetylcrinamidine perchlorate" (m.p. 205–206° dec.), respectively. We were not able to obtain any

(1) Previous paper, Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

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(5) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **90**, 369 (1957).

(6) W. C. Wildman, *Chem. & Ind.*, 1090 (1956).

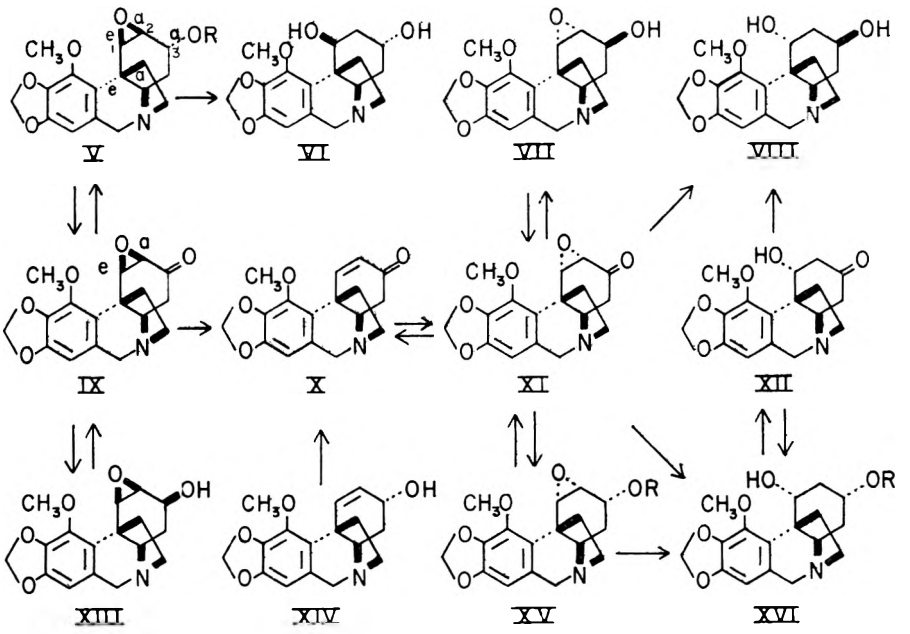
(7) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

(8) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3368 (1960).

(9) H.-G. Boit and H. Döpke, *Chem. Ber.*, **92**, 2582 (1959).

(10) E. W. Warnhoff and W. C. Wildman, *Chem. & Ind.*, 1293 (1958); *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(11) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, p. 115, John Wiley and Sons, Inc., New York (1948).



Series a, R=H; b, R=CH_3; c, R=2 TETRAHYDROPYRANYL

evidence that crinamidine formed an *O,O*-diacetyl derivative under these acetylating conditions, and the nature of the *O,O*-diacetate reported by Boit and Ehmke[5] remains uncertain.

A second degradative sequence supporting structure Va for crinamidine was found in the oxidation of crinamidine with manganese dioxide. It has been our experience that usually one gram of activated manganese dioxide will oxidize completely one millimole of an alkaloid containing the allylic alcohol group within three hours. In contrast, saturated alcohols, *e.g.*, α-dihydroundulatine[10] and nerbowdine,[2] require several days for even partial oxidation. With crinamidine, oxidation was found to proceed as rapidly as it had for powelline. While this observation might be considered to support the Boit and Ehmke structure (IIa), the spectral and analytical data derived from the oxidation product were consistent with structure IX, rather than II (R = O) which would result from the oxidation of IIa. The oxidation product, oxocrinamidine (IX), showed carbonyl absorption at 1724 cm.$^{-1}$ The α,β-unsaturated ketone derived from the oxidation of IIa would be expected to absorb near 1681 cm.$^{-1}$, the frequency found earlier for X. No hydroxyl absorption was found in the 5000–3000 cm.$^{-1}$ range. The ultraviolet absorption spectrum was nearly identical with that of the starting material. At 230 mμ, where intense absorption due to an α,β-unsaturated ketone group would be expected if IIa were the structure of crinamidine, oxocrinamidine, and crinamidine differed in ε values by only 800.[12] These data are incompatible with formulation of oxocrinamidine as II (R = O). Reduction of oxocrinamidine with sodium borohydride gave largely (85%) an epimeric alcohol (XIII), along with a trace of crinamidine. The epimeric nature of the C_3 hydroxyl in XIII was demonstrated by the facile reoxidation of XIII to IX by manganese dioxide. Although the oxidation of cyclopropylcarbinols to ketones by manganese dioxide has been reported,[13,14] the utility of this reagent in the oxidation of α,β-epoxyalcohols has not been appreciated. It would appear that a combination of the steric strain due to the epoxide group and the electronegative nature of the heterocyclic oxygen atom provides activation comparable to that of a double bond.

In the presence of zinc and acetic acid at room temperature, oxocrinamidine was converted to oxopowelline (X). When the reduction was carried out at reflux temperature, dihydroöxopowelline was the predominant product. Presumably reduction occurs first at the C_2—O bond to form a β-hydroxy ketone which is dehydrated to X in the acidic reaction medium. Further reduction of X to dihydroöxopowelline at reflux temperature is feasible, as pure X afforded dihydroöxopowelline under these conditions.[15] The isolation of X from this degradative sequence may be taken as an alternate proof for the (+)-powellane nucleus of the alkaloid and the C_3 location of the hydroxyl group of crinamidine.

(12) 1-Acetoxy-2-lycorinone possesses a similar arrangement of functional groups to II (R = O) and shows $\lambda_{max.}^{C_2H_5OH}$ 235 mμ (ε 15,800) and 290 mμ (ε 5000); the unsaturated carbonyl band is at 1675 cm.$^{-1}$. Y. Nakagawa and S. Uyeo, *J. Chem. Soc.*, 3736 (1959).

(13) R. M. Evans, *Quart. Revs.*, **13**, 61 (1959).

(14) G. Ohloff, H. Farnow, W. Philip, and G. Schade, *Ann.*, 625, 206 (1959).

With oxocrinamidine established as IX, it seemed possible that some oxocrinamidine might be formed when oxopowelline (X) was treated with hydrogen peroxide and alkali. The reaction product proved to be a single, crystalline epoxide. Analytical data showed that one atom of oxygen had been introduced, and the infrared and ultraviolet spectra were in agreement with the change of an α,β-unsaturated ketone to an α,β-epoxycyclohexanone. However, the product was not identical with oxocrinamidine as shown by differences in melting point, optical rotation, and infrared spectrum. Like oxocrinamidine, this product was converted to oxopowelline with zinc and acetic acid. Because it can differ from oxocrinamidine only in the configuration of the epoxide group, this epoxy ketone is assigned structure XI. The stereochemistry of the epoxy group of epoxyoxopowelline (XI) is in accord with an initial axial attack of HOO^- at C_1 of X on that side of ring C which is unhindered by the 5,10b-ethano bridge.

It has been reported that lithium aluminum hydride reduces undulatine (Vb) to a mixture of IIIb and IVb.[16] In a comparable manner, the free hydroxyl of cinamidine was protected by conversion to a mixture of diastereomeric 2-tetrahydropyranyl ethers (Vc). Subsequent reduction of the mixture with lithium aluminum hydride afforded two alcohols (IIIc). These alcohols differed in the configuration at C_2 of the tetrahydropyranyl protecting group, as both isomers gave the same diol (IIIa) upon mild acid hydrolysis. The vicinal nature of the diol was apparent from the consumption of 1.05 equivalents of periodic acid. The relative slowness of the reaction ($t_{1/2}$ = 86 min.) may be indicative of the *trans* arrangement of the hydroxyl groups, but the failure to obtain a *cis* isomer from analogous reactions with either XIII or XV for comparison makes any conclusion based on this observation of dubious value. It is unlikely that the configuration of the hydroxyl of crinamidine has been altered during the reaction sequence, and it is still *cis* to the phenyl and axial in IIIa and IIIc. The hydroxyl at C_2 would be expected to retain the configuration (axial) present in the epoxide group before reduction. Proof that the hydroxyls at C_2 and C_3 are *trans* diaxial is obtained from the infrared spectra of IIIa and IIIc, neither of which showed any evidence of intramolecular hydrogen bonding.[16]

Crinamidine, possessing an unprotected hydroxyl at C_3, behaved in a different manner when reduced with lithium aluminum hydride. The product, dihydrocrinamidine (VI), was a nonvicinal diol as determined by periodate titration. It formed an amorphous *O,O'*-diacetyl derivative which was stable to distillation at 130° (1 μ). The infrared spectrum of VI in the 5000–3000 cm.$^{-1}$ range showed only one stretching frequency at 3625 cm.$^{-1}$, characteristic of an unbonded hydroxyl group. The positions and stereochemistry of the hydroxyl groups of VI are in accord with the supporting data cited above and are derived from the precursor (Va) by attack of hydride ion at C_2. Analogous reductions have been cited in the steroid series.[17] No reduction occurred when either epicrinamidine (XIII), epicrinamidine perchlorate, or the 3-(2-tetrahydropyranyl) ether of epicrinamidine was treated with lithium aluminum hydride under conditions comparable to those which were successful in the reduction of crinamidine.

As might be expected, two diols were formed when XI was reduced with lithium aluminum hydride. Neither diol (VIII or XVIa) was vicinal as shown by lack of oxidation by periodic acid. Prolonged stirring of a chloroform solution of XVIa with manganese dioxide resulted in a 50% yield of a hydroxy ketone (XII). The structure of XII was proved through a facile conversion of XII to X by aluminum *t*-butoxide in refluxing toluene. An attempt to prepare the 2,4-dinitrophenylhydrazone of XII resulted in the formation of the 2,4-dinitrophenylhydrazone of X. Barring an unlikely epimerization at C_1 during the reduction of XI, the configuration of the C_1 hydroxyls of XVIa and VIII would be *cis* to the phenyl. When XII was reduced with sodium borohydride, both XVIa and VIII were produced. This conversion demonstrates that XVIa and VIII have the same hydroxyl configuration at C_1 and are epimeric at C_3. Finally, XVIa was established as the *cis* diol because it formed a monomeric *O,O'*-carbonate. The infrared spectrum of the carbonate showed carbonyl absorption at 1748 cm.$^{-1}$, characteristic of the carbonate of a 1,3-glycol.[18] With regard to ring C, the hydroxyls of XVIa should be *cis* to the phenyl if the lithium aluminum hydride reduction of XI proceeds with no inversion of the C_1 oxygen function. If ring C of XVIa is in the chair form, both hydroxyls are axial.

Reduction of XI with the milder reagent sodium borohydride gave two epimeric epoxy alcohols, epoxypowelline (XVa) and epiepoxypowelline (VII). Both could be reoxidized by manganese dioxide to XI, indicating that the compounds were epimeric at C_3. The hydroxyl configurations at C_3 of VII and XVa are assigned from the reduction of each with lithium aluminum hydride; epoxypowel-

(15) This reduction is in contrast to a recent report on the action of zinc and acetic acid on several 4,5-unsaturated 3-oxo steroids, where loss of the oxygen atom and double bond migration were observed. *Cf.* J. McKenna, J. K. Norymberski, and R. D. Stubbs, *J. Chem. Soc.*, 2502 (1959).

(16) A critical analysis of the 3650–3400 cm.$^{-1}$ region of the infrared spectra for oxygenated derivatives of crinane and powellane will be reported in the near future.

(17) Pl. A. Plattner, H. Heuser, and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1885 (1948).

(18) Carbonates of 1,2-glycols show carbonyl absorption near 1817 cm.$^{-1}$; J. L. Holes, J. I. Jones, and W. Kynaston, *J. Chem. Soc.*, 618 (1957).

line (XVa) afforded a 65% yield of XVIa, while VII gave a 77% yield of VIII.

Structure XVIa is significant in another respect. From the bulbs of *Nerine bowdenii* W. Wats. and one unidentified *Brunsvigia* species we have isolated an alkaloid, $C_{17}H_{21}NO_5$, which was named nerbowdine.[2] From deductions provided by the analytical and spectral data, the alkaloid was tentatively considered to be a dihydroxypowellane. A comparison of XVIa prepared from oxopowelline with nerbowdine isolated from *N. bowdenii* showed the two substances to be identical.[19]

Studies on the structure of flexinine were limited in scope because of the scant supply of *Nerine flexuosa*. This alkaloid, $C_{16}H_{17}NO_4$, was isolated first from this source by Boit and Ehmke.[5] It was reported by them to contain one methylenedioxy and one hydroxyl group but no methoxyl. Acetylation of flexinine afforded a monoacetylflexinine, the infrared spectrum of which showed no hydroxyl absorption. A solution of flexinine in dilute hydrochloric acid absorbed no hydrogen in the presence of a platinum catalyst. We have confirmed these observations and found that flexinine was oxidized by manganese dioxide to a ketone, oxoflexinine, which, like oxocrinamidine, showed infrared carbonyl absorption at 1724 cm.$^{-1}$ and no band attributable to a hydroxyl group. The ultraviolet spectrum showed only the normal methylenedioxyphenyl absorption which was present in the parent alkaloid. In the presence of zinc and acetic acid, oxoflexinine was converted to oxocrinine (X, no OCH_3). This conversion establishes the basic ring system, (−)-crinane,[8] of flexinine and locates the hydroxyl group at C_3. To accommodate the molecular formula $C_{16}H_{17}NO_4$, flexinine must contain either a double bond or a sixth ring. As flexinine is stable to catalytic reduction and oxoflexinine is a saturated cyclohexanone containing no free hydroxyl, a 1,2-epoxide is in accord with the experimental facts. Although these data do not provide complete proof of the stereochemistry of the 1,2-epoxide of flexinine, the evidence that flexinine and crinamidine occur together in *N. flexuosa*, possess strikingly similar infrared spectra, and undergo identical reactions indicates a close relationship between them. Also, epoxyoxocrinine (XI, no OCH_3) prepared by the alkaline epoxidation of oxocrinine is isomeric but not identical with oxoflexinine, and the epimeric nature of the epoxide group in the two derivatives thereby is established. By analogy with this relationship in the powelline-crinamidine series, the epoxide group of flexinine is established as *trans* to the phenyl, and flexinine is *ar*-demethoxycrinamidine (Va, no OCH_3).

(19) In a recent paper [A. Goosen and F. L. Warren, *J. Chem. Soc.*, 1097 (1960)] an alkaloid "buphanitine," possessing the same melting point behavior, optical rotation, and empirical formula as nerbowdine, has been reported to be a 1,3-dihydroxy derivative of 5,10b-ethanophenanthridine in which the B:C ring fusion is *cis* rather than *trans* as in XVIa. As nerbowdine can be synthesized from oxopowelline and degraded *via* XII to oxopowelline, it is impossible for XVIa to have a B:C ring fusion other than that of oxopowelline. Overwhelming evidence from our laboratory that oxopowelline (as well as powelline and crinine) has a B:C *trans* ring fusion has been cited in earlier papers.[8,10,20-24] The same degradations, reasoning and conclusions as those presented in these papers have been published in recent articles by Warren and his associates.[25,26]

(20) P. F. Highet and W. C. Wildman, *J. Org. Chem.*, **25**, 287 (1960).

(21) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960).

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EXPERIMENTAL[27]

Isolation. Isolations of crinamidine from the seeds of *Crinum moorei* J. D. Hook. and the bulbs of *Nerine bowdenii* W. Wats. have been reported previously.[2] Flexinine, ambelline, crinamidine, lycorine, and undulatine were obtained from *Nerine flexuosa* Herb. The same major alkaloids were reported from this source by Boit and Ehmke.[5]

Flexinine (V, no OCH_3). The alkaloid was recrystallized twice from ethanol to give long prisms, m.p. 230–231°, and finally sublimed in vacuum for analysis, m.p. 232–234°, $[\alpha]_{589}^{25}$ −12.7°, $[\alpha]_{436}^{25}$ −38.8° (*c* 0.82); reported[5]: m.p. 221–222°, $[\alpha]_{589}^{25}$ −14° (*c* 0.85); λ_{max} 238 mμ (ε 3900) and 295 mμ (ε 5550).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88; OCH_3, 0.00. Found: C, 66.92; H, 5.93; N, 4.85; OCH_3, 0.00.

Crinamidine (Va). The physical constants of crinamidine have been reported in an earlier paper.[2] In addition, 0.27% active hydrogen was found (calcd. for one hydroxyl, 0.32%).

O-Acetylcrinamidine. A solution of 207 mg. of crinamidine in 5 ml. of anhydrous pyridine was treated with 1 ml. of acetic anhydride and allowed to stand 5 days at 0°. The mixture was poured into water. Sodium bicarbonate was added and the mixture was extracted with chloroform. Evaporation of the chloroform left 255 mg. of oil which was chromatographed over ethyl acetate–washed alumina and eluted with 5% ethyl acetate in benzene. The *O-acetylcrinamidine* was crystallized from ether-cyclohexane, 210 mg. (89%), m.p. 133–136°. One recrystallization from ether raised the m.p. to 137–139°, $[\alpha]_{589}^{23}$ +15°, $[\alpha]_{436}^{23}$ +32° (*c* 1.0). The compound exhibited no absorption from 5000–3000 cm.$^{-1}$ but showed an *O*-acetyl band at 1733 cm.$^{-1}$ and λ_{max} 287 mμ (ε 1600).

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; (1) $OCOCH_3$, 11.98. Found: C, 63.72; H, 6.06; $OCOCH_3$, 12.08.

(27) All melting points were observed on a Kofler microscope hot-stage and are corrected. The boiling points are uncorrected. Unless otherwise noted, rotations were measured in chloroform solution on a Rudolph photoelectric polarimeter, using a 2-dm. tube, and ultraviolet spectra were obtained in absolute ethanol solution on a Cary model 11 MS recording spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer model 21 double-beam spectrophotometer, in chloroform solution unless noted to the contrary. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

A sample was converted to the *perchlorate* with aqueous perchloric acid and recrystallized from water to form small prisms, m.p. 157–160°. Another sample, prepared in the same way, melted at 200–206°. The two polymorphs exhibited identical infrared spectra in chloroform although their spectra in potassium bromide were dissimilar. A mixture of the two forms melted at 200–208°. The compounds exhibited maxima at 3508 cm.$^{-1}$ (N^+—H) and 1739 cm.$^{-1}$ (*O*-acetate) in chloroform.

Anal. Calcd. for $C_{19}H_{21}NO_6.HClO_4$: C, 49.62; H, 4.82; (1) $OCOCH_3$, 9.36. Found, polymorph m.p. 157–160°: C, 49.32; H, 4.99; $OCOCH_3$, 10.11. Found, polymorph m.p. 200–206°: C, 49.47; H, 5.00; $OCOCH_3$, 9.75.

Oxocrinamidine (IX). A solution of 500 mg. of crinamidine in 50 ml. of chloroform was combined with 3.0 g. of activated manganese dioxide and allowed to stir for 6 hr. The oxidant was removed by filtration, and the solvents were evaporated, leaving 500 mg. of crude ketone which was crystallized from ethyl acetate to yield 327 mg. (65%) of prisms, m.p. 202–212°. An additional 85 mg., m.p. 190–195°, was obtained from the filtrates. A sample was recrystallized from ethanol, m.p. 208–211°, and sublimed at 200° (0.1 mm.), m.p. 210–212°, $[\alpha]_{589}^{26}$ −64.8°, $[\alpha]_{436}^{25}$ −141° (*c* 0.88), λ_{max} 287 mμ (ε 1540). The compound lacked absorption from 5000–3000 cm.$^{-1}$ (Nujol) but showed a strong band at 1724 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.86; H, 5.29; N, 4.53.

Sodium borohydride reduction of oxocrinamidine. An ice cold solution of 252 mg. of oxocrinamidine and 500 mg. of boric acid in 25 ml. of methanol was treated with 500 mg. of sodium borohydride. The mixture was allowed to warm to room temperature, acidified with acetic acid, then made basic with sodium hydroxide and extracted with chloroform. On evaporation, the extracts yielded 257 mg. which was chromatographed over Florisil and eluted with 1–10% methanol in chloroform. Early fractions consisted of a 1:1 mixture of crinamidine and epicrinamidine which was separated into its components by preparative-scale paper chromatography on Whatman No. 3 filter paper using a solvent system consisting of *n*-amyl alcohol:water:acetic acid (8:1:1). The section containing crinamidine (R_f 0.51) was separated from that containing epicrinamidine (R_f 0.39), and the crinamidine was eluted with ethanol. The solvent was evaporated; the residue was made basic with alkali and extracted with chloroform. Evaporation left crystals of *crinamidine* which were recrystallized from ethyl acetate and found identical in infrared spectrum (potassium bromide), m.p. (236°) and mixture m.p. with authentic material.

Further elution of the original column provided 215 mg. (85%) of *epicrinamidine hydrate* (XIII), m.p. 114–118°, which was strenuously dried at 100° (0.1 mm.) before analysis, $[\alpha]_{589}^{25}$ −35°, $[\alpha]_{436}^{25}$ −86° (*c* 1.0), λ_{max} 287 mμ (ε 1488).

Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 64.34; H, 6.04; neut. equiv., 317. Found: C, 64.27; H, 6.01; neut. equiv., 316.

Epicrinamidine did not sublime at 140° (10 μ). At higher temperatures, it formed an insoluble glass.

A solution of 68 mg. of epicrinamidine in 5 ml. of chloroform was oxidized with 500 mg. of activated manganese dioxide by the procedure described for the oxidation of crinamidine. Evaporation of the solvent gave amorphous *oxocinamidine* which was crystallized from ethyl acetate, m.p. 208-211° alone or when mixed with authentic material. An infrared spectrum (potassium bromide) confirmed the identity of the product.

O-3,5-Dinitrobenzoylepicrinamidine. The free base (XIII) was mixed with an equal weight of 3,5-dinitrobenzoyl chloride in pyridine. The mixture was allowed to stand overnight at room temperature and then was poured into aqueous sodium bicarbonate and extracted with benzene. Recrystallization from ethanol produced yellow prisms, m.p. 246–249° dec.

Anal. Calcd. for $C_{24}H_{21}N_3O_{10}$: C, 56.36; H, 4.14. Found: C, 56.16; H, 4.10.

Dihydrocrinamidine (VI). A solution of 247 mg. of crinamidine in tetrahydrofuran was refluxed with an excess of lithium aluminum hydride for 3 hr. After decomposition with ethyl acetate and water, the mixture was extracted with chloroform and the chloroform was evaporated. The residue was crystallized from ethanol to yield 177 mg. (72%) of fine prisms, m.p. 255–260°, $[\alpha]_{589}^{24}$ +22.7°, $[\alpha]_{436}^{24}$ +52.6° (*c* 0.5, ethanol), λ_{max} 286 mμ (ε 1479).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39; vic. glycol, 0.00. Found: C, 64.02; H, 6.62; N, 4.34; vic. glycol, 0.00.

O,O'-Diacetyldihydrocrinamidine. Preparation in the usual manner gave an oil which refused to crystallize. A sample was distilled at 130° (1 μ) for analysis, $\lambda_{max}^{C_2H_5OH}$ 287 mμ (ε 1550).

Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; $OCOCH_3$, 21.34. Found: C, 62.53; H, 6.39; $OCOCH_3$, 21.09.

2-Tetrahydropyranyloxycrinamidine (Vc). A solution of 630 mg. of crinamidine in 6 ml. of freshly distilled dihydropyran and 5 ml. of chloroform was cooled to 5° and treated with sufficient hydrogen chloride to render the mixture distinctly acid to congo red paper. The solution stood 4 hr. at room temperature and was poured into dilute sodium hydroxide. The basic and neutral compounds were extracted with chloroform. The oil remaining after evaporation of solvents was chromatographed over alumina. Neutral compounds were removed with 5% ethyl acetate in benzene while 25% ethyl acetate in benzene eluted a basic, amorphous solid which could not be induced to crystallize. This oil possessed no absorption in the hydroxyl region from 3400–3800 cm.$^{-1}$ but exhibited a profusion of intense bands in the 1030–1124 cm.$^{-1}$ region characteristic of cyclic ethers.[28]

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78. Found: C, 65.87; H, 6.82.

α- and β-2-Tetrahydropyranyloxyisodihydrocrinamidine (IIIc). A solution of 850 mg. of Vc in 15 ml. of tetrahydrofuran was refluxed overnight with 2.0 g. of lithium aluminum hydride. The mixture was decomposed with ethyl acetate and sodium hydroxide and extracted with chloroform. Evaporation of the extracts left 792 mg. of an oil which yielded 351 mg. of crystals on trituration in acetone, m.p. 235–250°. Chromatography over alumina or Florisil did not change the melting point, but after many recrystallizations from ethanol and ethyl acetate, a pure sample of the α-isomer was obtained, m.p. 252–254°, $[\alpha]_{589}^{22}$ +11°, $[\alpha]_{436}^{22}$ +28° (*c* 0.62), $\lambda_{max}^{C_2H_5OH}$ 287 mμ (ε 1790). The infrared spectrum (chloroform) of the pure material was nearly identical with that of the initial product, indicating that the initial product contained only traces of a persistent impurity.

Anal. Calcd. for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.25; neut. equiv., 403. Found: C, 65.49; H, 7.34; neut. equiv., 409.

The *β-isomer* was obtained from the filtrates of the α-isomer by recrystallization from ethyl acetate and chromatography over alumina. The yield was 119 mg. (14%), m.p. 225–227°, $[\alpha]_{589}^{24}$ −75.7°, $[\alpha]_{436}^{24}$ −142° (*c* 0.53), $\lambda_{max}^{C_2H_5OH}$ 287 mμ (ε 1820). The infrared spectra (potassium bromide) of the two isomers were different although in chloroform they were identical. The β-compound depressed the melting point of the α-isomer.

Isodihydrocrinamidine (IIIa). A solution of 20 mg. of either isomer of IIIc was warmed briefly with 0.5 ml. of 4*N* hydrochloric acid. The mixture was made basic with sodium hydroxide and extracted with chloroform. The extracts were evaporated, and the residue was crystallized from acetone as fine needles, m.p. 245–247° after recrystallizing as short prisms at 210°, $[\alpha]_{589}^{24}$ −25°, $[\alpha]_{436}^{24}$ −46° (*c* 0.58, C_2H_5OH), $\lambda_{max}^{C_2H_5OH}$ 287 mμ (ε 1690). In excess 0.4% aqueous potassium

(28) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, Inc., New York (1958), p. 119.

periodate (*p*H 6.5) at 25°, the diol exhibited a pseudo first-order rate constant of 1.34×10^{-1} sec.$^{-1}$

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; neut. equiv., 319; glycol, 1.0 mole. Found: C, 63.75, 63.71; H, 6.73, 6.67; neut. equiv., 316; glycol, 1.05 mole.

Conversion of oxocrinamidine to oxopowelline (X). A stirred solution of 200 mg. of oxocrinamidine in 15 ml. of 50% acetic acid was treated with 3 g. of zinc dust in small portions over 30 min. at room temperature; 3 ml. of ethanol was added and stirring continued for 10 min. The solution was filtered, made strongly basic with sodium hydroxide, and extracted with chloroform. Evaporation of the extract left 180 mg. of an oil which was dissolved in ethyl acetate and passed through a small column of alumina to produce 166 mg. of crystalline *oxopowelline*, m.p. 165–166°. This proved to be a lower melting polymorph of oxopowelline since it recrystallized when seeded with authentic oxopowelline[7] (m.p. 179–180°) and remelted at 179–180°. A mixture with authentic oxopowelline showed no depression of m.p., and the infrared spectra (chloroform) of the two materials were identical, $[\alpha]^{24}_{589}$ −273°, $[\alpha]^{24}_{436}$ −727° (*c* 0.5); reported[7]: $[\alpha]^{25}_{589}$ −258°, $[\alpha]^{25}_{436}$ −697°.

A solution of 27 mg. of oxopowelline and 27 mg. of 2,4-dinitrophenylhydrazine was refluxed in 4 ml. of ethanol with the addition of 3 drops of 12*N* hydrochloric acid. After 5 min., water and ammonia were added; the orange precipitate was collected, washed with water, and dried. The *oxopowelline 2,4-dinitrophenylhydrazone* was recrystallized from chloroform-ethanol to form bright red prisms, m.p. 246–247°.

Anal. Calcd. for $C_{23}H_{21}N_5O_7$: C, 57.62; H, 4.42. Found: C, 57.32; H, 4.68.

Epoxyoxopowelline (XI). A solution of 0.5 ml. of 30% hydrogen peroxide was added dropwise to a stirred solution of 540 mg. of oxopowelline and 400 mg. of potassium carbonate in 50 ml. of 80% ethanol at 0°. After 15 min. a small amount of palladium-on-charcoal was added to destroy excess hydrogen peroxide, and the mixture was extracted with chloroform. Evaporation of the solvents left 515 mg. of residue which spontaneously crystallized, m.p. 190–200°. One recrystallization from ethanol produced fine prisms, m.p. 199–200°, $[\alpha]^{23}_{589}$ −147°, $[\alpha]^{23}_{436}$ −382° (*c* 0.4), λ_{max} 287 mμ (ε 1820). The infrared spectrum in chloroform differed from that of oxocrinamidine and showed absorption at 1709 cm.$^{-1}$ (potassium bromide).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; neut. equiv., 315. Found: C, 64.77; H, 5.50; neut. equiv., 310.

Nerbowdine (XVIa) *and/or epinerbowdine* (VIII). (a) *From oxonerbowdine* (XII). A solution of 175 mg. of oxonerbowdine (XII) was treated with an equal weight of sodium borohydride in 10 ml. of methanol at 0°. After standing 10 min. at 0° and 2 min. at reflux temperature, the mixture was acidified with acetic acid and subsequently made basic with ammonia. The solution was extracted with chloroform, and the extracts were evaporated to leave 167 mg. of an oil which was chromatographed on Florisil. Elution with 2–5% methanol in chloroform produced 88 mg (50%) of *nerbowdine* (XVIa), identified by infrared spectrum. Finally, 10–20% methanol in chloroform eluted 54 mg. (31%) of *epinerbowdine* (VIII).

Epinerbowdine recrystallized from wet benzene as an ill-defined hydrate, m.p. 150–165°, $[\alpha]^{23}_{589}$ −77°, $[\alpha]^{23}_{436}$ −166° (*c* 0.74), $\lambda^{C_2H_5OH}_{max}$ 287 mμ (ε 1210). The hygroscopic nature of the product prevented satisfactory analytical results; however, from one strenuously dried sample, a neut. equiv. of 321 (calcd. 319) was obtained.

Epinerbowdine picrate crystallized as fine prisms from water, m.p. 162–169°.

Anal. Calcd. for $C_{23}H_{24}N_4O_{12}$: C, 50.36; H, 4.41. Found: C, 50.15; H, 4.49.

A sample of epinerbowdine, recovered from the picrate by passage over IRA-400 resin in ethanol, showed properties identical with those of recrystallized material. Epinerbowdine (15 mg.) was irreversibly adsorbed from a chloroform solution on 200 mg. of activated manganese dioxide.

(b) *By reduction of epoxyoxopowelline* (XI). A solution of 208 mg. of epoxyoxopowelline in 10 ml. of distilled tetrahydrofuran was refluxed 4 hr. with a large excess of lithium aluminum hydride. After decomposition of excess hydride with ethyl acetate and water, the bases were extracted with chloroform and the extracts dried over sodium sulfate. Evaporation of the chloroform left a residue which was chromatographed on alumina with 0–5% ethanol in chloroform. The first product eluted, 72 mg. (34%), proved to be identical in melting point, mixture melting point and infrared spectrum (potassium bromide) with *nerbowdine* (XVIa). Further elution gave 97 mg. (41%) of epinerbowdine (VIII). This was confirmed by the preparation of *epinerbowdine picrate*, m.p. 162–169° alone or on admixture with authentic material. Infrared spectra (potassium bromide) also confirmed the identity of these picrates.

(c) *From epoxypowelline* (XVa). A solution of 20 mg. of epoxypowelline in 5 ml. of tetrahydrofuran was refluxed overnight with 200 mg. of lithium aluminum hydride. The hydride was decomposed with ethyl acetate, acidified with dilute hydrochloric acid, and extracted with benzene. The acidic layer was made basic with sodium hydroxide, extracted with chloroform, and the extracts dried with sodium sulfate. Evaporation of the solvent left 13 mg. of nerbowdine, m.p. 233–238° alone or on admixture with an authentic sample. Infrared spectra (potassium bromide) confirmed their identity.

Under identical conditions, 100 mg. of epiepoxypowelline hydroperchlorate monohydrate was recovered unchanged.

(d) *From epiepoxypowelline* (VII). A solution of 48 mg. of VII was refluxed with excess lithium aluminum hydride in tetrahydrofuran for 4 hr. and processed as above to yield 37 mg. (77%) of an oil possessing an infrared spectrum identical with that of *epinerbowdine*. A picrate prepared from the oil melted at 162–169° alone or on admixture with authentic *epinerbowdine picrate*.

Nerbowdine O,O′-carbonate. Nerbowdine (200 mg.) was dissolved in 5 ml. of pyridine and cooled to 0°. A large excess of phosgene in benzene was added to the pyridine solution which was allowed to stand overnight at 0°. The mixture was then poured onto ice, neutralized with sodium bicarbonate, and extracted with chloroform. The dried solutions were evaporated, leaving 210 mg. of a partially crystalline residue which was chromatographed over ethyl acetate–deactivated alumina. Elution with 15% ethyl acetate in benzene produced a crystalline carbonate (82 mg., 38%) which was recrystallized from ethyl acetate as small tablets, m.p. 249–250°, $[\alpha]^{25}_{589}$ −146°, $[\alpha]^{25}_{460}$ −263° (*c* 0.66), λ_{max} 287 mμ (ε 1510). A maximum was observed at 1748 cm.$^{-1}$ (chloroform).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 62.60; H, 5.55; mol. wt., 345. Found: C, 62.75; H, 5.46; mol. wt. (Rast), 352.

Oxonerbowdine (XII). A solution of 400 mg. of nerbowdine in 20 ml. of chloroform was allowed to stir for 36 hr. with 4.0 g. of activated manganese dioxide. On filtration and evaporation, 380 mg. of a glass was obtained which exhibited only one band at 1720 cm.$^{-1}$ in the carbonyl region. This was chromatographed over activated, basic alumina with chloroform; 37 mg. of *oxopowelline*, m.p. and mixture m.p. 176–178°, was obtained, presumably by β-elimination of the hydroxyl group during chromatography. Subsequent elution with 2–4% methanol in chloroform produced 199 mg. (50%) of pure *oxonerbowdine*. One recrystallization from ethyl acetate gave fine prisms, m.p. 208–212°, $[\alpha]^{23}_{589}$ −104°, $[\alpha]^{23}_{436}$ −226° (*c* 0.52), λ_{max} 287 mμ (ε 1590).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; neut. equiv., 317. Found: C, 64.31; H, 6.29; neut. equiv., 316.

An attempt to prepare the 2,4-dinitrophenylhydrazone of oxonerbowdine in ethanolic hydrochloric acid gave the *2,4-dinitrophenylhydrazone* of *oxopowelline*, m.p. 246–247°, presumably by acid-catalyzed β-elimination of the hydroxyl group. The derivative was identical in melting point, mix-

ture melting point and infrared spectrum (potassium bromide) with an authentic sample.

Conversion of oxonerbowdine to oxopowelline. A solution of 80 mg. of oxonerbowdine and 80 mg. of aluminum *t*-butoxide in 5 ml. of toluene was refluxed 4 hr. The toluene layer was washed with water and evaporated, leaving 46 mg. of oil which was chromatographed over alumina. Elution with 50% benzene–ethyl acetate produced 20 mg. of crystals, m.p. 176–178° alone or on admixture with authentic *oxopowelline*.

Sodium borohydride reduction of epoxyoxopowelline. A solution of 670 mg. of epoxyoxopowelline (XI) in 30 ml. of methanol at 0° was reduced with 500 mg. of sodium borohydride in the usual manner. The oil was chromatographed twice over ethyl acetate–deactivated alumina. Elution with 2% methanol in ethyl acetate furnished a total of 231 mg. (35%) of crude *epoxypowelline* (XVa) which was crystallized from ethyl acetate to form bladed prisms, m.p. 195–195.5°, $[\alpha]^{23}_{589}$ −30.8°, $[\alpha]^{23}_{436}$ −65.5° (*c* 0.36), λ_{max} 287 mμ (ε 1620).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04. Found: C, 64.48; H, 6.17.

Further elution with 2–3% methanol in ethyl acetate produced a total of 220 mg. (33%) of *epiepoxypowelline* (VII). Rechromatography of this material over Florisil and examination of the infrared spectra (chloroform) of the various fractions suggested that the compound was pure, but it resisted crystallization as did its picrate, perchlorate,[29] and 3,5-dinitrobenzoate. It could not be distilled at 170° (1 μ) and at higher temperatures formed an insoluble glass. The infrared spectrum differed in many respects from that of epoxypowelline, and there was ample evidence for the absence of epoxypowelline in the product. A sample that had been subjected to 100° (1 μ) for one day showed $[\alpha]^{24}_{589}$ −32.5°, $[\alpha]^{24}_{436}$ −64° (*c* 0.6).

When solutions of either epoxypowelline or epiepoxypowelline were allowed to stir for 5 hr. with activated manganese dioxide in chloroform, epoxyoxopowelline was formed in yields of 67% and 76%, respectively. The product was identified by infrared spectrum (potassium bromide) and m.p. 198–199° alone or on admixture with authentic material.

2-Tetrahydropyranyloxyepoxypowelline (XVc). By the same method used in the preparation of 2-tetrahydropyranyloxycrinamidine, 763 mg. of epoxypowelline (XVa) was converted to its 2-tetrahydropyranyl ether, an amorphous solid purified by chromatography on alumina and distilled at 160° (1 μ) for analysis.

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78. Found: C, 65.62; H, 6.88.

3-(2-Tetrahydropyranyloxy)nerbowdine (XVIc). A solution of 981 mg. of XVc was allowed to reflux overnight with 2.0 g. of lithium aluminum hydride in tetrahydrofuran. The mixture was decomposed with sodium hydroxide and extracted with chloroform. On evaporation, the residue was purified by chromatography over basic alumina with benzene–ethyl acetate to yield 705 mg. (72%) of a product which could not be crystallized. A sample was distilled at 130° (<1 μ) for analysis.

(29) A compound previously referred to as *epiepoxypowelline hydroperchlorate monohydrate* [W. C. Wildman in R. H. F. Manske, *The Alkaloids*, Vol. VI, p. 407, Academic Press, New York (1960)], m.p. 153–155°, $[\alpha]^{25}_{589}$ −33°, $[\alpha]^{25}_{436}$ −69° (*c* 0.4, ethanol), has been found to be the hydroperchlorate of another substance. This material could be formed by allowing the methanol-borohydride reduction mixture to evaporate to dryness on the steam bath before isolation of the basic materials as described above. It neither was oxidized by manganese dioxide to epoxyoxopowelline nor was affected by lithium aluminum hydride in tetrahydrofuran. It may be a dimeric dioxane caused by condensation of the epoxy alcohol functions.

Anal. Calcd. for $(C_{17}H_{19}NO_5.HClO_4.H_2O)_x$: C, 46.85; H, 5.09. Found: C, 47.02; H, 5.18; vic. glycol, 0.0.

Anal. Calcd. for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.25; neut. equiv., 403. Found: C, 65.38; H, 7.17; neut. equiv., 402.

A sample of the ether was hydrolyzed in 2*N* hydrochloric acid to produce a high yield of *nerbowdine* as the only product.

Oxoflexinine (IX, no OCH_3). By the method described for oxocrinamidine, 225 mg. of flexinine was oxidized by 2.0 g. of activated manganese dioxide to give 220 mg. of oxoflexinine which showed carbonyl absorption at 1724 cm.$^{-1}$ and no absorption due to a hydroxyl group between 4000–3000 cm.$^{-1}$ Because the product resisted crystallization, it was converted to the *hydroperchlorate monohydrate* and recrystallized from water to yield prisms which gradually decomposed from 200–260°.

Anal. Calcd. for $C_{16}H_{15}NO_4.HClO_4.H_2O$: C, 47.59; H, 4.49. Found: C, 47.83; H, 4.59.

Another sample was dried at 137° (vac.) before analysis.

Anal. Calcd. for $C_{16}H_{15}NO_4.HClO_4$: C, 49.81; H, 4.18. Found: C, 49.70; H, 4.30.

The free base, recovered from the hydroperchlorate, possessed an infrared spectrum (chloroform) identical with that of the crude oxidation product.

Oxocrinine (X, no OCH_3). A solution of 100 mg. of oxoflexinine in 8 ml. of 50% acetic acid was treated with 1.5 g. of zinc dust and worked up according to the procedure outlined for oxocrinamidine. A yield of 93 mg. of product showing an infrared spectrum (chloroform) identical with that of oxocrinine was obtained. Two recrystallizations from ether provided prisms, m.p. 186–187° alone or on admixture with authentic oxocrinine, $[\alpha]^{24}_{589}$ −321°, $[\alpha]^{24}_{436}$ −885° (c 1.3); reported[7]: m.p. 184–186°, $[\alpha]^{24}_{589}$ −307°, $[\alpha]^{24}_{436}$ −848°.

Epoxyoxocrinine (XI, no OCH_3). By the method used in the conversion of oxepowelline to epoxyoxopowelline, 390 mg. of oxocrinine was converted to 320 mg. of crude epoxyoxocrinine. This was chromatographed over deactivated alumina to yield 210 mg. (51%) of epoxyoxocrinine which crystallized from ethanol as a solvate, irregular prisms, m.p. 62–75°, $[\alpha]^{24}_{589}$ −156°, $[\alpha]^{24}_{436}$ −402° (*c* 0.50), λ_{max} 237 mμ (ε 3590) and 294 mμ (ε 4920). The unsolvated base was an oil exhibiting maxima due to the unconjugated carbonyl group at 1709 cm.$^{-1}$ (chloroform) and no absorption in the hydroxyl region.

Anal. Calcd. for $C_{16}H_{15}NO_4.C_2H_5OH$: C, 65.24; H, 6.39; neut. equiv., 331. Found: C, 65.02; H, 6.33; neut. equiv., 329.

A sample was dried at 100° in vacuum, forming a glass.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30. Found: C, 67.17; H, 5.37.

cis-1,3-Dihydroxycrinane (XVIa, no OCH_3). A solution of 103 mg. of XI (no OCH_3) in 10 ml. of tetrahydrofuran was refluxed overnight with 100 mg. of lithium aluminum hydride. After decomposition with sodium hydroxide and extraction with chloroform, 89 mg. of semicrystalline product was obtained. Three recrystallizations from ethanol furnished bladed prisms which recrystallized on the hot-stage at 250° and finally melted at 266–267°, $[\alpha]^{24}_{589}$ −88°, $[\alpha]^{24}_{436}$ −198° (c 0.67, ethanol), λ_{max} 235 mμ (ε 3460) and 292 mμ (ε 4820).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; neut. equiv., 289. Found: C, 66.57; H, 6.54; neut. equiv., 287.

cis-1,3-Dihydroxycrinane O,O'-carbonate. A solution of 7 mg. of XVIa (no OCH_3) was treated with phosgene in benzene and pyridine under the conditions used in the formation of nerbowdine *O,O'*-carbonate. The product crystallized on evaporation of the solvents, m.p. 252–256°. The total sample was sublimed at 160° (1 μ), forming rectangular plates, m.p. 254–256°. A maximum was observed at 1748 cm.$^{-1}$ due to the cyclic carbonate.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.37; mol. wt., 315. Found: C, 64.85; H, 5.37; mol. wt. (Rast), 329.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XV.[1] Stereochemical Control of Methyl-Metallo Additions to 9-Oxobenzomorphans

EVERETTE L. MAY AND HIROSHI KUGITA

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Reaction of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (I) with methylmagnesium iodide produces an 80% yield of α-9-hydroxy-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan methiodide II which on pyrolysis in 1-nonanol gives the base VI. The stereochemistry of this addition is almost completely reversed by reaction of methylmagnesium iodide with the base V and is completely reversed by employing methyllithium and V, affording the β-isomer IX. That the hydroxyl group of II and VI was *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system was proved by its conversion to the *cis*-fused furano compound (IV) in two Hofmann elimination reactions. Similar degradation of IX yielded what appears to be the *trans*-fused furan derivative (XIV). Spectral data were also consistent with th eVI, IX and XIV assignments. *O*-Demethylation of VI and IX produced the phenolic compounds VII and X, respectively, which may be considered as analogs of 14-hydroxydihydromorphinone (XVIIIb). Compound VI has also been converted to the corresponding phenolic *N*-phenethyl analog XI which along with VI, VII, IX, and X have been evaluated for analgesic effectiveness in mice.

In a previous communication[2] we reported that methylmagnesium iodide adds to the carbonyl group of 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide to yield only one of the two possible methyl carbinols in 80% yield. Such a reaction with the corresponding 2′-methoxy compound (I) would not only give benzomorphan analogs of the potent analgesics 14-hydroxydihydro-codeinone (XVIIIa)[3] and -morphinone (XVIIIb)[4] but would also provide an intermediate which might be useful for the synthesis of a neuropharmacologically promising benzomorphan derivative diastereoisomeric (at C-9) with XVII,[2] isolated in very low yield in the Grewe synthesis of XVII.[5] Furthermore, it was conceivable that the stereochemistry of addition to the ketonic function of I could be reversed by varying reagents or that appropriate equilibration of II or the base VI might produce some inversion at C-9 to give a diastereoisomer (IX) which would be of pharmacological and chemical interest. Results obtained in applying some of the above-mentioned thoughts are herein presented.

Reaction of the methobromide I with excess ethereal methylmagnesium iodide[6] afforded in 80% yield the methiodide II to the apparent exclusion of any diastereoisomer in agreement with our experience in the *de*-methoxy series.[2] Pyrolysis of II in boiling 1-nonanol gave VI which, with methyl iodide, could be reconverted nearly quantitatively to II. When the free base V and methylmagnesium iodide were brought to reaction only a 15% yield of VI resulted, the principal product (57% yield) being the diastereoisomer IX. The use of methyllithium instead of methylmagnesium iodide gave, as a characterizable product, only IX in 70% yield.

Degradation of II by two Hofmann elimination reactions according to Schöpf and Borkowsky[7] for XVIIIa afforded a nitrogen-free compound (70% yield from II) whose infrared, ultraviolet and NMR spectra and elemental analyses are accomodated by structure IV. Furthermore, hydrogenation of IV with the uptake of one molar equivalent of hydrogen gave a compound VIII showing only phenyl absorption in the ultraviolet and an infrared band at 9.34 μ characteristic of tetrahydrofurans.[8] These facts it seemed permitted the assignment of the hydroxyl group as *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system inasmuch as molecular models indicated unfavorable geometry for a tetrahydrofuran ring *trans*-fused to the dihydronaphthalene moiety. However, identical double-Hofmann degradation of the isomer IX produced a nitrogen-free monomolecular compound (70% yield from the methiodide of IX) devoid of either a free hydroxyl or vinyl group as shown by infrared and NMR spectral determinations. Hydrogenation of this product resulted in the absorption of only one molar equivalent of hydrogen and disappearance of the 3,4-dihydro-6-methoxynaphthalene chromophore present in each IV and XIV. These findings of course cast doubt upon the validity of our assign-

(1) Communication XIV, J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(2) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(3) M. Freund and E. Speyer, *J. Prakt. Chem.*, [2], **94**, 135 (1916).

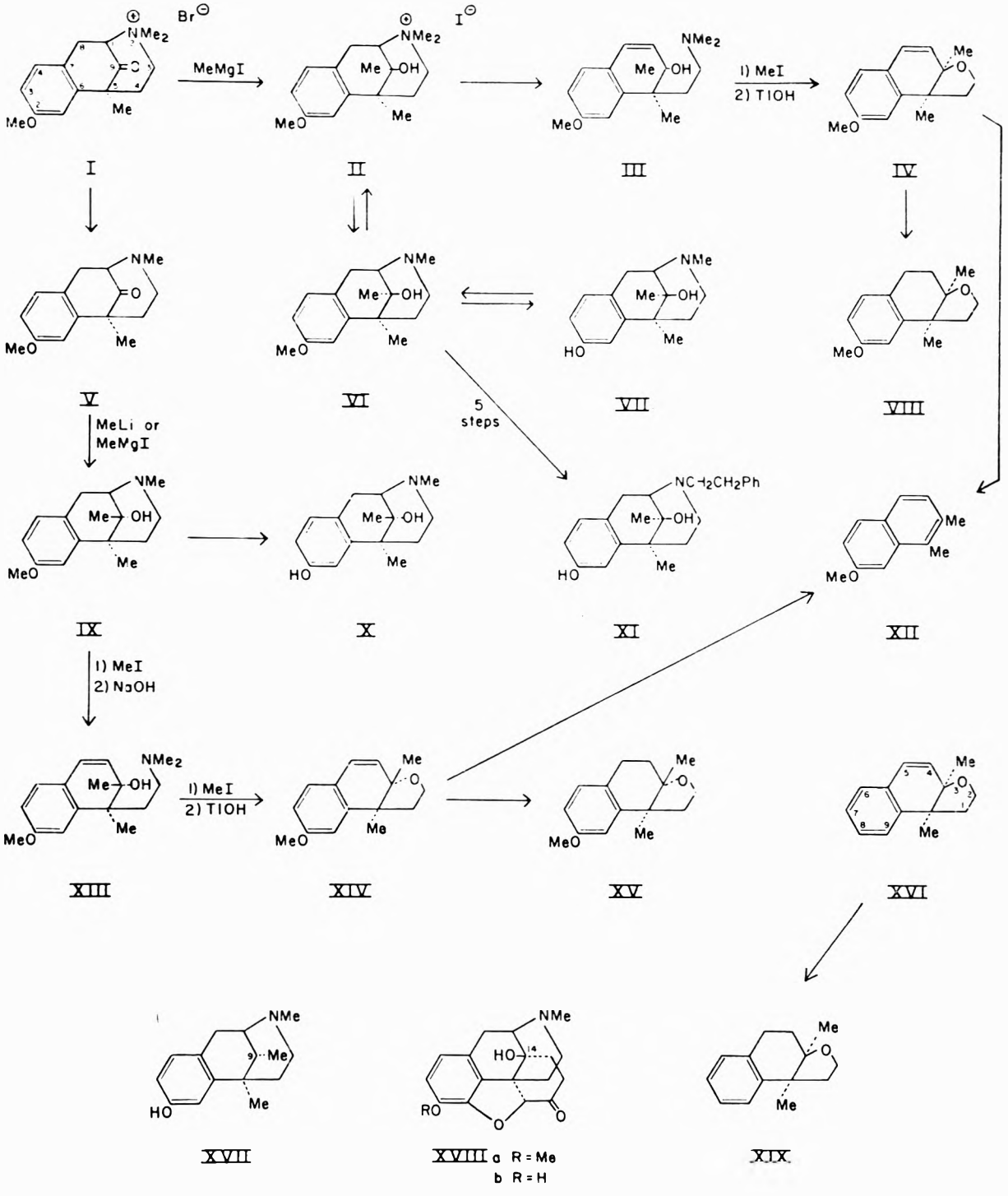
(4) (a) U. Weiss, *J. Am. Chem. Soc.*, **77**, 5891 (1955); (b) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Orgn.*, **17**, 569 (1957). The international, nonproprietary names oxydocone and oxymorphone have been assigned to XVIIIa and XVIIIb respectively.

(5) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(6) Methyllithium and I gave only a low yield of VI after pyrolysis of the crude II first isolated) and no IX.

(7) C. Schöpf and F. Borkowsky, *Ann.*, **452**, 249 (1927).

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 104.



ments for VI and IX. To dispel this doubt the *de*-methoxy analog[2] of II was converted by the same series of reactions to the IV and VIII *de*-methoxy counterparts which proved to be identical with 1,2,3a,9b-tetrahydro-3a,9b-dimethylnaphtho (2,1-b) furan (XVI) and its hydrogenation product (XIX) synthesized by Fry[9] and almost certainly containing a *cis*-fused tetrahydrohydrofuran ring.[10]

Furthermore, examination of infrared spectra of VI and IX (the OH values for which were independent of dilution) determined in the Beckman IR-7 (carbon tetrachloride as solvent) revealed that VI exhibits a broad maximum at 3450 cm.$^{-1}$ typical of OH—N bonding,[11] while IX gave a weak but sharp maximum at 3622 cm.$^{-1}$ (free OH) and a

(9) E. M. Fry, *J. Org. Chem.*, 22, 1710 (1957).

(10) The results of the degradation of the *de*-methoxy analog of II will appear in a later paper.

(11) Compare these results with those of R. E. Lyle, *J. Org. Chem.*, 22, 1280 (1957), B. L. Zenitz, C. Martini, M. Priznar, and F. Nachod, *J. Am. Chem. Soc.*, 74, 5564 (1952), and E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, 75, 68 (1953).

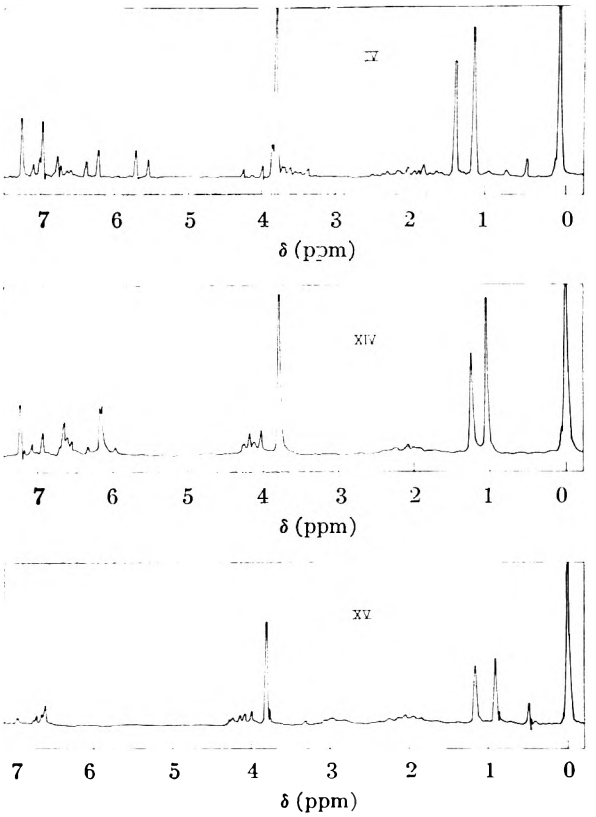


Fig. 1. Nuclear magnetic resonance spectra (deuterochloroform as solvent, tetramethylsilane as internal 0 reference) at 60 Mc.

much stronger broader band at 3585 cm.$^{-1}$ characteristic of OH—π bonding.[12] Molecular models indicate the plausibility of such bonding. These results combined with the degradative experiments outlined above leave little doubt about the stereochemical correctness of the VI and IX assignments.

All data that we have accumulated to date appear to be consistent with the formulation of XIV as a *trans*-fused tetrahydrofurano compound. (i) The yield of XIV from XIII (84%), comparable to that in going from III to IV, would indicate participation by a fairly acidic hydrogen, implicating the hydroxyl as the proton donor.[13] (ii) The ultraviolet absorption spectrum of IV shows a maximum at 270 mμ compared with 279 mμ for XIV which might be interpreted as a bathochromic shift due to conjugation of the 6-methoxy-3,4-dihydronaphthalene chromophore of XIV with a strained,[14] *trans*-fused tetrahydrofuran ring, which, according to molecular models, lies in essentially the same plane[15] as this chromophore; in the *cis*-fused furan (IV) there appears to be little if any strain in the oxygen-containing ring which lies well out of the plane of the principal chromophore. A similar effect was noted in the NMR spectra as described below. The ultraviolet spectra of the reduced compounds VIII and XV are virtually identical. (iii) Infrared and NMR data are entirely consistent with structures XIV and XV assigned to the products arising from XIII and incompatible with other possible formulations. (iv) Palladium-charcoal aromatization of either IV or XIV gave 7-methoxy-1,2-dimethylnaphthalene (XII) while treatment of either with acetic anhydride–sulfuric acid mixture afforded in each instance an oily, monoacetoxy derivative characterized only by its infrared spectrum.

Regarding the NMR spectra[16] of IV, XIV, and XV, each gives a sharp intense line at 3.78–3.82 p.p.m. due to CH_3O. Intense lines in the high-field region are unquestionably assigned to CH_3C< groups (not CH_3CH< or CH_3C=) on the basis of intensity, chemical shift, and absence of spin splitting. The lower-field line (at 1.38) in IV is assigned to the CH_3 adjacent to the >C—O— and >C—C=C groups. The difference between IV and XIV could arise from change of configuration (*e.g.*, crowding of methyls seems to cause a shift to low field in 6-methyl steroids).[17] The shift of these lines on reduction of XIV is reasonable. The nonequivalence quartet in IV arises from styrene type protons (δ = 5.65 and 6.32). On the basis of comparison with *cis*-propenylbenzene,[18] 6.32 is α to the benzene ring, 5.65 β. In XIV the pattern has changed, indicating a barely resolved nonequivalence quartet with components centered at 6.13 and 6.25, the spin-coupling remaining at 10 c.p.s., reasonable for *cis*-olefinic protons. The line due to the proton farther from the benzene ring (β) has thus been shifted to be nearly coincident with the nearer proton line (α).[19] In XV, of course, there is no absorption in this region. Absorption in the region 6.5–7.2 p.p.m. is

(12) *Cf.* M. St. C. Flett, *Spectrochim. Acta*, **10**, 21 (1957); H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960). We gratefully acknowledge the aid and counsel of Drs. Fales and Wildman in these spectral determinations on VI and IX.

(13) Inversions during the degradations in both series appear unlikely because of the excellent yields of homogeneous products obtained in both steps.

(14) L. Dorfman, *Chem. Rev.*, **53**, 51 (1953); W. W. Robertson, J. F. Music, and F. A. Matsen, *J. Am. Chem. Soc.*, **72**, 5260 (1950); R. N. Moore and G. S. Fisher, *J. Am. Chem. Soc.*, **78**, 4362 (1956).

(15) W. J. Bailey and W. B. Lawson, *J. Am. Chem. Soc.*, **77**, 1606 (1955).

(16) We are greatly indebted to Mr. Robert Bradley and Dr. Edwin Becker of this Institute for the determination and complete analysis and interpretation of these spectra.

(17) G. Slomp, Jr., and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959).

(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, Toronto, London, 1959, p. 238.

(19) Such a shift to nearer equivalence of the vinyl protons of XIV than those of IV appears to be in harmony with the ultraviolet spectral differences noted and due to strain in XIV.

due to the three aromatic protons. The detailed pattern depends upon the nonequivalence of these protons due to substituents on the ring and spin coupling (differing for *o*, *m*, and *p* positions of the protons in relation to each other). The changes in pattern between compounds reflects small changes in the chemical environment of some of the protons. For example, reduction of the double bond will almost certainly cause a shift of the proton *ortho* to that double bond; and in IV one of the methyl groups appears to interfere sterically with one of the aromatic protons, probably causing a shift to low field relative to an unhindered proton (*e.g.*, that in the *trans*-compound XIV).[20] A more detailed interpretation of the aromatic pattern is not feasible. The group of lines centered ~3.82 in IV and ~4.20 in XIV and XV must arise from the CH_2O group spin-coupled to the adjacent CH_2 group. The patterns are complex—evidently because the two protons of one or both of the CH_2 groups are nonequivalent. The groups of lines in all three compounds 1.7–2.3 arise from the remaining CH_2 group. Of course XV has one additional CH_2 group in this region and one at 3.0 due to reduction of the double bond of XIV. Overall the spectra of XIV and XV are entirely consistent with the proposed structure involving the *trans* ring closure.

The Grignard reactions described in this paper constitute, we believe, a special case of stereochemical control of assymmetric induction[21] in which, with relatively small radicals involved, the electrical environment (charge on a neighboring heterocyclic nitrogen) appears to play a major role in the direction of addition to a carbonyl function. Further support of this view will be presented in the following paper dealing with the addition of hydrogen to the carbonyl group of I and V.

Conversion of VI and IX to the phenolic analogs VII and X respectively was effected in 65–70% yield with boiling 48% hydrobromic acid. Methylation of VII with diazomethane regenerated VI proving no inversion at C-9. The base VI was also converted by standard reactions[22] to the *N*-phenethyl compound XI. Deliberate attempts to convert II to the methiodide of IX by equilibration in 0.5*M* perchloric acid[23] gave only unchanged II and decomposition products. There was no indication of inversion.

Compounds VI, VII, IX, X, and XI have been tested in mice for analgesic effectiveness.[24] The phenolic compounds VII[25] and X lie between morphine and meperidine in analgesic potency, are half as active as XVII, and vastly inferior to XVIIIb. The methyl ether, VI, was comparable to codeine by parenteral administration but about three times more potent than codeine by the oral route. Diastereoisomer IX had little activity at subtoxic doses. The *N*-phenethyl derivative XI, surprisingly, was slightly less potent than the *N*-methyl counterpart VII.

A more detailed report on the pharmacology of these compounds will be published later.

EXPERIMENTAL

Melting points were taken in a capillary (Hershberg apparatus, total-immersion thermometers). Microanalyses are by Paula Parisius, Elizabeth Fath, Evelyn Peake, and Byron Baer of the Institute's service analytical laboratory, Harold McCann, director, and infrared determinations (Perkin-Elmer, 21) are by Harold K. Miller, Richard Brown, and Ann Wright of this Institute unless otherwise noted.

α-9-Hydroxy-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan methiodide (II).[26] Five grams of I[1] was covered with dry ether and treated rapidly (stirring) with 50 ml. of 1.7*M* ethereal methylmagnesium iodide. Stirring was continued until all solid had disappeared. The ether was then distilled. Water was added gradually to the sirup (ice-cooling, nitrogen atmosphere), followed by 15 ml. of 6*N* hydrochloric acid, and 5.0 g. of potassium iodide in 10 ml. of water. After stirring for 2 additional hr. 4.4 g. (74%) of II, m.p. 217–224° was obtained; plates from alcohol-acetone, m.p. 233–235°, λ_{max}^{nujol} 3.0 μ.

Anal. Calcd. for $C_{17}H_{26}INO_2$: C, 50.63; H, 6.50. Found: C, 50.58; H, 6.47.

When methyllithium was used instead of methylmagnesium iodide the yield of II was only 20%; no other identifiable products could be isolated. The II thus obtained could not be readily purified but was converted to the easy-to-purify VI as described below.

α-9-Hydroxy-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan (VI) *picrate*. 1-Nonanol (8 ml.) and 1.4 g. of II were refluxed for 10–15 min., cooled under nitrogen, and extracted thrice with 5% hydrochloric acid. The combined extracts were made alkaline (ammonium hydroxide) and extracted with ether. The dried ether extracts were evaporated giving an oil, which with 8 ml. of alcohol and 1.0 g. of picric acid, yielded 1.4 g. (82%) of VI picrate, m.p. 195–199°; yellow rods from alcohol-acetone, m.p. 197–199°, λ_{max}^{nujol} 2.9 μ.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 53.60; H, 5.39.

The hydrochloride of VI crystallized from alcohol-ether in prisms apparently as the monohydrate, m.p. 160–163° (after drying at 40°/75 mm.).

Anal. Calcd. for $C_{16}H_{24}ClNO_2 \cdot H_2O$: C, 60.84; H, 8.30. Found: C, 60.87; H, 8.20.

In carbon tetrachloride (Beckman IR.7),[12] VI showed a broad maximum of medium intensity at 3450 cm.$^{-1}$

(20) Molecular models clearly demonstrate that in IV the 1′ proton and 9b methyl are very close together and much farther apart in XIV.

(21) For leading references on assymmetric induction *cf.* D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); N. H. Cromwell, *J. Am. Chem. Soc.*, **81**, 4702 (1959).

(22) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(23) C. A. Bunton, A. Konasiewicz, and D. R. Llewellyn, *J. Chem. Soc.*, 604 (1955).

(24) N. B. Eddy, Chief, Section on Analgesics of this Institute and staff by a method previously described; *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). Statistical analysis of the data are by Wendy Ness.

(25) The diacetoxy derivative of VII has twice the potency of morphine and shows relatively low (if any) physical dependence capacity in the monkey (private communication from Dr. G. Deneau, University of Michigan).

(26) This compound was first synthesized by J. Harrison Ager of this Institute. The α (OH *cis*- to iminoethano system) and β-designations were chosen arbitrarily.

which was independent of concentration (OH—N bonding)[11] and no free OH absorption.

Treatment of VI in warm alcohol with excess methyl iodide regenerated II almost quantitatively.

β-9-Hydroxy-2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan (IX) *picrate.* V (0.8 g.)[1] in 10 ml. of dry ether was treated (stirring) during 2–5 min. with 7.0 ml. of 1.3*M* ethereal methyl lithium. The mixture was refluxed for 20 min. and poured into ice water. The dried ether layer was evaporated and the residue treated with 15–20 ml. of alcohol and 1.0 g. of picric acid. On heating to homogeneity and cooling to 5°, 1.1 g. (70%)[27] of the picrate of IX, m.p. 210–213°, was obtained as the sole product; yellow cubes from alcohol-acetone, m.p. 213–214° dec., λ_{max}^{nujol} 2.93 μ.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 54.02; H, 5.34.

The *hydrobromide* of IX crystallized from 95% ethanol in prisms of m.p. 259–260° dec.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.14; H, 7.07. Found: C, 55.96; H, 7.18.

The *methiodide* of IX formed sluggishly with excess methyl iodide in acetone or refluxing alcohol; rosettes from absolute ethanol, m.p. 213–216°, λ_{max}^{nujol} 2.96 μ.

Anal. Calcd. for $C_{17}H_{26}INO_2$: C, 50.63; H, 6.50. Found: C, 50.43; H, 6.33.

The base (IX) crystallized from ligroin (30–60°) in prisms, m.p. 90–91°, $\lambda_{max}^{CHCl_3}$ 2.79 μ (3586 cm.$^{-1}$), $\nu_{max}^{CCl_4}$ (Beckman IR.7) 3622 cm.$^{-1}$ (weak, sharp), 3586 cm.$^{-1}$ (strong, broad, OH—π bonding).[12]

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.67; H, 8.97.

1,2-Dihydro-2-hydroxy-7-methoxy-cis-1,2-dimethyl-1-(2-dimethylaminoethyl)naphthalene (III). II (300 mg.) and 5 ml. of 10% sodium hydroxide were refluxed gently for 20 min. The liberated oil was dried in ether and distilled (bath temperature 140–150°) at 0.2 mm. to give 180 mg. (88%) of colorless, oily III, $\lambda_{max}^{C_2H_5OH}$ 275 mμ (ε 12,560) and showing associated hydroxyl absorption (chloroform) in the 3 μ region.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 74.01; H, 9.03.

1,2,3a,9b-Tetrahydro-8-methoxy-cis-3a,9b-dimethylnaphtho(2,1-b)furan (IV). III (170 mg.), 0.05 ml. of methyl iodide, and 2 ml. of methanol were refluxed for 1 hr. Distillation of solvent and washing the residue with ether left 220 mg. (86%) of white amorphous III methiodide which was dissolved in 2 ml. of hot water and treated with 2.3 ml. of 0.23*M* thallium hydroxide.[28] The mixture was digested on the steam bath for 20 min. and filtered from thallium iodide. The filtrate was evaporated to dryness at the water pump. The residual methohydroxide was dry-distilled at 110–120° (air bath temperature)/0.3 mm. Colorless needles of nitrogen-free product (IV) sublimed in a yield of 90 mg. (78%), m.p. 62.8–63.1°. Resublimation did not change the melting point and the material was chromatographically homogeneous. The infrared spectrum showed bands at 9.37, 9.79, and 11.42 μ (tetrahydrofuran characteristics)[8] and no hydroxy or vinyl group absorption; $\lambda_{max}^{C_2H_5OH}$ 271 mμ (ε 14,200).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.41; H, 8.11.

1,2,3a,4,5,9b-Hexahydro-8-methoxy-cis-3a,9b-dimethylnaphtho(2,1-b)furan (VIII). IV (80 mg.) 10 mg. of platinum oxide and 5 ml. of methanol absorbed rapidly 1 molar equivalent of hydrogen to give after distillation at 0.3 mm. (bath temperature 110–115°) 80 mg. of VIII, $\lambda_{max}^{CHCl_3}$ 9.28, 9.72, and 11.40 μ, $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 2680).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.75; H, 8.70.

1,2-Dihydro-2-hydroxy-7-methoxy-trans-1,2-dimethyl-1(2-dimethylaminoethyl)naphthalene (XIII). The methiodide of IX (0.8 g.) and 10 ml. of 10% sodium hydroxide were kept on the steam bath for 20–30 min. The liberated oil was dried in ether and distilled at 0.3 mm. (bath temperature 140–150°) giving 0.5 g. (88%) of colorless XIII, $\lambda_{max}^{CHCl_3}$ 2.8 μ,[29] $\lambda_{max}^{C_2H_5OH}$ 277 mμ (ε 8940).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 73.25; H, 9.29.

1,2,3a,9b-Tetrahydro-8-methoxy-trans-3a,9b-dimethylnaphtho(2,1-b)furan (XIV). The methiodide of XIII (0.65 g. prepared in 94% yield as a noncrystalline powder as described for that of III above), 7.3 ml. of 0.23*M* thallium hydroxide, and 5 ml. of water gave 0.30 g. (80%) of pure XIV as described above; m.p. 63.4–64.2°, $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 12,080), $\lambda_{max}^{CHCl_3}$ 9.44, 10.09, 10.40, and 11.09 μ (no hydroxyl band).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88; M.W., 230.3. Found: C, 77.80; H, 7.76; M.W. (Rast), 216.

1,2,3a,4,5,9b-Hexahydro-8-methoxy-trans-3a,9b-dimethylnaphtho(2,1-b)furan (XV). During 80 min. 200 mg. of XIV, 10 mg. of platinum oxide and 5 ml. of methanol absorbed 1 molar equivalent of hydrogen and reduction ceased. By distillation at 0.2 mm. (bath temperature 95–105°) 185 mg. of XV was obtained; $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 2,450). In the infrared (chloroform) there were strong bands at 9.43, 9.98, 10.40, and 11.13 μ and no hydroxyl absorption.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.44; H, 8.59.

1,2,3a,9b-Tetrahydro-cis-3a,9b-dimethylnaphtho(2,1-b)furan (XVI).[9] By a series of reactions identical with those described in the preparation of IV from II, 9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan methiodide (obtained in the reaction of methylmagnesium iodide with 2,5,9-trimethyl-9-oxo-6,7-benzomorphan methobromide)[2] yielded XVI, $\lambda_{max}^{C_2H_5OH}$ 263 (ε 9630) whose infrared spectrum was identical with that of the XVI synthesized by Fry.[9] The synthetic XVI almost certainly contains a *cis*-fused tetrahydrofuran ring.[10] Furthermore, hydrogenation of our XVI from degradation resulted in the absorption of one molar equivalent of hydrogen affording XIX, $\lambda_{max}^{C_2H_5OH}$ 272 mμ (ε 520) also identical in the infrared with the synthetic hydrogenation product.[9]

7-Methoxy-1,2-dimethylnaphthalene picrate. Either IV or XIV (0.2 g.) and 0.5 g. of 5% palladium charcoal were kept at 300–330° (bath temperature) for 20–30 min. and extracted with ether. Evaporation of the ether left an oil which gave 70 mg. (20%) of picrate (from alcoholic picric acid), m.p. 134–135° which proved to be identical with 7-methoxy-1,2-dimethylnaphthalene picrate described previously.[5] By the same procedure XVI afforded a 30% yield of 1,2-dimethylnaphthalene picrate.[2]

Acetic anhydride–sulfuric acid[30] *treatment of* VIII *and* XV. To 80 mg. of VIII in 2 ml. of acetic anhydride was added one drop of concd. sulfuric acid and the solution left at 25° overnight. After decomposition of the acetic anhydride with water and treatment with ammonium hydroxide the liberated oil was dried in ether and distilled at 0.2 mm. (bath temperature 130–140°); yield 30–40%, $\lambda_{max}^{CHCl_3}$ 5.75 μ. Similar treatment of XV likewise gave an oil which absorbed at 5.75 μ. Both products analyzed for one *O*-acetyl group (15.5 and 16.3%, calcd. 15.7%) based on the empirical formula $C_{17}H_{22}O_3$. The near identity of the infrared spectra indicate

(27) When ethereal methylmagnesium iodide was used in place of methyllithium there was obtained a 57% yield of the less soluble IX picrate and a 15% yield of the picrate of VI.

(28) We are grateful to Dr. L. J. Sargent of this laboratory for suggesting thallium hydroxide which proved vastly superior to silver hydroxide: *cf.* L. J. Sargent and L. F. Small, *J. Org. Chem.*, 16, 1031 (1951).

(29) The hydroxyl of XIII is apparently π-bonded in contrast to the strongly intramolecularly associated (with nitrogen) hydroxyl of III.

(30) T. Kitagawa, S. Uyeo, and N. Yokoyama, *J. Chem. Soc.*, 3741 (1959).

that the monoacetoxy derivatives are the same compound or isomers.

α-2′,9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan. (VII). VI (0.75 g.) and 8 ml. of 48% hydrobromic acid were refluxed gently for 15 min., cooled, and made alkaline with ammonium hydroxide. Addition of sodium chloride and extraction of the mixture with 20 ml. of chloroform in five portions gave, after drying and evaporation of the solvent *in vacuo* and crystallization of the residue from 1 ml. of acetone and 1 ml. of ligroin (30–60°), 0.5 g. (70%) of VII, m.p. 155.5–157°; prisms, λ_{max}^{nujol} 2.9 μ (sharp, strong), shoulder at 2.83 μ, $\lambda_{max}^{CHCl_3}$ 2.78 (sharp, medium), 3.0 (broad, strong).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.55. Found: C, 72.84; H, 8.35.

The *hydrobromide* salt crystallized from absolute ethanol-ether in prisms of m.p. 238–240°, λ_{max}^{nujol} 2.78 (weak), 3.07 (strong), 3.21 μ (medium).

Anal. Calcd. for $C_{15}H_{22}BrNO_2$: C, 54.87; H, 6.76. Found: C, 54.89; H, 6.86.

Methylation of 50 mg. of VII in methanol with ethereal diazomethane regenerated VI, isolated as the picrate in 70% yield, showing no inversion at C-9 or rearrangement during the 48% hydrogen bromide treatment.

