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Participation of a Neighboring Keto Group in the Nucleophilic Displacement of Halogen. Solvolysis of a γ,δ-Dibromo Ketone

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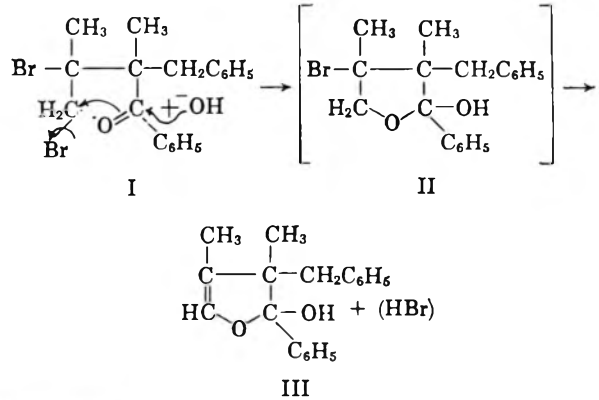
Under varying conditions, solvolysis of a γ,δ-dibromo ketone is shown to lead to a 2,7-dioxabicyclo[2.2.1]-heptane system, in addition to other products including a bromohydrin and a glycol. The latter two form as cyclic hemiketals. The dioxabicycloheptane system also forms in small yield in an unusual alkylation of a ketone with epichlorohydrin. Evidence is presented for the participation of the neighboring keto group in the nucleophilic displacement of bromide ion.

The normal reaction between an alkene dibromide and dilute, aqueous alkali is the formation of the corresponding glycol.[2,3g] If the alkali is omitted, the glycol that forms may undergo rearrangement to an aldehyde or a ketone.[3]

When a carbonyl group is located near a vicinal dibromo system, the action of aqueous alkali produces results that vary markedly with the location of the carbonyl relative to the bromines. α,β-Dibromo acids behave only partially as ordinary vicinal dibromides with respect to product types (*i.e.*, glycols). Decarboxylation is an important result and vinyl bromides are isolated. Formation of α-bromo α,β-unsaturated acids also has been reported.[4] Action of aqueous base on β,γ-dibromo acids usually produces butenolides.[5] The present brief review is concerned primarily with dihalo systems, but mention must be made of the extensive work of Zaugg and co-workers who have discovered several neighboring group reactions in monohalo-lactonic systems.[5g]

α,β-Dibromo aldehydes and ketones react rapidly with aqueous bases to give products which woldd be expected from the simple vicinal dibromo system. Both glycols and unsaturated monobromo ketones form.[6]

The first reported study of the action of aqueous base on a β,γ-dibromo ketone disclosed significant involvement of the carbonyl.[7] Action of dilute sodium hydroxide in refluxing, aqueous dioxane on 3,4-dibromo-1-phenyl-2-benzyl-2,3-dimethyl-1-butanone (I) gave 48% of 3-benzyl-3,4-dimethyl-1,2-dihydro-1-furanol (III). The mechanism proposed for this change



I II III

(1) (a) We are pleased to acknowledge generous support of this work by the National Science Foundation, Grant G-17559; (b) to whom inquiries should be sent.

(2) N. I. Dolgorukova-Dobryanska, *J. Russ. Phys. Chem. Soc.*, **57**, 283 (1925); *Chem. Abstr.*, **20**, 2311 (1926).

(3) (a) A. Eltekoff, *J. Russ. Phys. Chem. Soc.*, **10**, 214 (1878); *Chem. Zentr.*, 516 (1878); (b) A. Eltekoff, *Ber.*, **6**, 558 (1873); (c) W. Ipatieff, *J. prakt. Chem.*, [2]**53**, 257 (1891). (d) K. Krassuski, *J. Russ. Phys. Chem. Soc.*, **33**, 791 (1902); *Chem. Zentr.*, **I**, 628 (1902); (e) W. Froebe and A. Hochstetter, *Monatsh.*, **23**, 1075 (1902); *Chem. Zentr.*, **I**, 384 (1903); (f) W. L. Evers, H. S. Rothrock, H. M. Woodburn, E. E. Stahly, and F. C. Whitmore, *J. Am. Chem. Soc.*, **55**, 1136 (1933); (g) C. M. Suter and H. D. Zook, *ibid.*, **66**, 738 (1944). (h) These constitute a partial list of references. For a review of the literature to 1954 of the reactions of vicinal dibromides with alkaline reagents, see J. R. Holum, Ph.D. thesis, University of Minnesota, 1954; *Univ. Microfilms* (Ann Arbor, Mich.), Publ. No. 14554.

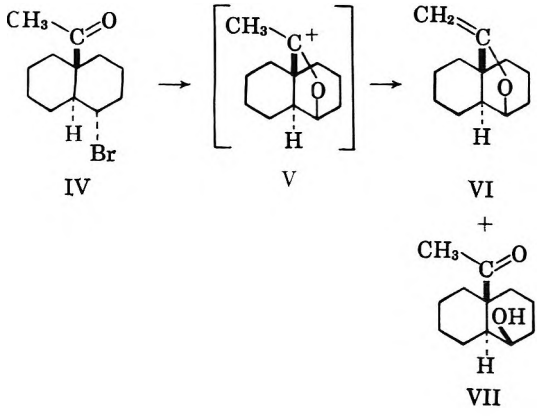
(4) (a) G. B. Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933); (b) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935); (c) A. A. Alberts and G. B. Bachman, *ibid.*, **57**, 1284 (1935); (d) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632, 2645 (1953); (e) E. Grovenstein, Jr. and D. E. Lee, *ibid.*, **75**, 2639 (1953); (f) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Sauers, *J. Org. Chem.*, **27**, 2339 (1962).

(5) (a) R. Fittig and C. Geisler, *Ann.*, **208**, 45 (1881); (b) J. Thiele and W. Wedemann, *ibid.*, **347**, 137 (1906); (c) A. Courtot, *Bull. soc. chim.*, [3]**35**, 657, 969 (1906); (d) E. E. Blaise and A. Courtot, *ibid.*, [3]**35**, 989 (1906); (e) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **93**, 139 (1931); (f) J. C. Bardhan, *J. Chem. Soc.*, 2607 (1928); (g) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567 (1962), and leading references to earlier papers cited therein.

(6) (a) J. Pastureau, *Bull. soc. chim.*, [4]**5**, 226 (1909); (b) P. L. Viguier, *Ann. chim. et phys.*, [8]**28**, 454 (1913); (c) C. F. H. Allen and C. O. Edens, Jr., *Org. Syn.*, **25**, 92 (1945); (d) J. Pauly and H. Lieck, *Ber.*, **33**, 500 (1900); (e) T. Hellthaler, *Ann.*, **406**, 155 (1914); (f) C. Weygand, E. Bauer, H. Gunther, and W. Heynemann, *ibid.*, **459**, 107 (1928); (g) N. H. Cromwell, D. J. Cram, and C. E. Harris, *Org. Syn.*, **27**, 9 (1947).

(7) L. I. Smith and J. R. Holum, *J. Am. Chem. Soc.*, **78**, 3417 (1956).

involved attack of hydroxide ion at the carbonyl carbon followed by nucleophilic attack of the carbonyl oxygen at the γ-carbon and formation of the intermediate bromohemiketal (II). This, then, according to the mechanism, lost hydrogen bromide to yield III. Operation of the *gem*-dimethyl effect[8] may have been decisive for the course of the reaction. A similar participation of the neighboring keto group in the nucleophilic displacement of bromide ion was reported by Baddeley, Baylis, Heaton, and Rasburn.[9] Unimolecular solvolysis of the γ-bromo ketone (IV) in aqueous acetone containing sodium bicarbonate gave the vinyl ether (VI) and the alcohol (VII). On the basis of



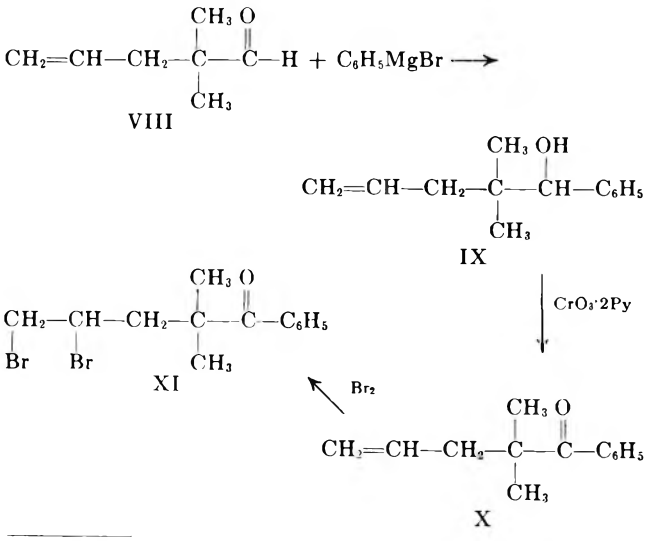
IV V VI + VII

kinetic data, they postulated the formation of the cation (V) as the rate-determining step.

This paper is a report of a study of the behavior of a γ,δ-dibromo ketone toward water and toward aqueous alkali.

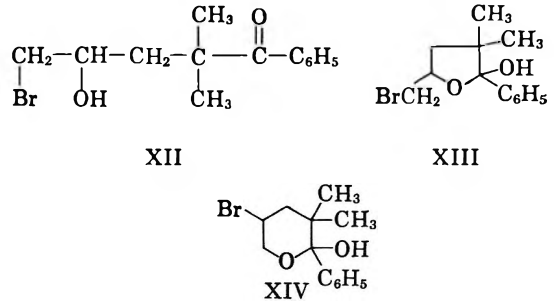
Results

Preparation and Hydrolysis of a γ,δ-Dibromo Ketone.—4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI) was selected for study because it would give opportunity for operation of the *gem*-dimethyl effect and because it happened to be rather easily preparable. The unsaturated precursor to the dibromo ketone (X), 2,2-dimethyl-1-phenyl-4-penten-1-one, was prepared by the route VIII to X as shown.[10] 2,2-Dimethyl-4-pentenal (VIII) was available from another study during which it had been synthesized from isobutyraldehyde and allyl alcohol by the method of Brannock.[11] The oxidation of the unsaturated alcohol with the chromium trioxide–pyridine complex[12,13] was accomplished in 90% yield on a 0.2-mole scale. The reagent, therefore, is rather easily adaptable to fairly large-scale (60 g. of chromium trioxide) laboratory preparations.



VIII IX XI X

The dibromo ketone (XI) was exceptionally unstable when exposed to humid air, confirming the observations of Haller and Ramart-Lucas.[14] They reported that, when freshly prepared dibromo ketone (XI) was left exposed to (moist) air, crystals formed which analyzed for a bromohydrin, $C_{13}H_{17}BrO_2$, and for which they assigned structure XII, 5-bromo-2,2-dimethyl-1-phenyl-4-pentanol-1-one. They also reported that the



XII XIII XIV

same compound formed when the parent unsaturated ketone (X) was allowed to react with a solution of bromine in aqueous acetone. Their structural assignment, therefore, was consistent with Markownikoff-addition of hypobromous acid to the alkene linkage in compound X.

We could not isolate a pure sample of the dibromo ketone (XI). The crude material was an oil that fumed strongly in even slightly humid air. The residue left after the removal of solvent (anhydrous carbon tetrachloride) following the addition of bromine to the ketone (X) gave a precipitate (presumably sodium bromide) and iodine, when it was added to sodium iodide in acetone.[15] That fact plus the well-known nature of the interaction of bromine with a double bond constituted the chief evidence that a dibromide of structure XI did in fact form. The infrared spectrum of a film of the crude dibromo ketone showed that it absorbed in the carbonyl region at 1680 cm.$^{-1}$. The relative intensity of this absorption was not so strong as expected when it was compared with the spectrum of the unsaturated ketone (X). Further, there were weak to moderate absorptions at 3500 and 3580 cm.$^{-1}$. Evidently some hydrolysis of the dibromo ketone had already occurred in spite of great effort to exclude moisture. This would explain the absorptions in the hydroxyl region *and* the weakened intensity of the carbonyl band. As shall be described shortly, hydrolysis

(8) G. S. Hammond, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 460.

(9) G. Baddeley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961).

(10) A reported alternative synthesis of the ketone X consisted of direct alkylation of isobutyrophenone by allyl chloride using sodium amide as the base [A. Haller and E. Bauer, *Compt. rend.*, **148**, 73 (1909)].

(11) K. C. Brannock, *J. Am. Chem. Soc.*, **81**, 3379 (1959).

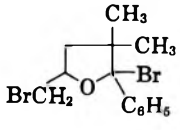
(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 425 (1953).

(13) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

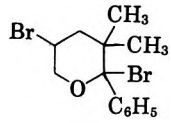
(14) A. Haller and P. Ramart-Lucas, *Compt. rend.*, **171**, 144 (1920).

(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, New York, N. Y., 1956, p. 158.

of the dibromo ketone leads to disappearance of the carbonyl group. (After the infrared analysis when the cell was disassembled, the film of dibromo ketone fumed strongly, and in less than a minute it had changed to crystals of what later proved to be a bromohydrin.) In view of subsequent developments and because of the work of Arnold, Campos, and Lindsay,[16,17] we could not lightly assign the open-chain structure XI to the dibromo ketone. Heterocyclic structures XV and XVI had to be considered. We were satisfied, however, that neither of these cyclic structures was correct.



XV



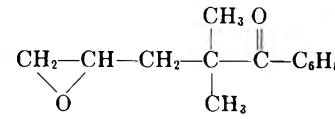
XVI

Exposure of the dibromo ketone (XI) to the moderately humid air of the laboratory produced a bromohydrin, $C_{13}H_{17}BrO_2$, melting at 101–103°. The same compound was obtained by first adding a stoichiometric amount of bromine (dissolved just before use in dioxane) to a solution of the unsaturated ketone (X) in dioxane followed by the addition of water. The bromohydrin's infrared spectrum showed no absorption between 1600 and 2850 cm.$^{-1}$. Bands at 3500 and 3650 cm.$^{-1}$ indicated the presence of a hydroxyl group. On this basis, the bromohydrin must have formed as a cyclic hemiketal, either XIII, 5-bromomethyl-3,3-dimethyl-2-phenyltetrahydro-2-furanol, or as XIV, 5-bromo-3,3-dimethyl-2-phenyltetrahydro-2-pyranol.

The action of sodium iodide in acetone[15] produced no precipitate with the bromohydrin. Alcoholic silver nitrate[18] reacted very slowly with it at 50°. These results did not permit a clear choice between the pyranol form XIV and the furanol form XIII. (However, they did rule out those isomers of XIV and XIII in which locations of bromines and hydroxyls are exchanged giving the bromine in either case a tertiary, benzylic, and α-halo ether position.)

The proton magnetic resonance spectrum of the bromohydrin will be described later in the paper together with that of the glycol related to it. Briefly, the observed chemical shifts did not permit an unambiguous choice between XIII and XIV. However, the spin-coupling pattern was inconsistent with any reasonable conformer of pyranol form XIV, but it was appropriate for furanol form XIII. Therefore, we have assigned structure XIII to the bromohydrin.

Action of Aqueous Alkali on the γ,δ-Dibromo Ketone (XI).—When freshly prepared dibromo ketone (XI) was added to a mixture of 10% aqueous sodium hydroxide in dioxane and the mixture was refluxed several hours, there was obtained in 55% yield a bromine-free solid melting at 58°, analysis $C_{13}H_{16}O_2$. Haller and Ramart-Lucas[19] obtained a 59°-melting compound, also $C_{13}H_{16}O_2$, by the action of epibromohydrin on the sodium salt of isobutyrophenone. To their product

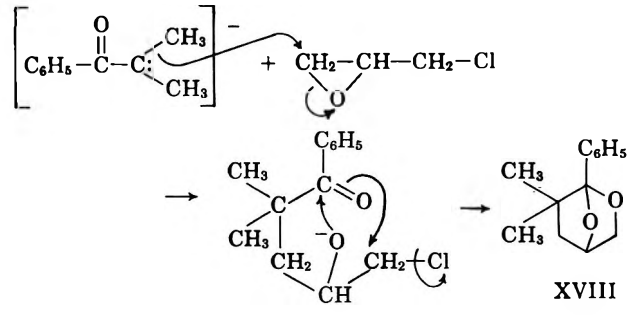


XVII

they assigned structure XVII, 4,5-epoxy-2,2-dimethyl-1-phenyl-1-pentanone. When we repeated their synthesis[20] we isolated in low yield a solid melting at 57.5–58.5°. A mixture melting point of this with our 58°-melting solid obtained from the dibromo ketone was not depressed. Further, the infrared spectra of the two were identical. The two substances, therefore, were the same, but the structure could not be represented by XVII.

The infrared spectrum of the 58°-melting compound possessed no bands characteristic of a carbonyl group, a hydroxyl group, or a carbon-to-carbon double bond. Application of the periodic acid test[21] gave positive results only after the elapse of some time. When the periodic acid test included the presence of acetic acid, conditions under which epoxides (and by inference, cyclic ketals of 1,2-glycols) are attacked,[22] the test was positive in the usual time limit.

Supported by analytical values, origin, spectrum, and chemical behavior, we have assigned to the 58°-melting compound structure XVIII, 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane. This assignment was consistent further with the reported behavior of the 58°-melting compound toward sodiomalonic ester or sodium amide. Haller and Ramart-Lucas[19] observed that these strong nucleophiles did not react with their 59°-melting compound, a behavior inconsistent with epoxide structure XVII, for epoxides are reactive toward such reagents.[23] Such inertness, however, would be expected of a ketal system as in XVIII.



XVIII

Formation of a dioxabicycloheptane system (XVIII) *via* alkylation of a ketone with epichlorohydrin is without precedent as far as we can ascertain. The basic system itself is known. Levene and Walti[24] reported that 1,2-hexanediol-5-one, when heated at 150° for several hours, lost water. On the basis of analytical values, molar refractivity, and the parachor, they proposed for their product structure XIX, 1-methyl-

(16) R. T. Arnold, M. Campos, and K. L. Lindsay, *J. Am. Chem. Soc.*, **75**, 1044 (1953).

(17) They reported that bromination of γ,δ-unsaturated esters gave δ-bromo-γ-lactones instead of γ,δ-dibromo esters.

(18) *Cf.* ref. 15, page 136.

(19) P. Ramart-Lucas and A. Haller, *Compt. rend.*, **158**, 1302 (1914).

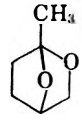
(20) We used epichlorohydrin. They used epibromohydrin, although they stated, without giving details, that epichlorohydrin did not give better results. Presumably it gave the same 59°-melting product.

(21) *Cf.* ref. 15, p. 129.

(22) R. Fuchs, R. C. Waters, and C. A. Vanderwerf, *Anal. Chem.*, **24**, 1514 (1952).

(23) *Cf.* work by W. Traube and E. Lehmann, *Ber.*, **32**, 720 (1899), or A. Haller's earlier work, *Bull. soc. chim.*, 564 (1899).

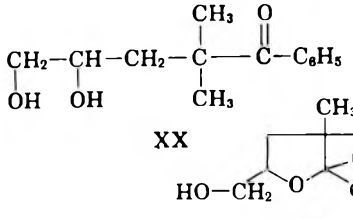
(24) P. A. Levene and A. Walti, *J. Biol. Chem.*, **88**, 771 (1930).



XIX

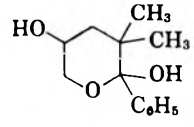
2,7-dioxabicyclo[2.2.1]heptane. The system is also quite well-known in carbohydrate chemistry.[25] The suggested mechanism shown for the formation of XVIII parallels well-known instances in which sodio derivatives of active methylene compounds attack epichlorohydrin at C-1.[26]

According to Haller and Ramart-Lucas,[19] their 59°-melting compound (now shown to have been XVIII) could be hydrolyzed to a glycol, $C_{13}H_{18}O_3$, melting at 100°, to which they assigned structure XX, 4,5-dihydroxy-2,2-dimethyl-1-phenylpentanone. The same compound was obtained when the unsaturated ketone (X) was hydroxylated by action of dilute, slightly alkaline potassium permanganate.[27] By repeating this procedure we obtained the glycol, $C_{13}H_{18}O_3$, melting at 98–100°. Since its infrared spectrum was essentially transparent in the carbonyl region between 1600 and 2000 cm.$^{-1}$, it could not have had structure XX. Cyclic, hemiketal structures XXI and XXII were considered. The glycol could be made to form, but with difficulty, by action of a boiling aqueous dioxane solution of sodium hydroxide on the bromohydrin (XIII). The yield was low and much unchanged bromohydrin was recovered. Since the bromohydrin most probably is represented by a furanol system, we have assigned the furanol form (XXI), 2-hydroxy-5-hydroxymethyl-3,3-dimethyl-2-phenyltetrahydrofuran, to the glycol.



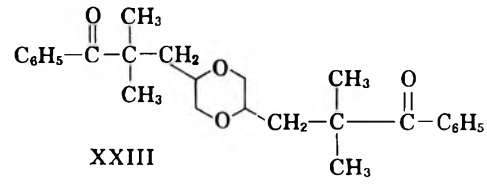
XX

XXI

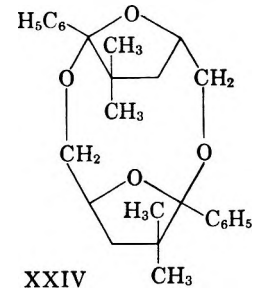


XXII

Under certain circumstances, notably acid catalysis, a dimer of the 58°-melting compound (XVIII) forms. Haller and Ramart-Lucas[19] obtained a compound, $C_{26}H_{32}O_4$, melting at 214–215°, when they added traces of acids to their 59°-melting substance. It also was obtained when attempts were made to prepare a benzoate derivative or a urethane of the glycol.[27] We did not repeat these experiments, but we did obtain the dimer, $C_{26}H_{32}O_4$, melting at 219–221°, in one experiment when chromatography onto silica gel (rather than the usual alumina) was used in an effort to isolate XVIII. The silica gel we used gave a slightly acidic reaction with water. Haller and Ramart-Lucas[19] tentatively assigned structure XXIII to the dimer. The dimer we obtained, almost certainly the same substance as theirs, did not absorb in the carbonyl region of the infrared spectrum. Bands characteristic of a hydroxyl group also were absent. In analogy with structural assignments in the carbohydrate field,[25c] we tentatively propose structure XXIV for the dimer. Our dimer gave



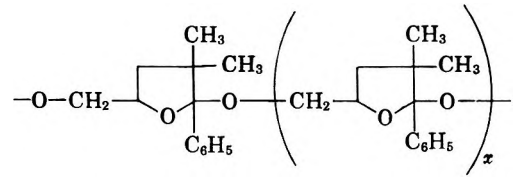
XXIII



XXIV

in the presence of acetic acid (and only in its presence) a positive periodic acid test.[21,22] A compound of structure XXIII would not be expected to do this but XXIV, being a diketal of a 1,2-glycol, could.

In addition to XVIII (or its dimer), another substance was isolated from the action of aqueous base in refluxing dioxane on the dibromo ketone (XI). This was eluted from alumina by ether and it constituted from 25–30% of the crude product's mixture. It was an amorphous solid of ill-defined melting point. Its chemical and spectral properties indicated that it might be a polymeric substance of the general type shown by XXV, in which the value of x is probably small and



XXV

varied. Weak absorption at 3550 cm.$^{-1}$ in the infrared indicated the presence of hydroxyl (*e.g.*, at chain terminals). No absorption occurred corresponding to a carbonyl group. In acetic acid it gave a positive periodic acid test. XXV could form by the splitting out of hydrogen bromide from the bromohydrin (XIII) externally, while the same loss internally would produce XVIII.

N.m.r. Spectra of the Bromohydrin (XIII) and the Glycol (XXI).[28]—The proton magnetic resonance spectra of the bromohydrin and the glycol are shown in Fig. 1. In selecting reasonable candidates for the structures of the pyranol form of the bromohydrin, only chair forms were considered. It was further reasoned that the several bulky groups present on the ring would effectively inhibit interconversion of conformers at room temperature; the system would be quite rigid. Structure XXVI represents the bromine and hydroxyl *cis* to each other, and it has both the bromine and the phenyl in equatorial positions. (The alternative, both

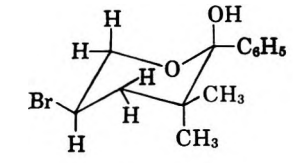
(25) (a) H. Hibbert and C. P. Burt, *J. Am. Chem. Soc.*, **50**, 1411 (1928); (b) R. J. Dimler, *Advan. Carbohydrate Chem.*, **7**, 37 (1952); (c) E. Vis and H. G. Fletcher, *J. Am. Chem. Soc.*, **79**, 1182 (1957); (d) E. Vis and H. G. Fletcher, *J. Org. Chem.*, **23**, 1393 (1958); (e) V. N. Nigam, Hsien-Gieh Sie, and W. H. Fishman, *J. Am. Chem. Soc.*, **82**, 1007 (1960).

(26) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1950, p. 26.

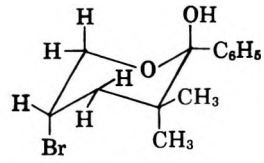
(27) J. Meyeringh and A. Haller, *Compt. rend.*, **158**, 1957 (1914).

(28) The n.m.r. spectra were obtained and interpreted for us by Dr. Donald P. Hollis of Varian Associates, Palo Alto, Calif.

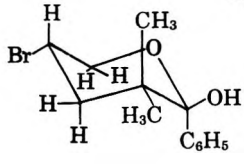
bromine and phenyl in axial positions, was regarded as a most unlikely conformer, and it was not considered.) Structures XXVII and XXVIII represent the two chair conformers of the *trans* orientation of bromine and hydroxyl. Structures XXIX and XXX show *cis* and *trans* orientations, respectively, for the bromomethyl group and the hydroxyl in the furanol form.



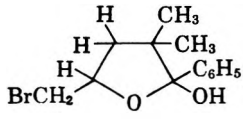
XXVI



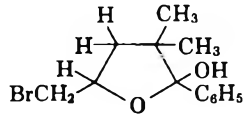
XXVII



XXVIII



XXIX



XXX

In the spectrum of the bromohydrin (Fig. 1a), the signals at 0.6 and 1.2 p.p.m., representing three protons each, correspond to the two *gem*-dimethyl groups. They have slightly different chemical shifts because of *cis–trans* relationships to the neighboring phenyl group. The patterns centered at 2.1 and 3.5 p.p.m. correspond to two protons each. The signals at 2.1 p.p.m. were assigned to the protons at position 4; those at 3.5 p.p.m., to the protons at position 6. These assignments could apply to any of the structures XXVI through XXX. The pattern at 4.5 p.p.m. corresponds to the one proton at position 5, either the tertiary proton α to the bromine and β to the ring oxygen in the pyran system (XXVI–XXVIII) or α to the ring oxygen and β to the bromine in the furan system (XXIX–XXX). α-Protons in tetrahydrofuran have $\delta = 3.75$ p.p.m. An additional 0.2–0.3-p.p.m. increase in δ could easily result from β-effects and from the fact that the C-5 proton is tertiary, not secondary. Tertiary bromine in cyclohexyl bromide has $\delta = 4.1$ p.p.m. (All δ-values are with reference to tetramethylsilane.) With the lack of chemical shift data on sufficiently similar, known systems, the observed $\delta = 4.5$ p.p.m., therefore, does not permit an unambiguous choice between the pyranol and the furanol forms.

Study of the spin-coupling pattern at $\delta = 4.5$ p.p.m., however, does appear to distinguish the two ring types. In both XXVI and XXVIII, the axial proton at C-5 has two axial and two equatorial neighbors. This arrangement is expected to produce a resonance consisting of a triplet of triplets, since the diaxial couplings are expected to be about 8–10 c.p.s., while axial–equatorial couplings are only 2–3 c.p.s. The pattern at 4.5 p.p.m., however, is either a perturbed quintet or a quartet of doublets. Hence XXVI and XXVIII are ruled out. Structure XXVII, having no diaxial neighbors for the proton at position 5, should exhibit a resonance pattern with all coupling constants in the

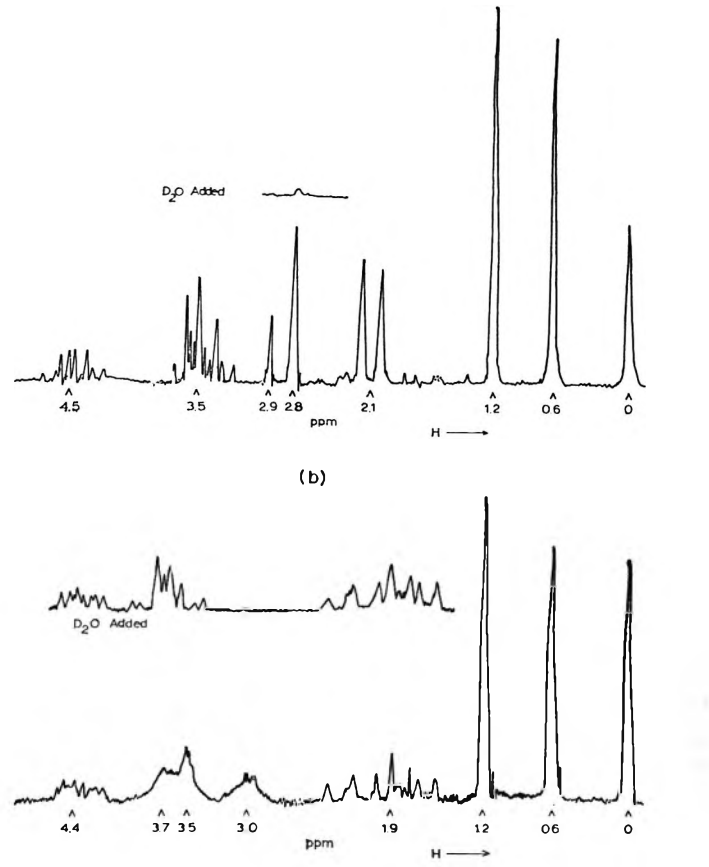


Fig. 1.—N.m.r. spectra of (a) bromohydrin XIII and (b) glycol XXI at 60 Mc. in deuteriochloroform with tetramethylsilane as the internal reference.

2–4-c.p.s. range. Hence, structure XXVII does not seem likely either.

The furanol system (XXIX or XXX), on the other hand, could very well give the pattern observed at 4.5 p.p.m. In either form, all four protons neighboring the one at position 5 would couple to it with about the same coupling constant of about 4–7 c.p.s. There are two singlets for the hydroxyl proton of the bromohydrin, one at 2.8 p.p.m. and the other at 2.9 p.p.m. The assignment followed from the change in the spectrum when deuterium oxide was added to the solution. Two signals instead of one indicates that a mixture of XXIX and XXX are present in a ratio of roughly 3:1 (based on relative peak intensities), but which isomer is the more abundant cannot be determined from the spectrum. On other grounds it would seem that XXIX with the phenyl and bromomethyl groups *trans* to each other would be more abundant than the *cis* isomer in XXX. The *trans* isomer (XXIX) could lead to the dioxabicycloheptane system (XVIII) and the dimer (tentatively XXIV), whereas the *cis* isomer (XXX) could lead to the polymer (tentatively XXV).

The spectrum of the glycol (Fig. 1b) is not inconsistent with the five-membered ring system, an assignment compatible with the chemical evidence that the bromohydrin can be converted into the glycol in a basic medium. Here, however, there appears to have been slight changes in some of the coupling constants for the protons at positions 4, 5, and 6, and, although the chemical shifts for these protons are virtually the same as in the spectrum of the bromohydrin, the patterns are not. We note especially the very complicated

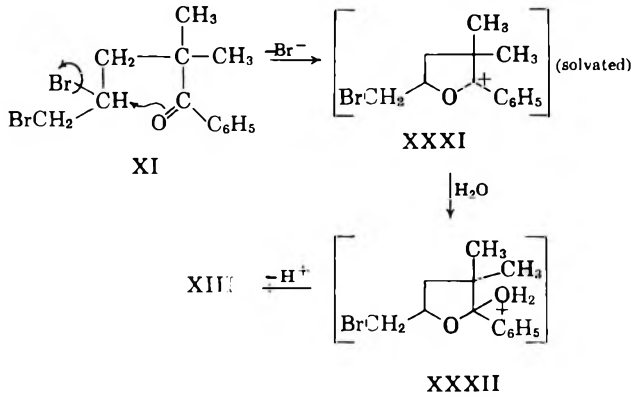
pattern centered at about 1.9 p.p.m. in the spectrum of the glycol assigned to the two C-4 protons. In the bromohydrin spectrum, these appeared as a doublet. In view of the changes in the spectrum of the glycol when deuterium oxide was added to the sample, the signals centered at 3 and 3.7 p.p.m. are assigned to the two hydroxyl groups. In summary, then, the n.m.r. spectra and chemical evidence support tetrahydrofuran systems for both the bromohydrin and the glycol, represented respectively without regard to *cis–trans* isomerism by XIII and XXI.

Discussion of Results

The formation of the bromohydrin (XIII) from the dibromo ketone (XI) conceivably could have occurred in such a way that the keto group did not significantly affect the rate-determining step. Thus, simple solvolysis of the dibromo ketone to the open-chain bromohydrin (XII) might have occurred. Ring closure would then be unsurprising, for it is well-known that γ- and δ-hydroxy aldehydes and ketones often exist largely in cyclic, hemiacetal, or hemiketal forms.[29]

What was unusual, however, about the dibromo ketone was its extreme reactivity toward even the moisture in humid air. This behavior was not consistent with a simple 1,2-dibromo system, even if one of the bromines were secondary. Suter and Zook,[3g] for example, reported that first-order hydrolysis of 2,3-dibromo-2-methylbutane occurred at a convenient rate at 45°, at which temperature they conducted kinetic studies. The initial product was the bromohydrin, 3-bromo-2-methyl-2-butanol. Thus, even the tertiary bromine in their vicinal dibromide was not unusually reactive in the way our dibromo ketone (XI) was.

The kinetic studies made by Baddeley, Baylis, Heaton, and Rasburn,[9] described earlier (*cf.* IV to VII), provided a way of rationalizing both the reactivity of our dibromo ketone toward water as well as the bromohydrin it formed. We suggest the following mechanism.



The solvated carbonium ion (XXXI) would receive stabilization through delocalization of the charge both into the phenyl ring and to the oxygen. Such stabilization of a similar carbonium ion was postulated by Oae[30] to explain the reactivity of 4-bromo-1-phenyl-1-butanone toward mercuric nitrate. Depending upon how a water molecule became attached to position-2 of the ring, isomers XXIX or XXX would form.

Experimental[31]

2,2-Dimethyl-1-phenyl-4-penten-1-ol (IX).—2,2-Dimethyl-4-pentenal (VIII) was prepared by Brannock's procedure B[11] in 74% yield from isobutyraldehyde and allyl alcohol and had b.p. 124–126.5°, $n^{27}D$ 1.4176; lit.[11] b.p. 124–126°, $n^{20}D$ 1.4200. The infrared spectrum of this compound showed absorptions at 1725 (m–s) and 2700 cm.$^{-1}$ (w) for an aldehyde. Bands at 920 (s), 988 (m–s), and 1640 cm.$^{-1}$ (w) correlated with a terminal double bond. The strongest band in the spectrum was at 1160 cm.$^{-1}$.

A solution of 2,2-dimethyl-4-pentenal (67 g., 0.6 mole) in anhydrous ether (120 ml.) was added over a period of 30 min. to a stirred, chilled, freshly prepared solution of phenylmagnesium bromide (from 104 g., 0.66 mole of bromobenzene and 16.1 g., 0.66 g.-atom of magnesium turnings) in ether (270 ml.). The mixture remained at room temperature, protected by a drying tube, over a weekend. It was hydrolyzed with 10% sulfuric acid and the layers were separated. The ether layer was washed with saturated sodium chloride and dried (potassium carbonate). Removal of the ether left an oil which was distilled. Material boiling between 116–133° (1 mm.), $n^{27}D$ 1.5227, was used in the subsequent oxidation with chromium trioxide–pyridine. An analytical sample was prepared and had b.p. 90° (0.75 mm.), $n^{26}D$ 1.5225.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.81; H, 9.53.

The infrared spectrum of this compound (10% in carbon tetrachloride/carbon disulfide) had its strongest band at 703 cm.$^{-1}$. A sharp band at 3670 cm.$^{-1}$ (m–w) together with a broader band at 3540 cm.$^{-1}$ (m–w) indicated hydroxyl. Bands at 915 (s), 1000 (m), and 1640 cm.$^{-1}$ (m–w) supported the inclusion of a vinyl group in the structure.

2,2-Dimethyl-1-phenyl-4-penten-1-one (X).—The chromium trioxide–pyridine complex was made by adding chromium trioxide (63.5 g., 0.64 mole) *in small portions* during a 45-min. period *to well-stirred*, chilled (ice bath) anhydrous pyridine (720 ml.). A Hershberg stirrer rather than a blade or a magnetic capsule must be used. (See also ref. 12 and 13.) 2,2-Dimethyl-1-phenyl-4-penten-1-ol (39 g., 0.21 mole) was added using small portions of pyridine (total, 15 ml.) for rinsing. The mixture was stirred for 15 min. as it slowly darkened, and then it was left in a stoppered flask undisturbed at room temperature for 22 days. The mixture was poured into water (1 l.) and extracted with three 300-ml. portions of ether. The ether layers were combined and washed with four 200-ml. portions of 10% hydrochloric acid, seven 50-ml. portions of water, and two 50-ml. portions of 10% sodium carbonate. The solution was dried (sodium sulfate), the ether was removed at the aspirator, and the residue was fractionated. Oil (31 g., 0.18 mole, 90%), boiling at 74–85° (0.45–0.7 mm.), was shown to be homogeneous by refractive indices on three portions, taken at the beginning ($n^{25}D$ 1.5200), in the middle ($n^{25}D$ 1.5196), and near the end ($n^{25}D$ 1.5195) of the temperature range. In another experiment on a smaller scale (0.1 mole) and a shorter reaction time (4 days), the yield was 92%. For an analytical sample, a small portion was fractionated with a small spinning-band column (Nester and Faust) and had b.p. 61–61.5° (0.2 mm.), $n^{21}D$ 1.5215.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.19; H, 8.57.

The infrared spectrum of this compound (as a film) showed that it absorbed intensely at 1680 (aromatic ketone[32]) and at 917 (s),

(29) *Cf.*, for example, C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(30) S. Oae, *ibid.*, **78**, 4031 (1956).

(31) Infrared spectra were determined with a Perkin-Elmer Infracord Model 137. "Carbon tetrachloride/carbon disulfide" means that carbon tetrachloride was the solvent between 4000 and 1300 cm.$^{-1}$ and carbon disulfide was the solvent between 1300 and 665 cm.$^{-1}$. In all spectra taken of solutions, sodium chloride cells of 0.1-mm. thickness were used. Unless otherwise specified, a 0.025-mm. spacer was used for spectra of liquid films. Structure spectra correlations were based usually on data found in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1958.

All melting points were uncorrected and were determined on a Fisher–Johns melting point apparatus.

Carbon–hydrogen analyses were obtained at the Microanalytical Laboratory, University of Minnesota.

(32) J. L. Adelfang, P. H. Hess, and N. H. Cromwell, *J. Org. Chem.*, **26**, 1402 (1961).

996 (m), and 1640 cm.$^{-1}$ (m–w), bands characteristic of a vinyl group. (These bands disappeared when bromine was added to this compound.)

4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI).—2,2-Dimethyl-1-phenyl-4-penten-1-one (2.0 g., 0.011 mole) was dissolved in anhydrous carbon tetrachloride (10 ml., Baker analyzed), and the solution was cooled to ice-bath temperature. A solution of bromine (1.7 g., 0.011 mole) in anhydrous carbon tetrachloride (40 ml.) was added slowly. The reaction was very rapid, yet the solution was allowed to remain undisturbed for 30 min. Removal of the solvent in a rotating evaporator left a pale yellow oil. Attempts to purify it further were unsuccessful. A drop of this oil added to freshly prepared sodium iodide in acetone reacted to produce a precipitate (presumably sodium bromide) and an iodine coloration.

An infrared spectrum of this oil (as a film) showed that it absorbed in the infrared at 1680 cm.$^{-1}$ (m). There was a slightly weaker band near this at 1710 cm.$^{-1}$ which we cannot explain. Weak bands at 3580 and 3500 cm.$^{-1}$ indicated that absorption by hydroxyl had occurred. The oil film on the sodium chloride windows changed to crystals within a minute after the windows were separated. This was accompanied by very obvious fuming of hydrogen bromide. A spectrum of a Kel-F mull of the crystals had no bands between 1510 and 2800 cm.$^{-1}$. A sharp band occurred at 3490 cm.$^{-1}$ (m). Broad, strong, unresolved absorption occurred between 1100 and 1250 with other strong bands centered at 900 to 1060 cm.$^{-1}$.

The dibromo ketone (XI) was prepared in dioxane just before use and not isolated in all experiments in which it was allowed to react with aqueous sodium hydroxide in dioxane.

5-Bromomethyl-3,3-dimethyl-2-phenyltetrahydro-2-furanol (XIII, "Bromohydrin").—A solution of bromine (3.84 g., 0.024 mole) in dioxane (30 ml.) was added dropwise (15 min.) to 2,2-dimethyl-1-phenyl-4-penten-1-one (X) (4.52 g., 0.024 mole). Water (5 ml.) was added, and the mixture was stirred 15 min. It was neutralized with 10% sodium bicarbonate and the solution was concentrated *in vacuo* at room temperature. The residue, largely solid, was taken up in ether–ligroin, washed with water, and dried. Removal of the solvent left tan crystals (5.94 g., 0.019 mole, 80%) melting at 94–99°. An analytical sample was prepared by crystallization of this crude material five times from ether–ligroin. It melted at 101–103°. (Haller and Ramart-Lucas[14] reported a melting point of 106° for their bromohydrin to which they, not having infrared spectrophotometers, quite reasonably assigned structure XII, the open-chain form of XIII. We were certain that our bromohydrin was the same substance as theirs.)

Anal. Calcd. for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.57; H, 5.99.

The infrared spectrum of this material (10% in carbon tetrachloride/carbon disulfide) showed no absorption between 1600 and 2850 cm.$^{-1}$. Bands at 3500 (m–w) and 3650 cm.$^{-1}$ (m–w) indicated a hydroxyl group. The strongest absorption occurred at 1030 with side bands at 1010, 1040, and 1055 cm.$^{-1}$.

This compound gave no precipitate with sodium iodide in acetone at 50°. In alcoholic silver nitrate, it produced a cloudiness; boiling the solution did not materially affect this result.

2-Hydroxy-5-hydroxymethyl-3,3-dimethyl-2-phenyltetrahydrofuran. (XXI, "Glycol").—A solution of 3% potassium permanganate in 1% potassium hydroxide was added slowly to a stirred suspension of 2,2-dimethyl-1-phenyl-4-penten-1-one (5.0 g., 0.027 mole) in water (50 ml.). The permanganate color gave way to a sludge of manganese dioxide very quickly. The solids were collected on a filter and washed with ether. Removal of the ether left a solid (3.8 g.) which was recrystallized five times from petroleum ether (b.p. 30–60°) containing a trace of ether and had m.p. 98–100°. (By the same procedure, Haller and Meyeringh[27] prepared a glycol, m.p. 100°, to which they assigned structure XX.)

The solid was insoluble in 10% sodium hydroxide, and no precipitate was obtained by acidification of the aqueous filtrate obtained from this operation. In water, the solid gave a negative periodic acid test, but in the presence of acetic acid, the test was positive.[21,22] It did not decolorize bromine in carbon tetrachloride.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.15. Found: C, 69.99; H, 8.21.

The infrared spectrum (5% in carbon tetrachloride/carbon disulfide) showed that it absorbed at 3450 cm.$^{-1}$ with an intensity equal to the intensity of absorption at 2960 cm.$^{-1}$, the most intense band in the C–H stretching region. The relative intensity of absorption by hydroxyl in the glycol was considerably greater than in the bromohydrin. In a Kel-F mull, the hydroxyl peak was at 3370 cm.$^{-1}$ with a slightly larger relative intensity. The strongest absorption (as with the bromohydrin) occurred at 1030 cm.$^{-1}$. Strong to moderate side bands were at 1000 (m), 1055 (s), 1075 (m), and 1105 cm.$^{-1}$ (m).

1-Phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII).

A. From 4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI).—A solution of bromine (4.25 g., 0.027 mole) in dioxane (25 ml. m.p. 10–11°) was added to a solution of 2,2-dimethyl-1-phenyl-4-penten-1-one (X) (5 g., 0.027 mole) in dioxane (10 ml.) to form a dioxane solution of the dibromo ketone (XI). This solution was added in one portion to a mixture of 10% sodium hydroxide (25 ml., approx. 0.062 mole of sodium hydroxide) in dioxane (125 ml.). The mixture was stirred and refluxed for 4 hr. A brown aqueous layer was separated from the dioxane layer, and the latter was poured into water (1 l.) and extracted with four 200-ml. portions of ether. The ether layers were combined and washed with two 100-ml. portions of water and three 40-ml. portions of saturated sodium chloride. Removal of the ether left an oil (5.62 g.) which was chromatographed from petroleum ether onto alumina (120 g., Fisher A-540, 80–200 mesh). Elution with petroleum ether and with 10:1 petroleum ether–ether gave a white, crystalline solid (2.98 g., 55%) which proved to be 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). Elution with ether gave an amorphous solid (1.73 g.). Elution with ethyl acetate yielded a thick viscous material (0.37 g.).

The crystalline solid eluted largely by petroleum ether was crystallized several times from petroleum ether to a constant melting point of 58°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.67; H, 8.01.

The infrared spectrum of this solid (10% in carbon tetrachloride/carbon disulfide) showed no absorption between 1600 and 2850 and between 3100 and 4000 cm.$^{-1}$. Hence, both hydroxyl and carbonyl groups were absent. Several needle-sharp absorptions occurred between 850 and 1140 cm.$^{-1}$, the strongest in the entire spectrum being at 975 cm.$^{-1}$. Others were at 1130 (m), 1065 (s), 1035 (m–s), 1025 (m), 1005 (m–w), 996 (s), 985 (m), 963 (m–s), 955 (m), 915 (m–w), and 860 cm.$^{-1}$ (w, broad). These bands were undoubtedly associated with the C–O and C–C of the ketal system. (Steroidal sapanogens, wherein the ketal group is part of a spiro- rather than a dioxabicyclo system, also show several sharp absorptions in this region.[33]) In addition to these bands, three sharp, strong bands appeared at 700, 734, and 770 cm.$^{-1}$.

This compound did not react with either aqueous potassium permanganate or with bromine in carbon tetrachloride. In acetic acid, the periodic acid test was positive.[21,22]

The amorphous solid eluted with ether could not be purified to a sharp melting point. The best melting point, 84–87°, was of slightly cream-colored material obtained directly from the chromatographic column. It was not analyzed for carbon and hydrogen. It was very soluble in petroleum ether, ether, alcohol, and acetone. Cooling of these solutions or evaporating the solvents in each attempt gave a sticky material that hardened to a very viscous glass. Its infrared spectrum (in both 10 and 20% solutions in carbon tetrachloride/carbon disulfide) showed that it absorbed at 3550 cm.$^{-1}$, indicating hydroxyl. Strongest absorptions occurred between 980 and 1110 cm.$^{-1}$, and though resolution was poor, specific bands could be discerned at 980 (shoulder), 1010, 1050, 1080, and 1095 cm.$^{-1}$. No absorption for carbonyl was found between 1600 and 2800 cm.$^{-1}$. A sharp, moderate band occurred at 910 cm.$^{-1}$.

In acetic acid, the amorphous solid gave a positive periodic acid test.[21,22]

B. From Isobutyrophenone and Epichlorohydrin.—All reagents were used as commercially available without further purification. Sodium amide was obtained from City Chemical Corporation, New York.

A suspension of sodium amide (7.8 g., 0.2 mole) in anhydrous ether (100 ml.) was stirred, as isobutyrophenone (29.6 g., 0.2 mole) in anhydrous ether (30 ml.) was added in one portion. The mixture was refluxed and stirred for 5.5 hr. and allowed to remain at room temperature overnight, protected by a soda-lime tube. Epichlorohydrin (18.4 g., 0.2 mole) in ether (30 ml.) was

(33) C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

added, and the mixture was stirred and refluxed for 7 hr. and allowed to remain at room temperature overnight. The mixture was poured into an equal volume of water and the layers were separated. The ether layer was washed free of alkaline substances with eight 20-ml. portions of water and dried (sodium sulfate). Removal of the ether *in vacuo* at room temperature left an oil (30.8 g.) which was fractionated. Isobutyrophenone (15.9 g., 54%) was recovered at 51° (0.5 mm.). A fraction boiling at 93–98° (0.4 mm.), 6.1 g., possessed an infrared spectrum that indicated it was a mixture of isobutyrophenone and 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). Accordingly, a portion (5.0 g.) of this fraction was chromatographed from petroleum ether onto alumina (120 g., Alcoa F-20). Elution with petroleum ether gave 1.4 g. of isobutyrophenone (identified by comparing its infrared spectrum with the spectrum of an authentic sample), followed by 0.40 g. of XVIII. Additional XVIII, 1.34 g. (total, 1.74 g.), was obtained by elution with 9:1 petroleum ether–ether. A center fraction melted without further purification at 57.5–58.5°; mixture melting point with the 58°-melting solid obtained in procedure A was 57–57.5°. The infrared spectra of the two were identical. The total yield of pure XVIII by this method was 4% based on original isobutyrophenone taken. Attempts to isolate and to characterize any other products from this reaction were not made.

Action of Aqueous Base on the Bromohydrin (XIII).—A mixture of the bromohydrin (XIII, 1.5 g., 5.3×10^{-3} mole), 10% sodium hydroxide (2.5 ml., estimated 6.3×10^{-3} mole of sodium hydroxide), and dioxane (50 ml.) was stirred and refluxed for 4 hr. It was poured into water (1 l.), and this mixture was extracted with four 200-ml. portions of ether. The ether extracts were combined and washed with five 100-ml. portions of water and three 40-ml. portions of saturated sodium chloride. Removal of the ether at room temperature left an orange oil (1.22 g.) which was chromatographed from petroleum ether onto alumina (37 g., Alcoa F-20). Elution with petroleum ether and with 10:1 petroleum ether–ether gave 0.75 g. (50%) of a white solid, m.p. 99–100°, which proved to be starting material (bromohydrin) by comparing its infrared spectrum with that of an authentic sample. Elution with ether gave a white solid (0.36 g., 30%), melting at 97–98°, which was glycol XXI, according to its infrared spectrum. Material with analysis agreeing with XVIII was not isolated.

In another experiment in which the crude oil obtained from the reaction was heated on the steam bath before it was chromatographed, only the amorphous solid, identified by its infrared spectrum, also obtained in procedure A in the previous synthesis, was isolated.

Dimer of XVIII (XXIV).—In one experiment designed to prepare XVIII, silica gel (Baker, 80–200 mesh) was used instead of alumina as the adsorbant for chromatography. The silica gel, when mixed with water, liberated enough acid to test with indicator paper. The principal product (4 g. from an initial 5 g., 0.027 mole of unsaturated ketone X) was a white solid, m.p. 219–221°, after recrystallization from ligroin.

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 75.83, 75.96; H, 7.96, 8.03.

Our molecular weight determinations (cryoscopic in benzene), while giving reasonable results with naphthalene (Calcd. for $C_{10}H_8$: 128. Found: 125, 125, 118, 118.) and with *p*-dibromobenzene (Calcd. for $C_6H_4Br_2$: 236. Found: 223, 221, 224, 220.), gave low results for the dimer, $C_{26}H_{32}O_4$ (Calcd., 408. Found: 371, 342, 335.). That our product was indeed the dimer seemed evident from the work of Haller and Ramart-Lucas[19] who obtained a compound, $C_{26}H_{32}O_4$ (m.p. 214–215°; mol. wt. found, 396). Although they assigned structure XXIII to their compound, the origin was such that their 214–215°-melting material and our 219–221° substance were almost surely the same.

The compound did not react with bromine in carbon tetrachloride. In acetic acid it gave a positive periodic acid test.[21,22]

The infrared spectrum of the product (as a 5% solution in carbon tetrachloride/carbon disulfide) showed that it did not absorb between 1600 and 2800 or between 3100 and 4000 cm.$^{-1}$. Several sharp bands occurred between 970 and 1110 cm.$^{-1}$, the two strongest at 1050 and 1065 with others at 1115 (s), 1085 (m–s), 1035 (w), 1015 (m–s), 995 (w) and 980 cm.$^{-1}$ (w). Three sharp bands appeared at 705 (s), 748 (w), and 777 cm.$^{-1}$ (m). The spectrum was significantly different from either that of the "monomer" (XVIII) or of the amorphous material, both described earlier.

Acknowledgment.—We wish to express our gratitude to Dr. Donald P. Hollis and Varian Associates of Palo Alto, California, for the n.m.r. analyses.

The Structure of Isomaltol[1]

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Isomaltol is shown to be 3-hydroxy-2-furyl methyl ketone. Isomaltol *O*-methyl ether was ammonolyzed to produce both a pyrrole (3-methoxy-2-pyrrolyl methyl ketone) and a pyridine derivative (4-methoxy-2-methyl-3-pyridinol). Removal of the *O*-methyl group of the pyridinol gave the same 3-hydroxy-2-methyl-4-(1*H*)-pyridone that was obtained by ammonolysis of maltol *O*-methyl ether (3-methoxy-2-methyl-4*H*-pyran-4-one) to 3-methoxy-2-methyl-4-(1*H*)-pyridone, followed by removal of the *O*-methyl group. Oxidative degradation of the acetyl side chain of isomaltol *O*-methyl ether gave 3-methoxy-2-furoic acid, which was decarboxylated to the known 3-methoxyfuran. The acidity of isomaltol is attributed to a carboxylic acid-like resonance that extends from the carbonyl group to the enolic hydroxyl group and that diminishes the aromaticity of the furan nucleus. The infrared spectra indicate isomaltol to be strongly hydrogen bonded as a dimer in the crystalline state, and possibly also as a dimer, or intramolecularly, in organic solvents.

Isomaltol first was isolated from bread as a crystalline enol by Backe.[3] He obtained it in trace amounts from the steam distillate of a bread baked from a special flour that contained dried milk. He named the compound isomaltol because some of its properties were similar to those of isomeric maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one). Backe suggested a 4-pyrone structure for isomaltol.

Hodge and Nelson[4] produced isomaltol β-D-galactopyranoside from lactose by the same reaction with secondary amine salts that gave the amino-hexose-reductones from hexoses.[5] The *O*-galactoside was easily hydrolyzed to yield Backe's isomaltol. How-

(1) Presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

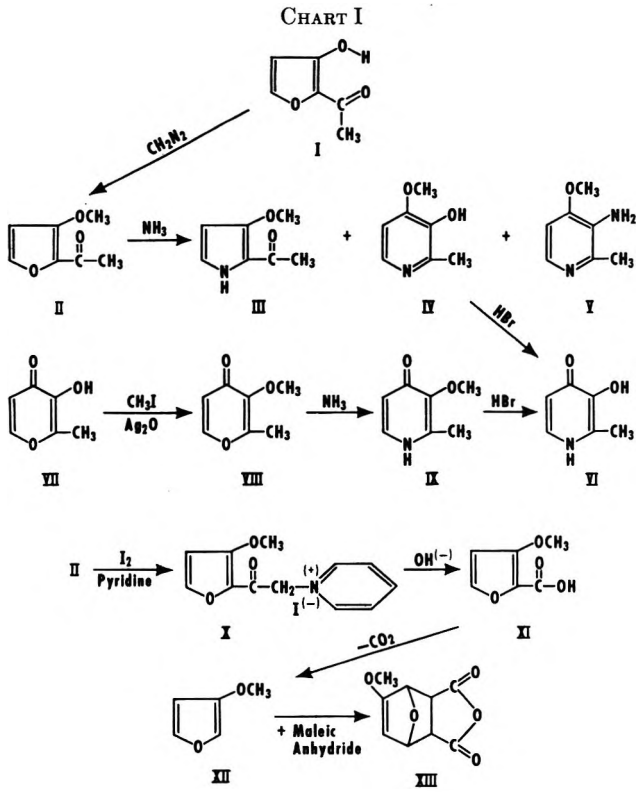
(2) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture; article is not copyrighted.

(3) A. Backe, *Compt. rend.*, **150**, 540 (1910); **151**, 78 (1910).

(4) J. E. Hodge and E. C. Nelson, *Cereal Chem.*, **38**, 207 (1961).

(5) (a) J. E. Hodge, U. S. Patent 2,936,308 (May 10, 1960); (b) J. E. Hodge, E. C. Nelson, and B. E. Fisher, unpublished results; (c) F. Weygand, H. Simon, and W. Bitterlich, and also J. E. Hodge and B. E. Fisher, *Tetrahedron*, **6**, 123 (1959).

CHART I

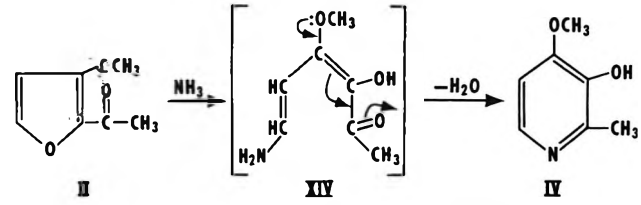


ever, from the instability of isomaltol to mineral acids (in contrast to the known stability of maltol and other 4-pyrones), the rather strong acidity of the enolic hydroxyl group, the demonstration of a reactive carbonyl group apart from the enol function, and the ultraviolet and infrared spectra, they concluded that isomaltol could not have the pyrone structure proposed by Backe. Instead, the 3-hydroxy-2-furyl methyl ketone structure (I) was proposed.[4] Proof of structure was undertaken because knowledge of the complex group of reactions involved in the browning decomposition of sugars by amine salts would be extended,[6] and because the strong caramel flavor of isomaltol indicated some possible uses as a flavoring agent.[7]

The structure (I) now has been proved by the series of transformations presented in Chart I. Ammonolysis of the *O*-methyl ether of isomaltol (II) gave the pyridinol derivative (IV), and, by demethylation of IV, 3-hydroxy-2-methyl-4-(1*H*)-pyridone (VI) was obtained. The same pyridone (VI) was synthesized by a known route (VII → VIII → IX → VI)[8] from maltol, for which the structure has been established unequivocally as 3-hydroxy-2-methyl-4*H*-pyran-4-one (VII).[8] Furthermore, degradation of the side chain of isomaltol *O*-methyl ether (II) through the pyridinium salt (X) and 3-methoxy-2-furoic acid (XI), with decarboxylation of XI, gave 3-methoxyfuran (XII).[9] Identity of the pyridones (VI) was shown by infrared spectra and X-ray diffraction patterns, by melting points, and by the melting point of a mixture of *O*-acetyl derivatives. Identity of our 3-methoxyfuran with that of Gronowitz and Sörlin was established by comparison of the infrared and n.m.r. spectra.[9]

Reaction of 3-methoxyfuran with maleic anhydride gave the crystalline adduct analyzing as XIII. However, several attempts to convert the adduct to the known 4-hydroxyphthalic anhydride with acetic anhydride and zinc chloride, or with hydrobromic acid in glacial acetic acid, were unsuccessful.

Leditschke[10] demonstrated that formation of 3-pyridinols by ammonolysis of 2-acylfurans is a general reaction. Others[11,12] have isolated both 2-methyl-3-pyridinol and methyl 2-pyrrolyl ketone after heating 2-furyl methyl ketone in aqueous or alcoholic ammonia. When 2-furyl methyl ketone is ammonolyzed in aqueous ammonia, the 3-pyridinol is isolated in 47% yield with a very low yield of the pyrrole derivative.[13] In contrast, aqueous ammonolysis of isomaltol *O*-methyl ether gave only 1.2% of 4-methoxy-2-methyl-3-pyridinol (IV), and 24% of 3-methoxy methyl 2-pyrrolyl ketone (III). Ammonolysis of II in aqueous methanol gave 2.0% of IV, 25% of III, and 0.4% of an unidentified compound of empirical formula $C_7H_{10}N_2O$. A plausible explanation for the low yield of IV is that the flow of electrons from the methoxyl oxygen of the postulated intermediate XIV decreases the electropositive character



of the carbonyl carbon. This decrease impedes nucleophilic attack of the nitrogen atom on the carbonyl carbon.

The pyrrole derivative (III) gave a positive color reaction with Ehrlich reagent and a blood-red color by the well-known pine splinter test. Structure III is supported by ultraviolet and infrared spectra. The ultraviolet absorption spectrum of III in methanol discloses a single peak at 290 mμ with E_m (l. mole^{-1} cm.$^{-1}$) 21,300. This peak coincides with the major peak reported for methyl 2-pyrrolyl ketone in methanol at 290 mμ, E_m 16,400.[14] The minor peak at 251 mμ, E_m 4100 that was reported for methyl 2-pyrrolyl ketone did not appear in the spectrum of III. However, disappearance of the minor peak (with a corresponding increase in the extinction coefficient of the major peak) also occurs when the furan nucleus is substituted with a methoxyl group in the β-position. For example, 2-furyl methyl ketone in methanol gives E_m 15,000 at 268 mμ and E_m 2500 at 226 mμ,[15] whereas, 3-methoxy-2-furyl methyl ketone (II) in methanol gives only one peak with E_m 17,400 at 281 mμ.[4] The infrared spectrum of III shows N–H stretching vibrations at 3495 and 3270 cm.$^{-1}$ and carbonyl stretching at 1640–1645

(6) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Am. Soc. Brewing Chemists Proc.*, 84 (1963).

(7) J. E. Hodge and H. A. Moser, *Cereal Chem.*, **38**, 221 (1961).

(8) A. Peratoner and A. Tamburello, *Gazz. chim. ital.*, **36**, 33, 50 (1906).

(9) Shortly after our presentation of this synthesis of 3-methoxyfuran (Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, p. 1D), G. Gronowitz and G. Sörlin [*Acta Chem. Scand.*, **15**, 1419 (1961); *Arkiv Kemi*, **19**, 515 (1962)] published a synthesis of 3-methoxyfuran from 3-iodofuran. Comparisons of the infrared and n.m.r. spectra were made by correspondence with Dr. Gronowitz, who kindly provided the spectra he had obtained before they were published.

(10) H. Leditschke, *Chem. Ber.*, **86**, 123 (1953).

(11) A. P. Dunlop and S. Swadesh, U. S. Patent 2,636,882 (April 28, 1953); U. S. Patent 2,672,461 (March 16, 1954).

(12) H. Sugisawa and K. Aso, *Chem. Ind.* (London), 887 (1958).

(13) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 667.

(14) U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

(15) Spectra were measured at this laboratory by Mr. C. A. Glass.

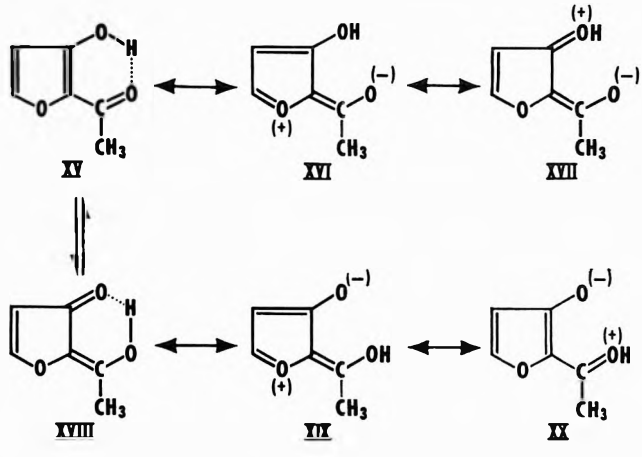
cm.$^{-1}$. This conforms to the recorded spectrum of methyl 2-pyrrolyl ketone, which shows N–H vibrations at 3425 and 3270 and carbonyl stretching at 1640 cm.$^{-1}$.[16] Furthermore, the band of III at 1515 cm.$^{-1}$ is in the region (1475–1600 cm.$^{-1}$) assigned to a ring vibration of pyrroles.[16] The methoxyl group of III was indicated by a clear, sharp band at 2830 cm.$^{-1}$, a frequency assigned to the C–H stretching vibrations of methoxyl groups.[17]

Huebner's method[18] for the paper chromatographic separation and identification of pyridines indicated the ammonolysis product, $C_7H_{10}N_2O$, to be a pyridine derivative. Proof of structure was not attempted because of the limited quantity of material available; however, *a priori* reasoning allows tentative assignment of the 3-amino-4-methoxy-2-picoline structure (V).

Isomaltol reacts as a strongly acidic enol. It gives an immediate deep red color with ferric chloride, and it liberates carbon dioxide from sodium bicarbonate solution.[4] It has one-tenth the acidity of acetic acid (pK_a 5.7 determined by electrometric titration). In ether solution isomaltol reacts rapidly with diazomethane to give II in 68% yield.[4] Whereas 2-furyl methyl ketone is very easily hydrogenated with a platinum catalyst,[19] isomaltol resisted hydrogenation under 3 atm. of hydrogen pressure at 25 and at 60° in the presence of prereduced platinum oxide catalyst. No significant uptake of hydrogen was observed.[20]

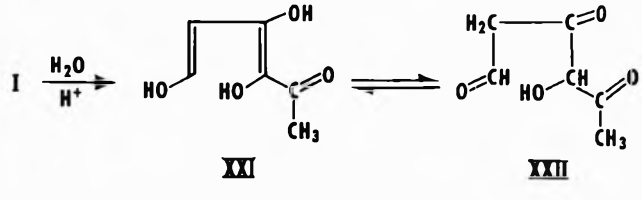
The only well-characterized β-hydroxyfurans that have been shown to exist predominantly in the enol form are diethyl and dimethyl 3,4-dihydroxy-2,5-furan dicarboxylate.[21,22] Hoehn[23] alkylated the dimethyl ester with dimethyl sulfate and isolated both mono- and dimethoxy derivatives of the dienol. Stable disodium and diammonium salts of the dienol also were isolated from the diethyl ester. No keto derivatives were reported. On the other hand, a series of 2-alkyl-3-hydroxyfurans prepared recently have been shown to exist almost completely in the keto form.[22] The side-chain β-carbonyl groups in the furan-2,5-dicarboxylic esters, therefore, can be considered to induce enolization of the ring carbonyl groups. In view of the stronger electron-withdrawing property of the acetyl carbonyl of isomaltol in comparison with the carbonyl of these esters, the existence of isomaltol as an enol is not surprising. However, a question arises on the mode of induction of enolization and stabilization of the enol by the carbonyl group. Does it occur by intramolecular hydrogen bonding of the conjugate chelate type,[24] as suggested by Dunlop and Peters[21]; or does it occur without such bonding, by resonance stabilization, as in carboxylic acids and vinylogs of carboxylic acids like "*trans* fixed" β-diketones?[25]

The relatively strong acidity of isomaltol coupled with its resistance to hydrogenation indicates that resonance through the enol and β-carbonyl functions is probably more important than the enol–chelate structure in stabilizing the enol form. Much weaker acidity and a much slower reaction with diazomethane would exist if only the intramolecularly bonded structures XV and XVIII were present.[24] Some structures that would



contribute to the resonance hybrid are given by XV, XVI, XVII, and (especially if intramolecular hydrogen bonding does occur) XVIII, XIX, and XX. The strong acidity suggests a relatively high contribution of structures XVII and XX and corresponding resonance structures of the anion.[25b,26]

Isomaltol in water alone at pH 3.5 reduces a limited amount of 2,6-dichloroindophenol in the cold in the manner of *aci*-reductones.[4] Hydrolysis of the furan ring[27] would yield the enediol-α-carbonyl compound XXI with strong acidic and reducing properties. Ex-



istence of the reductone XXI in water does not satisfactorily explain the observed acidity of isomaltol, however, because isomaltol is strongly acidic in ether solution as shown by its rapid methylation with diazomethane.[4] Hydrolysis of isomaltol by strong acid, as in the Elek–Harte method of determining acetyl groups,[28] gives a nearly quantitative yield of acetic acid together with a small amount of formic acid.[4] Both acids would be produced by C–C bond hydrolyses in the open-chain β-triketone XXII.

Evidence for a hydrogen-bonded conjugate chelate structure, such as XV ⇌ XVIII, was sought by meas-

(16) U. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

(17) H. B. Hinbest, G. D. Meakins, B. Nicholls, and A. A. Waglund, *ibid.*, 1462 (1957).

(18) C. F. Huebner, *Nature*, **167**, 119 (1951).

(19) T. Kariyone, *J. Pharm. Soc. Japan*, **515**, 1 (1925); *Chem. Abstr.*, **20**, 412 (1926).

(20) By E. C. Nelson of this laboratory.

(21) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 180 ff.

(22) (a) C. H. Eugster, K. Allner, and R. E. Rosenkranz, *Chimia* (Aarau), **15**, 516 (1961); (b) C. H. Eugster, R. E. Rosenkranz, K. Allner, and A. Hoffman, *Angew. Chem.*, **73**, 737 (1961); (c) R. E. Rosenkranz, K. Allner, R. Good, W. v. Phillipsborn, and C. H. Eugster, *Helv. Chim. Acta*, **46**, 1259 (1963).

(23) W. M. Hoehn, *Iowa State Coll. J. Sci.*, **11**, 66 (1936).

(24) (a) B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Chem. Ber.*, **84**, 156 (1951); (b) B. Eistert and E. Merkel, *ibid.*, **86**, 895 (1953); (c) B. Eistert, W. Reiss, and H. Wurzler, *Ann.*, **650**, 133 (1961); (d) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

(25) (a) B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 92, 108 (1954); (b) B. Eistert and F. Geiss, *Tetrahedron*, **7**, 1 (1959).

(26) R. B. Woodward and G. Small, Jr., *J. Am. Chem. Soc.*, **72**, 1297 (1950).

(27) Because of the resonance that extends to two electronegative oxygen atoms outside the ring, the aromaticity of the ring is diminished. Increased double bond character within the ring promotes hydrolysis of the vinyl ether linkage under mildly acidic conditions. Hydrolysis to the reductone was not observed in cold alkaline solutions.[4]

(28) A. Elek and R. A. Harte, *Ind. Eng. Chem., Anal. Ed.*, **8**, 267 (1936).

urements of the infrared spectra in various media.[15] In the crystalline state in potassium bromide disks (Fig. 1A), isomaltol does show broad, merged, and strongly shifted bands for the hydroxyl and carbonyl stretching vibrations at 3100–2650 and 1610–1550 cm.$^{-1}$, respectively; however, these bands should not be interpreted as representing the chelated structure XV. According to Martin,[29] these wide bands are too strong to represent intramolecular hydrogen bonding of a conjugate chelate type. They closely resemble bands that correspond to O–H· · ·O bonding in dimers of carboxylic acids.[29–31] No such strong, shifted bands appear in the spectrum of isomaltol in carbon tetrachloride solution (Fig. 1B).