α-2′,9-Diacetoxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide. VII (0.4 g.) and 3.5 ml. of acetic anhydride were refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residue was treated with cold, dilute ammonium hydroxide and extracted with ether. Drying and evaporating the ether left an oil which was distilled at 0.2 mm. (bath temperature 165–175°). The 0.55 g. of distillate in 5 ml. of acetone was treated with 30% hydrobromic-acetic acids to Congo-Red acidity. The hydrobromide crystallized in a yield of 0.63 g. after overnight standing; wedges from absolute ethanol-ethyl acetate, m.p. 264–265° dec.

Anal.[31] Calcd. for $C_{19}H_{26}BrNO_4$: C, 55.34; H, 6.35; Br, 19.38. Found: C, 55.66; H, 6.57; Br, 19.07.

β-2′,9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan (X). This compound was prepared from IX (55% yield after sublimation at 0.1 mm., bath temperature 180°) as described above for VII; prisms from acetone, m.p. 194–195°, λ_{max}^{nujol} 3.03 μ (strong, broad).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.55. Found: C, 72.67; H, 8.58.

The *hydrobromide* crystallized from 95% ethanol in triangular plates, m.p. 258–260° (dec.), λ_{max}^{nujol} 2.99, 3.11 μ (strong, sharp).

Anal. Calcd. for $C_{15}H_{22}BrNO_2$: C, 54.87; H, 6.76; Br, 24.34. Found: C, 55.23; H, 6.52; Br, 24.30.

α-9-Hydroxy-2′-methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. VI (1.1 g.) in 7 ml. of chloroform was added during 30 min. to a stirred solution of 0.45 g. of cyanogen bromide in 4 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness at the water pump. The residual crude cyanamide derivative, and 20 ml. of 6*N* hydrochloric acid were refluxed for 7 hr. The cooled mixture was made alkaline with potassium carbonate, extracted with ether, and the extracts washed with water, dried, and evaporated leaving 1.05 g. of crude secondary amine. To this was added 15 ml. of methanol, 5 ml. of water and 0.8 g. of potassium carbonate. The mixture was stirred while adding 0.8 ml. of phenylacetyl chloride during 7 min., then stirred an additional 3 hr. Water and ether were added and after thorough shaking the ethereal layer was washed with dilute hydrochloric acid,[32] then aqueous sodium carbonate, dried and evaporated. To the resultant 1.1 g. of *N*-phenylacetyl compound in 20 ml. of dry ether was added carefully (stirring) 15 ml. of *M* ethereal lithium aluminum hydride. After stirring and refluxing for 6–8 hr. 2 ml. of water was added carefully and inorganic material filtered. The filtrate was extracted with dilute hydrochloric acid and these extracts made alkaline to give after extraction with ether 0.46 g. of crude XI methyl ether. In another identical run using 0.43 g. of the VI recovered above, 0.25 g. more XI methyl ether was obtained. The combined products in 5 ml. of acetone were treated with 30% hydrobromic-acetic acid to Congo-Red acidity and cooled to −5° to give 0.4 g. of the hydrobromide, m.p. 200–201°. Concentration of the filtrate and washings gave an additional 0.1 g.; pillars from absolute ethanol-ethyl acetate, m.p. 199–201°.

Anal. Calcd. for $C_{22}H_{30}BrNO_2$: C, 63.89; H, 6.98. Found: C, 63.99; H, 6.98.

α-2′,9-Dihydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (XI) *hydrobromide.* The methyl ether of XI (0.48 g.) and 4 ml. of 48% hydrobromic acid were refluxed gently for 15 min. After vacuum distillation to dryness, the residue was washed several times with ether and triturated with acetone. Filtration gave 0.39 g. of XI hydrobromide, m.p. 261–263°, which was dissolved in hot ethanol. The solution was filtered, concentrated, and treated with Norit. The filtrate deposited 0.25 g. (55%) of colorless granules of pure XI hydrobromide, m.p. 265–267° (dec.).

Anal. Calcd. for $C_{22}H_{28}BrNO_2$: C, 63.16; H, 6.74. Found: C, 63.16; H, 6.82.

BETHESDA 14, MD.

(31) Sample dried for 6 hr. at 60°.

(32) On making these washings alkaline, 0.45 g. of VI, identified as the picrate, was recovered. Thus, the *N*-demethylation of VI was only about 50% complete indicating hindrance by the 9-hydroxy substituent. In the *N*-demethylation of the methyl ether of XVII [E. L. May and N. B. Eddy, *J. Org. Chem.*, 24, 1435 (1959)], by a similar procedure, only small yields of starting *N*-methyl compound were recovered.

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE]

Cyclization of Some *O*-Substituted Derivatives of *N*-(3,4-Dimethoxy-β-phenylethyl)glycolamide; Synthesis of (±)-Calycotomine

F. BENINGTON AND R. D. MORIN

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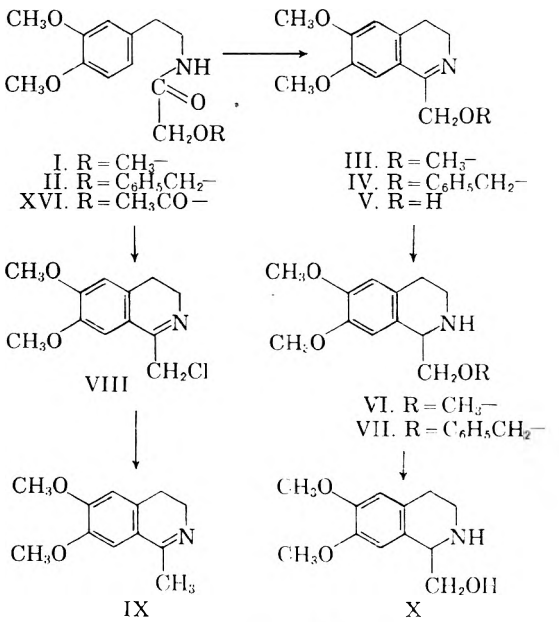
Attempts to cyclize *N*-(3,4-dimethoxy-β-phenylethyl)alkoxyacetamides with phosphorus oxychloride or phosphorus pentoxide resulted in extensive decomposition and tar formation rather than formation of the desired 1-alkoxymethyl-3,4-dihydroisoquinolines. Cyclization was effected by phosphorus pentachloride, but, in addition, cleavage occurred and a 1-chloromethyl-3,4-dihydroisoquinoline was formed. A possible mechanism for this reaction is discussed. A synthesis of (±)-calycotomine was achieved by cyclization of *N*-(3,4-dimethoxy-β-phenylethyl)acetoxyacetamide with phosphorus oxychloride followed by catalytic hydrogenation.

In the course of certain studies of the synthesis of isoquinoline compounds, we have had the occasion to examine various routes for preparing 1-hydroxymethylisoquinolines from readily available intermediates. At the beginning of this investigation, an examination of the literature concerning the Bischler-Napieralski ring closure[1] of *N*-acyl-β-phenethylamines failed to show any cyclizations which had given 1-hydroxymethyl-3,4-dihydroisoquinolines as end products.

The present study was undertaken to examine the possibility of cyclizing *N*-alkoxyacetylhomoveratrylamines (I and II) to the corresponding 1-alkoxymethyl-3,4-dihydroisoquinolines (III and IV) *via* the Bischler-Napieralski method; subsequent ring hydrogenation and ether cleavage of III and IV would accordingly be expected to yield (±)-1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-dimethoxyisoquinoline[2] (X).



The starting *O*-alkylglycolylamides I and II were obtained in good yield by treating an excess of homoveratrylamine respectively with methoxyacetyl chloride and benzyloxyacetyl chloride. As both amides are suitably activated for electrophilic ring closure by methoxy groups, it was expected that cyclization would occur readily in the presence of phosphorus pentoxide or phosphorus oxychloride.[1] However, neither I nor II was found to undergo cyclization to the corresponding 1-alkoxymethyl-3,4-dihydroisoquinoline III or IV when refluxed with either of these reagents in toluene or benzene. Polyphosphoric acid[3] was likewise ineffective in bringing about the cyclization of II to IV. In a further variation of conditions for the Bischler-Napieralski cyclization, II was subjected to the action of phosphorus pentachloride in chloroform solution at room temperature for about fifteen hours; the hydrogen chloride which was liberated during the first two hours of the reaction was taken as evidence of cyclization. The purified reaction product, obtained as a yellow hydrochloride salt, which was thought to be the dihydroisoquinoline V, was then hydrogenated in methanol solution over a 10% palladium-on-charcoal catalyst. The resulting hydrogenation product (free base) was found to give an incorrect analysis for X, and was subsequently identified as 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX), which had been described previously by Kaufmann and Radosevic.[4] The unhydrogenated cyclization product of II was shown to be identical with 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII) hydrochloride prepared by the cyclization of *N*-chloroacetylhomoveratrylamine as described by Child and Pyman.[5] The free base VIII on standing at room temperature undergoes

(1) R. Adams, *Org. Reactions*, VI, 74 (1951).

(2) Compound X is the naturally occurring alkaloid (±)-calycotomine, first isolated by E. P. White, *New Zealand J. Sci. Tech.*, 25B, 152 (1944), from *Calycotome Spinosa*. Well after our study had been initiated, A. R. Battersby and T. D. Edwards, *J. Chem. Soc.*, 1909 (1959), described the first synthesis of X *via* cyclization of ethyl *N*-3,4-dimethoxyphenethyloxanilate followed by reduction of the resulting 3,4-dihydroisoquinoline ester to X with lithium aluminum hydride.

(3) N. J. Leonard and J. H. Boyer, *J. Am. Chem. Soc.*, 72, 2980 (1950).

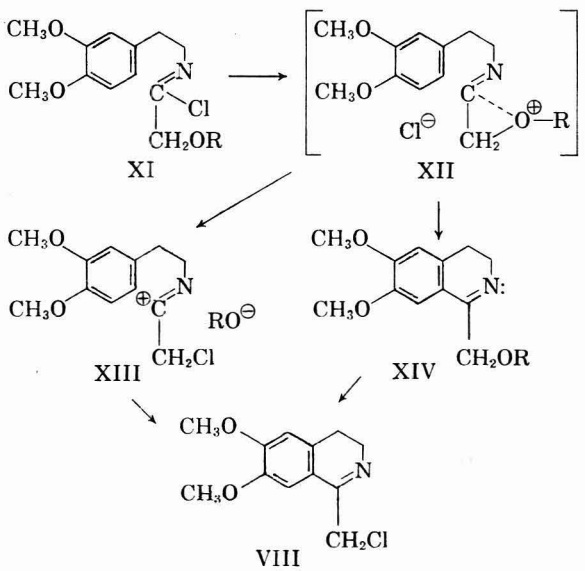
(4) A. Kaufmann and R. Radosevic, *Ber.*, 49, 675 (1916).

(5) R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931).

an intermolecular reaction to form a dark, water-soluble quarternary salt which was not further characterized.

It was at first assumed that the ether cleavage which occurred during the cyclization of II to VIII was due to the tendency of reactive benzyl ethers to undergo scission with certain Lewis acids *via* a weak oxonium salt. However, when *N*-methoxyacetylhomoveratrylamine (I) was subjected to the action of phosphorus pentachloride under the same conditions used in the cyclization of II, the same reaction product, namely, 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII), was again obtained.

This evidence suggests two possible reaction mechanisms as being operative in the cyclization of *N*-alkyloxyacetylhomoveratrylamines with phosphorus pentachloride. The first step in the Bischler-Napieralski cyclization is the formation of an imino chloride, XI, resulting from the elimination of hydrogen chloride from the unstable grouping $ArCH_2CH_2NHCCl_2R$. An inductive shift then gives rise to the intermediate cyclic oxinium ion XII, in which the accompanying chloride anion shifts to the terminal carbon atom. The resulting shift takes place with the elimination of an alkoxyl anion, producing the carbonium ion XIII which, in turn, internally cyclizes to the final cyclic 1-chloromethyl compound VIII *via* an electrophilic



attack on the aromatic ring. A second mechanism would involve the direct cyclization of XI through the elimination of hydrogen chloride to form the 1-alkoxymethyl compound XIV. This, in turn, could undergo an S_N2-type nucleophilic displacement with Cl^- to form the same final 1-chloromethyl compound VIII. The fact that none of the 1-alkoxymethyl compound XIV was isolated would seem to favor occurrence of electrophilic cyclization prior to ether cleavage.

Several attempts were made to convert the 1-chloromethyl compound VIII to the corresponding 1-hydroxymethyl and 1-acetoxymethyl compounds. Refluxing VIII in methanol with silver hydroxide failed to give the desired compound V; instead, intractable tars were formed. Similarly, refluxing VIII with sodium acetate in the same solvent failed to give the corresponding 1-acetoxymethyl derivative.

In an alternative approach to obtaining X, *N*-acetoxyacetylhomoveratrylamine (XVI) was prepared by treating acetoxyacetyl chloride with homoveratrylamine. Refluxing XVI in dry toluene with phosphorus oxychloride resulted in a low yield of 1-hydroxymethyl-5,6-dimethoxy-3,4-dihydroisoquinoline (V). This result was somewhat surprising in that the acetyl group was eliminated during this reaction. Reduction of V in ethanol solution over 10% palladium-on-charcoal catalyst afforded (±)-1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-dimethoxyisoquinoline (X), identical in properties with (±)-calycotomine described by White[2] and Battersby.[2] The picrate salt of X prepared by us was higher in melting point than the (±)-calycotomine picrate described by White as a hydrated salt; our derivative, prepared under anhydrous conditions, gave a correct analysis for the picrate of X.

EXPERIMENTAL[6]

N-(3,4-Dimethoxy-β-phenylethyl)methoxyacetamide (I). A mixture of 45 g. of methoxyacetic acid and 59.5 g. of thionyl chloride was warmed at 40 to 60° on a water bath for 3.5 hr. while passing a slow stream of dry nitrogen through to remove sulfur dioxide and hydrogen chloride. The mixture was distilled under reduced pressure, and the fraction boiling at 46–49°/62 mm. was collected as methoxyacetyl chloride (reported[7] b.p. 51°/69 mm.); yield, 31.1 g. (57%). A solution of 22.7 g. of this acid chloride in 50 ml. of dry benzene was added gradually to a stirred solution of 75.7 g. of 3,4-dimethoxy-β-phenethylamine in 200 ml. of dry benzene. After stirring an additional 15 min., the precipitated amine hydrochloride was removed by filtration, benzene was stripped from the filtrate, and the residue was distilled under reduced pressure to recover pure *N*-(3,4-dimethoxy-β-phenylethyl)methoxyacetamide; b.p. 185–190°/0.5 mm.; yield, 47.9 g. (86%).

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.5. Found: C, 61.3; H, 7.4.

N-(3,4-Dimethoxy-β-phenylethyl)benzyloxyacetamide (II). To a stirred solution of 23 g. of clean sodium cut into small pieces in 475 g. of redistilled benzyl alcohol (stirring for 20 hr. and warming to 70° were required to effect complete solution) was added gradually 123 g. of freshly distilled ethyl chloroacetate with water bath cooling. The mixture was then stirred and heated at about 80° for 2 hr., cooled, treated with water, and the oil which separated was extracted from the aqueous layer with ether. The ether extract was dried (anhyd. magnesium sulfate), the solvent was removed, and the residue was distilled under reduced pressure to obtain a mixture of ethyl and benzyl esters of benzyloxyacetic acid, b.p. 50–165°/0.3 mm.; yield, 128 g. The mixed esters were saponified by refluxing for 1.5 hr. with a mixture of 150 ml. of methanol and 60 ml. of 45% potassium hydroxide. After

(6) Melting points are uncorrected.

(7) R. Leimu, *Ber.*, **70B**, 1049 (1937).

the methanol was removed by evaporation, the residue was diluted with water and then extracted with ether to remove unchanged benzyl alcohol; acidification of the aqueous phase released the crude benzyloxyacetic acid, which was taken up in ether and purified by distillation under reduced pressure; b.p. 135–140°/0.2 mm. (reported,[8] 136°/0.2 mm.); yield 63 g. (38%). The amide of this acid melted at 92–93° (reported,[8] m.p. 91°).

A mixture of 31.5 g. of benzyloxyacetic acid and 42 g. of thionyl chloride was refluxed for 35 min. and the acid chloride formed was purified by distillation under reduced pressure; b.p. 81–83°/0.6 mm.; yield, 34 g. (97%). To a stirred and cooled (ice bath) solution of 67 g. of 3,4-dimethoxy-β-phenethylamine in 600 ml. of dry ether was added portionwise 33.6 g. of benzyloxyacetyl chloride. After stirring a few minutes longer, the copious white precipitate which had formed was filtered by suction and washed with water to remove amine hydrochloride. When the solid had been washed free of chloride ion, it was dried in a vacuum oven at 50° to obtain 54.4 g. (91%) of crude II as a white solid, m.p. 61–63°. After recrystallization from benzene-ether-petroleum ether (b.p. 30–60°), a sample melted at 72–73°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; N, 4.26. Found: C, 69.1; H, 6.8; N, 4.18.

Attempted cyclization of I *and* II *with phosphorus oxychloride or phosphorus pentoxide.* A mixture of 26.5 g. of II, 160 ml. of dry toluene, and 120 g. of phosphorus oxychloride was refluxed for 6 hr., during which time hydrogen chloride was evolved. As no hydrochloride separated on cooling, the mixture was poured into ice water and the aqueous layer was separated and made alkaline with 20% aqueous sodium hydroxide. A brown oil separated and solidified to a dark resinous mass which was insoluble in most solvents and could not be induced to crystallize. Similar results were obtained with phosphorus pentoxide in boiling benzene by the method described by Battersby.[2] Treatments of the amide I with phosphorus oxychloride or phosphorus pentoxide in benzene or toluene also resulted in the formation of intractable tars from which none of the desired dihydroisoquinolines could be isolated.

Action of phosphorus pentachloride on I *and* II; *1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline* (VIII). To a cold solution of 15 g. of II in 125 ml. of chloroform was added in portions 22 g. of phosphorus pentachloride. The phosphorus pentachloride gradually dissolved, and a yellow solid deposited. After standing overnight at room temperature, a clear brown solution was obtained. Most of the chloroform was removed by evaporation, and the residue was dissolved in 50 ml. of water with cooling. After extraction with ether, the aqueous solution was treated with concd. ammonia solution until alkaline, extracted thrice with ether, and the ether solution was washed with water and dried (anhydrous magnesium sulfate). Treatment of the dried ether solution with dry hydrogen chloride precipitated a yellow gum, which was separated from the supernatant ether by decantation and dissolved in boiling alcohol. On cooling a yellow crystalline solid deposited; yield, 9.7 g. of a product, m.p. 200–202° dec. Recrystallization from alcohol gave 7.9 g. (64%) of yellow crystals, m.p. 209–210° dec. This product was identified as 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride, first reported by Child and Pyman[5] (reported m.p. 217° dec.).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_2$: C, 52.2; H, 5.4; Cl (ionic), 12.9. Found: C, 52.2; H, 5.4; Cl (ionic), 12.8.

Catalytic hydrogenation of 6.8 g. of VIII hydrochloride in 150 ml. of methanol over 1 g. of 10% palladium-charcoal at 3 atm. and room temperature gave 5.4 g. of a product m.p. 200–201° as the hydrochloride and m.p. 105–106° as the free base, which contained no halogen. This compound was identified as 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX) (reported[4] m.p. 108° for free base and 200° for hydrochloride).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.3; H, 7.3; N, 6.8. Found: C, 70.2; H, 7.4; N, 6.7.

An authentic specimen of VIII hydrochloride was prepared for comparison purposes by cyclization of *N*-(3,4-dimethoxy-β-phenylethyl)chloroacetamide, m.p. 95–96° (reported,[5] m.p. 96°), as described by Child and Pyman.[5] By refluxing a mixture of 12.9 g. of the amide in 40 ml. of dry toluene and 13 ml. of phosphorus oxychloride there was obtained 11.2 g. (81%) of VIII hydrochloride, m.p. 209–210° dec., which did not depress the melting point of the product obtained from II and phosphorus pentachloride.

Treatment of 10 g. of the amide I in 50 ml. of chloroform with 8 g. of phosphorus pentachloride at 5° for 3 days also resulted in the formation of VIII, which was isolated as the hydrochloride, m.p. 209–210° dec.

N-(3,4-Dimethoxy-β-phenylethyl)acetoxyacetamide. A mixture of 57 g. of glycolic acid and 114 g. of acetyl chloride was refluxed for 3 hr., when evolution of hydrogen chloride had ceased. The mixture was stripped under reduced pressure to remove excess acetyl chloride, and the residue (86 g.) was refluxed for 2 hr. with 119 g. of thionyl chloride. The reaction product was distilled under reduced pressure, and the fraction boiling at 58–61°/19 mm. was collected as acetoxyacetyl chloride; yield, 51 g. (50%); (reported[9] b.p. 51°/14 mm.).

To a stirred solution of 23.3 g. of acetoxyacetyl chloride in 25 ml. of dry benzene was added gradually a solution of 62.7 g. of 3,4-dimethoxy-β-phenethylamine in 300 ml. of dry benzene. After stirring a few minutes longer, the precipitated amine hydrochloride was removed by filtration and washed with additional benzene. The solvent was distilled from the filtrate, and the residue was distilled under reduced pressure; b.p. 212–214°/0.2 mm.; yield, 34.7 g. (73%) of a colorless oil.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.8. Found: C, 60.0; H, 6.9.

(±)-*Calycotomine* (X). A mixture of 21.2 g. of *N*-(3,4-dimethoxy-β-phenylethyl)acetoxyacetamide, 150 ml. of dry toluene, and 112 g. of phosphorus oxychloride was refluxed for 2 hr. Dilution of the cooled solution with petroleum ether (b.p. 30–60°) precipitated a black viscous oil from which the hydrocarbon layer was decanted after settling. The black oil was treated with ice and water, and the resulting solution extracted with ether and then made alkaline with sodium hydroxide solution. The dark oil which separated was extracted with four ether extractions; the ether solution was dried and treated with hydrogen chloride to precipitate a dark-brown gummy hydrochloride. This was dissolved in methanol and the solution treated with small portions of ethyl acetate and ether to give, after standing overnight, three crops of brown crystals. After two recrystallizations from methanol-ether, the product was obtained pure; m.p. 199–200° dec.; yield, 3.1 g. (16%). Analysis showed that the acetyl group had been removed by hydrolysis, and the product isolated was *1-hydroxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride.*

Anal. Calcd. for $C_{12}H_{16}ClNO_3$: C, 56.0; H, 6.2; Cl, 13.8; N, 5.4. Found: C, 56.4; H, 6.2; Cl, 13.6; N, 5.3.

A solution of 1 g. of this hydrochloride in 50 ml. of methanol was shaken with 3 atm. of hydrogen in the presence of platinum oxide catalyst for 30 min. The catalyst was removed by filtration, and the solvent evaporated to a volume of 10 ml. Cooling and treatment with ether induced crystallization, and 800 mg. (80%) of a colorless solid was obtained; m.p. 195–196°, after one more recrystallization from methanol-ether (reported[2] for (±)-calycotomine hydrochloride, m.p. 194–195°). Treatment of a water solution of the hydrochloride with dilute sodium hydroxide gave (±)-calycotomine, m.p. 134–135°, after recrystallization from benzene (reported[2] for (±)-calycotomine, 133–134°).

(8) W. Wenner and J. T. Plati, *J. Org. Chem.*, 11, 751 (1946).

(9) R. Anschutz, *Ber.*, 36, 467 (1903).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.6; N, 6.3. Found: C, 64.4; H, 7.5; N, 6.2.

The *picrate* melted at 203–204°.

Anal. Calcd. for $C_{20}H_{22}N_4O_{11}$: C, 47.8; H, 4.4. Found: C, 47.6; H, 4.5.

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BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO

[CONTRIBUTION FROM THE BIOCHEMISTRY DIVISION, DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF ILLINOIS]

The L-Glyceric Acid Monophosphates

FINN WOLD

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The syntheses of L-glyceric acid 2- and 3-phosphate from L-arabinose are described. The two new phosphate esters have been characterized by comparison with the previously synthesized D-isomers.

Studies of the effect of the unnatural isomers of substrates and substrate analogues on enzymatic reactions have given information about the configuration of the enzymes' catalytic sites.[1] With the intention of applying this kind of studies to the enzyme enolase, it was of interest to prepare the pure L-isomers of glyceric acid 2- and 3-phosphate. The D-isomers have been prepared previously from D-galactose,[2] but as L-galactose is not readily available as a starting material, a new synthetic route leading to the glyceric acid monophosphates was developed, starting with a more common L-sugar, L-arabinose.

The key intermediate, methyl 2-*O*-benzyl-L-glycerate, was obtained from L-arabinose by the following reaction sequence:

L-arabinose (I) → benzyl β-L-arabinopyranoside (II) → benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (III) → benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-β-L-arabinopyranoside (IV) → 2-*O*-benzyl-L-arabinose (V) → 2-*O*-benzyl-L-arabitol (VI) → 2-*O*-benzyl-L-glyceric acid (VII) → methyl 2-*O*-benzyl-L-glycerate (VIII).

VIII could be phosphorylated in the 3-position and unblocked in the usual manner[2-4] to give the 3-phosphate ester, or it could be benzoylated, debenzylated, phosphorylated, and unblocked again according to standard procedures[2-4] to give the 2-phosphate ester.

II, III, and IV were prepared in good yield, the first according to published methods,[5,6] and were obtained as readily characterizable crystalline products. The hydrolysis of IV to give V was not as easy to accomplish. The hydrolysis conditions must be chosen to give a minimum of hydrolysis of the benzyl ether, and yet be drastic enough to cleave the relatively stable benzyl glycoside. By refluxing for two to three hours with 1*N* hydrochloric acid moderately good yields of V could be obtained. During the first fifteen to twenty minutes of refluxing, the compound would slowly go into solution as the acetal was hydrolyzed. (If the reaction were cooled at this stage, a near quantitative yield of benzyl 2-*O*-benzyl-β-L-arabinoside would crystallize out of the aqueous solution.) After the removal of the acetal, the reducing power of the reaction mixture would slowly increase leveling off after two to three hours. At this time the acid was neutralized and the reaction mixture was taken to dryness. The product could be extracted into hot chloroform, leaving the inorganic salt and some free arabinose behind. A low and variable yield of crystals could be obtained from the chloroform solution upon concentration, and it was found that a drop of concentrated hydrochloric acid would increase the amount of crystalline material, indicating mutarotation and crystallization of one of the anomeric forms. This phenomenon was not investigated further. In practice the chloroform solution was taken to dryness, and if benzyl 2-*O*-benzylarabinoside and free arabinose were shown to be absent by paper chromatography, the sirup was used in the subsequent step without further purification. After reduction to VI and periodate cleavage to give 2-*O*-benzylglyceraldehyde, perpropionic acid oxidation[7] of the aldehyde to the acid was attempted; however, this led to cleavage of the benzyl ether. The iodine oxidation previously described[2] was therefore used giving variable yield.

The two monophosphate esters of L-glyceric acid were characterized by chromatography, titration, and optical rotation, in comparison with the known

(1) M. London, R. McHugh, and P. B. Hudson, *Arch. Biochem. Biophys.*, **73**, 72 (1958); L. I. Pizer and C. E. Ballou, *J. Biol. Chem.*, **234**, 1138 (1959).

(2) C. E. Ballou and H. O. L. Fischer, *J. Am. Chem. Soc.*, **76**, 3188 (1954).

(3) C. E. Ballou, *J. Am. Chem. Soc.*, **79**, 984 (1957).

(4) F. Wold and C. E. Ballou, *J. Am. Chem. Soc.*, 81, 2368 (1959).

(5) E. Fischer and H. Beensch, *Ber.*, **27**, 2478 (1894).

(6) C. E. Ballou, S. Roseman, and K. P. Link, *J. Am. Chem. Soc.*, **73**, 1140 (1951).

(7) R. Barker, Doctorate thesis, University of California, Berkeley, 1958; J. d'Ans and W. Frey, *Ber.*, **45**, 1845 (1912).

TABLE I

SPECIFIC ROTATION OF THE L- AND D-GLYCERIC ACID MONOPHOSPHATES

	1*N* HCl	10% Neutral Molybdate	10% Neutral Molybdate after 30 Min. at 100° in 1*N* HCl
L-Glyceric acid 2-P	−12.0 (c^a 0.7)	+9 (c^a 1)	+590 (c^a 0.06)
L-Glyceric acid 3-P	+12.0 (c^a 0.7)	+690 (c^a 0.06)	+580 (c^a 0.06)
D-Glyceric acid 2-P[2]	+13.0	+5	−600
D-Glyceric acid 3-P[2]	−14.5	−725	−610

[a] Concentration of the free acid.

D-isomers. The optical rotations determined for the L-isomers are given in Table I, together with the values reported for the D-glyceric acid monophosphates.[2]

EXPERIMENTAL

The melting points reported are all uncorrected. A flash evaporator operating at 45° and 15 mm. pressure was used for solvent removal unless other conditions are specified. The optical rotations were read in a Rudolf Polarimeter.

Benzyl β-L-arabinopyranoside. Fifty grams of L-arabinose C.P. (Pfanstiehl Laboratories, Inc.) was suspended in 250 ml. of freshly redistilled benzyl alcohol. The mixture was cooled in an ice bath, saturated with dry hydrochloric acid, and shaken for 24 hr. at room temperature. Four hundred milliliters of ethyl ether was added and after several hours at −10° the voluminous crystalline product was collected by filtration, washed with ether, and air dried. Recrystallization in two batches from 1 l. of boiling ethanol gave 71 g. (88%) of product, m.p. 168–171°, ($[\alpha]_D^{25}$ +206° (*C* 0.3, water)) in good agreement with the literature values.[6] The compound showed a rapid periodate consumption of 1.85 moles of periodate, confirming the pyranose structure.

Benzyl 3,4-O-isopropylidene-β-L-arabinopyranoside. Thirty grams of the benzyl arabinoside was dissolved in 1.5 l. of acetone (C.P. acetone from a previously unopened bottle was used without further drying) and the solution was shaken with 1 ml. of concd. sulfuric acid and 150 g. of cupric sulfate (dried at 90° for 24 hr.) for 25 hr. The acid was neutralized with dry ammonia and the inorganic salts were removed by filtration through Celite. The filtrate was taken to dryness, redissolved in ether, and a purple color removed by extraction with water. The ether phase was dried over sodium sulfate and upon removal of the ether, 34.99 g. (86%) of a colorless sirup which crystallized slowly was obtained. The product did not react with periodate, but after a short exposure to hot aqueous acid, a positive periodate test was obtained. Recrystallization from ether–petroleum ether (b.p. 30–60°) at −10° gave large rosettes melting at 59–59.5°; $[\alpha]_D^{25}$ +222 (*c* 1, chloroform).

Anal. Calcd. for $C_{15}H_{20}O_5$ (280.3): C, 64.3; H, 7.15. Found: C, 64.28; H, 7.31.

Benzyl 2-O-benzyl-3,4-O-isopropylidene-β-L-arabinopyranoside. To a solution of 30 g. of the crystalline mass obtained above in 120 ml. of toluene in a three neck flask equipped with a mechanical stirrer was added 50 g. of powdered potassium hydroxide and 175 ml. of freshly redistilled benzyl chloride. The reaction mixture was left on a steam bath with rapid stirring for 5 hr. and allowed to cool. The solution was transferred to a separatory funnel with 200 ml. of benzene and extracted with water to remove the base. The organic phase was dried over sodium sulfate and the excess benzyl chloride was distilled off at 150° and 15 mm. (water aspirator). The product was collected by distillation (160–190° at 0.3 mm.) and crystallized from a small volume of ethanol giving 33.5 g. (80%) of crystalline material. It was later found that the residue after the unchanged benzyl chloride has been removed, can be crystallized directly and that the distillation step thus can be eliminated. Recrystallization from hot ethanol gave prisms melting at 77°; $[\alpha]_D^{25}$ +199 (*c* 2, chloroform).

Anal. Calcd. for $C_{22}H_{26}O_5$ (370): C, 71.4; H, 7.03. Found: C, 71.46; H, 7.15.

2-O-Benzyl-L-arabinose. Fourteen grams of the fully blocked arabinoside from above was refluxed with 210 ml. of 1*N* hydrochloric acid. During the first 30 min. the reaction mixture was shaken frequently to disperse the oil of the melted starting material, which slowly disappeared as the isopropylidene group hydrolyzed and acetone distilled out. [Upon cooling at this stage, a near quantitative yield of benzyl 2-*O*-benzyl-β-L-arabinopyranoside crystallized from the aqueous solution. It could be recrystallized from chloroform–petroleum ether (b.p. 60–90°) melted at 127–128°, $[\alpha]_D^{25}$ +207° (c 1, chloroform).]

Anal. Calcd. for $C_{19}H_{22}O_5$ (330): C, 69.1; H, 6.67. Found: C, 67.8; H, 6.60.

As the compound dissolved, the reducing power, as tested by the Willstätter-Schudel method,[8] increased, and reached a constant value after about 2.5 hr. After cooling, the solution was brought to *p*H 7 with concd. potassium hydroxide (bromthymol blue end point) and taken to dryness. None of the characteristic very voluminous precipitate of benzyl 2-*O*-benzyl-β-L-arabinopyranoside appeared during the concentration. The dry semisolid sirup was extracted twice with hot chloroform, and after removal of the chloroform, 8 g. of a semicrystalline, colorless sirup was obtained (88%). Ascending paper chromatography in butanol-water (3:2) containing enough acetic acid to give a single phase, gave a spot with R_f = 0.85. In this solvent system arabinose, benzyl arabinopyranoside and benzyl 2-*O*-benzyl-arabinopyranoside have R_f values of 0.35, 0.85, and 0.95 respectively, but the reaction product could be distinguished from benzyl arabinoside by the latter's negative reducing test (benzidine spray[9]).

It may be of interest to note that hydrochloric acid gave a nice compact spot with R_f = 0.5 in this system. It gave a yellowish-brown spot with the periodate-benzidine spray reagent.[10]

The above sirup was dissolved in hot chloroform containing a drop of concd. hydrochloric acid, and upon cooling, 3.7 g. of crystals were obtained melting at 109–112°, $[\alpha]_D^{25}$ +87° after 5 min., and +75 after 90 min. (*c* 1, ethanol).

Anal. Calcd. for $C_{12}H_{16}O_5$ (240): C, 60.0; H, 6.67. Found: C, 59.6; H, 6.65.

Continuous boiling and concentration of the mother liquors would give additional crops of crystals, but the total yield of crystalline product was never over 60% of the original sirup.

(8) F. J. Bates and Associates, *Polarimetry, Saccharimetry and the Sugars*, Circular of the National Bureau of Standards C440, U. S. Government Printing Office, Washington, 1942, p. 210.

(9) R. H. Horrocks, *Nature*, **164**, 444 (1949).

(10) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).

2-O-Benzyl-L-glyceric acid. Six grams of crystalline 2-*O*-benzyl-L-arabinose was dissolved in 100 ml. of water and the *p*H was adjusted to 10 with potassium hydroxide. Sodium borohydride (500 mg.) in about 2 ml. of water, adjusted to *p*H 10, was added and the solution was left for 10 hr. After treatment with Dowex 50 H^+ to remove the excess borohydride, the solution was nonreducing.

After concentration to a small volume, the borate was removed as the methyl ester by taking the product to dryness repeatedly from methanol. The final semicrystalline colorless sirup weighed 6 g. (100%) and was oxidized without further purification. For the oxidation 10.64 g. of sodium periodate was dissolved in 100 ml. of water and the solution was cooled in an ice bath. A concentrated aqueous solution of 6 g. of benzyl arabitol was then added slowly with rapid stirring, the addition being completed in about 30 min. Ten minutes later a couple of drops of glycerol were added and the reaction mixture was extracted three times with 100 ml. of ether. The dry ether solution was concentrated and gave 4.6 g. (100%) of a reducing, colorless sirup. This sirup (2-*O*-benzyl-L-glyceraldehyde) was dissolved in 100 ml. of water and a solution of 9.6 g. of iodine and 11.7 g. of potassium iodide in 15 ml. of water was added followed immediately by a solution of 8.9 g. of potassium carbonate and 6.9 g. of potassium bicarbonate in 80 ml. of water. After 2 hr. in the dark, the reaction mixture was acidified with 5*N* sulfuric acid, and the excess iodine was destroyed with thiosulfate. The product was extracted into ether, and after drying the ether solution over sodium sulfate, the ether was removed, yielding 2.7 g. (55%) of a colorless sirup, having a neutralization equivalent corresponding to that of 2-*O*-benzyl-glyceric acid. The cyclohexylammonium salt could be crystallized from absolute ethanol and gave a melting point of 156–157°.

L-Glyceric acid 2-phosphate. One and seven tenths grams of the above sirup of 2-*O*-benzyl-L-glyceric acid in 20 ml. of ether was treated with an excess of etheral diazomethane, and upon concentration 1.8 g. of the methyl ester was obtained as a sirup (100%). The sirup was dissolved in 15 ml. of dry pyridine, and 2 ml. of benzoyl chloride (10% excess) was added slowly to the ice cold pyridine solution. After 20 hr. at 4°, a few drops of water was added, followed by 50 ml. of chloroform. The chloroform phase was washed with 50 ml. portions of 1*N* hydrochloric acid, 1*M* potassium bicarbonate and water, and the pyridine free, neutral chloroform solution was dried over sodium sulfate. Upon removal of solvent (high vacuum at 50°), 2.8 g. of methyl 3-*O*-benzoyl-2-*O*-benzyl-L-glycerate (100%) was obtained as a sirup. The benzyl group was next removed by catalytic hydrogenation with palladium on carbon in ethanol solution. The theoretical uptake of hydrogen (210 ml.) was completed in 2 hr., and after removal of catalyst and solvent, 2 g. of a semicrystalline residue of methyl 3-*O*-benzoyl-L-glycerate was obtained (100%). This was phosphorylated directly in 20 ml. of dry pyridine with 2 g. of diphenyl phosphorochloridate at ice bath temperature. After 10 hr. at 4°, the reaction mixture was freed of pyridine hydrochloride and excess reagent as indicated in the benzoylation step, yielding finally 2.5 g. of a sirupy product (66%) of methyl 3-*O*-benzoyl-2-*O*-diphenyl phosphonyl-L-glycerate. The phenyl groups were removed by hydrogenation with 500 mg. of platinum oxide catalyst and the theoretical uptake of 1430 ml. of hydrogen was completed in 90 min. The ethanol solution was freed of catalyst and 20 ml. of 1*N* sodium hydroxide was added to saponify the methyl and benzoyl esters. The ethanol was removed and another 5 ml. of base was added to complete the saponification. Attempts to obtain the crystalline sodium salt of L-glyceric acid 2-phosphate failed, and the product was converted to the tricyclohexylammonium salt which crystallized from water-acetone. One and three tenths grams of crystals was collected (50%). The product was indistinguishable from authentic D-glyceric acid 2-phosphate[2] on paper chromatography in several solvents. After conversion to the free acid it titrated with 3 equivalents of base, and its optical rotation was numerically very similar to that of the D-isomer (Table I).

L-Glyceric acid 3-phosphate. One and eight tenths grams of methyl 2-*O*-benzyl-L-glycerate was phosphorylated as above with 1.9 ml. of diphenyl phosphorochloridate in 10 ml. of pyridine. The product after the workup (3.05 g. of methyl 2-*O*-benzyl-3-*O*-diphenylphosphonylglycerate) was reduced with palladium and hydrogen (170 ml. in 1 hr.) and platinum and hydrogen (1400 ml. in 2 hr.) and after saponification with 20 ml. of 1*M* sodium hydroxide, the tricyclohexylammonium salt of L-glyceric acid 3-phosphate (1.8 g., 71% yield) was collected. Again the product was indistinguishable from the authentic D-isomer by its titration and chromatographic properties, and numerically the optical rotation checked well with that of the D-isomer (Table I).

Acknowledgment. This work was supported by a U. S. Public Health Grant, RG-6370. Some of the experiments were done in the laboratory of Dr. C. E. Ballou, Department of Biochemistry, University of California, Berkeley, Calif.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CREIGHTON UNIVERSITY]

Long Carbon-Chain Sugars. Condensation of Diethyl Acetonedicarboxylate with Aldoses in Concentrated Hydrochloric Acid at 0°

PHILIPPOS E. PAPADAKIS

Received May 6, 1960

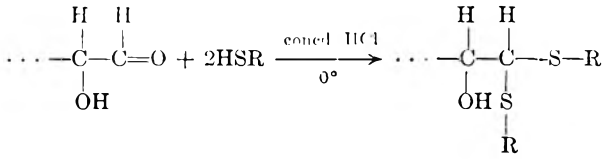
Diethyl acetonedicarboxylate condenses with D-glucose, L-arabinose, and D-xylose, respectively, in concentrated hydrochloric acid at 0°, producing carbethoxy derivatives of long chain unsaturated keto sugars.

The molar proportion of the ester to the aldose condensed was 1:1 or 1:2 depending on the relative concentration of the reagents and the reaction time.

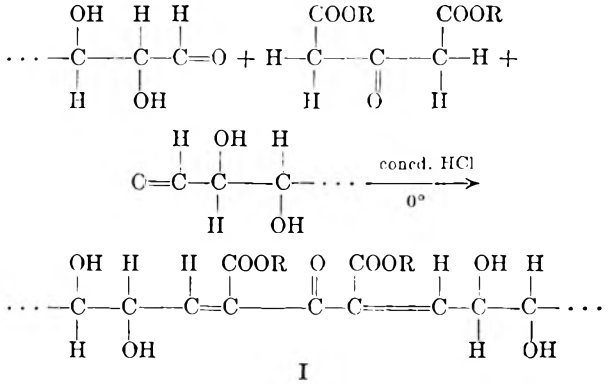
The products were converted and characterized as phenylhydrazine or 2,4-dinitrophenylhydrazine derivatives.

In a previous publication[1] the condensation of diethyl acetonedicarboxylate with 1,2-*O*-isopropylidene-D-xylopentadialdose, using piperidine as a catalyst was described. It was pointed out then, that this method favored the formation of long chain sugars. In view of the method used in the

(1) P. E. Papadakis, *J. Org. Chem.*, **20**, 630 (1955).



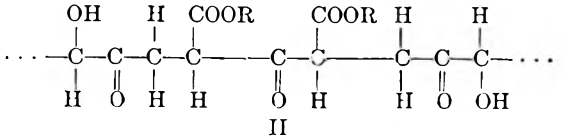
preparation of glucose diethyl thioacetal[2] it seemed reasonable that with similar reagents and conditions which apparently favored the aldehyde form of glucose, the latter may react with the methylene group of β-dicarbonyl compounds such as diethyl acetonedicarboxylate or other carbonyl compounds having *alpha* carbon hydrogens to produce derivatives of long carbon chain sugars.



I

Depending on the concentration of the reagents and on the time of the reaction at 0° one may expect that the product may be the result of a reaction of one aldose to one ester or of two aldoses to one ester. Such products, due to structural reasons, would be expected to be partially soluble in ethyl acetate and in water. The product of one aldose to one ester would be, relatively, more soluble in ethyl acetate than the product of the reaction of two aldoses to one ester and the latter more soluble in hot water.

Under alkaline conditions and with a reagent such as phenylhydrazine structure I by tautomerization of hydrogens may be converted to structure II which will react with a greater proportion of phenylhydrazine than compound I. Besides the

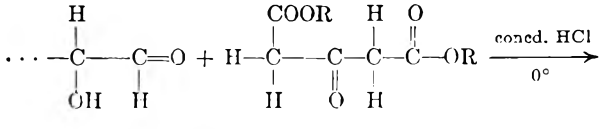


II

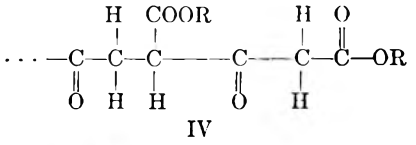
phenylhydrazone formation with each of the keto groups in formulas I and II, excess phenylhydrazine and a longer period of heating may produce phenylhydrazide derivatives with the ester groups. The experimental part furnishes evidence that such transformations take place.

In the present paper diethyl acetonedicarboxylate was treated with reducing sugars D-glucose, L-arabinose, and D-xylose in concentrated hydrochloric acid at 0°. In the preliminary experiments the reaction time period was three hours. In later experiments the time period was extended to three days as excess of the aldose and longer reaction time period favored the reaction of the molar proportion of two aldoses to one ester. After the reaction time period the hydrochloric acid was either neutralized with cold alkali solution or it was allowed to react with ether to remove any unchanged diethyl acetonedicarboxylate; thereafter the procedure was varied to suit the purpose of the respective experiments.

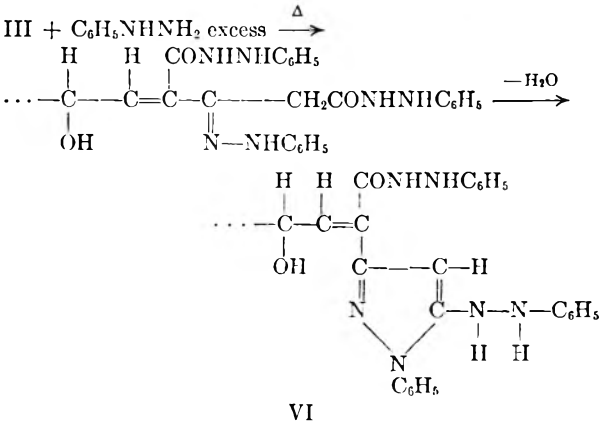
In an experiment with glucose (reaction time period three hours) after the ether extraction the mixture was extracted several times with ethyl acetate. After evaporation of the solvent the residue was processed with phenyl hydrazine. In another experiment the mixture without extracting with ethyl acetate was treated with phenylhydrazine. The derivative melts at 202°, and the carbon, hydrogen, and nitrogen analyses correspond to the formula $C_{29}H_{32}O_6N_6$, formula VI. This may be explained as follows:



III

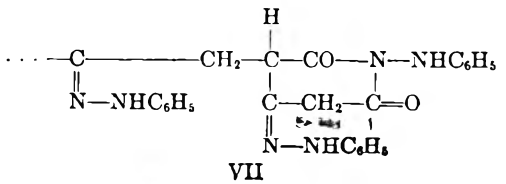


IV



VI

Compound IV with phenyl hydrazine may form an isomeric compound VII.

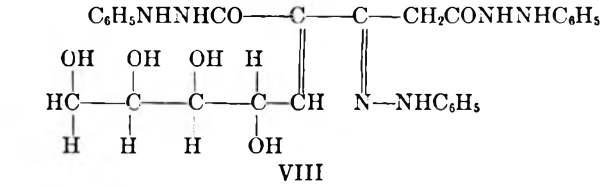


VII

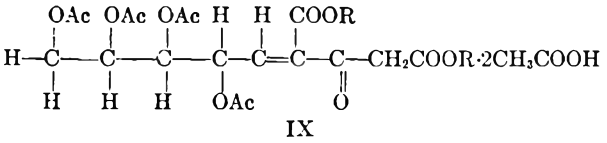
(2) E. Fischer, *Ber.*, 27, 673 (1894).

A similar experiment with L-arabinose (reaction time period three hours) rendered a phenylhydrazine derivative of the material extracted by ethyl acetate which may be represented by formula VIII. After the ethyl acetate extraction the water solution was evaporated and the residue was acetylated. The analysis of the acetylated product corresponded to formula IX. Part of the acetylated product was dissolved in methanol and treated with 2,4-dinitrophenylhydrazine according to the method described by Cheronis.[3]

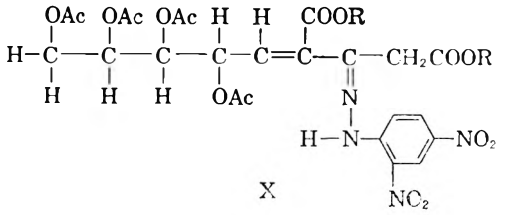
The product corresponds to formula X. With excess 2,4-dinitrophenylhydrazine and longer period of heating the analysis of the product obtained corresponds to formula XI.



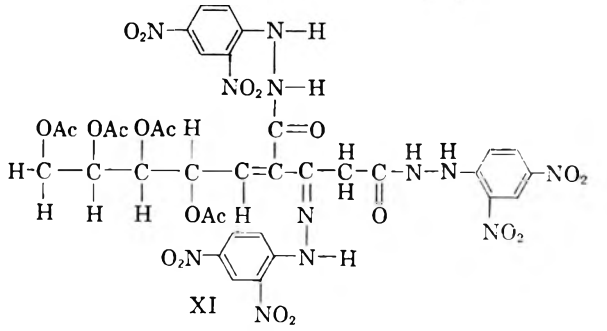
VIII



IX



X

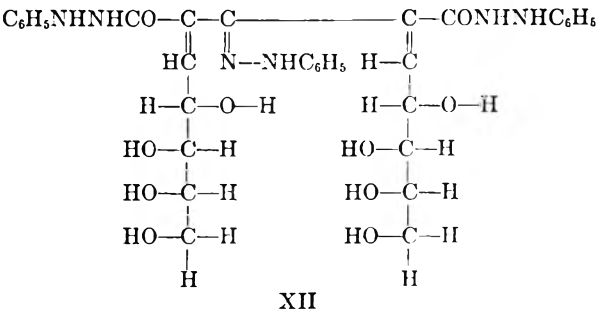


XI

The results indicate that under the conditions of the experiments the reaction of the L-arabinose to diethyl acetonedicarboxylate took place in a 1:1 molar proportion.

In later experiments with L-arabinose the reaction time period was extended to three days. After the addition of the sodium acetate the ether and ethyl acetate did not extract any significant amount of material. The water solution containing the product (inorganic salts and acetic acid) was evaporated and the residue was treated with phenylhydrazine (phenylhydrazine hydrochloride + excess sodium acetate solution), and the derivative was processed and isolated.

In one experiment analysis of the product for nitrogen gave the values 12.21, 12.40, and 12.38; calculated for $C_{33}H_{40}O_{10}N_6$, nitrogen is 12.31% which may be represented by formula XII.



XII

In another experiment where excess phenylhydrazine was used with longer period of heating the product obtained was divided into two parts, A and B, where the A part was the more readily soluble in alcohol. The analysis of the material from A corresponds to formula XIII. The analysis of the material from B may be represented by formula XIV. (See previous discussion concerning formula II.)

The experiment was repeated and the product obtained was recrystallized from boiling water and then dried under 3 mm. pressure and room temperature for four hours. The analysis of the product corresponded to a dihydrate of formula XIV. A similar experiment with D-xylose rendered a phenylhydrazine derivative the analysis of which for carbon, hydrogen, and nitrogen corresponds to $C_{46}H_{52}O_8N_{10}.2H_2O$ and may be represented by formula XV. Further work is in progress.

EXPERIMENTAL

The reaction of diethyl acetonedicarboxylate with D-*glucose in concentrated hydrochloric acid at 0°.* To a solution of 3.6 g. of glucose dissolved in cond. hydrochloric acid at 0°, 2.02 g. of diethyl acetonedicarboxylate was added with stirring. This mixture was neutralized with cold sodium hydroxide solution. The mixture was extracted with ether to remove any unchanged diethyl acetonedicarboxylate. The water solution containing the product was treated with phenylhydrazine, (phenylhydrazine hydrochloride + sodium acetate solution). A yellow precipitate formed which was filtered, then dissolved in alcohol, and reprecipitated with distilled water. The precipitate was filtered and dried *in vacuo* and 100° temperature, m.p. 202°. formula VI.

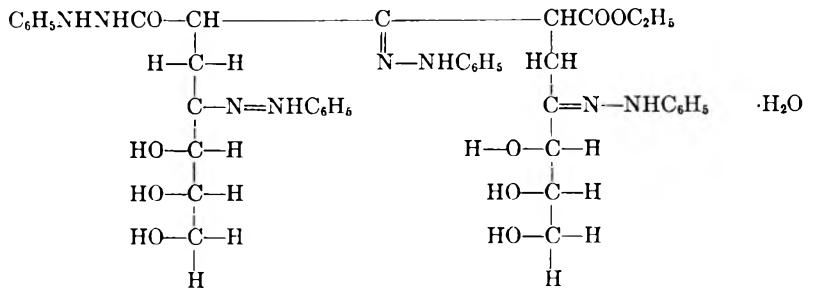
Anal. Calcd. for $C_{29}H_{32}O_6N_6$: C, 62.11; H, 5.71; N, 14.99. Found: C, 61.81; H, 5.80; N, 14.98; 14.83.

The experiment was repeated. Instead of neutralizing the hydrochloric acid with sodium hydroxide, sodium acetate was used, and the material was dried at room temperature and atmospheric pressure in a desiccator. The rest of the procedure was the same as before. The phenylhydrazine derivative thus obtained melted at 186°, formula V.

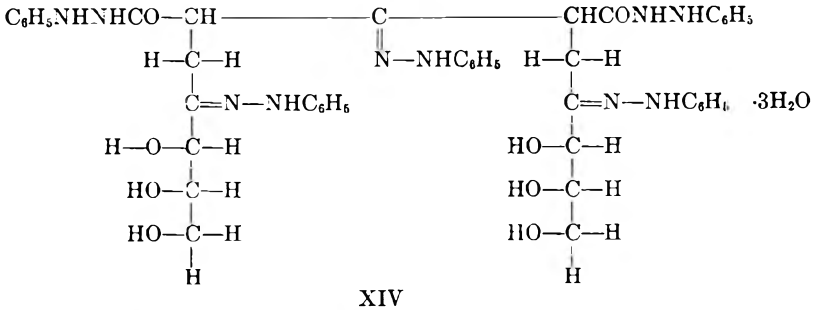
Anal. Calcd. for $C_{29}H_{34}O_7N_6$: C, 60.20; H, 5.88. Found: C, 60.15; H, 6.30.

The reaction of diethyl acetonedicarboxylate with L-*arabinose in concentrated hydrochloric acid at 0°.* To a solution of 21 g.

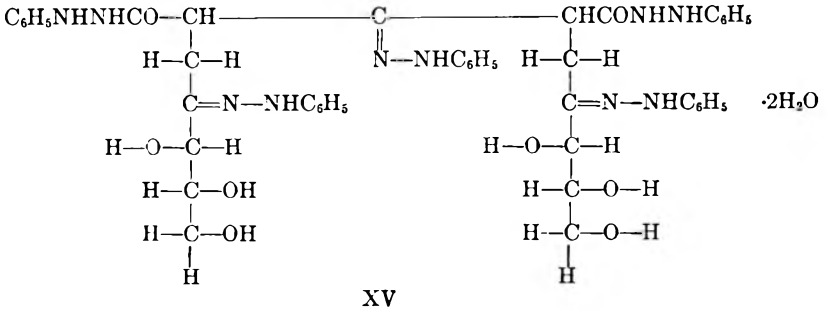
(3) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, Thomas Y. Crowell Co., New York, N. Y., 1947, p. 247.



XIII



XIV



XV

of L-arabinose in concd. hydrochloric acid at 0°, 14 g. of diethyl acetonedicarboxylate was added with stirring; the mixture was kept at 0° for 3 hr. then it was extracted several times with 30-ml. portions of ethyl acetate. The combined ethyl acetate was shaken with silver oxide, filtered, and the filtrate concentrated to a thick sirup. The latter was stirred with ether and petroleum ether (b.p. 39.9–44.5°) to extract any uncharged diethyl acetonedicarboxylate.

The part that did not dissolve in the ether was treated with phenyl hydrazine acetate. A yellow precipitate formed and some gum which rendered a brown powder after drying. The brown material was washed with ether, then it was dissolved in alcohol and reprecipitated with distilled water. A brown orange material resulted, formula VIII.

Anal. Calcd. for $C_{28}H_{30}N_6O_6$: C, 61.52; H, 5.53. Found: C, 61.28; H, 5.40.

To the water solution after the ethyl acetate extraction enough sodium acetate was added to react with the hydrochloric acid. The water of the solution was distilled *in vacuo*. The mixture was subjected to acetylation using acetic anhydride. The acetylated material was stirred with ice water, filtered and dried; m.p. 97°, formula IX.

Anal. Calcd. for $C_{26}H_{38}O_{17}\cdot 2CH_3COOH$: C, 50.15; H, 6.15. Found: C, 49.90; H, 5.87.

Part of the acetylated product was dissolved in methanol and treated with a methanol solution of 2,4-dinitrophenylhydrazine.[3] A light yellow precipitate formed which was recrystallized from methanol, m.p. 127°, formula X.

Anal. Calcd. for $C_{28}H_{34}O_{16}N_4\cdot H_2O$: C, 48.00; H, 5.18. Found: C, 47.68; H, 5.08.

With excess 2,4-dinitrophenylhydrazine and longer heating and standing a red brown precipitate was formed which began to sinter at 144° and melted at 166°, phenylhydrazide derivative of formula XI.

Anal. Calcd. for $C_{36}H_{34}O_{22}N_{12}\cdot 3H_2O$: C, 41.54; H, 3.87. Found: C, 41.73; H, 3.60.

In the following experiments the method was varied. The molar proportion of the L-arabinose to the ester was 2:1. The reaction time period was extended from 3 hr. to 3 days. The temperature was 0°. Little more than the calculated amount of sodium acetate was used to neutralize the concd. hydrochloric acid. The water solution was extracted with petroleum ether and with ethyl acetate. The water layer containing the product and inorganic salts was treated with phenylhydrazine solution in the usual way and the precipitate formed was filtered, dissolved in alcohol, and reprecipitated with distilled water. It was dried and analyzed for nitrogen; Formula XII.

Anal. Calcd. for $C_{33}H_{40}N_6O_{10}$: %N, 12.31. Found: %N, 12.21; 12.40; 12.38.

The experiment was repeated using excess of phenylhydrazine and heating a longer period of time. The product was processed as before but in the process of purification, the phenylhydrazine derivative was divided in two portions. The part which was more readily dissolved in alcohol was marked A and the less soluble was marked B. The material processed from A, m.p. 146° gave the following analysis: Formula (XIII).

Anal. Calcd. for $C_{41}H_{50}O_6N_8\cdot H_2O$: C, 60.27; H, 6.01; N, 13.71. Found: C, 60.72; H, 6.42; N, 13.62.

The material from B gave the following analysis: Formula (XIV).

Anal. Calcd. for $C_{45}H_{52}O_8N_{10}\cdot 3H_2O$: C, 59.08; H, 6.34; N, 15.31. Found: C, 58.98; H, 6.37; N, 14.95.

The experiment was repeated as above with the following modification. Instead of separating the phenylhydrazine derivative on the basis of its solubility in alcohol into fractions A and B, the product was recrystallized from boiling distilled water. The material obtained was dried first on porous tile and second under reduced pressure, 3 mm., at room temperature; Formula XIV—H_2O.

Anal. Calcd. for $C_{45}H_{52}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.25; N, 15.60. Found: C, 60.04; H, 5.98; N, 15.77.

The reaction of diethyl acetonedicarboxylate with D-*xylose in concentrated hydrochloric acid at 0°.* To a solution of 3 g. of xylose in concd. hydrochloric acid at 0°, 2 ml. of diethyl acetonedicarboxylate was added with stirring. The mixture was placed in a refrigerator and allowed to stand for 3 days, then the calculated amount of sodium acetate was added to neutralize the hydrochloric acid. The mixture was shaken with ether and petroleum ether to remove any unchanged ester. The product in the water layer was converted to a phenylhydrazine derivative in the usual way. The precipitate was dissolved in alcohol and reprecipitated with distilled water. The precipitate was filtered and dried in a desiccator, m.p. 176°; Formula (XV).

Anal. Calcd. for $C_{45}H_{50}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.29; N, 15.60. Found: C, 60.14; H, 5.95; N, 15.91.

Further work is in progress with other reagents having active *alpha* carbon hydrogen adjacent to a carbonyl or other appropriate group, with the aldoses, ketoses, and dialdehyde monoses.

Acknowledgment. The author wishes to express his appreciation to his student, Marshall Jacks, for his cooperation.

OMAHA, NEB.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Hydrolysis of 5,5-Disubstituted Barbituric Acids

MORRIS FREIFELDER, ADOLPH O. GEISZLER, AND GEORGE R. STONE

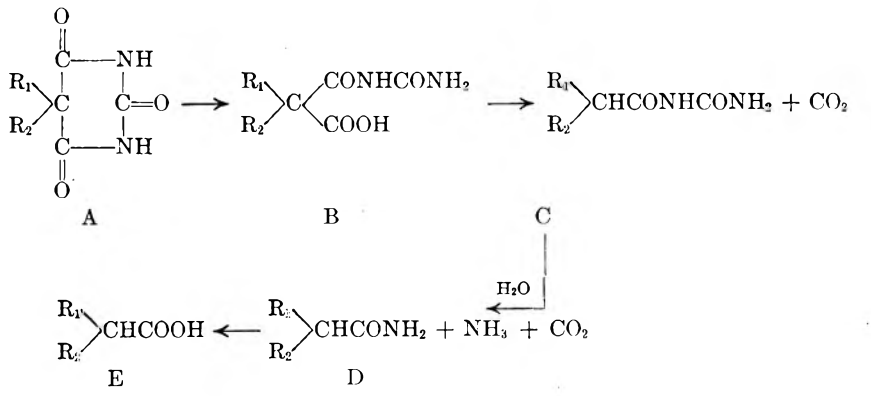
Received May 18, 1960

A rapid and simple method of hydrolysis of 5,5-disubstituted barbituric acids to the corresponding amides is reported. High yields are obtained when the reactions are carried out in dilute aqueous ammonia at 200° for five to ten minutes. In only one case was acylated urea obtained. Twenty-three of the compounds reported are new.

Amides of the type $R_1R_2CHCONH_2$ (where R_1 and R_2 are one or both of alkyl, unsaturated alkyl, and cycloalkyl groups) are widely reported. They normally are prepared from disubstituted acetic acids $-R_1R_2CHCOOH-$ by classical methods. The substituted acetic acids generally are obtained by hydrolysis and decarboxylation of dialkylated malonic or cyanoacetic esters.

The conversion of these esters to the corresponding acetic acids is time consuming and often troublesome.[1a,b] However, it is well known that the condensation of such esters with urea in the presence of sodium ethoxide[2] gives 5,5-disubstituted barbituric acids in good yield. Therefore it appeared advantageous to investigate their hydrolysis as a method of preparing disubstituted acetamides.

The hydrolysis of barbituric acids proceeds first by opening of the pyrimidine ring and decarboxylation to form an acylurea (C), followed by decomposition to the corresponding amide (D), carbon dioxide, and ammonia. More vigorous hydrolysis leads to E.



The alkaline hydrolysis of A at atmospheric conditions and at 100° in a bomb[1b] has been reported to give ureas (C). In a study of the hydrolysis of 5-substituted barbituric acids at 5–10 atmospheres pressure under various *p*H conditions Ruhkopf[3] obtained both ureas and amides. He

(1) (a) F. F. Blicke and P. Centolella, *J. Am. Chem. Soc.*, 60, 2923 (1938), (b) E. H. Volwiler and D. L. Tabern, *J. Am. Chem. Soc.*, 58, 1352 (1936) report on the difficulty of hydrolyzing certain higher substituted malonic esters.

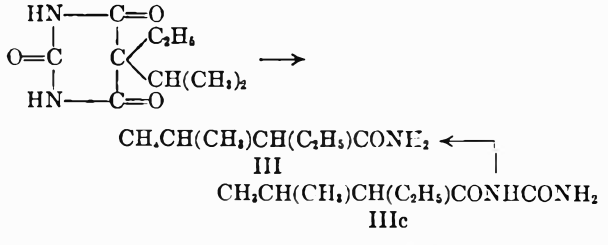
(2) W. J. Doran, *Medicinal Chemistry*, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 5.

(3) H. Ruhkopf, *Ber.*, 73, 938 (1940). The author also cites references describing the path of hydrolysis.

suggests that formation of either is dependent on pressure and the buffer.

The formation of two gaseous products of hydrolysis, ammonia and carbon dioxide, the volume of reactants, and the void of the reaction vessel will all have an effect on the pressure temperature relationship. As the size of the autoclave is not mentioned in Ruhkopf's experimental data, placing dependence on pressure could lead to erroneous conclusions.

We therefore thought more reliable results would follow if the course of the reaction were observed and the temperature and pressure noted. We found that at about 200° a significant surge of pressure took place. This rise, up to 25 atmospheres and above, suggested that this temperature was the point of optimum hydrolysis to the amide. This observation led us to conclude that most intermediate ureas would not be stable under such conditions. The absence of any urea (IIIc) in the hydrolysis of 5-ethyl-5-isopropylbarbituric acid and a comparison of this hydrolysis with that of α-ethyl-β-methylbutyrylurea in excess dilute aqueous ammonia for five to ten minutes reaction time at 200° seems to support this conclusion. From each reaction III was obtained in 91.8 and 93.5% yields, respectively.

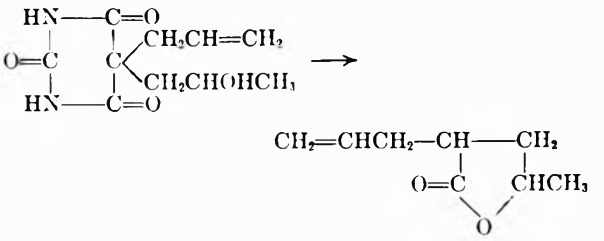


In order to determine the best reaction medium we hydrolyzed 5-ethyl-5-(1-methylpropyl)barbituric acid in water or with an equivalent of aqueous sodium hydroxide, and in excess dilute aqueous ammonia for the five to ten minute period at 200°. When Ruhkopf's conditions[3] were used with this same barbituric acid, the yield obtained compared well with the other procedures. However, its purity was questionable, as it melted over a wide range. When the reaction temperature was raised to 200° for six hours, a good product resulted.

Hydrolysis in water proved satisfactory only if the reaction were carried out at higher temperature and for a longer heating period (one hour). At 200° 95% of the starting barbituric acid was recovered. Lower yield was obtained with sodium hydroxide. The use of excess sodium hydroxide in hydrolysis is known to give malonamides.[4] When the best yield of X (90%) was obtained by hydrolysis of 5-ethyl-5-(1-methylpropyl)barbituric acid in dilute aqueous ammonia, we used this medium as the one of choice in most of the experiments.

With a few exceptions, hydrolysis at 200° with aqueous ammonia gave good yields (75–97.5%). In only one experiment was any acrylurea obtained. When 5-(1-methylbutyl)-5-propargylbarbituric acid was hydrolyzed we were able to isolate and identify 2-propargyl-3-methylhexanoylurea in addition to compound XXX. It should be noted that, while we were able to obtain an amide (XXIII) from the corresponding thiobarbituric acid, in general hydrolysis of this group of compounds gave materials difficult to purify.

Of particular interest was the hydrolysis of 5-allyl-5-(β-hydroxypropyl) barbituric acid. Even under the mildest conditions (at 120°) the lactone was formed and in no instance were we able to isolate either amide or urea.



EXPERIMENTAL

The barbituric acids used in this work were prepared by literature methods or were commercially available.

The following is an example of the preferred method of hydrolysis. *2-Ethyl-3-methylpentamide* (X). Twenty grams (0.0945 mole) of 5-ethyl-5-(1-methylbutyl)barbituric acid was dissolved in 50 cc. of water and 50 cc. of concd. aqueous ammonia (29%). The solution was placed in a 183-cc. stainless steel rocker type bomb and heated for 5-10 min. at 200°. The vessel was removed from the source of heat and cooled to at least 70° before opening. The contents were cooled thoroughly, filtered, and washed with cold water. The product melted at 112° and weighed 13.3 g. (almost quantitative). After recrystallization from dilute alcohol the melting point rose to 113.5–114° and the yield was 90%. In general, the saturated amides were recrystallized from dilute alcohol or water. The unsaturated amides were recrystallized from petroleum ether (b.p. 63–68°).

Hydrolysis in water. Fifty grams (0.236 mole) of 5-ethyl-5-(1-methylpropyl)barbituric acid was placed in a 1 l. stainless steel rocker type bomb along with 500 cc. of water. The mixture was heated for 1 hr. at 225°. The reaction vessel was removed from the source of heat immediately and cooled. After opening, the contents were cooled thoroughly and filtered. The amide melting at 112° was obtained in 82% yield. Recrystallization from dilute alcohol raised the melting point to 113–115°. When this reaction was run at 200° for 10 min., 95% of the barbituric acid was recovered.

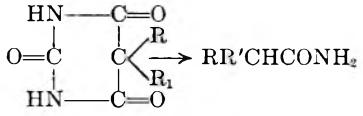
Method of Ruhkopf.[3] The same experiment was carried out at 180°[5] for 6 hr. After thoroughly cooling the contents of the reactor, the precipitate was filtered and washed with cold water and dried. An 85.8% yield of product melting from 90–105° was obtained. It was suspended in dilute sodium hydroxide, stirred, filtered, and washed with cold

(4) H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.*, **20**, 16 pp. (1955) or *Chem. Abstr.*, **50**, 11351 (1956) reports that hydrolysis at 100° with two or more equivalents of sodium hydroxide leads to malonamides. With 5,5-diethylbarbituric acid at 200° we obtained diethylmalonic acid.

(5) The pressure resulting from heating water in a closed system at 180° is about 10 atm.

TABLE I

HYDROLYSIS TO AMIDES



	Amides		Yield,			Carbon, %		Hydrogen, %		Nitrogen, %	
	R	R_1	%	M.P.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	C_2H_5	C_2H_5	74.5	112[a]	$C_8H_{14}NO$						
II	C_2H_5	CH_2=$CHCH_2$	63	75–77	$C_7H_{12}NO$	66.10	66.03	10.30	10.06	11.01	11.00
III	C_2H_5	$(CH_3)_2CH$	91.8	137.5[b]	$C_7H_{15}NO$						
IV	$CH_3CH_2CH(CH_3)$	CH_3	80.2	90–91	$C_7H_{15}NO$	65.17	65.43	11.72	11.96	10.86	10.57
V	CH_2=$CHCH_2$	CH_2=$CHCH_2$	75	84–85[c]	$C_8H_{13}NO$	69.03	69.07	9.41	9.56	10.06	10.10
VI	CH_2=$CHCH_2$	$(CH_3)_2CH$	82	108–110[d]	$C_8H_{15}NO$	68.04	67.81	10.71	10.72	9.92	9.73
VII	CH_2=$C(CH_3)CH_2$	C_2H_5	70	67–68	$C_8H_{15}NO$	68.04	67.91	10.71	10.88	9.92	9.76
VIII	CH_2=$CHCH_2$	C_3H_7	87	95–96	$C_8H_{15}NO$	68.04	67.99	10.71	10.71	9.92	10.11
IX	C_4H_9	C_2H_5	86	101.5[e]	$C_9H_{17}NO$	67.09	67.39	11.96	11.88		
X	$CH_3CH_2CH(CH_3)$	C_2H_5	90	113.5–114[f]	$C_8H_{17}NO$						
XI	CH_2=$C(CH_3)CH_2$	CH_2=$CHCH_2$	81	69–70	$C_9H_{15}NO$	70.55	70.85	9.87	10.11	9.14	9.35
XII	$CH_3CH_2CH(CH_3)$	CH_2=$CHCH_2$	84	92	$C_9H_{17}NO$	69.63	69.83	11.04	11.16	9.02	9.16
XIII	C_4H_9	CH_2=$CHCH_2$	78.5	92–92.5	$C_9H_{17}NO$	69.63	69.50	11.04	11.03	9.02	9.22
XIV	$(CH_3)_2CHCH_2$	CH_2=$CHCH_2$	97.5	78–79	$C_9H_{17}NO$	69.63	69.73	11.04	11.23	9.02	9.17
XV	$(CH_3)_2CHCH_2CH_2$	C_2H_5	88	110–111[g]	$C_9H_{19}NO$	68.74	68.87	12.18	11.94	8.91	9.02
XVI	$CH_3CH_2CH(CH_3)CH_2$	CH_2=$CHCH_2$	74	68–69	$C_{10}H_{19}NO$	70.96	70.92	11.32	11.56	8.28	8.38
XVII	C_5H_{11}	CH_2=$CHCH_2$	90	70–71	$C_{10}H_{19}NO$	70.96	71.11	11.32	11.50	8.28	8.30
XVIII	$C_3H_7CH(CH_3)$	CH_2=$CHCH_2$	91.8	79.5–80[h]	$C_{10}H_{19}NO$[i]	70.96	71.11	11.32	10.89	8.28	8.42
XIX	$C_2H_5CH(C_2H_5)CH_2$	C_2H_5	81.8	50–52	$C_{10}H_{21}NO$	70.11	69.80	12.36	12.60	8.18	8.00
XX	C_6H_{13}	C_2H_5	93.3	103.5–104	$C_{10}H_{21}NO$	70.11	70.36	12.36	12.52	8.18	8.42
XXI	$C_3H_7CH(CH_3)$	C_3H_7	81.5	108.5–110[j]	$C_{10}H_{21}NO$	70.11	70.16	12.36	12.45	8.18	8.35
XXII	$C_6H_{11}CH_2$	C_2H_5	78.5	99	$C_{11}H_{21}NO$	72.07	71.86	11.55	11.68	7.64	7.74
XXIII	C_5H_{13}	CH_2=$CHCH_2$	58[k]	79–81	$C_{11}H_{21}NO$	72.07	72.10	11.55	11.55	7.64	7.49
XXIV	C_4H_9	$C_3H_7CH(CH_3)$	89.8	95–96[l]	$C_{11}H_{23}NO$	71.29	71.16	12.51	12.71	7.56	7.84
XXV	C_5H_{11}	$(CH_3)_2CHCH_2$	95.2	69–71	$C_{11}H_{23}NO$	71.29	71.39	12.51	12.71	7.56	7.49
XXVI	$(CH_3)_2CHCH_2CH_2$	$(CH_3)_2CHCH_2$	87.6	82–83	$C_{11}H_{23}NO$	71.29	70.98	12.51	12.71	7.56	7.54
XXVII	C_6H_{11}	C_4H_9	94.8	117–118	$C_{11}H_{23}NO$[m]	71.29	71.01	12.51	12.71	7.56	7.68
XXVIII	$CH_3CH(CH_3)CH_2CH(CH_3)CH_2$	C_2H_5	85	50–52[n]	$C_{11}H_{23}NO$	71.29	71.38	12.51	12.71	7.56	7.63
XXIX	$C_4H_9CH(C_2H_5)CH_2$	C_2H_5	96.9	58–59.5	$C_{12}H_{25}NO$	72.31	71.96	12.64	12.64	7.03	7.12
XXX	$C_3H_7CH(CH_3)$	CH≡CCH_2	50.2	Oil[o]	$C_{10}H_{17}NO$						

[a] M. Freund and P. Hermann, *Ber.*, **23**, 190 (1890) gives m.p. of 105°, 107° recorded by E. Fischer and A. Dilthey, *Ber.*, **35**, 844 (1902). [b] Described m.p. 134–134.5°, A. W. Crossley and H. R. Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900). [c] Described 82.5°, E. Oberreit, *Ber.*, **29**, 2005 (1896). [d] Reported as 107° by J. D. Riedel, German Patent **461,814** (1930). [e] H. S. Raper, *J. Chem. Soc.*, **91**, 1831 (1907) gives 101.5°; F. F. Blicke and A. P. Centolella, *J. Am. Chem. Soc.*, **60**, 2924 (1938) report 106–107° (from water). [f] N. M. Katznelson and M. S. Kondakova, Russ. Pat. *40850* (1934) report 114–115°. [g] Ref. 1b gives 106–108°. [h] Ref. 1b gives 90–91°. [i] Also analyzed for oxygen. Calcd., 9.44. Found, 9.72. [j] First distilled at 195° (2 mm.), then recrystallized from dil. alcohol. [k] This amide was prepared from the corresponding thiobarbituric acid. [l] See ref. 1b, m.p. 97–98°. [m] Also analyzed for oxygen. Calcd., 8.69. Found, 8.61. [n] Distilled at 127–129° (1.5–1.7 mm.). The product solidified and melted at 48°. The distilled product appeared to pick up moisture and equilibrate at about 0.25 H_2O. Calcd. for hydrate: C, 69.61; H, 12.47; O, 10.54. Found: C, 70.11; H, 12.42; O, 10.65. After 48 hours drying m.p. rose to 50–52° and analysis was satisfactory for dried compound. [o] Liquid boiling at 140° (2.8 mm.). The distilled product seems to be hygroscopic and equilibrates at about 0.25 H_2O. Calcd. for hydrate: C, 69.90; H, 10.27; N, 8.15; O, 11.54. Found: C, 69.92; H, 10.27; N, 8.31; O, 10.99.

water. The yield dropped to 70.5% and the product still melted poorly (103–110°). However, after recrystallization from dilute alcohol the melting point was satisfactory. When this same experiment was carried out at 200° for 6 hr. an 83.5% yield of X was obtained. It melted at 110–113° before recrystallization.