In dilute carbon tetrachloride and in bromoform and tetrachloroethylene solutions, the hydroxyl stretching band of isomaltol lies at 3295 ± 5 cm.$^{-1}$; therefore, the hydroxyl group is not free. The hydroxyl group of phenols, *p*-acylphenols, and catechols is free in dilute carbon tetrachloride solutions, and the O–H stretching band occurs in the 3760–3580-cm.$^{-1}$ region.[32–34] Because dilutions from 1.4 down to 0.1% in the organic solvents did not alter the frequency or form of the isomaltol hydroxyl band, this stability rules out intermolecular hydrogen bonding of the type observed in liquid *p*-hydroxyacetophenone,[35] but which is lost in dilute carbon tetrachloride solution.[33]

The hydroxyl band of isomaltol in carbon tetrachloride (Fig. 1B) is relatively weak, broadened, and merged with the C–H bands. This band is just as broad and weaker in the more polar bromoform and tetrachloroethylene solvents. Weakness and breadth of a hydroxyl band, with shift into the C–H region and with no significant shift in three solvents of differing polarity,[36] are indications of intramolecular hydrogen bonding of a conjugate chelate type.[29] Some additional evidence was obtained in the region of carbonyl absorption.

The carbonyl band of 2-furyl methyl ketone in carbon tetrachloride lies at 1700 cm.$^{-1}$; 3-methoxylation (II) shifts the band to 1685 cm.$^{-1}$, and 3-hydroxylation (I) shifts the band by 45 to 1655 cm.$^{-1}$. The shifts to lower wave numbers for both the hydroxyl and carbonyl frequencies are not so great as the shifts observed for *o*-acylphenols and catechols,[31–35] but the carbonyl shift of 45 cm.$^{-1}$ does approach that of 55 cm.$^{-1}$ observed for 2-acetyl-1-naphthol in carbon tetrachloride,[37] and a 45-cm.$^{-1}$ shift observed for the same compound in chloroform.[33] Only a 28-cm.$^{-1}$ shift was observed for 2-acetyl-3-naphthol.[37] Methoxylation eliminates the possibility of conjugate chelation, yet a small shift is observed. Such a shift was observed also for *o*-methoxyacetophenone and was attributed to resonance of the type exemplified by XVI and XVII, structures which presumably exist also for the *O*-methyl ether.[35]

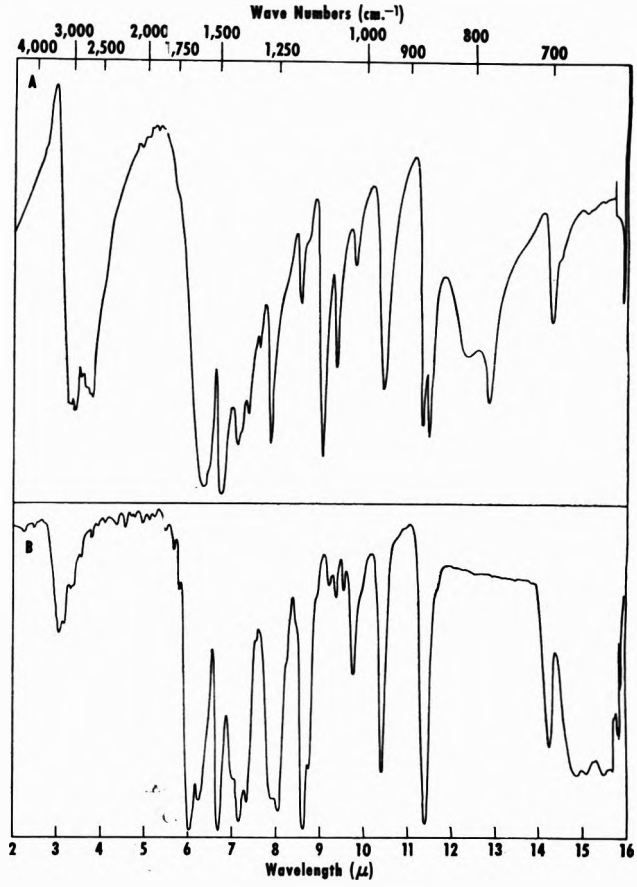


Fig. 1.—Infrared spectra of isomaltol (A) in potassium bromide disks, 14.0 g./l. and (B) in carbon tetrachloride solution, 13.5 g./l.

Carpenter and Snyder[38] found that a dimeric 2-carboethoxy-3-hydroxythiophene derivative, quite analogous to isomaltol, gave in chloroform a hydroxyl band at 3290 cm.$^{-1}$, the same frequency given by isomaltol in bromoform. As with isomaltol, no evidence was obtained from the infrared spectra for a breakdown of the thiophene dimer in organic solvents upon dilution. Therefore, the relatively small frequency shifts observed could be due to an unusually stable hydrogen-bonded dimer of the type proposed by Carpenter and Snyder, to intramolecular conjugate chelation, or to the unusual combination of furan and enolized β-diketone resonance systems. Further investigation of this matter, using infrared and n.m.r. measurements, is in progress with the collaboration of C. A. Glass of this laboratory.

Experimental

Materials and Methods. Isomaltol and isomaltol *O*-methyl ether were prepared by the methods previously described.[4] The maltol used was an especially purified commercial product, m.p. 160–161.5°. 2-Furyl methyl ketone was prepared by the method of Hartough and Kosak,[39] redistilled, and sublimed for the infrared analyses.

Infrared absorptions were determined in a Perkin-Elmer Model 21[40] twin-beam spectrometer with rock salt prism. The solvents used were spectral grade. Approximately 0.1 *M* solutions were

(29) A. E. Martin, *Nature*, **166**, 474 (1950).
(30) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brittain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).
(31) M. St. C. Flett, *J. Chem. Soc.*, 962 (1951).
(32) L. L. Ingraham, J. Corse, G. F. Bailey, and F. Stitt, *J. Am. Chem. Soc.*, **74**, 2297 (1952).
(33) N. M. Cullinane, R. A. Woolhouse, and V. V. Bailey-Wood, *Rec. trav. chim.*, **80**, 116 (1961).
(34) W. I. Awad, M. F. El-Newaihy, and S. F. Selim, *J. Org. Chem.*, **25**, 1333 (1960).
(35) H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).
(36) L. J. Bellamy and H. E. Hallam, *Trans. Faraday Soc.*, **55**, 220 (1959).
(37) I. M. Hunsberger, *J. Am. Chem. Soc.*, **72**, 5626 (1950).
(38) W. Carpenter and H. R. Snyder, *ibid.*, **82**, 2592 (1960).
(39) H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3093 (1947).
(40) Mention of instrument models and makers does not constitute endorsement by the U. S. Department of Agriculture over similar products not mentioned.

exposed in 1.0-mm. cells with automatic compensation for the absorption of the solvent. The potassium bromide pellets of isomaltol were 1.22 mm. thick, containing 0.1 *M* concentrations of the sample. The n.m.r. spectrum of 3-methoxyfuran was recorded on a Varian A-60 spectrometer.

All melting points were determined in capillary tubes and are corrected.

3-Methoxy-2-pyrrolyl Methyl Ketone (III).—Isomaltol *O*-methyl ether (II), 14.0 g. (0.1 mole), was dissolved in methanol (150 ml.) and concentrated ammonium hydroxide (150 ml.); the solution was heated in an autoclave at 140–145° for 20 hr. After cooling, the dark brown solution was washed from the autoclave with distilled water and concentrated at reduced pressure to *ca.* 100 ml. The crystals which separated were collected, and the filtrate was acidified to congo red with concentrated hydrochloric acid and extracted with three 50-ml. portions of benzene. The combined extracts were dried over anhydrous magnesium sulfate and evaporated to a crystalline residue. This material was added to the initial crystals, and the entire crop was recrystallized twice from water with the aid of charcoal to yield colorless needles, 3.5 g. (25%), of 3-methoxy-2-pyrrolyl methyl ketone, m.p. 115–116°. The compound gave a positive pine splinter test and a blood-red color with Ehrlich reagent, and had λ_{max}^{MeOH} 290 mμ (ε 21,300); $\nu_{max}^{CCl_4}$ 3500, 3270 (N–H); 2960 (C–H of C–CH_3); 2833 (C–H of O–CH_3); 1653–1625 (C:O); and 1515 cm.$^{-1}$ (pyrrole).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1; OCH_3, 22.3. Found: C, 60.4; H, 6.42; N, 10.1; OCH_3, 22.1.

Benzylidene Derivative of III.—3-Methoxy-2-pyrrolyl methyl ketone, 1.3 g., and benzaldehyde, 1.0 g. in 10% potassium hydroxide (20 ml.), were heated on a steam bath for 1 hr. The crystalline product which separated on cooling was recrystallized from aqueous ethanol, yielding 1.0 g. (45%) of 3-methoxy-2-pyrrolyl styryl ketone, m.p. 151–152°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77; N, 6.16. Found: C, 73.7; H, 5.61; N, 6.24.

3-Amino-4-methoxy-2-picoline (?) (V).—The aqueous mother liquor from the isolation of 3-methoxy-2-pyrrolyl methyl ketone was made alkaline with 50% potassium hydroxide and evaporated to dryness at reduced pressure. The residue was dissolved partially in boiling benzene (200 ml.). After evaporation of the benzene, the oily crystalline material which remained was purified by sublimation at 120° (3 mm.). Two recrystallizations from toluene gave 60 mg. of glistening flakes, m.p. 102–104.5°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.9; H, 7.24; N, 20.3; OCH_3, 22.5. Found: C, 61.1; H, 7.37; N, 19.9; OCH_3, 21.9; *C*-methyl,[41] 0.90 per 138.2 mol. wt.

4-Methoxy-2-methyl-2-pyridinol (IV).—The undissolved residue from the boiling benzene extraction was taken up in water (20 ml.), acidified with acetic acid, evaporated to dryness at reduced pressure, and extracted with boiling benzene (200 ml.). After removal of the solvent, the gummy residue was purified by sublimation at 120° (3 mm.) and recrystallized from toluene, yielding 270 mg. of 4-methoxy-2-methyl-3-pyridinol as colorless needles, m.p. 161–163°. The melting point was raised to 162.5–163.5° after one additional recrystallization from toluene, and the product showed λ_{max}^{MeOH} 310 mμ (ε 1270) and 270 (4980); in 0.1 *N* methanolic sulfuric acid, λ_{max} 277 mμ (ε 9730) and 242 (3280); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 290 mμ (ε 7010) and 252 (7930).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1. Found: C, 60.4; H, 6.38; N, 10.2; *C*-methyl,[41] 0.57 per 139 mol. wt.

Ammonolysis of isomaltol *O*-methyl ether (II), 5.0 g., in 100 ml. of concentrated ammonium hydroxide at 140° for 20 hr. yielded III, 1.2 g. (24%); IV, 60 mg. (1.2%); and V, 50 mg. (not purified).

3-Hydroxy-2-methyl-4(1*H*)-pyridone (VI).—4-Methoxy-2-methyl-3-pyridinol (190 mg.) was dissolved in 48% hydrobromic acid (3 ml.) and heated in a sealed tube at 140° for 4 hr. The solution was concentrated to a crystalline mass which was dissolved in 5 ml. of distilled water and neutralized with sodium bicarbonate. The crystals that separated on cooling to 5° were recrystallized from water, yielding 60 mg. which decomposed above 250° without melting. An alcohol solution of the compound gave an initial red color with alcoholic ferric chloride. The red color changed to violet and then to blue on further addition of ferric chloride solution. The compound showed λ_{max}^{MeOH} 278 mμ (ε 13,500); in 0.1 *N* methanolic sulfuric acid, λ_{max} 274 mμ (ε 8600) and 242 (3080); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 306 mμ (ε 4090), 275 (5355), and 247 (5570).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.9; H, 5.60; N, 11.2.

3-Methoxy-2-methyl-4*H*-pyran-4-one (VIII).—Maltol, 25.2 g. (0.2 mole), was dissolved in dimethylformamide (150 ml.), and 85.2 g. (0.6 mole) of methyl iodide was added.[42] Moist silver oxide (45 g.) was added portionwise while the solution was stirred vigorously. The flask was stoppered and mechanically shaken for 44 hr. The mixture was filtered through kieselguhr, then diluted with 500 ml. of distilled water; potassium cyanide (20 g.) was added, and the solution was extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated to a residual oil. This crude residue was chromatographed on an acid-washed aluminum oxide column (150 g.) and distilled at reduced pressure, yielding 11.2 g. (40%) of colorless hygroscopic liquid, b.p. 78–79° (4 mm), $n^{21}D$ 1.5168, λ_{max}^{MeOH} 259 mμ (ε 9,840).

Anal. Calcd. for $C_7H_8O_3$: C, 60.0; H, 5.71; OCH_3, 22.2. Found: C, 59.7; H, 5.83; OCH_3, 22.0.

3-Methoxy-2-methyl-4(1*H*)-pyridone (IX).—3-Methoxy-2-methyl-4*H*-pyran-4-one (4.0 g.) dissolved in concentrated ammonium hydroxide (120 ml.) was heated on a steam bath for 2 hr. The solvent was removed at reduced pressure, and the crude product was recrystallized from acetone, yielding 2.0 g. (50%) of 3-methoxy-2-methyl-4(1*H*)-pyridone, m.p. 155–156.5°, lit.[8] 149°; λ_{max}^{MeOH} 266 mμ (ε 13,370); in 0.1 *N* methanolic sulfuric acid, λ_{max} 259 mμ (ε 5320) and 241 (5580); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 245 mμ (ε 10,130).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1. Found: C, 59.5; H, 6.56; N, 10.1; *C*-methyl,[41] 0.87 per 139 mol. wt.

3-Hydroxy-2-methyl-4(1*H*)-pyridone (VI).—3-Methoxy-2-methyl-4(1*H*)-pyridone (1.5 g.) dissolved in 48% hydrobromic acid (30 ml.) was heated in a sealed tube 3.5 hr. at 140°. The solution was concentrated to a crystalline salt which was dissolved in distilled water (25 ml.) and neutralized with sodium bicarbonate. The crystals, which separated on cooling to 5°, were recrystallized from water to yield 970 mg. (72%) of 3-hydroxy-2-methyl-4(1*H*)-pyridone which decomposed above 250° without melting. The infrared spectrum and X-ray diffraction pattern were identical with those of 3-hydroxy-2-methyl-4(1*H*)-pyridone from IV. The product showed λ_{max}^{MeOH} 278 mμ (ε 13,400); in 0.1 *N* methanolic sulfuric acid, λ_{max} 274 mμ (ε 7970) and 242 (2870); in 0.1 *N* methanolic potassium hydroxide, λ_{max} mμ (ε 4020), 275 (5080), and 247 (5240).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.3; H, 5.64; N, 11.2.

Acetyl Derivative of VI. A.—3-Hydroxy-2-methyl-4(1*H*)-pyridone (50 mg.) from IX in 0.5 ml. of acetic anhydride was heated 0.5 hr. on a steam bath. The excess acetic anhydride and acetic acid were removed in a vacuum desiccator over potassium hydroxide pellets, and the sirupy residue was sublimed at 170–180° (2.5 mm.). Recrystallization of the sublimate from ethyl acetate gave 36 mg. of colorless 3-acetoxy-2-methyl-4(1*H*)-pyridone, m.p. 205–208°, lit.[8] 204–205°. An aqueous solution of the compound did not give a color with ferric chloride solution.

Anal. Calcd. for $C_8H_9NO_3$: N, 8.38. Found: N, 8.41.

B.—3-Hydroxy-2-methyl-4(1*H*)-pyridone (50 mg.) from IV, treated with acetic anhydride as in A, gave 10 mg. of 3-acetoxy-2-methyl-4(1*H*)-pyridone, m.p. 204–208°. A mixture melting point with the *O*-acetyl derivative of A showed no depression.

Anal. Calcd. for $C_8H_9NO_3$: N, 8.38. Found: N, 8.53.

3-Methoxy-2-furoylmethylpyridinium Iodide (X).—Isomaltol *O*-methyl ether, 14.0 g. (0.1 mole), was dissolved in dry pyridine (35 ml.), then 25.4 g. (0.1 mole) of iodine was added.[43] The mixture was heated 0.5 hr. on a steam bath. The crystals that formed at 5° overnight were collected, washed with ether and ethanol, and recrystallized from aqueous ethanol to yield 16.0 g. (40%) with m.p. 203° dec.

Anal. Calcd. for $C_{12}H_{12}INO_3$: C, 41.8; H, 3.50; N, 4.06. Found: C, 41.9; H, 3.63; N, 4.10.

(41) W. F. Barthel and F. B. LaForge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944).

(42) Method of R. Kuhn, I. Löw, and H. Trischmann, *Chem. Ber.*, **88**, 1492 (1955).

(43) Method of L. C. King, *J. Am. Chem. Soc.*, **66**, 894 (1944).

3-Methoxy-2-furoic Acid (XI).—3-Methoxy-2-furoylmethylpyridinium iodide (10.0 g.) was dissolved in 80 ml. of 6% aqueous potassium hydroxide. The solution was heated on a steam bath 5 min., cooled, and acidified with dilute hydrochloric acid. The acidified solution was extracted with three 100-ml. portions of ether, and the ether extracts were dried over anhydrous sodium sulfate. After distillation of the solvent at atmospheric pressure, 750 mg. of 3-methoxy-2-furoic acid, m.p. 161–163° dec., was obtained. A sample for analysis was recrystallized twice from ether and had m.p. 169–170° dec.; λ_{max}^{MeOH} 258 mμ (ε 14,500); ν_{max}^{KBr} 3365 w, 3125–2780 s, 2700–2530 s (O–H · · · O); 1710–1667 vs (C:O); 1610 vs (furan); 1495 vs cm.$^{-1}$ (furan).

Anal. Calcd. for $C_6H_6O_4$: C, 50.7; H, 4.26; OCH_3, 21.8; neut. equiv., 142.1. Found: C, 50.4; H, 4.23; OCH_3, 22.3; neut. equiv., 143.3.

Methyl 3-Methoxy-2-furoate (Methyl Ester of XI).—Crude 3-methoxy-2-furoic acid (500 mg.) was dissolved in dry tetrahydrofuran (10 ml.), and an ether solution of diazomethane was added. The solvents were removed on a steam bath, and the crude ester was recrystallized from ether–petroleum ether, yielding 320 mg. (58%) of methyl 3-methoxy-2-furoate, m.p. 51.5–52.5°.

Anal. Calcd. for C_7H_8O: C, 53.9; H, 5.17. Found: C, 53.9; H, 5.16.

3-Methoxyfuran (XII).—3-Methoxy-2-furoic acid (2.3 g.) was dissolved in 12 ml. of dry quinoline in a 50-ml. distilling flask. Cupric oxide catalyst (0.3 g.) was added, and the mixture was heated to boiling. The colorless liquid which distilled was dried over anhydrous sodium sulfate and redistilled twice. The yield of colorless volatile liquid, b.p. 109–110° (760 mm.), was 985 mg. (62%); $n^{20}D$ 1.4499; ν_{max} 3135 m (furan C–H); 2930 s, 2825 m (C–H); 1605 vs (furan C=C); 1515 s, 1468 s, 1458 s, 1395 vs, 1247 s, 1198 m, 1173 vs, 1070 vs, 1010 vs, 970 s, 865 vs, 764–746 vs, and 687 w cm.$^{-1}$; n.m.r. (CCl_4): τ 6.33 (OCH_3), 3.82 (C_4H), 2.92 (C_5H), 2.78 (C_2H).

Anal. Calcd. for $C_5H_6O_2$: C, 61.2; H, 6.17. Found: C, 61.6; H, 6.33.

4-Methoxy-3,6-*endo*-oxo-1,2,3,6-tetrahydrophthalic Anhydride (XIII).—3-Methoxyfuran (0.56 g.) dissolved in ether (10 ml.) was added to a solution of maleic anhydride (0.56 g.) in ether (10 ml.). The solution was kept at 5° overnight. The crystalline Diels–Alder adduct was washed with ether and air-dried to a weight of 0.6 g. (45%), m.p. 97–99°.

Anal. Calcd. for $C_9H_8O_5$: C, 55.1; H, 4.11. Found: C, 55.0; H, 4.32.

3-Methoxy-2-furyl Styryl Ketone.—Isomaltol *O*-methyl ether, 28.0 g. (0.2 mole), was dissolved in ethanol (150 ml.) and distilled water (120 ml.). Benzaldehyde, 21.0 g. (0.2 mole), was added and the solution was cooled to 5°. Sodium hydroxide (10 g. in 30 ml. water) was added while the solution was stirred mechanically. Stirring was continued for 6 hr. at 0°, and the crystals were collected and washed with cold 50% aqueous ethanol. The product was recrystallized from 50% ethanol, yielding 15.5 g. (68%) of pale yellow needles, m.p. 80–82.5°. A sample for analysis was recrystallized twice from 50% ethanol and had m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.30. Found: C, 73.7; H, 5.41.

3-*p*-Toluenesulfonyloxy-2-furyl Methyl Ketone.—Isomaltol, 6.3 g. (0.05 mole), and *p*-toluenesulfonyl chloride, 10.5 g. (0.055 mole), were dissolved in dry pyridine (100 ml.) at 0°. The solution was kept at room temperature for 72 hr., then the pyridine was removed by distillation at reduced pressure. The residue was taken up in chloroform (100 ml.), extracted with dilute hydrochloric acid, dilute potassium carbonate solution, and distilled water. After drying the chloroform phase over anhydrous magnesium sulfate, the solvent was removed at reduced pressure, and the crude crystals were recrystallized from absolute ethanol, yielding 9.0 g. (64%) of product with m.p. 62–65°. The melting point was raised to 69–70° after one additional recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{12}O_5S$: C, 55.7; H, 4.31. Found: C, 55.8; H, 4.46.

An attempt to cleave the tosyl ester to 2-furyl methyl ketone by a Kenner desoxygenation was unsuccessful.[44]

3-Methoxy-2-furyl Methyl Ketone Oxime.—The oxime was prepared from isomaltol *O*-methyl ether and hydroxylamine hydrochloride by the method described by Vargha for 2-furyl methyl ketone.[45] The yield was 80% and the melting point was 124–125°.

Anal. Calcd. for $C_7H_9NO_3$: C, 54.2; H, 5.85; N, 9.03. Found: C, 54.7; H, 5.91; N, 9.17.

Acknowledgment.—We are indebted to the following chemists of this laboratory: Mrs. Clara E. McGrew and Mrs. Bonita Heaton for the microanalyses; Mr. Curtis Glass for determining n.m.r., infrared, and ultraviolet absorption spectra; Mr. Henry Zobel for the X-ray diffraction patterns; and Dr. Charles Russell for the sample of 2-furyl methyl ketone. The Dow Chemical Company, Midland, Michigan, supplied the sample of maltol. This work was conducted under the general supervision of Dr. R. J. Dimler.

(44) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S 178 (1949).

(45) L. Vargha, J. Ramonczai, and P. Bite, *J. Am. Chem. Soc.*, **70**, 371 (1948).

Synthesis of Resin Acid Intermediates. 8α,10β-Dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 and 8α,10β-Dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2

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Condensation of 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone with acetone gives a small yield of dienone from which pure 8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 (XI) has been isolated. Condensation of 2,6-dimethyl-2-carbomethoxycyclohexanone with N,N-diethylaminobutanone-3 methiodide afforded a mixture of bicyclic unsaturated ketones from which pure 8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2 (XVI) has been isolated, converted to XI, and shown to have stereochemistry as designated.

As part of a research program directed toward synthesis of diterpene resin acids *via* bicyclic intermediates possessing the difficultly accessible *gem*-methylcarboxyl grouping and suitable functionality for elaboration to a variety of natural substances, we have investigated ring extension from a "preformed ring A" unit, such as 2,6-dimethyl-2-carbomethoxycyclohexanone (I).[2] Bicyclic material of potentially useful structure was obtained both by condensation of I with methyl vinyl ketone and by condensation of 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone (II) with acetone, and it is these results which are described in this paper. However, in view of the better yields obtained in other preparations of similar bicyclic intermediates,[3] no further pursuit of these two routes is planned.

The condensation of II with acetone was investigated first. 2-Methyl-2-carbomethoxycyclohexanone[4] was converted to its hydroxymethylene derivative[5] (III), m.p. 36–40°, in 68% yield with methyl formate and sodium methoxide in methanol under conditions which permitted precipitation of the enolate salt of III, thereby preventing alkoxide cleavage of the fully substituted β-keto ester moiety.

Methylation of 2-methyl-6-hydroxymethylenecyclohexanone (IV) yields a product suitable for subsequent condensation with acetone, only about 20% of the enol ether being formed.[6] In the present case, however, methylation of III with methyl iodide in acetone using potassium carbonate as catalyst always afforded at least 50% enol ether V. The amount of this O-alkylation product could be determined easily by comparing the ultraviolet absorption of the crude product with that of pure V, λ_{max}^{EtOH} 280 mμ (ε 7500). The amount of desired C-alkylation product (II)[7] present was very difficult to ascertain, for attempted isolation afforded only V and I, presumably produced by decarbonylation of II. Therefore, the crude methylation product was used directly in the next step.

The reason for the difference in the C- *vs.* O-alkylation ratio between IV[6] and III can be seen from a conformational consideration of the respective anions undergoing alkylation, if one assumes that C-alkylation occurs more readily with an axially approaching electrophilic center.[8] Such approach of methyl iodide to the π-cloud of the anion of 2-methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (VI) will necessarily generate a 1,3-diaxial interaction with either the methyl or carbomethoxyl group. In the anion of 2-methyl-6-hydroxymethylenecyclohexanone (VII), on the other hand, a hydrogen can be in the 1,3-diaxial relationship to the incipient C-methyl group. Thus, C-methylation will be less favored with the larger axial group of VI and O-methylation becomes the more likely reaction path.

The condensation of the crude methylation mixture with acetone was conducted, as is the custom,[9] in two steps: first, refluxing with piperidine and acetic acid to effect condensation at the aldehyde, and, second, treatment with stronger base to effect ring closure to the dienone. The first step afforded a crude product which had ultraviolet absorption at 220–225 mμ (ε 2000), corresponding to a yield of *ca.* 8% from III of α,β-un-

(1) (a) Recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, 1960–1962; Dartmouth College Senior Fellow, 1961–1962. (b) National Science Foundation Undergraduate Research Participant during the 1961–1962 and 1962–1963 academic years.

(2) Similar and essentially identical ring A units have been used as starting materials for an A → A–C phenylethylcyclohexanol → A–B–C (by acid-catalyzed ring closure) approach to resin acids and related compounds [see, *e.g.*, R. D. Haworth and R. L. Barker, *J. Chem. Soc.*, 1299 (1939); R. D. Haworth and B. P. Moore, *ibid.*, 633 (1946); B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945); F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind.* (London), 113 (1956), and *J. Chem. Soc.*, 573 (1957); J. A. Barltrop and N. A. J. Rogers, *ibid.*, 2566 (1958); U. R. Ghatak, *Tetrahedron Letters*, 19 (1959); U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Am. Chem. Soc.*, **82**, 1728 (1960)].

(3) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, to be published.

(4) W. E. Bachmann and A. S. Dreiding, *J. Org. Chem.*, **13**, 317 (1948).

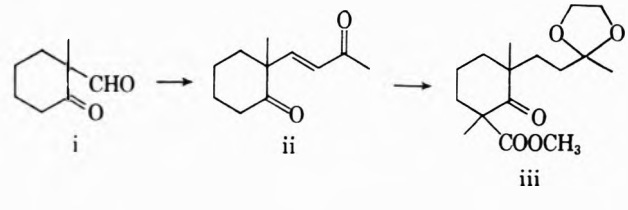
(5) E. W. Garbisch, Jr. [*J. Am. Chem. Soc.*, **85**, 1696 (1963)], has presented evidence that enolized β-keto aldehydes may exist to a significant or even preponderant degree at equilibrium in the "aldo enol" form rather than in the "hydroxymethylene ketone" form. The β-keto aldehyde species described in this paper are shown in the customary hydroxymethylene ketone form; obviously, no inference can be drawn about the actual equilibrium composition from the reactions of the species.

(6) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).

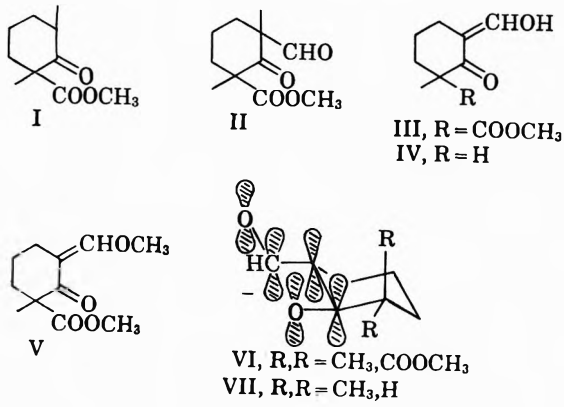
(7) The C-methylation of VI can, of course, generate a pair of diastereoisomers, with the 2- and 6-methyl groups *cis* and *trans*. Structure II is an expression for this mixture.

(8) Ample precedent exists for the assumption of stereoelectronic control of enolate methylation [see, *e.g.*, R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962)].

(9) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1716 (1946); R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950); see also ref. 11. While exploring an approach to diterpene intermediates outlined below (i → ii → iii) we found that piperidine and acetic acid, under the conditions of Woodward and Singh (*op. cit.*), actually cause cyclization of ii to 10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2, for the product absorbed at 240 mμ, and its hydrogenation product gave a 2,4-dinitrophenylhydrazone with m.p. 125–127°, (lit. m.p. 125–127°). However, in cases where the ring-closing aldol condensation is at a more hindered carbonyl (as in VIII–IX → XI–XII), the separate strong base step is necessary.

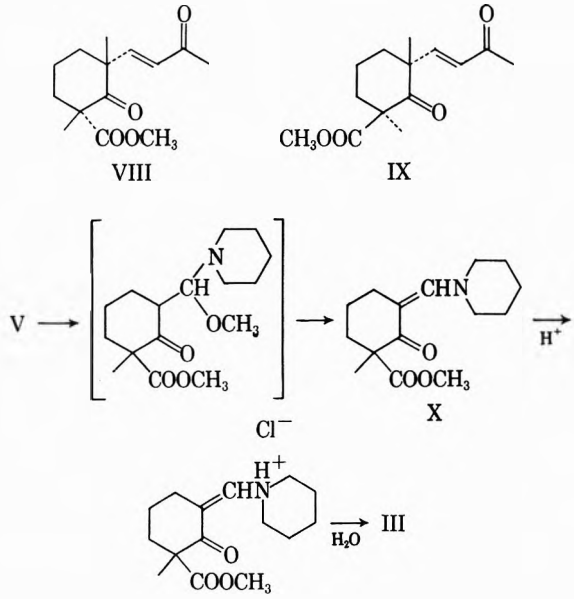


i ii iii



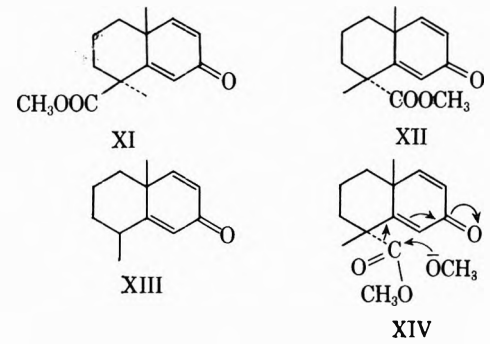
saturated ketones VIII and IX, based on an assumed ϵ of 10,000 for pure material.[10] Chromatography effected concentration of the chromophoric material (maximum ϵ attained was 8100), separating it from an easily eluted, mobile oil which was fractionally distilled to afford a small amount of mesityl oxide (undoubtedly formed by self-condensation of acetone during the 90-hr. treatment with piperidine and acetic acid) and higher-boiling material, judged by boiling point, refractive index, and infrared spectrum to be composed predominantly of I and 2-methyl-2-carbomethoxycyclohexanone.

The major portion of enol ether V had been assumed to have been removed from the product during work-up by acid hydrolysis to III, followed by extraction of this substance with base. However, another path of removal of V came to light when it was observed that the aqueous acid wash layer, initially homogeneous, deposited upon standing an oil which proved to be essentially pure III. This "recovered" material undoubtedly found its way into the aqueous acid *via* the enamine X, as shown below.



Treatment of the mixture containing VIII and IX with strong basic catalysts afforded material with absorption at 243 mμ, as expected for dienones XI and XII. The yield in the cyclization was never good; using purified starting material (ϵ 8100), the crude product (*ca.* 65%) had λ_{max} 243 mμ with ϵ 4000 to 4500 depending on conditions. The over-all yield of crude dienone from III thus may be estimated at 2%. Chromatography of the product from potassium *t*-butoxide-catalyzed cyclization afforded a very small amount of crystalline dienone, m.p. 90–91°, which was subsequently shown (*vide infra*) to be the isomer with the axial carbomethoxyl group (XI). The epimeric dienone XII was never obtained pure.

When the cyclization catalyst was sodium methoxide, there was isolated, in addition to XI, 8,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 (XIII), the dienone prepared by Bloom[11] by condensation of 2,6-dimethyl-2-formylcyclohexanone[6] with acetone. This dienone could arise by decarbomethoxylation as depicted in XIV, and its isolation can be taken as a possible indication of the presence of XII in the cyclization product, since nucleophilic attack (as in XIV) at the axial carbomethoxyl group of XI is unlikely (*vide infra*).[12] In view of the low yield in all the steps from III to the crude mixture of XI and XII, further conversions of these substances were not attempted, and attention was turned to the alternate approach, the Robinson annelation reaction of I.



In order to test the feasibility of Michael addition of I, we first tried the excellent acceptor acrylonitrile in the presence of potassium *t*-butoxide and obtained 51% of purified cyanoethylated product. This consisted of the two diastereoisomers of XV, one of which solidified, m.p. 64–65°. No attempt was made to identify the stereochemistry of these isomers[13] nor to use them for formation of the B ring *via* modification of the nitrile group.

That the reaction of I with methyl vinyl ketone did not proceed equally as smoothly was not unexpected. The Robinson annelation reaction applied to 2-methylcyclohexanone affords at best about 30% of 10-methyl-$\Delta^{1,9}$-octalone-2,[14] and in the case of I there is additional steric hindrance to both initial Michael addition and cyclization, plus the presence of a base-sensitive β-keto

(10) 3-Penten-2-one shows λ_{max}^{EtOH} 224 mμ (ϵ 9700); K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(11) S. M. Bloom *J. Am. Chem. Soc.*, **80**, 6280 (1958). We wish to thank Dr. Bloom for kindly sending us a copy of the infrared spectrum of XIII and a sample of its 2,4-dinitrophenylhydrazone.

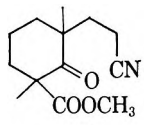
(12) Dienone XIII could arise by other pathways, *e.g.*, decarbomethoxylation of VIII and/or IX followed by cyclization, so that its isolation alone is by no means conclusive evidence for the presence of XII.

(13) By analogy to the Michael addition to I of methyl vinyl ketone, which afforded predominantly XVI the predominant, crystalline cyanoethylation product would have the 2- and 6-methyl groups *trans*. If XVI arises by axial attack of the Michael acceptor, reaction occurs preferentially with methyl rather than carbomethoxyl in the "3-axial" position.

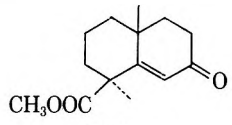
(14) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953); A. L. Wilds, C. H. Hoffman, and T. H. Pearson, *ibid.*, **77**, 647 (1955).

ester moiety.[15] With N,N-diethylaminobutanone-3 methiodide under conditions similar to those of Cornforth and Robinson[16] there was obtained from I a yield of 11% (on the basis of ultraviolet absorption) of bicyclic unsaturated ketone, presumably a mixture of XVI and XVII.

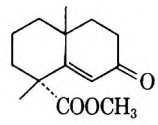
Extensive column chromatography effected considerable concentration but very incomplete separation of XVI and XVII, for only a small amount of one crystalline isomer, m.p. 89.5–90.5°, was obtained. Vapor phase chromatography showed that there were two major components in the chromophoric fractions, and that the preponderant one was the crystalline isomer. Since this isomer was adsorbed less strongly (elution or v.p.c.), it was very tentatively assigned structure XVI, with the carbomethoxyl group axial. Selenium dioxide oxidation of this crystalline isomer yielded the previously isolated crystalline dienone, suggesting that the latter was XI.



XV



XVI



XVII

Confirmation of these stereochemical assignments was sought in the resistance which a tertiary carboalkoxyl in a 1,3-diaxial relationship to a methyl should exhibit to basic hydrolysis, as found in the cases of podocarpic[17] and agathic[18] esters and in a similar bicyclic system.[19] To this end, XVI was hydrogenated over palladium on carbon to yield a dihydro compound, m.p. 77.0–77.5°, which was assigned the *trans* structure XVIII by analogy to results of hydrogenation of similar systems.[20]

The saponification resistance of this keto ester was tested, but it was found that XVIII was converted by refluxing aqueous base to oily material whose infrared spectrum was consistent with products resulting from cleavage (reverse Michael reaction) as shown in XIX. When the ketone group of XVIII was first reduced with sodium borohydride (to give presumably largely XX) and the product then subjected to refluxing 3 *N* sodium hydroxide solution for 24 hr., no ester hydrolysis occurred; neutral material identical in the infrared with the starting hydroxy ester was recovered in 95% yield.

(15) Evolution of gas upon acidification of the reactions of I in the presence of potassium *t*-butoxide suggested that either β-keto acids or *t*-butyl esters may have been formed; *cf.* H. O. House, *et al.*, *J. Am. Chem. Soc.*, **84**, 2614 (1962).

(16) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

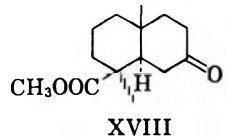
(17) I. R. Sherwood and W. F. Short, *ibid.*, 1006 (1938).

(18) L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, **14** 203 (1931).

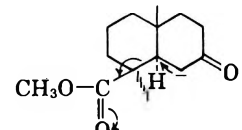
(19) C. L. Graham, F. J. McQuillin, and P. L. Simpson, *Proc. Chem. Soc.*, 136 (1963), and references cited therein.

(20) See, *e.g.*, G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); F. Sondheimer and D. Elad, *ibid.*, **79**, 5542 (1957); B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958); and, particularly, W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963). Some caution is necessary, however, in making the assumption that, in the words of E. Wenkert and B. G. Jackson [*J. Am. Chem. Soc.*, **80**, 211 (1958)], "... for obvious steric reasons hydrogenation of a $\Delta^{5,6}$ linkage in the presence of an axial angular methyl group and an axial C-4 substituent results in an A/B *trans* system," because in certain cases *cis* fusion has been obtained [see S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963); T. G. Halsall, W. J. Rodewald, and D. Willis, *J. Chem. Soc.*, 2798 (1959); N. B. Haynes and C. J. Timmons, *Proc. Chem. Soc.*, 345 (1958)]. Even if reduction of XVI unexpectedly did afford *cis* fusion, the combination of saponification and n.m.r. evidence (*vide infra*) still serves as proof of the structure of XVI.

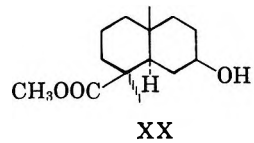
On the other hand, when some of the oil containing primarily the isomeric unsaturated ketone XVII was subjected to the same sequence—hydrogenation, sodium borohydride reduction, and basic hydrolysis—saponification occurred; *ca.* 60% of acidic material was obtained which solidified to afford a substance, m.p. 201–203°, possessing an elemental analysis consistent with the expected principal product of this sequence, XXI.



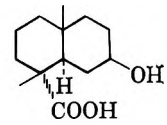
XVIII



XIX



XX



XXI

The n.m.r. spectra of XVI and XVIII[21] also confirmed the axial nature of the carbomethoxyl group in these substances, since the angular methyl resonance appeared at a higher field than expected for an epimeric substance like XVII, owing to transannular shielding by the axial carbomethoxyl.[22] The details of the argument will be deferred until a future publication when the n.m.r. spectra of similar intermediates[3] will be discussed.

Experimental

Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were taken either in an open capillary or on a micro hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 21 recording spectrophotometer.

2-Methyl-2-carbomethoxycyclohexanone.—2-Carbomethoxycyclohexanone was prepared in 40–45% yield by condensation of cyclohexanone with diethyl oxalate in methanol containing sodium methoxide, followed by pyrolysis of the intermediate glyoxylate, in a modification of the procedure of Snyder.[23] Methylation was performed by the method of Bachmann[4] in *ca.* 90% yield.

2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (III).—To a mixture of 173 g. (1.02 moles) of 2-methyl-2-carbomethoxycyclohexanone, b.p. 77–80° (0.8 mm.) (possibly contaminated with a small amount of the corresponding ethyl ester), and 300 g. (5 moles) of methyl formate (Brothers Chemical Co.) in a 2-l., three-necked flask equipped with mechanical stirrer, reflux condenser, and thermometer, and cooled to −8° in an ice–acetone bath was added dropwise over a 45-min. period a solution of 23 g. (1 mole) of sodium in 200 ml. of anhydrous methanol. Another 300 g. of methyl formate was added to the yellow-orange mixture which was then stirred with cooling for 3

(21) We wish to thank Professor Walter L. Meyer of Indiana University for determining these spectra and providing valuable interpretative discussion concerning them.

(22) R. W. J. Carney, Ph.D. thesis, Iowa State University, 1962, provides numerous examples of such an effect in resin acid derivatives; it also has been observed in resin acids and bicyclic substances in this laboratory.

(23) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

hr. and at room temperature for 15 hr. A voluminous white precipitate formed during the first hours of reaction.

The reaction was cooled to −8° in an ice–acetone bath again and 500 ml. of water was added slowly through a dropping funnel, with the temperature kept below 0°. The mixture, which at this point consisted of a yellow solution covered by an oily layer, was extracted twice with chloroform to remove neutral organic material. The aqueous layer was acidified carefully to *ca.* pH 5 by the addition of solid sodium dihydrogenphosphate and dilute hydrochloric acid, with stirring. Then the mixture was extracted thoroughly with benzene (some emulsion trouble), which was washed with water and saturated sodium chloride solution. The benzene was removed on the steam bath under reduced pressure, and the residue was distilled under nitrogen. 2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone was obtained as a slightly yellow oil, b.p. 103–107° (1.4 mm.); the yield was 136.5 g. (68%). This product gave an immediate deep purple color with ferric chloride solution and solidified on standing to give crystals which melted, after washing with ether, at 36–40°. Redistillation afforded colorless material, b.p. 79° (0.25 mm.); $n^{25}D$ 1.4992; λ_{max}^{EtOH} 289 mμ (ε 8000); λ_{max} 5.73, 6.05, and 6.26 μ.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.64; H, 7.04.

When the condensation with methyl formate was conducted in a larger amount of methanol, so that the enolate salt of the product did not precipitate, the yield was reduced to 15–20%. Sodium hydride and potassium *t*-butoxide as catalysts gave only poor yields of hydroxymethylene compound.

Methylation of 2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone.—The procedure used was a modification of that of Johnson and Posvic.[6] To a 2-l., three-necked flask were added 95 g. (0.69 mole) of potassium carbonate (reagent grade, anhydrous), 870 ml. of acetone (reagent grade, previously dried over potassium carbonate), 136 g. (0.69 mole) of 2-methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (b.p. 103–107° at 1.4 mm.), and 65 ml. (148 g., 1.04 mole) of methyl iodide (Brothers Chemical Co.). The mixture was mechanically stirred at room temperature for a total of 45 hr. After 19 hr. an additional 30 ml. of methyl iodide was added. The yellow mixture was diluted with 700 ml. of anhydrous ether, allowed to stand for a few hours, and filtered. The filtrate was reduced in volume under reduced pressure to afford 141 g. of orange oil which had λ_{max}^{EtOH} 278 mμ (ε 3600), indicating that it contained *ca.* 48% O-methylated product, and λ_{max} 3.68 μ, indicating presence of an aldehyde proton. This oil was customarily used directly in the next step; attempted isolation or concentration of the desired 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone failed. When the methylation was run at reflux, the per cent of O-methylated material in the isolated product was higher, and no 3.68-μ band could be detected.

Fractionation of one methylation product prepared as described above afforded two distinct fractions. The first, b.p. 59–61° (0.2 mm.), had an infrared spectrum (λ_{max} 5.73 and 5.82 μ), a refractive index ($n^{25}D$ 1.4570, lit.[24] $n^{24}D$ 1.4571), and an elemental analysis (Found: C, 65.91; H, 8.79.) that showed it to be I. The second (and principal) fraction was redistilled to give colorless material with b.p. 100–101° (0.2 mm.) which was pure **2-methyl-2-carbomethoxy-6-methoxymethylenecyclohexanone** (V) which had λ_{max}^{EtOH} 280 mμ (ε 7500); λ_{max} 5.73, 5.93, and 6.24 μ.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; OCH_3, 29.24. Found: C, 62.19; H, 7.67; OCH_3, 28.96.

Condensation of the Methylation Mixture with Acetone.—To 141 g. of crude neutral oil obtained from the methylation procedure was added 675 ml. of acetone, 45 g. (0.53 mole) of piperidine, b.p. 105–106°, and 31.8 g. (0.53 mole) of glacial acetic acid. The light yellow solution was refluxed for a total of 87.5 hr. During this time, at *ca.* 20-hr. intervals, aliquots were removed, worked up as described below, and examined for ultraviolet absorption: the ε at 220–225 mμ was *ca.* 2000 at each interval, and there also was present a peak of unknown origin at 300 mμ (ε 1000). The reaction mixture was concentrated under reduced pressure and partitioned between water and ether. The ether layer was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, water, and saturated sodium chloride solution, was dried over sodium sulfate, and evaporated, leaving 95 g. of red oil.

The hydrochloric acid wash deposited upon standing an oil which proved to be III, λ_{max} 288 mμ (ε 7400). Reaction of III with piperidine in benzene at reflux yielded a product with λ_{max} 339 mμ (ε 13,500), presumed to be the enamine X.

In many condensation attempts the entire crude product was subjected to strong base cyclization. In the present instance 95 g. of oil was chromatographed on 1500 g. of acid-washed alumina, using ether–hexane as the eluent system. First to be eluted was a large amount of liquid (*ca.* 30 g.) in three fractions with consecutively stronger absorption at 238 mμ. Fractional distillation of these fractions afforded (1) a small amount (<1 g.) of mesityl oxide, identified by comparison of infrared spectrum and 2,4-dinitrophenylhydrazone with those of an authentic sample, and (2) material with b.p. 121–123° (27 mm.), $n^{25}D$ 1.4530, and an infrared spectrum that was consistent with the presence of large amounts of I (lit.[24] $n^{25}D$ 1.4571) and 2-methyl-2-carbomethoxycyclohexanone (lit.[4] $n^{25}D$ 1.4570). Further identification was not attempted. After this material, there were eluted oils with λ_{max} *ca.* 224 mμ, and these were used for cyclization studies. The over-all yield of dienone was not improved by using these laboriously purified fractions rather than the entire crude product.

In a typical procedure, 2.6 g. of oil with λ_{max} 224 (ε 8100) (*ca.* 80% VIII and IX), was dissolved in 35 ml. of dry *t*-butyl alcohol and added to a solution of 0.31 g. of potassium in 45 ml. of dry *t*-butyl alcohol, under nitrogen. The dark red solution was refluxed for 21 hr. The cooled mixture then was poured into 250 ml. of ice-cold water and extracted with ether. The ether was washed with dilute sodium hydroxide solution and water, dried, and evaporated to yield 1.6 g. of oil, λ_{max} 243 (ε 4000). The loss in weight was characteristic of the base-catalyzed cyclizations. If the reaction mixtures were acidified, effervescence was observed.[15]

The 1.6 g. of oil was chromatographed on acid-washed alumina. With 2:3 ether–hexane was eluted *ca.* 0.5 g. of material which yielded 0.2 g. of crystals, m.p. 80–90°. Recrystallization from ether–pentane gave needles of **8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2** (**XI**), m.p. 90.0–91.0°; λ_{max}^{EtOH} 243 (ε 13,700); $\lambda_{max}^{CHCl_3}$ 5.74, 5.99, and 6.13 μ.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.62.

The 2,4-dinitrophenylhydrazone of XI had m.p. 130–132°.

When the cyclization was run with sodium methoxide as catalyst (2.5-hr. reflux), chromatography afforded a small amount (*ca.* 0.1 g. from 7.0 g. of III) of solid, m.p. 45–57°, eluted before XI. After repeated recrystallization from hexane this substance had m.p. 57–59°; λ_{max}^{EtOH} 243 mμ (ε 11,200). Comparison of infrared spectrum[11] and mixture melting point of the 2,4-dinitrophenylhydrazone, m.p. 172–173° (m.p. 120–123° until seeded with authentic sample,[11] m.p. 171–172°), showed that it was XIII.

2,6-Dimethyl-2-carbomethoxycyclohexanone (I).—2-Methylcyclohexanone was prepared by oxidation of commercial 2-methylcyclohexanol with sodium dichromate in sulfuric acid in *ca.* 75% yield and was converted to I in one operation by sequential treatment with sodium methoxide in methanol, dimethyl carbonate, and methyl iodide, in *ca.* 15% yield, according to a procedure of Shafer.[25]

Cyanoethylation of I.—To a solution of 0.45 g. (0.012 mole) of potassium in 35 ml. of anhydrous *t*-butyl alcohol (distilled from calcium hydride) was added a solution of 10 g. (0.054 mole) of 2,6-dimethyl-2-carbomethoxycyclohexanone, b.p. 118–128° (30 mm.), $n^{25}D$ 1.4530, in 10 ml. of *t*-butyl alcohol with magnetic stirring. The resulting yellow solution was allowed to stand for 10 min., and then a solution of 4.3 g. (0.081 mole) of acrylonitrile (b.p. 77°) in 10 ml. of *t*-butyl alcohol was added over a 10-min. period. The mixture, which turned orange, was stirred for 12 hr. at room temperature. Then 1.65 ml. of acetic acid was added, and the mixture was partitioned between water and chloroform. The organic layer was washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution, dried, and stripped of solvent. Fractionation of the residue afforded 6.54 g. (51%) of colorless oil, b.p. 126–127° (0.1 mm.); $n^{25}D$ 1.4680; λ_{max}^{film} 4.44, 5.72, and 5.83 μ. Upon standing, the oil partially crystallized affording 2.85 g. of material, m.p. 45–55°. Recrystallization from hexane yielded large clear crystals of one stereoisomer of **2,6-dimethyl-2-carbomethoxy-6-cyanoethylcyclohexanone** (**XV**), m.p. 64.5–65.2°.

(24) D. K. Banerjee and S. N. Mahapatra, *Tetrahedron*, 11, 234 (1960).

(25) P. R. Shafer, private communication.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.87; H, 7.93; N, 6.00.

The oil remaining after separation of the 64–65° material had an infrared spectrum very similar, both in principal bands and detail, to that of the crystalline material and is presumed to be the diastereoisomeric cyanoethylation product.

Condensation of I with Methyl Vinyl Ketone.—The annelation procedure was based on that of Cornforth and Robinson.[16] To a well-cooled solution of 23.3 g. (0.163 mole) of 1-diethylaminobutanone-3,[26] b.p. 66–68° (10 mm.), $n^{25}D$ 1.4318, in 150 ml. of dry ether was added, over a 30-min. period, 23.2 g. (0.163 mole) of methyl iodide with constant swirling. The ether then was removed under reduced pressure while swirling was continued, leaving a coating of white crystalline methiodide around the inside of the flask. Then a solution of 30 g. (0.163 mole) of 2,6-dimethyl-2-carbomethoxycyclohexanone, b.p. 118–128° (30 mm.), in 70 ml. of anhydrous *t*-butyl alcohol was added. While the flask was swirled in an ice bath, a solution of 7.63 g. (0.195 g.-atom) of potassium in 180 ml. of anhydrous *t*-butyl alcohol was added dropwise over a 30-min. period. The light yellow mixture was stirred magnetically in an ice bath for 20 min. and at room temperature for 5 hr., during which time it became light brown and cloudy. Excess acetic acid then was added, and the mixture was partitioned between ether and water. The aqueous layer was thoroughly extracted with ether, and the combined organic layers were washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution, dried, and stripped of solvent, yielding 31 g. of orange oil, λ_{max} 241 mμ (ε 1700) (11% yield of XVI and XVII based on ε of pure XVI). Attempts to enhance ε at 240 mμ by further treatment of small samples with potassium *t*-butoxide, pyrrolidine–acetic acid, and other bases failed. The entire product was chromatographed on acid-washed alumina. Elution with 1:4 ether–hexane gave *ca.* 4 g. with λ_{max} 240 (ε 8000–9000). Rechromatography gave 0.578 g. of oily crystalline material. Three recrystallizations from hexane gave 0.221 g. of **8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2 (XVI)**, m.p. 87.5–90.0°; the analytical sample had m.p. 89.5–90.5°; λ_{max}^{EtOH} 241 mμ (ε 12,500); $\lambda_{max}^{CHCl_3}$ 5.78, 6.00, and 6.21 μ; n.m.r.,[21] in carbon tetrachloride containing tetramethylsilane: τ 8.65 and 8.92 (–$\overset{|}{C}CH_3$), 6.38 (O–CH_3), and 4.12 (–$\overset{|}{C}$=$\overset{|}{C}$H).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.33; H, 8.63.

Vapor phase chromatographic analysis (typically on a Wilkens A-90-P2 chromatograph with a silicone SE-30 column at 250°, using carbon tetrachloride solutions) showed that the chromophoric chromatographic fractions consisted primarily of two components, the first of which was identified by retention time as XVI. The later fractions contained progressively more of the other, minor (ratio <1:2) component, which had λ_{max}^{EtOH} 240 mμ and λ_{max}^{film} 5.75, 5.96, and 6.20 μ.

Selenium Dioxide Oxidation of XVI.—The oxidation of XVI to the dienone XI was conducted according to the procedure of Baran.[27] To a solution of 0.03 ml. of glacial acetic acid and 0.065 g. (5.0×10^{-4} mole) of selenous acid (Fisher, reagent grade) in 3 ml. of anhydrous *t*-butyl alcohol was added 0.118 g. (5.00×10^{-4} mole) of the α,β-unsaturated ketone XVI, m.p. 89.5–90.5°. The mixture was refluxed for 5 hr.; then 0.02 g. (1.6×10^{-4} mole) of selenous acid was added and refluxing was continued for 16 hr. The resulting yellow solution was filtered from a brown-black precipitate and concentrated *in vacuo*, and the residue was partitioned between methylene chloride and water. The organic layer was washed with dilute sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residual oil was chromatographed on 10 g. of Merck acid-washed alumina. Elution with 4:1 hexane–ether gave 0.076 g. (65%) of crude crystalline material. After recrystallization from hexane there was obtained 27 mg. (23%) of material with m.p. 88–92°. Further recrystallization gave material with m.p. 90–91°, which had an infrared spectrum identical with that of the previously prepared dienone XI. The mixture melting point was 89.5–91.0°.

8α,10β-Dimethyl-8β-carbomethoxy-*trans*-decalone-2 (XVIII).—A mixture of 0.050 g. (2.1×10^{-4} mole) of the unsaturated ketone XVI, m.p. 89–91°, and 0.05 g. of 10% palladium on carbon in 20 ml. of ethyl acetate was hydrogenated until the absorption maximum at 240 mμ disappeared (*ca.* 1 hr.). The mixture was filtered, and the filtrate was evaporated to give 0.051 g. of crude product which solidified on standing, m.p. 56–73°. Two recrystallizations from hexane afforded 0.025 g. of colorless needles, m.p. 76.5–77.5°; $\lambda_{max}^{CHCl_3}$ 5.80–5.87 μ; n.m.r.[21]: τ 8.85 and 9.07 (–$\overset{|}{C}CH_3$) and 6.36 (–OCH_3).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.35; H, 9.54.

Sodium Borohydride Reduction of XVIII.—To a solution of 0.051 g. (2.1×10^{-4} mole) of ketone XVIII, m.p. 76.5–77.5°, in 3 ml. of absolute ethanol was added a solution of 0.080 g. of sodium borohydride in 3 ml. of absolute ethanol dropwise over a 15-min. period. The mixture was stirred magnetically at room temperature for 3 hr. (In an earlier run, a 45-min. reaction period yielded a product which v.p.c. analysis indicated to contain about one-third unreduced ketone.) The reaction mixture was then acidified with dilute hydrochloric acid and partitioned between water and chloroform. The organic layer, after drying and evaporation, yielded 0.056 g. of light yellow oil, λ_{max} 2.9, 5.80 μ. This product, which failed to solidify, was chromatographed on 1.3 g. of acid-washed alumina. V.p.c. analysis (Ucon polar column at 220°) of all fractions showed only a trace of unreduced ketone and two principal components: a minor one, absent in later fractions, with shorter retention time, and the major component, presumably XX. Suitable fractions, *i.e.*, almost all XX, were combined for attempted saponification.

Treatment of Sodium Borohydride Reduction Product from XVIII with Sodium Hydroxide Solution.—To a solution of 0.020 g. of the chromatographically purified sodium borohydride reduction product in 2 ml. of methanol was added 4 ml. of 3 *N* sodium hydroxide solution, and the mixture was refluxed for 24 hr. The reaction mixture was diluted with water and extracted with two 10-ml. portions of chloroform. The organic layer, after drying and evaporation, afforded 0.0195 g. of nearly colorless oil which had an infrared spectrum identical with that of the sodium borohydride product used as starting material. The original aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform in the same manner to yield 0.0015 g. of dark brown oil.

Reduction and Saponification of Crude XVII.—A sample from a chromatographic fraction from the reaction of I with methyl vinyl ketone, consisting primarily (*ca.* 90% by v.p.c. analysis on a silicone SE-30 column at 275°) of a substance other than XVI and assumed from the striking similarity of its infrared spectrum (λ_{max}^{film} 5.75, 5.96, and 6.20 μ) to that of XVI to be XVII, was reduced catalytically in the same manner as XVI. The uptake of hydrogen was much slower. The resulting oil (λ_{max} 5.80–5.84 μ) was treated with excess sodium borohydride in the same manner as XVIII. A 0.023-g. sample of the oily product from this reaction was refluxed with 4 ml. of 3 *N* sodium hydroxide solution and 2 ml. of methanol for 6 hr. Work-up in the usual manner afforded 0.013 g. of acidic material and 0.009 g. of neutral material. The acidic material crystallized to afford 0.006 g. of white solid, m.p. 200–202°. Recrystallization from acetone–hexane gave pure XXI, m.p. 201–203°; $\lambda_{max}^{CHCl_3}$ 2.9 (sh), 3–4 (broad), and 5.90 μ.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.86; H, 9.69.

Acknowledgment.—The authors are grateful for the financial support provided by Public Health Service Research Grant AM-05014 and by the Research Corporation.

(26) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).
(27) J. S. Baran, *ibid.*, **80**, 1687 (1958).

Condensation of Diethyl Malonate with Methyl Vinyl Ketone

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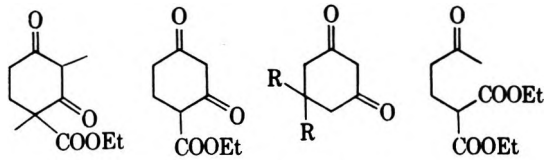
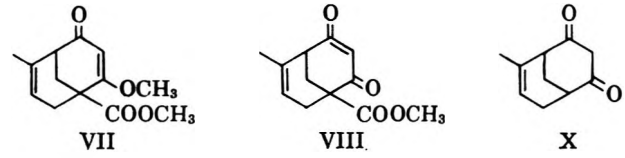
Ethoxide-catalyzed reaction of diethyl malonate with methyl vinyl ketone yields 1-carboxy-6-methylbicyclo-[3.3.1]non-6-ene-2,4-dione (VI) and, after hydrolysis, 1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI). The separately prepared mono-Michael adduct (V) can be cyclized in very good yield to a mixture of 4-carboethoxycyclohexane-1,3-dione (II) and 3-ethoxy-6-carboethoxy-Δ^2-cyclohexenone (XIII).

We have been engaged in a study of the synthesis of 4-carboalkoxycyclohexane-1,3-diones for use in elaboration of terpenoid carbocyclics, such as the diterpene resin acids (for which I would be a potential precursor) and isocamphorquinone.[2] The classical methods for preparing such systems consist in Michael addition of a suitably substituted malonic or acetoacetic ester to an α,β-unsaturated ketone or α,β-unsaturated ester, respectively, followed by ring-closing Claisen condensation. This paper reports the results of our investigation of the parent case of the first type: the reaction of diethyl malonate with methyl vinyl ketone. We were interested both in preparing 4-carboethoxycyclohexane-1,3-dione (II) and in the possibility of a simple one-step synthesis of dihydroresorcinol (III) that was analogous to the preparation of dimedone (IV) from mesityl oxide and diethyl malonate.[3] We were encouraged in the latter hope by the report of Mannich and Fourneau[4] that III could be isolated from sodium ethoxide treatment of the adduct V formed from diethyl malonate and N,N-diethylaminobutanone-3. However, when equimolar amounts of diethyl malonate and methyl vinyl ketone were subjected to the conditions of the first step in the preparation of dimedone,[3] the only pure products isolated were both the result of bis-Michael addition.



I II III, R = H; IV, R = CH_3 V

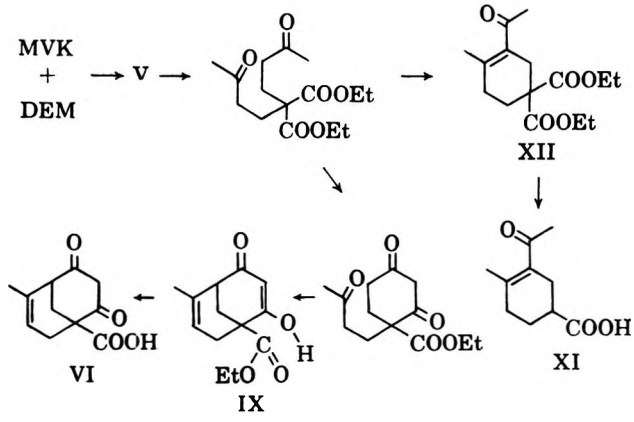
An acidic substance, m.p. 190–191° (with effervescence), was obtained in 20% yield; this had an elemental analysis indicating a formula $C_{11}H_{12}O_4$. Of the several structures with this formula which can be derived hypothetically from methyl vinyl ketone and diethyl malonate, only VI was consistent with the observed properties, which included neut. equiv. 107 (diacid), λ_{max} 270 mμ (ϵ 11,200), and λ_{max} 5.86, 6.14, and 6.4 μ (enolized β-diketone). The substance reacted with 2 moles of diazomethane to afford a compound, m.p. 87.5–88.5°, which was, accordingly, either VII or VIII. The n.m.r. spectrum of this diazomethane product was crucial in the assignment of structure VI



VII VIII X

to the diacid, for it showed bands completely consistent with the major structural features of VII or VIII.[5] The formation of VI from diethyl malonate and methyl vinyl ketone could occur as shown in Chart I. That the free acid VI rather than the ester IX was isolated can perhaps be explained as a case of the unusually facile hydrolysis (by water eliminated during condensation or upon work-up) undergone by enolized, hydrogen-bonded acetoacetic esters.[6a]

CHART I[6b]



When VI was heated at its melting point it yielded a substance, m.p. 120.5–121.5°, with an elemental analysis and ultraviolet and infrared spectra consistent with the decarboxylation product X. Similar decarboxylation of a bridgehead carboxyl in a bicyclo-[3.3.1]nonane β-keto acid has been observed when the participating ketone carbonyl is in a three-carbon bridge of the bicyclic system.[7]

The neutral material from this condensation of diethyl malonate with methyl vinyl ketone consisted of 23% recovered diethyl malonate and a higher-boiling fraction which afforded, upon saponification, a crystalline acid, m.p. 76.5–77.0°. The properties

(1)(a) National Science Foundation Undergraduate Research Participant, academic year, 1960-1961; recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, summer, 1961. (b) National Science Foundation Undergraduate Research Participant, academic year, 1962-1963, and summer, 1963.

(2) T. A. Spencer and M. D. Newton, *Tetrahedron Letters*, 1019 (1962).

(3) R. L. Shriner and H. R. Todd, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 200.

(4) C. Mannich and J. P. Fourneau, *Ber.*, **71**, 2090 (1938).

(5) On the basis of a multiplet due to a single proton at τ 8.1, assigned to the methinyl proton of the 87–88° compound, we prefer structure VIII over VII, for, if this proton were adjacent to a carbonyl group (as in VII), it should appear at a lower field. See, *e.g.*, L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 57.

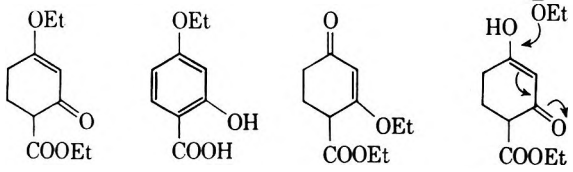
(6)(a) See M. L. Bender [*Chem. Rev.*, **60**, 70 (1960)] for a consideration of the exceptional reactivity toward nucleophiles of enolizable β-keto esters and for references. In Chart I, structure IX is shown in one such enolized, hydrogen-bonded form. (b) MVK, methyl vinyl ketone; DEM, diethyl malonate.

(7) H. Meerwein, *et al.*, *J. prakt. Chem.*, **104**, 163, 166 (1922).

of this substance, *e.g.*, ultraviolet absorption at 248 mμ (ε 7000),[8] readily showed that it was 1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI), which could be formed as indicated in Chart I. Wichterle[9] has reported the same structure for a compound, m.p. 97°, derived by treatment of diethyl bis(γ-chlorocrotyl)-malonate with concentrated sulfuric acid, followed by hydrolysis. He also reported preparation of the semicarbazone, m.p. 145–148°, of the cyclized malonic ester precursor XII. We were unable to obtain a semicarbazone of an α,β-unsaturated ketone from the neutral material which yielded XI upon hydrolysis, so that we were not thus able to check if the discrepancy between melting points for XI is due to dimorphism. Our spectral data (see Experimental) leave little room for doubt that at least our structural assignment is correct.

It was evident that, unlike mesityl oxide, methyl vinyl ketone very readily forms a bis-Michael adduct with diethyl malonate. It seemed that successful preparation of 4-carboethoxycyclohexane-1,3-dione would depend upon finding appropriate conditions, *e.g.*, those which would precipitate the enolate anion of II,[10] for cyclization of previously prepared mono-Michael adduct V. An improved method (71% yield) for the preparation of V was found in an adaptation of the method of Tsuruta[11] for the addition of methyl vinyl ketone to dimethyl malonate.

When V was treated with an equivalent of sodium ethoxide in a minimum amount of refluxing ethanol, a thick precipitate formed, which, upon acidification, afforded 79% of crude 4-carboethoxycyclohexane-1,3-dione. Pure II melted at 61.5–62.5° and absorbed at 256 mμ (ε 15,000) and at 5.77 and 6.2–6.3 μ. The structural assignment was confirmed by hydrolysis and decarboxylation to afford dihydroresorcinol (III) in 63% yield. Our hope of developing a convenient synthesis of III was frustrated, however, by the fact that, in subsequent cyclizations, the voluminous precipitate was not solely the anion of II but often largely the sodium salt of another solid substance, m.p. 98–99°, which proved to be the enol ether XIII



XIII XIV XV XVI

This structural assignment was made on the basis of elemental analysis and spectra, particularly the n.m.r. spectrum, which showed two nonequivalent ethyl groups, and by conversion of the substance in excellent yield (95%) to 4-ethoxysalicylic acid (XIV)[12] by treatment with N-bromosuccinimide, followed by basic hydrolysis, thereby establishing the location of the ethoxy group and showing that the substance was not the isomeric enol ether XV. Attempted basic hydrolysis of XIII led to no isolable product; mild acid hydrolysis gave II. Formation of XIII presumably occurs *via* II as indicated in XVI. Reaction variables which controlled the relative amounts of II and XIII formed upon cyclization of V were not found. Initiation of precipitation of a given enolate anion is probably important, for II is certainly a much stronger acid than XIII, and would be expected to form the predominant anion in an over-all equilibrium process.

(8) R. B. Turner and D. M. Voitle [*J. Am. Chem. Soc.*, **73**, 1403 (1951)] report that 1-methyl-2-acetylcyclohexene-1 has λ_{max} 249 mμ (ε 6890).

(9) O. Wichterle, *Chem. Zentr.*, 348 (1944).

(10) In all cases of cyclization to cyclohexane-1,3-diones which we have investigated (see, *e.g.* ref. 2), no reasonable yield of desired product could be obtained unless conditions for enolate precipitation were found. Otherwise, reverse Michael reactions, other condensations, etc., occurred, as in the formation of VI and XI.

(11) T. Tsuruta, *Bull. Inst. Chem. Research Kyoto Univ.*, **31**, 190 (1953).

(12)(a) R. J. W. Byrde, D. F. Downing, and D. Woodstock, *Biochem. J.*, **72**, 344 (1959); (b) Ng. Ph. Buu-Hoï, N. D. Xuong, and D. Lavit, *Rec. trav. chim.*, **74**, 729 (1955); (c) R. Kuhn, F. Klliken, and H. Trischmann, *Ber.*, **83**, 304 (1950).

Experimental[13]

Reaction of Diethyl Malonate with Methyl Vinyl Ketone at Reflux in the Presence of an Equivalent of Sodium Ethoxide.—In a modification of the procedure of Shriner and Todd,[3] 80.0 g. (0.50 mole) of freshly distilled diethyl malonate, b.p. 115–116° (65 mm.), was added to a solution of 11.5 g. (0.50 g.-atom) of metallic sodium in 200 ml. of absolute ethanol (distilled from calcium hydride) under a nitrogen atmosphere. While the clear solution was stirred in a water bath heated to 50° to prevent precipitation of the sodium enolate, 35.0 g. (0.50 mole) of methyl vinyl ketone (Matheson Coleman and Bell, technical) was added dropwise over 1 hr. The resulting light orange mixture was then brought to reflux, and after 2 hr. a salt began to precipitate. When the mixture had refluxed for 4 hr., it was reduced to a reddish brown slurry by evaporation of most of the ethanol *in vacuo*. This residue was then partitioned between 200 ml. of water and 250 ml. of chloroform. The chloroform layer was dried over magnesium sulfate and evaporated to yield 50 g. of mobile yellow oil, which was distilled to give two distinct fractions: 18 g. (23%) of recovered diethyl malonate, b.p. 55–62° (1 mm.), $n^{25}D$ 1.4118; and 3.5 g. of material with b.p. 115–120° (1.5 mm.).