Hydrolysis with sodium hydroxide. When the sodium salt of the barbituric acid in water (*p*H 9.0) was heated at 200° for 5–10 min. a 78% yield of X melting at 110–112° was obtained. However, when the free acid was hydrolyzed in the presence of an equivalent of sodium hydroxide under the same conditions, the yield dropped unless the *p*H of the solution had been adjusted with acetic acid to about *p*H 9.0 before reaction.

2-Allyloctanamide (XXIII). *Hydrolysis of 5-allyl-5-hexylthiobarbituric acid.* 5-Allyl-5-hexylthiobarbituric acid (8.05 g., 0.03 mole) in 25 cc. of water and 25 cc. of concd. aqueous ammonia were placed in a glass lined Hastelloy bomb and heated for 5–10 min. at 200°. After cooling, the vessel was vented. A strong odor of hydrogen sulfide was noted. The white crystalline solid was filtered and washed with cold water. It did not give satisfactory analysis after recrystallization from petroleum ether (b.p. 63–68°). It was then dissolved in anhydrous ether, filtered from insoluble material, and dried in a rotary drier with slight warming while under reduced pressure. After thorough drying, the product gave a satisfactory analysis (see Table I).

Several other thiobarbituric acids were subjected to the same conditions, but isolation difficulties caused us to abandon any further work with them.

2-Propargyl-3-methylhexanoylurea. A solution of 9.0 g. (0.038 mole) of 5-propargyl-5-(1-methylbutyl) barbituric acid in 40 cc. of water and 40 cc. of concd. aqueous ammonia was heated for 5–10 min. at 200°. After removal from the source of heat and cooling as in the other examples a crystalline solid plus some oily material was obtained. The mixture was treated with anhydrous ether and filtered. The solid was ether insoluble. The filtrate was further extracted for work up and distillation and isolation of compound XXX.

The ether insoluble product weighing 2.0 g. was recrystallized from dilute alcohol. It melted at 200°.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.82; H, 8.62; N, 13.32. Found: C, 62.92; H, 8.85; N, 13.32.

α-Allyl-γ-methylbutyrolactone. Thirty-three grams (0.146 mole) of 5-allyl-5-(2-hydroxypropyl)barbituric acid was hydrolyzed in 75 cc. of water and 75 cc. of concd. aqueous ammonia for 5–10 min. at 200°. The resulting product was an oil which was extracted from the reaction mixture with ether. The ether extract was dried over anhydrous magnesium sulfate and then the ether was removed. The residue was distilled and the fraction boiling at 77–80°; 1 mm., n^{25}_D 1.4519 was collected. The yield amounted to 60%.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.87; H, 8.77.

Similar runs at 150° and even at 120° yielded the same product. All were shown to be identical by infrared analysis.

α-Ethyl-β-methylbutyramide (III). A mixture of 17.2 g. (0.1 mole) of α-ethyl-β-methylbutyrylurea and 75 cc. of water was heated in a 183 cc. stainless steel bomb for 5–10 min. at 200°. After cooling the bomb and contents, 12.0 g. (93.5% yield) of III melting at 137° was obtained.

In a similar experiment with 5-ethyl-5-isopropylbarbituric acid in diluted aqueous ammonia 91.8% yield of III melting at 137.5° was obtained. The melting point did not change after recrystallization from water.

Acknowledgment. The authors are indebted to Mr. E. F. Shelberg and Mr. O. F. Kolsto and staff for the microanalyses. They also wish to thank Mr. W. Washburn and his group for infrared analysis.

North Chicago, Ill.

[Contribution from the Animal Research Institute, Research Branch, Canada Department of Agriculture]

Syntheses of N^{ϵ}-Tosyl-L-lysine Peptides[1a]

JOHN D. CIPERA

Received March 18, 1960

A novel approach to the incorporation of N^{ϵ}-tosyl-L-lysine into the peptide chains is outlined. The syntheses of several sequences appearing in the ACTH and MSH molecules are described in detail.

Lysine figures prominently in the active portions of the adrenocorticotropic hormones,[1b] melanotropic hormones,[2] and other biologically active peptides.[3] Thus, efficient methods for linking lysine into peptide chains are of considerable interest. Such methods must, however, take into account the difficulties inherent in the condensation reactions involving the carboxyl group of lysine.[4] These difficulties are compounded when two lysine moieties are to be coupled together.

Best results with this general type of reaction have been reported when both α- and ε-amino groups of lysine were protected by a carbobenzyloxy radical.[4,5] However, such products cannot be used effectively for selective reactions involving only one of the two amino groups, since both amino groups are protected by the same

(1) (a) Supported by a grant from the American Cancer Society, this investigation was carried on in the Biochemistry Department of the School of Medicine, University of Pittsburgh. It was presented in part at the 136th Meeting of the American Chemical Society in Atlantic City, N. J., September 1959.

(1) (b) P. H. Bell, *J. Am. Chem. Soc.*, **76**, 5565 (1954).

(2) I. I. Geschwind, C. H. Li, and L. Barnafi, *J. Am. Chem. Soc.*, **79**, 620 (1957).

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radical. Consequently the possibilities of selective introduction of these products into longer peptide chains are limited.

The choice of protecting groups was determined, beside the usual considerations of high yield and a lack of racemization, by their positioning on particular amino groups and by the requirement that they should be selectively removable. On the basis of these considerations it was decided to use *p*-toluenesulfonyl (tosyl) radical for protecting the ϵ-amino groups and the carbobenzyloxy radical for the α-amino groups.

While the carbobenzyloxy radical can be removed by catalytic hydrogenation,[6,7] the tosyl radical resists this cleavage. Thus, the α-amino group can be freed whenever it is required for linking with a carboxyl of another amino acid or peptide. The protecting action of the tosyl radical on the ϵ-amino group will be needed until the whole intended peptide is assembled. It can then be removed *e.g.* by the action of sodium in liquid ammonia.[8]

The selective tosylation of ϵ-amino group was made possible by immobilizing the α-amino group in a copper complex.[9] The N^{ϵ}-tosyl and N^{α}-carbobenzyloxy-N^{ϵ}-tosyl derivatives of L-lysine were prepared by procedures similar to those described by Roeske, *et al.*[10]

In the choice of coupling methods the primary consideration was the possible degree of racemization. Therefore the azide method was chosen for the first coupling experiments with the above-mentioned derivatives. The intermediate, N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine hydrazide, which is a novel compound,[11] was found to be useful for introducing the N^{ϵ}-tosyl-L-lysine moiety into a peptide chain. For example, it was used to introduce lysine into the position 11 of the α-MSH type peptide.[11] However, side-reactions apparently accompanied this type of coupling reaction as indicated by the need for extended purification of the products.

In a more difficult case, when it was attempted to couple this azide with another N^{ϵ}-tosyl-L-lysine moiety, the product failed to crystallize. No crystals were obtained even after subsequent saponification and catalytic hydrogenation.

Results similar to the above were obtained also when other methods of carboxyl activation, *e.g.*, the mixed carboxylic–carbonic acid anhydride[12] or the carbodiimide[13a] methods, were tested.

The chromatographic studies confirmed the presence of unwanted side-reactions during the attempted couplings of two N^{ϵ}-tosyl-L-lysine moieties by the carboxyl-activating methods. When aliquots of these products were saponified, decarbobenzoxylated by catalytic hydrogenation, and subjected to paper chromatography in either acidic or basic solvent systems,[13b] the chromatograms of products from all three methods (azide, mixed anhydride, or diimide) were very similar. In the acidic solvent system two spots appeared, a weaker one of R_f 0.75, which is the same as that of N^{ϵ}-tosyl-L-lysine, and a stronger one of R_f 0.90, which was later found to be the R_f value of N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine. In the basic solvent system four spots appeared, a weaker one of R_f 0.53, which is the same as that of N^{ϵ}-tosyl-L-lysine, a stronger one of R_f 0.65, which was later found to be the R_f value of N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine, and two weaker spots of R_f 0.74 and 0.89, the origin of which can only be conjectured. Since these two spots did not appear in the acidic solvent system, there is a possibility that they were formed by the effect of alkaline *p*H on the side-products. Another possible explanation is that these two compounds were not resolved by the acidic solvent system and stayed combined in either one of the two spots.

The possible character of these side-reactions is indicated by the relative ease with which the ϵ-amino group can be brought to close proximity with the carboxyl group. Although the lactam-formation is most facile when the amino and carboxyl groups are in a δ-position with respect to each other, thus producing a single-plane five-membered ring, the lactam forming tendency of the compounds with amino and carboxyl groups farther apart cannot be discounted as a significant factor, particularly when one or both of these groups are activated.[14] Even the tosyl-protected amino groups may undergo such reactions.[15]

In order to eliminate these side-reactions, it was decided to avoid the carboxyl-activating methods and to attempt the formation of the peptide bond by activating the α-amino group instead. Of the methods for activation of the amino group, the best known are those employing

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(12) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 1389 (1951); Th. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(13) (a) J. C. Sheehan and G. B. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1958).

(13) (b) Acidic solvent system (Partridge): upper phase of 1-butanol–acetic acid–water (4:1:5); basic solvent system: 2-butanol–3% ammonia (3:1).

(14) F. Wrede, *Z. Physiol. Chem.*, **206**, 146 (1932); D. W. Adamson, *J. Chem. Soc.*, 39 (1943).

(15) C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, 706 (1940).

the isocyanates,[16] the phosphazo compounds,[17,18] and the amides of phosphoric,[19] phosphorous,[7,18,20] and arsenous[21] acid. The most promising appeared to be that based on the phosphorous acid derivative, the pyrophosphite method of Anderson.[7] Using freshly prepared phosphorous acid anhydride (pyrophosphite) and following the "amide", *i.e.*, the amino-group activating procedure of the Anderson method, crystalline derivatives were easily obtained even in the case when two N^{ϵ}-tosyl-L-lysine moieties were coupled together into a dilysine derivative.

A brief test of an analogous method employing phosphorus pentoxide[19] had shown it to be inferior to the Anderson method.

Two methods for the preparation of the tetraethylpyrophosphite, that of Arens[22] and Anderson,[7] appeared to be superior to the other ones. Application of the Arens method would involve a rather risky preparation of acetylene ether. Therefore it was decided to use the Anderson method. Since the present modification of the Anderson method of the preparation of tetraethylpyrophosphite resulted in its improved yield, this procedure is also described here. Each batch of tetraethylpyrophosphite was tested on a condensation of benzoic acid with aniline. The yields of these trial runs were used to compute the amounts of tetraethylpyrophosphite used for the peptide bond formations.

A speculative thought about a possible means of synthesizing such a symmetric dipeptide, like N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine, from the corresponding diketopiperazine derivative[23] led toward the experiments testing the feasibility of preparing this type of cyclic intermediates. A marked difference was found in the behavior of the free esters of N^{ϵ}-tosyl-L-lysine and of N^{ϵ}-carbobenzyloxy-L-lysine. While the latter were easily converted into ninhydrine-negative crystals, the esters of N^{ϵ}-tosyl-L-lysine did not undergo any apparent change whatsoever, except for darkening at very high temperatures.

The product obtained from the N^{ϵ}-carbobenzyloxy-L-lysine was of little interest, since cleavage of the carbobenzyloxy group would be expected under the conditions necessary for the opening of the diketopiperazine ring. Further experiments in this direction were not pursued following the successful application of the pyrophosphite amide method to the preparation of the desired compounds.

Syntheses of those peptides, sequences of which appear in the ACTH and MSH molecules, are described in the experimental section. They were all tested for purity, subjected to elementary analyses by outside laboratories, and their sterical configurations were tested by the digestibility by leucine aminopeptidase and chromatography of the digestion products.

EXPERIMENTAL

Tetraethylpyrophosphite. Following the original procedure of Anderson, *et al.*,[7] it was observed that triethylammonium chloride continued to separate as a precipitate even during the removal of tetraethylpyrophosphite from the reaction mixture by distillation. Therefore the reaction time was prolonged from 30 min. to 3 hr., when no further precipitation occurred during the distillation. The yields were increased from 40% with the original procedure to 55% with the modified procedure. Further prolongation of the reaction time did not increase the yield but, on the contrary, tended to decrease it. Private communication from Dr. Anderson confirmed that his group also obtained higher yields when they allowed more time for the reaction to proceed.

The products were tested for refractive indices which varied between n_D 1.430 to 1.434°, and for %-yields of benzanilide obtained by the tetraethylpyrophosphite reaction.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. N^{ϵ}-Tosyl-L-lysine ethyl ester hydrochloride[10] (1.25 g.) was dissolved in 5 ml. of diethyl hydrogen phosphite. Triethylamine (0.50 ml.) was added which resulted in a formation of a white precipitate. The mixture was heated on a steam bath and tetraethylpyrophosphite (1.26 g.) was quickly added to it. Heating on steam was continued for 2 min., after which time a solution of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine (1.46 g.) in 2 ml. of diethyl hydrogen phosphite was added. After 30 min. of continuous stirring and heating on steam, the solution, which was clear and almost colorless, was diluted by 50 ml. water. This resulted in a separation of an oil, which was decanted. Since this oil did not yield crystals on trituration with 5% aqueous sodium bicarbonate (*cf.* the preparation of other dipeptides described below), it was dissolved in ethyl acetate and extracted first with 2*N* hydrochloric acid, then with 5% aqueous sodium bicarbonate. The ethyl acetate layer was then washed with water till the washings were neutral, dried over anhydrous magnesium sulfate, and evaporated on the flash evaporator with the bath temperature kept below 40°. The residue, which before the treatment in ethyl acetate weighed 2.24 g. (89.5% yield), now amounted to 2.08 g. (93% recovery). It was dissolved in methanol and water was slowly added till permanent turbidity was reached. The mixture was placed in a refrigerator, where well defined white crystals began to form. They were separated by filtration and dried *in vacuo* over phosphorus pentoxide to constant weight, 1.4 g. (56% yield), m.p. 114–116°. Recrystallization of an aliquot of this product from methanol and water increased the m.p. to 116.5–117°; $[\alpha]_D^{28}$ −10.5° (c, 1.12 in methanol).

Anal. Calcd. for $C_{36}H_{48}O_9N_4S_2$: C, 58.04; H, 6.49; S, 8.61. Found: C, 58.06; H, 6.40; S, 8.48.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine methyl ester. This methyl ester was prepared in the same way as the ethyl ester above. It was found that the crystallization of methyl ester took more time than that of the ethyl ester.

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The yield of the former was about two-thirds that of the latter.

The product melted at 110–111°; $[\alpha]_D^{28}$ −8.5° (*c*, 1.04 in methanol).

N^{ϵ}-Tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine. Saponification of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ester (either methyl or ethyl) by shaking it with *N* sodium hydroxide, acidification of the aqueous solution and extraction with ethyl acetate yielded an oil from which no crystals could be obtained.

Hydrogenation of this oil in 15% solution of glacial acetic acid in anhydrous methanol, with palladium as a catalyst, yielded a glossy residue which was not readily soluble in water. Addition of absolute ethanol resulted in formation of crisp, white microcrystals, m.p. 167–168°.

The product was ninhydrin-positive and gave a single spot on a paper chromatogram developed either with the Partridge solvent system (R_f 0.90) or with the 2-butanol–ammonia (3:1) system (R_f 0.65). The sterical configuration of the product was confirmed by the leucine aminopeptidase digestion which completely hydrolyzed the dipeptide leaving only N^{ϵ}-tosyl-L-lysine in the digest. The elementary composition of the product was also confirmed.

Anal. Calcd. for $C_{26}H_{38}O_7N_4S_2$: C, 53.28; H, 6.57; N, 9.61. Found: C, 52.92; H, 6.63; N, 9.72.

Carbobenzyloxyglycyl-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester hydrochloride was prepared from its N^{α}-carbobenzyloxy derivative by a catalytic hydrogenation in methanol in the presence of equimolecular amount of *N* hydrochloric acid, with palladium as a catalyst. An oil was obtained in a virtually quantitative yield, which gave a single ninhydrin spot in either of the above-described solvent systems. Leucine aminopeptidase hydrolysis of the oil gave a single ninhydrin spot of N^{ϵ}-tosyl-L-lysine.

This oil was coupled with an equimolecular amount of carbobenzyloxyglycine by the carbodiimide method; *i.e.*, N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester hydrochloride (1.25 g.), carbobenzyloxyglycine (0.41 g.), triethylamin (0.30 ml.) and dicyclohexylcarbodiimide (0.41 g.) were dissolved in dioxane (20 ml.). The mixture was left to stand overnight at room temperature. A precipitate formed which was removed by filtration (0.40 g., corresponds to 2.05 mmoles of dicyclohexylurea). The filtrate was evaporated *in vacuo* to dryness (40° bath temp.) and the oily residue dissolved in ethyl acetate. This solution was purified in the usual way (washed consecutively with 2*N* hydrochloric acid, *N* sodium bicarbonate, followed with distilled water until the washings were neutral), then dried over magnesium sulfate, and evaporated *in vacuo* to dryness. An oily residue (1.15 g.) was obtained. This residue was dissolved in methanol and water was added until permanently turbid. On standing overnight crystals appeared. Slow addition of water yielded more crystals. Both crops (0.82 g., 53% yield) had a melting point of 121–124°. Recrystallization of an aliquot increased the m.p. to 125.5–126°; its optical rotation was $[\alpha]_D^{23}$ −12.6° (*c*, 1.06 in ethanol).

Anal. Calcd. for $C_{35}H_{51}O_{10}N_5S_2$: C, 56.90; H, 6.41; N, 8.73; S, 7.99. Found: C, 56.77; H, 6.29; N, 8.80; S, 8.00.

Catalytic hydrogenation of the aliquot produced in virtually a stoichiometric yield an oil, R_f 0.91 (Partridge), 0.85 (2-butanol–ammonia), completely digestible by leucine amino peptidase, amino acid ratios in digest $gly_{1.0}$-ϵ-tos-$lys_{1.9}$.

Dicarbobenzyloxy-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester was prepared from dicarbobenzyloxy-L-lysine and the ethyl ester of N^{ϵ}-tosyl-L-lysine hydrochloride following the procedure described above for the preparation of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. On addition of water to the reaction mixture an oil was obtained. Trituration of this oil with 5% aqueous sodium bicarbonate resulted in a formation of crystals. These were washed twice with water, filtered, and dried *in vacuo* over phosphorus pentoxide; 72.4% yield, m.p. 115–118°. Recrystallization from methanol and water increased the m.p. to 121–122° $[\alpha]_D^{27.5}$ −11.3° (*c*, 2.47 in methanol).

Anal. Calcd. for $C_{37}H_{48}O_9N_4S$: C, 61.30; H, 6.67; S, 4.42 Found: C, 61.19; H, 6.85; S, 4.33.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-L-valine methyl ester was prepared from N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine (2.27 g.) and the methyl ester of L-valine hydrochloride (1.05 g.) following the procedure described above for N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. The yield (1.81 g.) was 63.4%; m.p. 97.5–98.5°, on recrystallization from methanol-water raised to 99.5–100°; $[\alpha]_D^{25}$ −14.3° (*c*, 2.51 in ethanol).

Anal. Calcd. for $C_{27}H_{37}O_7N_3S$: C, 59.21; H, 6.81; S, 5.85. Found: C, 59.14; H, 6.64; S, 5.84.

Catalytic hydrogenation of a small aliquot resulted in an almost quantitative yield of decarbobenzoxylated dipeptide, R_f = 0.89 (Partridge), single spot in (2-butanol–ammonia), completely digestible by LAP, amino acid ratios in digest ϵ-tos-lys_1val_1.

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OTTAWA, CANADA

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, COLGATE-PALMOLIVE CO.]

Distribution of *para* and *ortho* Isomers in Some Model Long Chain Alkylbenzenesulfonates

FREDERICK W. GRAY AND IRVING J. KREMS[1a]

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A series of long chain 1-phenyl- and 2-phenylalkanes has been prepared and sulfonated. The sulfonate distribution was about 80% *para*, 15% *ortho* for the 1-phenylalkanes and about 90% *para*, 7% *ortho* for the secondary 2-phenylalkanes. The isomers were characterized by conversion to their *S*-benzylisothiuronium salts and by infrared spectra. Some physical properties of the alkylbenzenesulfonates are described.

The preparation and properties, including surface activity, of some isomeric sodium alkylbenzenesulfonates were described in a previous publication.[1b] The position of the sulfonate group in the

(1a) Present address: Medical Faculty, University of Vienna, Vienna, Austria.

(1b) F. W. Gray, J. F. Gerecht, and I. J. Krems, *J. Org. Chem.*, **20**, 511 (1955).

benzene ring, the location of the phenyl group and the length of the alkyl chain were factors shown to affect the surface active properties of these compounds. The present work extends our study of model primary and secondary isomeric alkylbenzenesulfonates and also includes an examination of model tertiary alkylbenzenesulfonate.

The method of synthesis used for the primary and secondary alkylbenzenes was the same as previously reported. To synthesize the model tertiary alkylbenzene, 2-phenyl-2-methylundecane, two routes were investigated. In the first, α-methylstyrene was treated with hydrogen chloride to form α-chlorocumene. This intermediate was condensed with nonylmagnesium bromide and a 30% yield of crude product was obtained. When this material was distilled through a Podbielniak column, fractions having a wide boiling range were obtained and the indexes of refraction varied considerably. The purity of the alkylbenzene was not satisfactory for our purpose.

In the second route, the method of Weinmayr was used.[2] Benzene was alkylated with methallyl chloride to form neophyl chloride. The Grignard reagent prepared from this compound was treated with octanal. The resultant carbinol, 2-phenyl-2-methyl-4-undecanol, was isolated in a 76% yield. The alcohol was dehydrated and reduced to 2-phenyl-2-methylundecane.

$$ArH \xrightarrow{CH_2=C(CH_3)CH_2Cl} CH_3C(CH_3)CH_2Cl \xrightarrow[(ii)\ RCHO]{(i)\ Mg} CH_3C(CH_3)CH_2CHOHR \xrightarrow[(ii)\ H_2]{(i)\ KHSO_4} CH_3C(CH_3)CH_2CH_2R$$

(Ar)

$$R = C_7H_{15}$$

Under the sulfonation conditions used, the primary and secondary hydrocarbons were sulfonated in about 98% yields. The sulfonate isomer distribution for the 1-phenylalkanes was about 80% *para* and 15% *ortho;* whereas for the 2-phenylalkanes, the sulfonate content was about 90% *para* and 7% *ortho*. The *para* isomers in both series were white crystalline non-tacky compounds. The *ortho* sulfonates in the 1-phenyl series were slightly yellow in color, were less crystalline than the *para* isomers and they were hygroscopic and tacky. The *ortho* sulfonates in the 2-phenyl series were light brown in color and at room temperature were viscous tacky pastes.

The sulfonation of the model tertiary compound, 2-phenyl-2-methylundecane, with 20% oleum offered no difficulty and proceeded in the same way as the primary and secondary alkylbenzenes. The neutralized white crystalline product, sodium (1,1-dimethyldecyl)benzenesulfonate, possessed strong infrared absorption bands at 12.00 μ and 13.12 μ. These same absorption bands are present in mixtures of *para* and *ortho* secondary alkylbenzenesulfonates. On recrystallization of such a mixture, the *para* sulfonate isomer (12.00 μ) separates as a crystalline compound whereas the *ortho* sulfonate isomer (13.12 μ) is amorphous and difficult to obtain in a purified state. Attempts to accomplish a similar separation with the sulfonation product of 2-phenyl-2-methylundecane were not successful. After repeated recrystallizations, the 12.00 μ and 13.12 μ bands remained unchanged. A phase solubility analysis was undertaken to determine the homogeneity of the compound. The results unambiguously demonstrated the product to be essentially a single compound. It appears that in the isolated compound, sodium (1,1-dimethyldecyl)benzenesulfonate, the tertiary structure of the alkylbenzene and not the presence of *ortho* sulfonate substitution is responsible for the 13.12 μ absorption band.

A detailed discussion of the sodium alkylbenzenesulfonates in conjunction with their wetting, detergency, and foaming properties and a comparison of their behavior in these respects to commercial sodium (tetrapropylene)benzenesulfonate is to appear in another publication. In respect to sulfonate isomerism, the results obtained support the observation previously reported[1b] that the *para* sulfonates are superior in detergency but inferior in wetting action to their respective *ortho* isomers. In regard to foaming, however, it is now found that *para* rather than *ortho* substitution tends generally to favor better foaming action. This conclusion corrects the statement made in the earlier paper, based on relatively few experiments, that the *ortho* orientation is the favored position for foam height.

The extreme insolubility of sodium *p*-dodecylbenzenesulfonate places a restriction on the study of the surface active behavior of primary alkylbenzenesulfonates. Sodium *p*-octylbenzenesulfonate and sodium *p*-decylbenzenesulfonate have better solubility properties but the surface activity properties examined are not as good as for the higher molecular weight compound. When the phenyl group is shifted from the 1- to the 2-position in an alkylbenzenesulfonate, an appreciable increase in solubility occurs in the isomer. Consequently, higher molecular weight sulfonates may be utilized for detersive studies in the secondary series than was found possible for the primary alkylbenzenesulfonates.

The foaming ability of the *para* sulfonates of the secondary 2-phenylalkanes is dependent upon chain length as well as concentration. The foam height obtained for sodium *p*-(1-methyldodecyl)-benzenesulfonate is greater than obtained for sodium (tetrapropylene)benzenesulfonate but the height of foam obtained with sodium *p*-(1-methylhexadecyl)benzenesulfonate is less than for the commercial product at all concentrations ex-

(2) V. Weinmayr, U. S. Patent 2,467,170 (1949).

amined (0.015–0.045%). In detergency, however, sodium *p*-(1-methyldodecyl)-, sodium *p*-(1-methyltetradecyl)-, and sodium *p*-(1-methylhexadecyl)-benzenesulfonate are superior to commercial sodium (tetrapropylene)benzenesulfonate. The tertiary compound, sodium *p*-(1,1-dimethyldecyl)benzenesulfonate, has overall surface active properties that closely resemble commercial sodium (tetrapropylene)benzenesulfonate and its wetting ability is superior to the sodium *p*-sulfonates of the 1-phenylalkanes and 2-phenylalkanes.

EXPERIMENTAL

Phenylalkanes. 1-Phenyloctane, 1-phenyldecane, and 1-phenyldodecane were prepared by condensing the acid chlorides of octanoic, decanoic, and dodecanoic acids with benzene under Friedel Crafts conditions followed by reduction of the resulting ketones to hydrocarbons by the Wolff-Kishner reaction. 2-Phenylundecane, 2-phenyltridecane, 2-phenylpentadecane, and 2-phenylheptadecane were prepared by conversion of the appropriate fatty acids to acid chlorides and then to the phenones by using the Friedel Crafts reaction. The phenyl ketones thus obtained were treated with Grignard reagent and hydrolyzed. The tertiary alcohols formed were dehydrated and the phenylalkenes produced were hydrogenated to the desired products.[1b]

2-Phenyl-2-methylundecane was prepared by the general procedure described by Weinmayr.[2] Neophylmagnesium chloride was prepared from 75.5 g. of neophyl chloride[3] and 12.0 g. of magnesium in 425 ml. of ethyl ether. The chloride was added in a period of 3 hr., and the mixture refluxed for an additional 2 hr. A solution of 50 g. of octanal in 75 ml. of ethyl ether was then added in 35 min., the mixture refluxed for 2 hr., and then allowed to stand overnight at room temperature. The reaction mixture was poured into 500 g. of cold water and acidified with hydrochloric acid. The ether layer was washed with 5% sodium bicarbonate solution and the solvent removed by distillation. The residue was heated for 2 hr. at 200–290° in the presence of potassium acid sulfate. The reaction mixture was filtered and 64 g. of material, presumably a mixture of 2-phenyl-2-methyl-3-undecene and 2-phenyl-2-methyl-4-undecene, was obtained upon distillation. To a 40-g. fraction (b.p. 111°/1 mm.) was added 200 g. of glacial acetic acid and 0.4 g. of 5% palladium on charcoal catalyst. The reaction mixture was placed in a Parr apparatus and the theoretical amount of hydrogen was absorbed within 4 hr. at room temperature and 1–3 atm. pressure. The catalyst was removed by filtration and the acetic acid by distillation. At 128–130° (1.5–2.0 mm.) there was obtained 35.5 g. of hydrocarbon. This material was washed three times with 96% sulfuric acid, then with sodium bicarbonate. The purified product was re-distilled at 123° (1 mm.) to yield 27.2 g. The physical properties of the alkylbenzenes used for sulfonation are listed in Table I.

TABLE I

PHYSICAL PROPERTIES OF ALKYLBENZENES

Hydrocarbons	B.P.	Mm.	d_4^{25}	n_D^{25}
1-Phenyloctane	87–88	1	0.8541	1.4825
1-Phenyldecane	112	1	0.8520	1.4812
1-Phenyldodecane	148	1	...	1.4818[a]
2-Phenylundecane	92–94	0.2	0.8507	1.4804
2-Phenyltridecane	132–133	0.8	0.8612	1.4794
2-Phenylpentadecane	192	5	0.8577	1.4796
2-Phenylheptadecane	156–158	0.8	0.8522	1.4782
2-Phenyl-2-methylundecane	123	1	0.8599	1.4848

[a] Refractive index taken at 20.

2-Phenyl-2-methyl-4-undecanol. The neophylmagnesium chloride and octanal condensation product prepared in the manner described in the preparation of 2-phenyl-2-methylundecane was hydrolyzed in cold dilute aqueous acid solution. The reaction product was extracted with ethyl ether and dried over magnesium sulfate. The product distilled in 76% yield at 150–155° (1.5 mm.); d_4^{25} 0.9234; n_D^{25} 1.5010.

Sulfonation of phenylalkanes. The 1-phenylalkanes and 2-phenylalkanes were sulfonated in about 98% yields with 20% oleum, neutralized with sodium hydroxide, ether extracted, inorganic salt removed, and the *ortho-para* isomers isolated under conditions essentially the same as previously described for 1-phenyloctane and 2-phenyltridecane.[1b] The *para* and *ortho* sulfonate yields are given in Table II.

TABLE II

YIELD AND DISTRIBUTION OF SULFONATE ISOMERS

Alkylbenzene	Sulfonation Yield, %[a]	Isomer Distribution	
		para, %	*ortho*, %
1-Phenyloctane	98	81	15
1-Phenyldecane	99	80	15
1-Phenyldodecane	98	81	14
2-Phenylundecane	99	86	7
2-Phenyltridecane	98	91	6
2-Phenylpentadecane	98	90	7
2-Phenylheptadecane	98	89	7

[a] Yield based upon recovered unsulfonated material.

The isomers were identified by derivative formation and by infrared spectral data. The *para* sulfonates of the primary alkylbenzenes exhibit a doublet at 11.90, 12.28 μ while the *ortho* sulfonates exhibit a single absorption band at 13.36 μ. These characteristic isomer peaks were established from the properties of isomeric sodium dodecylbenzenesulfonates that were prepared by an unequivocal method of synthesis. The *para* sulfonates of the secondary alkylbenzenes possess a single *para* absorption at about 12.00 μ whereas the *ortho* sulfonates have a strong absorption at about 13.12 μ. Conceivably, an isomerization of secondary to tertiary structure during sulfonation could account for the small amount of sulfonate having an absorption band at 13.12 μ. However, the physical characteristics and the infrared spectrum of the sulfonation product obtained from the tertiary compound, 2-phenyl-2-methylundecane, do not support the possibility that such an isomerization occurs. The melting points and elemental analyses for the *S*-benzylisothiuronium salts of isomeric primary and secondary alkylbenzenesulfonates are given in Table III.

Sulfonation of 2-phenyl-2-methylundecane with 20% oleum offered no difficulty and presented the same appearance as the acid mixes of the primary and secondary alkylbenzenes. The reaction mixture was neutralized with sodium hydroxide, dried, and extracted with anhydrous ethyl ether. The ether soluble material was transferred to a separatory funnel and partitioned between equal volumes of water and ethyl ether. The ether layer contained less than 1% unsulfonated material while the water layer, which was recovered by evaporation to dryness, was found to contain an 80% yield of sodium (1,1-dimethyldecyl)benzenesulfonate. A recrystallization of 10.0 g. of the product from 100 ml. of water gave 7.8 g. of a crystalline, white and odorless compound (I). Its infrared spectrum suggested an *ortho-para* isomer mixture since absorption peaks were present at 13.12 (*ortho*) and 12.00 (*para*) μ. However, repeated recrystallizations and extraction procedures did not cause the 13.12 μ absorption peak to disappear. To establish the degree

(3) W. T. Smith, Jr., and J. T. Sellas, *Org. Synthesis*, **32**, 90 (1952).

TABLE III

S-BENZYLISOTHIURONIUM SALTS OF ISOMERIC ALKYLBENZENESULFONATES

R′ RCHC$_6$H$_4$SO$_3$Na				M.P.	Nitrogen, %		Sulfur, %	
Orientation	R	R′	M.P.[a]	(Ref. 1b)	Calcd.	Found	Calcd.	Found
p	C_7H_{15}	H	125.6–125.8	125.6–126.0	...	...	...	...
o	C_7H_{15}	H	98–99[b]	105.5–106	...	...	...	...
p	C_9H_{19}	H	94.2–95.3	...	6.03	6.20	13.78	13.23
o	C_9H_{19}	H	113–114	...	6.03	5.94	13.78	13.95
p	$C_{11}H_{23}$	H	117–118	117–118	...	...	...	...
o	$C_{11}H_{23}$	H	101–103	101–103	...	...	...	...
p	C_9H_{19}	CH_3	104.0–104.4	...	5.85	5.66	13.37	13.98
o	C_9H_{19}	CH_3	108.6–109	...	5.85	5.72	13.37	13.46
p	$C_{11}H_{23}$	CH_3	105.9–106.2	105–106	5.53	5.43	12.63	12.93
o	$C_{11}H_{23}$	CH_3	86–86.5	...	5.53	5.38	12.63	12.90
p	$C_{13}H_{27}$	CH_3	106–106.9	...	5.24	5.06	11.97	12.05
o	$C_{13}H_{27}$	CH_3	113.7–115	...	5.24	5.15	11.97	12.07
p	$C_{15}H_{31}$	CH_3	109–109.4[c]	...	4.98	4.91	11.38	11.48
o	$C_{15}H_{31}$	CH_3	92.2–93.2	...	4.98	4.60	11.38	11.24

[a] All melting points were taken after drying at least six hours over phosphorus pentoxide at 78 (2 mm.). [b] On resolidification of the melt, the melting point was 106–106.8. [c] *p*-Toluidine derivative had a melting point of 119.1–119.5. *Anal.* Calcd. for $C_{30}H_{49}NO_3S$: N, 2.78; S, 6.35. Found: N, 2.73; S, 6.36.

of purity a phase solubility analysis[4] was conducted with I. The results of the analysis show conclusively that the compound isolated is essentially a single component with a 5.5% solubility in water at 46.5°. The *S*-benzylisothiuronium derivative of I, which is presumably the *para* isomer, melted at 126–128°.

Anal. Calcd. for $C_{26}H_{40}N_2O_3S_2$: N, 5.60; S, 13.62. Found: N, 5.63; S, 13.40.

(4) W. J. Mader, *Organic Analysis*, Interscience Publishers Inc., New York, Vol. II., 253 (1954).

Acknowledgment. The authors appreciate the helpful discussions and suggestions of R. B. Wearn, A. I. Gebhart, J. F. Gerecht, W. G. Alsop, J. V. Schurman, and C. D. Hurd throughout this work. We are also grateful to the Analytical Section for analyses and to L. Angilella and W. Mihalik for their help in the experimental and evaluation work.

JERSEY CITY 2, N. J.

[CONTRIBUTION FROM THE BENZOL PRODUCTS CO.]

Isomer Distribution of Some Chloromethylated Alkylbenzenes

STANLEY K. FREEMAN

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Some alkylbenzenes were chloromethylated and the isomer contents of the resulting products examined by infrared spectrometry and gas-liquid chromatography. *meta*-Substitution occurred and in increasing amounts for ethyl-, methyl-, *i*-propyl, and *t*-butylbenzenes.

Ingold,[1] in commenting upon the data of Le Fèvre,[2] stated that it was inconceivable that no *meta* compounds were formed when ethyl- and *i*-propylbenzenes were mononitrated. It was later found[3] that not inconsiderable quantities of the *meta* isomers actually did result and that there was increasing *meta* substitution in the series methyl-, ethyl-, *i*-propyl-, *t*-butylbenzenes. H. C. Brown[4] recently reported analogous behavior for acetylation and benzoylation.

Nazarov and Semenovskii[6] determined the isomer distribution of chloromethylated ethyl-, *i*-propyl-, and *t*-butylbenzenes by oxidation to the corresponding dicarboxylic acids. No *meta* substituted compounds were recovered, but it is apparent that small quantities could have escaped detection by their semiquantitative oxidation technique. We decided to investigate the isomeric products of the chloromethylation reaction by hydrogenolysis and subsequent examination by means

(1) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953, p. 257.

(2) R. J. W. Le Fèvre, *J. Chem. Soc.*, 1501 (1934).

(3) H. C. Brown and W. H. Bonner, *J. Am. Chem. Soc.*, **76**, 605 (1954).

(4) H. C. Brown and G. Marino, *J. Am. Chem. Soc.*, 81, 5611 (1959).

(6) I. N. Nazarov and A. V. Semenovskii, *Izvest. Akad. Nauk. S.S.S.R. Otdel. Khim. Nauk.*, 100–111 (1957) [*Chem. Abstr.*, **51**, 10400 (1957)].

TABLE I

ISOMER DISTRIBUTIONS OF CHLOROMETHYLATED ALKYLBENZENES

Chloromethyl Benzene	% meta		% para		% ortho	
	IR	GLC	IR	GLC	IR	GLC
Methyl[a]	1.1	—	54.0	55[b]	45.0	45.4
Ethyl	1.9	—	69.2	70.0[b]	29.0	30.0
i-Propyl	3.2	3.4	84.0	84.4	12.0	12.2
t-Butyl	5.8	6.4	94.0	93.6	*ca.* 0.1	

[a] H. C. Brown and K. L. Nelson[9] reported 1.3% *m*-, 64.0% *p*-, and 34.7% *o*-. C. D. Shacklett and H. A. Smith[10] reported 3.0% *m*-, 54% *p*-, and 43% *o*-. [b] Includes *meta*.

of infrared spectrometry and gas-liquid chromatography.

The results of this study (Table I) show that *meta* substitution does indeed occur and in increasing amounts for ethyl-, methyl-, *i*-propyl-, and *t*-butylbenzenes. This increase is probably due to a combination of inductive effects[7] and dispersion forces.[8] The amount of *meta-t*-butylbenzyl chloride found agrees well with the value expected based on Brown's "Selectivity Factor."[5] Benzoylation

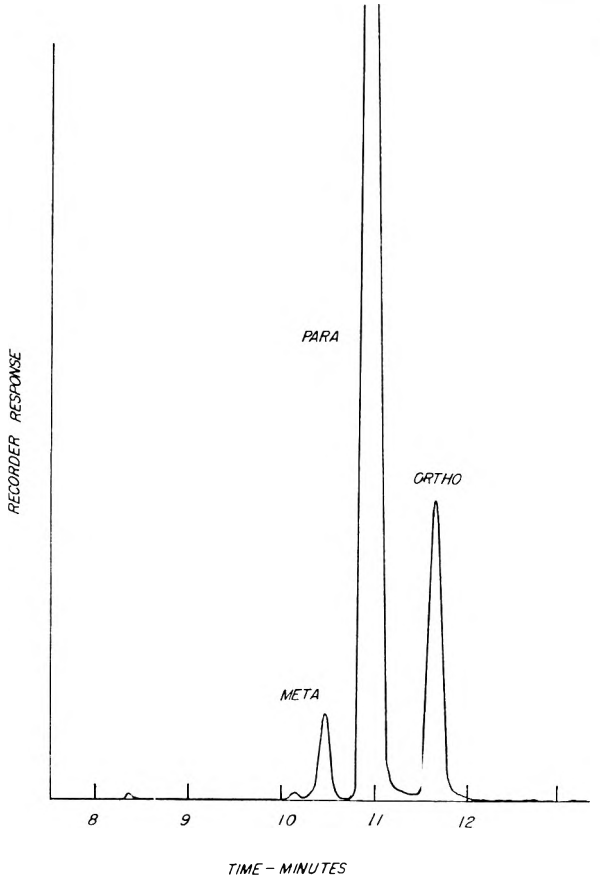

Fig. 1. Gas-liquid chromatogram of the isomeric *i*-propyltoluenes: 100 ft. by 0.01 in. stainless steel Ucon 50 HB 2000 capillary column, 135° column temp., 20 p.s.i. helium, 0.2 μl sample

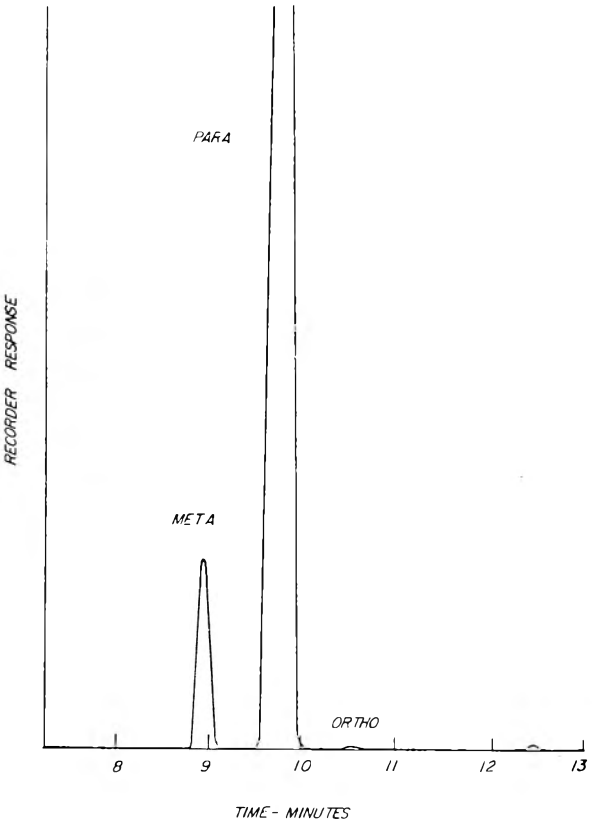

Fig. 2. Gas-liquid chromatogram of the isomeric *t*-butyltoluenes: 100 ft. by 0.01 in. stainless steel Ucon 50 HB 2000 capillary column, 135° column temp., 30 p.s.i. helium, 0.2 μl sample

(S_f 2.1)[12] yields 5.4% *meta*[4] and chloromethylation (S_f 1.99)[12] is reported here to form 6.1% of the *meta* isomer. The quantity of *meta* compound increases with decreasing selectivity of the entering group. The insignificant quantity of *ortho* substitution formed by the chloromethylation of *t*-butylbenzene indicates that the steric requirements of the chloromethyl group is rather large. A comparison among the amounts of *ortho* isomers resulting from the benzoylation, bromination, and chloromethylation reactions leads to the conclusion that

(7) H. C. Brown and M. Dubeck, *J. Am. Chem. Soc.*, 81, 5608 (1959).

(8) T. L. Brown, *J. Am. Chem. Soc.*, 81, 3229 (1959).

(5) H. C. Brown and C. R. Smott, *J. Am. Chem. Soc.*, 78, 6255 (1956).

(12) L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, 81, 3323 (1959).

(9) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, 75, 6292 (1953).

(10) C. D. Shacklett and H. A. Smith, *J. Am. Chem. Soc.*, 73, 766 (1951).

the chloromethyl group lies between the larger benzoyl group and bromine.

The disparity between the quantities of *ortho* and *para* isomers found in the chloromethylation of toluene as reported by H. C. Brown[9] and this work may result because the former's reaction was carried out in glacial acetic acid. Rather good agreement with Shacklett and Smith[10] has been obtained by us. Rapp and Kornev[11] recently reported nearly equal amounts of *ortho* and *para* chloromethyl toluenes arising from the chloromethylation reaction.

EXPERIMENTAL

A Perkin-Elmer Model 21 Infrared Spectrometer was used for the qualitative and quantitative examination of the alkyltoluenes. The gas-liquid chromatographic work was performed on a Perkin-Elmer Fractometer 154B equipped with a $^1/_4$-in. × 10-foot silicone oil (Dow Corning 550) column and thermal conductivity cells. In addition, a Barber-Coleman capillary column chromatograph was employed with a 100-foot Ucon 2000 capillary column and an ionization gauge detector. The packed column instrument effectively separated the *ortho* and *para* isomers but failed to resolve the *meta* from the *para*. Of many columns examined, only 7,8-benzoquinoline was somewhat effective for the separation of the isomeric xylenes. The capillary column coupled with ionization gauge nicely resolved all of the isomers (Figs. 1, 2). The chromatographic assays were obtained by the normalization technique and practically no area correction factors were necessary when using the Perkin-Elmer instrument. The infrared analytical wave lengths selected were as follows:

Alkyltoluene	*ortho*	*meta*	*para*
Methyl	13.46 μ	13.02 μ	12.55 μ
Ethyl, *i*-propyl, *t*-butyl	13.18–13.25	12.74–12.76	12.25–12.27

Known mixtures bracketing the values obtained by gas-liquid chromatography were prepared and standard curves drawn. *i*-Octane solutions were used for determining the major components and neat spectra recorded for the minor constituents.

The alkylbenzenes used as starting materials were of commercial quality and ranged between 95 and 98% pure. The chloromethylation reaction was carried out according to the method of Shacklett and Smith[10] and yielded products with analyses (alkaline hydrolysis) of over 99%. A.P.I. alkyltoluenes were used for the infrared standard curves.

The chloromethyl derivatives were transformed into the analogous alkyltoluenes by shaking 30 ml. of 50% ethanolic solution with 0.3 g. of 10% palladium–barium sulfate catalyst for 1 hr. at 50 p.s.i. hydrogen in a Parr hydrogenation apparatus. About 90% of the theoretical amount of hydrogen was absorbed. In all instances between 5 and 8% (determined by GLC) of unchanged chloromethylated material was found in the reduced product. A second reduction was carried out after filtering, driving off the hydrochloric acid and adding fresh catalyst. This sufficed to eliminate the unchanged residue. There was no difference in the isomer ratios of the alkyltoluenes when the first and second reductions were compared, indicating that the isomers of a particular alkyl chloromethyl benzene were hydrogenolyzed at the same rate. The analyses were carried out subsequent to filtering of the solutions, neutralizing with sodium carbonate and stripping off the alcohol.

Acknowledgment. The author expresses his appreciation to Professor H. C. Brown of Purdue University for some helpful comments concerning this investigation.

We are indebted to Dr. M. J. Schlatter of the California Research Corp. for supplying purified samples of the isomeric *i*-propyltoluenes.

NEWARK 5, N. J.

(11) L. B. Rapp and K. A. Kornev, *Ukrain. Khim. Zhur.*, **25**, 351–353 (1959) [*Chem. Abstr.*, **54**, 1368 (1960)].

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Solvent and Catalytic Effects in the Reaction of Ferric Chloride with Aromatic Compounds[1]

PETER KOVACIC AND CHISUNG WU

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A large number of metal halides were investigated for their influence as solvents or catalysts upon the reaction of anhydrous ferric chloride with simple aromatic compounds. Yield and isomer distribution of products, and rate of the various reactions which occur were affected by certain of the metal halides. The significance of the results is discussed.

It has been reported[2] that compounds of the Friedel-Crafts catalyst type, present either in small amounts or as solvents, decrease the temperature at which reaction occurs ("initiation temperature") and alter the isomer distribution in the chlorination of chlorobenzene by ferric chloride. Moreover, nitrobenzene, a solvent which would be expected to coordinate strongly with ferric chloride, retarded the reaction. These effects were interpreted as evidence for a polar mechanism. Catalytic influences in the ferric chloride–benzene system are treated elsewhere.[3]

Our intention in the present work was to make

(1) Paper V in the series, "Reactions of Metal Halides with Organic Compounds"; an abstract of a portion of the Ph.D. thesis of C. Wu, Case Institute of Technology, 1960.

(2) P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, **76**, 5491 (1954).

(3) P. Kovacic and C. Wu, forthcoming publication.

a more thorough investigation of solvent and catalytic effects in the reaction of ferric chloride with simple aromatic compounds.

RESULTS

Halobenzenes. The reaction of chlorobenzene with ferric chloride was studied principally. The catalysts examined included aluminum chloride, cupric chloride and bromide, cuprous chloride, mercuric chloride, zinc chloride, titanium tetrachloride, and antimony pentachloride (Table I). Addition of these substances resulted invariably in a lowering of the "initiation temperature." A number of them (mercuric chloride, zinc chloride, aluminum chloride) were found to have little or no effect on the isomer distribution of the product, whereas the copper halides increased the amount of *ortho* substitution. In some cases (aluminum chloride, titanium tetrachloride, antimony pentachloride), there were indications of the operation of temperature effects, *i.e.*, decreased *ortho* substitution at lower temperatures. Less than 1% of the *meta* isomer was obtained in all cases.

Some of the metal chlorides, such as titanium tetrachloride, antimony trichloride, stannic chloride, and arsenic trichloride, when used as diluent, were found to lower the initiation temperature and promote the reaction remarkably. The initiation temperatures were 50°, 92°, 116°, and 120°, respectively. In titanium tetrachloride, dichlorobenzene was obtained in 85% yield at 132° in fifteen minutes, and 74% at 100° in 1.8 hours. In contrast, no detectable reaction occurred at 120° in the absence of the solvent, a temperature of at least 125–130° being required. Reaction failed to take place at 132° in the presence of large amounts of pyridine or nitrobenzene, but dichlorobenzene was formed in low yield in nitrobenzene at higher temperatures (168–180°). In titanium tetrachloride (Matheson Coleman and Bell) and antimony trichloride, there was increased *ortho* substitution. It is interesting that in titanium tetrachloride from the Baker Chemical Co. decreased *ortho* substitution was observed (Table I).

In earlier work,[2] interaction of bromobenzene and ferric chloride was apparent at 126° yielding 93% of chlorobromobenzene ($o/m/p$ = 13/<1/87). In the presence of large amounts of titanium tetrachloride, reaction began at 55° and gave a 79% yield ($o/m/p$ = 23/<1/77). No reaction was observed previously between fluorobenzene and ferric chloride at the reflux temperature (85°), and only traces of chlorofluorobenzene were obtained on heating the reaction mixture at 100° for four hours in a pressure vessel.[2] In titanium tetrachloride solvent, however, a 7% yield was realized at 47–97° in two hours.

Alkylbenzenes. While some metal chlorides (titanium tetrachloride, antimony trichloride, cupric chloride) used in small amounts or as solvent, were found to influence orientation in the chlorination of chlorobenzene, these same adjuncts did not exert any appreciable effect on isomer distribution in the toluene reaction (Table II). Titanium tetrachloride solvent and aluminum chloride catalyst were effective in favoring chlorination at the expense of polymerization. However, in titanium tetrachloride temperatures above 100° were necessary to maintain the reaction at a rapid rate. Antimony trichloride and nitrobenzene both retarded the chlorination, allowing facile polymerization.

TABLE I

FERRIC CHLORIDE AND CHLOROBENZENE[a]

Solvent	Temp.	Time, hr.	Dichlorobenzene, % Yield	*ortho*[b]	*para*
None	131–132	2.0	69	11	89
$TiCl_4$[c]	129–132	0.25	85	21	79
$TiCl_4$[d]	128–132	0.25	77	5	95
$TiCl_4$[e]	100	1.8	74	24	76
$SbCl_3$	128–132	1.0	71	21	79
$AsCl_3$	118–122	3.0	63	12	88
$SnCl_4$	118–120	2.0	57	7	93
C_5H_5N	130–132	2.0	0	..	..
$C_6H_5NO_2$	130–132	2.0	0	..	..
$C_6H_5NO_2$[e,f]	168–180	1.5	9	15	85
Catalyst					
$AlCl_3$	130–134	1.0	60	11	89
$AlCl_3$	130–134	2.0	72	11	89
$AlCl_3$[f,g]	119–134	2.0	83	7	93
$TiCl_4$[e]	78–132	1.8	82	6	94
$SbCl_5$[f,h]	112–138	1.25	88	9	91
$HgCl_2$	117–134	2.5	72	11	89
$CuCl_2$	115–126	1.1	84	18	82
$CuCl_2$[i]	105–122	1.8	83	18	82
Cu_2Cl_2	118–120	1.1	78	16	84[j]
$CuBr_2$	122–128	1.1	86	18	82[j]
$ZnCl_2$	90–138	1.7	64	10	90[j]

[a] Chlorobenzene (1 mole), ferric chloride (0.5 mole), and solvent (1 mole) or catalyst (0.02 mole). [b] Less than 1% of *meta* isomer by infrared analysis. [c] Matheson Coleman and Bell. [d] Baker Chemical Co. [e] Chlorobenzene (0.6 mole), ferric chloride (1.0 mole), and nitrobenzene (250 g.). [f] Ref. (2). [g] Chlorobenzene (2 moles), ferric chloride (1 mole), and aluminum chloride (0.02 mole). [h] 0.05 mole. [i] 0.15 mole. [j] Determined by the m.p.–f.p. method; see Experimental.

The reaction of *p*-chlorotoluene with ferric chloride took place with vigor at 104°, yielding among the products 9% of dichlorotoluene and a large quantity of red tar.[2,4] In titanium tetrachloride as solvent, the reaction proceeded quite smoothly at the same temperature with an increased yield (38%) of dichlorotoluene and negligible amounts of tar.

An energetic reaction of *m*-xylene with ferric chloride occurred at 17°, yielding 23% of chloro-*m*-xylene in addition to 2,2′,4,4′-tetramethylbiphenyl and polymer (Table III). Aluminum chloride in catalytic amounts acted in favor of nuclear chlorination. In small quantities titanium tetrachloride exerted little influence, but when used as a solvent favored chlorination at the expense of poly-

(4) P. Kovacic, C. Wu, and R. W. Stewart, *J. Am. Chem. Soc.*, 82, 1917 (1960).

TABLE II

FERRIC CHLORIDE AND TOLUENE[a]

Solvent or Catalyst,	Moles	Temp.	Time, hr.	Chlorotoluene, % Yield	*ortho*	*meta*	*para*	Polymer, g.
None	...	110	0.5	27	15	1	84	10
None[b]	...	45–68	4	40	13	1	87	6.5
$TiCl_4$	1	110	2	61	15	1	84	0
$SbCl_3$	1	110	1	3	14	1	85	12
C_5H_5NO	1	110	1	3	15	1	84	12
$CuCl_2$	0.01	60–64	1	19	13	1	87	10
$AlCl_3$[c]	0.09	40–60	3	62	11	1	89	..[d]
$AlCl_3$[b,e]	0.02	37–70	3	88	...[d]	...	...	0.5
BF_3[b,e]	0.02	31–104	2	52	...[d]	...	...	6.5

[a] Ferric chloride (0.5 mole) and toluene (1 mole). [b] Extrapolated from a double scale run. [c] Ferric chloride (1 mole) and toluene (3.5 moles). Ref. (2). [d] Not determined. [e] Experiment by F. J. Donat.

TABLE III

FERRIC CHLORIDE[a] AND *m*-XYLENE

C_8H_{10}, Mole	Solvent or Catalyst	Moles	Temp.	Time, hr.	C_8H_9Cl, %	High boiler, g.	Polymer,[b] g.
2	None	...	17–26	1.0	23	8[c]	16[d]
2	None[e]	...	17–82	5.5	33	2	16
2	$AlCl_3$[c]	0.02	47–71	3.5	77	2	3
2	$TiCl_4$	0.02	24–90	5.0	37	2	18
0.5	$TiCl_4$	1.3	40–98	4.5	50	10[f]	1

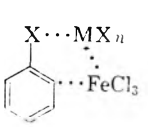
[a] 1 mole. [b] Residue from steam distillation of the reaction mixture. [c] 2,2′,4,4′-Tetramethylbiphenyl.[6] [d] Residue from fractional distillation. [e] Ref.[6]. [f] 4,6-Dichloro-*m*-xylene, b.p. 221° (743 mm.), m.p. 70–70.5°, leaflets from ethanol; lit.[7] b.p. 223–224°, m.p. 68.5°.

merization. In this same medium some of the chloro-*m*-xylene initially formed was converted to the dichloro stage.

DISCUSSION

In accord with previous findings,[2,6] catalytic amounts of aluminum chloride facilitated nuclear chlorination by ferric chloride, while decreasing the extent of polymerization. Other metal halides also possessed the ability, in common with aluminum chloride, to lower the initiation temperature. A somewhat related phenomenon has been observed[8] in the Friedel-Crafts reaction wherein one metal halide can increase the activity of another. Several plausible explanations may be offered to account for the pronounced catalytic action of aluminum chloride. Studies of the ArH-AlX_3-HX system[9] have established that a polar complex is formed, which may provide a favorable medium for ionic reactions—a category which apparently[2] includes chlorination by ferric chloride. Alternatively, reaction may be favored by the existence of complexes of the type $Cl_2FeCl \rightarrow AlCl_3$. However, the low *meta* isomer content does not indicate any large increase in "activity"[9] of the attacking species on addition of aluminum chloride.

Chlorobenzene and toluene are completely miscible with the metal chlorides used as solvents, but ferric chloride is at most only slightly soluble in these organic and inorganic media. Whether ferric chloride is more soluble in the aromatic–metal chloride solution is not known. In general, the metal chloride solvents promoted the chlorination of chlorobenzene by ferric chloride and in some cases altered the isomer distribution of the product. With toluene, titanium tetrachloride favored chlorination whereas antimony trichloride favored polymerization. In both cases the isomer distribution of the chlorotoluene remained unchanged, as was also the case for cupric chloride catalyst. These results suggest that the halogen atom on the aromatic nucleus may play a vital role in the altered isomer distribution produced by adjunct metal chlorides. The increased *o/p* ratio from chloro- and bromobenzene in titanium tetrachloride (Matheson Coleman and Bell), from chlorobenzene in antimony trichloride, and from chlorobenzene in the presence of copper chloride catalysts may result from formation of a complex in which *ortho* substitution is facilitated. The wide dis-



(5) P. Kovacic and C. Wu, forthcoming publication.
(6) R. W. Stewart, M.S. thesis, Case Institute of Technology, 1957.
(7) E. Koch, *Ber.*, **23**, 2318 (1890).
(8) C. C. Price, *Org. Reactions*, III, 1 (1946).
(9) K. L. Nelson and H. C. Brown, in *The Chemistry of Petroleum Hydrocarbons*, Reinhold Publishing Corp., New York, N. Y., 1955, Vol. 3, p. 465.

crepancy in results with titanium tetrachloride from different sources may possibly be due to differences in trace impurities present.

Several experiments were concerned with the rearrangement of aromatic chlorides by a Friedel-Crafts catalyst. Our results, together with the findings of Mattano,[10] show that rearrangement of *o*-dichlorobenzene by aluminum chloride leads to appreciable amounts of the *meta* isomer. It is significant that under the conditions used for chlorination by ferric chloride the proportion of *meta* isomer in the dichlorobenzene product is extremely low (about 1%).

Although the isomer distribution from the ferric chloride–antimony trichloride–chlorobenzene system resembles fairly closely that[2] from antimony pentachloride–chlorobenzene, the analogy does not hold in the case of ferric chloride–antimony trichloride–toluene and antimony pentachloride–toluene.

We have shown[3] that co-catalysts play an important role in the formation of polymer from benzene–ferric chloride. Since added titanium tetrachloride very pronouncedly inhibited benzene polymerization, its effect was attributed[3] to destruction of traces of co-catalyst. The ability of titanium tetrachloride to reduce polymer formation from alkylbenzenes may be similarly interpreted.

Nitrobenzene and pyridine markedly retarded or completely inhibited nuclear chlorination, presumably because of their ability to coordinate strongly with ferric chloride. This type of complex formation should decrease the Lewis acid strength of ferric chloride and therefore interfere with the electrophilic chlorination reaction[4] effected by this reagent. On the other hand, nitrobenzene did not inhibit the formation of polymer in the toluene reaction. The alkyl side-chain is very likely involved in the polymerization reaction, although our studies with benzene suggest that a nuclear polymerization might also occur. The reaction of ferric chloride with alkane is known[11] to proceed in the presence of nitrobenzene. These results lead us to believe that ferric chloride is involved in quite different ways in the chlorination and polymerization processes.

At the present stage many aspects of the action of catalysts and solvents in this heterogeneous system are little understood.

EXPERIMENTAL

Materials. High purity, commercial materials were used. Unless otherwise specified, the source of titanium tetrachloride was Matheson Coleman and Bell.

General procedure. The general procedure described in a previous report[4] was used with slight adaptations. Usually the aromatic compound (1 mole) was mixed with ferric chloride (0.5 mole), and the solvent[12] (1 mole) or catalyst (0.02 mole) was then added at room temperature. The reaction mixture was heated with stirring to the initiation temperature, the temperature at which hydrogen chloride was first detected. For the constant temperature reactions (in Table II and the titanium tetrachloride solvent experiments in Table I), the aromatic compound and the solvent were heated to the desired temperature, and then ferric chloride was quickly added. In the aluminum chloride catalyst experiments at 130–134° in Table I, the reaction mixture was quickly heated to the indicated temperatures.

Ferric chloride and bromobenzene in titanium tetrachloride. A mixture of bromobenzene, ferric chloride, and titanium tetrachloride was heated to 120° during 1 hr. with vigorous stirring. Hydrogen chloride was first detected at 55°. After an additional hour at 120–128°, the reaction mixture was poured onto ice and worked up in the usual manner. Bromochlorobenzene (38 g., 79%; $o/m/p$ = 23/< 1/87) was collected at 96–97° (33 mm.).

Ferric chloride and fluorobenzene in titanium tetrachloride. The reaction mixture was heated at 47–97° for 2 hr. The evolution of hydrogen chloride was slow. A 7% yield of chlorofluorobenzene (b.p. 129–130°) was obtained.

Ferric chloride and p-chlorotoluene in titanium tetrachloride. *p*-Chlorotoluene was added from a dropping funnel to a mixture of ferric chloride and titanium tetrachloride at 104°. After 1.5 hr. at 104–108°, the reaction mixture was steam distilled. Fractionation of the dried distillate yielded dichlorotoluene (14 g., 36%), b.p. 190–196°. Infrared analysis showed it to consist of 2,4- and 3,4-dichlorotoluene with the former predominating. The residue from fractionation was 1 g. of oil whose infrared spectrum resembled that[4] of (*p*-chlorobenzyl)-4-chlorotoluene. There was no tarry material.

Isomerization studies. A mixture of chlorobenzene (0.5 mole), *o*-dichlorobenzene (0.5 mole), and aluminum chloride (1 mole) was stirred at 130–133° for 3 hr., with dry hydrogen chloride being introduced beneath the surface of the reaction mixture. After work-up, infrared examination of the dichlorobenzene fraction revealed the presence of *meta* and *para* bands with the former being more intense.

In a similar manner, a mixture of toluene, *o*-chlorotoluene, and aluminum chloride was treated with hydrogen chloride at 60–63° for 3 hr. The infrared spectrum of the reaction product exhibited pronounced *meta* bands.

Analytical procedure.[4] The isomer distributions were determined by the infrared method. The wave lengths (μ) used for the determination of dichlorobenzene were 13.38 (*o*), 12.78 (*m*) and 12.23 (*p*); those for chlorotoluene were 13.38 (*o*), 12.78 (*m*) and 12.43 (*p*). In some cases, the isomer distributions of dichlorobenzene were determined by the melting–freezing point method of Holleman and van der Linden.[13] These results were found to deviate from the infrared analyses by no more than ±1% for the *p*-isomer. For the determination of chlorobromobenzene, the melting–freezing point method[13] was used.

Acknowledgment. We gratefully acknowledge the support of this work by the National Science Foundation.

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(10) L. A. Mattano, U. S. Patent 2,727,075 (1955); *Chem. Abstr.*, 50, 9444 (1956).

(11) P. Kovacic and H. C. Volz, *J. Am. Chem. Soc.*, 81, 3261 (1959).

(12) Denotes a liquid adjunct present in molar quantities, which may also act as a catalyst.

(13) A. F. Holleman and T. van der Linden, *Rec. trav. chim.*, 30, 305 (1911).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LOUISIANA STATE UNIVERSITY IN NEW ORLEANS]

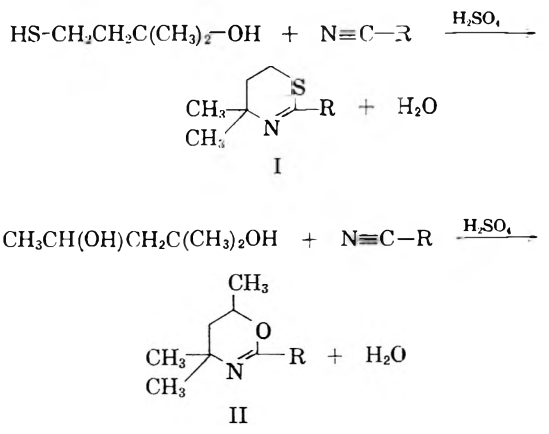
An Infrared Examination of the C=N Link in Dihydro-1,3-oxazines and Dihydro-1,3-thiazines[1]

ALBERT I. MEYERS

Received April 28, 1960

A series of dihydro-1,3-oxazines and dihydro-1,3-thiazines has been investigated with respect to the effects of various 2-substituents on the stretching frequency of the C=N link. It was observed that the C=N link in the thiazine derivatives exhibit a band at longer wavelengths than the C=N link in similarly substituted oxazines. This is attributed to the enhanced polarizability of the sulfur atom which effects a lower C=N bond order and results in a decrease in its stretching frequency.

As part of a continued study[2] on the spectral position of the C=N link in heterocyclic compounds, a series of previously unreported dihydro-1,3-thiazines (I) and dihydro-1,3-oxazines (II) was investigated. These heterocyclic bases were obtained *via* a new synthetic route[3] which involves the addition of various tertiary alcohol derivatives to a solution of nitriles in concentrated sulfuric acid.

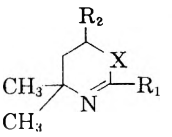


As a result of this ring closure reaction, the infrared spectra of sixteen heterocyclic compounds were examined and their absorption in the 6 μ region, which is the region containing the C=N stretching band, is given in Table I. Comparison of the oxazine and thiazine derivatives is made with respect to the influence exerted by the 2-substituent on their respective C=N linkages.

Table II contains the physical constants of several newly prepared oxazines to allow just comparison with all the correspondingly substituted thiazines. The physical constants for all other compounds used in this study have already been reported.[3,4]

TABLE I

INFRARED ABSORPTION OF THE C=N LINK IN DIHYDRO-1,3-THIAZINES AND DIHYDRO-1,3-OXAZINES



Compound	R_1	R_2	X	μC=N
III	CH_3	H	S	6.11
IV	C_2H_5	H	S	6.16
V	C_2H_5	CH_3	S	6.17
VI	$CH{=}CH_2$	H	S	6.32
VII	C_6H_5	H	S	6.22
VIII	2-$CH_3C_6H_4$	H	S	6.16
IX	4-$CH_3C_6H_4$	H	S	6.24
X	4-$H_2NC_6H_4$	H	S	6.25
XI	CH_3	CH_3	O	6.00
XII	C_2H_5	CH_3	O	6.01
XIII	CH_2CH_2CN	CH_3	O	6.00
XIV	$CH{=}CH_2$	CH_3	O	6.22
XV	C_6H_5	CH_3	O	6.10
XVI	2-$CH_3C_6H_4$	CH_3	O	6.04
XVII	4-$CH_3C_6H_4$	CH_3	O	6.09
XVIII	4-$H_2NC_5H_4$	CH_3	O	6.15

Examination of Table I reveals that the dihydro-1,3-thiazines (III–X) exhibit a single strong band in the 6 μ region. This region has been previously reported to contain the C=N stretching band in 1-pyrrolines,[2] 2-thiazolines,[5] dihydro-1,3-oxazines,[6] and other *N*-heterocyclic systems.[7] When the dihydro-1,3-thiazines containing 2-alkyl substituents (III–V) are considered, only one strong band in the 6.11–6.17 μ region appears. This is attributed to the stretching mode of the cyclic unconjugated C=N link. When the 2-substituent is the conjugated vinyl group (VI) a weak band at 6.14 μ and a strong band at 6.32 μ appears. These are

(1) A portion of this work was presented at the 15th Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec. 3–5, 1959.

(2) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

(3) A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1960).

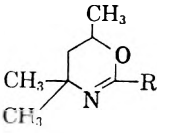
(4) J. J. Ritter and E. J. Tillmanns, *J. Org. Chem.*, **23**, 839 (1957); J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

(5) H. M. Randell, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Compounds*, Van Nostrand, New York, 1949. p. 211; W. Otting and F. Drawert, *Ber.*, **88**, 1469 (1955). A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

(6) A. I. Meyers, *J. Org. Chem.*, **25**, 142 (1960).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., J. Wiley and Sons, Inc., New York, 1958, p. 268.

2-SUBSTITUTED 4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3-OXAZINES



Compound	R_1	B.P.	mm.	n_D^{30}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XII	CH_2CH_3	67–68	20	1.4385	$C_9H_{17}NO$	69.67	10.96	69.62	10.91
XIII	CH_2CH_2CN	104–106	3.5	1.4544	$C_{10}H_{16}N_2O$	66.66	8.88	66.57	8.84
XVI	2-$CH_3C_6H_4$	118–119	1.3	1.5246	$C_{14}H_{19}NO$	77.41	8.75	77.32	8.68
XVII	4-$CH_3C_6H_4$	1.5	1.5	1.5403	$C_{14}H_{19}NO$	77.41	8.75	77.38	8.69
XVIII	4-$H_2NC_6H_4$	124–126[a]			$C_{13}H_{18}N_2O$	71.55	8.25	71.43	8.29

[a] Melting point. Recrystallized from 50% aqueous ethanol.

considered to represent the stretching frequency of the CH_2=CH and C=N linkages, respectively. As expected, the bond order and therefore the stretching frequency of the C=N link is lowered by virtue of its conjugation with the vinyl group.

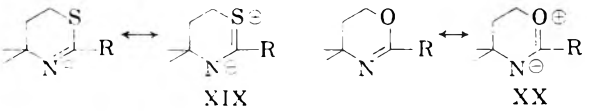
Substitution of an aromatic ring in the 2-position (VII–X) produces a shift of the C=N band to longer wave lengths than that observed for 2-alkylthiazines, but not as pronounced as the shift resulting from the introduction of the 2-vinyl group. The fact that the vinyl substituent produces a greater C=N bond shift than the aromatic substituent has been observed in several previous studies of this type.[2,5]

Another substituent effect which is plainly evident from the data in Table I is the fact that the C=N absorption for the 2-(*o*-tolyl)dihydrothiazine (VIII) appears at shorter wave lengths than it does for the 2-(*p*-tolyl) derivative (IX). This can be explained by considering the configuration of the molecule about the 2-position. For the *ortho* isomer there apparently exists considerable crowding between the methyl group and the thiazine ring and this would force the aromatic ring somewhat out of the plane of the thiazine ring. This results in partial destruction of the conjugative effect by making maximum *pi* electron overlap difficult. In the case of the *para* isomer, there exists no crowding between the phenyl substituents and the thiazine ring and this fact is obvious by comparing the C=N absorption of (VIII, II, and X).

By examining the spectra of the dihydro-1,3-oxazines, only a single strong band is found for the 2-alkyl derivatives (XI–XIII) in the 6 μ region whereas several bands appear in this region for the aryl and vinyl derivatives (XIV–XVIII). However, for the latter compounds, only one strong band is observed which is much greater in intensity than any of its nearest neighbors. It is this strong band which is believed to arise from the stretching frequency of the C=N link. The other bands of intermediate intensity present for the aryl derivatives in the 6 μ region are undoubtedly due to the aromatic C=C vibrations.

Comparing the C=N absorption of the dihydro-1,3-oxazines the effects produced by their 2-substituents appear to closely parallel the effects produced by similar substituents in the thiazine series. Thus, a 2-vinyl group (XIV) causes the C=N band to shift to a greater extent than a 2-aryl group (XV–XVII) and an *ortho*-substituted aryl group (XVI) on the oxazine ring yields a C=N band at shorter wave lengths than that derived from a *para*-substituted (XVIII) or unsubstituted aryl group (XV).

The one major difference, seen in Table I, between the dihydro-1,3-oxazines and the dihydro-1,3-thiazines is clearly evident by the overall absorption at longer wavelengths by the latter group. If each dihydro-1,3-oxazine and dihydro-1,3-thiazine containing identical 2-substituents is compared, it is obvious that the C=N link in the latter compound has a lower stretching frequency. The differences in the spectral position of the C=N link for each pair of identically 2-substituted heterocycles is approximately 0.1 μ. This decrease in the bond order of the dihydro-1,3-thiazine C=N linkage is attributed to the enhanced polarizability of the divalent sulfur atom and therefore the significant contribution of the canonical structure, XIX, to the thiazine hybrid. This behavior has been previously observed in fluorine-containing thioesters in which the carbonyl stretching frequency is shifted towards longer wave lengths than the carbonyl frequency in oxygenated esters.[8]



XIX XX

In the case of dihydro-1,3-oxazines, canonical forms such as XX must make little or no contribution to the hybrid and thus the bond character of the C=N link remains virtually unaltered. It is noteworthy to mention that the C=N link in unconjugated 1-pyrrolines containing a 2-alkyl group exhibits a single intense band[2,9] between 6.05–6.06 μ, whereas the dihydro-1,3-oxazines containing the same 2-alkyl group show a C=N band

(8) M. Hauptschein, C. S. Stokes, and E. A. Nodiff, *J. Am. Chem. Soc.*, **74**, 4005 (1952).

(9) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

at 6.00–6.01 μ (XI–XIII). If the Pauling electronegativities[10] of carbon (2.5) and oxygen (3.5) are considered, then it appears reasonable that the stronger electronegative element, oxygen, will "tighten" the C=N link by its inductive effect to a greater extent than the carbon atom. It has been found that for some cases group frequency shifts parallel electronegativities of the atoms concerned.[11] This fact is borne out herein when the 1-pyrrolines, dihydro-1,3-thiazines, and dihydro-1,3-oxazines are compared.[12]

In order to exclude the possibility that the comparison of the dihydro-1,3-thiazines and dihydro-1,3-oxazines reported herein is not valid because of the presence of a 6-methyl group in the oxazine system, a dihydro-1,3-thiazine containing a 6-methyl group (V) was compared with one not containing this substituent (IV). The C=N absorption of both these compounds revealed no significant differences.

(10) L. Pauling, *The Nature of the Chemical Bond*, Cornell Univ. Press, Ithaca, New York, 1948, p. 60.

(11) See ref. 7, p. 394.

(12) It is considered reasonable here to compare a five-membered ring (1-pyrrolines) containing the C=N link with the two six-membered ring systems (oxazines and thiazines) since it has been found that 2-thiazolines containing the same 2-substituents as the dihydro-1,3-thiazines exhibited C=N absorptions in exactly the same spectral region. Compare data of thiazines given in Table I with data of thiazolines reported in ref. 2.

EXPERIMENTAL[13,14]

All the infrared spectra were performed in a Perkin-Elmer 21 Recording Spectrophotometer using sodium chloride optics. All the samples were studied in a 5–7% solution in chloroform.

2-Substituted 4,4,6-trimethyldihydro-1,3-oxazines. The method of preparation of these compounds was taken from the procedure described by Ritter and Tillmanns.[4]

2-Ethyl-4,4,6-trimethyldihydro-1,3-thiazine (V). This compound was prepared by treating the corresponding dihydro-1,3-oxazine with phosphorus pentasulfide and the details are described in a previous communication;[3] b.p. 66–67° (1.5 mm.), n_D^{30} 1.4842, picrate, m.p. 113–114°.

2-Substituted 4,4-dimethyldihydro-1,3-thiazines. The experimental details describing the preparation of these compounds have recently been reported.[3]

Acknowledgment. The author wishes to express his gratitude to the National Institutes of Health (RG-6248) for funds granted to support a study of which the present work is a part.

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(13) All melting points and boiling points are uncorrected.

(14) Microanalyses performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE LABORATORY]

Absorption Spectra and Positions of Protonation of 2-Arylindoles

MORTIMER J. KAMLET AND JOSEPH C. DACONS

Received April 14, 1960

Structure-spectra correlations are drawn for the 2-arylindoles. It is shown that substitution at the 3-position causes a "type 1" steric effect, substitution on the nitrogen a "type 2" steric effect. At the 4(6)- and 5-positions substituents exert electromeric effects and shift maxima accordingly. In acid media the spectra are consistent with the indoleninium salt structure (XXIV).

In order to lay the groundwork for a proposed study of the more complex spectral behavior of indole alkaloids related to alstonilline and sempervirine, it was deemed desirable to determine the ultraviolet spectra in neutral and acidic media of a number of 2-arylindoles and related compounds. These spectra were of interest *per se*, as they illustrated electronic and steric effects in this series and offered evidence regarding the position of protonation. In Table I are listed the positions and extinction coefficients of maxima and minima determined in the course of the present investigation.[1]

(1) The method used to describe spectra conforms with the recommendations of the Editorial Board of Organic Electronic Spectral Data, Inc., J. D. Cawley and H. E. Ungnade, *Anal. Chem.*, **31**, No. 2, 42A (1959).

EXPERIMENTAL

Materials. 3-Phenylindole (II), 1-methyl-2-phenylindole (III) and 2-(*p*-biphenylyl)indole (XII) were kindly supplied to us by Dr. B. Witkop, National Institutes of Health. They had been prepared by the Fisher indole synthesis using polyphosphoric acid.[2] Dr. K. Schofield, Washington Singer Laboratories, Exeter, was good enough to furnish us a sample of 6-nitro-2,3-diphenylindole (XI), prepared by the cyclization of desoxybenzoin *m*-nitrophenylhydrazone.[3] The compound had decomposed slightly on arrival, but a single recrystallization from ethanol gave a pure sample as orange crystals, m.p. 227° (lit.,[3] m.p. 225–227°). 2-Phenylindole (I) was commercially available from K. and K. Laboratories, Long Island City, N. Y. The material melted at 187.5–188° (lit.,[2] m.p. 187–188°) after one recrystallization from ethanol.

(2) H. M. Kissman, D. W. Farnsworth, and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952).

(3) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 3175 (1957).

TABLE I

SPECTRA DETERMINED IN PRESENT INVESTIGATION

Compound	Solvent[a]	λ_{max}(log ϵ)[b]	λ_{min}(log ϵ)	Compound	Solvent[a]	λ_{max}(log ϵ)[b]	λ_{min}(log ϵ)
2-Phenylindole (I)	CH_3OH	240(4.23)	268(3.58)	4(6)-Chloro-2,3-diphenylindole (VII)	CH_3OH	249(4.46)	236(4.43)
		309(4.39)[c]				258s(4.41)	276(3.95)
	H_3PO_4	264(3.83)	278(3.64)			313(4.27)	
		343(4.34)[d]			H_3PO_4[f]	324(4.18)[h]	288(4.04)
3-Phenylindole (II)	CH_3OH[e]	201(4.47)	210(4.46)	5-Chloro-2,3-diphenylindole (VIII)	CH_3OH[e]	207(4.55)	226(4.37)
		224(4.56)	245(3.95)			244(4.43)	270(3.86)
		269(4.25)				309(4.28)	
		280s(4.21)			H_3PO_4[f]	339(4.20)[d]	295(4.01)
1-Methyl-2-phenylindole (III)	CH_3OH[e]	207(4.44)	214(4.45)	4(6)-Methoxy-2,3-diphenylindole (IX)	CH_3OH	242s(4.32)	251(4.29)
		224(4.46)	264(3.68)			259(4.30)	280(3.92)
		237s(4.33)				325(4.23)	
		298(4.26)			H_3PO_4	331(4.1)	
	H_3PO_4	250(3.48)	260(3.30)			380s(3.9)[f,j]	
		322(4.18)[d]			HCl	272(4.04)	289(3.81)
2,3-Diphenylindole (IV)	CH_3OH	248(4.34)	268(3.96)			328(4.14)	
		308(4.22)				390s(3.90)	
	H_3PO_4	255(3.93)	279(3.68)	5-Methoxy-2,3-diphenylindole (X)	CH_3OH	255s(4.20)	271(4.02)
		344(4.20)[d]				317(4.34)	
	H_2SO_4[f]	343(4.20)			H_3PO_4	266(4.02)	306(3.65)
	HCl	255(3.94)	279(3.68)			381(4.18)[d]	
		342(4.19)			HCl	268(4.06)	310(3.69)
4(6)-Methyl-2,3-diphenylindole (V)	CH_3OH	250(4.35)	238(4.33)			383(4.17)	
		314(4.24)	274(3.96)	6-Nitro-2,3-diphenylindole (XI)	CH_3OH	250(4.34)	229(4.21)
	H_3PO_4[f]	345(4.14)[d]				292(4.09)	285(4.09)
	HCl	260(3.95)	285(3.59)			342(4.02)	317(3.98)
		343(4.14)				396(4.13)	355(4.02)
5-Methyl-2,3-diphenylindole (VI)	CH_3OH	243(4.37)	241(4.36)	2-(*p*-Biphenylyl)indole (XII)	CH_3OH[e]	208(4.60)	240(4.09)
		249(4.39)	246(4.36)			257(4.25)	278(3.82)
		255(4.39)	252(4.37)			329(4.58)	
		313(4.29)	274(4.00)	2,3-Diphenylbenzofuran (XIII)	CH_3OH	235(4.36)	256(3.79)
	H_3PO_4	254(3.88)	256(3.87)			302(4.36)	
		261(3.94)	284(3.40)			315s(4.25)	
		365(4.14)[g]		5-Methyl-2,3-diphenylbenzofuran			
	HCl	255(4.10)	239(3.87)	(XIV)	CH_3OH	238(4.31)	230(4.26)
		261(4.12)	258(4.09)			306(4.39)	256(3.73)
		363(4.16)	284(3.72)			320s(4.29)	
				trans-Stilbene (XV)	CH_3OH	295(4.47)	242(3.10)
						306(4.45)	
						319s(4.26)	

[a] Absolute methanol, spectrum covers range 220–400 mμ; syrupy (85%) phosphoric acid containing 2% absolute methanol, 250–400 mμ; concentrated hydrochloric acid containing 12% methanol, 220–400 mμ. [b] Wave length followed by s denotes shoulder, plateau or inflection. [c] Blades and Wilds (ref. 15) report 241(4.34), 309(4.47). The present values were determined in duplicate and agree closely with data reported by Wiegand and Merkel (ref. 13). [d] Position of maximum substantially unchanged after three days standing. [e] Spectra determined on Cary, Model 14. Range 200–400 mμ. [f] Only long wavelength maximum recorded. [g] After three days standing position of maximum shifted to 345 mμ. [h] After three days, maximum 336 mμ. [i] After three days no maximum above 300 mμ. [j] Extinction coefficients could not be accurately determined because of poor solubility.

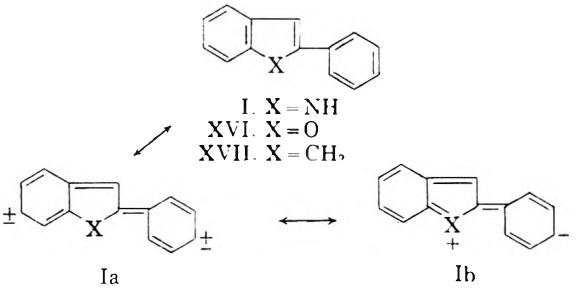
The 2,3-diarylindoles IV–X were prepared in the laboratories of Dr. E. F. Pratt, University of Maryland, by the cyclization of α-anilino-α-phenylacetophenones (desyl anilines) in refluxing *p*-cymene.[4] Melting points of the 5-methyl (VI), 5-chloro (VIII), and 5-methoxy (X) derivatives agreed closely with values reported by Ockenden and Schofield,[3] who prepared these compounds by Fisher indole syntheses from the desoxybenzoin *p*-X-phenylhydrazones. As the question of whether the α-(*m*-X-anilino)-α-phenylacetophenones cyclize *ortho* or *para* to X is as yet unresolved[5,6] the structures of V, VII and IX cannot be assigned with certainty. The weight of evidence[6] favors the 4-methoxy-2,3-diphenylindole structure for IX. Because electronic effects of 4- and 6-substituents on spectra would be expected to be about the same, further consideration of this problem will be deferred to a forthcoming publication by Pratt and Kamlet. Details of syntheses and physical properties will also be discussed together with the kinetics and mechanism of the cyclization reaction.

Fusion of equimolar *p*-cresol and benzoin with catalytic amounts of zinc chloride at 180° for 1.5 hr. gave mainly unchanged benzoin together with small amounts of 5-methyl-2,3-diphenylbenzofuran (XIV), which was separated by virtue of its greater solubility in ether. After several recrystallizations from ethanol the product melted at 114.5° (lit.,[7] m.p. 114°). A similar procedure using phenol gave 2,3-diphenylbenzofuran (XIII), m.p. 123–124° (lit.,[7] m.p. 123°), also in poor yields. Attempts to prepare these and other substituted 2,3-diphenylbenzofurans by refluxing cymene solutions of benzoin, the appropriately substituted phenol, and *p*-toluenesulfonic acid, yielded only tetraphenylfuran, m.p. 169–170°, which has been described as arising from benzoin by a series of oxidation-reduction and autocondensation reactions.[8]

Absorption spectra. The spectra were measured in 1-cm. silica cells using either a Cary Model 14 or a Beckman DU Spectrophotometer. To check for instrumental errors several spectra were determined on both machines and agreed within 1% in extinction coefficients and within one half millimicron in positions of the maxima. Solutions were $4.0 \pm 0.1 \times 10^{-5} M$ and previously described precautions[9] were taken to guard against photochemical transformations which are quite common at these low concentrations.

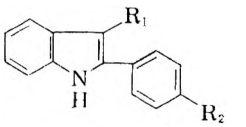
DISCUSSION

2-Phenylindole (I) shows two regions of intense absorption above 220 mμ in the ultraviolet. A secondary B-band[10] with a maximum at 240 (4.23),[11] probably arising from a styryl "partial," is superimposed on high intensity shorter wave length absorption so that the manner in which it shifts with substitution in the indole nucleus is often obscured. The primary B-band maximum at 309(4.39), however, is sufficiently remote that the variation in its position and intensity is less influenced by complications due to band overlap. The latter band may derive from the *trans*-stilbene chromophore (Ia) shifted bathochromically due to resonance contributions by structures like Ib. *trans*-Stilbene (XV) exhibits twin maxima at 295(4.47) and 306(4.45).



2-Phenylbenzofuran (XVI) and 2-phenylindene (XVII), which incorporate the same chromophore with resonance stabilization by structures like Ib, have spectra resembling I. For XVI splitting of the primary B-band persists with maxima at 302(4.39) and 315(4.28)[12] while XVII, like I, shows fusion of the maxima with a single peak at 305-(4.40, dioxane).[13] The displacement of the B-bands with changing X is as anticipated,[14] NH> O>CH_2. For comparison, 3-phenylindole has a spectrum reminiscent of the alkylindoles with maxima at 224(4.56) and 269(4.25) and a weak inflection at 280 (4.2).

The 3-substituent of 2-arylindoles influences only slightly the position of the primary B-band maximum, but affects strongly its intensity; the greater the bulk of the grouping, the lower is ϵ_{max}. Thus the band corresponding to 309(4.39) for I has its maximum at 307.5(4.32)[15] for 3-methyl-2-phenylindole (XVIII), at 306(4.21)[16] for 2-phenyltryptophane (XIX), and at 308(4.22) for 2,3-diphenyl-



I. R_1 = H, R_2 = H
IV. R_1 = C_6H_5, R_2 = H
XVIII. R_1 = CH_3, R_2 = H
XIX. R_1 = $CH_2CH(NH_2)COOH$, R_2 = H
XX. R_1 = CH_3, R_2 = Cl
XXI. R_1 = H, R_2 = Cl

(4) M. J. Kamlet, Ph.D. thesis, University of Maryland, 1954.

(5) A. H. Orr and M. Tomlinson, *J. Chem. Soc.*, 5097 (1951).

(6) H. J. Tauber and K. Schnee, *Ber.*, **91**, 2089 (1958).

(7) B. T. Arventi, *Bull. Soc. Chim. France*, [5] **3**, 598 (1936).

(8) O. Dischendorfer, *Monatsh.*, **74**, 287 (1943).

(9) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957).

(10) The band nomenclature system is that of W. F. Forbes, *Can. J. Chem.*, **36**, 1350 (1958). The B-band corresponds to the "primary band" of Doub and Vandenbelt, the "C-band" of Klevins and Platt, and the "K-band" of the European school.

(11) The same system of denoting positions and extinction coefficients of maxima is used in the text as in Table I; wave lengths are given in millimicrons followed by log ε in parentheses. Unless otherwise stated spectra from the literature were determined in ethanol.

(12) P. Yates, *J. Am. Chem. Soc.*, **74**, 5376 (1952).

(13) C. Wiegand and E. Merkel, *Med. u. Chem.*, **4**, 585 (1942).

(14) E. A. Braude in E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, New York, 1955, pp. 153–154.

(15) C. E. Blades and A. L. Wilds, *J. Org. Chem.*, **21**, 1013 (1956).

(16) H. M. Kissman and B. Witkop, *J. Am. Chem. Soc.*, **75**, 1967 (1953).

indole (IV). Similarly 2-(*p*-chlorophenyl)-3-methylindole (XX), 310.5(4.36)[15] shows a slight hypsochromic shift and diminished intensity relative to 2-(*p*-chlorophenyl)indole (XXI), 313.5(4.43).[15]

This corresponds to the steric effect referred to by Braude and co-workers as "type 1" behavior,[17] *i.e.*, a reduction in intensity without a significant shift in position of λ_{max} due to substitution in a vicinal atom by a nonconjugating group. Spectral bands exhibiting "type 1" behavior are believed to derive from transitions between ground states where the energetically preferred conformation is nonplanar and excited states where the preferred conformation is planar or near planar. In this series the 3-substituents, by increasing the angle of deviation from planarity of the 2-phenyl grouping with reference to the indole nucleus in the preferred ground state conformation, decrease the transition probability with a corresponding decrease in ϵ_{max}. Preferred interplanar angles, θ, calculated from Braude's equation, $\cos^2\theta = \epsilon/\epsilon_0$ where ϵ is the molar extinction coefficient of the 3-substituted derivative and ϵ_0 that of the parent compound,[18] are listed in Table II.

TABLE II

STERIC EFFECTS IN 3-SUBSTITUTED 2-ARYLINDOLES

Indole	ϵ/ϵ_0	θ
2-Phenyl (I)	1.000	0°
3-Methyl-2-phenyl (XVIII)	.846	23
2-Phenyltryptophane (XIX)	.650	36
2,3-Diphenyl (IV)	.680	34
2-(*p*-Chlorophenyl) (XXI)	1.000	0°
2-(*p*-Chlorophenyl)-3-methyl (XX)	.842	23

A similar, albeit weaker, effect is noted with the benzofurans. The 2,3-diphenyl derivative (XIII) shows a maximum at 302(4.36) and an inflection at 315(4.25) compared with twin maxima at 302-(4.39) and 315(4.28)[12] for the parent compound XVI. From this the interplanar angle is calculated to be 15°.

While substitution at the 1-position has about the same effect on intensity as it does at the 3-position, the displacement of λ_{max} is far more pronounced, *N*-methylation resulting in a hypsochromic shift of 10 to 15 mμ. Thus 1-methyl-2-phenylindole (III) has its primary maximum at 298(4.26), $\Delta\lambda = -11$ mμ, $\epsilon/\epsilon_0 = 0.73$ and 2-(p-chlorophenyl)-1-methylindole shows λ_{max} at 298.5(4.32), $\Delta\lambda = -15$ mμ. $\epsilon/\epsilon_0 = 0.77$. The magnitude of these effects is about the same as has been observed with the 2-arylbenzimidazles,[19] whose geometry and conjugated system closely resemble the present series. The *N*-methyl-2-phenyl, *N*-methyl-2-(*p*-hydroxyphenyl), *N*-methyl-2-(*p*-anisyl), and *N*-methyl-2-(*p*-aminophenyl) derivatives all showed hypsochromic shifts of 13–16 mμ relative to the parent *N*-hydrogen compounds with ϵ/ϵ_0 values of 0.70–0.76.

It seems likely that these shifts derive from steric rather than electronic causes[20] and conform with the effect described by Braude[17] as "type 2" behavior, *i.e.*, reduction in intensity coupled with a pronounced hypsochromic displacement. Such behavior is a consequence of the vicinal substituent completely inhibiting adoption of the uniplanar conformation required for maximal electronic interaction between the rings. The energy of the noncoplanar electronic excited state is raised relative to that of the noncoplanar ground state with a consequent increase in transition energy and lowering of λ_{max}. We cannot with certainty explain why a methyl group should cause a "type 1" effect on a vicinal carbon atom but a "type 2" effect on a vicinal nitrogen. The problem may relate to the geometry at the 1- and 3-positions. The angle between the carbon atoms of the 3-methyl and the 2- and 3-positions is probably greater than 120° and within the plane of the indole nucleus. On the other hand, the angle formed by the carbon of the 1-methyl group, the nitrogen, and the carbon at the 2-position may be less than 120° and out of the plane.

To determine effects of substitution in the indole nucleus the spectra of a number of 4(6)- and 5-substituted 2,3-diphenylindoles were determined. For these compounds in methanolic solution the order of increasing λ_{max} was H (IV), 308(4.22)<5-Cl (VIII), 309(4.28)<4(6)-Cl (VII) 313(4.27) ≅ 5-CH_3 (VI), 313(4.29)<4(6)-CH_3 (V), 314(4.24)<5-OCH_3 (X), 317(4.34)<4(6)-OCH_3 (IX), 325(4.23).[21] The order and the magnitudes of the shifts were as might have been predicted. Substituents in the 4(6)-position, conjugated with the stilbene chromophore, caused greater bathochromic displacements than like substituents in the 5-position which is out of conjugation. For the 4(6)-substituted compounds the order of increasing λ_{max} corresponds with increasing electromeric polarizability of the substituent group; for the 5-substituted derivatives the order corresponds to the increase in the combined effects

(17a) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 1890 (1949). (b) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(18) Ref. 14, p. 174.

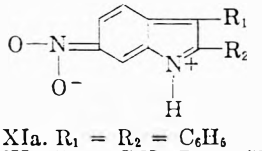
(19) A. Margini and F. Montanari, *Boll. sci. fac. chim. ind. univ. Bologna*, **14**, 36 (1956).

(20) On the latter basis it would be anticipated that the methyl group would by induction increase the availability of the free pair of electrons on nitrogen with a consequent bathochromic effect due to increased resonance stabilization by structures like Ib. Such an electronic effect is observed in comparing aniline, methylaniline, and dimethylaniline with maxima at 230, 244, and 250 mμ, respectively. F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956).

(21) 5-Amino-2-phenylindole absorbs maximally at 316.5 (4.36), R. Adams and W. P. Samuels, Jr., *J. Am. Chem. Soc.*, **77**, 5375 (1955). For comparison with the above series the 2,3-diphenyl derivative may be considered to absorb at about the same position.

of secondary resonance structures and induction.[22] The 17 mμ displacement of IX relative to IV compares with shifts of 13 mμ each for the maxima of *p*-methoxystilbene at 308(4.44) and 319(4.46) relative to the twin maxima of stilbene.[23] The increased extinction coefficients of V–X relative to IV reflect the greater tendency of the 2-phenyl group to retain the coplanar conformation as a result of resonance stabilization.[24]

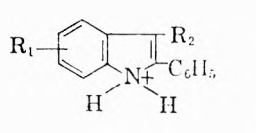
6-Nitro-2,3-diphenylindole (XI) was an interesting member of the above series which did not display the expected spectrum. By comparison with *p*-nitrostilbene, λ_{max} 350(4.42),[23] it was anticipated that the longest wave length band of XI would have its maximum 35–40 mμ lower than the observed position of 396(4.12). The problem was resolved on comparing the overall spectrum with that of 3-ethyl-2-methyl-6-nitroindole (XXII), λ_{max} = 251(3.96), 272(3.79) 340–350s(3.85), 397-(3.97).[25] From the overall similarity between the two it is apparent that the transition to the first electronic excited state in XI does not encompass the stilbene chromophore but more probably the 6-nitroindole chromophore represented by XIa.



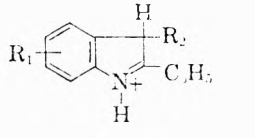
XIa. $R_1 = R_2 = C_6H_5$
XXIIa. $R_1 = C_2H_5$, $R_2 = CH_3$

The protonated indoles. It was considered that if the primary B-bands in this series did indeed derive from the stilbene chromophore with transition energies lowered by contributions from additional resonance structures like Ib, shifts to shorter wave lengths would result if the free electrons on nitrogen were tied up by protonation to the indolium salts (XXIII). By analogy with the anilinium ion which has its B-band maximum at exactly the same position as does benzene (203 mμ), we anticipated that the positions of the bands of I and IV in acidic media would approximate that for stilbene itself. When the spectra were measured in 85% phosphoric acid, there were observed instead bathochromic displacements to 343(4.34) and 344(4.20) mμ, respectively. To confirm that these spectra were not of mixtures of protonated and unprotonated material, the spectrum of IV was also determined in concentrated hydrochloric acid and in concentrated sulfuric acid. In both solvents the positions and intensities of λ_{max} were about the same, 342–344(4.19–4.20).

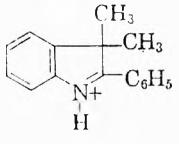
Although difficult to explain on the basis of structures XXIIIa and b, these shifts can readily be rationalized by assuming that the salts had the indoleninium structures XXIVa and b as a result of protonation at the 3-position. Witkop, Patrick, and Kissman[26] have shown that the primary B-band maximum of 3,3-dimethyl-2-phenylindolenine at 306(4.18) is shifted to 332(4.13) by protonation to the indoleninium salt XXV in alcoholic hydrochloric or *p*-toluenesulfonic acid. Both XXIV and XXV incorporate the protonated benzylideneaniline chromophore and the 10–12 mμ hypsochromic displacement and lowered absorption intensity of XXV relative to XXIVa or b are of such magnitudes as would be expected to result from a "type 2" steric effect caused by two neighboring methyl groups.



XXIIIa. $R_1 = R_2 = H$
b. $R_1 = H$, $R_2 = C_6H_5$



XXIVa $R_1 = R_2 = H$
b $R_1 = H$, $R_2 = C_6H_5$



XXV

With 1-methyl-2-phenylindole (III) the same sort of bathochromic displacement was observed. In 85% phosphoric acid, III showed λ_{max} at 322-(4.18), a red shift of 24 mμ relative to the unprotonated compound.

Further evidence regarding the position of protonation may be derived from the spectra of the 2,3-diphenylindoles V–X. In 85% phosphoric acid λ_{max} for this series increased in the order 4(6)-Cl (VII), 324(4.18)<4(6)-OCH_3 (IX), 328-(4.18)<5-Cl (VIII), 339(4.20)<H (IV), 344-(4.20)<4(6)-CH_3 (V), 345(4.14)<5-CH_3 (VI), 365-(4.14)<5-OCH_3 (X), 381(4.18). The spectra of V, VI, IX, and X were also determined in concentrated hydrochloric acid and showed about the same locations and intensities of maximal longer wave-length absorption.

(22) The nature and magnitudes of these effects are discussed by M. J. Kamlet and D. J. Glover, *J. Am. Chem. Soc.*, **77**, 5696 (1955).

(23) M. Calvin and H. W. Alter, *J. Chem. Phys.*, 19, 765 (1951).

(24) The relative extinction coefficients of the 5- and the 4(6)-substituted compounds may provide evidence regarding the positions of the substituents in the latter series. For each pair the 5-substituted derivative showed greater longer wavelength absorption intensity than the 4(6)-compound. In an extended search we were able to find no example of a class of compounds where substituents *meta* to a chromophoric system caused hyperchromic effects relative to the same substituents *para* to that chromophore (as would be the case here if the substituents were in the 6-position). If in the present series the substituents were in the 4-position, the diminution of intensity could be ascribed to a "type 1" steric effect resulting from buttressing of the 4-substituent against the 3-phenyl grouping.

(25) E. Shaw and D. W. Wooley, *J. Am. Chem. Soc.*, **75**, 1877 (1953).

(26) B. Witkop, J. B. Patrick, and M. Kissman, *Ber.*, 85, 953 (1952).

It has been pointed out that in neutral media compounds substituted at the 4(6)-position absorbed at longer wave lengths than the correspondingly substituted 5-derivatives because the former position was conjugated with the stilbene chromophore, the latter unconjugated. With protonation at the 3-position the chromophoric system changes and the 5- becomes the conjugated and the 4(6)- the unconjugated site with respect to the new benzylideneaniline chromophore. The spectra in acid media reflect this change. For each pair the 5-substituted compound now absorbed at longer wave lengths than the 4(6)- derivative, an inversion of their former relative positions.

This seems strong evidence that there was at least some protonation at the 3-position but does not necessarily imply that all seven compounds were converted exclusively to the indoleninium salts (XXIV, $R_2 = C_6H_5$), for on the latter basis it would be difficult to explain the hypsochromic positions of the maxima of VII and IX relative to IV.[27] It seems more likely that with I, III, IV, V, VI, VIII, and X the products were predominantly the indoleninium salts but that VII and IX were converted to mixtures of the latter with the indolium salts (XXIII), $R_2 = C_6H_5$).[28] The fact that the spectra of VII and IX were more diffuse than those of the others and a broad shoulder for IX at 360–390, which might be the manifestation of a bathochromic band, supports this suggestion.

To determine whether a rate versus equilibrium phenomenon was involved, the spectra of all compounds were redetermined after three days' standing in 85% phosphoric acid. The results were inconclusive. The maxima of I, III, IV, V, VIII, and IX remained at about the same place while that of VII shifted toward the red, that of VI shifted toward the blue and that of IX disappeared completely, probably because of decomposition. Details are given in the footnotes to Table I.

Indoles undergo Mannich[16] and Michael[29] reactions at the 3-position and it is the preferred site for alkylations, acylations, and other substitution reactions,[30] indicating a high electron density at this position. Protonation at the 3-position thus is consistent with the general tendency for electrophilic reactions. Indeed, the conversion of IV to XXIVb is exactly analogous with the reaction of 2,3-disubstituted indoles with methyl iodide. The products are the 2,3,3-trisubstituted iudolenines and the indoleninium salts corresponding to XXIV (H = R) are intermediates.

Acknowledgment. The authors are grateful to Drs. B. Witkop and K. Schofield for furnishing samples of the indoles and especially to Dr. E. F. Pratt for permission to publish preliminary information. Drs. L. A. Kaplan and R. E. Lyle contributed helpful discussions.

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(27) The positions of the maxima of both VII and VIII were strongly influenced by overlap with very high intensity bands showing maxima below 260 mμ so that the hypsochromic position for VIII relative to IV causes no concern. With VII the shift was too great to be ascribed to band overlap alone.

(28) Partial protonation at the imino position by VII and IX might be ascribed to stabilization of the stilbene chromophore by the substituent causing a tendency to keep that substituent in the conjugated position.

(29) W. E. Noland and P. J. Hartman, *J. Am. Chem. Soc.*, 76, 3227 (1954).

(30) *Cf.* Review by P. L. Julian, E. W. Meyer, and H. C. Printy in R. C. Elderfeld, *Heterocyclic Chemistry*, Volume III, John Wiley and Sons, New York, 1952.

[CONTRIBUTION NO. 28 FROM THE EXPLORATORY RESEARCH LABORATORY, DOW CHEMICAL OF CANADA, LIMITED]

Organic Fluorine Compounds. XXVI.[1a] Acetoacetyl Fluoride[1b]

G. A. OLAH AND S. J. KUHN

Received April 19, 1960

Acetoacetyl fluoride was prepared from diketene and anhydrous hydrogen fluoride. Its properties and chemical reactivity as an acetoacetylating agent were investigated.

Acyl fluorides have been reported to be stable in cases where the corresponding chlorides or bromides are nonexistent or unstable. Formyl fluoride[2] and perchloryl fluoride[3] are representative of the high stability of acyl fluorides.

Acetoacetyl chloride has been prepared by Hurd and Kelso[4] but was found to be unstable above −20°. It could not be distilled or stored without

(1a) Part XXV, *J. Org. Chem.*, 21, 1319 (1956).

(1b) Presented at the Symposium on Recent Advances in Fluorine Chemistry, at the 138th Meeting of the American Chemical Society, September 12, 1960. New York, N. Y.

(2) A. N. Nesmeyanov and E. J. Kahn, *Ber.*, 67, 370 (1934). G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, 82, 2380 (1960).

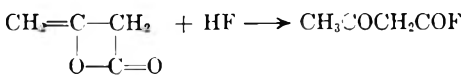
(3) A. Engelbrecht and H. Atzwanger, *Monatsheft.*, 83, 1087 (1952).

(4) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, 62, 1548 (1940).

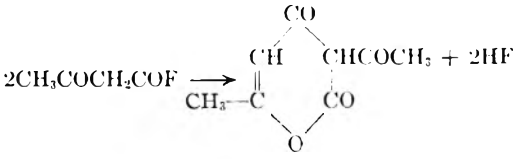
decomposition and its reactions could only be carried out at low temperatures.

We have now investigated the preparation, properties, and chemical reactivity of the previously unreported acetoacetyl fluoride.

Diketene was found to react with anhydrous hydrogen fluoride to give a 60% yield of acetoacetyl fluoride



The by-product of the reaction is dehydracetic acid, formed through condensation of acetoacetyl fluoride

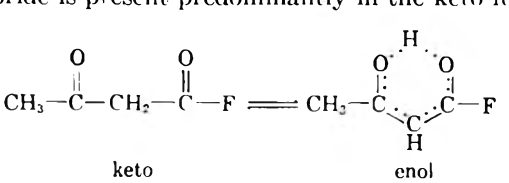


Acetoacetyl fluoride is a colorless fairly stable liquid with a somewhat sharp odor. The boiling point is 57–60° at 35 mm., 43° at 14 mm., 132–134° at atmospheric pressure with some decomposition, n_D^{25} 1.4052. At room temperature it decomposes upon standing in the course of some days to dehydracetic acid but when refrigerated it can be stored for weeks without decomposition. At first the colorless liquid turns yellow, then red. Later a solid precipitate forms (dehydracetic acid) and the whole sample becomes solid. Hydrogen fluoride liberated during the decomposition has a catalytic effect on the condensation.

The infrared spectrum of a thin liquid film (taken on a Baird double beam recording spectrometer with sodium chloride optics) gave the following bands, with tentative assignments in parentheses: 3676 w(2 × 1832), 3426 w, sh (2 × 1721), 3226 m, 2976 m (ν^a C—H), 2937 m (ν^s C—H), 1832 vs (ν C=O, —COF), 1721 vs (ν C=O, CH_3CO), 1626 s, 1425 s (δ C—H), 1412 s (δ C—H), 1366 (δ C—H), 1312 (δ C—H), 1233 s, 1200 s, 1168 s, 1121 s (ν C—F), 1110 s, sh, 1028 m, 945 w, 923 w,

The following abbreviations have been employed; w = weak, s = strong, sh = shoulder, m = medium, vs = very strong, b = broad; ν = stretching frequency (superscript a or s indicates symmetrical or antisymmetrical mode), δ = bending frequency.

According to the infrared spectrum acetoacetyl fluoride is present predominantly in the keto form.



keto enol

In order to establish the quantitative keto:enol ratio in acetoacetyl fluoride, the high resolution nuclear magnetic proton resonance spectrum was taken. The proton resonance spectrum was recorded as a function of the applied magnetic field at a fixed frequency of 30.008 Mc using the modified high resolution NMR spectrometer described by Baker and Burd.[5] A comparison of the intensity of the two principal CH_3 peaks indicates a mole ratio of 0.08 enol/keto (7.41% enol, 92.59% keto).

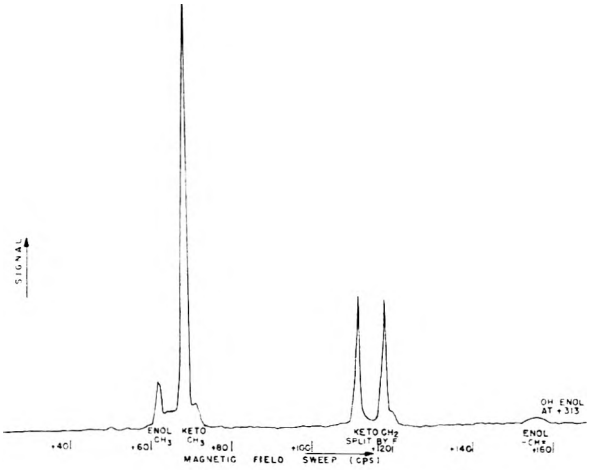
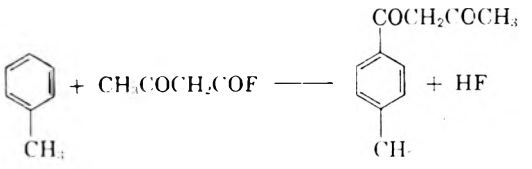


Figure 1

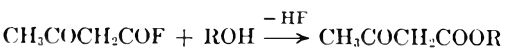
Acetoacetyl fluoride, when used as an acyl halide in attempted aromatic Friedel-Crafts acylation in the presence of boron trifluoride catalyst (most effective in acylation with other acyl fluorides) gives dehydroacetic acid as the main reaction product. Using aluminum chloride as catalyst, a 10% yield of methyl benzoylacetone was obtained in the Friedel-Crafts reaction of acetoacetyl fluoride with toluene.



Selfcondensation to dehydracetic acid is still the main reaction course.

Thus it seems that a Friedel-Crafts catalyst such as boron trifluoride promotes primarily enolization and subsequent selfcondensation by coördinating to oxygen rather than fluorine. This is made more obvious by the fact that no acetoacetylium tetrafluoroborate complex formations was observed in the system $CH_3COCH_2COF:BF_3$.

By treating acetoacetyl fluoride with alcohols in the presence of an acid binding agent, alkyl acetoacetates are formed in good yields:



(5) E. B. Baker and L. W. Burd, *Rev. Sci. Instr.*, 28, 313 (1957).

TABLE I

Amine	Acetoacetamide	B.P./Mm.	N, % Calcd.	N, % Found	Yield, %
Ethylamine	*N*-Ethyl acetoacetamide	170/18 (dec.)	10.90	10.84	70
n-Propylamine	*N*-Propyl acetoacetamide	131/1	9.77	9.69	93
i-Propylamine	*N*-*i*-Propyl acetoacetamide	105–106/0.5	9.77	9.83	91
n-Butylamine	*n*-Butyl acetoacetamide	128/0.5	8.92	8.90	86
Dicyclohexyl-amine	*N*,*N*-Dicyclohexyl aceto-acetamide	166–168/0.6	5.27	5.19	90

The known methyl, ethyl, *i*-propyl, *i*-butyl, *i*-amyl, and benzyl acetoacetate were obtained in yields varying from 68 to 86%.

Acetoacetyl fluoride reacts with primary and secondary amines to form the corresponding acetoacetamides.

$$CH_3COCH_2COF + 2RNH_2 \longrightarrow CH_3COCH_2CONHR + RNH_2.HF$$

The following previously known compounds were obtained with 56 to 87% yields: acetoacetamide, *N*-benzyl acetoacetamide, *N*-*o*-tolyl acetoacetamide, *N*-propyl acetoacetamide, and *N*-*o*-chlorophenyl acetamide. Properties of the new acetoacetamides prepared are summarized in Table I.

Acetoacetyl fluoride is hydrolyzed by water to acetoacetic acid, which itself loses carbon dioxide and gives acetone

$$CH_3COCH_2COF + H_2O \xrightarrow{-HF} CH_3COCH_2CO_2H \xrightarrow{-CO_2} CH_3COCH_3 + CO_2$$

In caustic medium the acetone formation is greatly accelerated.

EXPERIMENTAL

Diketene was purchased from the Aldrich Chemical Company, Milwaukee, Wis., and redistilled each time before use; b.p. 126–127.5°, m.p. −6.5°.

Preparation of acetoacetyl fluoride. To 100 g. (1.2 moles) of diketene 24 g. (1.2 moles) of anhydrous hydrogen fluoride was added in a silica flask, provided with a reflux condenser and protected by a calcium chloride tube from air moisture. The addition was started at −5° and as the freezing point of the diketene–acetoacetyl fluoride mixture dropped, so the temperature was lowered down to Dry Ice temperature. After the addition was completed the reaction mixture was allowed to warm up slowly to room temperature, 5 g. of anhydrous sodium fluoride was added to remove any possible excess of hydrogen fluoride. After filtering, the product was distilled *in vacuo;* yield, 81 g., 65%, b.p. 63–65°/35 mm., n_D^{25} 1.4052. From the residue 8 g. of dehydroacetic acid (m.p., 109°) was isolated.

Anal. Calcd. for $C_4H_5FO_2$ (104.08): C, 46.15; H, 4.83; F, 18.27. Found: C, 46.28; H, 4.80; F, 18.10.

Reaction of acetoacetyl fluoride with alcohols. Acetoacetyl fluoride, 5.7 g. (0.05 mole), was dissolved in 20 ml. of dry ether and 0.05 mole of the corresponding alcohol dissolved in 20 ml. ether was added at ice bath temperature. The reaction mixture was allowed to stand for 15 min. Thereafter, a solution of 3 g. of trimethylamine in 10 ml. ether was added, while the mixture was stirred with a magnetic stirrer. The precipitated amine hydrofluoride was filtered, the organic layer washed with water, dried, distilled to remove ether, and then fractionated. The following known alkyl acetoacetates were prepared: methyl (78% yield), ethyl (86%), *i*-propyl (83%), *i*-butyl (72%), *i*-amyl (79%) and benzyl (68%).

Reaction of acetoacetyl fluoride with amines. Acetoacetyl fluoride, 5.7 g. (0.05 mole), was dissolved in 20 ml. of dry ether and was added to a solution of 0.1 mole of amine dissolved in 25 ml. of ether, at ice bath temperature. The mixture was allowed to stay for 1 hr. The precipitated amine hydrofluoride was filtered. After removal of the ether, the remaining crude amine was either distilled under reduced pressure or recrystallized from ligroin or alcohol. The following known acetoacetamides were prepared: acetoacetamide (87% yield), *N*-benzyl (61%), *N*-phenyl (74%), *N*-*o*-tolyl (63%), and *N*-*o*-chlorophenyl (56%). Data of the new acetoacetamides prepared are summarized in Table I.

Friedel-Crafts acetoacetylation of toluene. Into the stirred mixture of 46 g. of toluene (0.5 mole), 50 g. of chloroform, and 33 g. of anhydrous aluminum chloride (0.25 mole), 20 g. of acetoacetylfluoride (0.2 mole) was added dropwise. The temperature was kept at 0° and the mixture stirred for 1 hr. There was strong hydrogen chloride evolution at first which gradually ceased. The mixture was then poured into ice water, the separated organic layer was washed three times with water, dried over calcium chloride, and distilled to remove the unchanged toluene. The residue was distilled under reduced pressure; b.p. 115–117°/1 mm. The infrared spectrum was identical with that of methyl benzoylacetone; yield 3.29g., 10% From the reaction residue, 10.5 g. dehydracetic acid (b.p. 109°) was isolated.

Acknowledgment. The authors are indebted to Dr. Denys Cook of this laboratory for the assignment of the infrared spectrum and to Dr. E. B. Baker, Physical Research Laboratory, the Dow Chemical Company, Midland, Mich., for obtaining and interpreting the NMR spectrum.

SARNIA, ONT.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE A AND M COLLEGE OF TEXAS AND FROM THE TEXAS ENGINEERING EXPERIMENT STATION]

The Reaction of 2,4-Dinitrophenylhydrazine with some Dicarbonyl Compounds and α-Substituted Carbonyl Compounds[1]

LOUIS A. JONES,[2] C. KINNEY HANCOCK AND ROBERT B. SELIGMAN[3]

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The reactions between eleven dicarbonyl compounds and eight α-substituted carbonyl compounds and 2,4-dinitrophenylhydrazine (DNPH) in 2*N* hydrochloric acid and ethanolic phosphoric acid have been studied. At room temperature and in 2*N* hydrochloric acid, glyoxal and pyruvaldehyde yielded bis-2,4-dinitrophenylhydrazones (DNP's) although paper chromatography indicated the latter compound formed a small amount of a mono-DNP. Butanedione and 2,3-octanedione gave a mixture of the mono- and bis-DNP's while benzil and 1-phenyl-1,2-propanedione produced only the mono-derivative, the DNPH attack occurring on the 2-carbonyl group. The 1,3-dicarbonyl compounds yielded 1-(2,4-dinitrophenyl)-3,5-disubstituted pyrazoles and 1,5- and 1,6-dialdehydes formed only bis-DNP's. A mono- and a bis-derivative could be prepared from 2,5-hexanedione. The other α-substituted carbonyl compounds, when treated with DNPH at elevated temperatures in ethanolic phosphoric acid, yielded the corresponding bis-DNP and 2,4-dinitroaniline, suggesting a Weygand-type of mechanism. Dichloroacetal gave only glyoxal-bis-DNP while chloral produced chloroglyoxal bis-DNP and ethyl glyoxylate-DNP. Benzotrichloride and benzal chloride produced the anomalous benzoyl chloride-DNP and benzaldehyde-DNP respectively, thus supporting the proposal that the S_N1 mechanism of halide hydrolysis applies to these reactions.

INTRODUCTION

The reaction between 2,4-dinitrophenylhydrazine (DNPH) and dicarbonyl compounds has not been studied as to the effect of structure on the formation of the mono-2,4-dinitrophenylhydrazones (DNP) in preference to the bis-DNP's although several mono-DNP's have been reported.[4] The same reaction with α-substituents other than carbonyl groups has received some attention recently. For example, the same bis-DNP has been obtained from 2-methoxy-[5] and 2-chlorocyclohexanones[6] and the chloro group in the mono-DNP of the latter compound could be replaced by a methoxy substituent by refluxing in methanol.[7] The failure of α-bromoacetophenone DNP to undergo analogous reactions was explained in terms of the different labilities of primary and secondary halogens.[8] Further, the attempted preparation of the DNP of chloral yielded a product which gave a nitrogen analysis for chloroglyoxal-bis-DNP[9] although only one ultraviolet absorption maximum was reported[10] in contrast to the two maxima characteristic of 1,2-dicarbonyl-bis-DNP's.[11] An analogous reaction was previously proposed for chloral and hydroxylamine but no experimental evidence was presented to support the proposal.[12]

In the reaction of excess DNPH with an α-substituted carbonyl-DNP (excepting dicarbonyls), it might be assumed that the replacement of the substituent by a solvolysis mechanism is the first step in the reaction as suggested by the formation of 2-methoxycyclohexanone-DNP from the 2-chloro-compound.[7] However, reaction of DNPH with this product should yield some disproportionation product similar to that found in the Weygand mechanism for osazone formation.[13] Further, such solvolysis of chloral would lead to an acyl chloride, an acid, or an ester, none of which would be expected to form a bis-DNP.

During the course of other investigations[11,14] it was necessary to prepare several DNP's. No literature could be found describing several of the DNP's and, in view of the unusual reactions observed in some cases, it was felt that the results obtained would be of interest. This article describes the products obtained in the reactions between DNPH and α-substituted acetals and carbonyl compounds, and from these data a new mechanism is proposed for certain α-substituted compounds.

(1) Taken from the Ph.D. Dissertation of L.A.J., A. and M. College of Texas, May, 1959, and presented in part at the 135th meeting of the American Chemical Society, Boston, Mass., April, 1959. A portion of this work was initiated at the Research Laboratories of Philip Morris and Co., Inc.

(2) Present address: Research Laboratories, Brown & Williamson Tobacco Corp., Louisville, Ky.

(3) Address: Research Laboratories, Philip Morris and Co., Inc., Richmond, Va.

(4) (a) H. Reich and L. Hefle, Jr., *J. Org. Chem.*, **21**, 708 (1956). (b) C. J. Timmons, *J. Chem. Soc.*, 508 (1957).

(5) H. Adkins and A. G. Rossow, *J. Am. Chem. Soc.*, **71**, 3836 (1949).

(6) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(7) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **74**, 4331 (1952).

(8) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953).

(9) K. Yamaguchi, S. Fukushima, T. Tabata, and M. Ito, *J. Pharm. Soc. Japan*, **74**, 1327 (1954).

(10) K. Yamaguchi, S. Fukushima, T. Tabata, and M. Ito, *J. Pharm. Soc., Japan*, **74**, 1335 (1954).

(11) L. A. Jones and C. K. Hancock, *J. Am. Chem. Soc.*, **82**, 105 (1960).

(12) A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896).

(13) (a) F. Weygand, *Ber.*, **73B**, 1259 (1940). (b) For an excellent proof of mechanism see E. M. Bamdas, K. M. Ermoldev, V. J. Maimud, and M. M. Shamyakin, *Chem. and Ind.*, 1195 (1959).

(14) L. A. Jones and C. K. Hancock, *J. Org. Chem.*, **25**, 226 (1960).

TABLE I

No.	Compound	DNP	M.P.[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Lit. M.P.	Minor Products
			DNP's Obtained from Procedure A				
1	Glyoxal	bis	313d. (Nb., Py.)	26.8	26.7	328[b]	None
2	Pyruvaldehyde	bis	298d. (Nb., HA.)	25.9	25.9	313[b]	mono-DNP
3	Butanedione	mono[c]	174 (Cf.-Mt.)	—	—	175[d]	bis-DNP
4	2,3-Octanedione	mono[e]	89 (Mt.-H_2O)	17.4	17.3	—	bis-DNP
5	1-Phenyl-1,2-propanedione	mono[f]	185 (Hp.)	17.1	17.1	—	None
6	Benzil	mono[g]	185 (Xy.)	—	—	185[h]	None
7	Succinaldehyde	bis	280 (MCS.)	—	—	280[i]	None
8	2,5-Hexanedione	bis	260d. (Xy., Py.)	23.6	23.2	259[b]	mono-DNP
9	Glutaraldehyde	bis	185 (Xy., Py.)	24.3	24.3	195[k]	None
10	β-Methyl glutaraldehyde	bis	198 (EA.)	23.6	23.6	203[k]	None
11	α-Hydroxyadipaldehyde	bis	219 (Dx.-H_2O)	22.9	22.1	—	None
			DNP's Obtained from Procedure B				
12	Butanedione	bis	316 (Nb., HA.)	25.1	25.2	315[b]	None
13	2,3-Octanedione	bis	221 (Nb., HA.)	22.3	22.4	213[b]	None
14	1-Phenyl-1,2-propanedione	bis	265 (Nb., HA.)	22.0	21.9	260[b]	None
15	Benzil	bis	311d. (Nm., HA.)	19.6	19.5	318[l]	None
16	Chloroacetal	reg.[m]	157 (Bz.)	—	—	157[n]	None
17	Chloro-2-propanone	reg.	126 (Hp.)	—	—	126[o]	None
18	Diethylaminoacetal	bis-1[p]	313d. (Nb., Py.)	—	—	—	DNA[q]
19	Diethylamino-2-propanone	reg.	85 (Bz.)	22.6	22.1	—	None
20	Phenoxyacetal	reg.	131 (Bz.-Hp.)	17.7	17.7	—	None
21	Dichloroacetal	bis-1	313d. (Nb., HA.)	—	—	—	None
22	Chloral	bis[r]	259d. (EA.)	24.8	25.0	264[s]	None
23	Benzoin	bis-6	311d. (Nm., Nb.)	19.6	19.8	318[l]	DNA
			DNP's Obtained from Procedure D				
16	Chloroacetal	bis-1 (97)[t]	313d. (Nb.)	—	—	—	DNA (74)[t]
17	Chloro-2-propanone	bis-2 (81)	298d. (Nb.)	—	—	—	DNA (67)
18	Diethylaminoacetal	bis-1 (94)	313d. (Nb.)	—	—	—	DNA (88)
19	Diethylamino-2-propanone	bis-2 (34)	298d. (Nb.)	—	—	—	DNA (10)
20	Phenoxyacetal	bis-1 (99)	313d. (Nb.)	—	—	—	C_6H_5OH (73)[u]
21	Dichloroacetal	bis-1 (25)	313b. (Nb.)	—	—	—	None
22	Chloral	bis[q]	259 (Ea.)	—	—	—	DNP of CHO—COOEt[t]

[a] All melting points are uncorrected. Data in parenthesis indicate recrystallizing solvents. Nb. = nitrobenzene, Py. = pyridine, HA. = glacial acetic acid, Cf. = chloroform, Mt. = methanol, Hp. = heptane, Xy. = *m*-xylene, MCS. = methylcellosolve, EA. = ethyl acetate, Dx. = *p*-dioxane, Nm. = nitromethane. [b] C. Neuberg and E. Strauss, *Arch. Biochem.*, **7**, 211 (1945). [c] $\nu_{C=O}$ = 1675 cm.$^{-1}$ [d] Ref. 4a. [e] $\nu_{C=O}$ = 1701 cm.$^{-1}$ [f] $\nu_{C=O}$ = 1653 cm.$^{-1}$ [g] $\nu_{C=O}$ = 1676 cm.$^{-1}$ [h] C. F. H. Allan, *J. Am. Chem. Soc.*, **52**, 2955 (1930). [i] L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946). [j] See Experimental for details of preparation. [k] C. W. Smith, D. G. Norton, and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5267 (1951). [l] D. Y. Curtin and V. R. Proops, *J. Org. Chem.*, **19**, 820 (1954). [m] reg. = regular derivative. [n] F. Weygand, G. Eberhardt, H. Linden, F. Shäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953). [o] G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953). [p] The number refers to compound 1. [q] DNA = dinitroaniline. [r] *Anal.* Calcd. for $C_{14}H_9N_3O_8Cl$: Cl, 7.8. Found: Cl, 7.5. [s] Ref. 9. [t] Data in parenthesis are average yields. [u] Isolated as the tribromo derivative by steam distilling from acid solution into bromine water.

EXPERIMENTAL

All materials used in this study were obtained from commercial sources and, where necessary, purified to obtain physical constants in agreement with literature values. All melting points are uncorrected.

Procedure A. One equivalent of the dicarbonyl compound was added to one equivalent of DNPH contained in a saturated DNPH 2*N* hydrochloric acid solution and the mixture shaken for 1–2 hr. at room temperature. The solid was filtered, washed with distilled water until the washings were neutral, and finally purified by column chromatography using 60–100 mesh silica-magnesia (Florisil, Floridin Co.) as the fixed phase and redistilled heptane as the eluent. Although the mono-DNP's were mobile in this system, no well-defined bands were apparent and the elution was accomplished by volume fractions, obscuring accurate data on yields. Infrared spectra were obtained as confirmation of structure.

Procedure B. The bis-DNP's of 1,2-dicarbonyl compounds were prepared in nearly quantitative yields by refluxing 1 equivalent with 2 equivalents of DNPH contained in ethanolic phosphoric acid (Johnson's Reagent).[15]

Procedure C. The α-substituted carbonyl compounds were refluxed for 8 hr. with 3 equivalents of DNPH (Johnson's Reagent).[15] Following filtration of the bis-DNP formed, the filtrate was neutralized with sodium carbonate and, if a solid appeared, filtered. The precipitate was recrystallized from heptane and a mixed melting point obtained with an authentic sample of 2,4-dinitroaniline while the bis-DNP was identified by mixed melting point determination with the derivatives prepared by Procedure B.

Procedure D. The α-substituted carbonyl compounds were treated with 1 equivalent of DNPH (Johnson's Reagent)[15] at room temperature and, following filtration, the solid derivatives were recrystallized from suitable solvents. The yields ranged from 96–99%.

The results of these procedures are shown in Table I.

(15) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

2,5-Hexanedione-mono-DNP. When the dicarbonyl compound was treated with DNPH in 2*N* hydrochloric acid, a mixture of the mono- and bis-DNP was obtained as evidenced by the large increase in melting point upon successive recrystallizations. Consequently, equivalent amounts of DNPH and 2,5-hexanedione were refluxed in a minimum amount of pyridine for 4 to 5 hr. and then stirred into 20 volumes of water and filtered. A typical preparation using 2.0 g. of DNPH and 1.3 g. of 2,5-hexanedione gave 0.7 g. of the mono-DNP after two recrystallizations from heptane, m.p. 116–117°.

Anal. Calcd. for $C_{12}H_{14}N_4O_5$: N, 19.0. Found: N, 18.8.

1-(2,4-Dinitrophenyl)-3,5-dimethylpyrazole was prepared in near quantitative yields from 2,4-pentanedione by Procedure A and gave yellow-green needles after recrystallization from methanol (m.p. 121.5°, lit.[16] m.p. 122°, 119–120°).

1-(2,4-Dinitrophenyl)-3-methyl-5-phenylpyrazole. One equivalent of DNPH in glacial acetic acid was refluxed for 24 hr. with 1-phenyl-1,3-butanedione and the solution evaporated to dryness on a steam bath. The solid, purified by Procedure A, gave yellow-green prisms in 70% yield (m.p. 133–134°, lit.[16b] m.p. 128–129°). The 3-phenyl-5-methyl-isomer was not found in the reaction mixture.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: N, 17.3. Found: N, 17.0.

1-(2,4-Dinitrophenyl)-3,5-diphenylpyrazole was prepared from 1,3-diphenyl-1,3-propanedione by the above procedure. Glacial acetic acid in heptane (20% v/v) failed to elute the product from a silica-magnesia column and, following extrusion of the column, the product was extracted from the fixed phase with methanol and the solution evaporated to dryness. Two recrystallizations from methanol gave yellow needles in 65% yield (m.p. 150.5–151.5°, lit.[17] m.p. 151–153°).

Benzoyl chloride-DNP. A mixture of redistilled benzotrichloride (10.0 g.) and 3.0 g. of DNPH was heated to 175° for 5 hr. and was accompanied by the steady evolution of hydrogen chloride. After cooling, the solution was taken up in 50 ml. of ether and filtered. Successive recrystallization of the solid from benzene and ethanol gave 2.6 g. (53.5%) of the DNP, m.p. 228.5–229°, $\lambda_{max}^{CHCl_3}$ 370 mμ, ε 2.70 × 10^4, λ_{max}^{NaOH} 457 mμ, ε 2.48 × 10^4.

Anal. Calcd. for $C_{13}H_9N_4O_4Cl$: N, 17.5; Cl, 11.1. Found: N, 17.4; Cl, 11.2.

Benzaldehyde-DNP was prepared by refluxing 20.0 g. of redistilled benzal chloride in 100 ml. of xylene with 5.0 g. of DNPH for 6 hr. Recrystallization of the precipitate from xylene and glacial acetic acid gave 4.8 g. (74%) of orange-red needles, m.p. 236–237°, which showed no melting point depression with an authentic sample and whose infrared and ultraviolet spectra were identical with those of the reference compound.

Ethyl glyoxylate-DNP. Chloral (3.0 g.) was refluxed 48 hr. with 100 ml. of Johnson's Reagent[15] diluted with 200 ml. of 95% ethanol. The solid, 3.4 g. of chloroglyoxal-bis-DNP, was filtered and the alcohol evaporated from the filtrate at room temperature. Filtration and recrystallization from cyclohexane of the resulting solid gave 2.6 g. of *ethyl glyoxylate-DNP*, m.p. 126–127°. The infrared spectrum showed a carbonyl absorption of 1702 $cm.^{-1}$ (m) and an ether linkage absorption at 1230 $cm.^{-1}$ (s). The ultraviolet and visible spectra in chloroform and alcoholic sodium hydroxide have been previously reported.[14]

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 42.6; H, 3.6; N, 19.9. Found: C, 42.6; H, 3.6; N, 19.9.

Pyruvaldehyde-mono-DNP was prepared by saturating 2 l. of distilled water with DNPH and adding 10 ml. of a 45% aqueous solution of pyruvaldehyde. The solution was allowed to stand for 2 weeks and then evaporated to a syrup. The residue was placed on a silica-magnesia column and eluted with chloroform, the eluent evaporated, and water added to precipitate the yellow-green solid. Filtration, followed by recrystallization from methanol-water gave 0.07 g. of yellow needles, m.p. 169–170°.

Anal. Calcd. for $C_9H_8N_4O_5$: C, 42.9; H, 3.2; N, 22.2. Found: C, 43.3; H, 3.6; N, 22.1.

The infrared spectrum contained a carbonyl stretching absorption at 1690 $cm.^{-1}$ and $\lambda_{max}^{CHCl_3}$ 345 mμ, ε 2.29 × 10^4, λ_{max}^{NaOH} 490 mμ; ε 3.08 × 10^4. Paper chromatography[18] of the derivative showed a single spot at an R_f previously observed for an unknown compound obtained from the pyruvaldehyde—Procedure A reaction product.

RESULTS AND DISCUSSION

Dicarbonyl compounds. Under the conditions described for Procedure A, glyoxal formed only the bis-DNP although, in the absence of acid, the mono-derivative has been prepared.[4a] Paper chromatography of the pyruvaldehyde reaction product showed the bis-derivative to be present in large amounts. In addition, however, the presence of a minute amount of a second compound (not DNPH) was observed at an R_f within the range of values obtained for other mono-DNP's of aliphatic 1,2-dicarbonyl compounds and subsequently shown to be the pyruvaldehyde-mono-DNP (see Experimental). Butanedione and 2,3-octanedione, when allowed to react with DNPH in 2*N* hydrochloric acid, yielded both the mono- and bis-DNP's in sufficient concentration to isolate and identify although only one of the two possible mono-DNP's of the latter carbonyl compound was isolated as indicated by the infrared spectrum. The mono-derivatives of 1-phenyl-1,2-propanedione and benzil were formed exclusively under these same conditions. bis-DNP's of the above carbonyl compounds were conveniently prepared by refluxing in Johnson's Reagent,[15] the aromatic compounds requiring six to eight hours of reflux as compared to two hours for the aliphatic carbonyl compounds.

The 1,3-dicarbonyl compounds yielded 1-(2,4-dinitrophenyl)-3,5-disubstituted pyrazoles when reacted with DNPH, and although the 3,5-dimethyl derivative could be produced by Procedure A, the aromatic analogues gave gummy products which produced crystalline pyrazoles on refluxing in glacial acid. Reaction of the 1,4- 1,5- and 1,6-dialdehydes with DNPH in 2*N* hydrochloric acid yielded only the bis-DNP's, while 2,5-hexanedione gave a mixture of mono- and bis-derivatives, the mono-DNP of which could be prepared in acceptable yield and purity using pyridine as the reaction solvent. Interestingly, attempts to recrystallize the bis-DNP's of 2,5-hexanedione and α-hydroxyadipaldehyde from acidic solvents resulted in tars and the aliphatic 1,2-dicarbonyl-mono-DNP's disproportionated to the bis-DNP's under the same conditions, similar to the results obtained with glyoxal-mono-DNP[4a].

Several interesting examples of polychromism were

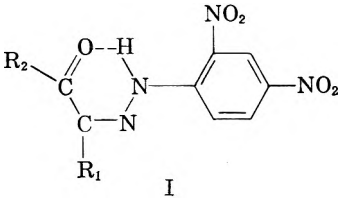
(16) (a) O. L. Brady, *J. Chem. Soc.*, 756 (1931). (b) W. Borsche and W. Reid, *Ann.*, **554**, 269 (1943).

(17) W. J. Croxall and J. O. Van Hook, *J. Am. Chem. Soc.*, **71**, 2422 (1949).

(18) R. B. Seligman, unpublished data.

found, the most striking being that of 1-phenyl-1,2-propanedione-bis-DNP, which gave orange-yellow needles when recrystallized from glacial acetic acid, red needles from nitrobenzene, and a mixture of the two from *m*-xylene. These had the same ultraviolet[11] and infrared spectra and identical melting points with no mixed melting point depression thus eliminating the possibility of *syn*- and *anti*-isomerism. The X-ray diffraction patterns indicated they were of different crystalline structures.[19]

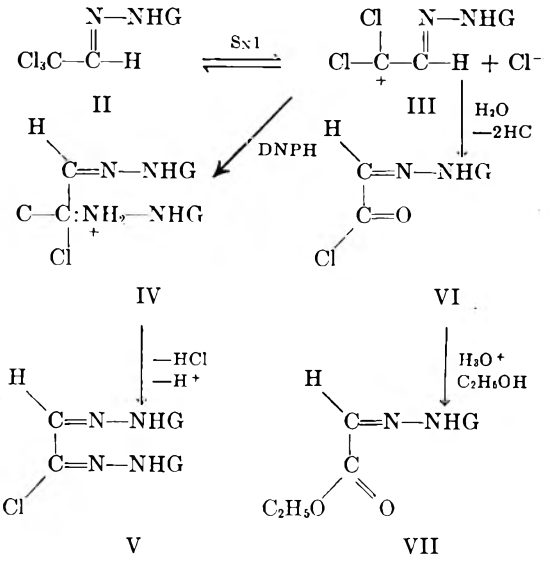
The infrared spectrum of 2,5-hexanedione-mono-DNP contains a carbonyl absorption at 1736 cm.$^{-1}$, characteristic of a nonconjugated carbonyl group. Suggestive of conjugative interaction between the C=O and the C=N moieties is the hypsochromic shift of 61 cm.$^{-1}$, observed in the carbonyl absorption of the corresponding derivative of butanedione. However, such interaction between C=C and C=N is reportedly small[20] and, by analogy, is probably small for the C=O and C=N linkages. Hence, the observed shift can be attributed to a combination of conjugation and hydrogen bonding of the type shown in I with no tautomeric shift of the *N*-hydrogen to the carbonyl oxygen occurring. These proposals are in accord with the ultraviolet spectra[11] and molecular models[21] of such derivatives.



I

In aromatic 1,2-dicarbonyl compounds the hydrazone formation occurs on the 2-carbonyl group as indicated by the carbonyl absorption occurring at 1653 cm.$^{-1}$ and the ultraviolet and visible spectra.[11] Further, 1-(2,4-dinitrophenyl)-3-methyl 5-phenyl-pyrazole could be formed only by the attack of DNPH on the 3-keto position of 1-phenyl-1,3-butanedione suggesting that the steric effect of the phenyl group is the determining factor in the position of the DNPH attack.

α-Substituted carbonyl compounds. The reaction of 1-chloro-2-propanone-DNP yielded pyruvaldehyde bis-DNP with excess DNPH, thus substantiating the proposal of Ramirez and Kirby that the action of DNPH on α-halo ketones involves the formation of an intermediate α-halo-DNP.[7] Isolation of 2,4-dinitroaniline and phenol following the reaction of excess DNPH with phenoxyacetal suggests the reaction proceeds by the same path as



G = 2,4-dinitrophenyl

Figure 1

osazone formation.[13] Benzoin reacted rapidly at room temperature to form the benzil-bis-DNP and α-hydroxyadipaldehyde-bis-DNP, on standing in a solution containing excess DNPH, slowly formed a solid which produced a blue color with alcoholic sodium hydroxide, characteristic of 1,2-dicarbonyl-bis-DNP's.[11] Attempts to increase the rate of reaction of α-hydroxyadipaldehyde-bis-DNP and DNPH by heating produced a tar and the reaction was not investigated further. From these reactions, however, it appears that α-hydroxy groups are particularly labile with respect to the disproportionation investigated.[13b]

Chloral and dichloroacetal, when allowed to react with DNPH, did not produce 2,4-dinitroaniline suggesting that the reaction does not proceed by the Weygand-type[13] mechanism. Further, the formation of chloroglyoxal-bis-DNP suggests that hydrolysis cannot be involved in the reaction since hydrolysis would yield an acyl halide which would not react to give the bis-DNP. With an excess of chloral, however, a mixture of chloroglyoxal-bis-DNP and ethyl glyoxylate-DNP was obtained and the reaction scheme shown in Fig. 1 appears reasonable in view of these results.

The equilibrium II ⇌ III is similar to that proposed for the S_N1 hydrolysis of benzyl halides[23] and the reaction VI → VII is in agreement with the proposed mechanism for the hydrolysis of benzotrichloride which produces benzoic acid.[24] The nucleophilic attack of DNPH on III must occur at a much faster rate than does the hydrolysis III →

(19) E. A. Meyers, unpublished data.

(20) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 268.

(21) Catalin Products, Ltd., Waltham Abbey, Essex, England.

(22) G. H. Stempel, Jr., and G. D. Schaffel, *J. Am. Chem. Soc.*, **66**, 1158 (1944).

(23) E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941). See also S. C. J. Olivier and A. P. Weber, *Rec. Trav. Chim.*, **53**, 869 (1934).

(24) J. Hine and D. E. Lee, *J. Am. Chem. Soc.*, **73**, 22 (1951).

VI, as no ethyl glyoxylate-DNP could be found when the reaction was carried out at room temperature with excess DNPH. The product V cannot reasonably be obtained except through the unstable hydrazonium intermediate IV, and, with excess chloral, once the formation of V is complete, the remaining "mono-DNP" undergoes the hydrolysis-esterification reaction to VII.[25] The chloroform solution spectrum of V contained absorption maxima at 385 mμ (ϵ 4.01 × 10^4) and 435 mμ (ϵ 4.81 × 10^4) while in alcoholic sodium hydroxide λ_{max} 540 mμ (ϵ 5.42 × 10^4), the results being in complete agreement with the spectral properties previously reported for other bis-DNP's of 1,2-dicarbonyl compounds.[11]

The above reaction scheme implies that the trichloromethyl-group is activated by the conjugated unsaturation of the DNP moiety and, further, that a similar π-electron system should react in an analogous fashion. To test this hypothesis, DNPH was treated at elevated temperatures with an excess of benzotrichloride and yielded the anomalous "benzoyl chloride-DNP." Similarly, benzal chloride was used in the preparation of the benzaldehyde derivative. These results offer support for the reaction mechanism proposed and indicate that the DNP portion of the derivative has an activating effect similar to that of the phenyl groups in the benzyl halides.[23]

Acknowledgments. The authors wish to thank Mr. Hugh C. Sutton for his technical assistance during a portion of this work and gratefully acknowledge the financial assistance of the Robert A. Welch Foundation.

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(25) The mono-DNP of chloral, m.p. 131°, has been reported by F. L. Roduta and C. Quiblan, *Rev. Filipina med. farm.*, **27**, 123 (1936), *Chem. Abstr.*, **31**, 98. As the derivative was prepared from methanol, it seems likely the methyl glyoxylate DNP was the derivative isolated.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF LOWELL TECHNOLOGICAL INSTITUTE AND THE LOWELL TECHNOLOGICAL INSTITUTE RESEARCH FOUNDATION]

Chemistry of the Silylamines. I. The Condensation of Monofunctional Silylamines with Monofunctional Silanols[1]

RONALD M. PIKE

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The rates of reaction of triphenyl- and triethylsilanol with a series of silylamines in bis(2-methoxyethyl) ether have been measured under a variety of conditions. The effect on the reaction rate of the structure of the reacting species, the addition of acid catalyst, and the observed second-order kinetics indicate a bimolecular type mechanism. This condensation reaction offers an alternate route for the formation of siloxane bonds.

Numerous reports in the literature indicate that silylamines are susceptible to attack by various nucleophilic reagents resulting in the cleavage of the silicon-nitrogen bond.

$$\mathrm{R{-}X{:}} + \equiv\mathrm{Si{-}N{=}} \longrightarrow \mathrm{R{-}X{-}Si{\equiv}} + \mathrm{H{:}N{=}}$$

(H on X; X may be O, NH, or S)

Rochow[2] states that an $-NH_2$ group attached to silicon is easily replaced by an —OH group upon hydrolysis, generating ammonia. The treatment of triethylsilylamine with hydrogen sulfide resulted in the formation of the corresponding thiol compound, triethylsilanthiol.[3] The reaction of hexamethyldisilazane with alcohols gives aliphatic trimethylsilyl ethers.[4] Langer and co-workers[5] have recently extended this reaction to prepare a large number of silyl ethers belonging to this class. Smith[6] has treated triethylsilanol with di-*tert*-butoxydiaminosilane and isolated $(C_2H_5)_3Si{-}O{-}Si{-}(t\text{-}C_4H_9O)_2{-}NH_2$.

In each of the above reactions of silylamines or silazanes with water, primary amines, alcohols, hydrogen sulfide, or a silanol, it appears that a nucleophilic displacement on silicon occurs,[5] which results in the formation of a new ≡Si—O—, ≡Si—N= or ≡Si—S— linkage.

Since this displacement reaction is of considerable practical importance for the synthesis of a variety of useful silicone intermediates and products, a program has been initiated in these laboratories to obtain fundamental information concerning the behavior of silylamines toward various nucleophilic reagents.

(1) Presented at the 137th meeting of the American Chemical Society, Division of Organic Chemistry, at Cleveland, Ohio, April 11, 1960.

(2) E. G. Rochow, *Chemistry of the Silicones*, John Wiley and Sons, New York, New York, 2nd ed., 1951, p. 58.

(3) E. Larsson and R. Mjorne, *Acta. Chem. Scand.*, **5**, 964 (1951).

(4) J. L. Speir, *J. Am. Chem. Soc.*, **74**, 1003 (1952).

(5) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

(6) B. Smith, *Svensk. Kem. Tidskr.*, **65**, 101 (1953); *Chem. Abstr.*, **48**, 9907g (1954).

The present paper describes a general experimental technique for measuring the rates of the displacement reactions on silylamines and illustrates this technique with a study of the condensation of monofunctional silanols with monofunctional silylamines.

$$R_3SiOH + R_3'SiNR''_2 \longrightarrow R_3Si{-}O{-}SiR_3' + HNR''_2$$

This condensation reaction offers an alternate route for the formation of siloxane linkages, ≡Si—O—Si≡. Furthermore, it offers an approach to the formation of siloxane linkages in which control of the structure of the end product may be exercised. Previous methods for forming siloxane bonds such as treatment of chlorosilanes with alkoxy or hydroxy silanes,[7] condensation of alkoxysilanes with silanols in the presence of metallic sodium,[8] condensation of selected silanols,[8] and the equilibration of preformed silicone cyclic intermediates[9] are mainly random type reactions.