The latter oil (1 g.) was stirred at room temperature for 24 hr. in 15 ml. of 1 *N* sodium hydroxide solution. Acidification of this mixture, followed by chloroform extraction in the usual manner, yielded 0.200 g. of white solid **1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI)**, m.p. 68–71°. Recrystallization from benzene yielded material, m.p. 76.5–7.70°, which was soluble in 1 *N* sodium bicarbonate solution, and which gave a positive iodoform test and a neutralization equivalent of 182 (calculated for $C_{10}H_{14}O_3$: 182). The material had λ_{max}^{EtOH} 248 mμ (ε 7000) and $\lambda_{max}^{CHCl_3}$ 5.85, 5.93, and 6.18 (w) μ; n.m.r.: singlet at τ −1.29 (−COO*H*), singlet at 7.85 (−C(=O)−*CH*$_3$), and singlet at 8.19 (−C=C−*CH*$_3$).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.92; H, 7.68.

The original aqueous solution obtained from the reaction of diethyl malonate and methyl vinyl ketone described above was cooled in an ice bath and acidified with 5 *N* sulfuric acid, whereupon a thick, dark oil precipitated. This gum was extracted with chloroform, leaving behind 15 g. of insoluble residue. The chloroform was dried over magnesium sulfate and evaporated to yield an oil which crystallized upon trituration with ether to give 10.5 g. (20%) of white crystalline **1-carboxy-6-methylbicyclo-[3.3.1]non-6-ene-2,4-dione (VI)**, m.p. 187–188° (with definite evolution of gas). Recrystallization from ether–methanol yielded the analytical sample, m.p. 190–191° dec.; λ_{max}^{EtOH} 270 mμ (ε 11,200), shoulder at 242 (6600); λ_{max}^{Nujol} 3.7 (broad), 5.86, 6.14, and 6.4 (broad) μ. The material was soluble in 1 *N* sodium bicarbonate solution, gave a negative iodoform test, and turned methanolic ferric chloride solution deep red; a neutralization equivalent of 107 was obtained (calculated for a $C_{11}H_{12}O_4$ diacid: 104).

(13) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Clark Microanalytical Laboratory, Urbana, Ill. Melting points were taken on a micro hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 21 recording spectrophotometer. N.m.r. spectra were determined on a Varian Model A-60 instrument in carbon tetrachloride solution using tetramethylsilane as reference.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.86.

Monomethyl Enol Ether of 1-Carbomethoxy-6-methylbicyclo[3.3.1]non-6-ene-2,4-dione.—To an ethereal solution of diazomethane (prepared from Du Pont precursor EXR-101), was added a solution of 1.36 g. (6.54 mmoles) of the bicyclic compound VI, m.p. 187–188° dec., in 25 ml. of methanol. Excess diazomethane was decomposed with glacial acetic acid, and the solvent was evaporated to yield a yellow oil, which crystallized from methanol at −20°, affording 0.980 g. (64%) of white crystals, m.p. 60–70°. Three recrystallizations from cold methanol raised the melting point to 87.5–88.5°; λ_{max}^{EtOH} 259 mμ (ε 9200), shoulder at *ca.* 240 (8000); $\lambda_{max}^{CHCl_3}$ 5.71, 6.00, and 6.17 μ; n.m.r.: multiplet at τ 4.7 (—C=C—*H*), singlet at 4.9 (CH₃—O—C=C—*H*), singlet at 6.3 (2 OC*H*₃), multiplets at 7.4 and 7.6 (2 —C*H*₂—), multiplet at 8.1 (—C=C—C—*H*), and 8.3 (—C=C— C*H*₃, split, presumably by remote coupling).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.12; H, 6.92.

6-Methylbicyclo[3.3.1]non-6-ene-2,4-dione (X).—A 0.200-g. (0.960 mmole) sample of the β-keto acid (VI), m.p. 190–191° dec., was placed in a small test tube filled with nitrogen and heated at 210° for 5 min. with the inert atmosphere maintained. The cooled contents of the tube crystallized upon addition of a small amount of ether. Four recrystallizations of the crude red product from acetone–hexane yielded 0.060 g. of colorless crystals, m.p. 120–121°. The analytical sample had m.p. 120.5–121.5°; λ_{max}^{EtOH} 270 mμ (ε 8400), shoulder at 240 (4400); $\lambda_{max}^{CHCl_3}$ 3.1 (broad), 5.86 (shoulder at 5.78), and 6.22 μ.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.90; H, 7.35.

Diethyl (3-Oxobutyl)malonate (V).—In an adaptation of the method of Tsuruta,[11] 525 g. (3.28 moles) of diethyl malonate (Matheson Coleman and Bell, practical) was added to a solution of 11.3 g. (0.49 g.-atom) of sodium in 492 ml. of absolute ethanol (distilled from calcium hydride) in a nitrogen atmosphere. The mixture was cooled to −10° and stirred vigorously while a mixture of 490 g. (3.06 moles) of diethyl malonate, 286 g. (4.08 moles) of methyl vinyl ketone, and 490 ml. of absolute ethanol was added dropwise, causing the mixture to turn light yellow. When the addition was complete, the mixture was kept at −10° for 30 min. and then allowed to stand at room temperature for 48 hr. At the end of this time the bright yellow mixture was neutralized with 6% aqueous acetic acid and extracted with ether in the usual manner. After evaporation of the dried ether extracts, the residual oil was distilled *in vacuo* to give 660 g. (71%) of diethyl (3-oxobutyl)malonate (V), b.p. 129–138° (2 mm.). Redistillation afforded 602 g. (65%) of product, b.p. 134–138° (2.5 mm.); $n^{25}D$ 1.4377; λ_{max} 5.8 (broad) μ. The **semicarbazone**, prepared in the usual manner and recrystallized from ethanol, had m.p. 112.5–113.5° (lit.[4] m.p. 118°, lit.[14] m.p. 113°).

Anal. Calcd. for $C_{12}H_{21}N_3O_6$: C, 50.16; H, 7.37; N, 14.63. Found: C, 50.36; H, 7.33; N, 14.78.

4-Carboethoxycyclohexane-1,3-dione (II).—To a solution of 0.50 g. (0.022 g.-atom) of sodium in 8 ml. of absolute ethanol, cooled in an ice–acetone bath and protected with a nitrogen atmosphere was added 5.00 g. (0.022 mole) of diethyl (3-oxobutyl)-malonate (V), b.p. 134–138° (2.5 mm.). The resulting bright yellow mixture was stirred at −10° for 30 min. and then brought to reflux. After 20–30 min. of reflux a precipitate formed in sufficient amount to make the reaction mixture very difficult to stir. This thick slurry was refluxed for 2 hr. longer, then cooled, and partitioned between 25 ml. of saturated sodium chloride solution and 100 ml. of ether. The aqueous layer was acidified with 5 *N* sulfuric acid and extracted with ether. Evaporation of the ether yielded 4.34 g. of yellow, viscous oil, λ_{max}^{EtOH} 256 mμ (ε 14,300). This oil crystallized in the freezer when triturated with ether to give 2.31 g. (57%) of 4-carboethoxycyclohexane-1,3-dione (II), a colorless solid, m.p. 56–60°. A further 0.90 g., m.p. 50–60°, was isolated from the ether washings, making the total yield 3.21 g. (79%). Recrystallization from ether gave the analytical sample with m.p. 61.5–62.5°; λ_{max}^{EtOH} 256 mμ (ε 15,000); $\lambda_{max}^{CHCl_3}$ 3.8 (broad), 5.77, and 6.2–6.3 μ.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.71; H, 6.64.

Conversion of II to Dihydroresorcinol.—A 0.208-g. (1.14 mmoles) sample of II was stirred for 24 hr. at 25° in 10 ml. of 3 *N* sodium hydroxide solution in a nitrogen atmosphere. The light yellow mixture was cooled, acidified with 5 *N* sulfuric acid, and partioned between 25 ml. of saturated sodium chloride solution and 300 ml. of chloroform. The chloroform was dried and evaporated to yield 0.080 g. (63%) of white solid, m.p. 87–95°. Recrystallization from benzene yielded a sample, m.p. 105–106°, which did not depress the melting point of an authentic sample of III, m.p. 105–106°.

3-Ethoxy-6-carboethoxy-Δ²-cyclohexenone (XIII).—Every time the cyclization of V was repeated, there was formed a mixture of II and, often as the predominant product, the enol ether XIII. For example, on a 5-g. scale, exactly as described above as far as we know, there was obtained a crude oily product which afforded, first, 1.1 g. of material, m.p. 84–87°, and then, from the mother liquors, a smaller amount of II. The ratio of XIII to II in different cyclizations varied and was not determined exactly.

The higher-melting material was recrystallized from ether to afford colorless crystals of XIII, m.p. 98–99°; λ_{max}^{EtOH} 252 (ε 16,000); $\lambda_{max}^{CHCl_3}$ 5.78, 6.06, and 6.24 μ; n.m.r.: singlet at τ 4.7 (—C=C—*H*), quartets centered at 5.8 and 6.1 (2 —O—C*H*₂-CH₃), multiplets at 6.8 (—C—*H*) and 7.6 (—CH₂—CH₂), and triplets centered at 8.6 and 8.7 (2 —O—CH₂—C*H*₃).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.70.

On one occasion a 1-kg. sample of V was cyclized, the crude product was saponified (hopefully to III), and the basic mixture was treated with methyl iodide. Only 30 g. of methyldihydroresorcinol could be isolated from this sequence.

Conversion of XIII to II.—A solution of 2.12 g. (0.010 mole) of XIII in 350 ml. of 1 *N* hydrochloric acid was stirred for 24 hr. at 25° in a nitrogen atmosphere. The mixture was then partitioned between saturated sodium chloride solution and chloroform. Evaporation of the chloroform afforded 1.0 g. of yellow oil which crystallized in the freezer to afford 4-carboethoxycyclohexane-1,3-dione (II), identified by infrared spectrum and melting point. Treatment of XIII with dilute base gave only a very small amount of chloroform-soluble material; no dihydroresorcinol was obtained.

Conversion of XIII to 4-Ethoxysalicylic Acid (XIV).—To a solution of 6.36 g. (0.0300 mole) of enol ether XIII, m.p. 97.5–99.0°, in 125 ml. of reagent grade carbon tetrachloride was added 5.34 g. (0.300 mole) of N-bromosuccinimide. The resulting mixture was refluxed while being illuminated with two 100-watt light bulbs. Hydrogen bromide was evolved during reflux. After 90 min., the original precipitate was completely replaced by supernatant succinimide, which was removed by filtration of the cooled mixture. Evaporation of the filtrate afforded 11 g. of gummy solid residue which was stirred with 300 ml. of 3 *N* sodium hydroxide solution at room temperature for 11 hr., and then the mixture was heated on the steam bath for 2 hr. to complete dissolution of the solid. After being cooled, the reaction mixture was acidified with 3 *N* sulfuric acid, causing formation of a white precipitate, which was collected by filtration. The solid product was dissolved in ether, and the solution was dried over sodium sulfate. Evaporation of the ether afforded 5.20 g. (95%) of tan solid, m.p. 146–149°. This material was recrystallized from benzene to afford 4.51 g. of off-white needles, m.p. 151–153°. Comparison with 4-ethoxysalicylic acid, m.p. 151–153°, prepared by the reaction of resorcylic acid with diethyl sulfate,[12a] showed the two samples to have identical infrared spectra and an undepressed mixture melting point.

Acknowledgment.—This investigation was supported in part by Public Health Service Research Grant AM-05014. The authors are very grateful to Professor Paul R. Shafer who generously obtained the n.m.r. spectra and provided valuable and extensive discussion concerning their interpretation and many other aspects of this work.

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Formation of Ketones in the Oxo Synthesis

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Ketones have been prepared by the reaction of hydrogen tetracarbonylcobaltate(−I) with monoolefins, conjugated and unconjugated diolefins. A mechanism is proposed for ketone formation in which only the last step of the hydroformylation mechanism for aldehyde formation has been changed from the decomposition involving hydrogen tetracarbonylcobaltate(−I) to one involving alkyl tetracarbonylcobaltate(−I).

Although the preparation of aldehydes from olefins and hydrogen tetracarbonylcobaltate(−I) in a stoichiometric reaction or a catalytic process is well-known, the preparation of ketones by such reactions is rare. Ketones have been observed as a major product when ethylene is subjected to oxo conditions and as a minor product when other olefins have been used.[2] In a reaction which would seem related, although it does not involve an olefin, Hieber[3] observed acetone in the decomposition of methyl tetracarbonylcobaltate(−I). While studying the coordination compounds formed by diolefins and hydrogen tetracarbonylcobaltate(−I), considerable amounts of oxygenated organic compounds were observed in several cases. Since identification of these compounds indicated that some were ketones, it was decided to investigate further the possibility of preparing ketones by such reactions.

Results and Discussion

Reactions were carried out by adding the olefin to an aqueous solution of potassium tetracarbonylcobaltate(−I) in an autoclave and then acidifying to produce hydrogen tetracarbonylcobaltate(−I). With conjugated diolefins, temperatures above 120° were necessary to decompose the somewhat stable complexes, substituted π-allyl tricarbonylcobaltates. With unconjugated diolefins, room temperature was sufficient; monoolefins at room temperature gave only aldehydes. At lower temperatures in pentane solvent, 1-butene gave predominantly ketones as oxygenated product.

The mechanism of aldehyde formation recently has been discussed by various workers.[4-7] Although there are several points of disagreement, the following sequence of reactions is compatible with available data.

$$RCH{=}CH_2 + HCo(CO)_4 = RCH_2CH_2Co(CO)_4$$

$$RCH_2CH_2Co(CO)_4 = RCH_2CH_2COCo(CO)_3$$

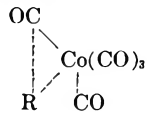
$$RCH_2CH_2COCo(CO)_3 + CO = RCH_2CH_2COCo(CO)_4$$

$$RCH_2CH_2COCo(CO)_3 + HCo(CO)_4 = RCH_2CH_2CHO + Co_2(CO)_7$$

The sequence is written for only one of the isomeric aldehyde products.

Acyl compounds, such as the one above, have been prepared by Heck and Breslow.[8,9]

The second and third steps may proceed by a concerted carbonyl insertion mechanism involving the following transition state.[4,10,11]



The entering carbon monoxide molecule attaches itself to cobalt while one of the original carbon monoxide ligands forms the acyl group.[12] Such a mechanism would eliminate the coordinately unsaturated acyl tricarbonylcobaltate(−I), and the last step would become the following.[1b,2]

$$RCH_2CH_2COCo(CO)_4 + HCo(CO)_4 = RCH_2CH_2CHO + Co_2(CO)_8$$

The mechanism proposed by Heck and Breslow[4] would involve $HCo(CO)_3$ and appears less likely in view of a mass spectrometric analysis of hydrogen tetracarbonylcobaltate(−I) which showed no hydrogen-containing fragments.[13]

The formation of ketones can be explained by a mechanism similar to the one above by assuming that the alkyl tetracarbonylcobaltate(−I) of step 1 can function in the same way as hydrogen tetracarbonylcobaltate(−I) in the decomposition that follows

$$RCH_2CH_2COCo(CO)_x + R'Co(CO)_4 \longrightarrow RCH_2CH_2CR'O + Co_2(CO)_{4+x}$$

where x is 3 or 4, depending on which mechanism is preferred, and R′ is RCH_2CH_2– or H. Since the decomposition would proceed through an intermediate or activated complex, steric factors would strongly favor R′ = H. However, the alternate reaction should become important when (1) R is small (R = H for ethylene), (2) the concentration of $HCo(CO)_4$ is low, or (3) the two reactants are held together (that is, an *intra*molecular decomposition).

Furthermore, the same decomposition can account for the formation of acetone from methyl tetracarbonylcobaltate(−I).[1a]

(1)(a) Esso Research Laboratories, Baton Rouge, La.; (b) University of Bergen, Norway.

(2) I. Wender, H. W. Sternberg, and M. Orchin, "Catalysis," Vol. 5, P. H. Emmett, Ed., Reinhold Publishing Corp., New York, N. Y., 1957, p. 85.

(3) W. Hieber, O. Vohler, and G. Braun, *Z. Naturforsch.*, **13b**, 192 (1958); W. Hieber, W. Beck, and E. Lindner, *ibid.*, **16b**, 229 (1961).

(4) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p. 658.

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(7) R. F. Heck and D. S. Breslow, *J. Am. Chem. Soc.*, **83**, 4023 (1961).

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(11) K. A. Keblys and A. H. Filbey, *J. Am. Chem. Soc.*, **82**, 4204 (1960).

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(13) H. W. Sternberg, I. Wender, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, **75**, 2717 (1953).

$$CH_3Co(CO)_4 \rightleftharpoons CH_3COCo(CO)_3$$

$$CH_3Co(CO)_4 + CH_3COCo(CO)_3 \rightleftharpoons CH_3COCH_3 + Co_2(CO)_7$$

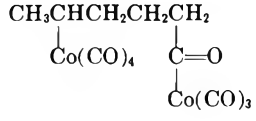
As no $HCo(CO)_4$ is present, the above is the only decomposition.

As mentioned previously, use of ethylene in an oxo reaction leads to considerable yield of ketone; with longer-chain olefins, ketone becomes only a minor by-product.

In the present study, when a large excess of butene-1 reacted with hydrogen tetracarbonylcobaltate(−I) at room temperature, only aldehyde product was isolated; when the reactants were mixed at −8° and then heated, about 90% of the oxygenated product was ketone. The low temperature mixing would favor formation of intermediates, both alkyl and acyl, and would use up the hydrogen tetracarbonylcobaltate(−I) before the decomposition reaction. The decomposition reaction would then involve the alkyl and acyl intermediates and result in ketone formation.

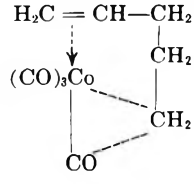
The reaction of 1,4-pentadiene at room temperature yielded a mixture of 5-hexenal (8% yield), 2-methylcyclopentanone (22% yield), and coordination compounds (3% yield). A small amount of cyclohexanone also was noted. The coordination compounds have been identified as isomers (*syn-* and *anti-*) of π-(1-ethylallyl)-tricarbonylcobaltate(−I).[14]

The formation of 5-hexenal would follow the usual aldehyde mechanism, with only one double bond being used. Under conditions which regenerate the hydrogen tetracarbonylcobaltate(−I), the other double bond would be expected to react as well; these reactions were carried out with a 1:1 mole ratio of hydrogen tetracarbonylcobaltate(−I) and diolefin. By the mechanism proposed, the cyclic ketone would result from formation of the alkyl and acyl intermediates within the same molecule.

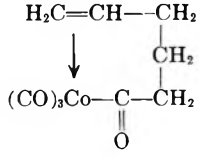


Owing to proximity of reactants, the ketone reaction would compete favorably with the aldehyde reaction.

An alternate scheme can explain the formation of ketone from diolefins. Starting with the intermediate $CH_2{=}CHCH_2CH_2CH_2Co(CO)_4$, the next step would be a cyclic transition state.



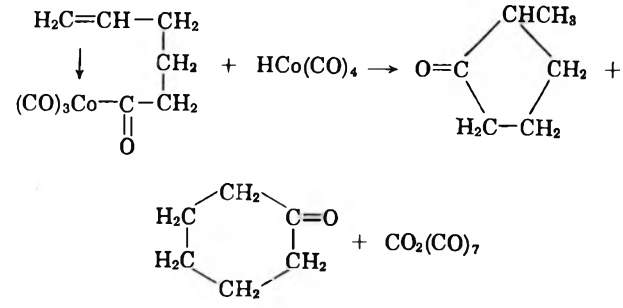
This transition state would yield the following complex.



(14) H. B. Jonassen, D. W. Moore, and J. A. Bertrand, *Inorg. Chem.*, **2**, 601 (1963).

Existence of such π-complexes at lower temperature has indeed been demonstrated by Heck.[15]

This intermediate presumably would be sufficiently stable to exist long enough for a hydrogen tetracarbonylcobaltate(−I) to interact with it, thus giving a cyclic ketone.



The predominance of the 2-methylcyclopentanone can be explained on the basis of the cyclic intermediate, which favors a closer approach of the carbonyl group to C-5 rather than to C-6 of the ring.

The reaction of 1,3-butadiene yielded, on decomposition of the complex at 120°, both saturated and unsaturated C_8 ketones. Only straight-chain ketones were observed; furthermore, when a similar reaction was carried out under a pressure of carbon monoxide only, the saturated 5-nonanone was obtained. Formation of ketone could proceed again through alkyl and acyl intermediates, formed from the π-complex under the reaction conditions. The alternate scheme is unlikely, since hydrogen tetracarbonylcobaltate(−I) probably is used up in forming the stable complex.

Experimental

1,4-Pentadiene Reaction.—A solution of 0.2 mole of potassium tetracarbonylcobaltate(−I) in 300 ml. of water was placed in a 1-l. steel autoclave, 120 ml. of concentrated phosphoric acid and 0.2 mole of 1,4-pentadiene were added without mixing, and the autoclave was closed, inverted to mix the reactants, and rocked for 24 hr. The vessel was opened under a stream of nitrogen and 100 ml. of hexane was added to extract the products. The hexane layer was separated, washed with distilled water, dried over sodium sulfate, and transferred to a distillation apparatus. The hexane was removed by aspirator vacuum; the product was distilled under high vacuum. The material distilling below 45° (1 mm.) was collected as one fraction; the material distilling at 45° was predominantly π-(1-ethylallyl)tricarbonylcobaltate(−I).

The first fraction was further separated into two pure compounds in a Beckman Megchrom gas chromatograph equipped with a silicone rubber column. The first component (8% yield) was identified as 5-hexenal. The infrared spectrum showed absorptions indicative of aldehyde and terminal unsaturation, and absorptions indicative of branching (methyl) were absent. The molecular weight of 98 (mass spectrum) checked for 5-hexenal. The 2-4 dinitrophenylhydrazone isolated according to the procedure of Kharasch, *et al.*,[16a] had m.p. 103°, lit.[16a] m.p. 103°; a mixture melting point with an authentic sample showed no depression.

The second component (22% yield) was identified as 2-methylcyclopentanone. The infrared spectrum was identical with that of an authentic sample and the phenylhydrazone melted at 60° dec., lit.[16c] m.p. 60° dec. A mixture melting point with the authentic phenylhydrazone showed no depression.

1,3-Butadiene Reaction.—A solution of 0.2 mole of potassium tetracarbonylcobaltate(−I) in 300 ml. of water was placed in the autoclave, and 120 ml. of concentrated phosphoric acid and 0.2

(15) R. F. Heck, *J. Am. Chem. Soc.*, **85**, 3116 (1963).

(16) (a) M. S. Kharasch, J. Kuderna, and W. Nudenberg, *J. Org. Chem.*, **18**, 1275 (1953). (b) "Dictionary of Organic Compounds," Vol. III, Heilbron Oxford Press, New York, N. Y., 1953; (c) p. 357.

mole of 1,3-butadiene were added without mixing. The autoclave was closed, inverted to mix the reactants, rocked at room temperature for 24 hr., and then heated to 120° for 2 hr. After cooling, the vessel was opened, the product was extracted with hexane, and the hexane layer was washed with distilled water and dried over sodium sulfate. After removing the hexane, the product was separated on the preparative scale gas chromatograph.

The first component (18% yield) was identified as 5-nonanone. The gas chromatographic retention time and infrared spectrum were identical with an authentic sample prepared by the method of Briese and McElvain,[17] and the molecular weight (mass spectrum) was correct for 5-nonanone. The semicarbazone melted at 90°, lit.[16b] m.p. 90°, and showed no depression when mixed with the authentic derivative.

The second compound (9% yield) was identified as 3-nonen-5-one. The infrared spectrum contained adsorptions characteristic of ketone carbonyl and conjugated unsaturation, and the molecular weight (mass spectrum) was 140. Satisfactory elemental analysis was not obtained because of sensitivity to air as reported by Powell and Nielsen.[18] However, hydrogenation of the carbon–carbon unsaturation as described by Powell and Nielsen[18] yielded 5-nonanone. The infrared spectrum was identical with the authentic sample prepared above, the molecular weight (mass spectrum) was 142 (calcd. for 5-nonanone, 142), semicarbazone had m.p. 90° (lit.[16b] m.p. 90°), and mixture melting point of semicarbazone with authentic derivative was 90°.

The above experiment was repeated, and carbon monoxide gas was added to a pressure of 1200 p.s.i. before heating. The product, treated as before, yielded only one major component, 5-nonanone (25% yield), in the gas chromatograph.

In both of the above experiments, minor peaks were observed by gas chromatography but were not separated. These corresponded in retention time to *n*-valeraldehyde, 2-methyl-1-butanal, and vinylcyclohexene.

1-Butene Reaction.—Gaseous hydrogen tetracarbonylcobaltate(−I) was prepared by slowly dropping an aqueous solution of potassium tetracarbonylcobaltate(−I) into concentrated phosphoric acid under nitrogen. The acid solution was constantly stirred while nitrogen was bubbled slowly through the mixture.

The hydrogen tetracarbonylcobaltate(−I) formed was passed through a drying tube filled with calcium chloride, then precooled in a U-tube immersed in an ice bath. The gas mixture then was bubbled slowly through a mixture of 60 ml. of 1-butene (*ca.* 0.7 mole) and 10 ml. of pentane kept at −6 to −8°. The trap was fitted with a condenser kept at −30° to minimize loss of olefin. A 250-ml. solution of potassium tetracarbonylcobaltate(−I) containing approximately 0.12 mole of cobalt was used; thus, a large excess of olefin was present. This favors the formation of alkyl and acyl cobaltates(−I) and prevents the interaction of excess hydrogen tetracarbonylcobaltate(−I) with the above complexes to yield aldehydes.

After the gas had been bubbled through for 2–3 hr., the reddish solution was transferred rapidly to the autoclave under nitrogen, and the autoclave then was closed and heated between 120 and 130° for 3 hr. in order to decompose the carbonylcobaltates present.

The solution then was distilled, and the solvent and excess olefin were removed by aspirator vacuum. The high boiling product, 0.50 g., distilled below 40° (1 mm.).

The distillate was analyzed on a Perkin-Elmer 154-L gas chromatograph with a polyethyleneglycol distearate column. Peaks corresponding to *n*-valeraldehyde, 2-methylbutanal, 3,5-dimethyl-4-heptanone, 3-methyl-4-octanone, and 5-nonanone were observed.

An infrared spectrum of the distillate showed strong carbonyl absorptions around 5.8 μ.

Based on semiquantitative gas chromatographic estimates, the above compounds contribute roughly 80% of the product, the ketone to aldehyde ratio being about 9:1.

In another experiment, when no excess of olefin was present, this ratio was considerably smaller.

Acknowledgment.—We gratefully acknowledge the financial support received from the Esso Research and Engineering Company. We wish to thank Dr. J. B. Zachry and Dr. D. R. McAdams of Esso Research Laboratories, Baton Rouge, Louisiana, for help with some of the identifications.

(17) R. R. Briese and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1697 (1933).

(18) S. G. Powell and A. T. Nielsen, *ibid.*, **70**, 3627 (1948).

The Addition of Silicon Hydrides to Olefinic Double Bonds. IX. Addition of *sym*-Tetramethyldisiloxane to Hexene-1, -2, and -3

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sym-Tetramethyldisiloxane adds to either hexene-2 or hexene-3 in the presence of chloroplatinic acid to establish Si–C bonds with the silicon attached chiefly to the 1-position but also to the 2- and 3-positions of the hexyl group in the products. Hexene-1 formed the 1-hexyl derivative almost exclusively. During the reaction a hexene becomes a mixture of hexene isomers.

In the presence of platinum catalysts, chlorosilicon hydrides seem to add to acyclic olefins so as to form only primary alkylsilanes, even from olefins such as pentene-2,[1] heptene-3,[2] or 2-methylbutene-2.[3]

sym-Tetramethyldisiloxane behaves somewhat differently from the chlorosilanes in being able to form secondary alkylsilicon derivatives from an internal olefin. Heptene-3 apparently formed 1-, 3-, and 4-heptylsilicon compounds[2] by addition of *sym*-tetramethyldisiloxane.

During all such addition reactions isomerization of olefins may be observed.[3] Recent experiments with trichlorosilane-*d* (Cl_3SiD)[4] show that extensive exchange between Si–D and the C–H of the olefins accompany the isomerization. A plausible mechanism has been postulated[4] to rationalize these data. This mechanism seemed to indicate that a reaction that produced a 1-, a 3-, and a 4-heptylsilicon derivative from heptene-3 and tetramethyldisiloxane[2] must have produced also the 2-heptyl isomer. Heptene-3 also should have formed a mixture of the isomeric heptenes during the reaction. It was not observed to do so.[2]

To reconcile the earlier data[2] with more recent results,[4] essentially the same experiments were repeated using hexene-3, which was assumed to be chemically

(1) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, **79**, 974 (1957).

(2) J. C. Saam and J. L. Speier, *ibid.*, **80**, 4104 (1958).

(3) J. C. Saam and J. L. Speier, *ibid.*, **83**, 1351 (1961).

(4) J. W. Ryan and J. L. Speier, *ibid.*, **86**, 895 (1964).

equivalent to heptene-3 for this purpose. To extend our data, hexene-1 and hexene-2 also were used.

In each experiment *sym*-tetramethyldisiloxane was added to one of the hexenes in the presence of chloroplatinic acid and converted into hexyltrimethylsilane as shown.

$$\text{Hexene} + \text{O}[\text{SiMe}_2\text{H}]_2 \xrightarrow{\text{Pt}} \text{O}[\text{SiMe}_2\text{C}_6\text{H}_{13}]_2$$

$$\text{O}[\text{SiMe}_2\text{C}_6\text{H}_{13}]_2 \xrightarrow[\text{H}_2\text{SO}_4]{\text{NH}_4\text{Cl}} 2\text{ClSiMe}_2\text{C}_6\text{H}_{13}$$

$$\text{ClSiMe}_2\text{C}_6\text{H}_{13} + \text{MeMgBr} \longrightarrow \text{Me}_3\text{SiC}_6\text{H}_{13}$$

Authentic samples of the 1-, 2-, and 3-hexyltrimethylsilanes were prepared. The ability of various vapor phase chromatography equipment was tested then for known mixtures of the three standards. No packed column available to us was able to separate the 2-hexyl from 3-hexyltrimethylsilane, although both of these were easily separable from the 1-hexyl isomer. Satisfactory separations of the three isomers were achieved with a capillary column. The column was then calibrated by means of the standards and used to gather the data in Table I.

Table I

1-, 2-, and 3-Trimethylsilylhexanes from the Addition *sym*-Tetramethyldisiloxane to Hexene-1, -2, and -3

	—% 1-, 2-, and 3-trimethylsilylhexane—		
Olefin	1-	2-	3-
Hexene-3[a]	76	10	14
Hexene-2[b]	88	7	5
Hexene-2[c]	87	7	6
Hexene-1[d]	99	Trace	None

[a] Addition was in a sealed tube at 100° 13 days. [b] Addition was in a sealed tube at 100° 19 days. [c] Addition was in a flask at reflux several days. [d] Addition was in a flask at reflux several hours.

These new data indicate that all the possible adducts form from hexene-2 or -3 with *sym*-tetramethyldisiloxane. Their separation was unambiguous and in each case excess hexene was recovered as a mixture of isomers. These new data indicate that the apparent absence of 2-heptylsilicon derivatives from the reaction of heptene-3 and tetramethyldisiloxane must be ascribed to inadequate analyses.

Experimental

Reagents.—Hexene-1 and hexene-2 were obtained from the Phillips Petroleum Company. Analysis by v.p.c. indicated that hexene-1 was at least 99% pure. Hexene-2 was a mixture of the *cis* and *trans* isomers containing a small amount of hexene-1. Hexene-3 was purchased from the Farchan Research Laboratory. V.p.c. and infrared analysis indicated it to be the *trans* isomer free of hexene-2 or -1. The catalyst was used as a 0.55 *M* solution of chloroplatinic acid hexahydrate in isopropyl alcohol.

Authentic samples of 1-, 2-, and 3-hexyltrimethylsilane were prepared. The first was made from 1-bromohexane, trimethylchlorosilane, and lithium in tetrahydrofuran below room temperature; the boiling point was 161.2°, n^{25}D 1.4142, d^{25}_4 0.7474,[5] R_D 0.3345, calcd. 0.3382.

2-Hexyltrimethylsilane was prepared in the same manner from 2-bromohexane, b.p. 158.2°, n^{25}D 1.4187, d^{25}_4 0.7494, R_D 0.3368, calcd. 0.3382.

3-Hexyltrichlorosilane was prepared by the addition of trichlorosilane to hexene-3 with benzoyl peroxide as the initiator essentially as previously described.[6] The 3-hexyltrichlorosilane was treated with excess methylmagnesium bromide in ether to give 3-hexyltrimethylsilane, b.p. 157.2° at 731 mm., n^{25}D 1.4252, d^{25}_4 0.7597, R_D 0.3366, calcd. 0.3382.

Anal. Calcd for 3-hexyltrimethylsitane: Si, 17.7. Found: Si, 17.2, 17.5.

Each of these samples was essentially pure by v.p.c. analysis and free from any isomers.

Analyses of mixtures of the 1-, 2-, and 3-hexyltrimethylsilanes were satisfactorily performed by a Perkin-Elmer Model 154C vapor phase chromatograph using nitrogen at 20 p.s.i. as the carrier and a 283 ft. × 0.02 in. stainless steel column with liquid paraffin N.F. as the adsorbent. A flame ionization detector was used with a Texas Instrument Company Recti/Riter recorder. A 2-μl. sample was split so that 1/500th passed through the column. Less than 1% of any of the isomers could be detected in mixtures of the three: retention times in minutes, 3-hexyl, 44.6 ± 0.4; 2-hexyl, 46.2 ± 0.5; 1-hexyl, 56.1 ± 0.4 at a column temperature of 40.5–41°.

Addition of *sym*-Tetramethyldisiloxane to Hexene-3.—Hexene-3 (11 g., 0.13 mole), *sym*-tetramethyldisiloxane (8.3 g., 0.62 mole), and 4.7 × 10^{-5} mole of chloroplatinic acid were heated in a 50-ml. ampule at 100° for 13 days. The mixture was devolatilized by removal of 2.7 g. of hexene. V.p.c. analysis of the recovered hexene showed it to be a mixture of isomers, mostly hexene-2 and -3.

The adduct (15.3 g.) was dispersed in 40 ml. of concentrated sulfuric acid, and ammonium chloride (10 g.) was stirred into the mixture in small portions. Hydrogen chloride was then bubbled through the mixture for 2 hr.

The top layer then was separated (18.5 g.) and added to methylmagnesium bromide (0.2 mole) in 140 ml. of ether. The mixture was heated to reflux 4 hr. and permitted to stand overnight. The mixture then was washed with dilute hydrochloric acid and then with water. The organic material was dried over calcium chloride and distilled to give a mixture of hexyltrimethylsilane (10.3 g., 65.7% over-all yield), n^{25}D 1.4178–1.4140. The properties of the combined fractions are n^{25}D 1.4150, d^{25}_4 0.7417, R_D 0.3376, calcd. 0.3382.

Anal. Calcd. for $C_9H_{22}Si$: Si, 17.7. Found: Si, 17.6, 17.7.

The distribution of isomers present in the mixture was determined by v.p.c. and was as indicated in Table I.