EXPERIMENTAL

General method. Ammonia or an amine is liberated when a silylamine reacts with a nucleophilic reagent. The rate of reaction, therefore, can be followed by measurement of the rate of formation of the amine. The method adopted for the present work is a modification of that described by Ma and Zuazaga,[10] concerned with the determination of nitrogen by a Micro Kjeldahl procedure. In this procedure the ammonia evolved on decomposition of the organic compound was absorbed in a 2 wt. % solution of boric acid and the liberated borate anion titrated with standard hydrochloric acid solution. To check this method for the present work, weighed samples of freshly distilled diethylamine were added to a 2 wt. % solution of boric acid followed by titration with a standard hydrochloric acid solution. The indicator used was methylpurple modified methylorange. Ninety-nine and four-tenths per cent of the diethylamine was accounted for using this technique.

The rate runs were carried out using bis(2-methoxyethyl) ether as the solvent. The amine, as it formed, was removed from the reaction site by a stream of nitrogen passing through the system at a constant rate. Duplicate runs of several of the condensation reactions were carried out; excellent duplication was obtained.

Apparatus. The rate studies were carried out in a 30-ml. round bottom flask fitted with an inlet tube and a 12-inch water condenser. An outlet tube was connected from the top of the condenser to a 125-ml. Erlenmeyer flask. The reaction vessel was immersed in a constant temperature bath, the temperature of which was controlled to within ±0.5°. The inlet tube reached to the bottom of the flask through which nitrogen gas was passed at a constant rate. The gas rate was held constant at two bubbles/sec. formed as the nitrogen swept out the reaction flask, through the condenser and outlet tube and passed through approximately 20 ml. of freshly prepared 2 wt. % boric acid solution contained in the Erlenmeyer flask. The amine generated during the reaction was thus removed from the reaction site. The borate anion was then titrated at regular intervals with standard hydrochloric acid solution.

Timing procedure. Timing of the reaction was begun when the silylamine was added to the solution of the silanol in bis(2-methoxyethyl) ether solution. Nitrogen was swept through this solution for 5 min. and passed into the boric acid solution before the amine was added. The boric acid solution was changed at timed intervals and titrated with standard hydrochloric acid. Duplication of runs gave excellent results as previously mentioned. This fact appears to justify the validity of the timing procedure outlined above.

Materials. Commercial triphenylsilanol was recrystallized from benzene. The resulting material had m.p. 148–150°; lit.,[11] 147–149°.

Triethylsilanol was prepared by the hydrolysis of triethylchlorosilane using a procedure similar to that described by Sommer[12] for the hydrolysis of triethylfluorosilane. Distillation of the isolated product through a semimicro column[13] gave b.p. 153°, n_D^{25} 1.4299; lit.,[12] b.p. 153.5°, n_D^{20} 1.4329.

N,N-Diethylaminotrimethylsilane was prepared by the treatment of trimethylchlorosilane with diethylamine as described by Sauer and Hasek.[14] The purified material had b.p. 126–127°, n_D^{25} 1.4032; lit.,[14] b.p. 126.3°, n_D^{20} 1.4112.

N-*n*-Butylaminotrimethylsilane was prepared by treatment of *n*-butylamine with hexamethyldisilazane.[5] The material had b.p. 132–136.6°, n_D^{25} 1.4060; lit.,[5] 132–135°, n_D^{20} 1.4058.

N-*tert*-Butylaminotrimethylsilane was obtained by treatment of trimethylchlorosilane with *tert*-butylamine using a procedure similar to that by which *N,N*-diethylaminotrimethylsilane was prepared.[14] The purified material had b.p. 120–121°, n_D^{25} 1.4054.

Anal. Calcd. for $C_7H_{19}SiN$: Neut. Equiv., 145. Found: Neut. Equiv. 148.5.

N,N-Diethylaminotriethylsilane was prepared by treatment of triethylchlorosilane with diethylamine using a procedure similar to that described for *N,N*-diethylaminotrimethylsilane.[14] The purified material had b.p. 198–200°, n_D^{25} 1.4360; lit.,[15] b.p. 200.5°, n_D^{20} 1.4400.

N-Ethylaminotriethylsilane was prepared from triethylchlorosilane and ethylamine. The purified material had b.p. 170.5°, n_D^{25} 1.4254; lit.[15] b.p. 170.3°, n_D^{20} 1.4290.

N-*N*-Diethylaminotri-*n*-butylsilane was prepared by treatment of tri-*n*-butylchlorosilane with diethylamine in ether solvent. The purified material had b.p. 118–128° (5.0 mm.), n_D^{25} 1.4450–1.4455.

Anal. Calcd. for $C_{16}H_{37}NSi$: Si, 10.32%. Found: Si, 10.2 ± 0.5%.

Commercial *n*-propylalcohol was dried over "Molecular Sieve" and distilled.[16]

Commercial bis(2-methoxyethyl) ether was passed through a 12-inch column of "Molecular Sieve" to remove water and peroxides.

Baker Chemical Company reagent grade boric acid was used throughout this investigation. For each time interval the 2 wt. % boric acid solution was freshly prepared using distilled water. It was necessary to prepare the solution immediately before use since on standing the *p*H of the boric

(7) D. T. Hurd, British Patent 585,400, February 6, 1947.

(8) W. T. Grubb, *J. Am. Chem. Soc.*, **76**, 3408 (1954).

(9) E. G. Rochow, *Chemistry of the Silicones*, John Wiley and Sons, New York, New York, 2nd ed., 1951, p. 69; A. R. Gilbert and S. W. Kantor, *J. Polymer Sci.*, **40**, 35 (1959).

(10) T. S. Ma and G. Zuazaga, *Ind. Eng. Chem. (Anal. Ed.)*, **14**, 280 (1942).

(11) A. G. Brooks and H. Gilman, *J. Am. Chem. Soc.*, **77**, 2322 (1955).

(12) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Am. Chem. Soc.*, **68**, 2282 (1946).

(13) C. W. Gould, Jr., G. Holzman, and C. Neimann, *Anal. Chem.*, **20**, 361 (1948).

(14) R. Sauer and R. Hasek, *J. Am. Chem. Soc.*, **68**, 241 (1946).

(15) B. N. Dolgov. N. P. Kharitonov, and M. G. Vorarkov, *Zhur. Obshchel Khim.*, **24**, 678 (1954); *Chem. Abstr.*, **49**, 5272 (1955).

(16) "Molecular Sieve" is available from the Linde Company, Union Carbide Corp., Tonawanda, N. Y.

TABLE I

CONDENSATION OF SILYLAMINES WITH SILANOLS[a]

System	Silanol	Silylamine	Concentration (mole/l.)[b] Silanol	Concentration (mole/l.)[b] Silylamine	Special Conditions	Specific Reaction[c] Rate Constant, k, (l-mole^{-1} sec^{-1})[f]
I	$(C_6H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.1810	0.1810	...	5.91×10^{-4}
II	$(C_6H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.1710	0.1775	Run at 40°	3.01×10^{-4}
III	$(C_6H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.1760	0.1805	$(CH_3)_2SiCl_2$ added[d]	7.85×10^{-4}
IV	$(C_6H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.2100	0.1900	$(n\text{-}C_4H_9)_3N$ added[e]	5.99×10^{-4}
V	$(C_6H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.3610	0.1715	...	5.32×10^{-4}
VI	$(C_6H_5)_3SiOH$	$(CH_3)_3SiNH\text{-}C_4H_9\text{-}t$	0.1845	0.1851	...	3.00×10^{-4}
VII	$(C_2H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.4065	0.1855	...	1.60×10^{-4}
VIII	$(C_2H_5)_3SiOH$	$(CH_3)_3SiN(C_2H_5)_2$	0.4130	0.3840	...	1.67×10^{-4}
IX	$(C_2H_5)_3SiOH$	$(CH_3)_3SiNH\text{-}C_4H_9\text{-}n$	0.3775	0.3805	...	7.15×10^{-5}
X	$n\text{-}C_3H_7\text{-}OH$	$(CH_3)_3SiN(C_2H_5)_2$	0.1934	0.1420	...	8.33×10^{-4}
XI	$(C_6H_5)_3SiOH$	$(C_2H_5)_2SiN(C_2H_5)_2$	0.1810	0.1505	...	3.11×10^{-4}
XII	$(C_6H_5)_3SiOH$	$(C_2H_5)_2SiNHC_2H_5$	0.1720	0.1575	...	2.86×10^{-4}
XIII	$(C_6H_5)_3SiOH$	$(C_2H_5)_2SiNHC_2H_5$	0.1850	0.1830	quinoline solvent	4.89×10^{-4}
XIV	$(C_6H_5)_3SiOH$	$(n\text{-}C_4H_9)_3SiN(C_2H_5)_2$	0.1905	0.1655	...	5.36×10^{-5}

[a] All runs were carried out at 50 ± 0.5° except for System II as noted. [b] The solvent in each run was bis(2-methoxyethyl) ether except in system XIII as noted. [c] k values were determined from the second order rate plots examples of which are shown in Fig. 1. [d] Concentration of $(CH_3)_3SiCl$, 0.0017 mole/l. [e] Concentration of $(n\text{-}C_4H_9)_3N$, 0.0014 mole/l. [f] The probable error in the k values is estimated to be ±10 0%.

acid solution was found to change as much as 1 *p*H unit over the course of a week.

RESULTS AND DISCUSSION

To investigate the cleavage of the ≡Si—N≡ bond in the subject condensation reaction, kinetic studies employing triphenyl- and triethylsilanol were carried out with a selected series of silylamine derivatives under a variety of conditions. The systems investigated are summarized in Table I. In order to compare the reactivity of an organic alcohol to the silanols, the condensation of 1-propanol with *N,N*-diethylaminotrimethylsilane was also investigated. Information as to the effect of temperature, concentration of the reacting species, added catalyst, and the structure of the silanol and silylamine on the rate of the condensation reaction was obtained.

Identification of reaction products. To establish that the condensation of silanols with silylamines results in the formation of a new ≡Si-O—Si≡ linkage, the product from the treatment of triphenylsilanol with *N,N*-diethylaminotrimethylsilane (Table I, System I) was isolated and identified. The treatment of a monofunctional silanol with a monofunctional silylamine should result in the formation of a disiloxane, *i.e.*, System I, should yield triphenyltrimethyldisiloxane. This disiloxane was isolated from the reaction mixture of System I by concentration of the product solution over a period of several weeks at room temperature. The material (0.75 g.) had m.p. 49-50°, lit.,[17] m.p. 49.5–51.0°. This reaction was carried to 82% completion, which theoretically should yield 1.04 g. (0.00298 mole) of triphenyltrimethyldisiloxane. The actual amount of product isolated (0.75 g.) corresponds to 72.5% conversion. This result may indicate that the main side reaction, *i.e.*, the self-condensation of the silanol,[8] occurs to a small extent in the subject systems. However, hexaphenyldisiloxane was not isolated.

Determination of specific reaction rates. As outlined in the experimental section, the rates of the subject condensation reactions were followed by measuring the rate at which the amine was evolved from the reaction mixture.

In the majority of the runs approximately the stoichiometric ratio of reactants was used. Second order kinetics were expected and, therefore, specific reaction rate constants, k, were obtained by the method of constructing second order rate plots[18] (as illustrated in Fig. 1) based on the equation $kt = \frac{x}{a(a-x)}$. From the slope of the lines the value for the second order rate constants were calculated employing the relationship, slope = $1/k$. (See Systems I, II, III, VI VIII, IX, XII, and XIII in Table I.) For the other runs summarized in Table I (Systems IV, V, VII, X, XI, and XIV) k values were obtained by constructing second order rate plots based on the equation $k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$ where slope = $\frac{2.303}{k(a-b)}$. The results clearly demonstrate that the rate of condensation of a silanol with a silylamine obeys second order kinetics. The general rate expression may be represented by $+ d[RNH_2]/dt = k$ [Silylamine] [Silanol] where RNH_2 represents the organic amine formed during the course of the reaction.

(17) W. H. Daudt and J. Hyde, *J. Am. Chem. Soc.*, **74**, 386 (1952); U. S. Patent, 2,444,555.

(18) S. Glasstone, *Textbook of Physical Chemistry*, D. Van Nostrand Co., Inc., New York, New York, 2nd ed., 1946, p. 1054.

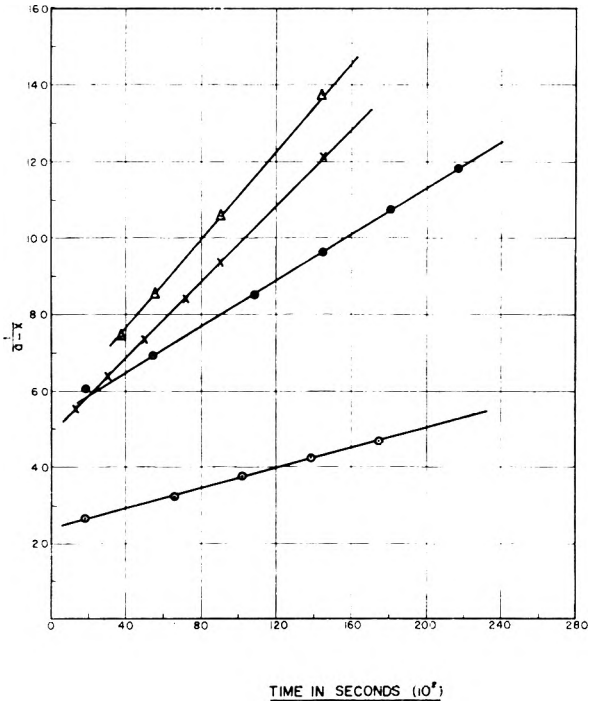


Fig. 1. Second order reaction rate plots. △ System I, ● System II, ○ System VIII, × System XIII

The effect of a change in the ratio of reactants on the subject condensation reactions is seen in a comparison of System I with V and System VII with VIII in Table I. Within experimental error, the k values obtained were similar.

Effect of temperature. In the present work the system *N,N*-diethylaminotrimethylsilane-triphenylsilanol (Table I, Systems I and II) was used to investigate the effect of temperature on the subject reaction. As noted in Table I, an increase in the temperature of 10° resulted in the rate constant being increased by a factor of 2. Since at 50° the majority of the reactions could be carried out over a convenient period of time, this temperature was used for the various systems in this work.

Effect of catalyst. Langer and co-workers[5] demonstrated the catalytic effect of acid catalyst on the condensation of silazanes with alcohols. As might be expected, a similar catalytic effect should operate in the present reactions. This was found to be the case. Comparison of the k values listed in Table I for Systems I and III shows that the addition of a trace of acid catalyst increases the rate constant from 5.91×10^{-4} to 8.34×10^{-4} 1-mole^{-1} sec.$^{-1}$; this is not a large difference, but higher concentrations of catalyst may result in a larger increase. It was also of interest to determine if an organic base might have a catalytic effect on the rate of the above system. It was found that the addition of a trace of tri-*n*-butylamine had no effect on the rate (compare Systems I and IV, Table I). However, the use of quinoline as a solvent did result in an increase in the rate of condensation (compare Systems XII and XIII).

Effect of structure. From the specific reaction rates summarized in Table I it is apparent that the nature of the organic groups attached to the silicon atom in the silanol and in the silylamine have an effect upon the rate of the reaction. The following general observations may be made from the data:

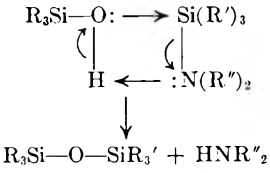
(1) The rate of condensation of a given silanol with monofunctional silylamines of the type $R_3SiNR_1R_2$, in which R remains constant and R_1, R_2 are varied, decreases in the order of —*N,N*-dialkyl > —NH-alkyl (compare System I with VI, System VIII with IX, and System XI with XII in Table I).

(2) The rate of condensation of a given silanol with monofunctional silylamines of the type $R_3SiNR_1R_2$, in which R is varied and R_1, R_2 remain constant, decreases in the order $(CH_2)_3Si$— > $(C_2H_5)_3Si$—> $(n$—$C_4H_9)_3Si$— (compare System I, System XII, and System XIV).

(3) The rate of condensation of monofunctional silanols toward a given silylamine decreases in the order of triaryl-> trialkyl- (compare System I with VIII in Table I).

(4) Toward the same silylamine, 1-propanol condensed at a faster rate than triphenyl- or triethylsilanol (compare System X with Systems I and VIII).

Mechanism. From the data accumulated in this investigation it appears that the condensation of silanols with silylamines involves an attack of the oxygen atom of the silanol on the silicon atom of the silylamine accompanied by deprotonization of the silanol. The result of this attack is the formation of an ≡Si—O—Si≡ linkage with cleavage of the ≡Si—N= bond in the silylamine molecule. Further investigation is necessary to formulate a detailed mechanism of the condensation reaction but on the basis of the accumulated evidence the reaction may be pictured involving a four centered type intermediate.



The data demonstrate that triphenylsilanol is a more effective condensation reagent than triethylsilanol toward the same silylamine. This order can be correlated with the acid strengths of the silanols. West and Baney measured the acid strengths of a series of silanols and showed triphenyl-silanol to be a stronger acid than a series of trialkylsilanols.[19,20] On this basis triphenylsilanol would be expected to give a faster rate than triethylsilanol. On the other

(19) R. West and R. H. Baney, *J. Inorg. & Nuclear Chem.*, **7**, 297 (1958).

(20) R. West and R. H. Baney, *J. Am. Chem. Soc.*, **81**, 6145 (1959).

hand, the more basic silylamine would be expected to condense at a faster rate. The observation that *N,N*-dialkylaminosilanes react at a faster rate than *N*-alkylaminosilanes can be correlated with the base strengths of the silylamines. Ebsworth and Emeléus[21] demonstrated that *N,N*-dimethylsilylamines are appreciably stronger bases than the monomethylated silylamines. Furthermore, a more basic solvent was shown to result in an increase in the rate of the reaction. It should be pointed out however, in comparing the *N,N*-dialkylsubstituted silylamines *vs.* the *N*-alkyl derivatives toward the same silanol that several of the *N*-alkyl types investigated are quite bulky. It is reasonable to expect that a steric factor may also account for the observed decrease in rate.

(21) E. A. V. Ebsworth and H. J. Emeléus, *J. Chem. Soc.*, 2150 (1958).

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LOWELL, MASS.

Notes

A department for short papers of immediate interest.

Organic Fluorine Compounds. XXVII.[1] Preparation of Acyl Fluorides with Anhydrous Hydrogen Fluoride. The General Use of the Method of Colson and Fredenhagen

G. A. Olah and S. J. Kuhn

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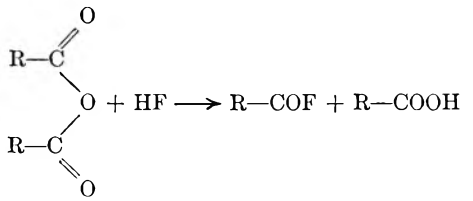
The preparation of acetyl and propionyl fluorides from the corresponding acid anhydrides and anhydrous hydrogen fluoride was described by Colson in 1897.[2] In 1933[3] Fredenhagen reported the quantitative formation of acetyl and benzoyl fluoride from the corresponding acyl chlorides and anhydrous hydrogen fluoride. No preparative investigation of the preparation of acyl fluorides based on anhydrous hydrogen fluoride, however, was reported, nor were the scope or experimental conditions of the reactions known. We therefore felt it useful to report briefly on the investigation of this method, which was found, with certain limitations, to be the most suitable way of preparing acyl fluorides. It is regrettable that so far the method of Colson and Fredenhagen has received little attention in the literature.

Our attention was directed to the method of Colson and Fredenhagen in connection with our previously reported investigation of the preparation of acyl fluorides from acyl chlorides and anhydrous potassium bifluoride.[4] We observed that both fluorine atoms of potassium acid fluoride reacted; thus potassium acid fluoride also acted as a source of hydrogen fluoride. A similar observation was made in the case of acid anhydrides and potassium acid fluoride by Mashentsev.[5] The reaction of potassium bifluoride with acyl chlorides and acid anhydrides needs higher temperatures which are sometimes inconvenient to apply. Therefore, we decided to investigate, in some detail, the reaction of anhydrous hydrogen fluoride with acyl chlorides (or bromides)

$$R{-}COCl + HF \longrightarrow R{-}COF + HCl$$

and acid anhydrides



$$(R{-}CO)_2O + HF \longrightarrow R{-}COF + R{-}COOH$$

The reactions were carried out at atmospheric pressure, generally at a temperature between −10 and + 5°. A slight excess of anhydrous hydrogen fluoride was added to the corresponding acid anhydrides or passed into the corresponding acyl chloride. This resulted in a vigorous evolution of hydrogen chloride. Table I shows the yields obtained for twenty-one acyl fluorides investigated.

TABLE I

Yields of Acyl Fluorides

Compound	B.P.	Yield, % from Anhydride	Yield, % from Acyl Chloride
(1) Formyl fluoride	−29	61.0	—
(2) Acetyl fluoride	20	93.6	—
(3) Propionyl fluoride	43	91.5	89.0
(4) Butyric fluoride	69	—	91.0
(5) Isobutyric fluoride	61	—	90.0
(6) Valeric fluoride	90	—	92.0
(7) Isovaleric fluoride	81	—	87.5
(8) Caproic fluoride	122	—	81.0
(9) Heptanoic fluoride	40/15 mm.	—	80.5
(10) Octanoyl fluoride	62/15 mm.	—	86.0
(11) Pelargonic fluoride	81/15 mm.	—	83.0
(12) Decanoic fluoride	92/15 mm.	—	85.0
(13) Fluoroacetyl fluoride	54	—	89.0
(14) Chloroacetyl fluoride	77	—	87.5
(15) Dichloroacetyl fluoride	85	—	84.0
(16) Trifluoroacetyl fluoride	−57	85.0	—
(17) Trichloroacetyl fluoride	67	—	79.0
(18) Bromoacetyl fluoride	104	—	82.0
(19) Benzoyl fluoride	157	78.0	94.0
(20) Phthaloyl fluoride	84/15 mm.	—	89.0
(21) Phenylacetyl fluoride	85/15 mm.	—	87.0

In the reaction of acid anhydrides with anhydrous hydrogen fluoride it was found that only acetic and propionic anhydride (or their halogenated derivatives such as trifluoroacetic anhy-

(1) Part XXVI, *J. Org. Chem.*, 26, 225 (1961).

(2) A. Colson, *Bull. soc. chim. France* [3] **17**, 55 (1897); *Ann. Chim.* [7] **12**, 255 (1897).

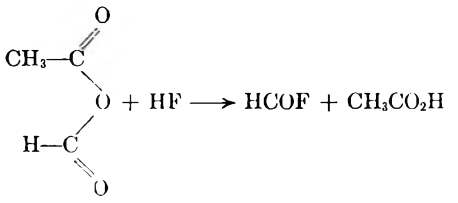
(3) K. Fredenhagen, *Z. phys. Chem. Abt.* **A164**, 189 (1933); K. Fredenhagen and G. Cadenbach, *Z. phys. Chem. Abt.*, **A164**, 201 (1933).

(4) G. Olah, S. Kuhn, and S. Beke, *Chem. Ber.* **89**, 862 (1956).

(5) A. I. Mashentsev, *J. Appl. Chem. (U.S.S.R.)* **11**, 816, 1135 (1941); *Chem. Abstr.* **37**, 1190, 2716 (1943); *J. Appl. Chem.* (U.S.S.R.) **15**, 915 (1945); *Chem. Abstr.*, **40**, 6443 (1946).

dride) react at hydrogen fluoride reflux temperature fast enough for this to be used as a preparative method at atmospheric pressure. The higher homologous acid anhydrides (with the exception of benzoic anhydride) need higher temperatures and, consequently, super-atmospheric pressures. The acyl chlorides, however, react at −10 to +5° rapidly and smoothly, thus allowing the halogen exchange to proceed at atmospheric pressure.

Such a preparation of acetyl fluoride is inconvenient, of course, as its boiling point is very similar to that of hydrogen fluoride. It is, therefore, obvious that the two types of starting materials complement one another. It was found possible to apply the reaction of acid anhydrides with anhydrous hydrogen fluoride to mixed anhydrides; this method was found to be extremely useful in the preparation of formyl fluoride.[6] By carrying out the reaction at atmospheric pressure, with continuous removal of the low boiling formyl fluoride, it was possible to make the reaction go entirely in this direction.



$$CH_3C(=O)OC(=O)H + HF \longrightarrow HCOF + CH_3CO_2H$$

A 61% yield of formyl fluoride was obtained, with a minimum formation of acetyl fluoride.

EXPERIMENTAL

The acyl fluorides were analyzed by gas chromatography and infrared spectroscopy. A Perkin-Elmer Model 154C Vapour Fractometer, having as column material a silicone high vacuum grease and a Perkin Elmer Model 221 infrared spectrograph with sodium chloride optics and silver chloride cells were used. As comparative standards, acyl fluorides described by us but prepared by known methods[4] were used. The yields, however, as shown in Table I, are those obtained in preparative scale experiments and represent the amount of isolated acyl fluoride and *not* VPC data. All operations were carried out with the usual precautions to exclude moisture.

Reaction of acid anhydrides with anhydrous hydrogen fluoride. Into 2.0 moles of the corresponding acid anhydride, 45 g. (2.25 moles) anhydrous hydrogen fluoride was added. The additon was carried out at approximately −10° with stirring by means of a Teflon covered magnetic stirrer. The mixture was kept at this temperature for an hour. It was then allowed to warm to room temperature and left standing for 2 hr. The mixture was then treated with 15 g. of anhydrous sodium fluoride to remove excess hydrogen fluoride, and distilled. Operations involving anhydrous hydrogen fluoride were performed in fused silica or plastic equipment. Plastic materials used included polyethylene, polypropylene, Teflon, and Kel-F.

Reaction of acyl chlorides with anhydrous hydrogen fluoride. Into 2.0 moles of the corresponding acyl chloride, kept at −5° to 0°, a continuous stream of anhydrous gaseous hydrogen fluoride was introduced at a rate of approximately 1 g./min. for 1 hr. It is also possible to carry out the reaction by adding the required amount of anhydrous liquid hydrogen fluoride to the stirred, cold acyl chloride. The reaction was then allowed to warm to room temperature and was kept there for 2 hr. To remove excess hydrogen fluoride, the reaction mixture was treated with dry sodium fluoride, filtered, and distilled.

(6) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.* **82**, 2380 (1960).

CONTRIBUTION NO. 30
EXPLORATORY RESEARCH LABORATORY
DOW CHEMICAL OF CANADA, LIMITED
SARNIA, ONT., CANADA

Oxidation of Olefins by Thallium Compounds

ROBERT R. GRINSTEAD

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Olefins have long been known to form complexes with various metallic compounds,[1] particularly those of platinum (II), mercury (II), palladium (II), and silver (I). In the case of mercury, a further reaction occurs in which the mercury compound adds across the double bond. For example, in glacial acetic acid, ethylene and mercuric acetate react as follows:[2]

$$C_2H_4 + Hg(OAc)_2 \longrightarrow AcOC_2H_4HgOAc \qquad (1)$$

Under certain conditions it is possible to effect an oxidation of the olefin, producing an inorganic mercurous salt and the oxidized carbon compound.[3] For example, in moderately strong (~2*M*) nitric acid solution, mercuric nitrate and 2-pentene react as follows:[3a]

$$CH_3CH{=}CHC_2H_5 + 2Hg^{++} \longrightarrow CH_3COC_3H_7 + 2Hg^{+} + 2H^{+} \qquad (2)$$

Lead (IV), which is isoelectronic with mercury (II), has also been reported to oxidize olefins, both to carbonyl compounds[4] and also to glycol derivatives.[5] This report describes a similar reaction of olefins with a third isoelectronic species, thallium (III). The reaction of thallium (III) solutions with both ethylene and 2-hexene was investigated, and both carbonyl products and glycols or their esters were obtained. The thallium was meanwhile completely reduced to thallium (I).

In nitrate solutions, the highest yield of ethylene glycol obtained was about 32% of the ethylene consumed. The yield of nonvolatile carbonyl com-

(1) P. H. Plesch, Ed., *Cationic Polymerization and Related Complexes*, Academic Press, New York, N. Y., 1953, p. 40. J. C. Bailar, *Chemistry of Coordination Compounds*, Reinhold, New York, N. Y., 1956, p. 487.

(2) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(3) (a) R. F. Morris, Thesis, University of Indiana, 1954. (b) F. E. Mertz and O. C. Dermer, *Proc. Oklahoma Acad. Sci.*, **30**, 134 (1949). (c) A. C. Cope, N. A. Nelson, and D. S. Smith, *J. Am. Chem. Soc.*, **76**, 1100 (1954). (d) W. Treibs, *Naturwiss.*, **35**, 125 (1948). (e) W. G. Toland, U. S. Patent **2,623,073** (1952).

(4) M. Finkelstein, *Ber.*, **90**, 2097 (1957).

(5) R. Criegee, *et al.*, *Ber.*, **90**, 1070 (1957).

pounds was estimated from the amount of 2,4-dinitrophenylhydrazone formed and was about 6% in this case. In the sulfate system the corresponding figures were 45% and 3%. Solutions of thallium (III) chloride reacted only slowly with ethylene, while acetate solutions appeared not to react at all. Acetaldehyde was formed in all cases as evidenced by its odor, but very little was found in the solution. It was suspected that further oxidation of acetaldehyde by thallic ion occurred and a separate experiment was carried out involving thallic sulfate and acetaldehyde. This oxidation proceeded more slowly than that of ethylene, but it was possible to show by means of spot tests and infrared spectra the presence of acetate and glycolate among the products. These same products were also found to occur in the oxidation of ethylene.

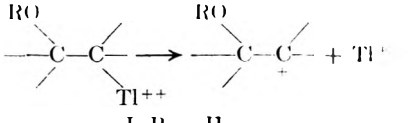
In the reaction between 2-hexene and thallium (III) acetate in acetic acid–water media the main products were acetate esters, principally the monoester, of hexane-2,3-diol, yields of which varied with the water content of the medium. With water contents of 2%, 10%, and 25% by volume the yields of esters were roughly 40%, 30%, and 7%, based on the thallium (III). Two per cent water corresponds to about one mole of water per mole of thallium, and in this experiment a trace of 2-hexanone was found. In the other two experiments substantial amounts of 2-hexanone were found.

The stoichiometry of the reaction between olefins and thallium (III) appears to be expressed by the equations

$$RCH{=}CHR' + Tl^{+++} + 2H_2O \longrightarrow RCHOHCHOHR' + Tl^{+} + 2H^{+} \quad (3)$$

$$RCH{=}CHR' + Tl^{+++} + H_2O \longrightarrow RCOCH_2R' + Tl^{+} + 2H^{+} \quad (4)$$

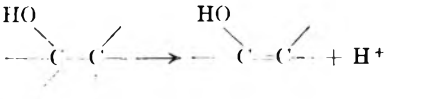
for the formation of glycols and ketones, respectively. It seems reasonable to suppose that the first step in these reactions is the formation of a thallium-olefin complex, similar to that occurring in the mercury-olefin system.[2] Upon reaction with a base, this complex forms an alkyl-thallium ion which, because of the strong oxidizing properties of thallium (III), decomposes, giving a carbonium ion:



(5)

I, R = H
II, R = CH_3CO

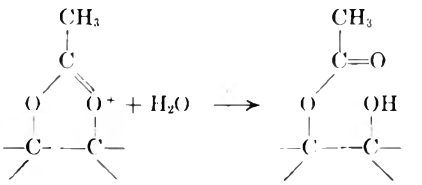
In aqueous media species I (R = H) will exist, and can, among other possibilities, pick up a hydroxyl ion or water molecule at the positive carbon to become a glycol. It can also lose a proton from the carbon bearing the hydroxyl group to become first an enol, then an aldehyde (or ketone):



(6)

This mechanism is in accord with the formation of both glycol and acetaldehyde in the oxidation of ethylene. A similar mechanism has been proposed for the reaction of lead (IV) with olefins.[5]

This mechanism can also be applied to the formation of a monoacetate glycol ester in acetic acid media, in which case the product of reaction 5 is II (R = CH_3CO). The reactions of carbonium ions of type II have been studied by Winstein,[6] who has shown that certain groups, such as acetate, are capable of a "bridging" effect, forming a carbonium ion of somewhat different nature (Equation 7). The C—O bonds of the ultimate glycol are already formed in the intermediate, and attack by a water molecule at the carboxyl carbon produces a monoacetate ester:



(7)

The extent to which reaction 5 produces II instead of I presumably depends upon the relative amounts of acetic acid and water in the system. Evidently, at the lowest water concentration reported here, the intermediate is almost entirely II, as judged by the absence of appreciable amounts of carbonyl compounds in the final products.

EXPERIMENTAL

Thallium solutions. C.P. grade thallium salts were obtained from Amend Drug Company, New York. To prepare solutions of thallium (III), a thallous compound (usually thallium chloride) was chlorinated in aqueous solution, and thallium hydroxide was precipitated by addition of sodium hydroxide. The hydroxide was then dissolved in the appropriate acid. For aqueous experiments this solution was used directly, and for experiments in acetic acid media the acetate solution was evaporated to dryness on a steam bath and taken up in glacial acetic acid.

Oxidation of ethylene. The reaction between ethylene and thallium (III) was carried out at ambient temperature in a constant-volume system, in which an atmosphere of ethylene was allowed to react with a stirred solution of a thallic compound, usually about 0.4*M* in thallium. In the nitrate and sulfate systems, absorption of ethylene occurred readily, 10 mmoles of thallium being completely reduced within a few hours. The reaction appeared to go most rapidly if sodium hydroxide were added to maintain the *p*H at the point of incipient precipitation of thallium hydroxide.

Oxidation of 2-hexene in glacial acetic acid. The oxidation of 2-hexene by thallium (III) acetate was carried out in glacial acetic acid. These experiments were performed using varying amounts of water in the system. The solutions were warmed gently for a few hours, which was sufficient to reduce the thallium completely.

Separation and determination of products. Thallium was first separated by addition of hydrochloric acid and filtration of insoluble thallium chloride. The determination of

(6) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, 65, 613 (1943); 64, 2787 (1942).

glycols was carried out by the periodate method[7] involving oxidation with excess periodate and determination of the residual periodate by addition of potassium iodide and titration with thiosulfate. This procedure also determines glyoxal and glycolaldehyde. In the ethylene experiments, where these compounds appeared to be present, a correction was made, based on the amount of 2,4-dinitrophenylhydrazone obtained. The latter compound was a reddish color, insoluble in most solvents, and melted above 300°. This description fits the glyoxal derivative, which is also obtained from glycolaldehyde. Infrared spectra of the residues obtained by evaporation of the water indicated the presence of glycolate and acetate salts. Oxalate, glyoxylic acid, formaldehyde, and formic acid were shown to be absent by chemical spot tests.[8] In one experiment the ethylene glycol was isolated by evaporating the aqueous solution to dryness, leaching the residue with propanol to reject inorganic salts, and evaporating the alcohol. The infrared spectrum of the liquid residue was identical with that of ethylene glycol.

The products of oxidation of 2-hexene were isolated by dilution of the system with water and extraction with ether, or by distillation of the solvent followed by partition between ether and water. From the ether was obtained a sweet-smelling liquid, whose infrared spectrum exhibited a strong alcoholic hydroxyl band at 2.88 μ, and another band at 5.75 μ, characteristic of the ester carbonyl group.

This data suggested that the liquid was a monoacetate ester of hexane-2,3-diol, and further evidence of its identity was sought. Monoacetate esters of this type are produced during the reaction of olefins with peroxyacetic acid,[9] and accordingly 2-hexene was oxidized by the procedure of Swern.[10] The product was purified on a vapor chromatography column, and its infrared spectrum was obtained. It was compatible with designation as a monoacetate ester of hexane 2,3-diol. A product from the thallium oxidation was chromatographed also, and the major product was found to behave identically on the chromatography column with the standard sample. Its infrared spectrum was also identical with that of the standard. In both chromatograms lesser amounts of a second component were observed, whose infrared spectra indicated it to be the diacetate ester. Approximate yields of the total ester product were obtained from the weight of product and the approximate purity as determined from the chromatograms.

A portion of the monoacetate prepared by the peroxidation procedure was hydrolyzed by refluxing 2 hr. in 10% sodium hydroxide solution, and the hexane-2,3-diol was isolated by extracting with ether, drying and evaporating the ether. An ester product from the thallium oxidation procedure was hydrolyzed in the same manner. The infrared spectrum of this hydrolysis product indicated it to be hexane-2,3-diol.

No attempt was made to ascertain whether the monoacetate was the 3-ester or the 2-ester of hexanediol. This point does not appear to have been studied in the peroxidation procedure either, and the question of the identity of the "standard" monoacetate is still open as well.

The carbonyl product obtained in the oxidation of 2-hexene in acetic acid was isolated from the distillate as the 2,4-dinitrophenylhydrazone, which was recrystallized from ethanol. It melted at 102–106°, compared to the literature values of 106° for the 2-hexanone derivative and 130° for the 3-hexanone derivative.

(7) G. O. Curme, *Glycols*, Reinhold, New York, N. Y., 1952, p. 337.

(8) F. Feigl, *Spot Tests*, Vol. II, *Organic Applications*, Elsevier, 4th ed., 1954.

(9) D. Swern, *Org. Reactions*, **7**, 378 (1953).

(10) D. Swern, G. W. Billen, T. W. Findley, and J. T. Scanlon, *J. Am. Chem. Soc.*, **67**, 1786 (1945).

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RESEARCH DEPARTMENT
DOW CHEMICAL COMPANY
PITTSBURG, CALIF.

Use of Cation Exchange Resins in Organic Reactions. I. The von Pechmann Reaction

E. V. O. JOHN AND S. S. ISRAELSTAM

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It has generally been the practice to use large quantities of concentrated sulfuric acid as a condensing agent in the preparation of hydroxycoumarins by the von Pechmann reaction, i.e. the condensation of phenols with malic acid or with β-keto esters.[1,2] It has, however, been shown by Grieg-Gass[3] and Barris and Israelstam[4] that such large amounts of acid are unnecessary, since comparable yields of coumarins are obtained by using relatively small quantities of acid. The use of cation exchange resins as condensing agents was therefore investigated and it has now been shown that certain hydroxycoumarins are readily formed in good yield in this reaction using such resins.

In recent years anion exchange resins have been used in organic reactions with some success.[5–7] Apart from the use of cation exchange resins as hydrolytic agents, there have been very few applications of such resins in synthetic work.[7–9]

The cation exchange resins used in this work were Zeokarb 225 and Amberlite IR.120. These resins are resistant to high temperatures and can be used continuously at 100°, or at higher temperatures for short periods. The main advantages of cation exchange resins are that they may be recovered and used again and that they simplify the purification of the final product. Since β-keto esters were found to be hydrolyzed by cation exchange resins, it is necessary to limit the weight of resin used, generally between 20 and 40% by

(1) H. von Pechmann, *Ber.*, **17**, 929 (1884).

(2) H. von Pechmann and C. Duisberg, *Ber.*, **16**, 2119 (1883).

(3) A. Grieg-Gass, M.S. dissertation, University of the Witwatersrand, 1932.

(4) E. Barris and S. S. Israelstam, *Chem. & Ind. (London)*, 1430 (1958).

(5) G. Durr, *Compt. rend.*, 242, 1630 (1956).

(6) C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.*, **44**, 1388 (1952).

(7) N. B. Lorette, *J. Org. Chem.*, **22**, 3346 (1957).

(8) S. Sussman, *Ind. Eng. Chem.*, **38**, 1228 (1946).

(9) B. Loev and J. T. Massengale, *J. Org. Chem.*, **22**, 8988 (1957).

TABLE I YIELDS OF COUMARINS OBTAINED

Coumarin R1	R2	R3	R4	R5	Phenol	β-Keto Ester	% Resin Giving Max. Yield: n-Hexane Without	% Resin Giving Max. Yield: n-Hexane With	Time of Reaction in Min.: n-Hexane Without at 150°	Time of Reaction in Min.: n-Hexane With at 120°	Maximum Yield: n-Hexane Without	Maximum Yield: n-Hexane With	Maximum Yield Lit.	M.P. Obtained	M.P. Lit.
			OH		Resorcinol	Ethyl acetoacetate	20.4	25.0	90	40	67.1	79.5	97.0[17]	185	185[17]
	OH		OH		Phloroglucinol	Ethyl acetoacetate	28.1	37.2	35	5	52.8	49.1	78.0[18]	284.5–5.0	282–4[18]
			OH	OH	Pyrogallol	Ethyl acetoacetate	18.7	26.7	45	20	37.8	50.8	32.0[19]	234–5	232–3[18]
			CH_3		Orcinol	Ethyl acetoacetate	25.0	28.9	60	15	21.1	33.3	91.0[20]	253	250[21]
CH_3			OH		Resorcinol	Ethyl-α-methylacetoacetate	39.0	42.7	60	15	47.0	50.6	None	256	256[21]
CH_3	OH		OH		Phloroglucinol	Ethyl-α-methylacetoacetate	36.5	36.6	60	10	36.9	25.6	None	288–9	288[3]
CH_3			OH	OH	Pyrogallol	Ethyl-α-methylacetoacetate	39.2	30.2	60	10	24.0	36.0	31.0[19]	272–3	272–3[3]
CH_3	OH		CH_3		Orcinol	Ethyl-α-methylacetoacetate	60.0	50.6	60	20	11.5	8.3	None	249	249[3]
C_2H_5			OH		Resorcinol	Ethyl-α-ethylacetoacetate	32.5	32.5	30	30	52.0	49.8	54[16]	196–7	198[3]
C_2H_5	OH		OH		Phloroglucinol	Ethyl-α-ethylacetoacetate	20.0	34.8	15	5	17.8	18.4	46[16]	217	217[16]
C_2H_5			OH	OH	Pyrogallol	Ethyl-α-ethylacetoacetate	24.0	31.0	30	30	32.0	24.4	None	217–18	219–20[3]
C_2H_5	OH		CH_3		Orcinol	Ethyl-α-ethylacetoacetate	33.4	19.0	25	40	4.4	9.0	None	207	207[3]

[a] Per cent resin means per cent by weight of resin of the total of phenol, β-keto ester and resin.

weight of the total reactants, in order to obtain the maximum yield of coumarins. (See Table I.) It is interesting to note that when a non-polar compound, such as *n*-hexane, was used as a solvent, the rate of reaction was increased quite substantially in many cases, the yields, too, being generally improved to some extent. This is probably due to the fact that there is an increased percentage of enol form of the β-keto ester in *n*-hexane,[10] *i.e.*, 63% as compared with the normal 7%.

Various mechanisms have been put forward to account for this reaction.[2,11–13] Since it has already been shown[6,4] that small quantities of acid are effective in bringing about the condensation, it would seem that the key factor in this reaction is the activity of the hydrogen ion. Bearing this point in mind the following mechanism is suggested:

Resorcinol as a result of resonance (1) has a center of high electron density at the position *ortho* to the hydroxyl group. Addition then takes place across the double bond in the enolic form of the β-keto ester as in (2)

The hydrogen ions produced by the resin (or from any acid for that matter) would cause dehydration and produce an olefinic bond, at the same time ethyl alcohol would be eliminated with ring closure.

The decrease in yield in the case of phloroglucinol is probably due to steric hindrance caused by the third hydroxyl group. The reactivity of pyrogallol is less than that of resorcinol since the third hydroxyl group deactivates the position *meta* to it for an electrophilic reagent. In the case of orcinol, the position *para* to a methyl group is deactivated for an electrophilic reagent. The activity of orcinol will therefore be less than that of resorcinol.

The substitution of the hydrogen atom on the α-carbon atom by methyl and ethyl groups lessens the activity of the β-keto ester in that order. Enolization of the β-keto ester takes place to a lesser extent when the hydrogen atoms are replaced by electron repelling groups. The ethyl-substituted ester is less reactive than the methyl substituted ester, due to a possible steric hindrance effect taking place. Conant and Thompson[14] have shown that the introduction of alkyl groups as substituents on the methylene group of ethyl acetoacetate decreases the degree of enolization.

The results given in Table I seem to bear out the above hypothesis.

After this investigation had been completed the authors noted a paper by Mastagli and Andric[15] who stated that they had used IRC-120 as a reagent in the von Pechmann reaction; but very low yields of coumarin were reported, due presumably to the low temperature at which the reaction was carried out, *viz.*, 90–100°.

EXPERIMENTAL

Preparation of cation exchange resin. The resin is crushed and washed free of smaller particles by decantation. It is allowed to soak for 10 min. in 10% hydrochloric acid and then washed with distilled water until the washings are neutral to litmus. The resin is then dried at 50° for 4 hr.

Preparation of hydroxycoumarins using exchange resin. The following is the general procedure used for the preparation of hydroxycoumarins:

Equimolecular quantities of phenol, β-keto ester, and a given quantity of resin (see table I) are heated with constant stirring in an oil bath at 150° under reflux until all reaction ceases. In many cases the coumarins separate out in the flask as a solid mass at the end of the reaction.

When *n*-hexane is used as the solvent, the reaction mixture is heated at 120°.

The effect of resin on the β-keto ester. In order to determine to what extent the resin hydrolyzes the β-keto ester, 26 g. of ethyl acetoacetate were heated under reflux, with varying amounts of resin, in an oil bath at 150°, a vigorous reaction occurring. After 1 hr. the acetone was distilled, and after washing and drying, the residual ethyl acetoacetate was weighed. The results are given in Table II.

TABLE II

HYDROLYSIS OF β-KETO ESTERS

Wt. Resin Used, g.	Wt. of Ester, g.	Wt. of Ester Hydrolyzed	% Ester Hydrolyzed
2.0	26.0	16.1	61.9
4.0	26.0	19.6	75.4
6.0	26.0	24.51	94.3
8.0	26.0	24.53	94.3

These results show that there is an optimum for the weight of resin used, beyond which there will be a decrease in yield of coumarin owing to the hydrolysis of the ester.

This was confirmed by a series of experiments with different phenols and β-keto esters in which varying amounts of resin were used.

Acknowledgment. One of the authors (E.V.O.J.) wishes to thank the S.A. Council for Scientific and Industrial Research for a grant and a research bursary.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG, SOUTH AFRICA

(10) R. J. W. Le Fevre and H. Welsh, *J. Chem. Soc.*, 1909 (1949).

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The Preparation of Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran

THOMAS J. PROSSER

Received April 29, 1960

Limited evidence found in the literature indicates that the base-catalyzed, exhaustive hydroxymethylation of ketones in which the carbonyl group is flanked by methylene groups gives rise to substituted tetrahydropyran-4-ols. Thus, the reaction of acetone and formaldehyde gives anhydroenneaheptitol (Ia),[1] whereas methyl ethyl ketone and diethyl ketone are reported to give tetrahydro-3,3,5-tris(hydroxymethyl)-5-methylpyran-4-ol (Ib) and tetrahydro-3,5-bis(hydroxymethyl)-3,5-dimethylpyran-4-ol (Ic), respectively.[2]

(1) M. Apel and B. Tollens, *Ber.*, **27**, 1089 (1894), *Ann.*, **289**, 46 (1896); C. Mannich and W. Brose, *Ber.*, **55**, 3155 (1922).

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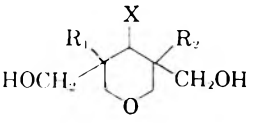
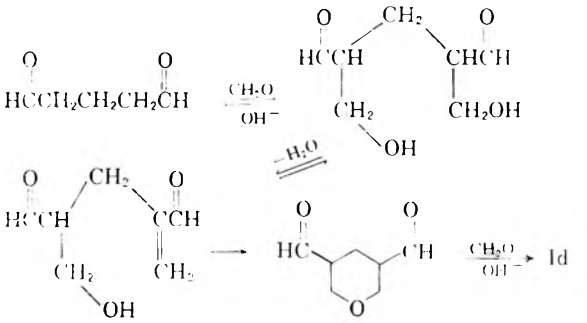


I

Ia. $R_1 = R_2 = CH_2OH$; X = OH
b. $R_1 = CH_2OH$; $R_2 = CH_3$; X = OH
c. $R_1 = R_2 = CH_3$; X = OH
d. $R_1 = R_2 = CH_2OH$; X = H

It has now been found that a similar reaction takes place in a 1,3-bis(methylene) system activated by terminal aldehyde groups rather than by a central ketone function. The exhaustive hydroxymethylation of glutaraldehyde gives the previously unreported tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)-pyran (Id). A general reaction mechanism would seem to apply to all of the above cases. The following scheme is proposed for the glutaraldehyde-formaldehyde reaction and is analogous to that suggested for the formation of dipentaerythritol in the preparation of pentaerythritol from acetaldehyde and formaldehyde.[3]



The tetraacetate, dibenzylidene acetal, and diisopropylidene ketal derivatives of Id were prepared.

EXPERIMENTAL[4]

Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). To 236 g. (3.30 moles) of 42% aqueous formaldehyde solution adjusted to *p*H 11.0 by addition of 50% sodium hydroxide solution was added 200 g. (0.50 mole) of 25% aqueous glutaraldehyde (Union Carbide Chemicals Co.) at 40–45° over a 1-hr. period. Thereafter, the temperature of the mixture was held at 50, 60, and 70° for 4, 3, and 2 hr., respectively. *p*H 11.0 was maintained throughout by intermittent addition of base. Theoretical base consumption was observed following the complete heating period. Deionization of the total crude reaction solution by passage through columns of Dowex 50 and Dowex 1 exchange resin, in that order, gave 60.6 g. of crystalline to semicrystalline product in the initial portions of effluent. Further rinsing gave an additional 10.3 g. of oily by-product considered to represent lower condensation products. The major portion of the latter material was absorbed by the exchange resin and not recovered. The main product contained 55.5% Id (32.6% yield) as determined by quantitative isolation of its dibenzylidene derivative. Preparation of an analytical sample of Id by water recrystallization gave a white crystalline solid; m.p. 176.5°.

Anal. Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.80; OH, 32.99; mol. wt., 206.23. Found: C, 52.64, 52.51; H, 8.80, 8.96; OH (acetylation), 32.3, 31.9; mol. wt. (cryoscopic in ethanol), 206, 206.

Derivatives of tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)-pyran (Id). (1) *Tetraacetate.* A mixture of 10 g. (0.049 mole) of Id, 40 g. (0.39 mole) of acetic anhydride, and 4 ml. of glacial acetic acid was heated under reflux for 1 hr., allowed to stand overnight, and then poured into 100 ml. of water. The crystalline white solid which separated amounted to 7.8 g. (43% yield), m.p. 91–95°, recrystallized from *n*-hexane, 94°.

Anal. Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00; mol. wt., 374.38; Sapon. No., 599.48. Found: C, 54.81, 55.00; H, 7.09, 7.17; mol. wt. (Rast), 386, 381; Sapon. No., 604.

(2) *Dibenzylidene acetal.* A mixture of 5.0 g. (0.024 mole) of impure Id, 25 ml. of water, 25 ml. of methanol, and 5 ml. of concd. hydrochloric acid was reacted with 10 ml. of benzaldehyde for 45 min. at steam bath temperature. There was obtained 8.14 g. (89% yield) of crude white solids which upon recrystallization from butyl acetate melted at 232–234°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.22; H, 6.85; mol. wt., 382.43. Found: C, 72.37, 72.47; H, 7.01, 7.02; mol. wt. (Rast), 388, 403.

Tests with pure Id showed the dibenzylidene reaction to be quantitative and applicable to the determination of Id in mixtures, or compounds hydrolyzed under the reaction conditions.

(3) *Diisopropylidene ketal.* A mixture of 10 g. (0.048 mole) of Id, 150 ml. of acetone, 5 drops of concd. sulfuric acid, and 15 g. of 2,2-dimethoxypropane (Dow Chemical Co.) was heated under reflux overnight. Concentration of the reaction mixture gave 11.6 g. (91.4% yield) of white crystals. Recrystallization from acetone gave a melting point of 201–205°.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.27, 63.25; H, 9.39, 9.29.

The Id content of the recrystallized product was determined by conversion to its dibenzylidene derivative: Calcd., 72.02; found, 71.2. Various samples of Id diisopropylidene ketal melted over a range of 153–206°, suggesting the presence of allotropic crystalline forms.

RESEARCH CENTER
HERCULES POWDER COMPANY
WILMINGTON, DEL.

(3) S. Wawzonek and D. A. Rees, *J. Am. Chem. Soc.*, **70**, 2433 (1948).

(4) All melting points are uncorrected.

Synthesis of Deuterated Biphenyls. II[1]

R. I. AKAWIE

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The synthesis of four deuterated isomers of biphenyl has been reported previously.[2] To complete the series studied by irradiation[3] and mass spectrometry[4] two new deuterium-substituted bi-

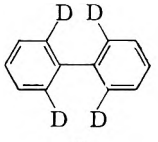
(1) This work was performed under AEC Contract AT(11-1)-GEN-8.

(2) R. I. Akawie, J. M. Scarborough, and J. G. Burr, *J. Org. Chem.*, **24**, 946 (1959). Two of these isomers have been reported by A. I. Shatenshtein, G. V. Peregudov, E. A. Izrailevich, and V. R. Kalinachenko, *Zhur. Fiz. Khim.*, **32**, 146 (1958); *Chem. Abstr.*, **52**, 12554e (1958).

(3) J. G. Burr and J. M. Scarborough, *J. Phys. Chem.*, in press.

(4) J. G. Burr, J. M. Scarborough, and R. H. Shudde, *J. Phys. Chem.*, in press.

phenyls have been prepared: biphenyl-2,2′,6,6′-d_4 (I), which has deuterium atoms in the four *ortho* positions, and biphenyl-2,2′,3,3′,5,5′,6,6′-d_8 (II), which has deuterium atoms in the four *ortho* and four *meta* positions. A simpler method has also been developed for the synthesis of biphenyl-d_{10}.



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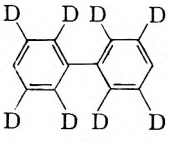
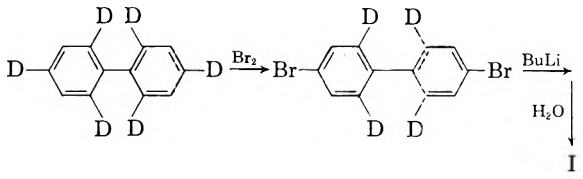


II

Compounds I and II were each prepared from previously synthesized deuterated biphenyls by the method used for the preparation of biphenyl-4,4′-d_2.[2] Biphenyl-2,2′,4,4′,6,6′-d_6 was brominated by the method of Buckles and Wheeler[5] to 4,4′-



I

dibromobiphenyl-2,2′,6,6′-d_4. This was converted by exchange with *n*-butyllithium in ethyl ether to the 4,4′-dilithium compound, which was hydrolyzed with water; the two-step yield of biphenyl-2,2′,6,6′-d_4 was 56%. Biphenyl-d_{10} was similarly converted to biphenyl-2,2′,3,3′,5,5′,6,6′-d_8 in 51% yield.

A modification of the method of Leitch[6] for the preparation of benzene-d_6 was used to synthesize biphenyl-d_{10} from biphenyl. Exchange between biphenyl and deuterium oxide was carried out over platinum black catalyst by heating to 150° and shaking in a pressure vessel made of stainless steel and copper. The water alone was removed from the reaction mixture and fresh deuterium oxide was added in each successive exchange. After several exchanges[7] there was obtained biphenyl-d_{10} of greater isotopic purity than that previously prepared.[2]

The deuterated biphenyls were found to be free of chemical impurities by gas chromatography. The isotopic content of the products was determined by mass spectrometry at an ionizing voltage high enough to ionize the molecules but too low to remove hydrogen atoms from the molecules.[8] The values for the isotopic purities are given in Table I. As the deuterium oxide used for the synthesis contained 0.3 atom percent hydrogen, the theoretical maximum purity is given in the last column of Table I.

TABLE I

ISOTOPIC COMPOSITION OF DEUTERATED BIPHENYLS

Compound	Isotopic Composition	Theoretical Maximum Purity
Biphenyl-d_4	$C_{12}H_6D_4$—98.2%	98.8%
	$C_{12}H_7D_3$— 1.6%	
	$C_{12}H_8D_2$— 0.2%	
Biphenyl-d_8	$C_{12}H_2D_8$—96.0%	97.6%
	$C_{12}H_3D_7$— 3.8%	
	$C_{12}H_4D_6$— 0.2%	
Biphenyl-d_{10}	$C_{12}D_{10}$— 96.2%	97.0%
	$C_{12}HD_9$— 3.8%	
	$C_{12}H_2D_8$— 0.0%	

EXPERIMENTAL[9]

4,4′-Dibromobiphenyl-2,2′,6,6′-d_4, m.p. 163.5–164.5°, was prepared from biphenyl-2,2′,4,4′,6,6′-d_6[2] by bromination with bromine vapor at room temperature.[5] A second crop of slightly less pure product, m.p. 162.5–164°, was obtained by concentrating the benzene mother liquor and adding methanol; the total yield was 84%.

Biphenyl-2,2′,6,6′-d_4 was prepared from 4,4′-dibromobiphenyl-2,2′,6,6′-d_4 by the method used to prepare biphenyl-4,4′-d_2.[2] From 45.8 g. (0.145 mole) of 4,4′-dibromobiphenyl-2,2′,6,6′-d_4 and *n*-butyllithium reagent (containing 0.58 mole of total base) there was obtained, after hydrolysis with ordinary water, 15.7 g. of product distilling at 124–128° at 13 mm. Two sublimations *in vacuo* gave 15.3 g. (67%) of white crystals, m.p. 69–70°.

4,4′-Dibromobiphenyl-d_8, m.p. 163–164°, was prepared from biphenyl-d_{10} in 81% yield by the procedure used for 4,4′-dibromobiphenyl-2,2′,6,6′-d_4.

Biphenyl-2,2′,3,3′,5,5′,6,6′-d_8. From 38.4 g. (0.120 mole) of 4,4′-dibromobiphenyl-d_8 and *n*-butyllithium (containing 0.48 mole of total base) there was obtained, after hydrolysis, distillation at 13 mm., and sublimation at 1 mm., 12.3 g. (63%) of product, m.p. 69–70°.

Biphenyl-d_{10}. The pressure vessel used for the exchanges was a cylinder (capacity 2.4 l.) made of stainless steel and copper which had a bellows valve and a metal thermometer soldered to it. The cylinder was charged with 100 g. of biphenyl, 200 ml. of 99.7% pure deuterium oxide, and 5 g. of platinum black (prepared by reducing platinic oxide with hydrogen). The exchange was carried out at 150° by shaking for 4 days (this may be longer than necessary). The reaction mixture was cooled, filtered with suction, and the solids were returned to the vessel with a fresh batch of deuterium oxide (200 ml.). When the exchanges were completed,[7] the mixture was cooled and filtered. The product was dissolved in benzene and filtered. After evaporation of the solvent, two sublimations *in vacuo* gave 40.3 g. of white crystals, m.p. 69–70°. The low yield was partly caused by a small leak in the pressure vessel during exchange.

Gas chromatography. The deuterated biphenyls were analyzed for chemical purity with a Perkin-Elmer model 154B Vapor Fractometer, using a 2 meter column of silicone oil on Celite. Holding the column at different temperatures changed the retention time of biphenyl, and thus made it easy to analyze for chemical impurities either more or less volatile than biphenyl.

(5) R. E. Buckles and N. G. Wheeler, *Org. Syntheses*, **31**, 29 (1951).

(6) L. C. Leitch, *Can. J. Chem.*, **32**, 813 (1954).

(7) The number of exchanges required when the reaction temperature is 150° is not known, as the first two exchanges were carried out at a lower temperature and the biphenyl was partially deuterated before the reaction temperature was changed to 150°.

(8) D. P. Stevenson and C. D. Wagner, *J. Am. Chem. Soc.*, **72**, 5612 (1950).

(9) Melting points and boiling points are uncorrected.

Mass spectrometry. The mass spectra at low ionizing voltage were determined with a modified Consolidated Electrodynamics Corporation model 21-620 mass spectrometer.

ATOMICS INTERNATIONAL
A DIVISION OF NORTH AMERICAN AVIATION, INC.,
CANOGA PARK, CALIF.

Allylic Rearrangements. XLVIII. The Absolute Configuration of (+)-α-Methylallyl Alcohol and (+)-α-Methylallyl Chloride[1]

WILLIAM G. YOUNG AND FREDERICK F. CASERIO, JR.[2]

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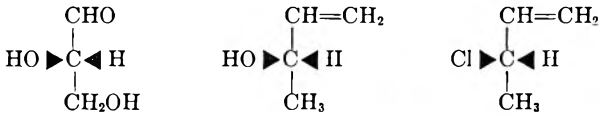
DISCUSSION

In connection with other studies[3,4] the determination of the relative configurations of optically active α-methylallyl chloride and α-methylallyl alcohol became necessary and this work is described below.

Catalytic hydrogenation of (+)-α-methylallyl alcohol yielded (+)-2-butanol which has the L-configuration[5] and therefore (+)-α-methylallyl alcohol is designated L- in agreement with the work of Wiberg.[6,7]

Reaction of thionyl chloride with D-(−)-α-methylallyl alcohol and tri-*n*-butylamine in ether yielded (+)-α-methyallyl chloride which was ozonized to (−)-α-chloropropionic acid known to possess the L-configuration.[8] It follows then that α-methylallyl alcohol and α-methylallyl chloride of like sign have like configurations about the asymmetric carbon. The absolute configurations are shown in Fig. 1.



L-(−)-Glyceraldehyde[9] L-(+)-α-Methylallyl alcohol L-(+)-α-Methylallyl chloride

Fig. 1 Absolute configuration of (+)-α-methylallyl alcohol and chloride

A lower limit for the rotation of optically pure L-(+)-α-methylallyl chloride of α_D^{25} +61° (for l = 1, neat) has been estimated from comparison of the rotation of the L-(−)-α-chloropropionic acid obtained in this work with that obtained by Lucas[10a,b] from the degradation of optically pure L-(+)-erythro-3-chloro-2-butanol. This comparison assumes that no racemization occurred during the present ozonization or Lucas' degradations, as the asymmetric centers under consideration were not directly involved in any reactions.

EXPERIMENTAL

dl-α-Methylallyl alcohol was prepared by the method of Delaby[11] as modified by Prevost,[12] b.p. 96–97°, n_D^{25} 1.4125.

Partial resolution of α-methylallyl alcohol was accomplished by the procedure of Kenyon and Snellgrove.[13] The purified alcohol had b.p. 97°, n_D^{25} 1.4121 and α_D^{27} +20.09 ± 0.02° (neat, l 1.0) which is 71.9% of optical purity based on α_D^{30} +13.8 (neat, l 0.5).[4] The mother liquors yielded a small amount of (−)-α-methylallyl alcohol of α_D^{25} −8.45° (neat, l 1.0).

Hydrogenation of (+)-α-methylallyl alcohol. A mixture having α_D^{25} +9.78 ± 0.02° (neat, l 1.0) of 2.21 g. of (+)-α-methylallyl alcohol and 2.36 g. of inactive 2-butanol was dissolved in 10 ml. of ether and hydrogenated at atmospheric pressure over 1.41 g. of 5% palladium on barium sulfate. Only about 30% of the theoretical hydrogen was absorbed. The solution was fractionated through a 30-cm. concentric tube column and yielded 1.8 g. of impure (+)-2-butanol in three fractions, the last of which had α_D^{24} +1.91 ± 0.02° (neat, l 1.0). The impurity was found to be methylethyl ketone which presumably arose from rearrangement of α-methylallyl alcohol caused by the catalyst. In another hydrogenation with Adam's catalyst, 80% of the theoretical hydrogen was absorbed.

(+)-α-Methylallyl chloride was prepared by dropwise addition of 16.5 g. (0.139 mole) of thionyl chloride over 50 min. to a stirred, ice cooled solution of 10.0 g. (0.139 mole) of (−)-α-methylallyl alcohol and 25.7 g. (0.139 mole) of tri-*n*-butylamine in 200 ml. of ether. Careful fractionation through a 30-cm. concentric tube column gave 3.3 g. of γ-methylallyl and 7.1 g. of (+)-α-methylallyl chlorides (83% yield).

Ozonization of (+)-α-methylallyl chloride. A solution of 8.39 g. (0.093 mole) of (+)-α-methylallyl chloride, α_D^{25} +5.87 ± 0.02° (neat, l 1.0) and 50 ml. of chloroform was ozonized at 0° with 2–3% ozone. After ozonization was completed, the solution was poured into 25 ml. of water. The mixture was stirred overnight at room temperature and then, after addition of 10 ml. of acetone, was heated cautiously to 50° for 4 hr. When cool, half of the mixture was saturated with magnesium sulfate then treated with 4.9 g. of potassium permanganate in about 100 ml. of water. The mixture was filtered, the filtrate saturated with sodium sulfate and acidified by addition of 2 ml. of concd. sulfuric acid. The colorless solution was extracted with ten portions

(1) This work was supported in part by a National Science Foundation grant.

(2) Standard Oil Company of California Predoctoral Fellow, 1952–1954.

(3) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 813 (1956).

(4) K. L. Olivier and W. G. Young, *J. Am. Chem. Soc.*, **81**, 5811 (1959).

(5) P. A. Levene, A. W. Walti, and H. Haller, *J. Biol. Chem.*, **71**, 465 (1927).

(6) K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3981 (1952).

(7) Wiberg designates the (+) stereoisomer as D- and has the vinyl group correspond to the hydroxymethyl group of glyceraldehyde. In the present work the vinyl group corresponds to the carboxaldehyde group of glyceraldehyde and thus the L- designation given here is consistent with Wiberg's D- designation.

(8) W. A. Cowdry, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

(9) J. J. Bijvoet, A. F. Peerdeman, and A. J. Van Bommel, *Nature*, **168**, 272 (1951).

(10) (a) H. J. Lucas and H. K. Garner, *J. Am. Chem. Soc.*, **70**, 991 (1948); (b) W. F. Fickett, H. K. Garner, and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 5063 (1951).

(11) R. Delaby, *Compt. Rend.*, **175**, 967 (1922).

(12) C. Prevost, *Ann. Chim.*, **10**, 113, 147 (1928).

(13) J. Kenyon and D. Snellgrove, *J. Chem. Soc.*, **127**, 1174 (1925).

of ether. The combined ether extracts were dried over sodium sulfate and concentrated by distillation. The residue was distilled at reduced pressure to give three fractions of (−)-α-chloropropionic acid weighing a total of 1.1 g. (22%) and all with b.p. 69.5° (1.2 mm.). The third fraction had α_D^{25} −1.73 ± 0.02° (neat, l 1.0) and neutral equivalent 110.5 (calcd.: 108.5). The neutral equivalent solution after titration with standard base was dextrorotatory.

The other half of the ozonide hydrolysis solution was treated with 5 g. of 30% hydrogen peroxide. The α-chloropropionic acid obtained after extraction and distillation amounted to about 1 g. (20%) and had α_D^{25} −1.46 ± 0.02° (neat, l 1.0) but appeared to be quite impure.

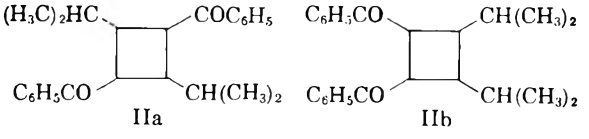
Department of Chemistry
University of California
Los Angeles 24, Calif.

The Structure of the Dimer of 1-Phenyl-4-methyl-2-penten-1-one

Ragini Anet

Received April 28, 1960

Kulka, *et al.* recently reported[1] that treatment of 1-phenyl-4-methyl-2-penten-1-one (I), (the condensation product of acetophenone with isobutyraldehyde), with aqueous methanolic alkali gave a dimer (II), m.p. 144.5–145°. Vacuum distillation of II in presence of catalytic amounts of sodium acetate gave back I. As attempts to detect an ethylenic linkage (catalytic hydrogenation, formation of a dibromide) failed, a 1,2,3,4-tetrasubstituted cyclobutane structure, IIa or IIb, was assigned to II. The formation of a dioxime and an infrared absorption band at 880 cm.$^{-1}$ were cited as evidence supporting such an assignment.



As the formation of such cyclobutane structures under alkaline conditions seemed surprising to us,[2] the structure of II was reinvestigated.

The NMR spectrum[3] of II, prepared according to Kulka, *et al.*, was determined in a deuterochloroform solution using tetramethylsilane as an internal standard,[4] and is shown in Fig. 1.

The spectrum rules out structures IIa and IIb and can only be interpreted on the basis of the structure given below.

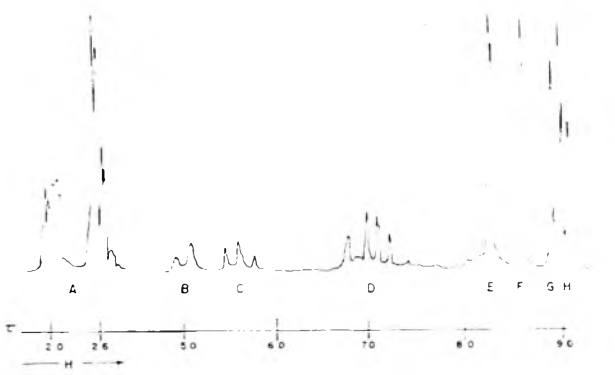


Fig. 1. The NMR spectrum of II in deuterochloroform (60 Mc/s)

$$C_6H_5CO-CH_2-\underset{\displaystyle C_6H_5CO-CH-CH=C(CH_3)_2}{\overset{\displaystyle CH-CH(CH_3)_2}{|}} \quad II$$

This structure is compatible in every detail with the NMR spectrum and is in fact the Michael addition[5] product of the conjugate anion $C_6H_5-\overset{\displaystyle O}{\overset{\|}{C}}-C^-H-CH=C(CH_3)_2$ of II to the α,β-unsaturated ketone I itself. The alkali-catalyzed dimerzation of the α,β-unsaturated ketones piperitone[6] and 3-methyl-cyclohex-2-en-1-one[7] has indeed been shown to occur *via* an initial Michael addition followed by further reactions.

The NMR spectrum clearly shows the presence of one isopropyl group. The bands G and H at highest field[8] (τ, 8.9, 9.0) are due to the two methyl groups split by a single hydrogen (J = 7.2 c.p.s.). The nonequivalence of the two methyl groups is due to the presence of an asymmetric center in the molecule, an observation made in the case of the alkaloid lunacrine.[9] The other two methyl groups (bands E and F) are not part of an isopropyl group, thus ruling out[10] structures IIa and IIb. Their position at low field (τ, 8.34, 8.60) corresponds to methyl groups attached to a doubly bonded carbon.[8] The magnitude of the splitting (1.3–1.5 c.p.s.) is too small for 1:2 coupling but is consistent with 1:3 coupling observed in olefinic compounds.[11]

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(2) Cyclobutane compounds are well known in the photodimerization of ethylenic compounds, *cf.* A. Schönberg, *Präparative Organische Photochemie*, Springer-Verlag, Berlin, 1958.

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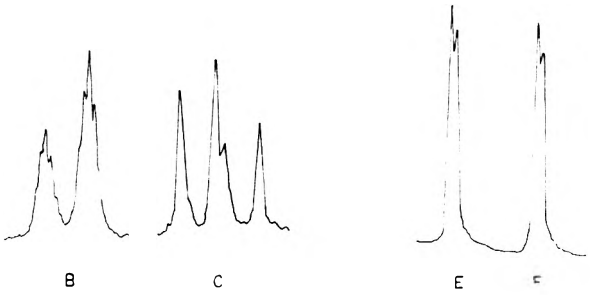

Fig. 2. Fine splitting in NMR spectrum of II

Confirmation of the double bond is obtained in band B (τ, 4.97) corresponding in position to an olefinic proton.[8] This is coupled to one adjacent hydrogen (10 c.p.s.) and shows further fine splitting (see Fig. 2) of the same magnitude as the methyl bands E and F. The unequal coupling with two methyl groups (1.5 for E and 1.3 c.p.s. for F) is due to the difference in the 1:3-*cis* and 1:3-*trans* coupling[12] and is consistent with the poorly resolved septets in band B. Band C can then be assigned to the proton coupled with the olefinic proton, as it shows the same spacing (10 c.p.s.) as in band B and is also at low field (τ, 5.6), being α to the carbonyl and β to the double bond.[11] If this deduction is correct then the fact that band C is a quartet is most simply explained by having the proton giving rise to band C coupled both to the olefinic proton (J = 10 c.p.s.) and to another proton (J = 8.75 c.p.s.).

The spectrum of the remaining protons is in bands A, D and under band E. The former is due to the aromatic protons which are similar to those of acetophenone and corresponds to ten protons. The spectrum of the tertiary hydrogen of the isopropyl group is only partially visible under band E as it is extensively split by the six hydrogens on the two methyl groups and also by adjacent hydrogen. Intensity measurements on band D show that it corresponds to three protons as compared with one each for B and C. The detailed analysis of this is not feasible by first-order treatment as the chemical shift is of the same order as the coupling constant resulting in an ABC system.[13]

The properties of the dimer II can be rationalized on the basis of the structure proposed. Although the double bond is only trisubstituted, models show considerable steric hindrance. The latter has been shown to confer unusual properties even to the disubstituted ethylene, 1,1-dineopentylethylene (III) which can be hydrogenated only at 130 atmospheres at 150° with Raney nickel.[14] The evolution of hydrogen bromide during attempts to brominate II[1] also finds parallel in the properties of III.[14] We have observed that the ethylenic linkage in II is attacked extremely slowly by potassium permanganate as has also been observed with III.

It is interesting that II is a β,γ-unsaturated ketone although it is formed under equilibrating conditions. This may be due to increased steric strain in going from an unconjugated to a conjugated structure. The structure II is consistent with the ultraviolet absorption spectrum which follows that of acetophenone. The formation of the monomer I can be easily visualized as a reverse Michael reaction[5] which needs no further comment.

ADDED IN PROOF: Dr. Kulka (personal communication) has now obtained acetone on ozonolysis of the dimer, in complete agreement with the structure proposed in this paper.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OTTAWA
OTTAWA, CANADA

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Cleavage of Ethyl 2,2-Diphenyl-4-pentenoylglycinate by Oxidants and Acids

WILLIAM B. LAWSON AND BERNHARD WITKOP

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The participation of amide groups in intramolecular displacement reactions has been utilized as a principle for the elaboration of selective methods to cleave peptide bonds next to γ,δ-unsaturated acids such as tryptophan[1,2] and tyrosine.[3] These degradative reactions may be used to advantage not only for analytical studies but also for the development of blocking groups in peptide synthesis. Indole-3-propionic[1] and phloretic acids[3] in principle are acceptable blocking groups for the synthesis of peptides that contain no functional groups whose rate of reaction with *N*-bromosuccinimide or *N*-bromoacetamide is faster than with that of the blocking groups. This note shows that by comparison observations on the use of a straightforward γ,δ-unsaturated acid such as 2,2-diphenyl-4-pentenoic acid (I) as a blocking group, though offering no immediate advantages with regard to yield, may serve as a guide for the development of groups removable not only by positive bromine but also by the controlled action of acid.

Bromination of acid I under anhydrous conditions has been found to lead to a bromolactone formulated as IV,[4] which has now also been obtained

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(2) L. K. Ramachandran and B. Witkop, *J. Am. Chem. Soc.*, **81**, 4028 (1959).

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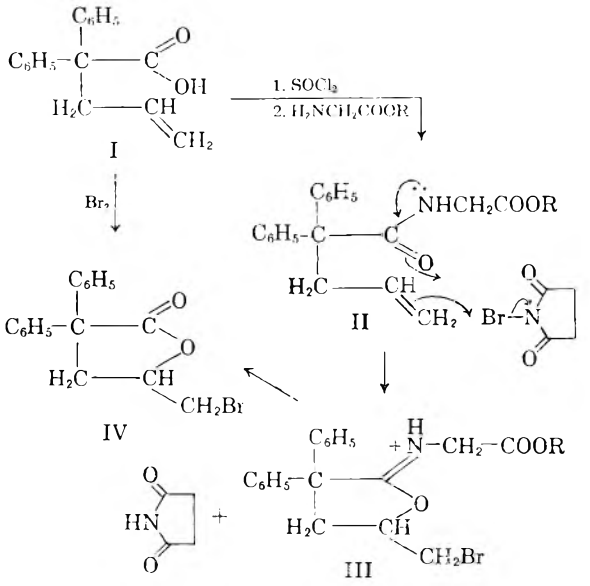

in 80% yield by the action of *N*-bromosuccinimide on the solution of the acid I in a mixture of acetonitrile and aqueous acetate buffer of *p*H 4.

The preparation of the corresponding amide II of glycine ethyl ester, unsuccessful by the mixed anhydride and carbodiimide methods, was achieved in 65% yield by the reaction of the acid chloride[4] of I with ethyl glycinate.

The cleavage of this peptide was carried out in ethanolic aqueous buffer solutions of varying *p*H or in dioxane or acetic acid saturated with hydrogen bromide. The colorimetric evaluation of the ninhydrin reaction according to Moore and Stein was used to follow the cleavage of the peptide bond. In buffer solutions of *p*H 4 cleavage to the extent of 20% was observed when the ratio of peptide to *N*-bromosuccinimide was about 1:1. Less than 5% or no cleavage occurred when glacial acetic acid was used as the reaction medium. By changing the *p*H of the buffer systems and using one mole of *N*-bromosuccinimide, the maximum yield of cleavage was constant (18–25%) between *p*H 1 and *p*H 6, and decreased steadily with higher *p*H, suggestive of alternate routes, *e.g.*, participation of nitrogen and formation of pyrrolidones.[5] The yields with acid alone in anhydrous systems did not exceed 32%.

Formation of stable iminolactones of type III has so far been observed only for tertiary amides derived from cyclohexylamine[5] dialkylamines and morpholine.[6]

EXPERIMENTAL

2,2-Diphenyl-4-hydroxy-5-bromopentanoic acid lactone (IV). To a solution of 500 mg. (1.98 mmoles) of 2,2-diphenyl-4-pentenoic acid (I) in a mixture of 25 ml. of acetonitrile and 25 ml. of 0.2*M* acetate buffer of *p*H 4 was added a solution of 374 mg. (2.1 mmoles; 5% excess) of *N*-bromosuccinimide. After 2 hr. at room temperature, the acetonitrile was evaporated and the neutral product was extracted into ether. The residue from the ether extract was crystallized from ethanol to give 480 mg. (73%) of lactone IV, m.p. 87–89° (reported[4] m.p. 87–88°). An additional 50 mg. was obtained from the mother liquors to give a total yield of 530 mg. (81%). In the infrared the compound has a peak at 5.65 μ, as would be expected for a five-membered lactone.

2,2-Diphenyl-4-pentenoylglycine ethyl ester (II). The crude acid chloride[4] from 1.09 g. (4 mmoles) of 2,2-diphenyl-4-pentenoic acid was allowed to react with a solution of 600 mg. (4.3 mmoles) of glycine ethyl ester and 1.1 ml. of triethylamine in chloroform for 2 days at 20°. The solution was extracted with 20 ml. of 1.0*N* hydrochloric acid and 20 ml. of 1.0*N* potassium bicarbonate, and evaporated to dryness. Crystallization from ethanol-water gave 870 mg. (65%) of II, m.p. 85–87°. Recrystallization, followed by drying *in vacuo* for 2 hr. at 55° afforded an analytical sample, m.p. 86.5–87.0°.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.79; H, 7.11; N, 4.29.

Cleavage of the peptide. The cleavage of the peptide was carried out in aqueous buffer systems with 1 mole of *N*-bromosuccinimide or in anhydrous systems saturated with hydrogen bromide and was followed by the method described by Patchornik, *et al.*[1] Table I summarizes the results. Total hydrolysis of the peptide in 6.0*N* hydrochloric acid for 15 hr. at 105° gave a quantitative yield of glycine.

TABLE I

EFFECT OF *p*H ON THE CLEAVAGE OF 2,2-DIPHENYL-4-PENTENOYLGLYCINE ETHYL ESTER AS ASSAYED BY COLORIMETRIC EVALUATION OF NINHYDRIN-POSITIVE MATERIAL

*p*H	Buffer or Solvent System	Yield of Glycine Ethyl Ester, %
1	Hydrochloric acid	25
2	Citrate	25
3	Citrate	21
4	Acetate	18
5	Acetate	20
6	Phosphate	23
7	Phosphate	13
8	Borate	8
9	Borate	8
Anhydrous HBr	Dioxane, saturated, 25°, 2 hr.	32
Anhydrous HBr	Glacial acetic acid, saturated, 25°, 1 hr.	26

In contrast to indole-3-propionyl peptides[7] the pentenoyl peptide II is not cleaved by the action of periodic acid at *p*H 1.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
BETHESDA, MD.

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(6) P. N. Craig, *J. Am. Chem. Soc.*, **74**, 129 (1952).
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Preparation and Pyrolysis of Methyl 12-Methylricinoleate[1]

WALTER J. GENSLER AND CAROLYN B. ABRAHAMS

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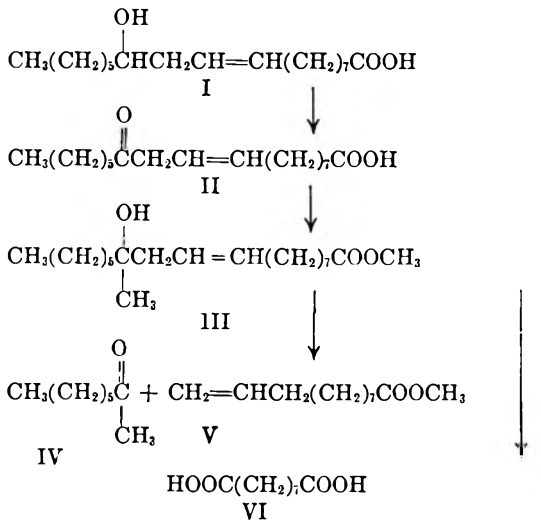
Methyl ricinoleate (the methyl ester of I) pyrolyzes to give heptaldehyde and methyl undecylenate.[2] We have now found that methyl 12-methylricinoleate (III) pyrolyzes analogously to give 2-octanone (IV) and methyl undecylenate (V). Accordingly, in agreement with the cyclic mechanism supported by Arnold and Smolinsky,[3] the hydrogen atom at the 12-position plays no essential role in the pyrolysis of methyl ricinoleate.



Methyl 12-methylricinoleate (III) was prepared from castor oil ricinoleic acid (I). Short exposure of ricinoleic acid to acid dichromate[4] gave 12-oxo-*cis*-9-octadecenoic acid (II), which after esterification with diazomethane, and reaction with methylmagnesium bromide furnished the desired product III. To show that no double bond migration occurred during the Grignard reaction, the methyl 12-methylricinoleate (III) was oxidatively cleaved. Since azelaic acid (VI) was the only dibasic acid isolated, the $\Delta^{9,10}$ formulation as in III was established.

(1) Abstracted from a portion of the dissertation submitted by Carolyn B. Abrahams to the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1957.

(2) *Cf.* A. Barbot, *Ann. chim.* (*Paris*), [11] 11, 519 (1939).

(3) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, 81, 6443 (1959); *J. Org. Chem.*, 25, 129 (1960). Also S. Isikawa, T. Tosimitu, A. Miyata, Z. Araki, and R. Someno, *Chem. Abstr.*, 34, 3240 (1940) [*Science Repts. Tokyo Bunrika Daigaku*, A3, 273 (1939)].

(4) J. Nichols and E. Schipper, *J. Am. Chem. Soc.*, 80, 5705 (1958).

EXPERIMENTAL[5]

12-Oxo-cis-9-octadecenoic acid (II). Crude castor oil fatty acids (100 g.) supplied by Baker Castor Oil Co. was oxidized essentially according to published directions.[4] The keto acid II obtained (54 g.; m.p. 39–40°) was more conveniently recrystallized from petroleum ether (b.p. 30–60°) than from 80% ethanol. The purified 12-oxo-*cis*-9-octadecenoic acid (II), m.p. 40–41°, weighed 51 g. The reported melting point is 40–40.5°.[4]

Methyl ester of 12-oxo-cis-9-octadecenoic acid (II). A distilled ethereal solution of diazomethane, prepared from 0.20 mole of *N*-methyl-*N*-nitrosourea,[6] was slowly added to a solution of 21.0 g. (0.071 mole) of freshly prepared keto acid II[7] in 30 ml. of ether. After standing overnight at room temperature, the yellow solution was distilled on the steam bath. The last traces of volatile material were removed under reduced pressure. The methyl ester of keto acid II, remaining as a brown oil, was used without further treatment.

Methyl 12-methylricinoleate (III). The keto methyl ester was transferred with 75 ml. of absolute ether to a 3-necked flask fitted with a dropping funnel, mechanical stirrer, and condenser. The reaction mixture was blanketed with pure nitrogen during the entire preparation. An ethereal solution of methylmagnesium bromide (25.5 ml. of a 4*M* solution, or 0.10 mole) was added by drops over a period of 1 hr. to the stirred keto ester solution at ice-salt temperatures. The reaction mixture, in which a dark red insoluble resin had appeared, was allowed to warm to room temperature, and was stirred for 15 hr.

Acetic acid (20 ml.) in cold water (100 ml.) was added slowly to the vigorously stirred, ice cold ether mixture. After the upper ether layer was separated, the aqueous layer was extracted with four 25-ml. portions of ether. The combined ether solutions were washed with water until the washings were neutral to litmus, and were then dried with sodium sulfate. Removal of all volatile material by distillation under reduced pressure on the steam bath left a yellow oil (16.1 g.; 70%).

Purified adduct III was obtained by placing 1.0 g. of this oil in 10 ml. of petroleum ether (b.p. 30–60°) on a 1.7 cm. chromatography column containing 25 g. of alumina (Merck, acid washed). Elution with 50 ml. portions of mixtures of petroleum ether–benzene in the volume proportions 4:1, 3:2, and 1:4 failed to remove nonvolatile material. Passage of 200 ml. of benzene did remove product, which was obtained solvent-free by distillation on the steam bath under a jet of pure nitrogen directed at the surface of the liquid. The residual, faintly yellow methyl 12-methylricinoleate (0.71 g.) was further purified by distillation in a 2 ml. short-path still. The distillate (0.56 g.) collected at b.p. 137–140° (0.02 mm.), was taken as pure product III, n_D^{25} 1.4670.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.6; H, 11.5.

Methyl 12-methylricinoleate (III), as neat liquid, showed strong infrared absorption peaks at 2.89 and 5.74 μ, but only negligible absorption in the 10.3 μ region.

In another preparation, 72 g. (0.24 mole) of 12-oxo-*cis*-9-octadecenoic acid (II) was esterified and treated with methylmagnesium bromide in a manner analogous to that described above. The crude adduct III (53.5 g.) was chromatographed on a 4 cm. column containing 500 g. of alumina to give 44.6 g. (57%) of faintly yellow methyl 12-methylricinoleate (III), n_D^{25} 1.4674, which was used without further purification.

(5) Temperatures are uncorrected. Elementary analyses were performed by Carol K. Fitz, 115 Lexington Ave., Needham Heights, Mass.

(6) F. Arndt, *Org. Syntheses*, Coll. Vol. II, 165 (1943).

(7) 12-Oxo-*cis*-9-octadecenoic acid (II) autoxidizes readily at room temperature. *Cf.* G. W. Ellis, *J. Chem. Soc.*, 9 (1950).

Treating 12-oxo-*cis*-9-octadecenoic acid (II) first with methylmagnesium bromide (3 molar proportions) and then with diazomethane gave the same product III, b.p. 139–144° (0.1 mm.), n_D^{25} 1.4667, but in only 20% yield.

Oxidative cleavage of methyl 12-methylricinoleate (III). Oxygen containing ozone was bubbled into a solution of 10 g. (0.031 mole) of methyl 12-methylricinoleate (III) in 70 ml. of chloroform (Baker Analyzed) at a rate of 0.36 mmole of ozone per min.[8] The reaction mixture was held at the temperature of solid carbon dioxide–kerosene. Ozonolysis was interrupted after 110 min., that is, after 0.040 mole of ozone had been introduced. At this time, the chloroform became blue, and iodine was liberated on passing the emergent gases into an acidified aqueous solution of potassium iodide.

Most of the chloroform was removed by distillation at room temperature under reduced pressure. Water (300 ml.) was added to the viscous residue, and the mixture was boiled for 2 hr. Five per cent aqueous potassium permanganate (150 ml.) and 10% aqueous sodium hydroxide (25 ml.) were added to the cooled mixture, which was boiled again and then cooled in an ice bath. Excess 5% sulfuric acid (200 ml.) was slowly introduced followed by enough 5% aqueous sodium hydrogen sulfite to transform all the permanganate and manganese dioxide to manganese(II). The colorless, faintly turbid solution was extracted with six 50-ml. portions of ether, and the combined extracts were extracted in turn with two 10-ml. portions of 10% aqueous sodium hydroxide. After the combined alkaline solutions were washed with two 20-ml. portions of ether (discard), concentrated hydrochloric acid was added dropwise with cooling until the *p*H was close to 1. The white, precipitated azelaic acid (VI) was collected on the funnel, was washed free of inorganic acid with ice water, and was air dried.

This product (3.7 g.; m.p. 94–97°), on crystallization from water yielded 3.3 g. (57%) of pure material, which melted either alone or admixed with authentic azelaic acid (m.p. 104.5–106°) at 105–106°. The observed neutralization equivalent, 95.0, agreed with the value calculated (94.1) for azelaic acid. The cleavage azelaic acid (VI) mixed with 7-carbon pimelic acid (m.p. 104–105°) showed m.p. 85–95°. The reported melting points of the 8-carbon suberic acid and the 10-carbon sebacic acid are 140° and 133°, respectively.[9]

Pyrolysis of methyl 12-methylricinoleate (III).[10] A 25-ml. flask fitted with a 25-cm. Vigreux column and condenser, and containing 10.0 g. (0.031 mole) of methyl 12-methylricinoleate (III) was dipped into a metal bath at 400°. After 10 min., distillation became slower, and the bath was heated to 525° and held at this temperature for 5 min. The pyrolysis products, which came over at vapor temperatures fluctuating between 270 and 330°, were collected in a receiver cooled with solid carbon dioxide.

Redistillation of the products through a 5-cm. Vigreux column afforded the following fractions: (a) 0.61 g. of a colorless, pungent liquid, b.p. 64–75° (atm. press.), n_D^{25} 1.3767; (b) 1.3 g. of faintly yellow liquid, b.p. 97–101° (54 mm.), n_D^{25} 1.4192; (c) 1.82 g. of faintly yellow liquid, b.p. 137–140° (25 mm.), n_D^{25} 1.4392; and (d) 3.2 g. of brown residue.

Fraction (b) was shown to be 2-octanone (IV) by formation of the semicarbazone.[9] The 2-octanone (0.50 g.) furnished 0.61 g. of once-crystallized white needles, m.p. 114–117°, which were recrystallized once from water. The pure derivative melted at 121–122°; its melting point was unchanged on admixture with an authentic sample of 2-octanone semicarbazone, m.p. 121.5–122°. The derivative was crystallized twice from water before analysis.

Anal. Calcd. for $C_9H_{19}N_3O$: C, 58.34; H, 10.34; N, 22.68. Found: C, 58.6; H, 10.5; N, 22.5.

Distillate fraction (c) was taken as methyl undecylenate (V). Purification by chromatography was effected by placing 0.77 g. of fraction (c) dissolved in 10 ml. of petroleum ether (b.p. 30–60°) on a 1.7 cm. chromatography column containing 15 g. of alumina (Merck, acid washed) and eluting with 120 ml. of petroleum ether. Each 20-ml. portion of eluate was freed of solvent by exposure at 100° to a jet of pure nitrogen. In this way, 0.32 g. of analytically pure methyl undecylenate (V) was obtained.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.5; H, 11.2.

The index of refraction, n_D^{25} 1.4372, agreed with the value, n_D^{25} 1.43727,[11] reported for methyl undecylenate. Infrared absorption curves taken with neat samples of pyrolysis methyl undecylenate (V) and of authentic methyl undecylenate were the same.

Under similar pyrolysis conditions, methyl ricinoleate gave heptanal and methyl undecylenate in roughly double the yields of 2-octanone (IV) and methyl undecylenate (V) from methyl 12-methylricinoleate (III).

Acknowledgment. We wish to thank the Baker Castor Oil Co. for the grant under which this work was performed and to acknowledge the encouragement and assistance of Don S. Bolley, Technical Director, The Baker Castor Oil Co. Dr. Joseph Nichols, of Ethicon, Inc. very kindly provided us with directions for the preparation of keto acid II before their publication.[4]

CHEMISTRY DEPARTMENT
BOSTON UNIVERSITY
BOSTON, MASS.

(8) The ozonolysis was modeled after the ozonolysis of ricinoleic acid (I), A. C. Noorduyn, *Rec. trav. chim.*, **38**, 323 (1919).

(9) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth edition, John Wiley & Sons, Inc., New York, New York, 1956.

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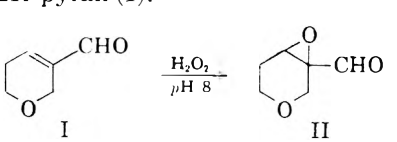
(11) J. T. Bornwater, *Rec. trav. chim.*, **26**, 409 (1907).

Alkaline Epoxidation of α,β-Unsaturated Aldehydes

GEORGE B. PAYNE

Received June 2, 1960

The technique recently described[1] for the epoxidation of acrolein and methacrolein by hydrogen peroxide has been applied to a variety of other α,β-unsaturated aldehydes. Table I summarizes the results obtained with crotonaldehyde, tiglaldehyde (2-methyl-2-butenal), cinnamaldehyde, citral, and the "acid dimer" of acrolein, 3-formyl-5,6-dihydro-2H-pyran (I).



I II

The epoxy aldehydes obtained from I, citral, and tiglaldehyde are new compounds. That from croton-

(1) G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959).

TABLE I

α,β-EPOXYALDEHYDES

R_1	R_2	Yield, %	B.P.	Mm.	n_D^{20}	Formula	Carbon, %		Hydrogen, %		Oxirane Oxygen, %		2,4-Dinitrophenylhydrazone Derivative			
							Calcd.	Found	Calcd.	Found	Calcd.	Found	M.P.	Formula	Nitrogen, % Calcd.	Found
CH_3	H	56[a]	60–61	80	1.4179	$C_4H_6O_2$	55.8	55.3	7.0	7.1	18.6	17.5[b]	136–138	$C_{10}H_{10}N_4O_5$	21.0	21.0
CH_3	CH_3	46	58–59	60	1.4198	$C_5H_8O_2$	60.1	60.4	8.1	8.1	16.0	14.6[b]	—[c]	—	—	—
C_6H_5	H	24	70–72	0.3	1.5448	$C_9H_8O_2$	73.0	73.1	5.4	5.6	10.8	7.2[c]	138–139	$C_{15}H_{12}N_4O_5$	17.0	16.9
Citral		75	63–67	1	1.4609	$C_{10}H_{16}O_2$	71.4	71.3	9.6	9.6	9.5	9.1[d]	—[c]	—	—	—
3-Formyl-5,6-dihydro-2H-pyran		70	56–57	2	1.4739	$C_6H_8O_3$	56.2	56.4	6.3	6.4	12.5	11.7[b]	136–136.5	$C_{12}H_{12}N_4O_6$	18.1	18.3

[a] Yield of anhydrous product; the yield of product as a flashed aqueous solution was 77%. [b] Hydrochloric acid in aqueous magnesium chloride; see J. L. Jungnickel, E. D. Peters, A. Polgar, and F. T. Weiss, *Organic Analysis*, Vol. 1, Interscience Publishers, Inc., New York, 1953, p. 134. [c] Hydrochloric acid in dioxane; see footnote (b), p. 135. [d] Hydrobromic acid in acetic acid; A. J. Durbetaki, *Anal. Chem.* **28**, 2000 (1956). [e] No pure derivative isolated.

aldehyde has been prepared by oxidation with hypochlorite,[2] while β-phenylglycidaldehyde was recently obtained from cinnamaldehyde in high yield by epoxidation using alkaline *t*-butyl hydroperoxide.[3]

For the epoxidation of relatively water-insoluble unsaturated aldehydes (I, citral and cinnamaldehyde), methanol was used as solvent. This meant that the *p*H as determined by a meter was generally about 1 unit higher than that determined by indicator paper; it varied somewhat with the amount of water (from the hydrogen peroxide and from the aqueous caustic used for *p*H control) introduced into the system.

EXPERIMENTAL

2,3-Epoxybutyraldehyde from crotonaldehyde. The procedure used was exactly the same as that described earlier for the epoxidation of methacrolein.[1] The crude yield of epoxide was 86% by titration for oxirane oxygen. Flashed aqueous epoxyaldehyde was secured in 77% yield based on crotonaldehyde charged. Anhydrous product was isolated in 56% overall yield, b.p. 60–61° (80 mm.); n_D^{20} 1.4179 (lit.[2] values: b.p. 66–68° (100 mm.); n_D^{20} 1.4185).

3-Formyl-3,4-epoxytetrahydropyran. To a 1-l., five-neck, round-bottom flask equipped with mechanical stirrer, dropping funnels, thermometer, and standard electrodes connected to a Beckman *p*H Meter were charged 300 ml. of methanol and 0.55 mole of 30% hydrogen peroxide. This mixture was stirred at 35–40° while 56 g. (0.50 mole) of 3-formyl-5,6-dihydro-2H-pyran[4] was added dropwise with cooling at a meter *p*H of about 9 (true *p*H of about 8 as determined by indicator paper) over a 10-min. period; *N* sodium hydroxide was used for *p*H control. After 1.5 hr. longer, an iodometric titration indicated the presence of only 0.03 mole of peroxide; 19 ml. of caustic had been consumed. The mixture was concentrated under vacuum to remove the bulk of the methanol; the concentrate was saturated with ammonium sulfate and extracted with three 150-ml. portions of chloroform. The combined chloroform extract, after a wash with saturated ammonium sulfate solution, was dried over magnesium sulfate and concentrated to low volume on the steam bath. Distillation through a 0.7 × 50 cm. glass spiral-packed column afforded 45 g. (70% yield) of 3-formyl-3,4-epoxytetrahydropyran, b.p. 56–57° (2 mm.).

β-Phenylglycidaldehyde from cinnamaldehyde. To a 2-l. flask equipped as above were charged 1000 ml. of methanol and 0.10 mole of 30% hydrogen peroxide. To this stirred mixture held at 35–40° were added simultaneously (a) a solution of 132 g. (1.0 mole) of cinnamaldehyde in 100 ml. of methanol, (b) 1.0 mole of 30% hydrogen peroxide and (c) 1*N* aqueous sodium hydroxide solution. The addition was made over 1 hr. with the peroxide leading the aldehyde; the meter *p*H was held at 11.0–10.5 (*true* *p*H 8–8.5 as determined by indicator paper). After an additional hour at meter *p*H 10.0–10.5 and 35°, an iodometric titration indicated the utilization of 1.01 mole of hydrogen peroxide.

The mixture was concentrated under vacuum to a volume of about 300 ml., diluted with 1 l. of water, and extracted with three 300-ml. portions of ether. The combined ether extract was washed with water, dried over magnesium sulfate, and concentrated at room temperature to a constant weight of 136 g. A titration for organic peroxide[5] indicated the presence of 0.08 mole of such material. In order to obviate any difficulty due to peroxide decomposition during

(2) C. Schaer, *Helv. Chim. Acta*, **41**, 614 (1958).

(3) G. B. Payne, *J. Org. Chem.*, **25**, 275 (1960).

(4) B. P. Geyer and R. H. Mortimer, U. S. Patent **2,514,156** (1950).

distillation, the residue was dissolved in 150 ml. of benzene and hydrogenated over 3 g. of 5% palladium on charcoal catalyst in a bottle shaken at 50 pounds pressure and room temperature. Hydrogenation was halted after 0.5 hr. and 0.09 mole absorption of hydrogen. After removal of catalyst by filtration, the solution was Claisen-distilled to give 79 g. of crude product, b.p. 65–90° (0.5 mm.). Redistillation through a 10-tray Oldershaw column afforded 34 g. (24% yield) of β-phenylglycidaldehyde, b.p. 70–72° (0.3 mm.); n_D^{20} 1.5448 [lit.[3] values: b.p. 66–68° (0.2 mm.); n_D^{20} 1.5447].

SHELL DEVELOPMENT CO.,
EMERYVILLE, CALIF.

(5) A sample was added to a mixture of 5 ml. of acetic acid and 50 ml. of 2-propanol; 2 ml. of saturated aqueous sodium iodide was added and the stoppered solution held in the dark for 30 min. at room temperature. The liberated iodine was titrated with 0.1*N* sodium thiosulfate to the disappearance of yellow color.

2,6-Diethyl Homologs of Bromobenzene, Benzonitrile, Benzamide, and Benzoic Acid

DONALD J. FOSTER AND D. E. REED, JR.

Received May 18, 1960

In connection with another project, we had occasion to prepare the heretofore unknown 2,6-diethylbenzoic acid. The conversion of the readily available[1] 2,6-diethylaniline to 2,6-diethylbenzoic acid was carried out by two alternate sequences of reactions. The 2,6-diethyl homologs of bromobenzene, benzonitrile, and benzamide are also unreported in the literature. These intermediates were isolated and their physical properties determined. The hydrolysis of 2,6-diethylbenzonitrile to 2,6-diethylbenzamide rather than 2,6-diethylbenzoic acid, even under the vigorous conditions employed, indicates a considerable steric factor.[2]

EXPERIMENTAL

2,6-Diethylbenzonitrile. 2,6-Diethylaniline was converted into 2,6-diethylbenzonitrile, b.p. 85–86° (1 mm.), n_D^{20} 1.5210; d_4^{27} 0.9614 in a 21% yield *via* the diazonium salt.[3] 2,6-Diethylbenzonitrile was also prepared from 2,6-diethylbromobenzene and cuprous cyanide[4] in an 86% yield.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 83.02; H, 8.2.

2,6-Diethylbromobenzene. 2,6-Diethylaniline was converted into 2,6-diethylbromobenzene, b.p. 234° (742 mm.); n_D^{20}, 1.5456; d_4^{27}, 1.264 in a 24% yield according to the general direction for the Gatterman reaction.[5]

Anal. Calcd. for $C_{10}H_{13}Br$: C, 56.36; H, 6.15. Found: C, 56.31; H, 6.2.

2,6-Diethylbenzamide. Basic hydrolysis[4] of 2,6-diethylbenzonitrile gave a 91% yield of 2,6-diethylbenzamide, m.p. 136–136.5°, after recrystallization from hexane or water. Hydrolysis of 2,6-diethylbenzonitrile with 90% sulfuric acid gave a 55% yield of 2,6-diethylbenzamide. There was no evidence for the formation of 2,6-diethylbenzoic acid in either the acidic or basic hydrolysis even after an extended reaction time.

Anal. Calcd. for $C_{11}H_{15}NO$: N, 7.90. Found: N, 7.82.

2,6-Diethylbenzoic acid. Eighteen grams (0.1 mole) of 2,6-diethylbenzamide was dissolved in 180 g. of 85% phosphoric acid and heated to 130°. Within 15 min. the clear reaction mixture became opaque and after 1-hr. two layers had formed. The organic layer solidified on cooling and after recrystallization from hexane 2,6-diethylbenzoic acid, m.p. 92–93°, was obtained in a 91% yield.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.36; H, 8.1.

2,6-Diethylbenzoic acid was also obtained in a 72% yield from the carbonation of 2,6-diethylphenyllithium, prepared from 2,6-diethylbromobenzene and lithium wire in ethyl ether. The physical and spectroscopic properties of 2,6-diethylbenzoic acid prepared by the two alternate methods were identical.

RESEARCH DEPARTMENT
UNION CARBIDE OLEFINS COMPANY
DIVISION OF UNION CARBIDE CORPORATION
SOUTH CHARLESTON, W. VA.

The Stereochemistry of the Free Radical Addition of Hydrogen Bromide to 1-Methylcycloheptene[1]

PAUL I. ABELL AND BRUCE A. BOHM

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Since the work of Goering[2] and his group on the stereochemistry of the radical addition of hydrogen bromide to 1-bromocyclohexene and 1-methylcyclohexene, in which stereospecific *trans* addition was observed, the use of cyclic olefins in the study of free radical reactions has become increasingly more important. The effect of a number of factors on radical additions to cyclic olefins has been studied. Of considerable interest has been the influence of ring size on the stereospecificity of the reaction. King Howe[3] reported that the free radical addition of hydrogen bromide to 1-methylcyclopentene afforded at least 94.3% of the *trans* addition product, *cis*-1-methyl-2-bromocyclopentane. Abell and Chiao[4] investigated the radical addition of hydrogen bromide to 1-bromocyclobutane, 1-bromocyclo-

(1) G. G. Ecke, J. P. Napolitano, A. H. Filbey, and A. J. Kolka, *J. Org. Chem.*, **22**, 639 (1957).

(2) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, p. 232.

(3) H. T. Clark and R. R. Read, *Org. Syntheses*, Coll. Vol. I, 514 (1941).

(4) H. R. Snyder, R. R. Adams, and A. V. McIntosh, *J. Am. Chem. Soc.*, **63**, 3280 (1941).

(5) L. A. Biglow, *Org. Syntheses*, Coll. Vol. I, 135 (1941).

(1) This work was performed under Contract No. DA-19-020-ORD-3171, OOR Project 1037, of the Office of Ordnance Research, U. S. Army. Support for this work is gratefully acknowledged.

(2) (a) H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.*, **74**, 3588 (1952). (b) H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **77**, 3465 (1955).

(3) King Howe, Ph.D. Thesis, University of Wisconsin, 1957.

(4) P. I. Abell and C. Chiao, *J. Am. Chem. Soc.*, **82**, 3610 (1960).

pentene, and 1-bromocycloheptene. The ratios of *cis* to *trans* isomers of the 1,2-dibromocycloalkanes obtained were, respectively, 79:21, 94:6, and 91:9. These results were explained in terms of a balance between preference for a *trans* addition process and steric inhibition to the formation of the *cis* isomers. The next step in the study seemed to be an extension of the ring-methyl series to include the seven-membered ring.

It is the purpose of this note to present the preliminary report of our work on the radical addition of hydrogen bromide to 1-methylcycloheptene. It was thought that the increased flexibility of the seven-membered ring might have some effect on the reaction, especially in the chain transfer step, where the cycloheptane ring should be capable of distorting slightly, enabling closer approach of the hydrogen bromide molecule.

Three products may result from the addition of hydrogen bromide to 1-methylcycloheptene, *cis*- and *trans*-1-methyl-2-bromocycloheptanes by the free radical process and 1-methyl-1-bromocycloheptane by the ionic process. The method of analysis employed in this work consisted of dehydrobromination of the free radical product followed by infrared analysis of the resultant olefins. The presence of ionic addition product, however, would interfere with this procedure, hence removal of this material was necessary. Preferential solvolysis of the tertiary bromide with aqueous acetone was found to give quite satisfactory results. According to Cristol[5] dehydrohalogenation proceeds preferentially by a *trans* elimination process. Therefore, *trans* addition of hydrogen bromide to 1-methylcycloheptene would give *cis*-1-methyl-2-bromocycloheptane, which would give the original olefin upon dehydrohalogenation. If *trans*-1-methyl-2-bromocycloheptane were formed in the addition reaction, 3-methylcycloheptene would be expected to be formed in the dehydrobromination. A mixture of these olefins would, of course, indicate the presence of both isomers of 1-methyl-2-bromocycloheptane and the absence of a stereospecific addition process.

Examination of the infrared spectra and the physical constants of the olefin from the dehydrobromination of the radical addition product and an authentic sample of 1-methylcycloheptene showed them to be virtually identical. The absence of absorption bands of 3-methylcycloheptene in the infrared spectrum and the fact that 3-methylcycloheptene does not isomerize to 1-methylcycloheptene under the conditions of the dehydrobromination reaction indicate that the free radical addition proceeds probably better than 95% by the *trans* mechanism. It would appear from these results that the increased flexibility of the seven-membered ring does not affect the addition process to any substantial degree.

(5) S. J. Cristol, *J. Am. Chem. Soc.*, **69**, 338 (1947).

EXPERIMENTAL

1-Methylcycloheptene. This compound was synthesized according to the method of Arnold, Smith, and Dodson[6] and Bartlett and Rosenwald[7] in 61.2% yield. The physical constants of this olefin were: b.p. 135.5–136.0°, n_D^{24} 1.4562 (lit.[8] b.p. 136°, n_D^{25} 1.4563).

3-Methylcycloheptene. This olefin was prepared according to the method of Arnold, Smith, and Dodson[6] by the Ziegler bromination of cycloheptene (47.2%) to give 3-bromocycloheptene, followed by coupling of this product with methyl magnesium iodide. Purification of the 3-methylcycloheptene gave a product with the following physical constants: b.p. 130–132°, n_D^{22} 1.4562.

Free radical additions. The addition reactions were run in a fused silica flask fitted with an addition funnel, a gas inlet adapter fitted with a fritted glass bubbler tube, and a reflux condenser protected from the atmosphere by a drying tube filled with anhydrous calcium sulfate. Energy for the homolysis of the hydrogen bromide was provided by a Hanovia type 30600, medium pressure, mercury vapor lamp. The reaction flask was partially immersed in a water bath which was held at about 70°. 1-Methylcycloheptene in *n*-heptane was added through the addition funnel which contained a glass wool pad upon which was placed a layer of sodium hydride. Hydrogen bromide, dried by passing over anhydrous calcium sulfate, was bubbled through the reaction mixture for 2–3 hr. The reaction product was isolated by removal of the solvent under reduced pressure followed by distillation of the residual material in one fraction. Analysis for tertiary halide (ionic addition product) was performed at this stage. The results of a number of runs are given in Table I.

TABLE I

FREE RADICAL ADDITION OF HYDROGEN BROMIDE TO 1-METHYLCYCLOHEPTENE

Run	Olefin Used, G.	Product, G.	Yield, %	B.P./Mm.	*tert*-Halide Analysis
4	8.7	11.2	74	91–95°/17	17.1
6	8.4	11.0	75	85–89°/16	19.3
7	10.0	14.6	84	95–97°/20	15.4
8	10.0	13.7	79	97–99°/25	22.1

Tertiary halide analysis. An accurately weighed bromide sample of about 0.2 g. was mixed with 5 ml. of a 4:1 acetone-water mixture and allowed to stand at room temperature for 0.5 hr. The mixture was diluted with a large excess of cold water and titrated against standard sodium hydroxide using a 1% solution of phenolphthalein in alcohol as indicator. The end point was taken when the color held for about 1 min.

Isolation of the free radical addition product. The free radical bromide was isolated by selective hydrolysis of the tertiary halide with a 4:1 acetone-water mixture. The mixture was allowed to stand at room temperature for 1 hr. After dilution with water, the organic material was extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Purification by distillation gave a product which had an analysis corresponding to less than 1% tertiary halide. The secondary halide (from run number 6) had the following physical properties: b.p. 106°/32 mm., n_D^{22} 1.5003.

(6) R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950).

(7) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934).

(8) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

Dehydrobromination of the free radical bromide. Dehydrobromination of the free radical bromide, purified as described in the preceeding paragraph, was done by refluxing 6 hr. with anhydrous pyridine. At the end of the heating period the mixture was poured into ice-cold water which had been acidified with hydrochloric acid. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Distillation at atmospheric pressure gave a product with b.p. 133–135°, $n_D^{25.5}$ 1.4560 (lit.[8] for 1-methylcycloheptene: b.p. 136°, n_D^{25} 1.4563).

Isomerization experiment. 3-Methylcycloheptene, prepared as indicated above, was refluxed in a pyridine–pyridine hydrobromide mixture to simulate the dehydrobromination reaction conditions. The reaction mixture was poured into cold, dilute hydrochloric acid, the olefin extracted with several portions of ether, and the ether extracts were combined and dried over anhydrous magnesium sulfate. After the ether was removed under reduced pressure the infrared spectrum of the residual oil was obtained, and this spectrum was found to be identical to the spectrum of an authentic sample of 3-methylcycloheptene.

Department of Chemistry
College of Arts and Sciences
University of Rhode Island
Kingston, R. I.

Decolorization of Triphenylmethyl Carbonium Ion by Ethyl Ether

William B. Smith and Parinam S. Rao

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In 1921 Hantzsch noted that the addition of ethyl ether to various solutions containing the triphenylmethyl carbonium ion caused a diminution of the characteristic yellow color of the ion.[1] This he attributed to a reversal of the ion forming reaction with the regeneration of the colorless precursor to the ion. Since solid triphenylmethyl perchlorate is itself highly colored this explanation can hardly hold for the decolorization of solutions of triphenylmethyl perchlorate.

Leffler, in speculating on these observations, proposed the formation of a colorless oxonium salt with the ether as a more likely possibility.[2] If so, then the formation of the complex should follow a regular diminution in color as a function of ether concentration, and one should be able to calculate an equilibrium constant for the complex formation. Such a study has been carried out for triphenylmethyl perchlorate in acetic anhydride and for triphenylmethyl chloride in nitromethane. The results are reported below.

Solutions of triphenylmethyl perchlorate in acetic anhydride were prepared *in situ* by the addition of a stoichiometric excess of perchloric acid to a solution of triphenylcarbinol. The characteristic spectrum of the triphenylmethyl carbonium ion in this solvent is given in Fig. 1A. The solution

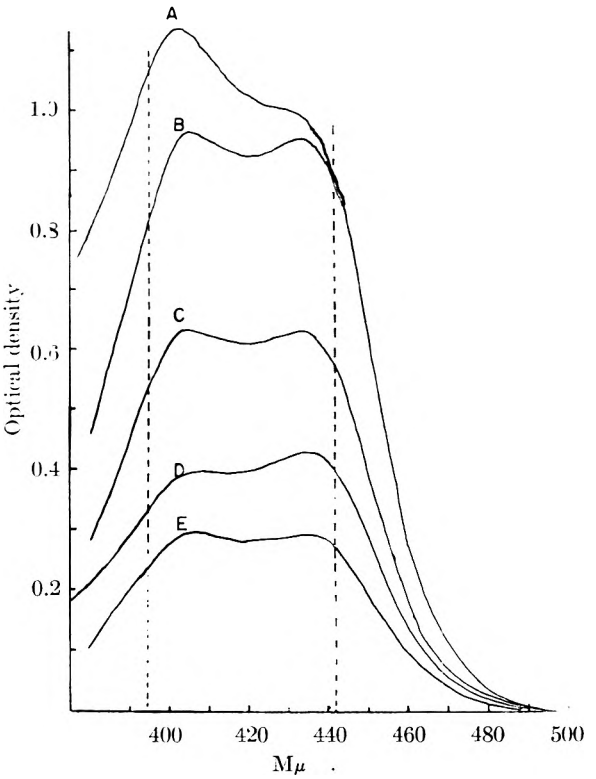

Fig. 1. The spectrum of the triphenylmethyl carbonium ion under various conditions: A, Ph_3CClO_4 ($2.75 \times 10^{-5}M$) in acetic anhydride; B, Ph_3CCl ($0.0804M$) in nitromethane; C, Ph_3CCl ($0.0777M$), Et_2O ($0.192M$) in nitromethane; D, Ph_3CClO_4 ($2.75 \times 10^{-5}M$) and Et_2O ($1.65M$) in acetic anhydride; and E, Ph_3CCl ($0.0791M$) and Et_2O ($0.736M$) in nitromethane

was stable for thirty to sixty minutes after which the bands due to the carbonium ion slowly decreased in intensity. After twenty-four hours the solution was still deep orange, but the carbonium ion band had entirely disappeared. The addition of ethyl ether lessened the intensity of the carbonium ion bands, Fig. 1C. The data for a series of ether concentrations are given in Table I as are the values

TABLE I

Effect of Ethyl Ether on a $2.75 \times 10^{-5}M$ Solution of Triphenylmethyl Perchlorate in Acetic Anhydride

$(C_2H_5)_2O$	$(Ph_3C^+) \times 10^5$	$[Ph_3C{-}O(C_2H_5)^+_2] \times 10^7$	K
0.0946	2.51	24	0.99
0.1519	2.42	33	0.90
0.3952	2.10	65	0.78
0.4600	1.85	90	0.94
0.8340	1.59	116	0.88
1.650	1.06	169	0.97
2.240	0.84	191	1.02
			$K_{av} = 0.93$

of the equilibrium constant calculated for the individual points assuming a one to one complex. The assumption of a two to one complex led to a great variation in the value of K. A plot of carbonium ion concentration *versus* the concentration

(1) A. Hantzsch, *Ber.*, **54**, 2573 (1921).

(2) J. E. Leffler, *The Reactive Intermediates of Organic Chemistry*, p. 97, Interscience Publishers, New York, 1956.

of complex divided by the ether concentration was linear. Assuming a one to one complex, one may write:

$$Ph_3C^+ + (C_2H_5)_2O = [Ph_3C{-}O(C_2H_5)_2^+]$$

$$K = \frac{[Ph_3C{-}O(C_2H_5)_2^+]}{(Ph_3C^+)[(C_2H_5)_2O]}$$

The value of K taken from the slope of the plot was 0.93 which agrees with the average value of K taken from the data for the individual points.

Solutions of triphenylmethyl chloride in nitromethane have varying degrees of stability depending on the history of the solvent. Leffler and Smith[3] found that the color of the carbonium ion rapidly decreased in carefully purified commercial nitromethane. On the other hand, Evans has reported that such solutions are stable for days.[4] Pocker reported stability for twenty-four hours; the implication being that the color of the ion decreased after this time.[5] Vapor phase chromatography of a sample of a popular brand of spectroscopic grade nitromethane, purified by the method of Evans, produced four bands other than that due to the solvent itself. Thus, it seems likely that the results reported earlier by Leffler and Smith reflect impurities in their nitromethane. In order to overcome the difficulties of purifying commercial nitromethane we synthesized our own by the usual procedure.[6] This material gave only one band on vapor phase chromatography. Solutions of triphenylmethyl chloride in this material were stable for at least one hour. Three determinations of the ionization constant gave an average value of 3.48×10^{-4} with a maximum error of 3%. This value agrees well with those reported by Evans[7] and Pocker.[5]

The data for a series of solutions of triphenylmethyl chloride and ethyl ester in nitromethane are given in Table II. The values of K were determined on the assumption that the following equilibria existed. The pertinent equations for calculation are also given (where the superscripts o and f mean original and final concentrations, respectively).

$$Ph_3CCl \overset{K_i}{=} Ph_3C^+Cl^- \quad K_i = \frac{(Ph_3C^+)}{(Ph_3CCl)} = 3.48 \times 10^{-4}$$

$$Ph_3C^+ + (C_2H_5)_2O \overset{K}{=} Ph_3C{-}O(C_2H_5^+)_2^+$$

$$K = \frac{(Ph_3C{-}O(C_2H_5)_2)}{(Ph_3C^+)[(C_2H_5)_2O]^f} \quad (1)$$

$$(Ph_3CCl)^f = \frac{(Ph_3C^+)}{K_i} \quad (2)$$

$$[Ph_3C{-}O(C_2H_5)_2^+] = (Ph_3CCl)^o - (Ph_3CCl)^f \quad (3)$$

$$[(C_2H_5)_2O]^f = [(C_2H_5)_2O]^o - [Ph_3C{-}O(C_2H_5)_2] \quad (4)$$

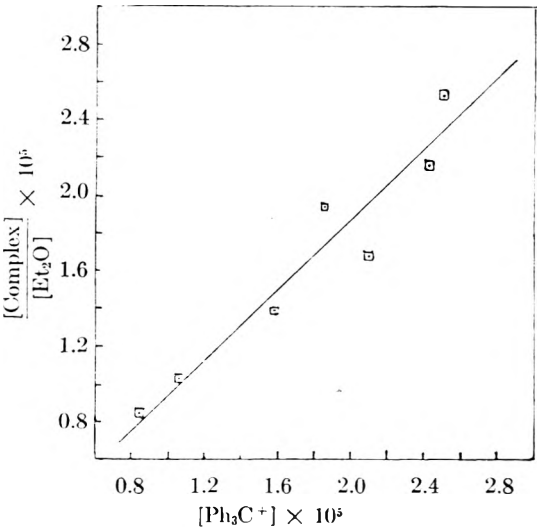

Fig. 2. A plot of the data obtained for the system triphenylmethyl perchlorate and diethyl ether in acetic anhydride

The values of K in nitromethane are not as self-consistent as those in acetic anhydride. This may be due to one or more of several reasons. The Equation 2 above may be an oversimplification. Pocker[5] has shown that solutions of triphenylmethyl chloride in nitromethane are more complex than simple ionization to an ion pair as stated by Evans.[7] For our purposes all that is required is that species other than the complex be controlled by the value of K_i and be nonabsorping in this region. In view of the constancy of K_i over a wide range of concentrations of the chloride this assumption would seem to be reasonable. Any possible variations in K_i over the concentration range of ether used in this study were ignored since no systematic variation in the values of K were noted.

Because we prepared our own nitromethane, smaller amounts were used in making up each sample than in the anhydride solvent. Thus, the variation may reflect the inaccuracies in preparing exact dilutions of ether in a small solvent sample.

Finally, solutions of triphenylmethyl chloride and ether in nitromethane were not so stable as those without the ether. The color of the carbonium ion started to decay within ten minutes after the solutions were prepared. An attempt was made to carry out a similar study with triphenylmethyl perchlorate in nitromethane. In the absence of ether the carbonium ion was stable for over a day. On the addition of ether the color decreased rapidly, and the characteristic spectrum of the carbonium ion was gone at the end of an hour.

The above data strongly support Leffler's suggestion of a covalent complex formed between the triphenylmethyl carbonium ion and ethyl ether. The great difference in equilibrium constants for complex formation in these two solvents is of in-

(3) Bill B. Smith and J. E. Leffler, *J. Am. Chem. Soc.*, **77** 1700 (1955).

(4) I. W. Bayles, A. G. Evans, and I. R. Jones, *J. Chem. Soc.*, 1020 (1957).

(5) Y. Pocker, *J. Chem. Soc.*, 240 (1958).

(6) W. J. Hickinbottom, *Reactions of Organic Compounds*, p. 237, Longmans, Green and Co., London, 1948.

(7) A. Bentley, A. G. Evans, and J. Halpern, *Trans. Faraday Soc.*, **47**, 711 (1951).

TABLE II

EFFECT OF ETHYL ETHER ON VARIOUS SOLUTIONS OF TRIPHENYLMETHYL CHLORIDE IN NITROMETHANE

$(Ph_3CCl)^o$	$[(C_2H_5)_2O]^o$	$(Ph_3C^+) \times 10^o$	$[Ph_3C—O(C_2H_5)_2^+]$	$K \times 10^{-4}$
0.0792	0.077	2.23	0.0151	1.09
0.0764	0.084	2.37	0.0083	0.46
0.0777	0.192	1.87	0.0239	0.76
0.0779	0.261	1.77	0.0270	0.65
0.0764	0.484	1.22	0.0412	0.76
0.0772	0.585	1.32	0.0393	0.55
0.0756	0.668	1.17	0.0420	0.57
0.0791	0.736	0.86	0.0544	0.93
0.0768	0.936	0.56	0.0607	1.24
0.0816	1.172	0.49	0.0675	1.25
				$K_{av} = 0.83$

terest. Gillespie and coworkers[8] have shown that acetic anhydride is a much stronger base than nitromethane in concentrated sulfuric acid. On this basis it would be expected that the anhydride would be more able to solvate the ion and would compete with the ether more avidly than nitromethane. The altered spectrum of the carbonium ion in acetic anhydride as opposed to the spectrum of the ion in nitromethane or sulfuric acid may reflect this solvation effect.

EXPERIMENTAL

Triphenylmethyl chloride was prepared in the usual fashion from triphenylmethylcarbinol,[9] m.p. 112–113°. Nitromethane was prepared from chloroacetic acid,[6] dried over phosphorous pentoxide and distilled, b.p. 99–100°. Acetic anhydride and ethyl ether were Mallinckrodt Analytical Reagent grade chemicals taken from freshly opened containers in each case.

Determinations of the carbonium ion concentrations were made with a Cary model 14 Spectrophotometer. All work was done at room temperature, 24–26°.

Triphenylmethyl perchlorate in acetic anhydride. A stock solution of triphenylmethylcarbinol ($5.50 \times 10^{-5}M$) in acetic anhydride was prepared. Aliquots (5.0 ml.) of this stock solution were taken, and the appropriate amount of ether was weighed in. The samples were then diluted to a final volume of 10 ml. with additional acetic anhydride. A silica cell (1 cm. thick) was filled with the sample, and 1 drop of 70% perchloric acid was added. The addition of 2 or 3 drops of acid did not alter the intensity of the carbonium ion absorption. The spectrum was then run immediately after the acid addition.

In view of the variance in the shape of the carbonium ion absorption curve at different concentrations, the area under the curves was taken between the limits of 395 mμ and 442 mμ. A standard sample of the carbonium ion in acetic anhydride was used to determine the relationship between area under the curve and the concentration of the carbonium ion. This method represents a compromise between the usual method of determining the concentration at one wave length and the more desirable practice of using oscillator strengths.

The various concentrations of ether used and the K's calculated therefrom are given in Table I.

Triphenylmethyl chloride in nitromethane. The desired amount of triphenylmethyl chloride was weighed into a 5 ml. volumetric flask, and a small amount of nitromethane was added. The ethyl ether was weighed into this flask, and the volume was brought up to 5.0 ml. with additional nitromethane. The flask was shaken to ensure solution. Determination of the carbonium ion concentration was as described above. The data are given in Table II. The method of calculation is given in the text. The determination of the initial concentration of carbonium ion in nitromethane alone was carried out in the same fashion as that used by Evans[7] and Pocker.[5] It was assumed that the extinction coefficient for the carbonium was the same as that of the ion in sulfuric acid; a value of 35,500 at 404 mμ was used.[3]

Several experiments were carried out with triphenylmethyl perchlorate in nitromethane. The perchlorate was generated *in situ* as previously described. These solutions were stable for over 24 hr., and the usual spectrum for the carbonium ion was observed. However, the addition of ethyl ether to these solutions caused an immediate diminution of the carbonium ion color, the resultant solutions were not stable. The color of the ion was completely discharged within 30–60 min.

DEPARTMENT OF CHEMISTRY
OHIO UNIVERSITY
ATHENS, OHIO

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The Equilibrium Composition of the Octahydronaphthalenes

ALLEN S. HUSSEY, JAMES-FREDERIC SAUVAGE, AND ROBERT H. BAKER

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The preparation of pure $\Delta^{9,10}$-octalin by way of the dehydration of 2-decalol, separation of the nitroso chloride derivative of the $\Delta^{9,10}$-isomer, and the regeneration of the olefin has been recently described.[1,2] Our procedure is essentially that described by Dauben and coworkers[1] except that the regeneration of the olefin from its purified nitroso chloride derivative by warming with *N,N*-dimethylaniline furnishes the pure olefin in 85–95% yield.

(1) W. G. Dauben, *et al.*, *J. Org. Chem.*, **23**, 1205 (1958).

(2) A. S. Hussey, J.-F. Sauvage and R. H. Baker, Abstracts, 134th Meeting, American Chemical Society, Chicago, Ill., September 7–12, 1958, p. 80P.

Our data for the acid-catalyzed equilibration of the $\Delta^{1,9}$- and $\Delta^{9,10}$- octalin mixture suggests that the apparent enrichment in the latter is more likely the result of removal of the former by polymerization side-reactions. Thus, while the ratio of $\Delta^{9,10}$-isomer to $\Delta^{1,9}$-isomer increases with time of exposure to phosphoric acid, the undistillable residue shows a corresponding increase (see Experimental).

This explanation is supported by the composition of the equilibrated system when a carbanion catalyst[3] is used. In contrast to strong protic acid catalysts, such carbanion catalysts cannot effect polymerization. A mixture composed of 72% $\Delta^{9,10}$-octalin, 26% $\Delta^{1,9}$-octalin and 2% *trans*-decalin after 42, 48, and 65 hours at reflux over a "benzylsodium" catalyst[3] had the constant composition 70% $\Delta^{9,10}$-, 20% $\Delta^{1,9}$-, 4% *trans*-$\Delta^{1,2}$-, 4% *trans*-$\Delta^{2,3}$-, and 2% *trans*-decalin. Thus the equilibrium ratio of $\Delta^{9,10}$- to $\Delta^{1,9}$-octalin is considerably smaller (7/2) than can be realized by the acid catalyzed "isomerization". The latter is really an enrichment of the unpolymerized octalin mixture by a preferential polymerization of the $\Delta^{1,9}$-isomer.

Our experience with the lithium-ethylamine reduction of tetralin or naphthalene by Benkeser's procedure[4] has been essentially that reported by Dauben.[1]

EXPERIMENTAL

Dehydration of 2-decalol. A mixture of 2-decalol isomers obtained from the hydrogenation of 2-naphthol over nickel-kieselguhr was added to three times its weight of 100% phosphoric acid with stirring and the system was rapidly raised to 150°. A slight vacuum was applied to the system and water was added dropwise while maintaining the temperature at 150°. After all of the steam-volatile product had distilled, considerable (*ca.* 20%) of the reaction product remained as nonvolatile residue. The volatile product was analyzed by vapor partition chromatography through a 1000 plate tri-*m*-cresyl phosphate-on-fire-brick column and was found to consist of 80% $\Delta^{9,10}$-octalin, 20% $\Delta^{1,9}$-octalin, yield 75–80%.

$\Delta^{9,10}$-Octalin nitroso chloride. Equimolar amounts of isoamyl nitrite and iced hydrochloric acid were mixed at −10° with 0.5 mole of the octalin mixture. After 1.5 hr. the blue precipitate was filtered and washed with ice cold ethanol; yield, 75%. Recrystallization from acetone-ether gave 55–65% of blue prisms, m.p. 91–92°.[5]

Regeneration of $\Delta^{9,10}$-octalin. The blue nitroso chloride, 19.0 g. (0.094 mole), and 30 ml. of *N,N*-dimethylaniline in a 100 ml. flask with a reflux condenser were slowly warmed to 70° when gas evolution began. (Caution! If the temperature is raised too rapidly to this point, gas evolution becomes violent.) The temperature was gradually raised to 85° and maintained there for 2.5 hr. at which time gas evolution was complete. Dilution with water, extraction with pentane, and washing of the pentane extracts with dilute hydrochloric acid served to isolate the product. This distilled at 77.5° at 14 mm., n_D^{20} 1.4990; yield 11–12 g. (85–95%). This product exhibited a single peak when analyzed on the tri-*m*-cresyl phosphate column.

Isomerization studies. A. *Over phosphorus pentoxide.* A 22.0-g. sample having the composition 53% $\Delta^{9,10}$-octalin, 9% $\Delta^{1,9}$-octalin and 38% *trans*-decalin was heated on the steam bath for 2 hr. over 10 g. of phosphorus pentoxide. It was then extracted with ether and distilled. The undistillable residue amounts to 5 g. The volatile product had the composition 47% of $\Delta^{9,10}$-, 7% $\Delta^{1,9}$-, and 46% *trans*-decalin. A second 2-hr. treatment of the mixture left 5.2 g. of polymeric residue. The volatile material had the composition 32% $\Delta^{9,10}$-, 4% $\Delta^{1,9}$-, and 64% *trans*-decalin.

B. Over "benzylsodium" catalyst.[3] A sample of mixed octalins having the composition 72% $\Delta^{9,10}$-, 26% $\Delta^{1,9}$, and 2% *trans*-decalin was refluxed with "benzylsodium" catalyst.[3] A sample was removed periodically for analysis on the 1000 plate tri-*m*-cresyl phosphate column. After 42 hr., the composition was constant at 70% $\Delta^{9,10}$-, 20% $\Delta^{1,9}$-, 4% *trans*-$\Delta^{1,2}$-, 4% *trans*-$\Delta^{2,3}$-, and 2% *trans*-decalin. Additional samples removed at 48 hr. and at 65 hr. had the same composition.

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILL.

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Are Organic Group Influences Additive in All Reactions of Aromatic Compounds?

ROBERT M. STONE[1] AND D. E. PEARSON[2]

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The consensus of opinion is that group influences are additive. Jaffé states in summary that the effect of multiple substitution in the reactivity of a functional group can be expressed in the Hammett equation by the sum of the substituent constants[3]: $\log K/K_0 = \rho\Sigma\sigma$. Since the publication of this work, Benkeser and co-workers[4] have shown that the sigma constants of 3,5-dialkyl groups, including the bulky *tert*-butyl group, are additive in the loss of a trimethylsilane group from an aromatic ring. The predicted dissociation constant of 3,5-di-*tert*-butylbenzoic acid, calculated in this laboratory from published data,[5] does not substantiate Benkeser's conclusions. As the data of Ref. 5 are less extensive and our calculation dependent on two different sources of information,

(1) In partial fulfillment of the requirements for the Ph.D. degree, Vanderbilt University, 1959. Dissertation Abstracts, 20(4), 1196 (1959), University Microfilms Inc., Ann Arbor, Mich.

(2) To whom correspondence should be sent.

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(4) R. A. Benkeser, R. A. Hickner, D. I. Hoke, and O. H. Thomas, *J. Am. Chem. Soc.*, **80**, 5289 (1958).

(5) Data from E. E. Betts and L. R. C. Barclay, *Can. J. Chem.*, **33**, 1768 (1955). Assuming that rho, the slope, is 1.24 in 50% aqueous methanol,[6] we calculate the dissociation constant of 3,5-di-*tert*-butylbenzoic acid to be 3×10^{-6}. Betts and Barclay report 1.66×10^{-6}. Thus, the *meta-tert*-butyl groups appear to be too strong as electron donors in this reaction.

(6) E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4939 (1951).

we place more confidence in the data of Benkeser. Crocker and Jones[7] claim that group influences are additive, except for groups adjacent to the methoxyl group, in the quaternization of dimethylanilines with allyl bromide. The abnormality of the methoxyl group under these conditions may be attributed to steric inhibition of resonance. Brown states that the prediction of relative rates in aromatic substitution of polyalkylbenzenes is "moderately satisfactory."[8] Such predictions are based inherently on additivity of the influences of the groups attached. Keefer and Andrews,[9] however, found that iodination of polyalkylbenzenes, compared to bromination, showed a retardation in rates, *i.e.*, the alkyl group influences were not additive. They attributed the retardation to a direct steric influence. Recently[10] we found a most striking deviation from the additivity of 3,4,5-trialkyl groups in the Beckmann rearrangement of substituted acetophenone oximes. The 3,4,5-trimethylacetophenone oxime rearranged at a rate 18% slower than predicted,[11] and the 3,4,5-triethyl oxime at a rate 30% slower than predicted.[10] As few trisubstituted derivatives have been studied in the conception of the idea of additivity,[12] we thought that nonadditivity of group effects might have escaped detection in other reactions. We therefore determined the dissociation constants of the trisubstituted benzoic acids by potentiometric titration.[13] The difficulties of determining dissociation constants in aqueous ethanol solution have been pointed out by Grunwald[6] and Kilpi.[14] But since the absolute dissociation constants for benzoic acid are now available for various aqueous ethanol solutions,[6] we made the assumption that all values determined in this paper could be corrected by application of the ratio 1.2/1.86 (Grunwald's value for benzoic acid in 57.6% ethanol divided by our value in the same solvent). Some doubt may be raised about the absolute values reported using this assumption, but very little doubt can be raised about the relative values.[6] In addition precaution was taken to minimize changes in activities of ions or in liquid junction potentials by using 57.6% ethanol for every solution including the standard alkali and the potassium chloride salt bridge.

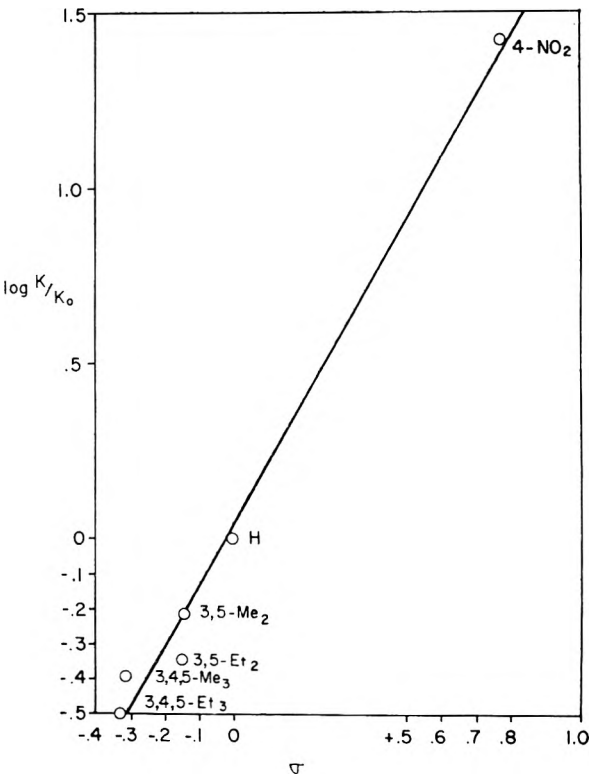

Fig. 1. Plot of log K/K_0 of substituted benzoic acids in 57.6% aqueous ethanol *vs.* sigma. The slope, rho, = 1.73; *s*, the standard deviation, = 0.078; *r*, the standard correlation coefficient, = 0.97.[17] Sigma for 4-ethyl = −0.16; σ for 4-methyl = −0.17; σ for 3-methyl and -ethyl = −0.07; σ for trimethyl = −0.31

The results are given in Table I and illustrated in Fig. 1. As can be noted, correlation of the dissociation constants with sigma is only moderately satisfactory—the 3,4,5-triethyl point falls on the line but the 3,4,5-trimethyl point falls above the line. At least we can say that no trend is established here where the points deviate further from the line as the groups become bulkier. Thus we arrive at the conclusion from our work and from the work summarized earlier that group influences are additive in predicting dissociation constants of acids having up to and including three adjacent ethyl groups. On the other hand, we have concluded previously[10] that in the Beckmann rearrangement, an electrophilic reaction,[15] group influences are not additive with three adjacent alkyl groups. A very definite trend was detected, *i.e.*, triethyl deviated more than trimethyl. This behavior may be general for all electrophilic reactions. Perhaps anions or molecules with free pairs of electrons which are necessary to solvate the transition complex of an electrophilic reaction are bulkier than the hydronium ions, protons, or Lewis acids necessary to stabilize the transition complexes of nucleophilic

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(15) Basing our definition on the Hammett equation, we define an electrophilic reaction as one with a significantly negative slope (rho), a nucleophilic reaction as one with a positive slope.

reactions. Thus, the former may be more sensitive to bulk effect of substituents. On the other hand, the explanation may be as simple as stating that the canonical forms with positive charges in the ring are more important in the transition complex hybrid of electrophilic reactions than the corresponding negative charges in nucleophilic reactions. If either or both of these explanations are true, they focus attention on the importance of solvation forces in attempts to study influences of groups remote from the reaction center.[10]

TABLE I

DISSOCIATION CONSTANTS OF SUBSTITUTED BENZOIC ACIDS[a]

Benzoic Acid	$K' \times 10^5$ (Uncorrected)	$K \times 10^5$ (Corrected) ($K' \times 1.20/1.86$)
Unsubstituted	1.86	1.20
3,5-$(CH_3)_2$	1.15	0.741
3,5-$(C_2H_5)_2$	0.851	0.588
3,4,5-$(CH_3)_3$	0.759	0.490
3,4,5-$(C_2H_5)_3$	0.589	0.380
4-Nitro	49.0	31.6

[a] In 57.6% aqueous ethanol at 25°.

EXPERIMENTAL

Materials. Baker and Adamson benzoic acid was twice recrystallized from water. The alkyl substituted benzoic acids were prepared by hypobromite oxidation of the corresponding ketones,[10] the melting points of the purified acids being as follows: 3,5-diethyl, 129–129.5°; 3,5-dimethyl, 171.5–172.5°; 3,4,5-trimethyl, 220.5–221.5°; 3,4,5-triethyl, 142–143°; 4-nitro, 242°. The water and ethanol each were refluxed and distilled, and the distillates stored under a nitrogen atmosphere.

The standard sodium hydroxide was prepared by dilution of 3.6 ml. of saturated sodium hydroxide solution with 330 ml. of carbonate-free water and 570 ml. of 95% ethanol. The solution was approximately 0.1*N* in 57.6% (by weight) of alcohol. It was tested daily for carbonate by adding 5 drops of 0.5*N* barium chloride solution to a 10-ml. aliquot.

Apparatus. Titrations were followed with a Leeds and Northrup *p*H meter, Model 7663-Al, using glass and calomel electrodes. The saturated potassium chloride bridge was made from 57.6% aqueous alcohol, and the glass electrode stored in aqueous alcohol of the same concentration. The *p*H meter was calibrated by means of the known *p*K of benzoic acid in 57.6% aqueous ethanol,[6] and the correction applied to all the other acids as shown in the procedure.

The titration system consisted of storage delivery bottles for water, ethanol, and sodium hydroxide solution, titration jar, and a nitrogen inlet, all in a closed system under about 2.5 lb./sq. in. pressure. The solution was stirred with a magnetic stirrer at a temperature maintained at 25° ± 0.5°.

Procedure. The amount of acid added was always sufficient to make the concentration of the acid one tenth that of the strength of the base.[16] The *p*H meter was checked by buffers at *p*H 7 and 4, and the base added to the 10 ml. buret under nitrogen pressure. After the acid was dissolved in 22 ml. of ethanol, 13 ml. of water was added to make the solution 57.6% aqueous ethanol. The jar was sealed with a rubber stopper containing electrodes, burette tip, and pressure line while the system was swept with nitrogen. The system was then maintained under about 2.5 lbs. of nitrogen pressure.

The *p*H of solution was recorded at 0.1-ml. intervals in the 40–60% neutralization range. Endpoints were also obtained to check the neutral equivalent of each acid. At two points on either side of the half-neutralization point and at the half-neutralization point itself, the five points averaging 0.1 ml. apart from each other, the *p*K was calculated from the formula

$$pK = pH - \log \frac{C_B + a_{H^+}}{C_A - a_{H^+}} + \frac{166\sqrt{\mu}}{1 + 1.65}$$

where C_B is concentration of base added, C_A is concentration of unneutralized acid, and a_{H^+} is the hydrogen ion activity. The formula was used in lieu of extrapolation of the acid dissociation constant to zero concentration.[13] The five values of *p*K were averaged, and the average value shown in Table I as K′ (uncorrected). As the value of *K* for benzoic acid in 57.6% aqueous alcohol is 1.2×10^{-5} as reported,[6] the correction factor, 1.20/1.86, was applied to all the other uncorrected dissociation constants. These values are given in the column for K (corrected). As a further check, the *p*K values were determined about a month after the initial values were obtained using new solutions and new electrodes. No difference in K was noted for any acid except *p*-nitrobenzoic acid. The new value was used in the table. Standard deviations and correlation coefficients were calculated by regular procedures.[17]

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DEPARTMENT OF CHEMISTRY
VANDERBILT UNIVERSITY
NASHVILLE, TENN.

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2-Ethyl-3-methylhexanamide

RICHARD E. STRUBE

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Two different melting points are reported in the literature for 2-ethyl-3-methylhexanamide. Volwiler and Tabern[1] found 97–98° while Maynert and Washburn[2] gave a melting point of 91–93°. This compound was also synthesized in these laboratories by the sequence of reactions formulated below. Although the "purified" end-product (VI) gave the correct analytical values it melted at 95–109°. Since 2-ethyl-3-methylhexanamide has two asymetric carbon atoms, it is likely that compound VI consisted of a mixture of racemates. The separation of the mixture into two racemic pairs was accomplished by chromatography on an aluminum oxide column. Two products were isolated, one melting at 89–90.5° and another at 123–124°. These melting points are uncorrected, and therefore, one may assume that the melting point of the lower melting product is in agreement with that reported by Maynert and Washburn.[2] The analytical

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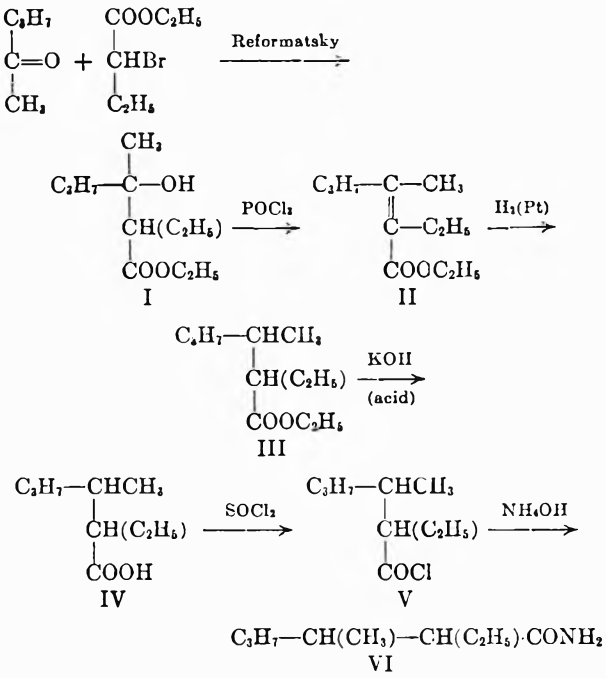

values of the product melting at 123–124° are in agreement with those calculated for 2-ethyl-3-methylhexanamide and, as expected, the infrared absorption curves of the two racemates are almost identical. The significant differences are in the intensities of the bands at 1160 and 1117 cm.$^{-1}$ The possibility of the existence of different crystal forms was excluded by the observation that crystallization of the molten compounds caused no change in melting points.

EXPERIMENTAL

Ethyl-2-ethyl-3-hydroxy-3-methylhexanoate (I). To 75.0 g. (1.15 g.-atoms) of zinc dust was added 20–30 ml. of a solution of 115.0 g. (1.34 moles) of *n*-propyl methyl ketone, 225.0 g. (1.15 moles) of ethyl-α-bromobutyrate in 150 ml. of dry benzene. The mixture was stirred and heated until the reaction started. The rest of the solution was introduced at such a rate that gentle refluxing occurred. After the solution was added, refluxing was continued for 45 min. The cooled reaction mixture was poured into 600 ml. of ice-cold 10% sulfuric acid with vigorous stirring. The acid layer was separated and the benzene solution washed twice with 100-ml. portions of ice-cold 15% sulfuric acid. The benzene solution was washed once with 25 ml. of cold 10% aqueous sodium carbonate, then with 25 ml. of cold 5% sulfuric acid, and finally with two 25-ml. portions of water. The benzene solution was dried with anhydrous magnesium sulfate, filtered and distilled, yield 184.5 g. (83%); b.p. 85–95° at 8 mm. This crude product was used in the next reaction.

Ethyl 2-ethyl-3-methyl-2-hexenoate (II). Compound I (184.5 g.) was dissolved in 600 ml. of benzene and 75 g. of phosphorus oxychloride was added. The mixture was heated on the steam bath for 3 hr. After cooling to room temperature the solution was extracted successively with an aqueous solution of sodium bicarbonate and water until neutral to litmus paper. After drying over anhydrous sodium sulfate, there was obtained 108 g. (64%) of compound II, b.p. 97–102° at 22 mm.

Ethyl 2-ethyl-3-methylhexanoate (III). Compound II (88.4 g.) was catalytically (platinum oxide) hydrogenated at an initial pressure of 50 lb./sq. inch. There was obtained 70.8 g. (80%) of compound III; b.p. 87–91° at 13–14 mm. [lit.[3] b.p. 197–198°].

2-Ethyl-3-methylhexanoic acid (IV). Compound III (70.8 g.) was hydrolyzed by refluxing under vigorous stirring with a solution of 55.0 g. of potassium hydroxide in 200 ml. of water for a period of 80 hr. After this time the ester layer had disappeared. The solution was acidified with hydrochloric acid (1:1) and extracted with ether. After drying over anhydrous magnesium sulfate there was obtained 51.0 g. (60%) of compound IV; b.p. 127–132° at 14 mm. (lit.[3] b.p. 230–232°).

2-Ethyl-3-methylhexanoyl chloride (V). Compound IV (51.0 g.) was added dropwise to 51 g. of thionyl chloride at 10–15°. After 1 hr. at room temperature the flask was heated for another hour at 50°. Then the excess of thionyl chloride was removed by distillation and the acid chloride distilled under reduced pressure; yield 53.0 g. (93%); b.p. 80–82° at 14 mm. (lit.[4] b.p. 87–89° at 25 mm.).

2-Ethyl-3-methylhexanamide (VI). Compound V (53.0 g.) was added under vigorous stirring to 300 ml. of cold concd. aqueous ammonia at such a rate that the temperature did not rise above 15°. After the addition stirring was continued for 1 hr. The precipitate formed was removed by filtration and dried *in vacuo;* yield 40.4 g. (87%). The product was recrystallized twice from dilute ethanol (100 ml. of ethanol and 150 ml. of water) and once from methylcyclohexane; yield 27.0 g. (60%); m.p. 95–109°.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.98; H, 12.14; N, 8.64.