Addition of *sym*-Tetramethyldisiloxane to Hexene-2.—With the exception that hexene-2 was used, the preceding experiment was repeated. The reagents were heated at 100° for 19 days. A mixture of hexene (2.4 g.) was recovered, and distillation gave the hexyltrimethylsilanes (52% over-all yield), n^{25}D 1.4160–1.4135. The properties of the combined fractions were n^{25}D 1.4140, d^{25}_4 0.7399, R_D 0.3377, calcd. 0.3382.

Anal. Calcd. for $C_9H_{22}Si$: Si, 17.7. Found: Si, 17.9, 18.0.

The isomers in this mixture were as shown in Table I.

In order to see if essentially the same results would be obtained under different conditions, hexene-2 (134 g., 1.6 moles), *sym*-tetramethyldisiloxane (100.5 g., 0.75 mole), and 7.5 × 10^{-5} mole of chloroplatinic acid were heated to reflux for 144 hr.

Distillation of this mixture gave 38.3 g. of isomeric hexenes, essentially the same as previously obtained, and hexyltetramethyldisiloxane (22.9 g., 0.1 mole), n^{25}D 1.4130, d^{25}_4 0.8088, R_D 0.3083, calcd., 0.3107.

Anal. Calcd. for $C_6H_{13}Me_2SiOSiMe_2H$: H (as SiH), 0.459. Found: H (as SiH), 0.455, 0.459.

V.p.c. analysis in a 0.25-in. packed column showed the presence of three compounds in this fraction, presumably the hexyl-1, -2, and 3-tetramethyldisiloxanes. They had nearly the same retention times, but did form three distinct closely spaced peaks on the chromatograph.

1,3-Dihexyltetramethyldisiloxane was obtained (126 g., 0.416 mole), n^{25}D 1.4281, d^{25} 0.8126, R_D 0.3143, calcd. 0.3157.

Anal. Calcd. for $C_{16}H_{38}OSi_2$: Si, 18.54. Found: Si, 18.5, 18.5.

All of the fractions boiling above hexene were recombined (165 g.), including intermediate fractions and nonvolatile residues, and converted to hexyltrimethylsilanes as described before: n^{25}D 1.4142, d^{25}_4 0.7422, R_D 0.3367, calcd. 0.3382. The isomers are shown in Table I.

Anal. Calcd. for $C_9H_{22}Si$: Si, 17.72. Found: Si, 17.7, 17.8.

(5) F. C. Whitmore, L. H. Sommer, P. A. Di Giorgio, W. A. Strong, R. E. Van Strien, D. L. Bailey, H. K. Hall, E. W. Pietrusza, and G. T. Kerr [*J. Am. Chem. Soc.* **68**, 475 (1946)] report b.p. 163° at 760 mm., d^{20}_4 0.7422, n^{20}D 1.4154.

(6) (a) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *ibid.*, **69**, 188 (1947); (b) J. L. Speier and J. A. Webster, *J. Org. Chem.*, **21**, 1044 (1956).

Addition of *sym*-Tetramethyldisiloxane to Hexene-1.—*sym*-Tetramethyldisiloxane (100.5 g., 0.75 mole) was added slowly (1.25 hr.) to refluxing hexene-1 (134 g., 1.6 moles) containing 7.5 $\times 10^{-5}$ moles of chloroplatinic acid. The reaction was noticeably exothermic. The mixture was kept at 140° for 4.5 hr. and distilled. The typical mixture of hexenes (17.1 g.) was recovered followed by 1,3-dihexyltetramethyldisiloxane (202 g., 90%), $n^{25}D$ 1.4265, d^{25}_4 0.8154, R_D 0.3142, calcd. 0.3157.

Anal. Calcd. for $C_{16}H_{38}OSi_2$: Si, 18.5. Found: Si, 18.6, 18.6.

This product was also converted to hexyltrimethylsilane as described; the properties are $n^{25}D$ 1.4132, d^{25}_4 0.7378, R_D 0.3379, calcd. 0.3382.

Anal. Calcd. for $C_9H_{22}Si$: Si, 17.7. Found: Si, 17.5, 17.9.

Acknowledgment.—The authors wish to express their appreciation to Robert Winger for assistance with analyses and to Joseph Cekada for making 1- and 2-hexyltrimethylsilanes.

Reactions of Enamines. IV. The Formation of Chloroiminium Salts from Certain Enamino Ketones[1]

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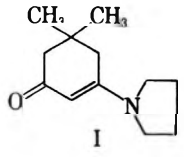
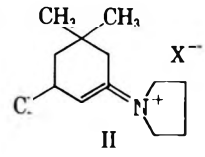
The reaction of enamino ketones with the acid chlorides of acids, the anions of which are also good leaving groups, or with phosphorus pentachloride, lead to chloroiminium salts. The proof of structure and mechanism of formation are discussed. A new synthesis of enamino ketones from β-chloro-α,β-unsaturated ketones is reported.

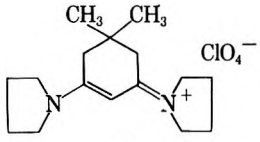
In our preliminary communication[2] it was shown that reaction of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) with trichloroacetyl chloride gave N-(3-chloro-5,-5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium chloride (II, X = Cl) as a hygroscopic solid readily converted to the stable crystalline perchlorate II (X = ClO_4). The structure of II was established by its ultraviolet spectrum[3] (see Table I) and by facile reaction of its perchlorate with 1 mole of pyrrolidine to give the known N-(5,5-dimethyl-3-N′-pyrrolidylcyclohex-2-en-1-ylidene)pyrrolidinium perchlorate (III).[4] Further proof of the structure of II was provided by hydrolysis. The chloroiminium salt II was found to be extremely stable to hydrolysis with aqueous mineral acids (the preferred method for the hydrolysis of iminium salts[5]). Mild alkaline hydrolysis, however, afforded the known 3-chloro-5,5-dimethylcyclohex-2-en-1-one (IV).[6]



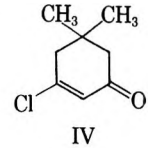
I



II

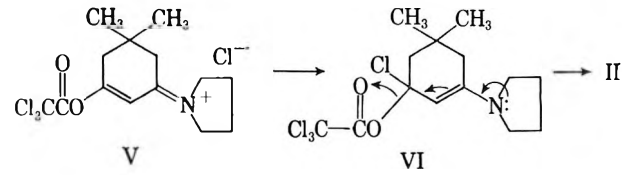


III



IV

It seemed to us, *ab initio*, that the formation of II must proceed by O-acylation of the enamino ketone I to the intermediate V.[7] Addition of chloride ion could then give VI from which the better leaving group (*i.e.*, trichloroacetate ion) would be eliminated.



V VI

It follows that the acid chloride of any acid, the anion of which is a good leaving group and a poor nucleophile, should undergo a similar reaction with I. To test this hypothesis, the enamino ketone I was heated with tosyl chloride in benzene solution. The hygroscopic salt, which was not fully characterized, gave II (X = ClO_4) in good yield when its aqueous solution was treated with perchloric acid or sodium perchlorate. In further support of our mechanism, picryl chloride underwent a similar reaction. Thus, reaction of I with picryl chloride in benzene solution, followed by treatment of the reaction mixture with water, afforded the picrate of the enamino ketone I and, as the minor product, the perchlorate II (X = ClO_4).

Indirect evidence for the reaction sequence is provided by reaction of I with diethylcarbamoyl chloride. It had been reported previously[8] that the enamino ketone I did not react with dimethylcarbamoyl chloride. While this may be true at lower temperatures, we have found that diethylcarbamoyl chloride reacts with I in refluxing chlorobenzene to give the N-(3-diethylamino-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium salt (VII), isolated as the perchlorate VII (X = ClO_4) and characterized by comparison of its physical properties with those of authentic material.[4]

The formation of VII can be rationalized by assuming reaction of the enamino ketone I with diethylcarbamoyl chloride to give the O-acylated intermediate VIII which can add chloride ion. Compound IX can then collapse to the chloroiminium cation, carbon dioxide,

(1) Part III: A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 3492 (1963).

(2) G. H. Alt and A. J. Speziale, *Tetrahedron Letters*, 111 (1663).

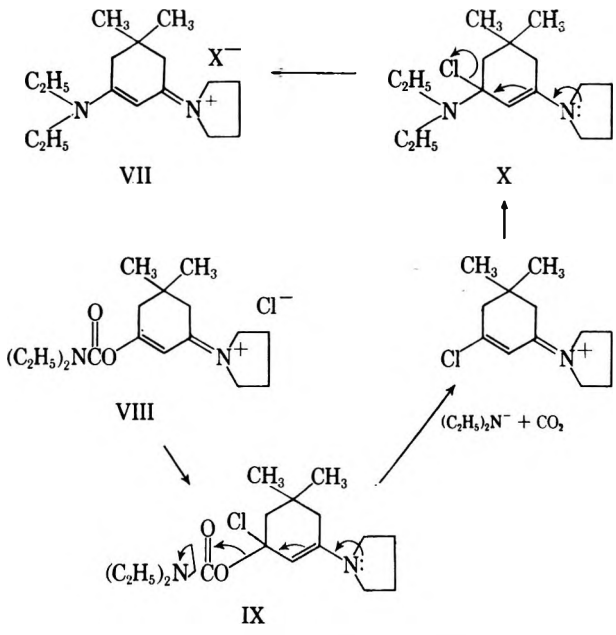
(3) J. L. Johnson, M. E. Herr, J. C. Babcock, R. P. Holysz, A. E. Fonken, J. E. Stafford, and F. W. Heyl [*J. Am. Chem. Soc.*, **78**, 430 (1956)] have reported λ_{max} 274–278 mμ (ε >20,000) for ternary iminium salts of the type $>C=C-\overset{|}{C}=\overset{+}{N}<$; see also G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962).

(4) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959).

(5) *Cf. inter alia:* G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85** 207 (1963).

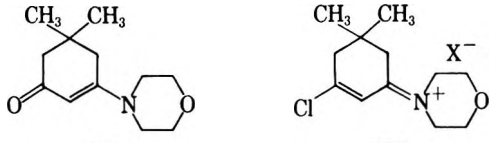
(6) A. W. Crossley and H. R. LeSueur, *J. Chem. Soc.*, **83**, 110 (1903).

(7) S. Hünig, E. Benzing, and E. Lücke [*Ber.*, **90**, 2833 (1957)] have observed the O-acylation of enamino ketones.

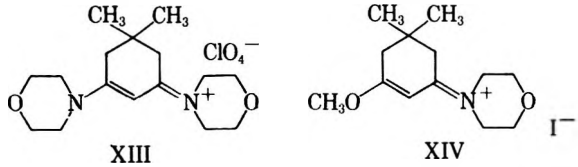


and diethylamine anion. Combination of cation and anion can give X, which is converted to VII by loss of chloride ion.

Since O-acylation is favored by pyrrolidine enamino ketones,[7,8] it seemed desirable to test the generality of our reaction by using the enamino ketone of a weaker base which would decrease the electron availability on oxygen. Treatment of 5,5-dimethyl-3-N-morpholinylcyclohex-2-en-1-one (XI) with trichloroacetyl chloride in carbon tetrachloride gave N-(3-chloro-5,5-dimethylcyclohex-2-en-1-ylidene)morpholinium chloride (XII, X = Cl) as a hygroscopic salt which afforded the stable



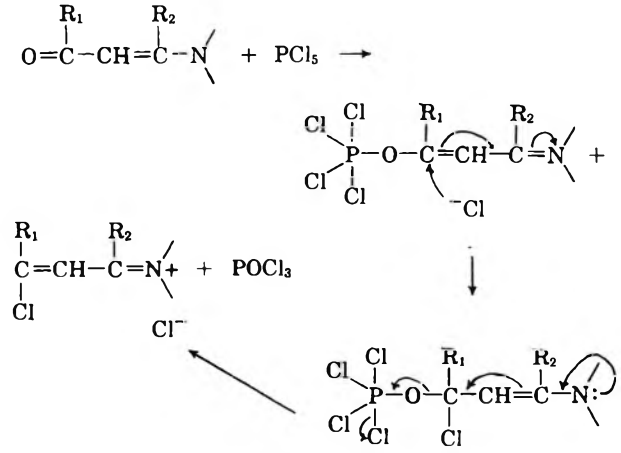
crystalline perchlorate XII (X = ClO_4). The same perchlorate was obtained by reaction of XI with tosyl chloride in benzene solution and treatment of the salt obtained with perchloric acid. The structure of XII was proven by the conversion of its perchlorate with 1 mole of morpholine to N-(5,5-dimethyl-3-N′-morpholinylcyclohex-2-en-1-ylidene)morpholinium per-



chlorate (XIII), which was identical with an authentic sample prepared from XI *via* the methiodide XIV. As expected by analogy with the chloroiminium salt II, mild alkaline hydrolysis of XII (X = Cl) gave the chloro ketone (IV).

An attempt was made to synthesize II and XII from the chloro ketone (IV) by treatment with the corresponding amines in benzenes olution. Instead of the chloroiminium salts there were obtained the hydrochloride salts of the enamino ketones I and XI, respectively, from which the enamino ketones could be obtained by treatment with base. This constitutes an alternative synthesis of enamino ketones which may be useful when they are not obtainable by conventional methods.

Finally it was found that the chloroiminium salts II and XII could be obtained in excellent yield by treatment of the corresponding enamino ketones (I and XI) with 1 mole of phosphorus pentachloride in refluxing benzene. As the enamino ketones may be regarded as vinylogous amides, the formation of the chloroiminium salts in this instance may proceed in a manner similar to the formation of amido chlorides by reaction of phosphorus pentachloride with N,N′-disubstituted amides.[9] At present, this method of preparation constitutes the best synthesis of chloroiminium salts.



All of the ultraviolet spectra (Table I) are entirely consistent with the structures assigned. However, a striking bathochromic shift of 9 ± 2 mμ was observed in the absorption maxima of the ternary iminium salts based on morpholine compared with those based on pyrrolidine. This shift was not observed in comparing the spectra of the enamino ketones I and XI or those of their hydrochlorides.[10]

In the n.m.r. spectra of compounds in Table I in deuteriochloroform solution the vinyl protons appear as sharp singlets. The position of the vinyl hydrogen varies considerably with the basicity of the amine, especially in the ternary iminium salts, in contrast with the position of the vinyl protons in enamines which are reported[5] to be essentially independent of the basicity of the amine.

Experimental[11]

5,5-Dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) was prepared according to the procedure of Leonard and Adamcik[4] and gave yellow prisms, m.p. 129–132°, lit.[4] m.p. 131–133°. The compound formed a yellow picrate, m.p. 185–186° (from chloroform–methanol).

(8) A. Brizzolara, Ph.D. thesis, Columbia University, 1960.

(9) (a) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 863 (1960); (b) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962).

(10) The absence of a bathochromic shift in the ultraviolet spectra of I (303 mμ) and XI (303 mμ), and of their hydrochlorides (298 and 301 mμ, respectively), together with the fact, that, if the hydrochlorides were protonated on nitrogen, they would be expected to absorb at a much lower wave length than the parent enamino ketones, leads to the conclusion that these compounds are protonated on oxygen, in agreement with the evidence of alkylation.[4]

(11) Boiling points and melting points are uncorrected. Melting points were taken on a Mel-Temp capillary melting point apparatus.

TABLE I

ULTRAVIOLET AND N.M.R. DATA

Compound	λ_{max} mμ[a]	ε	Position of vinyl proton in τ[b]
I	303	35,000	4.98
I HCl	298	27,000	3.69
II (X = Cl)	274	25,000	
II (X = ClO_4)	($CHCl_3$) 272	27,000	3.19
III	331[c]	46,000	4.92
	Shoulder 325	44,000	
IV			3.09
IV semicarbazone	272	20,000	
VII	335[d]	48,000	4.80
	Shoulder 325	43,500	
XI	303	32,000	4.72
XI HCl	301	28,000	
XII (X = Cl)	283	17,000	2.50
XII (X = ClO_4)	283	20,000	
XIII	342	46,000	
	Shoulder 332	43,000	
XIV	294[e]	24,000	3.68

[a] Beckman DK2A instrument in ethyl alcohol unless stated otherwise. [b] Varian A60 instrument in deuteriochloroform, TMS as internal standard. [c] Leonard and Adamcik (ref. 4) report λ_{max}^{EtOH} 331 mμ (ε 47,000) and shoulder at 325 (44,200). [d] Leonard and Adamcik (ref. 4) report λ_{max}^{EtOH} 332 mμ (ε 48,800) and shoulder at 326 (45,700). [e] Leonard and Adamcik (ref. 4) report λ_{max}^{EtOH} 286 mμ (ε, 24,300) for the corresponding compound based on pyrrolidine.

Anal. Calcd. for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.26. Found: C, 51.46; H, 5.32; N, 12.97.

N-(3-Chloro-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium Chloride (II, X = Cl).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was added a solution of trichloroacetyl chloride (2.3 g., 0.0127 mole) in benzene (20 ml.), and the mixture was heated at 70° for 2–3 hr. On cooling, 1.25 g. (20%) of a hygroscopic solid was isolated, taken up in chloroform, and reprecipitated with ether to give II (X = Cl^-), m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{19}Cl_2N_2$: C, 58.07; H, 7.72; Cl, 28.57; N, 5.64. Found: C, 57.99; H, 7.80; Cl, 28.40; N, 5.54.

N-(3-Chloro-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium Perchlorate (II, X = ClO_4). A. By Reaction of I with Trichloroacetyl Chloride.—To a solution of the enamino ketone I (9.65 g., 0.05 mole) in carbon tetrachloride (100 ml.) was added trichloroacetyl chloride (10 g., 0.055 mole) in carbon tetrachloride (50 ml.) over a period of 0.5 hr. There was no rise in temperature, but a solid started to precipitate. The reaction mixture was heated at 80° for 4 hr. more, cooled, and the solid was filtered. The sticky solid was washed with benzene and dried *in vacuo* and had m.p. 152–156°. The solid was taken up in water and 3 ml. of perchloric acid was added, giving a precipitate of the crystalline perchlorate (II, X = ClO_4, 3.5 g., 22.5%), which was recrystallized from ethyl acetate–ethanol, and had m.p. 187–188°.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO_4$: C, 46.16; H, 6.08; Cl, 22.75; N, 4.49. Found: C, 46.13; H, 6.19; Cl, 22.80; N, 4.55.

Evaporation of the filtrate gave 12.2 g. of an intractable gum.

B. By Reaction of I with Tosyl Chloride.—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was added tosyl chloride (4.8 g., 0.025 mole), and the mixture was heated under reflux for 4 hr. The solvent was removed by evaporation *in vacuo*. The sticky solid was taken up in 30 ml. of water and, upon addition of 3 ml. of 70% perchloric acid, an oil separated which solidified on seeding. Two recrystallizations from ethyl acetate–ethanol gave 1.1 g. (14%) of II (X = ClO_4), m.p. and m.m.p. 186–187°.

C. By Reaction of I with Picryl Chloride.—The enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was treated with picryl chloride (6.25 g., 0.025 mole) at the reflux temperature for 2 hr. The reaction mixture was cooled to room temperature and stirred with 50 ml. of water for 1 hr., during which time a solid precipitated. The solid (5.1 g., 48% of starting enamino ketone) was removed by filtration and recrystallized from ethyl acetate to give yellow plates, m.p. 183–185°, not depressed on admixture with an authentic specimen (see above) of enamino ketone picrate of the same melting point. The aqueous layer of the filtrate was separated and treated with 70% perchloric acid (1 ml.), giving a precipitate which was removed by filtration. Recrystallization from ethyl acetate–ethanol gave 400 mg. (5.1%) of N-(3-chloro-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium perchlorate (II, X = ClO_4), m.p. 185–187°, not depressed on admixture with an authentic sample (above) of the same melting point.

D. By Reaction of I with Phosphorus Pentachloride.—To a solution of the enamino ketone I (1.95 g., 0.01 mole) in benzene (50 ml.) was added phosphorus pentachloride (2.1 g., 0.01 mole), and the mixture refluxed for 3 hr. The reaction mixture was cooled and 50 ml. of water was added. After stirring for 15 min., the aqueous layer was separated and a solution of 3 g. of sodium perchlorate in 10 ml. of water was added. The product (1.8 g., 58%) was filtered. Recrystallization from ethanol–ethyl acetate gave II (X = ClO_4) as plates, m.p. and m.m.p. 185–187°.

N-(5,5-Dimethyl-3-N′-pyrrolidylcyclohex-2-en-1-ylidene)pyrrolidinium Perchlorate (III).—The perchlorate salt II (X = ClO_4, 0.85 g., 0.0027 mole) in 10 ml. of methanol was treated with pyrrolidine (0.20 g., 0.0028 mole) and the solution became warm. After heating the mixture on the steam bath for 5 min., the solvent was removed under reduced pressure, and the residue was recrystallized from ethyl acetate–methanol, giving 0.5 g. (54%) of III as needles, m.p. 193–195°, not depressed on admixture with authentic material[4] of the same melting point.

The chloride salt II (X = Cl) heated with pyrrolidine under the above conditions gave an oil which was converted with perchloric acid to III, m.p. 193–195°.

Hydrolysis of II. A.—To a solution of II (X = Cl^-, 2 g., 0.008 mole) in 30 ml. of water was added 10% sodium hydroxide solution (5 ml.), and the mixture was heated on the steam bath for 10 min. Extraction with chloroform gave 1.2 g. (95%) of an oil (b.p. 91° at 12 mm., $n^{25}D$ 1.4940) having an infrared spectrum superimposable with that of authentic 5,5-dimethyl-3-chlorocyclohex-2-enone (IV)[6] (below). Treatment of the oil with semicarbazide hydrochloride and sodium acetate in aqueous ethanol gave the semicarbazone, m.p. 199° dec., melting point not depressed on admixture with authentic semicarbazone of the same melting point (below).[6]

B.—One gram of II (X = ClO_4^-) in 50 ml. of 1 *N* sulfuric acid was heated at reflux temperature for 12 hr. On cooling, 900 mg. of II (X = ClO_4^-) crystallized from the reaction mixture.

C.—One-half gram of II (X = ClO_4^-) in 20 ml. of 10% sodium hydroxide solution was heated for 20 min. on the steam bath. Extraction with chloroform gave an oil, which, on treatment with semicarbazide hydrochloride and sodium acetate in aqueous ethanol, gave the semicarbazone of IV, m.p. 198° dec., not depressed on admixture with authentic material.

D.—One-half gram of II (X = Cl^-) in 20 ml. of 1 *N* sulfuric acid was heated to reflux for 4 hr. The sodium was cooled and added to 1 g. of sodium perchlorate. The precipitate which formed was filtered and recrystallized from ethyl acetate–ethanol giving 300 mg. of II (X = ClO_4^-), m.p. 187–188°, not depressed with material above.

5,5-Dimethyl-3-chlorocyclohex-2-enone (IV) was prepared by the procedure of Crossley and LeSueur[6] and had b.p. 87° (11 mm.), $n^{25}D$ 1.4944, lit.[6] b.p. 109–110° (14 mm.). The semicarbazone had m.p. 199° dec. (from ethanol), lit.[6] m.p. 199° dec.

Anal. Calcd. for $C_9H_{14}ClN_3O$: Cl, 16.44. Found: Cl, 16.61.

5,5-Dimethyl-3N-pyrrolidylcyclohex-2-en-1-one Hydrochloride A. From I.—A solution of 2 g. of I in 30 ml. of benzene was saturated with dry hydrogen chloride. The precipitated product was filtered and dried in a vacuum dessicator and had m.p. 229–230°.

Anal. Calcd. for $C_{12}H_{20}ClNO$: C, 62.72; H, 8.77; Cl, 15.43; N, 6.10. Found: C, 62.32; H, 8.77; Cl, 15.60; N, 6.13.

B. From IV.—A solution of 1.5 g. of IV in 20 ml. of benzene was treated with 0.71 g. of pyrrolidine at 80° for 10 min. The product (2 g., 87%) which crystallized on standing had m.p. 230–231°, not depressed on admixture with material above.[12]

One gram of the hydrochloride above in 20 ml. of water was treated with 5 ml. of 10% sodium hydroxide solution. The precipitated oily material was isolated by extraction with chloroform.

(12) See also G. Opitz and F. Zimmermann, *Ann.*, **662**, 178 (1963).

Evaporation of the chloroform *in vacuo*, and crystallization of the residue from benzene–methylcyclohexane gave the enamino ketone I, m.p. 130–132°.

N-(3-Diethylamino-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium Perchlorate (VII). A. By Reaction of I with Diethylcarbamoyl Chloride.—The enamino ketone I (4.9 g., 0.025 mole) in chlorobenzene (50 ml.) was treated with diethylcarbamoyl chloride (3.45 g., 0.0255 mole) in chlorobenzene (20 ml.), and the mixture refluxed (130°) for 7 hr. The reaction mixture was cooled, water (100 ml.) was added, and the solution was stirred for 20 min. The aqueous layer was separated and treated with 70% perchloric acid (approx. 2.5 ml.). The crude product was filtered, taken up in boiling water, treated with charcoal, and filtered. On cooling, N-(3-diethylamino-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium perchlorate, m.p. 130–132° (2.0 g., 23%), crystallized.

B. From II (X = ClO_4).—N-(3-Chloro-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium perchlorate (II, X = ClO_4, 312 mg., 0.001 mole) in methanol (5 ml.) was treated with diethylamine (5 drops). The reaction mixture became warm and was allowed to stand until it was again at room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from hot water with charcoal treatment. The product crystallized as long needles, m.p. 130–132° (200 mg., 58%), lit.[4] m.p. 131.5–132.5°.

5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one (XI).—A solution of 28.0 g. (0.2 mole) of 5,5-dimethylcyclohexan-1,3-dione and 19.2 g. (0.22 mole) of morpholine in 250 ml. of benzene was refluxed, and the water was removed azeotropically during 4 hr. The benzene was evaporated *in vacuo*, and the residue was recrystallized twice from benzene–methylcyclohexane to give 31.3 g. of XI (75%) as pale yellow plates, m.p. 127–129°.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.83; H, 9.20; N, 6.66.

5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one Hydrochloride. A. From XI.—A solution of the enamino ketone XI (2 g.) in 30 ml. of benzene was saturated with dry hydrogen chloride. The precipitated product was filtered and dried in a vacuum desiccator and had m.p. 234–236°.

Anal. Calcd. for $C_{12}H_{20}ClNO_2$: C, 58.65; H, 8.20; Cl, 14.43; N, 5.70. Found: C, 58.31; H, 8.45; Cl, 14.13; N, 5.88.

B. From IV.—A solution of 1.5 g. of IV in 20 ml. of benzene was treated with 0.88 g. of morpholine at 80° for 10 min. The product (2 g., 82%) crystallized on standing and had m.p. 234–236°, not depressed on admixture with material above.[12]

One gram of the hydrochloride above in 20 ml. of water was treated with 5 ml. of 10% sodium hydroxide solution. The precipitated oily material was isolated by extraction with chloroform. Evaporation of the chloroform *in vacuo* and crystallization from benzene–methylcyclohexane gave the enamino ketone XI, m.p. 126–128°.

N-(3-Chloro-5,5-dimethylcyclohex-2-en-1-ylidene)morpholinium Chloride (XII, X = Cl).—To a solution of the enamino ketone XI (5.25 g., 0.025 mole) in carbon tetrachloride (70 ml.) was added trichloroacetyl chloride (4.7 g., 0.0255 mole) in carbon tetrachloride over a period of 0.5 hr. The reaction mixture was heated under reflux for 3 hr. during which time a solid precipitated. The reaction mixture was cooled, and the solid (2.0 g., 30%) was filtered. The solid was washed with benzene and dried in a vacuum desiccator to give pure XII (X = Cl), m.p. 200–205° dec.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO$: C, 54.55; H, 7.25; Cl, 26.84; N, 5.30. Found: C, 54.10; H, 7.25; Cl, 26.94; N, 5.43.

Evaporation of the filtrate gave 7.5 g. of a colorless oil.

N-(3-Chloro-5,5-dimethylcyclohex-2-en-1-ylidene)morpholinium Perchlorate (XII, X = ClO_4). A. By Reaction of XI with Trichloroacetyl Chloride.—The solid, 1.3 g., from a preparation as above was taken up in 10 ml. of water, and a solution of 2 g. of sodium perchlorate in 15 ml. of water was added. The precipitated solid (approx. 1 g.) was filtered and recrystallized two times from ethanol to give 0.8 g. (50%) of pure XII (X = ClO_4), m.p. 254° dec.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO_5$: C, 43.91; H, 5.84; Cl, 21.54; N, 4.27. Found: C, 44.09; H, 6.01; Cl, 21.30; N, 4.37.

B. By Reaction of XI with Tosyl Chloride.—To solution of the enamino ketone XI (4.2 g., 0.02 mole) in benzene (70 ml.) was added tosyl chloride (4.0 g., 0.021 mole) and the mixture refluxed for 3 hr. The precipitated solid (5 g.) was filtered and dried in a vacuum desiccator. One gram of this solid was taken up in 10 ml. of water, and 3 ml. of 70% perchloric acid was added. The precipitated solid was filtered and recrystallized from ethanol to give XII (X = ClO_4), m.p. 254° dec., not depressed on admixture with material above.

C. By Reaction of XI with Phosphorus Pentachloride.—To a solution of the enamino ketone XI (2.1 g., 0.01 mole) in benzene (50 ml.) was added phosphorus pentachloride (2.1 g., 0.01 mole), and the mixture was heated under reflux for 3 hr. The reaction mixture was cooled, and 50 ml. of water was added. After stirring for 15 min., the aqueous layer was separated and a solution of 3 g. of sodium perchlorate in 10 ml. of water was added. The product (1.8 g., 55%) was filtered. Recrystallization from ethanol gave pure XII (X = ClO_4), m.p. 254° dec., not depressed on admixture with authentic material above.

Hydrolysis of XII.—To a solution of XII (X = ClO_4, 1.0 g., 0.003 mole) in 20 ml. of water was added 5 ml. of 10% sodium hydroxide solution, and the mixture was heated on the steam bath for 10 min. Extraction with chloroform gave an oil which was taken up in ethanol and treated with a solution of semicarbazide hydrochloride and sodium acetate in aqueous ethanol. The precipitated semicarbazone (0.45 g., 70%) was filtered and recrystallized from ethanol to give pure 3-chloro-5,5-dimethylcyclohex-2-en-1-one semicarbazone, m.p. 199° dec., not depressed on admixture with authentic material above.

N-(5,5-Dimethyl-3-N'-morpholinylcyclohex-2-en-1-ylidene)morpholinium Perchlorate (XIII). A. From XII.—The perchlorate XII (X = ClO_4, 1.0 g., 0.003 mole) in 10 ml. of methanol was treated with morpholine (0.27 g., 0.0031 mole) at the steam bath temperature for 5 min. The solvent was removed *in vacuo*, and the residue was crystallized from hot water to give XIII (0.65 g., 57%) as needles, m.p. 258° dec., not depressed on admixture with authentic material below.

B. From XIV.—To a solution of the methiodide XIV (1.75 g., 0.005 mole) in methanol (15 ml.) was added morpholine (0.49 g., 0.0056 mole) with evolution of heat. Ethyl acetate (20 ml.) was added, and the reaction mixture was evaporated *in vacuo*. The residue was recrystallized from methanol–ethyl acetate giving 1.9 g. (92%) of N-(5,5-dimethyl-3-N'-morpholinylcyclohex-2-en-1-ylidene)morpholinium iodide as pale yellow prisms, m.p. 280–282° dec.

Anal. Calcd. for $C_{16}H_{27}IN_2O_2$: C, 47.29; H, 6.70; I, 31.23; N, 6.90. Found: C, 47.50; H, 6.73; I, 31.34; N, 6.95.

The above iodide (0.81 g., 0.002 mole) in water (10 ml.) was heated with 0.5 ml. of 70% perchloric acid. The precipitated solid (0.70 g., 93%) was filtered and recrystallized from hot water to give XIII as needles, m.p. 258° dec.

Anal. Calcd. for $C_{16}H_{27}ClNO_6$: C, 50.72; H, 7.18; Cl, 9.36; N, 7.40. Found: C, 50.57; H, 7.08; Cl, 9.60; N, 7.60.

5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one Methiodide (XIV).—The enamino ketone XI (2.1 g., 0.01 mole) and methyl iodide (15 ml.) were heated under reflux for 24 hr. The product (3.3 g., 94%) was filtered and recrystallized from methanol–ethyl acetate giving pure XIV, m.p. 174–175° dec.

Anal. Calcd. for $C_{13}H_{22}INO_2$: C, 44.46; H, 6.31; I, 36.13; N, 3.99. Found: C, 44.78; H, 6.47; I, 35.85; N, 3.89.

Acknowledgment.—Our sincere thanks are due to Professor N. J. Leonard for many helpful and stimulating discussions.

Reactions of Enamines. V. The Acylation of Enamino Ketones[1]

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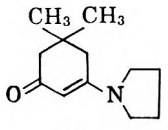
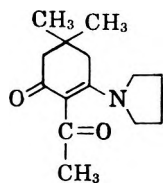
The acylation of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) and 5,5-dimethyl-3-N-morpholylcyclohex-2-en-1-one (V) with aromatic acid chlorides gives C-acylated products. Aliphatic acid chlorides react similarly except when they are capable of undergoing dehydrohalogenation to a ketene. Ketene or diketene does not react with I and V. 2-Nitrobenzenesulfenyl chloride with I afforded the 2-substituted sulfide (VII). The criteria for O- *vs.* C-acylation of enamino ketones are discussed.

The O- and C-alkylation of enamino ketones is well-established.[2] The only reported acylation of an enamino ketone must have involved O-acylation as shown by hydrolysis of the intermediate iminium salt to the enol ester of a 1,3-diketone.[3] Indirect evidence for O-acylation is provided by the formation of chloroiminium salts from enamino ketones.[1] On this basis,

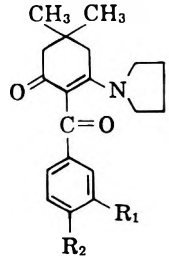


I



II

O-acylation would be expected in the reaction of enamino ketones with acid chlorides. Surprisingly, reaction of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) with acetyl chloride gave exclusively the C-acylated, 2-acetyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (II) with concomitant formation of an equimolar amount of the hydrochloride of I. The structure of II follows from the elemental analysis, the ultraviolet spectrum, and the n.m.r. spectrum which did not show a vinyl proton. Similar results were obtained by reaction of I with benzoyl, 3,4-dichlorobenzoyl, and *p*-nitrobenzoyl chlorides. In each

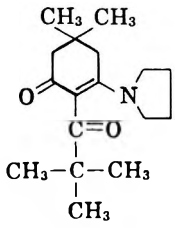


IIIa, $R_1 = R_2 = H$
b, $R_1 = R_2 = Cl$
c, $R_1 = H$; $R_2 = NO_2$

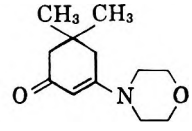
case the C-acylated product (IIIa, IIIb, IIIc, respectively) was obtained together with an equimolar amount of I hydrochloride. The formation of the hydrochloride of I rather than that of the C-acylated products (II or III) reflects the fact that enamino ketone I is a stronger base than II or III.