The infrared absorption cruves supported the structure λ_{max}^{Nujol} in cm.$^{-1}$: 3180, 3350 (NH); 1655 (amide CO); 1635 sh (amide NH); other max. 1302, 1255, 1160, 1145, 1117 (sh).

Chromatography. Two grams of compound VI was chromatographed on 200 g. of aluminum oxide (Merck, acid washed) using a column of approximately 1 in. diameter. The elution was done as shown below. Most fractions had a wide melting range. Fractions 13–24 melted completely below 100°; fraction 15 had a sharp melting point of 89–90.5°. Fractions 40–49 started to melt above 115°. These fractions were combined and recrystallized from dilute ethanol giving a product melting sharply at 123–124°.

Fractions	Solvents	Wt., mg.	Size of Fractions, ml.
1–12	Methylene chloride–Skellysolve B (1:1)	193	100
13–24	Methylene chloride–Skellysolve B (3:1)	321	100
25–36	Methylene chloride	123	100
37–41	Methylene chloride and 1% acetone	134	250
42–46	Methylene chloride and 5% acetone	268	250
47–51	Methylene chloride and 10% acetone	441	250
52–56	Methylene chloride and 20% acetone	219	250

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.42; H, 11.77; N, 9.09.

The infrared absorption curves of the two racemates were almost identical, the significant differences were the intensities of the bands at 1160 and 1117 cm.$^{-1}$

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DEPARTMENT OF CHEMISTRY
THE UPJOHN COMPANY
KALAMAZOO, MICH.

Synthesis of Some *N*-Benzyl-*N*-alkyl-*N*-*n*-octylamines

P. J. APICE[1]

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A recent research program of this laboratory involved the preparation of some new tertiary amines from the intermediate *N*-benzyl-*N*-*n*-octylamine. In general, the intermediate *N*-benzyl-*N*-*n*-octylamine can be prepared *via* reduction of the corresponding Schiff base,[2] or by the reaction of benzylamine with an *n*-oxtyl halide, or vice versa. In this work the second method was employed. This method is similar to that used by King and Work[3] in preparing various secondary and tertiary benzylamines.

The scope of the project involved only the *n*-alkyl halides from one to seven carbon atoms. The *N*,*N*-di-*n*-octyl compound was isolated from the intermediate secondary amine when the latter was produced.

The elemental analyses and physical properties are given in Tables I and II. It is worthy to note confirmation of the atomic factor value for the methylene group (D line) for the series synthesized. Calculations from the observed molecular refractivities over the range of one to eight carbon atoms give an M_D value of 4.617, while the generally accepted value is 4.618.[4]

Several attempts to prepare the usual derivatives of the tertiary amines of this series have thus far been unsuccessful. This difficulty is probably due mainly to steric effects.

EXPERIMENTAL[5]

N-Benzyl-N-n-octylamine. This base was obtained as the main product by the following process: Benzylamine, 286 g. (2.67 moles), was mixed with *n*-octyl bromide, 257 g. (1.33 moles), in a large beaker and allowed to stand at room temperature. The reaction is midly exothermic, and after 45 min. benzylamine hydrobromide was deposited as a white slush. The mixture was heated on a boiling water bath for 1 hr., cooled, diluted with dry ether, and the benzylamine

TABLE I

ELEMENTAL ANALYSES

Alkyl	Formula	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
H—	$C_{14}H_{25}N$	68	82.12	83.23	11.49	11.59	6.39	6.13
CH_3—	$C_{15}H_{27}N$	39	82.34	82.99	11.66	11.63	6.00	5.92
C_2H_5—	$C_{17}H_{29}N$	73	82.53	83.01	11.81	11.78	5.66	5.78
n-C_3H_7—	$C_{18}H_{31}N$	61	82.69	83.00	11.95	11.97	5.36	5.19
n-C_4H_9—	$C_{19}H_{33}N$	64	82.84	83.23	12.07	12.18	5.09	5.12
n-C_5H_{11}—	$C_{20}H_{35}N$	59	82.97	83.47	12.19	12.25	4.84	4.80
n-C_6H_{13}—	$C_{21}H_{37}N$	64	83.10	82.81	12.29	12.42	4.61	4.50
n-C_7H_{15}—	$C_{22}H_{39}N$	66	83.20	83.31	12.39	12.45	4.41	4.21
n-C_8H_{17}—	$C_{23}H_{41}N$	—	83.31	83.53	12.46	12.46	4.23	4.11

TABLE II

PHYSICAL PROPERTIES

Alkyl	B.P.,/Mm.	Sp. Gr. $\frac{20}{20}$	n_D^{20}	Molecular Refractivity	
				Calcd.	Obs.
H—	159–161.5/10	0.8914	1.4945	71.54	71.70
CH_3—	150–151.5/9	0.8825	1.4909	76.50	76.57
C_2H_5—	155.5–157/9	0.8796	1.4886	81.12	81.16
n-C_3H_7—	167–169/11	0.8758	1.4857	85.73	85.66
n-C_4H_9—	166–169/8	0.8722	1.4850	90.28	90.43
n-C_5H_{11}—	178.5–180.5/9	0.8702	1.4835	94.97	95.09
n-C_6H_{13}—	185–187.5/8	0.8688	1.4823	99.59	99.65
n-C_7H_{15}—	195–197/8	0.8682	1.4818	104.21	104.23
n-C_8H_{17}—	211–212/9	0.8679	1.4815	108.82	108.89

(1) Present address: Plastics and Coal Chemicals Division, Allied Chemical Corporation, Technical Department, Edgewater, N. J.

(2) R. E. Lutz, *et al.*, *J. Org. Chem.*, 12, 760 (1947).

(3) H. King and T. S. Work, *J. Chem. Soc.*, 401 (1942).

(4) H. Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. *II*, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1751.

(5) All melting and boiling points are corrected.

hydrobromide collected. Recrystallization of the hydrobromide from ethanol gave a material, m.p. 222–223°.

Anal. Calcd. for $C_7H_{10}NBr$: Br, 42.49. Found: Br, 42.43 and 42.46.

The ethereal solution was shaken with 150 ml. of 10% aqueous sodium hydroxide solution, separated, and dried over potassium hydroxide. The ether was removed by vacuum, and fractionation of the main material through a Vigreux column under reduced pressure gave: Benzylamine, 21 g., b.p. 62–67°/8–9 mm.; *N*-benzyl-*N*-*n*-octylamine, 220 g., b.p. 140–175°/11–12 mm.; and *N*-benzyl-*N*,*N*-di-*n*-octylamine, 45 g., b.p. 191–213°/10 mm. Separate redistillations through the Vigreux column of the latter two cuts gave the desired products. (See Tables I and II for analyses and physical properties.)

General method for preparing the N-benzyl-N-alkyl-N-n-octylamines. *N*-Benzyl-*N*-*n*-octylamine (21.9 g., 0.1 mole), alkyl halide (0.1 mole), and potassium hydroxide (7.7 g.) were added to a suitable flask and refluxed for 5 hr. The product was then cooled, shaken with 50 ml. of 10% aqueous sodium hydroxide solution, and separated. Fractionation of the colorless oily material through a Vigreux column under reduced pressure gave essentially the desired tertiary amine. The main product collected was then redistilled through the Vigreux column to give the *N*-Benzyl-*N*-alkyl-*N*-*n*-octylamine. (See Tables I and II for analytical data and physical properties.)

Acknowledgment. The author wishes to express his thanks to Mr. Anthony Cristino of the Plastics Division, Allied Chemical Corporation, Technical Department, Edgewater, N. J., for the elemental analyses. Gratitude is also expressed to Prof. S. P. Gimelli, Fairleigh Dickinson University, for making the overall research program possible.

CHEMISTRY DEPARTMENT
FAIRLEIGH DICKINSON UNIVERSITY
TEANECK, N. J.

Improved Syntheses of β-Alanine

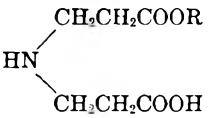
F. POPPELSDORF AND R. C. LEMON

Received May 12, 1960

One important group of β-alanine syntheses includes preparative procedures which involve the interaction at elevated temperatures and pressures of aqueous ammonia and acrylonitrile,[1] esters of acrylic acid,[2] or compounds RCH_2CH_2X which can yield acrylonitrile or acrylic acid by a simple, usually base-catalyzed, elimination reaction[3–6], $RCH_2CH_2X \rightarrow RH + CH_2 = CHX$ (X = CN or COOH). These reactions have generally been carried out between 125 and 250°. In each case, the β-alanine was directly isolated by precipitating it from the concentrated reaction products with a solvent in which it is sparingly soluble, *e.g.*, methanol. Where mentioned, the β-alanine thus obtained is claimed to be of high purity.

Preliminary investigations in this laboratory of syntheses of β-alanine by the interaction of aqueous ammonia and either ethyl or methyl acrylate[2] at 125 to 190°, or ethylene cyanohydrin[4] at 180 to 190°, showed, however, that quite impure β-alanine was invariably produced. In some instances, the product contained less than 70% of β-alanine. The prescribed isolation procedures[2,4] were followed in each case.

The impure products were found by titration to contain acidic and basic functions in almost equivalent amounts; moreover, the neutralization equivalents determined were only slightly greater than those calculated for β-alanine. Combined ammonia[7] (in the form of ammonium salts) was, however, present in appreciable quantities. No unsaturated compounds or tertiary amines were detected. These results, together with an analysis specific for the primary amino group,[8] indicated that the major impurity was probably the monoammonium salt of 3,3′-iminodipropionic acid (I).



I. R = NH_4
II. R = H

Pertinently, Ford[9] has pointed out that the monoammonium salt (I) and acid (II) are probable by-products in β-alanine syntheses of the type under discussion. Compounds I and II have solubilities similar to that of β-alanine in water and methanol,[9] the solvents employed for the isolation. Consequently, if these by-products are formed in large enough quantity they will crystallize with the β-alanine. Furthermore, the similarity of solubilities makes purification by fractional crystallization tedious and impractical.

A simple purification procedure for β-alanine made by syntheses based on an acrylate ester or ethylene cyanohydrin has now been found. Refluxing of either diisopropylamine or triethylamine with an aqueous solution of the crude β-alanine converted the impurities into methanol-soluble products but did not affect the β-alanine. Because β-alanine is sparingly soluble in methanol, the amine treatment followed by precipitation with methanol enabled the direct isolation of the amino-acid in a good degree of purity (95 to 98%). One crystallization of this product from water gave β-alanine in a purity of 99.9%.

(1) G. H. Carlson and C. N. Hotchkiss, U. S. Patent 2,377,401 (1945).
(2) S. H. Babcock, Jr., and B. R. Baker, U. S. Patent 2,376,334 (1945).
(3) P. M. Kirk, U. S. Patent 2,334,163 (1943).
(4) P. M. Kirk and J. H. Paden, U. S. Patent 2,364,538 (1944).
(5) J. H. Paden, U. S. Patent 2,414,389 (1947).
(6) P. M. Kirk, U. S. Patent 2,416,630 (1947).
(7) Determined by the method of K. G. Mizuch and A. Y. Savchenko [*Org. Chem. Ind. (U.S.S.R.)*, **7**, 24 (1940)].
(8) F. E. Critchfield and J. B. Johnson, *Anal. Chem.*, **29**, 1174 (1957).
(9) J. H. Ford, *J. Am. Chem. Soc.*, **67**, 876 (1945).

Prior separation of the crude β-alanine was found to be unnecessary because the amine treatment was equally satisfactory when performed on the concentrated ammonia–acrylate ester or concentrated ammonia–ethylene cyanohydrin reaction products.

The reaction conditions specified in the Experimental Section afforded optimum yields of β-alanine. First-pass yields approached 40%; however, the residues after removal of the β-alanine could be recycled with aqueous ammonia to give further quantities of the amino acid and over-all yields of about 85%.

EXPERIMENTAL

All melting points are uncorrected. β-Alanine purities were calculated from analyses for combined ammonia[7] and for the aliphatic primary amino group.[8]

Preparation of β-alanine from ethyl acrylate and aqueous ammonia. (a) Ethyl acrylate[10] (141.4 g., 153 cc., 1.415 moles), aqueous 28% ammonia (420 cc., 4.4 × 1.415 moles), water (830 cc.), and phenothiazine[11] (0.142 g.) were placed in a 3-l. stainless steel autoclave fitted with a rocking arrangement. The mixture was heated and rocked for 17 hr. at a pressure of 75 p.s.i.g. and an average temperature of 127°.

After being cooled, the reaction product was treated with charcoal (Norit A, 10.0 g.) and evaporated at reduced pressure at below 60° to a volume of 300 cc. Diisopropylamine (156 cc., 112 g.) and phenothiazine[11] (0.1 g.) were added and the mixture refluxed with stirring for 1.5 hr. At the end of this time the amine was distilled as quickly as possible at atmospheric pressure and the residue diluted with distilled water (50 cc.). The solution was treated with charcoal (Norit A, 10.0 g.) and most of the water evaporated therefrom under reduced pressure. Anhydrous methanol (150 cc.) was added to the final sirup and the mixture stirred at room temperature until precipitation of solid was complete (this took about 15 hr.). The solid was collected, washed twice with anhydrous methanol (30 to 35 cc. portions), and dried at 60° under reduced pressure. β-Alanine (43 to 48 g., 34 to 38% yield) was thus secured as colorless crystals, m.p. 194–196° dec.; mixed m.p. with authentic β-alanine, 196–198° dec.; ammonium salts were absent[7] and the purity varied between 96 and 98%.

This slightly impure product was dissolved in a hot aqueous solution previously prepared by saturating water at room temperature with β-alanine (material having a purity of 96 to 98% was suitable). The solution was then cooled to room temperature with gentle stirring and kept at this temperature for 3 hr. to give well-formed crystals of β-alanine (38 to 43 g., 30 to 34% yield), m.p. 199–201° dec.; the purity was 99.9%.

(b) The same quantities of reactants as were employed for the foregoing preparation were heated 8 hr. at 190° under an average pressure of 280 p.s.i.g.

After being cooled, the mixture was treated with charcoal (Norit A, 10.0 g.) and evaporated at reduced pressure at below 60° to a volume of 300 cc. The solution was treated once more with charcoal (Norit A, 10.0 g.) then evaporated to a sirup under reduced pressure. Anhydrous methanol (200 cc.) was added and the mixture stirred at room temperature until precipitation of solid was complete. The precipitate was collected, washed twice with methanol (50-cc. portions), and dried at 60° under reduced pressure. The product consisted of colorless crystals (58.5 g.), m.p. 133–147°, which contained 1.68% of combined ammonia and 75% of β-alanine.

This crude β-alanine (15.0 g.) was dissolved in distilled water (100 cc.). Diisopropylamine (56 cc., 40.2 g.) was added and the mixture refluxed with stirring for 1.5 hr. The excess of amine was distilled under reduced pressure, the residue dissolved in water (20 cc.), and the solution treated with charcoal (3.5 g.). Evaporation of most of the water from the filtrate under reduced pressure left a nearly colorless sirup. Anhydrous methanol (50 cc.) was added and the mixture stirred at room temperature for 16 hr. The precipitate was collected, washed twice with methanol (10 cc. portions), and dried at 60° under reduced pressure to give β-alanine (8.8 g.), m.p. 196–198° dec., which had a purity of 97%.

Preparation of β-alanine from ethylene cyanohydrin and aqueous ammonia. Ethylene cyanohydrin (68.0 cc., 71.1 g., 1 mole), aqueous 28% ammonia (345.0 cc., 5.0 moles), and water (501 cc.) were introduced into a 3-l. stainless steel autoclave equipped with a rocking device. The mixture was heated and rocked for 8 hr. at 190° under an average pressure of 285 p.s.i.g.

After being cooled, the reaction product was treated with charcoal (10.0 g.) and evaporated to low bulk at reduced pressure at below 60°. The residual sirup was stirred with anhydrous methanol (106 cc.) for 16 hr. at room temperature. The precipitated solid was collected, washed twice with anhydrous methanol (20-cc. portions), and dried at 60° under reduced pressure. A faintly pink solid (45.8 g.), m.p. 114–144°, was obtained; it contained 1.96% of combined ammonia and 78.1% of β-alanine.

The foregoing crude β-alanine (15.0 g.) was treated with diisopropylamine (56 cc., 40.2 g.) as described in the preceding experiment to give β-alanine (9.0 g.), m.p. 192–195° dec., in a purity of 95%.

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UNION CARBIDE CHEMICALS COMPANY
SOUTH CHARLESTON, W. VA.

(10) An equivalent quantity of methyl acrylate gave substantially the same yield of β-alanine.

(11) To inhibit polymerization.

A Simple Method for the Preparation of Oxindoleacetic and Propionic Acids from the Parent Indoles

WILLIAM B. LAWSON AND BERNHARD WITKOP

Received May 16, 1960

The known methods for the conversion of indoles into oxindoles involving oxidation with peracetic[1] or persulfuric[2] acids or hydrolysis of parent disulfides[3] leave much to be desired from a preparative point of view.

The smooth hydrogenolysis of the lactone III of 5-bromodioxindole-3-propionic acid, obtained by the action of *N*-bromosuccinimide on indole-3-propionic acid (II), to oxindole-3-propionic acid (V),[4] has now been

(1) B. Witkop, *Ann.*, **558**, 98 (1947).

(2) C. E. Dalgliesh and W. Kelley, *J. Chem. Soc.*, 3726 (1958).

(3) T. Wieland *et al.*, *Ann.*, **587**, 146 (1954); **592**, 69 (1955); K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 3191 (1957).

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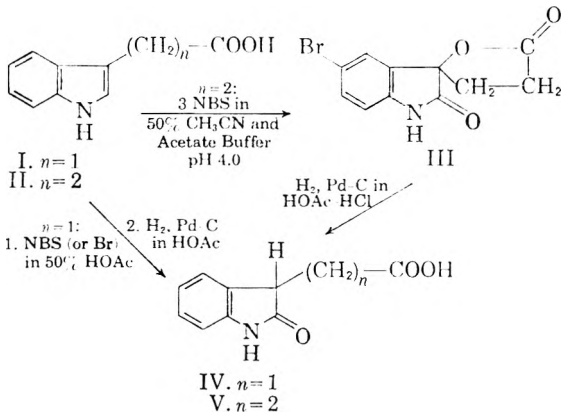

adapted to a direct conversion of indoles to oxindoles without isolation of intermediate (bromo)-dioxindoles. The rapid reaction of *N*-bromosuccinimide with indoles[4,5,6] from a preparative point of view is difficult to arrest at the oxindole stage under the conditions described. Further oxidation at the 3-position and aromatic substitution at the 5-position are invariably observed. The present one-step procedure uses an excess of brominating agent followed by simultaneous hydrogenolytic removal of the benzylic oxygen function of the 3-position and the aromatic bromine substituent in the 5-position of the benzene ring.

The preparation of oxindole-3-propionic acid (V) and of oxindole-3-acetic acid[7] (IV) previously prepared[8,9] only by multistep procedures, proceeds in minimal yields of 50% and better.

EXPERIMENTAL

Oxindole-3-propionic acid (V). To an ice cold solution of 3.0 g. (15.9 mmoles) of indole-3-propionic acid (II) in 100 ml. of 50% acetic acid, 5.65 g. (31.8 mmoles) of *N*-bromosuccinimide was added with constant swirling over a period of 5 min. After 15 min. at room temperature 1 g. of 10% palladium-on-charcoal was added, and the mixture was shaken in a hydrogen atmosphere for 18 hr. The filtered solution was evaporated. Crystallization of the residue from water, after treatment with charcoal, gave 1.60 g. (49%) of oxindole-3-propionic acid, m.p. 165–167° (reported[8] m.p. 169–170°), identical with an authentic sample prepared by hydrogenolysis of the crystalline lactone III.[5]

Oxindole-3-acetic acid (IV). To an ice cold solution of 1.0 g. (5.72 mmoles) of indole-3-acetic acid (I) in 50 ml. of 50% acetic acid was added 4.85 ml. of acetic acid containing 1.83 g. (11.4 mmoles) of bromine. After 1 hr. at room temperature, 500 mg. of 10% palladium-on-charcoal was added, and the mixture was shaken in an atmosphere of hydrogen for 17 hr. The solution was filtered, evaporated to dryness, and 15 ml. of water was added. The mixture was extracted three times with 25-ml. portions of ethyl acetate, and the dried (sodium sulfate) extract was evaporated to dryness. Crystallization of the residue from ether–petroleum ether (b.p. 50–60°) gave 686 mg. (63%) of oxindole-3-acetic acid (IV), m.p. 100–140° (this material probably contains some solvent; *cf.* ref. 9). Recrystallization from acetone-benzene, followed by drying for 45 min. *in vacuo* at 55° gave 536 mg. (49%) of colorless crystals, m.p. 140–142° (reported m.p. 147°, softening at 142°). The compound was further characterized by its smooth acid-catalyzed conversion to 3,4-dihydroquinolone-4-carboxylic acid, m.p. 210–214°.[9]

National Institute of Arthritis
and Metabolic Diseases
National Institutes of Health
Public Health Service
U. S. Department of Health,
Education and Welfare
Bethesda 14, Md.

(5) A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, 80, 4747 (1958); A. Patchornik, W. B. Lawson, E. Gross, and B. Witkop, *J. Am. Chem. Soc.*, 82, 5923 (1960).

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Some 6-Bis(2-chloroethyl)aminoalkyladenines[1]

Hsi Hu Lin and Charles C. Price

Received June 2, 1960

As it is a widely accepted hypothesis that nitrogen mustard gas [HN-2, bis(2-chloroethyl)methylamine] exerts its carcinostatic (and mutagenic) effects through attack on deoxyribonucleic acid (DNA), it seemed to us of some interest to prepare a variety of HN-2 analogs in which the methyl group was modified by incorporation of purine rings analogous to those naturally incorporated into DNA. To preserve the aliphatic character of the nitrogen mustard group, we did not wish to attach the mustard nitrogen directly to the purine ring system.

We report herein the preparation of two adenine nitrogen mustards, with a mustard group attached to the 6-amino group of adenine through an ethylene and a trimethylene chain. The compounds were extremely hygroscopic and difficult to purify. Against a number of mouse tumors, they showed moderate mustard-like activity. Details of the biological date will be reported elsewhere.

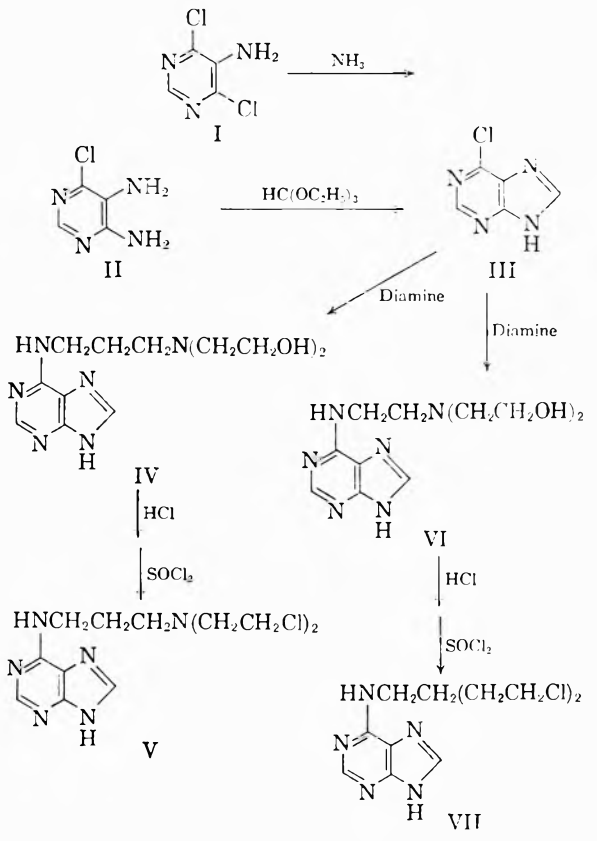
Incidental to the work, a convenient preparation of 4,5-diamino-6-chloropyrimidine has been worked out involving amination of 4,6-dichloro-5-aminopyrimidine.

EXPERIMENTAL

4,5-Diamino-6-chloropyrimidine (II). 4,6-Dichloro-5-aminopyrimidine (5 g., Cyclo Lab., Los Angeles) and 100 ml. of ethanolic ammonia were heated at 150° in a steel bomb for 3 hr. The mixture was evaporated to dryness, and the

(1) Supported in part by U. S. P. H. S. Grant No. CY-2714.

REACTION SCHEME



residue recrystallized from water to give 3.74 g. of light tan needles, m.p. 236–238°, (lit.,[2] m.p. 252°).

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.23; H, 3.48; N, 38.76; Cl, 24.53. Found: C, 33.20; H, 3.69; N, 38.62; Cl, 24.26.

6-{3-[Bis(2-hydroxyethyl)amino]propylamino}purine monohydrochloride (IV). 6-Chloropurine (7.73 g., prepared from II[3]) and 3-[bis(2-hydroxyethyl)amino]propylamine (8.10 g.) were dissolved in 120 ml. of 2-ethoxyethanol. The solution was refluxed with constant stirring for 5 hr. A light greenish solid precipitated upon cooling in a refrigerator. The solid removed by filtration was washed with chloroform and dried; yield, 7.0 g., m.p. 194–199°. The filtrate was distilled under reduced pressure to dryness and then extracted with chloroform to remove the unchanged chloropurine and diamine. Absolute ethanol (30 ml.) and chloroform (80 ml.) were added to the washed residue with constant stirring. The light brown powder which separated was filtered and dried; yield, 1.4 g. Another 2.2 g. of crude solid was recovered from the filtrate by repeating the same treatment. The combined crude yield was 10.6 g. (67%). A small portion was recrystallized from a mixture of ethanol and benzene, m.p. 203–205°.

Anal. Calcd. for $C_{12}H_{20}N_6O_2 \cdot HCl$: C, 45.49; H, 6.68; N, 26.53; Cl, 11.19. Found: C, 45.25; H, 6.92; N, 26.70; Cl, 11.07.

Ultraviolet absorption: 0.1*N* hydrochloric acid, λ_{max} 274.5 mμ, ε 16.8 × 10³; 0.1*N* sodium hydroxide, λ_{max} 273 mμ, ε 30.1 × 10³; ethanol, λ_{max} 268 mμ, ε 17.7 × 10³.

6-{3-[Bis(2-chloroethyl)amino]propylamino}-purine (V). Hydrogen chloride was passed through a suspension of 4 g. of IV in 150 ml. of absolute ethanol excluding moisture. The sticky mass which formed was stirred constantly to ensure contact with the gas. The mixture was distilled to dryness under reduced pressure. The viscous brown residue was refluxed in 150 ml. of thionyl chloride for 1 hr. Thionyl chloride was removed by distillation under reduced pressure. The brown residue was refluxed in 100 ml. of ethanol until all the solid went into solution. Activated charcoal was added to the solution and it was refluxed for 10 min. and filtered. Petroleum ether (b.p. 30–60°) was added slowly to the filtrate until slightly cloudy. Amber crystals separated upon cooling. The crystals were filtered, washed with petroleum ether and dried in vacuum; yield 1.56 g.; m.p. 100–112°. Another 1.8 g. of crude product was collected by adding an excess of petroleum ether to the filtrate. The combined yield was 3.36 g. (62.5%). A small sample was purified by dissolving in ethanol and reprecipitating with petroleum ether. After drying at 27° (3 mm.) it had an analysis corresponding to a dihydrate.

Anal. Calcd. for $C_{12}H_{18}N_6Cl_2 \cdot 2HCl \cdot 2H_2O$: C, 33.82; H, 5.68; N, 19.72; Cl, 33.28. Found: C, 33.68; H, 5.48; N, 20.19; Cl, 33.15. After further drying at 78° (3 mm.), it lost water and some hydrogen chloride.

Anal. Calcd. for $C_{12}H_{18}N_6Cl_2 \cdot 1.5HCl \cdot H_2O$: C, 36.96; H, 5.56; N, 21.55; Cl, 31.82. Ionic Cl, 13.64. Found: C, 36.78; H, 5.31; N, 21.72; Cl, 31.19. Ionic Cl, 15.40 (determined by conductometric titration).

Ultraviolet absorption: ethanol, λ_{max} 267 mμ, ε 14.4 × 10³.

6-{2-[Bis(2-hydroxyethyl)amino]ethylamino}purine hydrochloride (VI). 6-Chloropurine (2.15 g.) and 2-bis(2-hydroxyethyl)aminoethylamine (2.0 g.) were dissolved in 50 ml. of 2-ethoxyethanol and refluxed for 4 hr. The solution was boiled with activated charcoal and then filtered and distilled to dryness under reduced pressure. To the viscous residue, 15 ml. of absolute ethanol and 15 ml. of ether were added successively. On scratching, the residue solidified, was filtered and dried; yield, 2.1 g. Another 0.4 g. of solid crystallized from the filtrate upon standing overnight. The combined yield was 2.5 g. (62%), m.p. 157–162°. The crude product was recrystallized twice from 2-propanol to give light tan crystals, m.p. 163–165°.

Anal. Calcd. for $C_{11}H_{18}N_6O_2 \cdot HCl \cdot H_2O$: C, 41.18; H, 6.60; N, 26.20. Found: C, 41.45; H, 6.53; N, 26.82.

Ultraviolet Absorption: 0.1*N* hydrochloric acid, λ_{max} 274.5 mμ, ε 17.8 × 10³; 0.1*N* sodium hydroxide, λ_{max} 273 mμ, ε 27.6 × 10³; ethanol, λ_{max} 268 mμ, ε 16.3 × 10³.

6-{2-[Bis(2-chloroethyl)amino]ethylamino}purine (VII). Hydrogen chloride gas was passed through a suspension of 1.8 g. of VI in 60 ml. absolute ethanol, excluding moisture. The sticky mass formed was stirred constantly to ensure contact with the gas. The mixture was distilled to dryness under reduced pressure. The viscous brown residue was refluxed in 65 ml. of thionyl chloride for 1 hr. and then kept at room temperature overnight. The excess thionyl chloride was removed by distillation under reduced pressure. The brown residue was refluxed in 50 ml. of ethanol until all the solid dissolved. Upon cooling to room temperature, 400 ml. of anhydrous ether was added to the solution. The white solid which precipitated was filtered, washed with ether, and dried (30°, 3 mm.); yield, 1.63 g. (77%); m.p. 103–108°.

Anal. Calcd. for $C_{11}H_{16}N_6Cl_2 \cdot 1.5\ HCl \cdot 1.5H_2O$: C, 34.32; H, 5.37; N, 21.84; Cl, 32.24. Found: C, 34.12, 34.49; H, 5.25, 5.02; N, 21.90, 21.99; Cl, 32.60, 32.88. Upon further drying at 78° (3 mm.) it lost some water.

Anal. Calcd. for $C_{11}H_{16}N_6Cl_2 \cdot 1.5HCl \cdot H_2O$: C, 35.14; H, 5.23; N, 22.36; Cl, 33.01, Ionic Cl, 14.15. Found: C, 35.13, 35.06; H, 5.09, 5.05; N, 22.34, 22.41; Cl, 33.58, Cl, 33.58, 33.39; Ionic Cl, 15.95.

Ultraviolet absorption: ethanol, λ_{max} 266 mμ, ε 13.0 × 10³.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

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(3) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

Some 9-Bis(2-chloroethyl)aminoalkylpurines[1]

HSI HU LIN AND CHARLES C. PRICE

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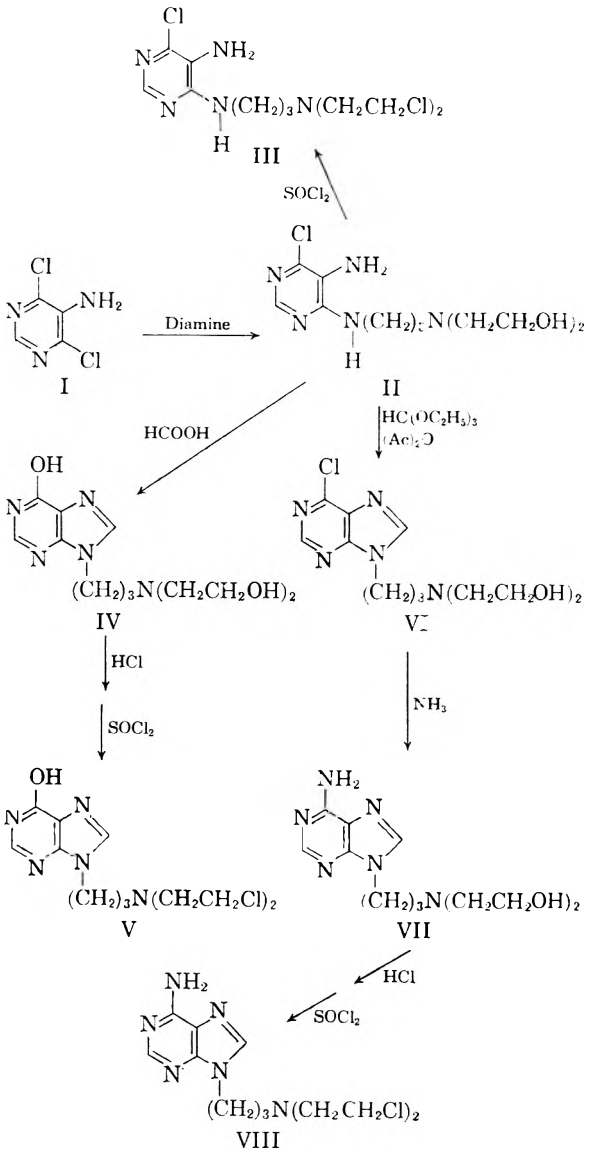
The purine mustard derivatives reported herein differ from those in the preceding paper in that the alkyl mustard side chain is attached in the 9-position, that normally involved in coupling with ribose or 2-deoxyribose in forming RNA or DNA.

The hypoxanthine derivative (V) has shown an interesting spectrum of activity against a number of experimental tumors in mice and will be given more extensive antitumor testing.

REACTION SCHEME



(1) Supported in part by U. S. P. H. S. Grant No. CY-2714.

EXPERIMENTAL

4-{3-[Bis(2-hydroxyethyl)amino]propylamino}-5-amino-6-chloropyrimidine (II). A mixture of 9.84 g. of 4,6-dichloro-5-aminopyrimidine and 19.44 g. of 3-[bis(2-hydroxyethyl)-amino propylamine in 130 ml. of water was refluxed for 5 hr. The aqueous solution was extracted with chloroform continuously for 20 hr. The chloroform extract was distilled to dryness under reduced pressure. The viscous residue solidified upon scratching the surface of the flask with a spatula. The crude solid was recrystallized from ethyl acetate to give 16 g. (92%) of yellowish white needles, m.p. 116–117°. This was recrystallized again from ethyl acetate to give colorless needles, m.p. 116–117°.

Anal. Calcd. for $C_{11}H_{20}N_5ClO_2$: C, 45.59; H, 6.95; N, 24.17; Cl, 12.24. Found: C, 45.61; H, 7.10; N, 24.65; Cl, 12.57.

Ultraviolet absorption: 0.1*N* sodium hydroxide, λ_{max} 263 mμ, ε 10.1 × 10³; λ_{max} 289 mμ, ε 9.9 × 10³; ethanol, λ_{max} 267.5 mμ, ε 12.2 × 10³; λ_{max} 294 mμ, ε 13.0 × 10³.

4-{3-[Bis(2-chloroethyl)amino]propylamino}-5-amino-6-chloropyrimidine hydrochloride (III). To a solution of 0.3 g. of II in 8.0 ml. of chloroform 10 ml. of thionyl chloride was added slowly. A yellow solid precipitated instantly. The mixture was refluxed excluding moisture for 1 hr. and was kept overnight at room temperature. The chloroform and the excess thionyl chloride were removed by distilling under reduced pressure. To the yellowish brown residue 15 ml. of absolute ethanol was added. The mixture was refluxed until all the residue went into solution. The solution, after being cooled to room temperature, was filtered. To the filtrate 80 ml. of anhydrous ether was added. A large amount of greenish yellow granular solid separated; after the solid settled to the bottom of the flask, the liquid was decanted. The residue was washed three times with anhydrous ether by decantation. The precipitate was filtered and quickly transferred into a drying apparatus and dried at room temperature (3 mm.) for 10 hr.; yield, 0.26 g. (70%); m.p. 54–65°.

A portion of the product was dried for 4 hr. at 56° (1.5 mm.).

Anal. Calcd. for $C_{11}H_{18}N_5Cl_3 \cdot HCl$: C, 36.38; H, 5.27; N, 19.29; Cl, 39.07. Found: C, 36.59; H, 5.59; N, 19.36; Cl, 36.40. Ionic Cl Calcd., 9.76. Ionic Cl found, 11.12 (determined by conductometric titration).

Ultraviolet absorption: ethanol, λ_{max} 295 mμ, ε 6.5 × 10³; λ_{max} 263 mμ, ε 6.2 × 10³.

9-{3-[Bis(2-hydroxyethyl)amino]propyl}-hypoxanthine (IV). A solution of 3.5 g. of II dissolved in 200 ml. of formic acid (98–100%) was refluxed for 6 hr. The formic acid was removed by distillation under reduced pressure. The brown viscous residue was heated on a steam bath for another hour under reduced pressure. To the viscous residue, 10 ml. of concd. ammonium hydroxide was added. The mixture was heated gently until all the viscous residue went into solution. To the solution, 150 ml. of absolute ethanol was added. The precipitate of ammonium formate and ammonium chloride was filtered. Light tan prism-like crystals precipitated upon leaving the filtrate in the refrigerator overnight; yield, 2.8 g. (80%); m.p. 165–170°.

The crude product was recrystallized from 95% ethanol, m.p. 171–172°. *Anal.* Calcd. for $C_{12}H_{19}N_5O_3 \cdot 2H_2O$: C, 45.41; H, 7.30; N, 22.08. Found: C, 45.42; H, 6.65; N, 22.23.

Ultraviolet absorption: 0.1*N* hydrochloric acid, λ_{max} 249 mμ, ε 12.1 × 10³; 0.1*N* sodium hydroxide, λ_{max} 255 mμ, ε 20.6 × 10³; ethanol, λ_{max} 250 mμ, ε 9.8 × 10³.

9-{3-[Bis(2-chloroethyl)amino]propyl}-hypoxanthine dihydrochloride (V). Hydrogen chloride gas was passed through a suspension of 1.8 g. of IV in 40 ml. of absolute ethanol for 5 min. The hydrochloride of the 9-substituted hypoxanthine became a sticky mass on standing in the hot ethanolic solution. The ethanol was removed by distillation under reduced pressure. To the brown viscous residue, 40 ml. of thionyl chloride was added and the mixture was refluxed for 40 min.

The excess thionyl chloride was removed by distillation under reduced pressure. To the residue, 50 ml. of absolute ethanol was added and the mixture was refluxed until all the residue went into solution. The solution, after being cooled to room temperature, was filtered and anhydrous ether was added dropwise until it became slightly cloudy. The cloudy solution was kept in the refrigerator overnight. Light yellow needles separated and were filtered and dried at room temperature (28°, 3 mm.) for 10 hr.; yield, 1.8 g. (72.6%); m.p. 264–266° (darkening at 183°). For microanalysis, the compound was dried at 78° (3 mm.) for 3 hr.

Anal. Calcd. for $C_{12}H_{17}N_6Cl_2O \cdot 2HCl \cdot C_2H_5OH$: C, 38.46; H, 5.76; N, 16.02; Cl, 32.44; Ionic Cl, 16.22. Found: C, 38.64; H, 5.80; N, 16.51; Cl, 31.69, 32.32; Ionic Cl, 16.48 (determined by conductometric titration).

Ultraviolet absorption: ethanol, λ_{max} 251 mμ, ϵ 11.4 × 10^3.

9-{3-[Bis(2-hydroxyethyl)amino]propyl}-6-chloropurine (VI). *Method A.* A solution of 10.2 g. of II in 50 ml. of diethoxymethyl acetate was boiled under reflux for 5 hr. The dark brown solution was distilled to dryness under reduced pressure. In order to remove the diethoxymethyl acetate completely, the viscous residue was vacuum dried at room temperature (0.5 mm.) for 2 hr. The brown viscous material, 9-{3-[bis(2-hydroxyethyl)amino]propyl}-6-chloropurine monoacetate, weighed 14 g. The residue was dissolved in 30 ml. of cold water. The solution was made alkaline (*p*H 11) with concd. ammonium hydroxide and extracted with three 200-ml. portions of chloroform. The chloroform extract, after being dried over anhydrous magnesium sulfate, was distilled to dryness under reduced pressure. The brown residue was further dried at room temperature (0.5 mm.) for 2 hr.; yield, 8.5 g. (84%).

Ultraviolet absorption: 0.1*N* hydrochloric acid, λ_{max} 263 mμ, ϵ 8.1 × 10^3; ethanol, λ_{max} 264 mμ, ϵ 6.5 × 10^3.

Method B. A solution of 1.1 g. of II in a mixture of 25 ml. of ethyl orthoformate and 25 ml. of acetic anhydride was refluxed for 2 hr. and then distilled to dryness under reduced pressure. The brown viscous residue was dried at room temperature (0.5 mm.) for 2 hr. in order to ensure the complete removal of acetic anhydride and ethyl orthoformate. The residue was dissolved in 15 ml. of water. The aqueous solution was made alkaline with concd. ammonium hydroxide. The basic solution was then extracted with three 50-ml. portions of chloroform. The chloroform solution, after being dried over anhydrous magnesium sulfate, was distilled to dryness under reduced pressure. The viscous residue was dried at room temperature (0.5 mm.) for 2 hr.; yield, 0.6 g. (53%).

Ultraviolet absorption: 0.1*N* hydrochloric acid; λ_{max} 263 mμ, ϵ 7.8 × 10^3; ethanol, λ_{max} 265 mμ, ϵ 6.0 × 10^3.

9-{3-[Bis(2-hydroxyethyl)amino]propyl}adenine (VII). A mixture of 3.0 g. of VI and 35 ml. of ammonium hydroxide saturated with ammonia gas at 3° was sealed in an autoclave and heated at 135° for 6 hr. The autoclave was cooled to room temperature overnight. The brown solution was evaporated to dryness on a steam bath. To the residue, 40 ml. of 2-propanol was added. The mixture stood in the open air for 2 days. The viscous residue solidified as a grayish granular solid, and some white crystals of 9-substituted adenine crystallized on the wall of the flask. Twenty milliliters more of 2-propanol was added to the mixture. The solid and crystals were collected by filtration, washed with solvent and dried; yield, 2.1 g. (67%); m.p. 166–171°. The crude solid was recrystallized from 2-propanol and water (95:5), to give white solid; m.p. 172–175°; yield, 1.9 g. (61%).

Anal. Calcd. for $C_{12}H_{20}N_6O_2 \cdot 2H_2O$: C, 45.56; H, 7.65; N, 26.57. Found: C, 45.35; H, 7.45; N, 26.60.

Ultraviolet absorption: 0.1*N* hydrochloric acid, λ_{max} 260 mμ, ϵ 14.2 × 10^3; 0.1*N* sodium hydroxide, λ_{max} 263 mμ, ϵ 26.9 × 10^3; ethanol, λ_{max} 261 mμ, ϵ 13.3 × 10^3.

9-{3-[Bis(2-chloroethyl)amino]propyl}adenine dihydrochloride (VIII). Hydrogen chloride gas was passed for a few minutes into a suspension of 0.5 g. of well pulverized 9-{3-[bis(2-hydroxyethyl)amino]propyl}adenine (0.5 g.) of VII in 20 ml. of absolute ethanol. Most of the adenine hydrochloride became a viscous mass on standing in the hot ethanol solution. The mixture was distilled to dryness under reduced pressure, 25 ml. of thionyl chloride was added to the viscous residue, and the mixture was refluxed for 0.5 hr. The excess thionyl chloride was removed by distillation under reduced pressure. The viscous residue was protected from moisture and refluxed in 60 ml. of absolute ethanol for 10 min. The undissolved brown solid was removed and the filtrate was kept in the refrigerator overnight. Orange crystals separated, m.p. 243–246°; yield, 0.35 g. (50%).

Benzene (5 ml.) was added to the filtrate. The solution was concentrated by distillation to half its volume and kept in the refrigerator overnight. More crystals separated; yield, 0.08 g.; m.p. 244–247°. The combined yield was 0.43 g. (61%). A portion of the product was further dried at room temperature (3 mm.) for 2 hr.

Anal. Calcd. for $C_{12}H_{18}N_6Cl_2 \cdot 3HCl \cdot H_2O$: C, 32.41; H, 5.21; N, 18.90; Cl, 39.87; Ionic Cl, 23.92. Found: C, 32.64, 32.52; H, 4.78, 4.90; N, 19.14, 19.24; Cl, 39.22, 39.08; Ionic Cl, 24.83 (determined by conductometric titration). After further drying at 56° (3 mm.) for 2 hr., it lost the molecule of water.

Anal. Calcd. for $C_{12}H_{18}N_6Cl_2 \cdot 3HCl$: C, 33.78; H, 4.96; N, 19.70; Cl, 41.56. Found: C, 34.29, 34.03; H, 5.05, 4.93; N, 19.74, 19.57; Cl, 37.32, 37.06.

The product was then dried at 78° (3 mm.) for 2 hr., and it lost a molecule of hydrogen chloride.

Anal. Calcd. for $C_{12}H_{18}N_6Cl_2 \cdot 2HCl$: C, 36.94; H, 5.17; N, 21.54; Cl, 36.35. Found: C, 36.74, 36.50; H, 5.06, 5.26; N, 21.88, 21.72; Cl, 35.15, 35.33.

Ultraviolet absorption: ethanol, λ_{max} 260 mμ, ϵ 14.8 × 10^3.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

Alkaloids of Tobacco Smoke. III. Methyl and Ethyl 3-Pyridyl Ketone as Constituents of Burley Tobacco Cigarette Smoke[1]

LOUIS D. QUIN, BETSY S. MENEFEE, AND NICHOLAS A. PAPPAS

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As we have concluded our work on the identification of the alkaloids of Burley tobacco smoke, we wish to report some results obtained since the appearance of the preceding paper[2] on this subject.

It has been found that previously unidentified Fractions 4 and 6 correspond to methyl 3-pyridyl ketone and ethyl 3-pyridyl ketone, respectively. A tentative identification was accomplished by comparative gas chromatography on two different columns of the isolated fractions and the known ketones. Confirmatory identification was obtained by comparative paper chromatography in two solvent systems of their 2,4-dinitrophenylhydrazones. The data are recorded in Table I. This marks the first identification of the methyl ketone

(1) Presented at the Organic Section of the Southeastern Regional, A. C. S. Meeting, Richmond, Virginia, November 6, 1959.

(2) L. D. Quin, *J. Org. Chem.*, 24, 914 (1959).

in tobacco smoke; the ethyl ketone has been reported previously.[3,4]

A determination of the amount of methyl 3-pyridyl ketone in the smoke condensate was made by gas chromatography. By a comparison of peak areas from known amounts of the ketone and the area on the alkaloid extract chromatogram, a value of 8 micrograms per cigarette smoked was obtained. The complexity of this chromatogram and the small amount of compound involved reduced the accuracy of the analysis; the figure quoted is the average of two complete determinations giving 6 and 9 micrograms per cigarette.

The amount of ethyl 3-pyridyl ketone was so small that a peak of measurable area could not be obtained for it. A very rough value was obtained by finding the amount of methyl 3-pyridyl ketone which gave visually the same slight inflection as noted on the chromatogram of the alkaloid extract for the ethyl derivative. This value was 1 microgram per cigarette.

The efficiency of the isolation and chromatographic procedures was evaluated in two ways. First, a synthetic mixture of nicotine and methyl 3-pyridyl ketone of appropriate relative amounts was placed through the entire extraction scheme used in the smoke analysis. The recovery of the ketone charged, as determined by gas chromatography, was 98%. In the second evaluation, known amounts of each ketone were added to a Burley smoke preparation immediately prior to the extraction procedures. Under these more realistic conditions, recoveries of charged methyl and ethyl 3-pyridyl ketone were 55% and 72%, respectively. It is thus concluded that the values reported for the content of the two ketones in the Burley smoke are of the right order of magnitude

Since completion of the above work, we have examined another lot of Burley tobacco cigarettes from a different source. We find no gas chromatographic evidence for either ketone in the smoke of these cigarettes. Apparently, the growth and history of the tobacco prior to smoking is of much importance in determining the concentration, or even the presence, of these ketones in the smoke.

EXPERIMENTAL

Isolation of Fractions 4 and 6. Humidified Burley tobacco cigarettes, 7.0 cm. in length, were smoked, and an alkaloid extract prepared from the smoke, in exactly the manner described previously.[2] A constant-time automatic smoking machine was used. Several 50–70 μl. aliquots of the extract were then processed on a 2 m. by 6 mm. column of polypropylene glycol (mol. wt. 1025) on Firebrick, 1:4, at 152° and a helium flow of 67 ml. per min. Those fractions corresponding to 4 and 6 of the original chromatogram[2] were collected as eluted. Between each sample injection, the column was flushed thoroughly to ensure removal of tailings from the preceding sample. The collected fractions were rinsed from the traps with ethanol and then benzene to a total volume of 100–150 μl.; this solution was then concentrated to about 50 μl., if gas chromatography were to be performed, or used directly for 2,4-dinitrophenylhydrazone formation.

Identification by gas chromatography. Data for the gas chromatography of known samples of methyl and ethyl 3-pyridyl ketone and of Fractions 4 and 6 are provided in Table I.

TABLE I

CHROMATOGRAPHIC DATA FOR THE IDENTIFICATION OF METHYL AND ETHYL 3-PYRIDYL KETONE

	Retention Min.		$R_f \times 100$ Values of Dinitrophenylhydrazones	
	I[a]	II[b]	I[c]	II[d]
Methyl 3-pyridyl ketone	19.9	11.8	50	40
Fraction 4	20.0	11.7	50	40
Ethyl 3-pyridyl ketone	30.0	14.9	62	48
Fraction 6	30.1	14.9	62	48

[a] On 1:4 polypropylene glycol (mol. wt. 1025)–Firebrick column, 2 m. × 6 mm. 152°. He, 67 ml. per min. [b] On 1:4 polyethylene glycol (mol. wt. 20,000)–Firebrick column. 1 m. × 6 mm. 153°. He, 67 ml. per min. [c] Chloroform-*n*-heptane, 40:15, v./v., as solvent. [d] Carbon tetrachloride as solvent.

Identification by paper chromatography of 2,4-dinitrophenylhydrazones. These derivatives were prepared by the procedure of Shriner and Fuson.[5] The acidic solutions so obtained were made slightly basic with 1*N* ammonia and extracted with chloroform. The extracts were concentrated if necessary to obtain solutions suitable for paper chromatography. These solutions were applied to Whatman's No. 1 paper and the paper placed in a chamber for ascending chromatography. Two solvent systems were used, chloroform-*n*-heptane 40:15, v./v., and carbon tetrachloride. Both solvents ascended fairly rapidly, and did not move the excess dinitrophenylhydrazine to any extent. As the problem at hand was to identify single compounds, no attempt was made to develop systems capable of resolving mixtures of the derivatives of the two ketones. Only small amounts could be placed on the paper or troublesome tailing occurred. It was then necessary to locate the spots on the paper by spraying with 10% sodium hydroxide, whereby a brown coloration resulted. Results are recorded in Table I.

Acknowledgment. Grateful appreciation is expressed to Dr. M. E. Hobbs for his interest and counsel during this work and to the Research Laboratories of The American Tobacco Company and the Liggett & Myers Tobacco Company for their cooperation.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.

(3) R. Schöller, *Fachl. Mitt. Österr. Tabak-Regie*, **2**, 2 (1933).

(4) F. Kuffner, K. Schick, and H. Bühn, *Monatsh.*, **87**, 749 (1956).

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Synthesis of 6α, 16α-Dimethylprogesterone

SEYMOUR BERNSTEIN, E. W. CANTRALL, AND J. P. DUSZA

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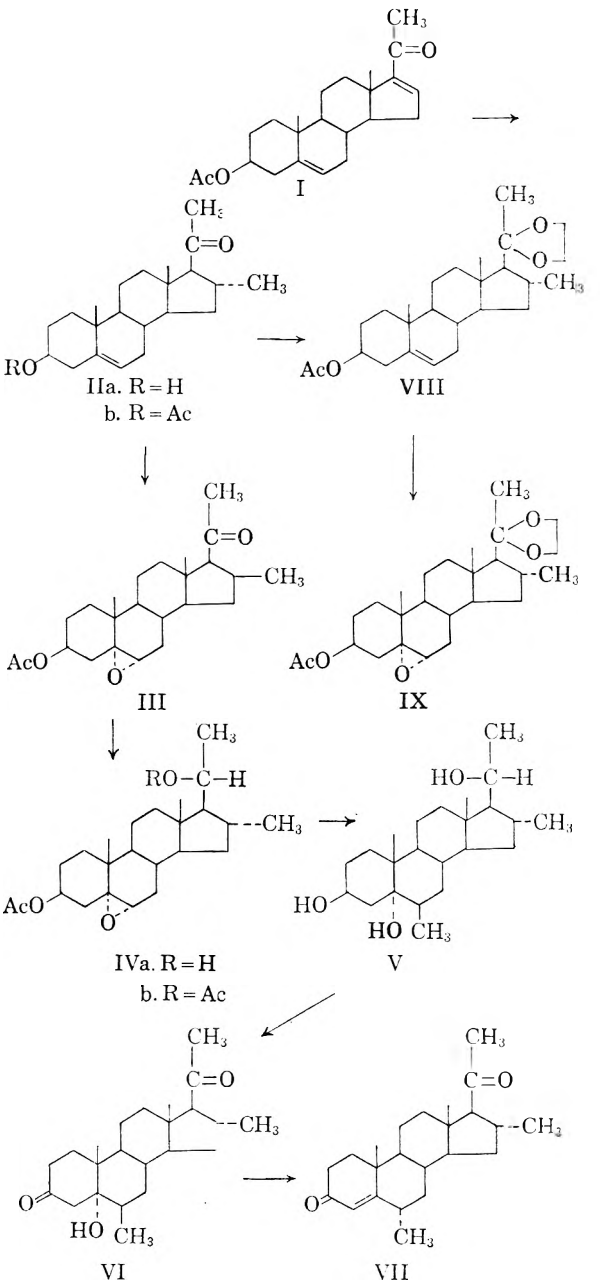
A C_6-methyl group is known to enhance both progestational[1] and anti-inflammatory[2] activities of steroid hormones. A C_{16}-methyl group markedly enhances anti-inflammatory activity.[3]

In view of these findings, it was of interest to examine the combined effect of C_6 and C_{16} methyl groups on the biological activities of steroid hormones. Initially, for this purpose we have synthesized 6α,16α-dimethylprogesterone (VII) details of which will be reported here.

The conjugate addition of methyl Grignard reagent to the Δ^{16}-20-one grouping of 3β-acetoxy-5, 16-pregnadien-20-one (I) gave the known 3β-hydroxy-16α-methyl-5-pregnen-20-one (IIa).[4] The product was not isolated as such but was converted directly into its acetate IIb, as the latter was found to be more readily purified than the free steroid. Treatment of IIb in methylene chloride at −5° with 1.2 equivalents of perbenzoic acid gave the corresponding 5α,6α-epoxide III in 63% yield. Reduction of III in methanol with sodium borohydride afforded 3β-acetoxy-5α,6α-epoxy-16α-methylpregnan-20β-ol (IVa).[5] Reaction of IVa with methylmagnesium bromide[6] gave 6β,16α-dimethylpregnane-3β,5α,20β-triol (V) in 72% yield. Oxidation of the latter with 8*N* chromic acid–sulfuric acid reagent[7] in acetone at 0° gave 5α-hydroxy-6β,16α-dimethylpregnane-3,20-dione (VI) in 85% yield. Dehydration under alkaline conditions[8] was accompanied by epimerization[1a,b]



of the 6β-(axial)-methyl group, and the desired product, 6α,16α-dimethylprogesterone (VII) was obtained in 87% yield.

Prior to the elaboration of the above pathway to VII, protection of the C_{20}-carbonyl group by ethylene ketal formation was considered. Accordingly, 3β-acetoxy-16α-methyl-5-pregnen-20-one (IIb) in benzene was converted to a ketal in the usual

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(3) (a) G. E. Arth, John Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, A. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, 80, 3161 (1958); (b) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, 80, 6687 (1958).

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(5) The newly formed hydroxyl group has been assigned the 20β-configuration based on the positive change in molecular rotation observed upon acetylation of IV_a [$M_D(IV_b)$-$M_D(IV_a)$ = +122°]. This assignment is in agreement with the literature values for the change in molecular rotation observed upon acetylation of 20β-hydroxypregnanes both substituted and unsubstituted at C-16 [R. H. Mazur and J. A. Cella, *Tetrahedron*, 7, 130 (1959)].

(6) See among others, E. Velarde, J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Org. Chem.*, 24, 311 (1959).

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(8) A. H. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, 80, 3091 (1958).

manner[9] with ethylene glycol and *p*-toluenesulfonic acid to the 20-ethylene ketal VIII. Conversion to the 5α,6α-epoxide IX was readily accomplished with perbenzoic acid. It was then planned to treat IX with methylmagnesium bromide, followed by ketal removal and dehydration of the 5α-hydroxyl group. At this point additional epoxide was required, but unfortunately the ketal reaction was for some inexplicable reason non-reproducible. Consequently this synthetic scheme was set aside.

In the Clauberg progestational assay (subcutaneous route) 6α,16α-dimethylprogesterone (VII) displayed an activity *at least* comparable to that of progesterone.[10]

EXPERIMENTAL

All melting points are uncorrected and unless noted otherwise were determined in open soft-glass capillaries. All rotations were measured in chloroform at 25°. The infrared spectra were determined in pressed discs of potassium bromide. The ultraviolet spectra were determined in methanol. The *petroleum ether* used boiled at 60–70° (Skellysolve B).

3β-Acetoxy-16α-methyl-5-pregnen-20-one (IIb). Nitrogen was bubbled through 1320 ml. of a *ca.* 3.0*M* solution of methylmagnesium bromide in diethyl ether containing 20.0 g. of cuprous chloride. A solution containing 200 g. of 16-dehydropregnenolone acetate (I) in 3 l. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added to the Grignard solution with stirring over 40 min. An additional 2 l. of tetrahydrofuran was added, and 1.1 l. of solution was distilled (reflux temperature 61°). Reflux under nitrogen was continued with stirring for 7.5 hr. The mixture was left to stand overnight at room temperature and was then poured into 12 l. of water containing 300 g. of ammonium chloride. The product was extracted with two 2-l. portions of methylene chloride. The combined extracts were washed with water and saturated sodium chloride solution and evaporated to a semicrystalline mass *in vacuo* on the steam bath. The crude product was heated on a steam bath for 1.75 hr. with a mixture of 1 l. of pyridine and 500 ml. of acetic anhydride. The excess acetic anhydride was decomposed with methanol, and the mixture was evaporated to a crystalline mass. The crude product was dissolved in 2 l. of ether: methylene chloride (3:1) and the solution was washed successively with 10% hydrochloric acid, water, 10% potassium bicarbonate, water, and saturated sodium chloride solutions. The solution was evaporated, and the residue was crystallized from methylene chloride–methanol to give 122.6 g. (58.6%) of colorless prisms, m.p. 176–180° (lit.[4] m.p. 173–175°). An additional 13.7 g. (6.5%, m.p. 175–179°) was obtained on working up the mother liquors.

3β-Acetoxy-5α,6α-epoxy-16α-methylpregnan-20-one (III). A solution containing 5.0 g. of 16α-methylpregnenolone acetate (IIb) in 100 ml. of methylene chloride was cooled to −5°, and 42 ml. of a 0.386*M* solution of perbenzoic acid in benzene was added dropwise with stirring over 10 min. The reaction mixture was kept at −5° for *ca.* 24 hr., following which it was washed successively with ice cold 5% sodium hydroxide solution, water, and saturated sodium chloride solution. The colorless solution was dried over anhydrous sodium sulfate and evaporated *in vacuo* to a colorless crystalline mass. On crystallization from acetone–petroleum ether, the crude product afforded 3.29 g. (63%) of colorless needles, m.p. 157.5–162°. An analytical sample had m.p. 167.5–168.5°; $[\alpha]_D$ −10°; ν_{max}^{KBr} 1745, 1710, 1370, 1250 and 1039 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 73.76; H, 9.33.

3β-Acetoxy-5α,6α-epoxy-16α-methylpregnan-20β-ol (IVa). A solution containing 512 mg. of sodium borohydride in 17 ml. of methanol was added dropwise, with stirring, over a period of 5 min. to a suspension of 1.30 g. of 3β-acetoxy-5α,6α-epoxy-16α-methylpregnan-20-one (III) in 35 ml. of methanol (most of the steroid dissolved before the addition of the reducing agent; all of it dissolved within *ca.* 2 min. after the first of the borohydride solution was added). The resulting solution was stirred for 10 min. at room temperature, and the excess borohydride was decomposed with a few drops of glacial acetic acid. The reaction mixture was evaporated *in vacuo* on a steam bath to a solid mass. The latter was taken up with *ca.* 75 ml. of ether–methylene chloride (2:1) and the extract was washed successively with water and saturated sodium bicarbonate solution. Concentration of the extract *in vacuo* afforded a solid mass, which on crystallization from acetone–petroleum ether gave 967 mg. (74%) of colorless blades, m.p. 178.5–180.5°.

A sample for analysis had m.p. 177–179.5°; $[\alpha]_D$ −76°; ν_{max}^{KBr} 1730, 1705, 1268, and 1042 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{38}O_4$ (390.54): C, 73.80; H, 9.81. Found: C, 73.92; H, 9.97.

5α,6α-Epoxy-16α-methylpregnan-3β,20β-dioldiacetate (IVb). Acetylation of 202 mg. of 3β-acetoxy-5α,6α-epoxy-16α-methylpregnan-20β-ol (IVa) with a mixture of 3 ml. of acetic anhydride and 3 ml. of pyridine and crystallization of the crude product IVb from aqueous acetone afforded 173 mg. of colorless needles, m.p. 146–147°. A sample for analysis was recrystallized from the same solvents, m.p. 147–148°; $[\alpha]_D$ −40°.

Anal. Calcd. for $C_{26}H_{40}O_5$ (432.58): C, 72.19; H, 9.32. Found: C, 71.80, 72.09; H, 9.54, 9.51.

6β,16α-Dimethylpregnan-3β,5α,20β-triol (V). To a solution containing 696 mg. of 3β-acetoxy-5α,6α-epoxy-16α-methylpregnan-20β-ol (IVa) in 30 ml. of benzene through which a slow stream of nitrogen was being bubbled was added 10 ml. of a *ca.* 3.0*M* solution of methylmagnesium bromide in diethyl ether. A grey solid precipitated, and the mixture was distilled until the reflux temperature had reached 65°. Reflux with stirring under a nitrogen atmosphere was continued for 3 hr. The mixture was treated with 10 ml. of saturated ammonium chloride solution, diluted with *ca.* 200 ml. of ether:benzene (3:1), and acidified with 10% sulfuric acid. The organic phase was washed successively with 5% sodium hydroxide, water, and saturated sodium chloride solutions. Evaporation *in vacuo* afforded a semicrystalline solid which crystallized from ethyl acetate–benzene to give 468 mg. (72%) of colorless needles m.p. 220–228° dec. An analytical specimen melted at 221–228° $[\alpha]_D$ −40°; ν_{max}^{KBr} 3430 and 1040 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{40}O_3$ (364.55): C, 75.77; H, 11.06. Found: C, 75.28; H, 11.01.

5α-Hydroxy-6β,16α-dimethylpregnan-3,20-dione (VI). A solution containing 5.0 g. of 6β,16α-dimethylpregnan-3β,5α,20β-triol (V) in 1 l. of acetone was cooled to −4°, and 15.0 ml. of an 8*N* solution of chromium trioxide in sulfuric acid was added dropwise over 25 min. The mixture was poured into a separatory funnel containing 3 l. of water, and the product was extracted with 1.5 l. of ether–methylene chloride (2:1) and twice with 500 ml. of ether. The combined extracts were washed with water and saturated sodium bicarbonate solution. Evaporation of the colorless extract *in vacuo* afforded a solid which crystallized from methylene chloride–methanol to give 3.58 g. (72%) of short needles, m.p. 260.5–262° dec. An additional 622 mg. (13%), m.p. 260–263° dec., was obtained on concentration of the mother liquors. The analytical specimen melted at 262.5–265° dec.; $[\alpha]_D$ +54°; ν_{max}^{KBr} 1705 cm.$^{-1}$

(9) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(10) This assay was carried out by the Endocrine Laboratories, Madison, Wis.

Anal. Calcd. for $C_{23}H_{36}O_3$ (360.51): C, 76.62; H, 10.07. Found: C, 76.35, 76.10; H, 10.27, 10.41.

6α-16α-Dimethylprogesterone (VII). A solution containing 150 mg. of 5α-hydroxy-6β,16α-dimethylpregnan-3,20-dione (VI) and 0.5 ml. of 5% sodium hydroxide in 10 ml. of methanol was heated to reflux for 1 hr. under nitrogen. The mixture was acidified with a few drops of acetic acid and concentrated to a colorless viscous oil *in vacuo* on a steam bath. The crude product was dissolved in *ca.* 30 ml. of ether, and ether solution was washed with 5% sodium hydroxide, water, and saturated sodium chloride solution. The extract was concentrated to a viscous oil, and the latter was crystallized from aqueous methanol to give 123 mg. (87%) of fine colorless needles, m.p. 109.5–113.5° (Kofler). A sample for analysis melted at 113–116.5° (Kofler); $[\alpha]_D$ +145°; λ_{max} 242 mμ (ε = 16,100); ν_{max}^{KBr} 1705, 1678 and 1610 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3$ (342.50): C, 80.65; H, 10.01. Found: C, 80.41; H, 10.32.

3β-Acetoxy-20-ethylenedioxy-16α-methyl-5-pregnene (VIII). To a solution containing 1.88 g. of 16α-methylpregnenolone acetate (I) and 49 mg. of *p*-toluenesulfonic acid (monohydrate) in 63 ml. of benzene was added 1.90 ml. of ethylene glycol. The resulting mixture was heated to reflux for 16 hr., and the water formed during the reaction was collected in a Dean-Stark apparatus. Pyridine (0.3 ml.) was added, and the solution was washed successively with ice-cold 5% sodium hydroxide, water, and saturated sodium chloride solutions. On evaporation *in vacuo* of the benzene solution, a semicrystalline solid was obtained which crystallized from methanol (containing a few drops of pyridine) to give 1.33 g. (63%) of fine, colorless needles, m.p. 134.5–140.5°. A sample for analysis melted at 144.5–146°; $[\alpha]_D$ −62.5°; ν_{max}^{KBr} 1740, 1255, 1238, and 1037 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{40}O_4$ (416.58): C, 74.96; H, 9.68. Found: C, 75.02; H, 9.83.

3β-Acetoxy-5α,6α-epoxy-20-ethylenedioxy-16α-methylpregnane (IX). To a solution containing 913 mg. of 3β-acetoxy-20-ethylenedioxy-16α-methyl-5-pregnene (VIII) in 20 ml. of benzene–methylene chloride (1:1) cooled to −10° was added 7.45 ml. of a 0.37*M* solution of perbenzoic acid in benzene dropwise with stirring over 17 min. The mixture was let stand at −5° for 23 hr. and washed successively with ice cold 5% sodium hydroxide, water, and saturated sodium chloride solutions. On evaporation *in vacuo* a semicrystalline solid was obtained. The latter on crystallization from methylene chloride–petroleum ether afforded 533 mg. of colorless needles, m.p. 169–171.5°. A sample for analysis melted at 171.5–172.5°; $[\alpha]_D$ −61°; ν_{max}^{KBr} 1730, 1243, 1218, 1100, 1047, and 1033 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.09; H, 9.56.

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ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES
A DIVISION OF AMERICAN CYANAMID COMPANY
PEARL RIVER, N. Y.

The Triterpenes of *Befaria racemosa* (Vent.)[1]

K. UEDA, WERNER HERZ,[2] AND IRWIN J. PACHTER[3]

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Befaria racemosa (Vent.), a striking shrub found in the pinelands of the Coastal Plain of Florida and Georgia, gave a negative test for andromedotoxin in a recent survey of *Ericaceae*,[4] but seems not to have been investigated in other respects. This note describes the isolation and identification of ursolic acid, taraxerol, β-amyrin, lupeol, and β-sitosterol. In addition there was isolated what appears to be crude α-amyrin and a poor yield (0.07%) of an alkaloid mixture which was reserved for future investigation.

The major triterpene constituents were ursolic acid (0.5%), of common occurrence in *Ericaceae* species,[5,6] and taraxerol (0.2%), which has recently been found in *Pieris japonica* (D. Don.)[7] The former was identified through preparation of acetylursolic acid, methyl ursolate, methyl ursolate acetate, and methyl ursolate benzoate. The latter was identified through the acetate and benzoate and by conversion to taraxerone. The other triterpenes were isolated in small amounts only and were identified by comparison with authentic samples of β-sitosterol, β-amyrin acetate, lupeol benzoate, and α-amyrin acetate.

EXPERIMENTAL

Dried *Befaria racemosa* (Vent.) leaves, collected near Tallahassee in summer 1959, 4.1 kg., were extracted continuously with 20 l. of 95% ethanol for 48 hr. The solution was concentrated to a small volume and filtered from crystalline material (precipitate A). The filtrate was concentrated almost to dryness, stirred with several portions of 3% phosphoric acid, the acid extract made basic with concd. ammonia, and extracted with chloroform until exhausted of alkaloids. The chloroform solution was concentrated to dryness at reduced pressure, the residue taken up in 50 ml. of fresh chloroform and diluted with ether to the point where an insoluble precipitate began to form. The solution was extracted repeatedly with 3% phosphoric acid, the acid extracts were made basic with ammonia and the alkaloids extracted with chloroform. Removal of chloroform left 3 g. of gummy residue (positive to Mayer's reagent) which paper chromatography showed to be a mixture of alkaloids.

Precipitate A was taken up in hot chloroform-ethanol, filtered and allowed to stand. There precipitated crude taraxerol which was recrystallized five times from chloroform-methanol, yield 2.5 g., m.p. 268–272° (Hershberg), 280–281° (Kofler), $(\alpha)_D^{25}$ +2.0 (c, 1.5, chloroform).[8]

The acetate, prepared by refluxing with acetic anhydride, crystallized from methanol as colorless scales, m.p. 302°

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(2) To whom correspondence should be addressed, Department of Chemistry, The Florida State University, Tallahassee, Fla.

(3) Smith, Kline and French Laboratories, Philadelphia 1, Pa.

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(Kofler), $(\alpha)_D^{23}$ +9.3 (*c*, 0.75, chloroform). The benzoate, prepared by the benzoyl chloride–pyridine method, crystallized from benzene as colorless needles, m.p. 292–293° (Kofler), $(\alpha)_D^{23}$ +35.7° (*c*, 0.7, chloroform). Oxidation in benzene with chromic acid–acetic acid at room temperature furnished taraxerone, colorless plates from chloroform-methanol, m.p. 240–201°, $(\alpha)_D^{25}$ +11.7° (*c*, 0.59, chloroform).

The filtrate from the taraxerol isolation was evaporated to dryness at reduced pressure, 64 g. (precipitate B). Precipitate B was worked up by two methods: (1) alkaline hydrolysis of 20 g. of B with 250 ml. of ethanol, 200 ml. of benzene, and 25 g. of potassium hydroxide followed by evaporation, dilution with water, and chloroform extraction gave chloroform-insoluble material which was filtered (precipitate C). The chloroform extract was evaporated, the residue was stirred with benzene, and the benzene-insoluble material (crude taraxerol) recrystallized repeatedly from ethanol-chloroform, yield of taraxerol 1.2 g., m.p. 280°. The benzene extract was evaporated and the residue chromatographed over 40 g. of neutral alumina (activity II, solvent and eluent petroleum ether–benzene). The first fractions gave 0.23 g. of paraffin-like material melting near 60° which gave a negative Liebermann-Burchard test and was discarded. Further elution gave a crystalline triterpene mixture of m.p. 95–160°, which gave a positive Liebermann-Burchard test and was separated through the acetates as described in Section 2.

Precipitate C, obviously a potassium salt, was neutralized upon dilution with water. Here separated 6.1 g. of amorphous material (precipitate D) giving a positive Liebermann-Burchard test. Crystallization from ethanol gave colorless needles of ursolic acid, m.p. 277°, which were converted to the acetate by refluxing with acetic anhydride. The product crystallized from methanol as colorless needles, m.p. 289–291°, $(\alpha)_D^{23}$ +67.5° (*c*, 1.23, chloroform).[9] Another portion of precipitate D, 1.7 g., was converted to the methyl ester by treatment with diazomethane. A solution of the crude ester, 1.4 g., in 170 ml. of benzene was chromatographed over 70 g. of neutral alumina (activity III). Elution with benzene–chloroform (3:1) furnished 1.2 g. of methyl ursolate, m.p. 160–167°, which after several crystallizations from methanol-water melted at 165–168°. The acetate crystallized from methanol as needles, m.p. 239–242°, $(\alpha)_D^{23}$ +63.1° (*c*, 1.49, chloroform). The benzoate was recrystallized from methanol, m.p. 234° (softening at 209–210°).

(2) Precipitate B, 24 g., was extracted thoroughly with 1500 ml. of ether. The ether extract was shaken repeatedly with 1*N* sodium hydroxide solution. There separated 9.5 g. of sodium urosolate which was filtered. The ether extract was washed, dried, concentrated to small volume, filtered from crude taraxerol (0.4 g.), passed through 80 g. of alumina, and eluted with 100 ml. portions of ether. Fractions 1–3 gave crystalline material, fractions 4–7 (ether) and 8–12 (ether-ethanol) gave only small amounts of gums.

Fractions 1–3 were combined and extracted with petroleum ether. The insoluble material was taraxerol, 0.8 g. The petroleum ether extract was chromatographed over 35 g. of alumina (activity III). Petroleum ether (b.p. 30–60°) (ten 30 ml. fractions) eluted 2.1 g. of a triterpene mixture, m.p. 130–160°. Elution with petroleum ether–benzene (1:1) eluted triterpene mixtures together with 58 mg. of taraxerol which was isolated by fractional crystallization from chloroform-methanol. Elution with benzene furnished 20 mg. of β-sitosterol, m.p. (from acetone) 133–136°, characteristic Liebermann-Burchard test. The acetate, prepared by the acetic anhydride–pyridine method, was purified by chromatography and recrystallization from methanol, m.p. 118–121°, $(\alpha)_D^{24}$ −39° (*c*, 0.59, chloroform), m.p. undepressed on admixture of an authentic sample. The infrared spectra were identical.