It has been reported[3] that the addition of triethylamine in the acylation of enamines avoids the loss of starting material as the hydrochloride. In the reaction of the enamino ketone I with acetyl chloride in the presence of triethylamine, a quantitative yield of triethylamine hydrochloride was obtained. However, no C-acylated product was isolated and I was recovered unchanged. This result is readily understood by allowing for the dehydrohalogenation of acetyl chloride by triethylamine to ketene which is rapidly converted to dimer under the reaction conditions.[4] In a control experiment it was shown that diketene does not react with I under the same conditions.[5]

For similar reasons reaction of propionyl chloride and I did not give the C-acylated product. A quantitative yield of I hydrochloride together with unchanged I was obtained. Thus, the enamino ketone I is a strong enough base to dehydrohalogenate propionyl chloride to methylketene before C-acylation can take place. Pivalyl chloride, which cannot undergo dehydrohalogenation, reacted normally to give C-acylated IV.

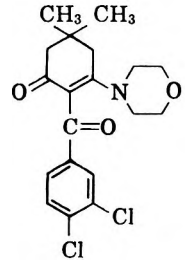


IV

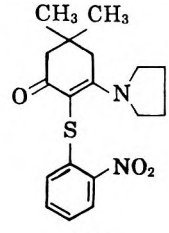


V

Reaction of 5,5-dimethyl-3-N-morpholylcyclohex-2-en-1-one (V) with 3,4-dichlorobenzoyl chloride afforded the C-acylated product (VI). However, a quantitative yield of the V hydrochloride and unchanged compound V were the only products from the reaction of V with acetyl chloride. Evidently dehydrohalogenation of acetyl chloride by the enamino ketone V had taken place. The difference in the behavior of I and V



VI



VII

(1) Part IV: G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964).

(2) *Cf.*, *inter alia*, (a) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959); (b) N. K. Kochetkov, *Izv. Ak. Nauk SSSR Otd. Khim. Nauk*, 47 (1954).

(3) S. Hünig, E. Benzing, and E. Lücke, *Ber.* **90**, 2833 (1957).

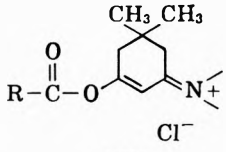
(4) J. C. Sauer, *J. Am. Chem. Soc.* **69**, 2444 (1947); see also W. E. Hanford and J. C. Sauer, "Organic Reactions," Coll. Vol. III, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 124.

(5) The reaction of enamines with ketene and diketene is well-known. See (a) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **26**, 4775 (1961); (b) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *ibid.*, **26**, 4776 (1961); (c) S. Hünig, E. Benzing, and K. Hübner, *Ber.*, **94**, 486 (1961); (d) G. Opitz and F. Zimmermann, *Ann.*, **622**, 178 (1963).

towards acetyl chloride must lie in the basicities of the amines as well as in the greater ease of formation of a trigonal atom in a five-membered ring compared with one in a six-membered ring in the transition state.[6] Thus, the more reactive (*i.e.*, in the acylation reaction) pyrrolidine enamino ketone reacts to give C-acylated product while the morpholine enamino ketone, which is less reactive, is nevertheless a strong enough base to effect the dehydrohalogenation of acetyl chloride. This difference in reactivity is well-illustrated by the reaction of I and V with acetic anhydride. The pyrrolidine enamino ketone (I) reacts with boiling acetic anhydride to give II while the morpholine enamino ketone (V) is recovered unchanged under the same conditions.[7]

The enamino ketone I also reacted smoothly with *o*-nitrobenzenesulfenyl chloride to give a compound (VII) having the *o*-nitrophenylthio group substituted in the 2-position. Again the equivalent of C-acylation had taken place.

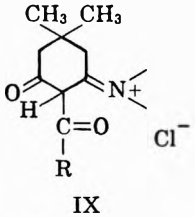
Since initial O-acylation must have taken place in the formation of chloroiminium salts,[1] it seems reasonable that in the present cases, O-acylation[8] also occurs, but does not lead to stable products. The O-acylated intermediate (VIII) can collapse to starting materials by attack of chloride ion at the carbonyl carbon.



VIII

In the formation of chloroiminium salts[1] (*e.g.*, VIII, R = $-CCl_3$) the inductive effect of the trichloromethyl group, although rendering the carbonyl carbon more positive, would also strengthen the bond to the ester oxygen. Hence, attack by chloride ion occurs at C-1 of the ring,[9] leading to chloroiminium salt and expulsion of trichloroacetate ion.

When C-acylation does occur, the intermediate IX can stabilize itself by loss of a proton from C-2 to give the observed product.



IX

Experimental[10]

2-Acetyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (II). A. Reaction of I with Acetyl Chloride.—To a solution of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I)[1,2a] (4.9 g., 0.025 mole) in benzene (70 ml.) was added acetyl chloride (1.0 g., 0.013 mole) in benzene (20 ml.). The reaction mixture was heated under reflux for 3 hr. during which time a solid precipitated. After cooling the solid was filtered giving 2.9 g. (100%) of the hydrochloride of the starting enamino ketone I, m.p. 225–228° (no depression with authentic I hydrochloride).[1] The filtrate was evaporated to dryness *in vacuo* giving 2.8 g. of sticky crystals, m.p. 140–146°, which on several recrystallizations from benzene or ethyl acetate–hexane mixture gave pure II (2.1 g., 72% based on enamino ketone reacted), m.p. 158–159°; λ_{max}^{EtOH} 274 mμ (ε 13,300), 310 (16,000); n.m.r. spectrum, τ 8.92 singlet, 8.05 multiplet, 7.75 singlet, 7.50 multiplet, 6.75 multiplet, no vinyl proton, with intensity ratios 6:4:2:5:4, respectively.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.47; H, 8.73.

Treatment of 400 mg. of II in 5 ml. of water with perchloric acid gave II perchlorate. Recrystallization from ethyl acetate–ethanol gave 200 mg., m.p. 164–165°; λ_{max}^{EtOH} 274 mμ (ε 12,700), 310 (17,000).

Anal. Calcd. for $C_{14}H_{22}ClNO_6$: C, 50.07; H, 6.61; Cl, 10.56. Found: C, 49.89; H, 6.50; Cl, 10.80.

In the reaction of I with 0.5 mole of acetyl bromide, I hydrobromide and unchanged I were the only products. If an excess of acetyl bromide (>1.0 mole) was used, II was isolated in low yield.

B. Reaction of I with Acetic Anhydride.—The enamino ketone I (2.45 g., 0.013 mole) in acetic anhydride (30 ml.) was refluxed for 3 hr. The acetic anhydride was removed by distillation *in vacuo*. The residue was recrystallized from benzene–hexane to give II (1.7 g., 59%), m.p. 157–159°, not depressed in admixture with authentic material above.

Reaction of I with Acetyl Chloride in the Presence of Triethylamine.—To a solution of the enamino ketone I (4.9 g., 0.025 mole) and triethylamine (3 g., 0.03 mole) in benzene (70 ml.) was added acetyl chloride (2.0 g., 0.0255 mole) in benzene (20 ml.), and the reaction mixture heated at 60–65° for 6 hr. On cooling, triethylamine hydrochloride (3.5 g., 0.0252 mole ≡ 100%) was removed by filtration, and the benzene filtrate was evaporated to give 6 g. of a very viscous oil. Chromatography or several recrystallizations from benzene–methylcyclohexane gave I (3.8 g.), m.p. 129–131°, not depressed in admixture with authentic starting material.

Attempted Reaction of I with Diketene.—The enamino ketone I (4.9 g., 0.025 mole) and freshly distilled diketene (2.2 g., 0.026 mole) in benzene (70 ml.) were heated at the reflux temperature for 5 hr. On evaporation, 7 g. of a solid mixed with tar were obtained. Recrystallization from benzene–methylcyclohexane gave I (3 g.), m.p. 130–132°, identical with authentic starting material.

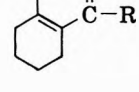
Attempted Reaction of I with Propionyl Chloride.—The enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was heated with propionyl chloride (1.2 g., 0.013 mole) in benzene (20 ml.) at 70° for 3 hr. On cooling, I hydrochloride (3.0 g., 0.013 mole ≡ 100%), m.p. 224–228°, was removed by filtration. Evaporation of the filtrate gave 3.0 g. of a yellow oil. Chromatography over alumina and crystallization from benzene–methylcyclohexane gave I (1.5 g.), m.p. 129–131°, not depressed in admixture with authentic material.

2-Benzoyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIa).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (50 ml.) was added benzoyl chloride (1.9 g., 0.0135 mole) in benzene (25 ml.), and the reaction mixture heated at 80° for 3 hr., during which time a solid precipitated. On cooling, filtration gave the hydrochloride of the starting enamino ketone (2.8 g., 98%), m.p. and m.m.p. 228–230°. The filtrate

(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(7) A. W. Crossley and J. Renouf [*J. Chem. Soc.*, **101**, 1525 (1912)] report that 5,5-dimethylcyclohexane-1,3-dione may be C-acylated with acetic anhydride in the presence of sodium acetate and O-acylated by rigid exclusion of base. In the reaction of I with acetic anhydride under the above conditions only C-acylation was observed.

(8) The O-acylation by Hünig, *et al.*,[3] is readily understood in view of the absence of a vinyl hydrogen in the enamino ketone involved.



Thus, C-acylation in this case would be equivalent to the disubstitution of this enamine at the same carbon, which has not been observed.[6]

(9) Attack at C-1 cannot be attributed to steric effects at the carbonyl carbon, because pivalyl chloride and I afford C-acylated product IV.

(10) Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Ultraviolet spectra were taken on a Beckman DK2A spectrometer in ethanol solution. N.m.r. spectra were taken with a Varian A60 instrument in deuteriochloroform solution using tetramethylsilane as internal standard.

evaporated *in vacuo* gave 3.7 g. (98%) of oily IIIa which was recrystallized from benzene–methylcyclohexane to give m.p. 164–165°, λ_{max}^{EtOH} 299 mμ (ε 23,000). The compound showed no carbonyl absorption in the infrared spectrum below 6.0 μ; n.m.r. spectrum, τ 8.85 singlet, 8.20 multiplet, 7.75 singlet, 7.48 singlet, 6.78 multiplet, 2.62 multiplet, no vinyl proton, with intensity ratios 6:4:2:2:4:5, respectively.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.32; H, 7.85; N, 4.20.

2-(3,4-Dichlorobenzoyl)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIb).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in 50 ml. benzene was added 3,4-dichlorobenzoyl chloride (5.3 g., 0.025 mole) in 40 ml of benzene. The reaction mixture was refluxed for 2.5 hr., during which time a solid precipitated. On cooling, filtration gave 7.3 g. of solid. The solid was boiled with 50 ml. of water when filtration gave 3.85 g. of yellow solid, m.p. 225–230°. Recrystallization from aqueous ethanol gave pure IIIb, m.p. 228–230°; λ_{max}^{EtOH} 298 mμ (ε 28,000); n.m.r. spectrum, τ 8.90 singlet, 8.17 multiplet, 7.80 singlet, 7.50 singlet, 6.82 multiplet, 2.60 multiplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:3, respectively.

Anal. Calcd. for $C_{19}H_{21}Cl_2NO_2$: C, 62.29; H, 5.78; N, 3.82; Cl, 19.36. Found: C, 62.03; H, 6.03; N, 3.89; Cl, 18.9.

The yield was 40% calculated on the starting enamino ketone or 80% if allowance is made for the enamino ketone used to take up hydrochloric acid. The aqueous filtrate above was evaporated to dryness, and the residue taken up in a minimum amount of water. Addition of perchloric acid gave a precipitate which, on crystallization from ethyl acetate–ethanol, had m.p. 179–181°, not depressed in admixture with the perchlorate of the starting enamino ketone of the same melting point.[2a]

2-(4-Nitrobenzoyl)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIc).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was added a solution of *p*-nitrobenzoyl chloride (2.3 g., 0.0125 mole) in benzene (10 ml.). The reaction mixture was heated at 50–60° for 4 hr. during which time a solid precipitated. Cooling and filtration gave the hydrochloride of the starting enamino ketone (2.8 g., 98%), m.p. and m.m.p. 228–230°. Evaporation of the filtrate gave crude IIIc (3.0 g., 70%), which recrystallized from ethanol as orange needles, m.p. 203–205°, λ_{max}^{EtOH} 300 mμ (ε 17,000). The compound showed no carbonyl absorption in the infrared spectrum below 6 μ; n.m.r. spectrum, τ 8.85 singlet, 8.08 multiplet, 7.75 singlet, 7.42 singlet, 6.75 multiplet, 1.95 quadruplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:4, respectively.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.71; H, 6.66; N, 7.97.

2-Pivalyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IV).—The enamino ketone I (3.9 g., 0.02 mole) and pivalyl chloride (2.5 g., 0.021 mole) in xylene (50 ml.) were heated under reflux for 4 hr. After cooling, the precipitated I hydrochloride (2.7 g., 0.0118 mole), m.p. 228–230°, not depressed in admixture with authentic material, was filtered. The filtrate was evaporated to dryness *in vacuo* and the residue chromatographed over alumina. Elution with benzene afforded crude IV (0.9 g., 30%), m.p. 138–142°. Recrystallization from chloroform–methylcyclohexane gave pure IV, m.p. 144–146°, as needles; λ_{max}^{EtOH} 305 mμ (ε 23,000); n.m.r. spectrum, τ 8.80 singlet, 8.72 singlet, 8.10 multiplet, 7.80 singlet, 7.58 singlet, 6.77 multiplet, no vinyl proton, with intensity ratios of 6:9:4:2:2:4, respectively.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.52; H, 10.00; N, 5.18.

2-(3,4-Dichlorobenzoyl)-5,5-dimethyl-3-N-morpolycyclohex-2-en-1-one (VI).—5,5-Dimethyl-3-N-morpholylcyclohex-2-en-1-one[1] (V, 4.2 g., 0.02 mole) and 3,4-dichlorobenzoyl chloride (2.1 g., 0.01 mole) in benzene (70 ml.) were heated under reflux for 3 hr. After cooling, the precipitated V hydrochloride (2.3 g., 98%), m.p. 234–236°, not depressed in admixture with authentic material,[1] was filtered. Evaporation of the filtrate gave a residue, which on recrystallization from chloroform–methylcyclohexane gave pure VI (2.0 g., 53%), m.p. 216–218°; λ_{max}^{EtOH} 302 mμ (ε 26,000), 255 (13,000).

Anal. Calcd. for $C_{19}H_{27}Cl_2NO_3$: C, 59.69; H, 5.54; N, 3.66; Cl, 18.55. Found: C, 59.29; H, 5.78; N, 3.58; Cl, 18.88.

Attempted Reaction of V with Acetyl Chloride.—The enamino ketone V (5.2 g., 0.025 mole) and acetyl chloride (1.0 g., 0.013 mole) in benzene (70 ml.) were heated under reflux for 2 hr. The precipitated V hydrochloride (3.1 g., 100%), m.p. 234–236°, not depressed in admixture with authentic material, was filtered after allowing the reaction mixture to cool. The filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized from benzene–methylcyclohexane to give V (2.0 g.), m.p. 127–128°, not depressed in admixture with authentic starting enamino ketone.

Attempted Reaction of V with Acetic Anhydride.—The enamino ketone V (2.1 g., 0.01 mole) in acetic anhydride (10 ml.) was heated under reflux for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was crystallized from benzene–methylcyclohexane to give starting material V, m.p. 126–128°, not depressed in admixture with an authentic sample.

2-(2-Nitrophenylthio)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (VII).—The enamino ketone I (1.95 g. 0.01 mole) and 2-nitrobenzenesulfenyl chloride (2.0 g., 0.0105 mole) in benzene (50 ml.) were heated at reflux temperature for 4 hr. After cooling, the precipitated solid (consisting of the product and I hydrochloride, 3.1 g.) was filtered. Recrystallization from aqueous methanol gave VII as orange needles (1.6 g., 92%), m.p. 176–178°; λ_{max}^{EtOH} 242 mμ (ε 11,500), 306 (19,500); n.m.r. spectrum, τ 8.85 singlet, 8.17 multiplet, 7.62 singlet, 7.47 singlet, 6.30 multiplet, 2.75 multiplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:4, respectively.

Anal. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09; S, 9.26. Found: C, 62.13; H, 6.34; N, 7.81; S, 9.09.

Treatment of a methanolic solution of VII with 70% perchloric acid gave a crystalline perchlorate as yellow needles, m.p. 212° dec.; λ_{max}^{EtOH} 242 mμ (ε 16,000), 309 (22,000).

Anal. Calcd. for $C_{18}H_{23}ClN_2O_7S$: C, 48.37; H, 5.19; N, 6.27; Cl, 7.93; S, 7.17. Found: C, 48.26; H, 5.16; N, 6.13; Cl, 7.81; S, 7.23.

Acknowledgment.—Our sincere thanks are due to Professor N. J. Leonard for many helpful and stimulating discussions.

Enamine Chemistry. IV. Cycloaddition Reactions of Enamines Derived from Aldehydes and Acyclic Ketones[1,2]

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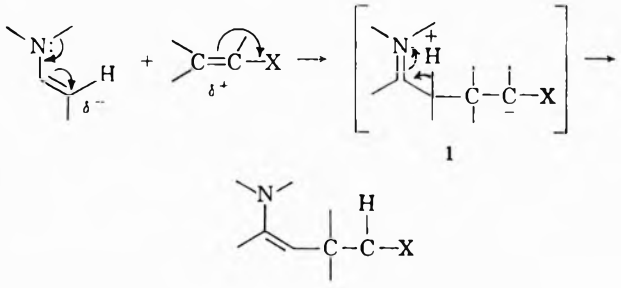
A variety of enamines, both with and without β-hydrogens, react with electrophilic olefins to give cyclobutane derivatives. This reaction is quite sensitive to steric effects, and its scope is discussed. Some further transformations of the cyclobutanes also are discussed.

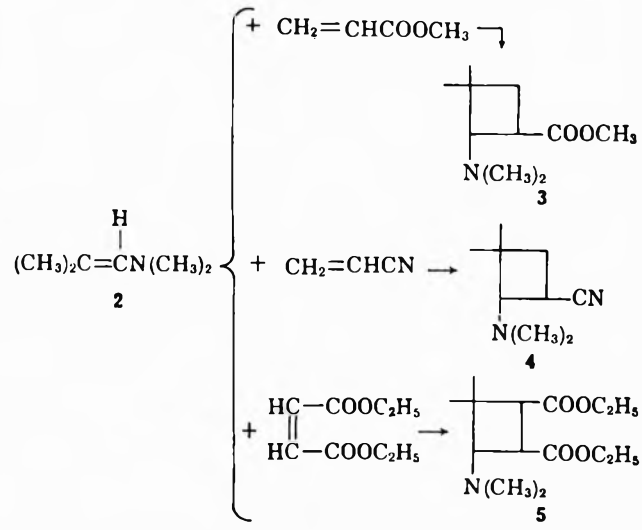
Since the work of Stork and his co-workers first appeared,[3] enamines have found increasingly important uses in organic syntheses. The Stork alkylation of enamines by electrophilic olefins depends on the presence of a β-hydrogen in the enamine. Thus, the transfer



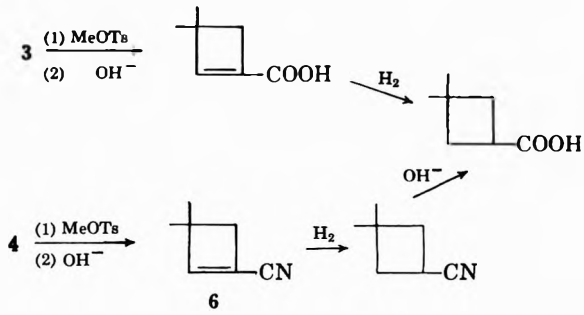
of the proton (which was originally the β-hydrogen of the enamine) in the zwitterionic intermediate (1) leads to its stabilization and to the products obtained by Stork. Our original purpose in the work described in this paper was to determine what course the reaction of electrophilic olefins with enamines containing no β-hydrogens would take. We found that reaction did indeed occur, leading to the formation of cyclobutanes, presumably *via* the collapse of a zwitterionic intermediate similar to **1**. We later found that the absence of β-hydrogens was not essential for cycloaddition to occur within certain limitations as to choice of reactants and conditions. The present paper deals with cycloaddition reactions of enamines derived from a variety of aldehydes and one acyclic ketone.

Cycloadditions of Enamines without β-Hydrogens.—We chose as a model compound the first of the series of enamines having no β-hydrogens: N,N-dimethylisobutenylamine (**2**), derived from isobutyraldehyde and dimethylamine. Compound **2** was found to react with methyl acrylate to give the cyclobutane **3** in 75% yield on heating the reactants for 2 hr. at 170° in an autoclave or, better, in 91% yield by refluxing for 2 hr. at 85° in acetonitrile.

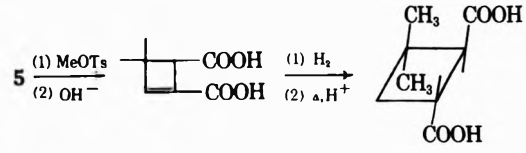
Similarly, **4** is obtained from **2** and acrylonitrile in 64% yield after 2 hr. at 170°, and **5** is obtained from **2** and diethyl maleate (or fumarate, since the maleate is rapidly converted to fumarate in the presence of the enamine) in 70% yield after 20 hr. at reflux, beginning at 110° and ending at 170°.[4]



The structures of **3** and **4** were confirmed by their conversion to 3,3-dimethylcyclobutanecarboxylic acid, as shown schematically.[5]



The structure of adduct **5** was confirmed by its conversion to *trans*-norcaryophyllenic acid.



(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) A preliminary announcement of this work has been made: K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(3) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954). For a more complete review, see G. Stork, H. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(4) Similar reactions between diethyl maleate and enamines with no β-hydrogens were reported by A. G. Cook, doctoral dissertation, University of Illinois, 1959.

(5) While the unsaturated nitrile **6** can be distilled readily under reduced pressure, attempted distillation at atmospheric pressure leads to a vigorous, exothermic reaction in which the Diels–Alder dimer of the ring-opened product is obtained. Caution should be used when subjecting compounds similar to **6** to elevated temperatures.

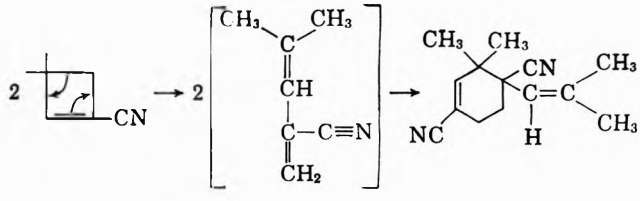
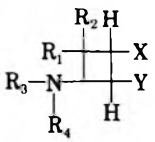
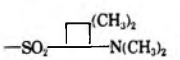
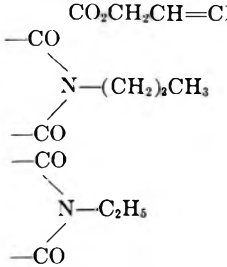


TABLE I

CYCLOBUTANES PREPARED FROM ENAMINES HAVING NO β-HYDROGEN ATOMS

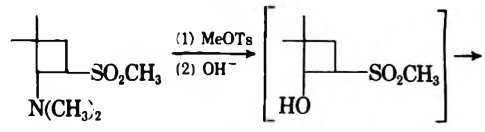


R_1	R_2	R_3	R_4	X	Y	B.p. °C.	B.p. mm.	M.p., °C.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Found C	Found H
CH_3	CH_3	$(CH_2)_5$		H	CN	73–77	1–2		1.4775	62	F	75.0	10.4	75.3	10.5
CH_3	CH_3	CH_3	CH_3	H	CN	44–45	0.5–1		1.4531	64	F	71.0	10.6	70.9	10.6
CH_3	CH_3	$(CH_2)_5$		H	CO_2CH_3	91–92	2		1.4705	72	F	69.3	10.3	69.4	10.5
CH_3	CH_3	CH_3	CH_3	H	$CO_2CH(CH_3)_2$	62–70	2		1.4418	51	F	68.7	11.1	68.7	11.3
CH_3	CH_3	C_2H_5	C_2H_5	H	$CO_2C_2H_5$	56–65	<1		1.4453	30	F	68.7	11.1	68.3	11.5
C_6H_5	C_2H_5	$(CH_2)_5$		H	CO_2CH_3	119–121	2		1.4788	20	F	71.0	10.7	71.1	10.7
CH_3	CH_3	$CH_2CH_2OCH_2CH_2$		H	CO_2CH_3	99–102	2.2		1.4711	35	F	63.5	9.3	63.4	9.2
CH_3	CH_3	*b*		H	CO_2CH_3			148		22	F	65.5	9.4	65.4	9.4
$(CH_2)_5$		$(CH_2)_5$		H	CO_2CH_3	115–120	1.5		1.4963	63	F	72.4	10.3	72.2	10.3
CH_3	CH_3	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	H	CO_2CH_3	98–110	1.5		1.4543	18	F	71.3	11.6	71.8	11.7
CH_3	CH_3	CH_3	$C_6H_5CH_2$	H	CO_2CH_3	96–105	1.5		1.5062	49	F	73.5	8.9	73.3	8.9
CH_3	CH_3	$(CH_2)_5$		$CO_2C_2H_5$	$CO_2C_2H_5$	113–120	1		1.4660	51	F	65.6	9.4	65.4	9.1
CH_3	CH_3	$(CH_2)_5$		C_6H_5	NO_2			71–73		68	E	70.8	8.4	70.6	8.5
CH_3	CH_3	CH_3	CH_3	C_6H_5	NO_2			90–92		94	E	67.7	8.1	67.9	8.3
CH_3	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	C_6H_5	NO_2			95–96.5		50	E	78.0	7.1	77.9	7.2
CH_3	CH_3	CH_3	CH_3	H	SO_2CH_3	100–103	0.5–0.6			91	F	52.7	9.3	52.2	9.2
CH_3	CH_3	CH_3	CH_3	CN	CN	99–100	0.75		1.4705	73	E	67.8	8.5	67.7	8.5
CH_3	CH_3	CH_3	CH_3	H				80–85		85	E	60.6	10.0	60.7	10.0
CH_3	CH_3	CH_3	CH_3	H	$CO_2CH_2CH{=}CH_2$	55.5–58	*ca.* 0.2		1.4528	75	F	68.3	10.0	67.9	10.0
CH_3	CH_3	CH_3	CH_3			110–120	*ca.* 0.5		1.4828	51	E	66.6	9.6	66.7	9.6
CH_3	CH_3	CH_3	CH_2			96–103	*ca.* 0.5		1.4853	53	E	64.2	9.0	63.9	8.6

$(CH_2)_5$	CH_3	H	CO_2CH_3	75–80	*ca.* 0.5	1.4765	83	F	68.9	10.3	69.2	10.0
CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$	H	CO_2CH_3	111–116	0.7–0.69	1.4904	*ca.* 75–80	F	72.4	10.3	72.1	10.4
CH_3	CH_3	H	CO_2CH_3	79–84	0.3–0.5		75	F	70.3	10.5	70.4	10.4
CH_3	C_6H_5	H	CO_2CH_3	102–108	0.3	1.5194	33	F	73.0	8.5	72.7	8.7
	$(CH_2)_5$	$CO_2C_2H_5$	$CO_2C_2H_5$	116–125	0.5	1.4753	71	F	65.6	9.4	65.9	9.4
CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	148–154	0.4–0.65	1.4830	72	F	68.3	9.5	68.1	9.4
CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$	$CO_2C_2H_5$	$CO_2C_2H_5$	120–125	0.5	1.4698	30	F	62.5	9.3	62.1	9.2
CH_3	$CH_2CH_2N(CH_3)CH_2CH_2$	H	CN	94	0.7		72	G	68.0	9.3	68.2	9.4
CH_3	$CH_2CH_2OCH_2CH_2$	$CH(CH_3)_2$	NO_2				74	E	61.6	10.3	61.7	10.3
CH_3	CH_3	H	CO_2CH_3	123–126	0.3	1.4960	68	G	68.6	10.1	68.9	10.3
CH_3	$CH_2N(CH_2)_4$	H	CO_2CH_3	60–61	0.3	1.4519	69	G	67.7	10.8	68.2	10.8
CH_3	$CH_3(CH_2)_2$	H	CO_2CH_3	45–47	0.3–0.4	1.4551	45	G	68.3	10.0	68.1	10.1
CH_3	CH_3	H	CO_2CH_3	120–123	0.1	1.5041	74	G	74.7	9.4	74.9	9.6
CH_3	CH_3	H	CO_2CH_3									
CH_3	CH_3	$CH_2=CHCH_2$	CO_2CH_3	92	7×10^{-6}[a]	1.4920	41	F	69.8	8.6	69.6	8.6
CH_3	CH_3	$C_6H_5CH_2CH(CH_3)$	$CO_2C_2H_5$	89–96	10^{-4}[a]	1.4979	45	G	70.4	8.9	70.2	8.6
CH_3	CH_3	$C_6H_5CH_2CH_2$	$CO_2C_2H_5$	93–96	*ca.* 0.1	1.4589	77	G	64.7	9.2	64.2	9.1
CH_3	CH_3	$C_6H_5CH_2CH(CH_3)$	$CO_2C_2H_5$	92	9×10^{-5}[a]	1.4848		G	65.6	9.4	65.3	9.4
CH_3	CH_3	$CH_2=CHCH_2$	$CO_2C_2H_5$	103–107	0.3	1.4559	44	F	64.2	9.8	64.1	9.8
CH_3	$CH_2N(CH_2)_4$	$(CH_2)_4$	$CO_2C_2H_5$									
CH_3	$CH_3(CH_2)_2$	CH_3	$CO_2C_2H_5$									

[a] Compound had to be molecularly distilled. [b] $(CH_2)_2$ $COOCH_3$ $-CH_2CH_2NCH_2CH_2$

Compound **2** reacted with methyl vinyl sulfone to give adduct **7** in 91% yield after 1.5 hr. at reflux, beginning at 90° and ending at 160°. Quaternization of **7** and treatment with base led to aldehyde **9**, presumably through dealdolization of **8**. Compound **9** was inde-



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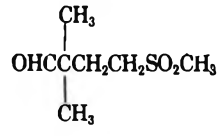
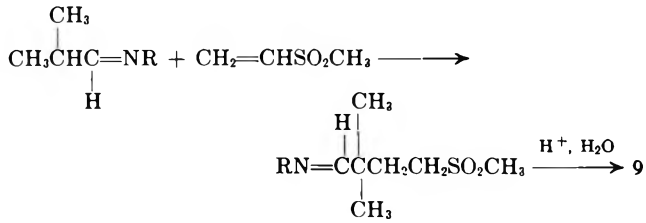
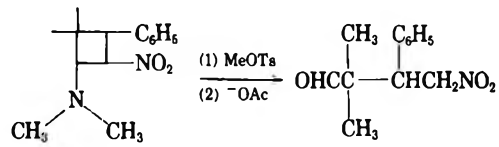


9

pendently prepared by the reaction of methyl vinyl sulfone with a Schiff base of isobutyraldehyde, followed by hydrolysis.



Compound **2** reacted vigorously with β-nitrostyrene to give adduct **10** in 94% yield. Quaternization of



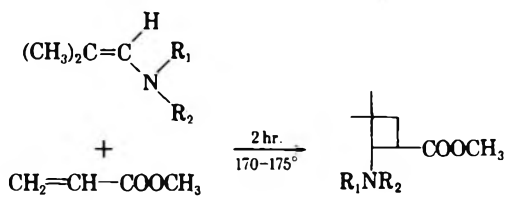
10

10 and treatment with a weak base, such as sodium acetate or bicarbonate, gave the ring-opened aldehyde in poor yield. A number of other adducts from enamines containing no β-hydrogens are listed in Table I.

Scope of the Reaction.—The effect of structure change in either the aldehyde or secondary amine from which the enamine is prepared is similar. Table II

Table II

Effect of Amine Moiety on Yield of Cyclobutane



R_1	R_2	Yield %
CH_2	CH_3	75
CH_3	—C=C—C—	45
C_2H_5	C_2H_5	30[a]
C_4H_9	C_4H_9	18
CH_3	$C_6H_5CH_2$	49
$R_1 + R_2$ =	$(CH_2)_5$	72
$R_1 + R_2$ =	$CH_2CH[CH_2CH_2]_2CHCH_2$	75
$R_1 + R_2$ =	$CH_2CH_2OCH_2CH_2$	35

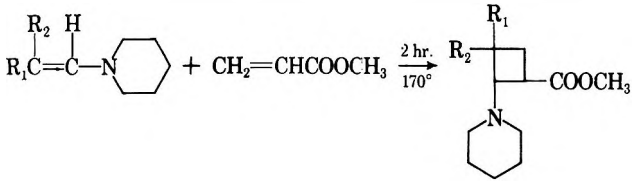
[a] Ethyl acrylate was used instead of methyl acrylate.

shows the yield of cyclobutane obtained from a series of isobutyraldehyde enamines and methyl acrylate under comparable reaction conditions, that is, 2 hr. at 170–175°. The yield falls off rapidly with increasing chain length of the aminoalkyl groups as shown for the first three adducts. The fifth enamine, from benzylmethylamine, is intermediate in reactivity, while the sixth and seventh, from piperidine and azabicyclononane, are comparable to the dimethyl enamine. Finally, the morpholine enamine is considerably less reactive in these cycloaddition reactions.

The effect of the structure of the aldehyde is illustrated in Table III for a series of piperidine enamines. As shown, the yield of adduct drops sharply on going from isobutyraldehyde to 2-ethylbutyraldehyde but rises again when the groups are tied into a ring as with cyclohexanecarboxaldehyde.

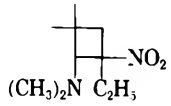
TABLE III

EFFECT OF ALDEHYDE MOIETY ON YIELD OF CYCLOBUTANE



R_1	R_2	Yield %
CH_3	CH_3	72
C_2H_5	C_2H_5	30
$R_1 + R_2$ =	$(CH_2)_6$	63

The effect of the structure of the electrophilic olefin on the cycloaddition reaction is indicated by the following observations. In the reactions involving α,β-unsaturated esters and nitriles, we have never isolated any cyclobutanes from methyl methacrylate, methyl crotonate, methyl cinnamate, or the corresponding nitriles. The reaction is, therefore, highly sensitive to steric effects, which can be overcome by using a more powerful electron-withdrawing group to activate the olefin. Typical of such groups is the nitro group, as in β-nitrostyrene or 2-nitro-1-butene. Like β-nitrostyrene, the latter reacts exothermically with **2** to give an excellent yield of the adduct **11**. This adduct, however, is

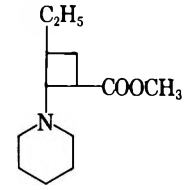


11

extremely sensitive to moisture, a property which appears to be characteristic of cyclobutanes which are derived from similar α-substituted electrophilic olefins. The reaction of **11** with water leads to the loss of dimethylamine and to ring opening, as will be discussed later.

Cycloadditions of β-Hydrogen-Containing Enamines.—We were surprised to find that β-hydrogen-containing enamines derived from aldehydes or the only acyclic ketone studied, 3-pentanone, also undergo cycloaddition reactions. In general, the reaction is carried out under milder conditions than those involving enamines containing no β-hydrogens because of the decreased stability of both the enamines and the cyclobutanes.

For example, the piperidine enamine of butyraldehyde gave, with methyl acrylate, the cyclobutane **12** in 83% yield when the reaction was carried out in acetonitrile for 2 days at room temperature, in 82% yield after 3 hr. of refluxing in acetonitrile, and in 57% yield after standing for 1 day in methanol[6] at room temperature.



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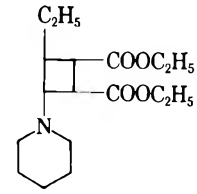
The butyraldehyde piperidine enamine reacted with diethyl maleate to give adduct **14** in 45% yield after standing for 1 day at room temperature in acetonitrile.