The triterpene mixture, 2.1 g., was refluxed with acetic anhydride for 2 hr. Fractional crystallization of the acetate mixture from methanol-chloroform furnished 43 mg. of β-amyrin acetate, m.p. 240–241°, $(\alpha)_D^{23}$ +80.9 (*c*, 2.2, chloroform), melting point undepressed on admixture of an authentic sample. The mother liquors from the recrystallization were combined, evaporated, dissolved in petroleum ether-benzene (2:1), and chromatographed over 50 g. of alumina (activity II). Elution with petroleum ether-benzene (2:1) gave a fraction which on crystallization from acetone gave an additional 7 mg. of β-amyrin acetate. The mother liquor was combined with the other eluates, the solvents removed and the residue, 1.8 g., saponified. The neutral product, 1.1 g., was converted to the benzoate. Crystallization of the crude benzoate from ethanol-chloroform, ethyl acetate, and petroleum ether gave colorless plates of lupeol benzoate, 28 mg., m.p. 265–268° $(\alpha)_D^{23}$ +60.6° (c, 2.08, chloroform), melting point undepressed on admixture of authentic lupeol benzoate. The infrared spectra were superimposable.

The mother liquors from the recrystallization of lupeol benzoate were combined and evaporated. The residue, m.p. 190–220°, 0.7 g. was chromatographed over alumina (activity III). Fractions 9–11 (20-ml. portions of petroleum ether) yielded 90 mg., m.p. 165–175°, fractions 12–16 (petroleum ether–benzene 9:1) 420 mg., m.p. 190–230° fractions 17–20 140 mg., m.p. 225–250°. Fractions 12–16 were rechromatographed over 20 g. of alumina. This chromatogram yielded fractions 6–9 (petroleum ether), 55 mg., 170–180°, fractions 10–15 (petroleum ether) 95 mg., m.p. 160–210°, fractions 16–20 (petroleum ether–benzene 4:1) 240 mg., m.p. 210–245°.

Fractions 9–11 of the first and 6–9 of the second chromatogram were combined and rechromatographed. Elution with petroleum ether–benzene (9:1) gave a fraction which after recrystallization from chloroform-methanol melted at 179–182°, $(\alpha)_D^{22}$ +89° (*c*, 1.3, chloroform). Hydrolysis gave crude α-amyrin, m.p. 155–177°, acetate m.p. 200°, $(\alpha)_D^{23}$ +74° (*c*, 0.58, chloroform). The rotations and infrared spectra were those of α-amyrin acetate (m.p. 226°, $(\alpha)_D$ +76°) and benzoate (m.p. 194°, (α) +94.6°) but the melting points remained low.

Fractions 17–20 of the original chromatogram and 16–20 of the second chromatogram exhibited the typical 1640 and 890 cm.$^{-1}$ bands of lupeol. They were combined, rechromatographed, and recrystallized m.p. 255–263°, yield 180 mg. Although the melting point was low, the infrared spectrum and rotation was identical with the infrared spectrum and rotation of lupeol benzoate. Hydrolysis furnished crude lupeol, m.p. 200°, $(\alpha)_D^{23}$ +23.4° (*c*, 1.37, chloroform) which was converted to the acetate 200–204°, $(\alpha)_D^{25}$ +37° (*c*, 1.6, chloroform). The infrared spectrum and rotation were similar to those of authentic lupeol acetate.

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Department of Chemistry
The Florida State University
Tallahassee, Fla.

Research and Development Division
The Smith Kline and French Laboratories
Philadelphia 1, Pa.

(9) For physical constants of ursolic acid and its derivatives, see ref. 5, p. 118 or ref. 8, Vol. 5, p. 114.

Alditol Arsenite Esters[1]

M. L. Wolfrom and M. J. Holm

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As one phase of a program initiated to explore the preparation of various partially nitrated alditols, the use of the cyclic arsenite esters of the alditols as possible intermediates appeared attractive. Although efforts to this end are not complete, a report on the preparation of several crystalline carbohydrate arsenites seems warranted at this time.

The cyclic arsenite esters of glycerol,[2–4] erythritol,[5] and pentaerythritol[5,6] have been described; only the last was isolated in crystalline form. Although the method of choice for the preparation of these compounds appears to be the reaction between arsenic trioxide and the polyhydroxy material under conditions which permit the removal of the water formed, other methods[4] have been described. More recently the use of arsenic trichloride has been suggested.[7]

Following Pascal and Dupire,[4] glycerol arsenite was prepared and on sublimation was found to afford a crystalline hygroscopic product (m.p. 66–70°) which appears to be the monomeric arsenite in contrast to the polymeric glassy solid described by the earlier workers.[4]

The crystalline diarsenite esters of D-mannitol (m.p. 226–227°) and galactitol (m.p. 266–267°) are reported for the first time. These monomeric derivatives were prepared by reaction of the alditol with arsenic trioxide in boiling dioxane with the water produced being removed by fractional distillation of the dioxane-water azeotrope. The reaction was found to be strongly catalyzed by mineral acid. Although these crystalline diarsenites are stable for short periods when exposed to moist air, the compounds must be considered quite sensitive toward hydrolysis by water. The positions of attachment of the cyclic arsenic rings to the hexitol chains have not been elucidated.

Attempts were made to prepare crystalline arsenites of 1,2,4-trihydroxybutane, erythritol, DL-threitol, xylitol, ribitol, and D-glucitol. In each case, the evolution of water and the solution of the arsenic trioxide in the dioxane indicated that reaction occurred but only sirups or glassy solids were obtained when the products were isolated.

EXPERIMENTAL

Glycerol arsenite. Arsenite trioxide (19.8 g.) and glycerol (glycerul, 18.4 g.) were placed in a flask and covered with 200 ml. of toluene. The mixture was refluxed and the water collected in a Dean and Stark receiver.[8] After 8 hr. of refluxing, distillation of the toluene gave a colorless, very viscous sirup which partially sublimed on heating to 120–140° at 0.3 mm. The sublimate was resublimed under similar conditions resulting in large, very hygroscopic crystals firmly affixed to the condensing surface; m.p. 66–70°.

Anal. Calcd. for $C_3H_5AsO_3$: As, 45.7. Found: As, 45.7.

D-*Mannitol diarsenite.* A mixture of D-mannitol (4.55 g., 25 mmoles), arsenic trioxide (4.95 g., 25 mmoles), dioxane (150 ml., peroxide-free), and concd. hydrochloric acid (0.25 ml.) were heated in a flask fitted with a fractionating column. When the temperature at the column head fell below the boiling point of dioxane, distillate was collected. Complete solution resulted after about 15 min. and the evolution of water ceased after 1 hr. The resulting solution was concentrated to dryness and the solid residue was dissolved in 200 ml. of chloroform. Concentration to a volume of 50 ml. initiated crystallization which was completed at 5°. Decantation of the liquid and drying gave a crude product; yield 6.9 g., m.p. 200–220°. The material that was insoluble in 75 ml. of refluxing chloroform was discarded. Cooling afforded crystalline hygroscopic material; yield 4.1 g. (50%) m.p. 224–225°. The analytical sample was obtained by two additional crystallizations from chloroform; m.p. 226–227°, $[\alpha]_D^{26}$ −72° (c 0.7, dioxane), infrared absorption[9]: 12.28 (95%), 9.52, 13.52B, 9.45, 9.92, 9.25, 9.96, 9.74, 15.65B, 10.65, 10.71, 12.07, 9.09 (50%), 11.86, 11.49, 10.52, 11.43, 7.45, 15.08B, 3.45, 8.90, 11.22, 3.38, 11.29, 14.15B, 10.34, 3.41, 10.24, 7.58, 7.76, 7.88, 8.31, 7.93, 7.66, 7.34, 8.22, 6.83 (5%). The substance sublimed readily at 170° and 0.1 mm.

Anal. Calcd. for $C_6H_8As_2O_6$: C, 22.11; H, 2.47; As, 46.0; mol. wt., 326. Found: C, 22.06; H, 2.41; As, 46.1; mol. wt., 350 (Rast).

Galactitol diarsenite. This preparation was carried out in the same manner as described above except that the D-mannitol was replaced by galactitol (dulcitol). The water removal was complete after 3 hr. (50 ml. of distillate). Cooling of the reaction mixture to room temperature completed precipitation of the slightly hygroscopic product, galactitol diarsenite; yield 7.1 g. (87%), m.p. 266–267°; infrared absorption[9]: 9.72 (95%), 10.72, 10.21, 9.87, 13.32, 14.72, 11.46, 15.60B, 9.07, 3.38 (50%), 3.46, 6.82, 12.60, 8.01, 7.88, 8.30, 8.25, 7.33, 6.92 (5%). Although the substance sublimes readily at 170° and 0.1 mm., the analytical sample was obtained by recrystallization twice from dioxane (melting point unchanged).

Anal. Calcd. for $C_6H_8As_2O_6$: C, 22.11; H, 2.47; As, 46.0. Found: C, 21.75; H, 2.60; As, 45.9.

Arsenite esters of other polyhydroxy alcohols. Application of the methods used for making the hexitol arsenites to 1,2,4-trihydroxybutane, erythritol, DL-threitol, xylitol, ribitol, and D-glucitol resulted in the evolution of water and dissolution of the arsenic trioxide. However, all efforts to isolate crystalline products failed. No sublimation products could be obtained from the ribitol and D-glucitol reaction products; a solid obtained from the xylitol reaction decomposed in

(1) This work was carried out under Contract DA-33-019-ORD-2025 between the Ballistic Research Laboratories of Aberdeen Proving Ground, Md., and The Ohio State University Research Foundation (Project 675).

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moist air. Efforts to prepare monoacyl derivatives of the glassy erythritol arsenite followed by hydrolysis of the arsenic function afforded mixtures which were not separated.

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DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

A New Synthesis of the Benzothiazole and Benzoxazole Rings

GLENN L. JENKINS, ADELBERT M. KNEVEL, AND CHARLES S. DAVIS

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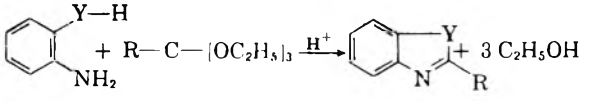
In an attempt to prepare a series of 2-(*N*-alkylamino)benzenethiols, ethyl orthoformate was treated with 2-aminobenzenethiol in a manner similar to that reported in *Organic Syntheses*[1] for the preparation of secondary amines. Although our attempt did not produce the desired product, we did discover a convenient method of preparing 2-substituted benzothiazole and benzoxazole rings (Table I) in 75–85% yields.

Table I lists the compounds prepared by treating 2-aminobenzenethiol or 2-aminophenol with the corresponding ortho-esters.

TABLE I

2-SUBSTITUTED BENZOTHIAZOLE AND BENZOXAZOLE COMPOUNDS



	Y	R	B.P. (mm.)[a] of Heterocycle	
1	S	H	183	(754)
2	S	CH_3	151	(15)
3	S	C_2H_5	132	(18)
4	O	H	182	(753)
5	O	CH_3	91	(18)
6	O	C_2H_5	129	(23)

[a] The physical properties of these compounds were in close agreement with those reported in the literature (Beilstein).

All of the above compounds were prepared according to the following procedure used for the synthesis of benzothiazole.

EXPERIMENTAL

In a 100 ml. round bottomed flask were placed 22 g. (0.17 mole) of 2-aminobenzenethiol, 37 g. (0.25 mole) of ethyl orthoformate, and 0.7 g. (0.007 mole) of concd. sulfuric acid. To the flask was attached a Vigreux column surmounted with a distillation head. The flask was heated in an oil bath and after the temperature reached 115–130° the ethanol began to distill. Heating was continued until the temperature reached 170–180°, at which time all of the ethanol and some yellow material had been removed (*ca.* 1 hr.). About 31 ml. of ethanol was collected. The reaction mixture was kept in the oil bath at 175–185° for an additional 45 min., after which time it was cooled and the product distilled under vacuum.

Anal. Calcd. for C_7H_5NS: C, 62.19; H, 3.73. Found: C, 62.45; H, 3.41.

The infrared spectrum of benzothiazole was identical with that obtained from a commercial product.

Acknowledgment. We are indebted to the American Cyanamid Company for the gift of 2-aminobenzenethiol used in this work.

RESEARCH LABORATORY
SCHOOL OF PHARMACY
PURDUE UNIVERSITY
LAFAYETTE, IND.

Reaction of Tertiary Mercaptans with Sulfur

PHILLIP S. LANDIS AND LYLE A. HAMILTON

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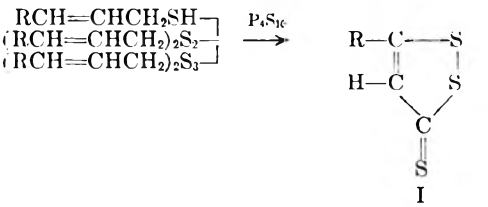
The interesting pseudoaromatic 1,2-dithiole-3-thiones have been prepared by the reaction of sulfur and/or phosphorus pentasulfide with aldehydes,[1] methyl substituted olefins or olefins easily converted to methyl substituted derivatives,[2,3] diolefins,[3] and unsaturated carbonyl compounds.[4] There are also scattered references to the synthesis of these systems from sulfur compounds. Allylic thiols, disulfides, and trisulfides[4] are reported to yield 5-alkyl-1,2-dithiole-3-thiones, I.



Wessely and Siegel[5] have reported low yields of thiones by reaction of sulfur with saturated aliphatic sulfides, disulfides and polysulfides. These workers have suggested a cleavage of the sulfide linkage as an initial intermediate on the route to the thione as well as to higher molecular weight products.

(1) R. M. Roberts and P. J. Vogt, *Org. Syntheses*, **38**, 29 (1958).

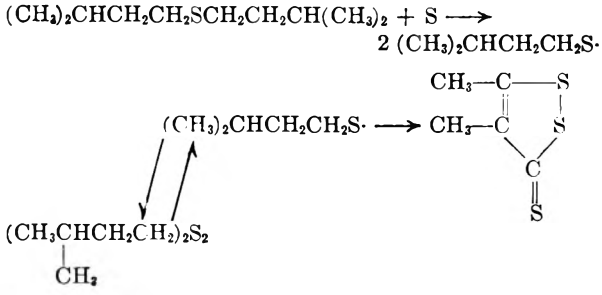
(1) G. A. Barbaglia, *Ber.*, **17**, 2654 (1884).

(2) M. L. Selker and A. R. Kemp, *Ind. Eng. Chem.*, **39**, 895 (1947).

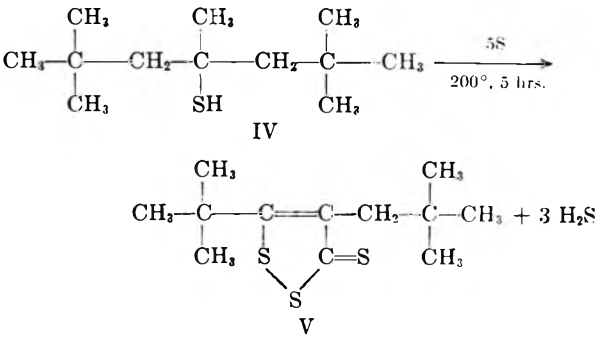
(3) B. Boettcher and A. Luttringhaus, *Ann.*, **557**, 89 (1947).

(4) A. Luttringhaus, H. B. Konig, and B. Bottcher, *Ann.*, **550**, 201 (1947).

(5) F. Wessely and A. Siegel, *Monatsh.*, **82**, 607 (1951).

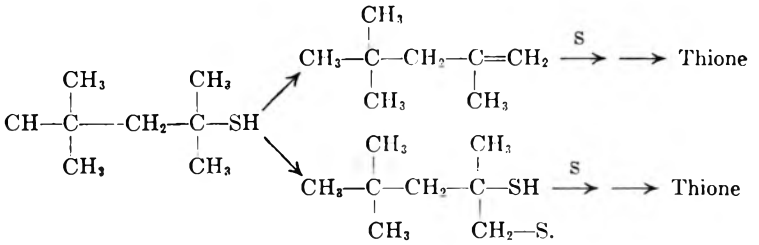


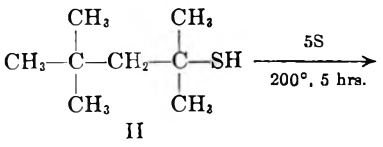
During the course of some investigations with thiols we have had occasion to study the reaction of tertiary thiols with sulfur and were surprised to find high yields of 1,2-dithiole-3-thiones. The thiols studied included 2,4,4-trimethyl-2-pentanethiol, II, and 2,2,4,6,6-pentamethyl-4-heptanethiol, IV. Reaction of II with sulfur yielded a mixture of 4-methyl-5-*t*-butyl-1,2-dithiole-3-thione and 4-neopentyl-1,2-dithiole-3-thione identical to that obtained by Spindt[6] from the direct sulfurization of diisobutylene, 2,4,4-trimethylpentene-1, or 2,4,4-trimethylpentene-2.

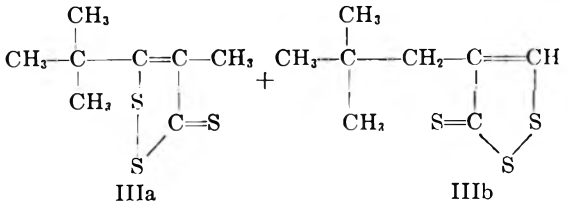


Compound V readily formed addition compounds with mercuric chloride, silver nitrate, bismuth chloride, and methyl iodide. Refluxing with alcoholic potassium hydroxide for extended periods of time yielded, among other products, two acids established as pivalic and γ,γ-dimethylvaleric acids. These acids presumably arise by hydrolytic cleavage of thiole ring to a β-keto acid, which readily undergoes base-catalysed C—C ring rupture.

The isolation of the thiones III and V from the indicated thiols suggest two alternatives in the initial reaction path to thione products.







Compound IV with sulfur at 200° gave 4-neopentyl-5-*t*-butyl-1,2-dithiole-3-thione, V identical with the product obtained by the reaction of triisobutylene with sulfur.[7]

Tertiary mercaptans are reported to eliminate hydrogen sulfide at 300°.[8] The presence of excess sulfur may enhance this elimination. Indeed we have found that heating sulfur in an inert solvent at 200°, dropping 2,4,4-trimethyl-2-pentanethiol onto the solution and rapidly removing volatile products in a side-arm takeoff trap produces small amounts of olefin, easily identified as diisobutylene. This observation suggests formation of olefin by loss of hydrogen sulfide before attack at a methyl group. By analogy the thiones from various sulfides reported by Wessely and Siegel must arise by thermal cleavage of the sulfide linkage, formation of a thiol by hydrogen abstraction and elimination of hydrogen sulfide prior to formation of the sulfur-containing intermediates on the route to dithiole-3-thione. In strong support of this suggestion is the observation that 2,4,4-trimethylpentanethiol yielded a mixture of thiones (IIIa and IIIb) in

(6) R. Spindt, D. Stevens, and W. Baldwin, *J. Am. Chem. Soc.*, **73**, 3693 (1951).

(7) P. Landis and L. Hamilton, *J. Org. Chem.* 25, 1742 (1960).

(8) C. Thompson, R. Meyer, and J. S. Ball, *J. Am. Chem. Soc.*, **74**, 3284 (1952).

about the same ratio as that obtained from the reaction of diisobutylene and sulfur.

EXPERIMENTAL

Reactions with sulfur. Two techniques were used to react sulfur with tertiary mercaptans. The first utilized the simple process of dropping mercaptan onto heated sulfur at 200° using an addition rate such that all of the low boiling mercaptan and intermediates were efficiently converted to higher boiling products. A second technique used the addition of preformed alkyl-1,2-dithiole-3-thione to the sulfur before addition of the mercaptan. The added thione served to reduce the viscosity of the sulfur, to increase the mutual solubility of the sulfur and mercaptan, and thus to provide increased conversions.

4-Neopentyl-1,2-dithiole-3-thione, IIIb *and 4-methyl-5-t-butyl-1,2-dithiole-3-thione*, IIIa. Sulfur (160 g., 5.0 moles) was placed in a 500-ml. four-necked flask fitted with a stirrer, thermometer, dropping funnel, and efficient condenser. The condenser was connected to a gas meter to measure evolution of hydrogen sulfide. The sulfur was heated and stirred at 200–220° and 2,4,4-trimethyl-2-pentanethiol (146 g., 1 mole) was added dropwise in 4 hr. Heating and stirring was continued for an additional hour at the end of which 3 moles of hydrogen sulfide had been evolved and reaction had essentially ceased. The crude product was vacuum distilled and after a forecut of intermediate sulfur compounds there was obtained 50 g. boiling at 145–155° (3 mm.). This fraction solidified on standing and was separated into two isomers by fractional recrystallization from pentane and ethanol. 4-Neopentyl-1,2-dithiole-3-thione IIIb, m.p. 85–86°, gave no melting point depression with a sample prepared by the method of Spindt, *et al.*[6] 4-Methyl-5-*t*-butyl-1,2-dithiole-3-thione IIIa, m.p. 79–80°, also was identical to that obtained by the method of Spindt.

Anal. IIIa. Calcd. for $C_8H_{12}S_3$: C, 47.01; H, 5.93; S, 47.06. Found: C, 47.05; H, 5.88; S, 47.00.

Anal. IIIb. Calcd. for $C_8H_{12}S_3$: S, 47.06; mol. wt. 204.3. Found: S, 47.19; mol. wt. 205.

4-Neopentyl-5-t-butyl-1,2-dithiole-3-thione, V. Sulfur (160 g.) and 2,2,4,6,6-pentamethyl-4-heptanethiol (212 g.) were placed in a three-necked 500-ml. flask fitted with a thermometer, stirrer, and a reflux condenser which was attached to a gas meter. The reactants were heated at 190–215° for 5 hr. and 67 l. of hydrogen sulfide were evolved. The crude product was vacuum distilled and 68 g. of thione, b.p. 150–170° (0.1–0.03 mm.) was obtained. This product was identical with that obtained from the direct sulfurization of triisobutylene.[7] Confirming analyses include infrared and ultraviolet spectra, metal complexes with mercuric chloride, silver nitrate, bismuth chloride, and methyl iodide, and the alcoholic potassium hydroxide hydrolysis to pivalic and 4,4-dimethylvaleric acids.[7]

Anal. Calcd. for $C_{12}H_{20}S_3$: S, 36.92; mol. wt. 260.5. Found: S, 36.22; mol. wt. 258, 265.

During the course of a large scale reaction (1 l.) of 2,4,4-trimethyl-2-pentanethiol with sulfur in di-*t*-butylbenzene a side-arm take-off trap was attached to the reflux condenser. This allowed removal of small samples of unreacted thiol and low boiling intermediates. Twenty-milliliter samples were thus removed every half hour and examined by vapor phase chromatography. Small (0.4–1.2%) but definite quantities of a C_8-olefin were observed during the entire course of the reaction (5 hr.). The identity of this olefin was confirmed by extraction of 200 ml. of low boiling condensate with aqueous caustic. The small caustic insoluble layer was separated by ether extraction, the ether extract washed with water, dilute caustic, dilute acid, and then dried over anhydrous sodium sulfate. After careful removal of the solvent the residue was distilled using a micro still and there was obtained 1.1 g. of mixed olefin easily identified by infrared as a mixture of 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2. Thermal treatment of the thiol II at reflux temperature gave no evidence for hydrogen sulfide evolution or the consequent formation of olefin.

RESEARCH DEPARTMENT
SOCONY MOBIL OIL CO.
PAULSBORO, N. J.

Vinylsilicon and 1,2-Dihaloethylsilicon Halogenoids and Esters[1]

HERBERT H. ANDERSON

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Earlier publications report the closely related halogenoids and perfluoroester $Si(NCO)_4$,[2] $Si(NCS)_4$,[3] $C_2H_5Si(NCO)_3$,[3] $CH_3Si(NCS)_3$,[3] $C_2H_5Si(NCS)_3$,[3] and $C_2H_5Si(OCOCF_3)_3$.[4] Addition of bromine or chlorine to vinyltrichlorosilane furnishes $CH_2BrCHBrSiCl_3$ and $CH_2ClCHClSiCl_3$ respectively,[5] while only a boiling point at diminished pressure and an analysis for silicon characterize $CH_2{=}CHSi(OCOCH_3)_3$.[6]

An E_2 elimination occurs in $CH_2ClCH_2Si(CH_3)_3$, in which the *beta* chlorine is titrated quantitatively with aqueous alkali.[7] Similarly, an acidic *beta* halogen titrates quantitatively in five new halogenoids and esters of the type $CH_2YCHYSiX_3$, in which Y is chlorine or bromine, presented in this paper.

Table I lists the boiling points, densities, refractive indices, molar refractions (calculated[4] and observed values show an average error of 0.46%), and analyses of the following eleven new compounds: $CH_2{=}CHSi(OCOCF_3)_3$, $CH_2{=}CHSi(OCOC_2F_5)_3$, $CH_2{=}CHSi(OCO\text{-}n\text{-}C_3F_7)_3$, $CH_2{=}CHSi(OCOC_2H_5)_3$, $CH_2{=}CHSi(NCO)_3$, $CH_2{=}CHSi(NCS)_3$, $CH_2BrCHBrSi(OCOCF_3)_3$, $CH_2BrCHBrSi(OCOC_2F_5)_3$, $CH_2BrCHBrSi(OCO\text{-}n\text{-}C_3F_7)_3$, $CH_2BrCHBrSi(NCO)_3$, and $CH_2ClCHClSi(NCO)_3$. There is also adequate data for $CH_2{=}CHSi(OCOCH_3)_3$. These colorless compounds all hydrolyze easily and many decompose sufficiently at the normal boiling point to limit the accuracy of the individual boiling point.

A typical perfluoroester such as $CH_2{=}CHSi(OCOCF_3)_3$ has a higher thermal stability and

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(1) Presented at 15th Southwest Regional A. C. S. Meeting, Baton Rouge, La., December, 1959.

(2) G. S. Forbes and H. H. Anderson, *J. Am. Chem. Soc.*, 62, 761 (1940).

(3) H. H. Anderson, *J. Am. Chem. Soc.*, 69, 3049 (1947); 71, 1801 (1949); 72, 196 (1950).

(4) H. H. Anderson and T. C. Hager, *J. Am. Chem. Soc.*, 81, 1584 (1959).

(5) C. L. Agre and W. Hilling, *J. Am. Chem. Soc.*, 74, 3895, 3899 (1952).

(6) K. C. Frisch *et al.*, *J. Am. Chem. Soc.*, 74, 4584 (1952).

(7) L. H. Sommer *et al.*, *J. Am. Chem. Soc.*, 68, 485 (1946); 70, 2871 (1948).

liquid density and a lower normal boiling point and refractive index than the corresponding halogen-free ester such as CH_2=$CHSi(OCOCH_3)_3$. Comparably, distillation under reduced pressure furnishes pure $CH_2BrCHBrSi(OCOCF_3)_3$ but decomposes the supposed $CH_2BrCHBrSi(OCOCH_3)_3$ completely; the latter compound appears to form through reaction of bromine and CH_2=$CHSi(OCOCH_3)_3$.

Bromination of perfluoroesters at a moderate rate only in sunlight suggests a free radical mechanism.[8] A withdrawal of electrons from the carbon-carbon double bond toward the many fluorine atoms may explain the need for free radicals.

In this paper there are three isocyanates (this term is without proof of structure), CH_2=$CHSi(NCO)_3$, $CH_2ClCHClSi(NCO)_3$, and $CH_2BrCHBrSi(NCO)_3$, and only one successful isothiocyanate, CH_2=$CHSi(NCS)_3$. There is no success in isolating either $CH_2BrCHBrSi(NCS)_3$ or CH_2=$CHSiCl_2NCS$. Gradual addition of silver isothiocyanate to excess CH_2=$CHSiCl_3$ furnishes only CH_2=$CHSi(NCS)_3$, although there is some indication of an unstable CH_2=$CHSiCl_2NCS$. Preparation of $SiCl_3NCS$ is quite straightforward, however.[9] E_2 eliminations[7,8] may possibly explain the reaction of $CH_2BrCHBrSi(NCO)_3$ with fluoride in antimony trifluoride to form silicon tetrafluoride, vinyl bromide, and bromide ion and the reaction of $CH_2BrCHBrSiCl_3$ and 48% aqueous hydrogen fluoride to form silicon tetrafluoride, vinyl bromide, and bromide and chloride ions.

EXPERIMENTAL

Starting materials included special preparations of silver cyanate, silver isothiocyanate, $AgOCOCH_3$, $AgOCOC_2H_5$, $AgOCOCF_3$, $AgOCOC_2F_5$, $AgOCO$-n-C_3F_7, and freshly sublimed antimony trifluoride, and included vinyltrichlorosilane from Dow Corning Corp., Midland, Mich. All reactions were in a room in which the partial pressure of water vapor was under 10 mm.

Vinyltri(iso)cyanatosilane. Reflux of 33 g. of AgNCO and 9.15 g. of CH_2=$CHSiCl_3$ in 35 ml. of carbon tetrachloride for 1 hr., followed by filtration, washing of silver salts and then fractional distillation gave 8.75 g. (85% yield) of CH_2=$CHSi(NCO)_3$, the center fraction of which had the properties in Table I.

Vinyltriisothiocyanatosilane. Similarly, 10.0 g. of CH_2=$CHSiCl_3$ and 40 g. of AgNCS in 30 ml. of carbon tetrachloride furnished 12.3 g. (86% yield) of CH_2=$CHSi(NCS)_3$; the center fraction had the properties in Table I.

Vinyltripropionoxysilane and vinyltriacetoxysilane. Similarly, CH_2=$CHSiCl_3$ and an excess of $AgOCOCH_3$ or $AgOCOC_2H_5$ in carbon tetrachloride furnished chlorine-free CH_2=$CHSi(OCOCH_3)_3$ or CH_2=$CHSi(OCOC_2H_5)_3$, respectively.

Vinyltris(trifluoroacetoxy)silane, vinyltris(pentafluoropropionoxy)silane, and vinyltris(heptafluoro-n-butyroxy)silane. Typically, 6.30 g. of CH_2=$CHSiCl_3$ and 34.2 g. (a 30% excess) of $AgOCOCF_3$ in 35 ml. of carbon tetrachloride similarly furnished 9.0 g. (60% yield) of CH_2=$CHSi(OCOCF_3)_3$.

TABLE I
PROPERTIES OF NEW (EXCEPT 4TH) HALOGENOIDS AND ESTERS

Compound	B.P.	d_4^{20}	$n^{20}D$	Mol. Refr.		Silicon, %[b]		Ester or Halide[c]		Distilled at	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Temp.	Mm.
CH_2=$CHSi(OCOCF_3)_3$	144.3	1.603	1.3217	52.37	52.22	7.13	7.15	86.0	85.8	84-86	70
CH_2=$CHSi(OCOC_2F_5)_3$	168	1.567	1.3112	67.36	67.16	5.16	5.34	89.9	89.5	97-98	50
CH_2=$CHSi(OCO$-n-$C_3F_7)_3$	198[d]	1.639	1.3122	82.35	82.16	4.05	4.04	92.1	92.0	117-118	32
CH_2=$CHSi(OCOCH_3)_3$[e]	231[d]	1.167	1.4226	50.80	50.64	12.09	12.20	76.3	76.3	112-113	1
CH_2=$CHSi(OCOC_2H_5)_3$	249[d]	1.098	1.4257	64.75	63.98	10.24	10.10	79.9	79.7	100-111	1
CH_2=$CHSi(NCO)_3$	176.3	1.251	1.4587	39.44	39.57	15.50	15.28	69.6	69.4	97-98	33
CH_2=$CHSi(NCS)_3$	276	1.292	1.6409	64.31[a]	64.04	12.25	12.20	76.0	76.0	117-118	1
$CH_2BrCHBrSi(OCOCF_3)_3$	195[d]	1.862	1.3799	68.27	68.95	5.07	5.18	61.2	61.4	131-132	58
$CH_2BrCHBrSi(OCOC_4F_9)_3$	219[d]	1.836	1.3555	83.26	83.68	3.99	4.05	69.5	69.5	91-92	1
$CH_2BrCHBrSi(OCOC_2F_5)_3$	241[d]	1.856	1.3486	98.25	98.64	3.29	3.39	74.8	74.8	110-111	1
$CH_2BrCHBrSi(NCO)_3$	261[d]	1.918	1.5357	55.35	55.43	8.24	8.39	37.0	37.0	137-138	1
$CH_2ClCHClSi(NCO)_3$	248[d]	1.481	1.4970	49.58	49.81	11.14	11.20	50.0	50.3	117-118	1

[a] In white light. [b] Weighed as silicon dioxide. [c] Average of two close values by titration. [d] Decomposition occurred during measurement of normal boiling point. [e] Using value for Si—NCS derived from Reference 3.

(8) Jack Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956. Especially pages 185 and 428.

(9) H. H. Anderson, *J. Am. Chem. Soc.*, 67, 223 (1945).

1,2-Dibromoethyltri(iso)cyanatosilane. Gradual addition of 3.39 g. of bromine to 3.88 g. of CH_2=$CHSi(NCO)_3$ in a 10-ml. stoppered flask, mainly in artificial light at 0° but with a little daylight at the end, left a slight excess of free bromine. After transfer and subsequent removal of free bromine under 30 mm. pressure, then fractional distillation as in Table I gave 6.15 g. (84% yield) of $CH_2BrCHBrSi(NCO)_3$, the center cut of which had a moderate viscosity and the properties listed.

1,2-Dichloroethyltri(iso)cyanatosilane. A slow, 80-min. passage of chlorine gas, until the solution no longer absorbed chlorine, into 9 g. of CH_2=$CHSi(NCO)_3$ at 0° in sunlight finally gave 11.8 g. (94% yield) of $CH_2ClCHClSi(NCO)_3$. Table I lists the center fraction, a portion of which hydrolyzed slowly at first but later moderately rapidly in water at 25°.

1,2-Dibromoethyltris(trifluoroacetoxy)silane, 1,2-dibromoethyltris(pentafluoropropionoxy)silane, and 1,2-dibromoethyltris(heptafluoro-n-butyroxy)silane. Typically, gradual addition of 2.46 g. of bromine to 6.40 g. of CH_2=$CHSi(OCOCF_3)_3$ at 0° in sunlight—the reaction was very slow in artificial light—left a very slight excess of free bromine. After transfer and then removal of bromine under 30 mm. pressure, fractional distillation showed the essential absence of CH_2=$CHSi(OCOCF_3)_3$ and furnished 7.9 g. (88% yield) of $CH_2BrCHBrSi(OCOCF_3)_3$, the center fraction having the properties in Table I. Similarly, 2.27 g., a slight deficiency, of bromine and 10.07 g. of CH_2=$CHSi(OCO\text{-}n\text{-}C_3F_7)_3$ gave 11.6 g. (94% yield) of $CH_2BrCHBrSi(OCO\text{-}n\text{-}C_3F_7)_3$. A comparable process furnished $CH_2BrCHBrSi(OCOC_2F_5)_3$.

Brominations of vinyltriacetoxysilane and vinyltriisothiocyanatosilane. Similarly, 3.52 g. of bromine and 5.19 g. of CH_2=$CHSi(OCOCH_3)_3$ easily furnished a colorless, very viscous liquid, presumably $CH_2BrCHBrSi(OCOCH_3)_3$, but distillation under 1 mm. pressure gave total decomposition and much solid residue. Bromine and CH_2=$CHSi(NCS)_3$ reacted, but distillation under 1 mm. pressure produced a liquid and also a solid, probably $Si(NCS)_4$.

Reactions of 1,2-dibromoethyltrichlorosilane. Carefully purified $CH_2BrCHBrSiCl_3$ had normal b.p. 220°, d_4^{20} 2.046, n^{20} 1.5369, mol. refr. 49.04 (calcd. 48.95), also b.p. 142–143° under 75 mm. pressure. A vigorous reaction between 16 g. of $CH_2BrCHBrSiCl_3$ and 16 g. of gradually added 48% hydrofluoric acid occurred at 10° in a polyethylene vessel; silicon tetrafluoride and hydrogen bromide were among the escaping gases and no organosilicon layer such as $CH_2BrCHBrSiF_3$ remained in the polyethylene vessel. Evidently the reaction products were silicon tetrafluoride, hydrogen chloride, hydrogen bromide, and vinyl bromide, all uncondensed gases.

Reflux of 10 g. of $CH_2BrCHBrSiCl_3$ in 30 ml. of carbon tetrachloride with 20 g. of AgNCO for an hour ultimately gave 2.0 g. of nearly pure $Si(NCO)_4$, b.p. 188°, d_4^{20} 1.450 and n^{20} 1.4629, and 2.6 g. of crude $CH_2BrCHBrSi(NCO)_3$, b.p. 254°, n^{20} 1.5160 and d_4^{20} 1.810, with large NCO and medium hydrolyzable bromide.

Similarly, $CH_2BrCHBrSiCl_3$ and $AgOCOCF_3$ finally gave a low fraction of b.p. 135° and n^{20} 1.302 and a small higher fraction of b.p. 174° and n^{20} 1.3166; both fractions were bromine-free and extremely hydrolyzable. Evidently a contaminated CH_2=$CHSi(OCOCF_3)_3$ was present.

Reaction of 1,2-dibromoethyltri(iso)cyanatosilane and antimony trifluoride. Six grams of $CH_2BrCHBrSi(NCO)_3$ and 3.8 g., an excess of freshly sublimed antimony trifluoride reacted spontaneously at 25° but formed no gases condensing at 0°. No organosilicon compounds remained in the mixture of antimony salts. Evidently the products were $Sb(NCO)_3$, antimony tribromide, silicon tetrafluoride and vinyl bromide, the latter perhaps swept through the condenser by the silicon tetrafluoride gas.

Analytical. All halogenoids or esters with the vinyl group gave satisfactory titrations with ethanolic sodium hydroxide. A light-medium orange-red of cresol red indicator stable for 15 seconds was satisfactory for the titration of $CH_2ClCHClSi(NCO)_3$ and the $CH_2BrCHBrSiX_3$ types; the endpoint fades with time. Because the *beta* halogen is quantitatively acidic, the halogen or ester attached to silicon is 75.0% of the observed acidity.

Acknowledgment. Mr. Abdolah Hendifar very kindly assisted in the preparation of many crude reaction products from vinyltrichlorosilane and silver salts.

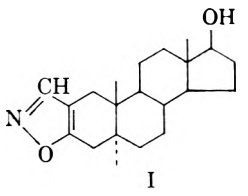
CHEMISTRY DEPARTMENT
DREXEL INSTITUTE OF TECHNOLOGY
PHILADELPHIA 4, PA.

Communications TO THE EDITOR

Steroidal[2,3-d]isoxazoles

Sir:

We have previously reported[1] the effect on endocrinological activity produced by the fusion of a pyrazole ring to the 2,3-positions of several hormonally active steroids. Noteworthy changes in the type of endocrinological activity, or in the separation of several activities, are also observed when an isoxazole ring is similarly fused to hormonally active steroids. The resultant steroidal[2,3-d]-



I

isoxazoles, (*e.g.*, I) constitute a new[2] class of modified steroids.

The reaction of 2-hydroxymethyleneandrostan-17β-ol-3-one[3] with hydroxylamine hydrochloride in ethanolic solution gave 17β-hydroxyandrostano-[2,3-d]isoxazole, I, m.p. 179.8–182.0°, $[\alpha]_D$ + 61.6°, λ_{max} 228 mμ (4900) (found: C, 75.93; H, 9.38; O, 9.90[4]). Treatment of I with cyclohexylpropionic anhydride in pyridine solution gave 17β-(3-cyclohexylpropionoxy)androstano[2,3-d]isoxazole, II, m.p. 140.4–141.8°, $[\alpha]_D$ + 40.6° (Found: C, 76.54; H, 9.63; N, 3.12).

Similarly, the reaction of hydroxylamine hydrochloride with the intermediate 2-hydroxymethylene-3-ketosteroids[1,5] gave 17β-hydroxy-17α-methylandrostano[2,3-d]isoxazole, III, m.p. 171.4–173.2°, $[\alpha]_D$ + 36.2° (found: C, 76.70; H, 9.55: O, 10.00), 17β-hydroxy-17α-methylandrost-4-eno[2,3-d]isoxazole, IV, m.p. 175.0–179.2°, $[\alpha]_D$ + 107.5°, λ_{max} 285 mμ (11,900) (found: C, 76.90; H. 8.77; O, 9.80), and 17β-hydroxy-17α-methylandrosta-4,6-dieno[2,3-d]isoxazole, V, m.p. 193.4–199.0°, $[\alpha]_D$ −187.8°, λ_{max} 245, 253, 319 mμ (3000, 2500, 19,800 respectively) (found: C, 77.19; H, 8.29; O, 10.05). From 2-hydroxymethylene-17α-methyl-19-norandrost-4-en-17β-ol-3-one[6] there was obtained the corresponding 17β-hydroxy-17α-methyl-19-norandrost-4-eno[2,3-d]isoxazole, VI, m.p. 160.2–161.0°, $[\alpha]_D$ − 43.3°, λ_{max} 287 mμ (10,400) (found: C, 76.78; H, 8.65; N, 4.51).

Compounds I, III, and IV proved to be very active when tested for myotrophic[7] and anabolic activities, and in addition they have low androgenic activity. Compound V, however, is a considerably less active myotrophic agent (and less androgenic) than either III or IV. In contrast to the corresponding steroidal[3,2-c]pyrazoles,[1] neither IV nor V show any estrogenicity.

Compound II is a very potent anabolic agent, with a long duration of action and minimal androgenicity. Peak response to this ester occurs from three to four weeks after a single subcutaneous injection.

Compound VI is progestational (equal in activity to progesterone intramuscularly, and at least as active as Ethisterone when given orally), highly active both anabolically and myotrophically, and in addition has a low degree of androgenic and estrogenic activities. The latter response, however, is atypical since considerable mucification and leucocytic infiltration accompany cornifying effects on the vaginal epithelium.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y.
R. O. CLINTON
A. J. MANSON
F. W. STONNER
R. G. CHRISTIANSEN
A. L. BEYLER
G. O. POTTS
AARON ARNOLD

Received July 20, 1960

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(2) F. Winternitz, C. Menou, and E. Arnal, *Bull. soc. chim. France*, 505 (1960), have recently prepared 2α-cyanocholestan-3-one *via* the intermediate cholestano-[2,3-d]isoxazole; the latter compound was not isolated.

(3) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959). The compound described as 2-hydroxymethylenedrostan-17β-ol-3-one by F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959) is actually the corresponding enol ether, 2-methoxymethyleneandrostan-17β-ol-3-one (data to be published from these laboratories).

(4) Melting points are corrected; rotations were taken in chloroform solution and ultraviolet spectra in 95% ethanol.

(5) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(6) J. Edwards and H. J. Ringold, ref. 3.

(7) Anabolic activity was determined by nitrogen retention, myotrophic activity by the growth response of the levator ani muscle, androgenicity by the gain in weight of the ventral prostate, and estrogenicity by vaginal cornification, all in rats. Progestational activity was evaluated by the Clauberg test in rabbits. Compounds I and II were administered by subcutaneous injection and compounds III, IV, and V were given orally.

A Convenient Synthesis of Alkyl Halides from Carboxylic Acids

Sir:

The salts of a variety of metals and carboxylic acids upon treatment with halogens lead to the halogenative decarboxylation reaction $RCOOM + X_2 \rightarrow RX + MX + CO_2$.[1] Of these reactions, that of the silver salt (generally termed the Hunsdiecker reaction) appears to be the most useful.[1] This reaction has the practical disadvantage that the silver salt must be relatively pure and must be scrupulously dry in order to obtain satisfactory yields. In the course of our studies[2] on the mechanism of the decomposition of the acyl hypobromite intermediate[1] in the Hunsdiecker reaction, we attempted to prepare this intermediate in another fashion. This has led to what appears to us to be a useful preparative method, as reagents and operations are much more convenient than the silver salt–bromine reaction.

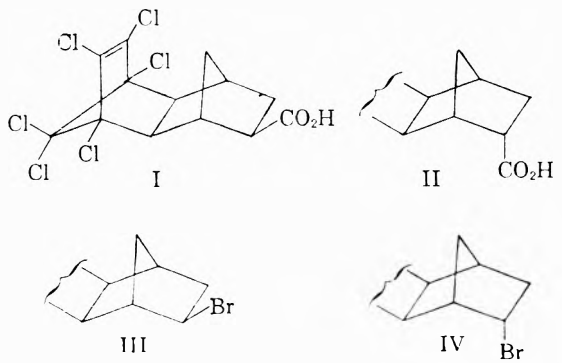
Treatment of a slurry of excess red mercuric oxide in a refluxing solution of an aliphatic carboxylic acid in carbon tetrachloride with approximately one equivalent of bromine in the dark led to excellent yields of the corresponding alkyl bromide. For example, treatment of 0.25 mole of stearic acid with 0.25 mole of bromine and 0.19 mole of red mercuric oxide in 150 ml. of carbon tetrachloride for one hour gave a 93% yield of crude heptadecyl bromide, m.p. 22° (lit.[3] m.p. 32° for pure material). The presumable stoichiometric equation is as follows:

$$2\ RCOOH + HgO + 2\ Br_2 \longrightarrow 2\ RBr + HgBr_2 + H_2O + 2\ CO_2 \quad (1)$$

Since our original observation, the reaction has been found to go in fair to excellent yields with cyclopropanecarboxylic acid and bromine,[4] with 9,10-dihydro-9,10-ethano-9-anthroic acid with bromine in carbon tetrachloride and with iodine in cyclohexane,[5] with lauric acid and bromine,[6] with stearic acid and iodine,[6] and in poor yield to give 1,3-dibromopropane from glutaric acid.[6] No γ-butyrolactone was found in the latter case.

The reaction gave poor yields with benzoic acid and bromine. Tetrachloroethane may also be used as solvent.[4] Silver oxide may not be substituted for mercuric oxide, and reaction in light gives polybromination.

When either *exo*- (I) or *endo*-5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8.8a-octahydro-*exo*-*endo*-1,4,5,8-dimethano-2-naphthoic acid (II)[2] was treated under these conditions, a mixture of 71% *exo*-(III) and 29% *endo*-bromides (IV)[2] was formed. This is precisely the same mixture of bromides obtained from the silver salt of either acid with bromine.[2] This suggests that both procedures lead to the same intermediate RCOOX. The reaction may involve the existence of the mercuric salt although (a) it has been reported[1a] that mercury salts of acids such as stearic acid do not give good yields following the normal Hunsdiecker reaction, and (b) glutaric acid does not give γ-butyrolactone, whereas the silver (and presumably the mercury) salt gives the lactone. It seems most likely that the mercuric oxide gives a positive halogen species,[7] which reacts with the carboxylic acid to give the acyl hypohalite. If this is the case, and if equation (1) represents the stoichiometry of the reaction, we do not understand why the water formed does not interfere with the reaction as it apparently does in the Hunsdiecker procedure where glassware and chemicals need to be scrupulously dry.[1] In any case, the preparative value of this procedure lies in its convenience and simplicity in comparison to those procedures involving preparation of silver or mercury salts.



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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLO.

STANLEY J. CRISTOL
WILLIAM C. FIRTH, JR.

Received October 21, 1960

(1) For leading references see: (a) H. Hunsdiecker and C. Hunsdiecker, *Ber*, **75**, 291 (1942); (b) R. G Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956); (c) C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

(2) S. J. Cristol, J. R. Douglass, W. C Firth, Jr., and R. E Krall, *J. Am. Chem. Soc.*, **82**, 1928 (1960).

(3) For comparable results with the silver salt see: J. W. H. Oldham, *J. Chem. Soc.*, 100 (1950).

(4) J. S. Meek and D. T. Osuga, unpublished work.

(5) J. S. Meek and P. W. Jennings, unpublished work.

(6) S. J. Cristol and J. S. Nelson, unpublished work.

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Free Radical Hydroxylations with Peracetic Acid

Sir:

We wish to report the reaction between peracetic acid and saturated hydrocarbons under conditions conducive to the formation of free radicals. While being irradiated with a 200-watt Hanovia high pressure quartz mercury arc in a Vycor well, excess cyclohexane was treated dropwise with a solution of peracetic acid[1] (23.5 weight %) in ethyl acetate at 22–25°. Vigorous evolution of gas was evident throughout the reaction period (13 hr.); by mass spectral analysis the gas was carbon dioxide, methane, and cyclohexane (52.2, 42.1, and 5.7 mole %, respectively). After neutralizing with aqueous potassium hydroxide and washing, the organic layer was fractionated to give, after recovery of excess cyclohexane, a mixture of cyclohexanol and cyclohexanone, b.p. 150–160°. The mixture contained 6.3% cyclohexanone (hydroxylamine titration) and 90.2% cyclohexanol (phthalic anhydride titration). (2,4-Dinitrophenylhydrazone, m.p. and mixed m.p. with cyclohexanone 2,4-dinitrophenylhydrazone, 156–158°; 3,5-dinitrobenzoate, m.p. and mixed m.p. with cyclohexanol 3,5-dinitrobenzoate, 111–112°.) The infrared spectrum of this mixture was consistent with this analysis. Yield of cyclohexanol was 38%.

cis-Decalin (b.p. 190–193°) treated similarly gave a mixture of isomeric decalols, of which a major portion was *trans*-9-decalol (b.p. 104–106°/20 mm., m.p. 52–54°, infrared peaks at 2.88 and 8.57 μ). *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76; mol. wt., 154.2. Found: C, 78.05; H, 11.74; mol. wt., 159. The yield of crude tertiary alcohol was 49%; total yield of all oxygenated products was much higher.

Compounds containing carbon-oxygen functions suffered further oxidation at such carbon atoms, as anticipated. γ-Valerolactone gave levulinic acid in 42% yield (b.p. 133–137°/10 mm., n 30°/D = 1.4333, acid equiv. calcd. 116, found, 110, m.p. and mixed m.p. of semicarbazone with authentic semicarbazone of levulinic acid, 190–191.5°). Di-(n-hexyl) ether gave caproic acid (b.p. 98°/10 mm., n 20°/D = 1.4171, m.p. of amide, 95–98°) in 56% yield; the coproduct was n-hexanol (b.p. 156–158°, n 20°/D = 1.4182, m.p. and mixed m.p. of 3,5-dinitrobenzoate with authentic 3,5-dinitrobenzoate of n-hexanol, 57.5–58°) in 67% yield.

Free radical hydroxylation with peracetic acid could also be effected thermally. *endo*-Tetrahydrodicyclopentadiene was heated to 185° and treated dropwise with peracetic acid solution; a high solution temperature was maintained by continuously removing ethyl acetate at the head of a column in the vessel. After washing to remove acid, the products were fractionated; a major product was the tertiary alcohol, *endo*-5,6-trimethylene-5-*exo*-norbornanol[2] [b.p. 125–130°/10 mm., m.p. (ligroin) 131–132°. *Anal.* Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.66; peak at 3.05 μ].

The previous literature provides little indication of such a reaction. The decomposition of perlauric acid in several solvents or in a melt has been found[3] to proceed predominantly by a non-radical mechanism to give lauric acid and oxygen, with small amounts of an ester that could have arisen by a radical mechanism. Recently, perlauric acid was reported[4] to decompose in a boiling solvent (40–70°) to give mainly products anticipated for a free radical decomposition, *viz.*, n-undecanol and carbon dioxide.

It is probable that a mechanism similar to the one proposed in both earlier publications[3,4] accounts for initiation of the present hydroxylation reaction. Relatively short chains appear to be involved. Chain propagation can be provided as in steps 2, 3, and 4. Several chain-terminating re-

$$CH_3CO_3H \longrightarrow CH_3CO_2\cdot + \cdot OH \quad (1)$$

$$CH_3CO_2\cdot \longrightarrow CH_3\cdot + CO_2 \quad (2)$$

$$CH_3\cdot + RH \longrightarrow CH_4 + R\cdot \quad (3)$$

$$R\cdot + CH_3CO_3H \longrightarrow ROH + CH_3CO_2\cdot \quad (4)$$

actions can occur, for most of which there is direct evidence. The reaction is inhibited completely by oxygen; it could be initiated by cobaltic ion, although poorer yields and more complex mixtures of products were obtained. These results will be detailed in forthcoming publications; the new reaction is general and extremely useful.

UNION CARBIDE CHEMICALS COMPANY
RESEARCH DEPARTMENT
SOUTH CHARLESTON, W. VA.
DONALD L. HEYWOOD
BENJAMIN PHILLIPS
HARRY A. STANSBURY, JR.

Received September 7, 1960

(1) B. Phillips, F. C. Frostick, Jr., and P. S. Starcher, *J. Am. Chem. Soc.*, 79, 5982 (1957).

(2) The proof of structure of this alcohol will be presented in a forthcoming publication by Paul von R. Schleyer.

(3) See W. E. Parker, L. P. Witnauer, and D. Swern, *J. Am. Chem. Soc.*, 80, 323 (1958), and references therein.

(4) D. Lefort, C. Paquot, and J. Sorba, *Bull. Soc. Chim. France*, 1385 (1959).

Reaction of *t*-Butyl Peresters with Thio Ethers

Sir:

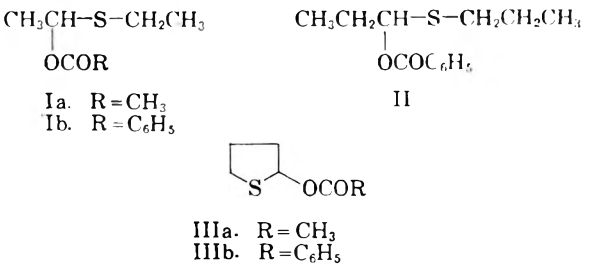
In a previous communication[1] the reaction of *t*-butyl peresters with aliphatic and cyclic ethers in the presence of cuprous bromide was described.

(1) G. Sosnovsky, *J. Org. Chem.*, 25, 874 (1960).

This work has now been extended to include thioethers.[2]

It is well known that sulfides react with various peroxy compounds such as hydrogen peroxide, peracids,[3] and hydroperoxides[4] to give good yields of sulfoxides or sulfones. In contrast, we have found that *t*-butyl peresters react smoothly with aliphatic and cyclic sulfides to give the corresponding acyloxy derivatives and that there is no oxidation of the sulfur atom under the chosen experimental conditions.

Specifically, the reaction of 0.3 mole of *t*-butyl peracetate with 0.35 mole of diethyl sulfide in benzene (50 ml.) in the presence of 0.35 mmole of cuprous bromide for 64 hr. at 80–85° yielded 44% of 1-acetoxy diethyl sulfide (Ia), b.p. 70–72°, 22 mm., n_D^{25} 1.4468, $\gamma_{C=O}$ 1730 cm.$^{-1}$ *Anal.* Calcd. for $C_6H_{12}O_2S$: C, 48.64; H, 8.16, S, 21.60; mol. wt., 148. Found: C, 48.84; H, 8.30; S, 21.97; mol. wt., 146.



Ia. R = CH_3
Ib. R = C_6H_5

II

IIIa. R = CH_3
IIIb. R = C_6H_5

Similarly, the reaction of 0.2 mole of *t*-butyl perbenzoate and 0.5 mole of diethyl sulfide in the presence of 0.35 mmole of cuprous bromide for 26 hr. at 80–90° yielded 31% of Ib, b.p. 75° at 0.1 mm., n_D^{25} 1.5266, $\gamma_{C=O}$ 1715 cm.$^{-1}$ *Anal* Calcd. for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22; mol. wt., 210. Found: C, 63.40; H, 6.98; S, 15.03; mol. wt., 216.

Under similar catalytic conditions, 0.4 mole of *t*-butyl perbenzoate reacted with 0.4 mole of di-*n*-propyl sulfide for 5 hr. at 85–97° to yield 69% of 1-benzoyloxy dipropyl sulfide (II), b.p. 90° at 0.04 mm., n_D^{25} 1.5175, $\gamma_{C=O}$ 1725 cm.$^{-1}$ *Anal.* Calcd. for $C_{13}H_{18}O_2S$: C, 65.53; H, 7.61; S, 13.47; mol. wt., 238. Found: C, 65.59; H, 7.73; S, 13.74; mol. wt., 231. The reaction of 0.3 mole of *t*-butyl peracetate with 0.5 mole of tetrahydrothiophene for 6 hr. at 90° gave 56% of 2-acetoxytetrahydrothiophene (IIIa), b.p. 60–62° at 0.1 mm., n_D^{25} 1.4893, $\gamma_{C=O}$ 1735 cm.$^{-1}$ *Anal.* Calcd. for $C_6H_{10}O_2S$: C, 49.31; H, 6.90; S, 21.90; mol. wt., 146. Found: C, 49.53; H, 7.16; S, 21.86; mol. wt., 141. Also, 0.25 mole of *t*-butyl perbenzoate with 0.5 mole of tetrahydrothiophene for 5 hr. at 90° gave 69% of IIIb, n_D^{25} 1.5650 (after chromatography on alumina), $\gamma_{C=O}$ 1735 cm.$^{-1}$ Because of thermal instability, IIIb could not be purified by distillation. *Anal.* Calcd. for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81; mol. wt., 208. Found C, 63.13; H, 6.02; mol. wt., 198.

In the absence of the catalyst the acyloxy compounds formed more slowly and in lesser quantity. Similar to the acyloxy derivatives of ethers, the sulfur compounds are sensitive to heat; they pyrolyze slowly at 100° and rapidly at slightly elevated temperatures. Thus, 2-benzoyloxytetrahydrothiophene (IIIb) at 110° for 2 hr. gave benzoic acid plus an 80% yield of 2,3-dihydrothiophene, b.p. 48° at 100 mm., n_D^{25} 1.5268.[5] *Anal.* Calcd. for C_4H_6S: C, 55.76; H, 7.03; mol. wt., 86. Found: C, 55.41; H, 7.21; mol. wt., 87. After several trap-to-trap distillations the product was shown by vapor phase chromatography to contain less than 1% impurities. Our method constitutes a new and improved synthesis of the 2,3-isomer of dihydrothiophene. When a mixture of IIIb and *t*-butyl alcohol was heated at reflux for about 100 hr., benzoic acid was eliminated quantitatively and an oil was isolated (yield 64%), b.p. 90° at 0.5 mm, n_D^{25} 1.6006. The elemental analyses and the molecular weight agree well with the formula for a dimer of dihydrothiophene. *Anal.* Calcd. for $C_8H_{12}S_2$: C, 55.80; H, 7.03; S, 37.17: mol. wt., 172. Found: C, 55.45; H, 6.77; S, 37.15; mol. wt., 179.

Thermal decomposition of the benzoyloxy derivatives of aliphatic sulfides in the presence of *t*-butyl alcohol gave a different result. Thus, Ib and II gave 1-mercaptoethyl diethyl sulfide and 1-mercaptopropyldipropyl sulfide, respectively.

The observations reported here are being investigated further and the details will be published at a later date.

Acknowledgment. The author is indebted to the Pennsalt Chemical Corporation for a sample of tetrahydrothiophene and to the Phillips Petroleum Company for samples of ethyl and propyl sulfides.

ARMOUR RESEARCH FOUNDATION GEORGE SOSNOVSKY
OF ILLINOIS INSTITUTE OF TECHNOLOGY
10 WEST 35TH STREET
CHICAGO 16, ILL.

Received October 14, 1960

(2) A brief account of this investigation was presented at the 138th Meeting of the American Chemical Society in New York, N. Y., September 1960.

(3) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Son, Inc., New York, N.Y., p. 801, 1953.

(4) K. R. Hargrave, *Proc. Roy. Soc., London*, **235A**, 55 (1956).

(5) S. F. Birch and D. T. McAllan, *J. Chem. Soc.*, 2556 (1951).

The Free Radical Chemistry of Epoxides: A Radical Rearrangement and Displacement

Sir:

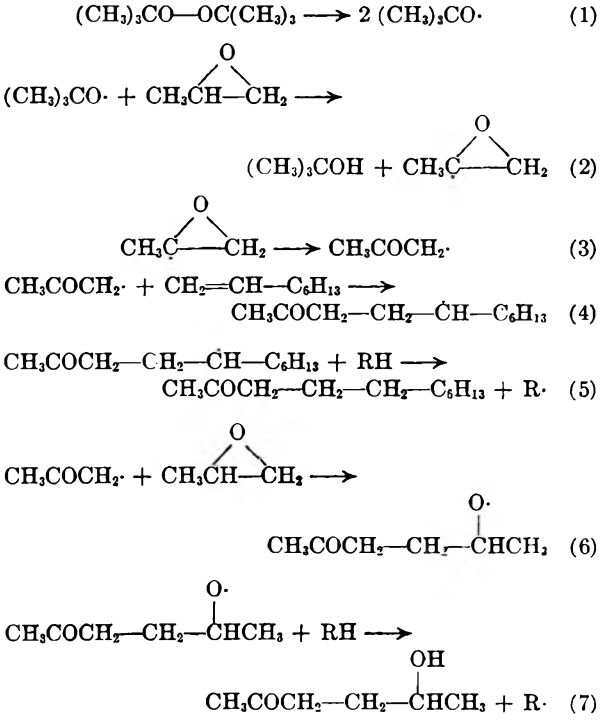
The attack of a free radical or atom on a double bond has long been known,[1] and the corresponding

(1) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957.

attack and ring opening of the three-membered carbon ring has recently been reported.[2] In support of the latter and to report an interesting electron realignment of a free radical, we wish to describe results obtained from a study of the free radical chemistry of the epoxide ring. It was found that the radical formed from propylene oxide by hydrogen atom abstraction isomerized to a keto-radical and that this keto-radical attacked both a double bond and the epoxide ring.

When propylene oxide, 1-octene, and *tert*-butyl peroxide were heated at 150° for 2 hr., a product, b.p. 50–57° (0.26 mm.), was obtained. This was shown to be a 4:1 mixture of 2-undecanone (8.3% yield based on 1-octene) and 5-hydroxy-2-hexanone (2% yield based on propylene oxide) by gas chromatography. When a similar reaction mixture was heated at 125° for 17 hr. the product was mainly the hydroxy ketone. The 2-undecanone gave a semicarbazone, m.p. 118–120°, reported 119–120°,[3] and the 5-hydroxy-2-hexanone was similar to the authentic compound.[4]

The following reaction scheme seems reasonable:



To test the mode of formation of the hydroxy ketone, propylene oxide was brought into reaction with other compounds which have reactive hydrogen atoms. In support of the postulate, toluene, propylene oxide, and *tert*-butyl peroxide gave bibenzyl, 5-hydroxy-2-hexanone, and 4-phenyl-2-butanol; cyclohexane, propylene oxide, and *tert*-butyl peroxide afforded 5-hydroxy-2-hexanone, 2,5-hexanedione, cyclohexylacetone, and 1-cyclohexyl-2-propanol; and ethanol, propylene oxide, and *tert*-butyl peroxide gave 5-hydroxy-2-hexanone and 2,4-pentanediol. All the product identifications were done by gas chromatography by comparison with authentic compounds.

Studies are in progress to determine if the displacement reaction on the epoxide ring (reaction 6) is a frontside or backside attack, and whether or not the *tert*-butoxy radical also gives the displacement.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CONNECTICUT
STORRS, CONN.

ROY J. GRITTER
THOMAS J. WALLACE[5]

Received October 12, 1960

(2) D. E. Applequist, G. F. Fanta, and B. W. Henrikson, *J. Am. Chem. Soc.*, 82, 2368 (1960).

(3) H. D. Dakin, *J. Am. Chem. Soc.*, 44, 47 (1910).

(4) R. M. Adams and C. D. Vanderwerf, *J. Am. Chem. Soc.*, 72, 4368 (1950).

(5) From the Ph.D. thesis and some post-doctoral research by T. J. W. whose present address is Esso Research and Engineering Co., Linden, N. J.

Photolysis of Aromatic Iodo Compounds as a Synthetic Tool

Sir:

Our interest in the chemistry of thyroxine and related substances[1] led us to examine the photochemical decompositions of certain iodinated thyronines and iodotyrosines. The behavior of these substances, on irradiation, is complex and the interpretation of the results required a prior study of simpler systems. Hence, we studied the photolysis of model substances, such as iodobenzene, *o*- and *p*-iodophenols, *p*-iodonitrobenzene, and 2,6-di-iodo-*p*-cresol under definitive conditions.

Our initial results suggest that photolysis of a variety of iodoaromatic compounds by essentially monochromatic light (2537Å), at or near room temperature, in dilute solution in an appropriate aromatic solvent, is a reaction which has broad synthetic and theoretical implications. While this work was in progress, reports by Szychlinski[2] and Blair and Bryce-Smith,[3] which deal with related reactions, also appeared, but to our knowledge it has not been previously shown that the reactions could be carried out in a synthetically useful manner and with a variety of substituted iodoaryl compounds (*e.g.*, the iodophenols).

(1) J. Roche, R. Michel, and Walter Wolf, *Bull. soc. Chim. France* 467 (1958); N. Kharasch and N. N. Saha, *Science* 127, 756 (1958).

(2) J. Szychlinski, *Roczniki Chem.* 34, 267 (1960).

(3) J. M. Blair and D. Bryce-Smith, *J. Chem. Soc.*, 1788 (1960).

The problem in adapting the photolysis of aromatic iodo compounds for synthetic purposes is to establish conditions which promote the scission of the carbon-iodine bonds without causing subsequent reactions of products, or undesired side reactions. Thus, the use of a quartz housing and a wide-spectrum light source lead to various side reactions.[3] However, by conducting the reaction at or near room temperature and using an ultraviolet source which provides energy at a wave length which essentially cleaves only the carbon iodine bond, the side reactions are minimized.

The synthesis of 2-hydroxybiphenyl in one step, in 60–70% yields of chromatographically pure product, is carried out as follows: *o*-Iodophenol (1g) in 50 ml. pure, dry benzene, was irradiated in a "Vycor"-7100 tube, by a helical cold-cathode, low pressure mercury lamp (manufactured by Dallons Laboratories, Los Angeles, California). After twenty hours of irradiation, the release of iodine, conveniently measured by titration with thiosulfate, was complete. Isolation of the product from the organic layer and purification by two passes through an alumina column gave 0.46 g. (60% yield) of pure 2-hydroxybiphenyl, fully characterized by its m.p.[4] and infrared spectrum.

By similar procedures, in syntheticaliy useful yields, we obtained the following products: diphenyl (from iodobenzene irradiated in benzene); 4-hydroxybiphenyl (from *p*-iodophenol irradiated in benzene); 4-nitrobiphenyl (from 4-iodo-nitrobenzene irradiated in benzene); a separable mixture of 2-methyl-4′-nitrobiphenyl and 4-methyl-4′-nitrobiphenyl (by irradiation of 4-iodonitrobenzene in toluene); and 2-methoxybiphenyl (by irradiation of iodobenzene in anisole). The irradiation of 1 g. of 2,6-di-iodo-*p*-cresol in benzene led to 712 mg. of a highly crystalline, *iodine-free* product, m.p. 66–7°, the infrared spectrum of which showed a phenolic group and polyphenyl absorption, but which has not yet been fully characterized. The structure of the fully-characterized products obtained are those to be expected for free radical attack on the substrates used.[5] These reactions, which occur at the wave lengths where iodoaromatic compounds show continuous absorption, can thus be considered as occurring, undoubtedly, by free radical mechanisms. The effective, low temperature generation of aryl radicals, and specifically of hydroxyaryl radicals, by this means, is novel. The use of diiodoarenes in this synthesis is also illustrated by the formation of *p* terphenyl from *p*-diiodobenzene and of *p*-quaterphenyl from 4,4′-diiodobiphenyl, irradiated in benzene.

We are continuing studies to determine the scope of these reactions, both as regards sources for aryl radicals, from iodo compounds, as well as solvents capable of capturing the radicals generated by the photochemical technique.

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Department of Chemistry Walter Wolf
University of Southern California
Los Angeles 7, Calif. Norman Kharasch

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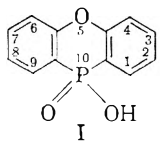
The Phenoxphosphinic Acid Ring System

Sir:

Only a few phosphinic acids are known in which the phosphorus atom is a member of a ring system.[1] In particular, the synthesis of phenoxphosphinic acid (I) or its derivatives has not been previously accomplished. Although phenoxarsinic acid is easily prepared by refluxing phenyl ether with arsenic trichloride and a small quantity of aluminum



I

chloride and then oxidizing the resulting chloroarsine with bromine water,[2] the analogous reaction with phosphorus trichloride yields *p*-phenoxyphenylphosphonic acid.[3] It is not clear why arsenic trichloride preferentially attacks the 2-position of phenyl ether, while phosphorus trichloride attacks the 4-position.

Numerous attempts in this laboratory to prepare phenoxphosphinic acid by the intramolecular dehydration of *o*-phenoxyphenylphosphonic acid have met with failure.[4] This compound is unaffected by polyphosphoric acid at 130° and is apparently sulfonated by concentrated sulfuric acid at 100°. The method of Campbell and Way,[5] whereby 2-biphenylylphenylphosphinic acid was cyclized to 9-phenyl-9-phosphafluorene 9-oxide by heating with an excess of phosphorus pentachloride in nitrobenzene, also failed with *o*-phenoxyphenylphosphonic acid. We can not explain the resistance of *o*-phenoxyphenylphosphonic acid to cyclization, but

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(2) W L Lewis, C. D. Lowry, and F. H. Bergeim, *J. Am. Chem. Soc.*, **43**, 891 (1921).

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the failure of *o*-biphenylylphosphonic acid to undergo cyclodehydration has been previously noted.[6]

We finally succeeded in preparing a derivative of phenoxphosphinic acid by heating *p*-tolyl ether with phosphorus trichloride in the presence of aluminum chloride, and then hydrolyzing the reaction mixture. Since the 4-positions of *p*-tolyl ether are blocked, the phosphorus trichloride attacked the 2-position.[7] The 10-chlorophenoxphosphine which was undoubtedly formed as an intermediate was presumably oxidized during the Friedel-Crafts reaction and subsequently hydrolyzed to 2,8-dimethylphenoxphosphinic acid. No attempt has yet been made to isolate these intermediate chloro compounds.

2,8-Dimethylphenoxphosphinic acid was characterized by analysis and ultraviolet absorption. The spectra of phenoxarsinic and 2,8-dimethylphenoxphosphinic acids are remarkably similar. The slight bathochromic shift exhibited by the phosphinic acid can probably be attributed to the methyl groups [phenoxarsinic acid: λ_{max} (95% ethanol) 214.5 (ϵ 34,400), 240.5 (ϵ 12,700), 275 (ϵ 3,560), 294 (ϵ 5260); 2,8-dimethylphenoxphosphinic acid: λ_{max} 218 (ϵ 35,700), 246 (ϵ 19,300), 297 (ϵ 5,000), 304 mμ (ϵ 5,630).]

In a typical experiment, 9.9 g. of *p*-tolyl ether, 17.4 ml. of phosphorus trichloride, and 8.5 g. of anhydrous aluminum chloride were placed in a 2-necked flask equipped with a sealed stirrer and a reflux condenser protected with a drying tube. The mixture was stirred and refluxed for about 22 hr. On pouring the reaction mixture over 400 g. of cracked ice, an oil was obtained which solidified rapidly. The solid was removed by filtration and washed thoroughly with water. After reprecipitation from 5% sodium hydroxide solution, the solid was recrystallized from 95% ethanol to give a 73% yield of pure 2,8-dimethylphenoxphosphinic acid; m.p. >300°. *Anal.* Calcd. for $C_{14}H_{13}O_3P$: P, 11.90; neut. equiv., 260.2. Found: P, 11.76; neut. equiv., 259.2.

VENEREAL DISEASE EXPERIMENTAL LABORATORY
COMMUNICABLE DISEASE CENTER
U. S. PUBLIC HEALTH SERVICE
SCHOOL OF PUBLIC HEALTH — LEON D. FREEDMAN
UNIVERSITY OF NORTH CAROLINA — G. O. DOAK
CHAPEL HILL, NORTH CAROLINA — JOYCE R. EDMISTEN

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(7) J. Reilly and P. J. Drumm, *J. Chem. Soc.*, 2814 (1927), have found that Friedel-Crafts acylation of *p*-tolyl ether yields 2-substituted compounds.

Auto-Transformation of D-Fructose

Sir:

The structural lability of fructose and the variability of its derivatives are well known. We have described a great number of compounds, which are formed by nitrating fructose by different methods and arise from anhydridization, polymerization or degradation.[1-3]

A striking demonstration of the extreme ease with which chemical changes occur in the fructose molecule, even when treated under very mild conditions, is given by treating the sugar with ethanol.

Ten grams of analytically pure, dried D-fructose (the purity of the material was checked chromatographically) was suspended in 10 ml. of absolute ethanol and dissolved by gentle heating to a temperature not exceeding 76°. The solution was kept at this temperature for 12 hr. under careful avoidance of superheating on the walls of the vessel. After cooling, the clear colorless solution was subjected to paper chromatography to yield a spectrum of at least eight spots besides the original spot of fructose. Of these, four had higher and four smaller Rf-values than fructose. By comparing them chromatographically with reference-substances, we were able to identify seven of these spots: methyl glyoxal[1]; difructose anhydride III[4]; methylglyoxal fructoside[1]; difructose anhydride I[4]; diheterolevulosan II[4-6]; diheterolevulosan I[4], β-ethyl fructupyranoside—the latter has also been isolated in substance.

The same results could be obtained in shorter time (in about 2–3 hr.) by boiling fructose with 95% ethanol, which caused immediate solution. The chromatogram in this case was identical with the former one.

A third method for effecting transformations of fructose even without heating, was to keep finely powdered, dried fructose with absolute ethanol at room temperature for some months. Eventually, complete solution occurred and the solution yielded a chromatogram which had besides the eight spots obtained by the first two methods, two additional spots which seemed to represent glucose derivatives.

It follows that under all these conditions, which exclude the action of bases or acids and avoid high temperatures, fructose undergoes anhydridization, dimerization, isomerization and degradation to C_3-fragments.

None of these effects could be observed in aqueous solution of fructose. Alcoholic solutions of glucose also failed to show any change under the conditions of our experiments.

DEPARTMENT OF BIOLOGICAL CHEMISTRY
THE HEBREW UNIVERSITY — A. H. SHAMGAR
JERUSALEM, ISRAEL — J. LEIBOWITZ

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