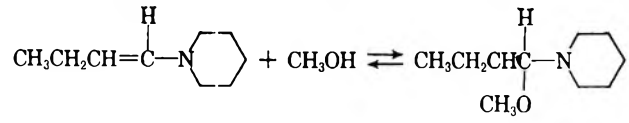
14

The cycloaddition products derived from the 3-pentanone enamine were perhaps the least stable thermally of any studied. Most of the β-hydrogen enamine adducts begin to dissociate at temperatures roughly in the range of 125–170°, depending on the structure, to the reactants from which they were prepared. Generally, if the reactants are not removed as formed, recombination can occur to give the products derived from the Stork-alkylation reaction. It is, therefore, sometimes necessary to resort to molecular distillation for purification, and sometimes the crude products must be used for further transformations.

The structure proofs of the β-hydrogen enamine adducts were analogous to those used for the no β-hydrogen enamine adducts, though the detailed experimental procedures were frequently different (see Experimental). Table IV lists some typical examples of cyclobutanes prepared from β-hydrogen enamines.

Mechanism of the Reaction.—Little can be said about the detailed mechanism of these cycloaddition reactions, but the following observations are pertinent. Enamines give with diethyl maleate (or fumarate) an orange-red color which fades considerably on completion of the cycloaddition reaction.[7] With the more reactive nitro olefins and acetylenic esters,[8] intense red

(6) As a point of interest, the piperidine enamine of butyraldehyde reacts exothermically with methanol to give the butyraldehyde O,N-acetal (**13**), which can be distilled at low pressure and temperature. The reaction is obviously reversible, however. The isobutyraldehyde enamine (**2**) did not



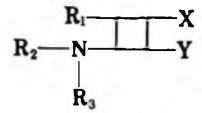
13

react spontaneously with methanol but did react on the addition of a trace of acid.

(7) This also was observed by A. G. Cook, ref. 4.

(8) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

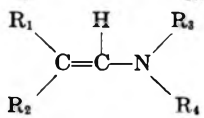
Table IV.—Cyclobutanes Prepared from Enamines Having a β-Hydrogen Atom



R_1	R_2	R_3	X	Y	B.p. °C.	B.p. mm.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5		$(CH_2)_5$	H	CO_2CH_3	87–89	0.5	1.4734	82	A	69.3	10.3		69.6	10.3	
CH_3		$(CH_2)_5$	H	CO_2CH_3	70–75	0.5	1.4741	67	A			6.6			6.6
C_2H_5	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	95–98	0.8	1.4482	78	B			4.9			5.2
CH_3	CH_3	CH_3	H	CO_2CH_3	55–58	3.0–3.5	1.4437	32	A	63.1	10.0		63.1	10.0	
C_2H_5	CH_3	CH_3	H	CO_2CH_3	52–53	1	1.4454	87	A			7.6			7.6
$(CH_3)_2NCH_2$	CH_3	CH_3	H	CO_2CH_3	78–82	0.75	1.4592	55	B	61.6	10.3		61.7	10.2	
C_5H_{11}	$CH_2CH_2OCH_2CH_2$		H	CO_2CH_3	125–130	1	1.4725	70	A			5.2			5.3
CH_3	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	86–87	0.5	1.4463	30	B	60.7	9.0		60 6	9.2	
C_2H_5		$(CH_2)_5$	$CO_2C_2H_5$	$CO_2C_2H_5$	69–70	10^{-4}[a]	1.4686	45	B			4.5			4.4
$(CH_3)_2NCH_2$	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	42–50	$(6 \times 10^{-6}$–$12 \times 10^{-6})$[a]	1.4562	33	B	60.0	9.4		59.9	9.2	
C_6H_5	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	78–80	10^{-6}[a]	1.5015	32	B	67.8	7.9		68.0	7.9	
C_2H_5		$(CH_2)_5$	H	CN	85–90	*ca.* 0.5	1.4830	53	B	74.9	10.5		74.8	10.4	
C_5H_{11}		$(CH_2)_4$	H	CN	116–120	*ca.* 0.5	1.4783	33	A	76.4	11.0		75.8	11.1	
CH_3		$(CH_2)_5$	H	SO_2CH_3	127–130	0.5	1.4954	57	A			6.6			6.1
$(CH_3)_2N$	CH_3	CH_3	H	CO_2CH_3	63–67	0.3–0.4	1.4586	40	A	60.0	10.0		59.8	10.0	
$CH_2N(CH_2)_5$		$(CH_2)_5$	H	CO_2CH_3	57	8×10^{-6}[a]	1.4990	39	B	69.3	10.3		69.2	10.3	
$CH_2N(CH_2)_5$		$(CH_2)_5$	$CO_2C_2H_5$	$CO_2C_2H_5$	66	6×10^{-6}[a]	1.4857	33	B	66.4	9.9		66.7	9.6	

[a] Compound had to be molecularly distilled.

Table V.—New Enamines Prepared in This Investigation

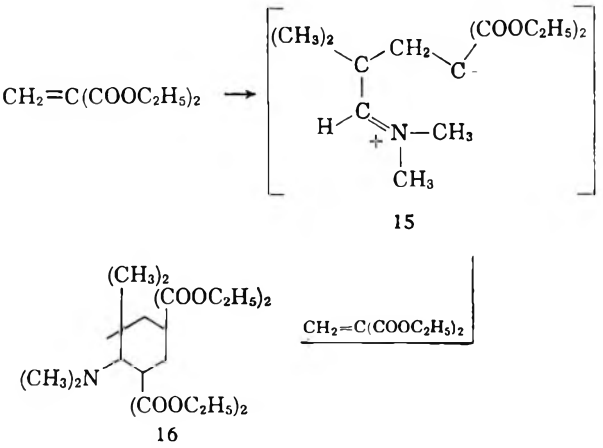


R_1	R_2	R_3	R_4	B.p. °C.	B.p. mm.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	CH_3	CH_3	40–45	200	1.4293	46	B			16.4			16.3
$(CH_2)_5$		CH_3	CH_3	171–172.5	atm.	1.4747	30	A	77.7	12.3		77.2	12.2	
CH_3	C_6H_5	CH_3	CH_3	51–53	0.2		66	A			8.7			8.5
CH_3	$CH_3CH_2CH_2$	CH_3	CH_3	134–136	atm.	1.4332	54	A			11.0			10.5
CH_3	CH_3	C_4H_9	C_4H_9	72	4.5–5.0	1.4409	63	C	78.6	13.7		78.4	13.7	
CH_3	CH_3	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	64	5.8	1.4375	57	C	78.7	13.7		78.5	14.1	
CH_3	CH_3	CH_3	$C_6H_5CH_2$	45	*ca.* 0.5	1.5145	80	C	82.3	9.8		82.3	10.0	
CH_3	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	110–114	0.8	1.5591	28	C	85.9	8.4		85.5	8.4	
CH_3	CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$		70–74	1.3–2.0	1.5008	85	C	80.5	11.7		80.4	11.8	
CH_3	CH_3	$CH_2N(CH_2)_5$		38–40	1	1.4718	82	C	70.2	11.8		70.6	11.6	
$(CH_2)_5$		$(CH_2)_5$		75–88	1.5–3.0	1.5042	85	C	80.3	11.8		80.2	12.1	
C_2H_5	C_2H_5	$(CH_2)_4$		92–97	26–31	1.4773	78	C	78.3	12.5		78.0	12.4	
CH_3	CH_3	$(CH_2)_6$		106–108	48–50	1.4823	67	C			9.1			8.9
CH_3	$CH_2N(CH_2)_4$	$(CH_2)_4$		91	0.2	1.5076	50	D	74.3	11.3		73.8	11.9	
CH_3	CH_3	CH_3	$C_6H_5CH_2CH(CH_3)$	61–64	0.1–0.2	1.5099	94	C	82.8	9.9		83.0	9.9	
CH_3	CH_3	CH_3	$C_6H_5CH_2CH_2$	61–65	0.6	1.5063	88	C	82.4	10.1		82.8	10.0	

colors of a highly transient nature are observed on admixture with enamines. These colored materials may be charge-transfer complexes, but no further study has been given to them.

Based on our qualitative observations, the enamine cycloadditions are much more polar in nature than the usual Diels–Alder reaction, since they occur at a remarkably faster rate in polar solvents such as acetonitrile.[9]

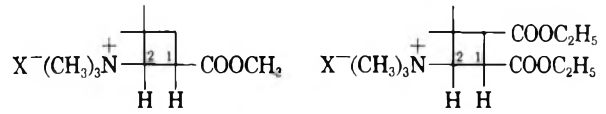
The polar nature of the intermediate is further illustrated by the fact that 2 (and related enamines) reacts with diethyl methylenemalonate to give the adduct **16** derived from 2 moles of ester and 1 mole of enamine, even when the enamine is used in excess.



Thus, when the anionic center of the intermediate **15** is sufficiently stabilized (as in this malonate anion) and the electrophilic olefin is sufficiently free of steric hinderance (as with a terminal methylene group), intermediate **15** may react with another mole of electrophilic olefin rather than collapse to form the cyclobutane.[10]

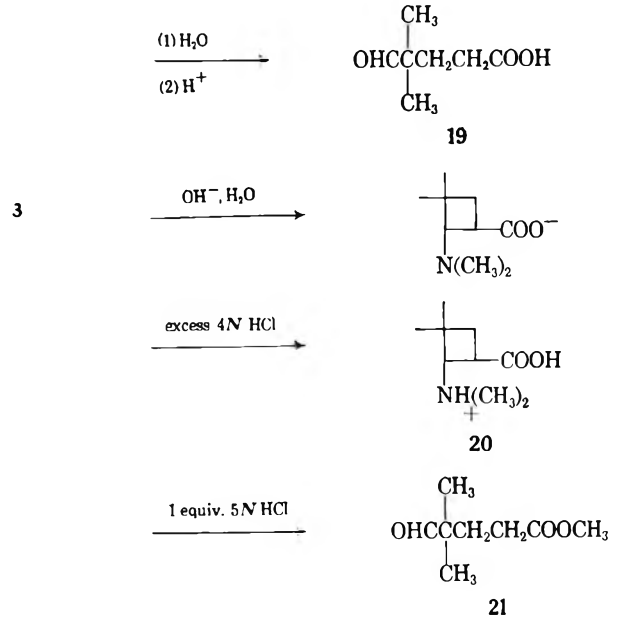
Stereochemistry of the Cyclobutanes.—As with the mechanism of the reaction, little can be said about the stereochemistry of the adducts. We did not observe any isomers of those adducts which are solids. Gas–liquid chromatography (g.l.c.) of adducts **3** and **5** did show the presence of *ca.* 5% of a second component in each adduct. This minor component also was found by g.l.c. to be less stable thermally than the major component and could be cracked almost preferentially to the reactants from which it was derived by raising the temperature of the vaporization chamber of the chromatography unit. The adducts corresponding to **3** and **5** but containing a piperidino group in place of the dimethylamino group showed a similar behavior, but with somewhat more of the less stable component. Whether these less stable isomers were formed in the original cycloaddition or arose by subsequent epimerization is not known.

The ease of elimination of trimethylamine from the quaternary salts of **3** and **5** led us to suspect that the hydrogen at C-1 is *trans* to the amine function at C-2.



Further evidence for this configuration was provided by treatment of **3** and **5** with hydrogen peroxide to prepare the amine oxides. If the hydrogen at C-1 were *cis* to the amine group, Cope elimination should occur quite readily. In both compounds, amine oxide formation took place along with a facile hydrolysis of the adjacent ester function, presumably with anchimeric assistance by the amine oxide. The resulting products (**17** and **18**) were quite stable.[11]

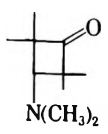
Some Reactions of the Cyclobutane Adducts.—Adduct **3** was found to undergo some remarkable ring-opening reactions. On refluxing with water, it gradually went into solution. Acidification then gave dimethylglutaraldehydic acid (**19**). Saponification with aqueous base apparently took place normally without ring opening, since acidification gave no insoluble material. Treatment of **3** with excess 4 *N* hydrochloric



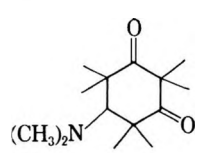
acid gave the amino acid hydrochloride (**20**),[12] while the use of an equivalent of 5 *N* hydrochloric acid gave the methyl ester of dimethylglutaraldehydic acid (**21**).

(9) For a similar observation involving cycloaddition reactions of tetracyanoethylene, see C. A. Stewart, Jr., *J. Am. Chem. Soc.*, **84**, 117 (1962). Unfortunately, nitromethane is not a good solvent for enamine reactions since it reacts with enamines.

(10) A borderline case is that reported by R. H. Hasek and J. C. Martin [*J. Org. Chem.*, **28**, 1468 (1963)] in which **2** reacts in nonpolar solvents with dimethyl ketene to give the cyclobutane, but in polar solvents such as acetonitrile to give the cyclobutane and some 2:1 adduct.



Cyclobutane



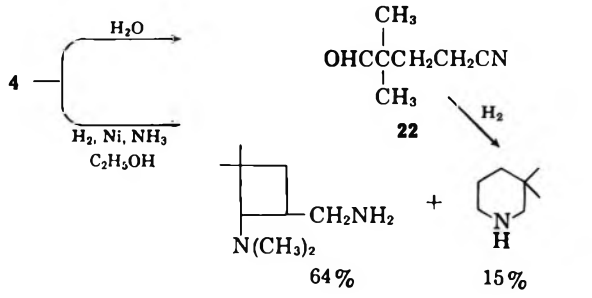
2:1 Adduct

(11) These experiments involving amine oxides were carried out by J. G. Thweatt and H. E. Davis.

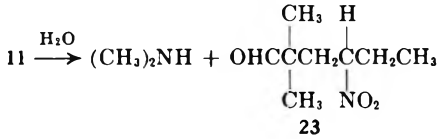
(12) We are indebted to Leonard Weintraub, of the Bristol-Myers Products Division, for disclosing this procedure to us.

With cyclobutanes derived from β-hydrogen enamines, ring-opening reactions analogous to the last one described would lead to the same products as those obtained by the usual Stork-alkylation procedure. This ring opening is not general, however, since adduct **5** does not undergo ring opening on heating with water or dilute acid.

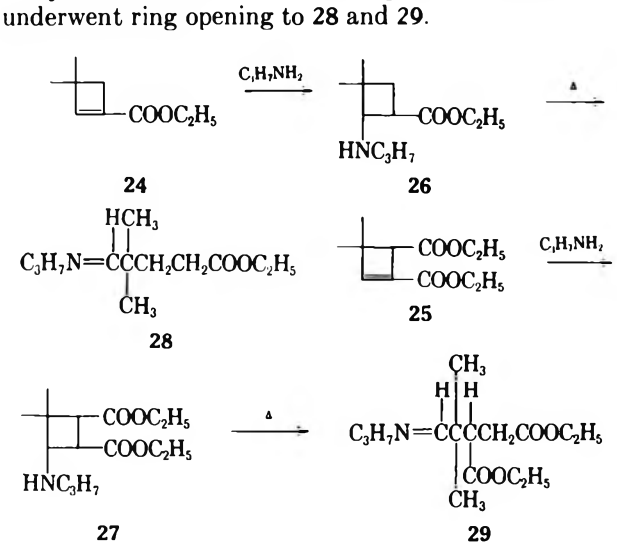
Adduct **4** also undergoes a hydrolytic ring opening to give the aldehydonitrile (**22**), while its hydrogenation over Raney nickel in alcohol and in the presence of anhydrous ammonia gives the expected amine along with some 3,3-dimethylpiperidine, which also is obtained by hydrogenation of **22**.



As mentioned previously, adduct **11** reacted so rapidly with moisture that it could not be purified for analysis. Exposure to air led to the loss of dimethylamine and the ring-opened aldehyde (**23**) was isolated as its 2,4-dinitrophenylhydrazone.



The cyclobutene esters (**24** and **25**) were both found to add primary amines (for example, propylamine) to give the unstable cyclobutanes **26** and **27**, respectively. Compounds **26** and **27** could be trapped as their stable acetyl derivatives, but on attempted distillation they underwent ring opening to **28** and **29**.



Products analogous to **28** and **29** were obtained by heating isobutyraldehyde Schiff bases with methyl acrylate and diethyl maleate, respectively. Although no enamine tautomer could be detected in these Schiff bases by n.m.r. spectroscopy, it is still interesting to consider the admittedly remote possibility that the Schiff bases react with the electrophilic olefins *via* cycloaddition of their enamine tautomers, followed by ring opening. A more plausible explanation, however, is the simple self-catalyzed Michael addition of the Schiff base to the unsaturated esters.

A number of derivatives of the cyclobutane adducts, which were prepared by standard methods and need not be discussed here, are described in the Experimental section.

Enamines.—The enamines used in this investigation are listed in Table V, and representative examples of their preparation are described in the Experimental section. It is of interest to note that 3,3-dimethylcyclobutanecarboxaldehyde reacted normally with piperidine to give the enamine, but cyclopropanecarboxaldehyde and piperidine gave the stable, distillable aminal, or N,N-acetal.[13]

Experimental[14]

Materials.—The following enamines were prepared by methods described in the literature: N,N-dimethyl-1-butenylamine,[15] 1-ethyl-N,N-dimethylpropenylamine,[16] N,N-dimethylstyrylamine,[17] N,N,N′,N′-tetramethyl-1-propene-1,3-diamine and 1,1′-propenylenedipiperidine,[18] 1-propenylpiperidine, 1-(1-butenyl)-piperidine,[19] 1-(1-heptenyl)morpholine,[20] 1-(1-heptenyl)pyrrolidine,[21] N-allyl-N-methylisobutenylamine,[22] N,N-dimethylisobutenylamine,[2] N,N-diethylisobutenylamine and 1-(2-ethyl-1-butenyl)piperidine,[23] 4-isobutenylmorpholine and N,N′-diisobutenylpiperazine,[24] and 1-isobutenylpiperidine.[19]

Table V contains a list of new enamines prepared during this investigation. Four different methods were employed; they are listed below with representative enamines prepared by the method.

Method A.—This method is the same as that previously described for the preparation of N,N-dimethylisobutenylamine.[22]

Method B.—N,N-Dimethylpropenylamine was prepared by adding propionaldehyde (191 g., 3.3 moles) over a 1.25-hr. period to a mixture of anhydrous dimethylamine (300 g., 6.6 moles), ether (250 ml.), and Linde No. 13X Molecular Sieve (300 g.), which had been cooled to −5°. During the addition, the mixture was stirred and its temperature was maintained at 0 ± 5°. The mixture was allowed to stand in a cold bath overnight and then was filtered. Distillation of the filtrate gave 130 g. (46%) of N,N-dimethylpropenylamine, b.p. 40–45° at 200 mm., $n^{20}D$ 1.4293.

Anal. Calcd. for $C_5H_{11}N$: N, 16.4. Found: N, 16.3.

Method C.—The method of Benzing[24] was used. It consists of refluxing a secondary amine with a slight excess of the appropriate aldehyde under a Dean–Stark trap and then recovering the enamine by distillation.

Method D.[25]—An ether solution of acrolein was treated with an excess of the secondary amine in the presence of potassium carbonate, and the enamine was recovered by distillation.

Cycloadditions of Enamines Containing No β-Hydrogen Atom.—A number of cyclobutanes were prepared from various electro-

(13) A similar observation has been made by Dr. Glenn A. Berchtold (private communication).

(14) Melting points were determined using a calibrated Fisher-Johns melting point apparatus. N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane. All structure assignments were supported by infrared and n.m.r. spectra. Spectral data for specific compounds are included when pertinent.

(15) S. Hünig, K. Hübner, and E. Benzing, *Ber.*, **95**, 92c (1962).

(16) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(17) J. W. Crary, Ph.D. thesis, Emory University, 1955.

(18) C. Mannich, K. Handke, and K. Roth, *Ber.*, **69**, 2112 (1936).

(19) C. Mannich and H. Davidsen, *ibid.*, **69**, 2106 (1936).

(20) P. L. de Benneville and J. H. Macartney, *J. Am. Chem. Soc.*, **72**, 3073 (1950).

(21) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

(22) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).

(23) G. Opitz, H. Hellmann, and H. W. Schubert, *Ann.*, **623**, 112 (1959).

(24) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(25) C. Mannich and H. Davidsen, *Ber.*, **69**, 2112 (1936).

philic olefins and isobutyraldehyde-type enamines, that is, enamines having no hydrogen atom in the β-position. These cyclobutanes are listed in Table I. The more reactive electrophilic olefins reacted spontaneously with enamines to form cyclobutanes (method E), whereas the less reactive ones required heating to effect cycloaddition. The heating was done without a solvent (method F) at atmospheric pressure or in an autoclave (depending upon the nature of the starting materials) or by refluxing the reactants in the polar solvent acetonitrile (method G) at atmospheric pressure. An example of each is given below.

Method E. 3-Dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarbonitrile.—To fumaronitrile (51 g., 0.65 mole) was added N,N-dimethylisobutenylamine (70 g., 0.71 mole). The temperature of the mixture rose to a maximum of 86° after standing for 45 min. with intermittent swirling. The mixture was heated to 150° over 10 min. and then allowed to stand at room temperature overnight. Distillation through a 6-in. Vigreux column gave a small forerun followed by 84 g. (73%) of 3-dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarbonitrile, b.p. 99–100° at 0.75 mm., $n^{20}D$ 1.4705. On standing, the material crystallized. Recrystallization from hexane gave a solid, m.p. 64–66°.

Anal. Calcd. for $C_{10}H_{15}N_3$: C, 67.8; H, 8.5. Found: C, 67.7; H, 8.5.

Method F. Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate (3).—A mixture of N,N-dimethylisobutenylamine and methyl acrylate was heated for 2 hr. at 170°. Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate, b.p. 49–50° at 1.5 mm., $n^{20}D$ 1.4448, was obtained in 75% yield.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.4; N, 7.6. Found: C, 64.7; H, 10.4; N, 7.5.

Method G. Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate (3).—A mixture of methyl acrylate (129 g., 1.5 moles), N,N-dimethylisobutenylamine (50 g., 0.5 mole), and acetonitrile (200 ml.) was refluxed for 9 hr. An infrared spectrum of the mixture, after 4.5 hr., showed no absorption bands in the >C=C—N= region (6–6.2 μ). The mixture was distilled to give 84 g. (91%) of methyl 3,3-dimethyl-2-dimethylaminocyclobutane-1-carboxylate, b.p. 35–39° at 0.5–1 mm., $n^{20}D$ 1.4438.

Methyl 3,3-Dimethyl-2-piperidinocyclobutanecarboxylate.—A mixture of 1-isobutenylpiperidine (208.5 g., 1.5 moles) and methyl acrylate (158 g., 1.87 moles) containing some hydroquinone was heated in an autoclave for 2 hr. at 175°. Distillation of the reaction product gave 244 g. (72%) of crude methyl 3,3-dimethyl-2-piperidinocyclobutanecarboxylate, b.p. 91–92° at 2 mm. A sample for analysis was obtained by redistillation and had b.p. 103° at 3.6 mm., $n^{20}D$ 1.4705.

Anal. Calcd. for $C_{13}H_{22}NO_2$: C, 69.3; H, 10.3; N, 6.2. Found: C, 69.4; H, 10.5; N, 6.2.

3,3-Dimethyl-1-cyclobutene-1-carboxylic Acid.—Methyl 3,3-dimethyl-2-piperidinocyclobutanecarboxylate (45 g., 0.2 mole) and methyl *p*-toluenesulfonate (40.9 g., 0.22 mole) were combined and heated on the steam bath for 7 hr. and then allowed to stand for 16 hr. at room temperature. A solution of potassium hydroxide (44.8 g.) in water (50 ml.) was added to the solid salt, and the mixture was stirred for 30 min. while being heated on the steam bath. The mixture was cooled, extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. Evaporation of the ether extracts on the steam bath left 20.5 g. (81%) of crude 3,3-dimethyl-1-cyclobutene-1-carboxylic acid, which crystallized on cooling. The crude material was recrystallized from hexane (with Norit treatment) by cooling the hexane solution in a Dry Ice–acetone bath to give 16 g. (63.5%) of the acid, m.p. 70–71°. A sample for analysis, recrystallized from pentane, melted at 71.5–72.5°, lit.[26] m.p. 54–55°.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.4; H, 8.0.

Hydrogenation of the unsaturated acid in pentane over 5% palladium on alumina at 2 atm. gave 3,3-dimethylcyclobutanecarboxylic acid, which gave a *p*-bromophenacyl ester identical with that obtained from the nitrile as described below.

3,3-Dimethyl-2-piperidinocyclobutanecarbonitrile.—A mixture of 1-isobutenylpiperidine (69.5 g., 0.5 mole) and acrylonitrile (26.5 g., 0.5 mole) containing a pinch of hydroquinone was heated for 2 hr. at 175° in an autoclave. Distillation of the reaction mixture gave 17 g. of recovered enamine, b.p. 28–32° at 2.5–3 mm., and 59.5 g. of 3,3-dimethyl-2-piperidinocyclobutanecarbonitrile, b.p. 73–77° at 1–2 mm., $n^{20}D$ 1.4775.

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 75.0; H, 10.4; N, 14.6. Found: C, 75.3; H, 10.5; N, 14.6.

Gas chromatography of the product on a Carbowax column at 200°, with the preheater at 200°, showed two components in approximately a 2:1 ratio. When the preheater temperature was raised to 300°, the second and smaller of the components was decomposed and appeared as two low-boiling components which were eluted rapidly from the column.

3,3-Dimethyl-1-cyclobutene-1-carbonitrile (6).—3,3-Dimethyl-2-piperidinocyclobutanecarbonitrile (108 g., 0.56 mole) and methyl *p*-toluenesulfonate (111 g., 0.6 mole) were combined and heated on the steam bath for 24 hr. Ethyl alcohol (100 ml.) was added to the glassy solid, and then a solution of potassium hydroxide (56 g., 1 mole) in 100 ml. of water was added. The mixture was stirred manually at 40–50° for 20 min. and then poured into 1 l. of water. The mixture was extracted with ether, which was then backwashed with dilute hydrochloric acid to remove the amine. Finally, after being washed with water, the ether layer was distilled to give 38.5 g. (64%) of 3,3-dimethyl-1-cyclobutene-1-carbonitrile, b.p. 52–53° at 20 mm., $n^{20}D$ 1.4440.

Anal. Calcd. for C_7H_9N: C, 78.5; H, 8.5; N, 13.1. Found: C, 78.2; H, 8.7; N, 12.9.

3,3-Dimethylcyclobutanecarbonitrile.—3,3-Dimethyl-1-cyclobutene-1-carbonitrile (9.8 g., 0.09 mole) in 50 ml. of pentane was hydrogenated over 0.1 g. of 5% palladium on alumina at 5–7° and 2 atm. After 15 min., 0.08 mole of hydrogen was absorbed. The reaction mixture was filtered and distilled to give 7.3 g. (74%) of 3,3-dimethylcyclobutanecarbonitrile, b.p. 85–86° at 53 mm., $n^{20}D$ 1.4289.

Anal. Calcd. for $C_7H_{11}N$: C, 77.0; H, 10.2. Found: C, 77.3; H, 10.3.

3,3-Dimethylcyclobutanecarboxylic Acid.—3,3-Dimethylcyclobutanecarbonitrile (6.5 g.) was combined with a solution of 10 g. of potassium hydroxide in 50 ml. of water and 25 ml. of ethyl alcohol and heated under reflux for 15 hr. An additional 25 ml. of water was added, and the alcohol was removed by distillation. The residue was acidified with concentrated hydrochloric acid and extracted with ether. The extract was distilled to give 6.8 g. of 3,3-dimethylcyclobutanecarboxylic acid, b.p. 98–99° at 9.5–10 mm., $n^{20}D$ 1.4363.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.9; H, 9.4.

The acid gave a *p*-bromophenacyl ester, m.p. 89–90°.

Anal. Calcd. for $C_{15}H_{17}BrO_3$: C, 55.4; H, 5.3. Found: C, 55.2; H, 5.3.

An authentic sample of 3,3-dimethylcyclobutanecarboxylic acid was prepared according to the method of Campbell and Rydon.[26] It gave an infrared spectrum identical with that obtained from the cyclobutane degradation product, as well as a *p*-bromophenacyl ester identical with the one above. Campbell and Rydon reported that the *p*-bromophenacyl ester melted at 93°.

Quaternization of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate with methyl *p*-toluenesulfonate, followed by treatment with potassium hydroxide, gave 3,3-dimethyl-1-cyclobutene-1-carboxylic acid in 81% yield.

2-Dimethylamino-3,3-dimethylcyclobutanecarbonitrile (4).—N,N-Dimethylisobutenylamine and acrylonitrile gave in 2 hr. at 170° a 64% yield of 2-dimethylamino-3,3-dimethylcyclobutanecarbonitrile, b.p. 44–45° at 0.5–1 mm., $n^{20}D$ 1.4531.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.0; H, 10.6; N, 18.4. Found: C, 70.9; H, 10.6; N, 18.1.

Quaternization of this product with methyl *p*-toluenesulfonate and treatment with base as previously described gave 3,3-dimethyl-1-cyclobutene-1-carbonitrile in 66% yield.

Rearrangement of 3,3-Dimethyl-1-cyclobutene-1-carbonitrile (6).—3,3-Dimethyl-1-cyclobutene-1-carbonitrile (22.5 g., 0.21 mole) was placed in a distillation flask and heated at atmospheric pressure under a reflux condenser. When the temperature reached *ca.* 190°, an exothermic reaction occurred and the temperature rose rapidly to 224°. Upon cooling, the contents of the flask crystallized. Recrystallization from hexane gave 18.6 g. (83%) of 2,2-dimethyl-1-(2-methyl-1-propenyl)-3-cyclohexene-1,4-dicarbonitrile, m.p. 83–84°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.5; H, 8.5; N, 13.1; mol. wt., 214. Found: C, 78.8; H, 8.6; N, 12.7; mol. wt., 208.

(26) A. Campbell and H. R. Rydon, *J. Chem. Soc.*, 3002 (1953).

The n.m.r. spectrum showed absorption for the ring olefinic proton at 6.80 (weakly split triplet), the side-chain olefinic proton at 5.70 (broad), and the side-chain methyl at 1.6 and 1.8 p.p.m. The broad, complex absorption due to the ring methylene protons indicated that these were on adjacent carbon atoms.

Rearrangement of Ethyl 3,3-Dimethyl-1-cyclobutene-1-carboxylate.—Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate (60 g., 0.39 mole) was heated as previously described for the 3,3-dimethyl-1-cyclobutene-1-carbonitrile. When the temperature reached *ca.* 210°, an exothermic reaction occurred and the temperature rose rapidly to 240°. After being cooled to room temperature, the material was distilled to give 50.5 g. (85%) of diethyl 2,2-dimethyl-1-(2-methyl-1-propenyl)-3-cyclohexene-1,4-dicarboxylate, b.p. 121–123° at *ca.* 0.1 mm., $n^{20}D$ 1.4913.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.2; H, 9.1. Found: C, 70.2; H, 9.2.

Diethyl 3,3-Dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate.—1-Isobutenylpiperidine (208.5 g., 1.5 moles) and diethyl maleate (322.5 g., 1.87 moles) were combined and heated for 5.5 hr. at 150°. Distillation gave 241 g. (51%) of diethyl 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate, b.p. 113–120° at *ca.* 1 mm., $n^{20}D$ 1.4660.

Anal. Calcd. for $C_{17}H_{29}NO_4$: C, 65.6; H, 9.4. Found: C, 65.4; H, 9.1.

Diethyl 4-Dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (5).—N,N-Dimethylisobutenylamine (82 g., 0.83 mole) and diethyl maleate (172 g., 1 mole) were combined. The temperature of the mixture rose slowly to 40° and then dropped back to room temperature (this heat effect is due to isomerization of the maleate to the fumarate). The mixture was then refluxed. It was held at 105–110° for 12 hr. by control of the Glascol heater voltage, then at reflux the temperature rose to 144° over the next 3.5 hr. At this point, an additional 35 g. of diethyl maleate was added and reflux was continued. Over the next 2.5 hr., the temperature rose to 162°. The mixture then was distilled to give 97.5 g. of diethyl fumarate, b.p. 59–60° at *ca.* 1.5 mm. (the infrared spectrum was practically identical with that of authentic diethyl fumarate), an 11.8-g. intermediate cut, and 150.5 g. (67%) of diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate, b.p. 93–94° at *ca.* 1.5 mm., $n^{20}D$ 1.4502. N,N-Dimethylisobutenylamine (19 g.) was present in the Dry Ice trap.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3; N, 5.2. Found: C, 61.8; H, 9.3; N, 5.0.

A product identical with that obtained from diethyl maleate was obtained in 78% yield when diethyl fumarate and N,N-dimethylisobutenylamine were refluxed for 11.5 hr.

4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylic Acid.—Diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (90 g., 0.33 mole) and methyl *p*-toluenesulfonate (65 g., 0.35 mole) were combined and heated on a steam bath for 16 hr. Over a 0.5-hr. period, a solution of potassium hydroxide (84 g., 1.5 moles) in 100 ml. of water was added with manual stirring and cooling to keep the temperature at *ca.* 50°. The mixture was heated for 1 hr. on the steam bath and acidified with hydrochloric acid. It was extracted ten times with 150-ml. portions of ether (evaporation of the tenth extract gave 0.5 g. of product), and the ether was removed by evaporation on the steam bath to leave a residue of 40 g. (71%) of crude 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylic acid. The acid was recrystallized from an ethyl acetate–hexane mixture with Darco treatment to give 25 g. (44%), m.p. 153–155°. A sample for analysis was recrystallized from an ethyl acetate–cyclohexane mixture, m.p. 154–155°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.5; H, 6.0.

***trans*-Norcaryophyllenic Acid.**—4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylic acid (5.1 g., 0.03 mole) in ethyl acetate (75 ml.) was subjected to hydrogenation over 0.25 g. of 5% palladium on alumina at 25° and 3 atm. Reduction was complete in less than 1 hr. The catalyst was removed by filtration, and the solvent was evaporated to give 5 g. of a solid, m.p. 106–115°, which was a mixture of *cis*- and *trans*-norcaryophyllenic acid. This mixture (4.5 g.) was combined with 15 ml. of 30% (by volume) sulfuric acid solution and heated in an autoclave for 12 hr. at 150°. The mixture was filtered, and the solid was dissolved in acetone and treated with Norit. This solution was filtered, the acetone was removed by evaporation, and the residue was recrystallized from benzene to give 4 g. of *trans*-norcaryophyllenic acid, m.p. 149–150°, lit.[27] m.p. 148–149°.

The dianilide was prepared and was found to melt at 239–240°, lit.[27] m.p. 238°.

N,N,2,2-Tetramethyl-4-(methylsulfonyl)cyclobutylamine (7).—N,N-Dimethylisobutenylamine (28 g., 0.28 mole) and methyl vinyl sulfone (28 g., 0.26 mole) were combined. The immiscible mixture was refluxed, and when the temperature reached 90°, the mixture became homogeneous. Reflux was continued for 1.5 hr. while the temperature rose from 90 to 160°. Distillation of the reaction mixture gave 49 g. (91%) of N,N,2,2-tetramethyl-4-(methylsulfonyl)cyclobutylamine, b.p. 100–103° at 0.5–0.6 mm., which crystallized in the receiver, m.p. 85–86°.

Anal. Calcd. for $C_9H_{19}NO_2S$: C, 52.7; H, 9.3. Found: C, 52.2; H, 9.2.

2,2-Dimethyl-4-(methylsulfonyl)butyraldehyde (9).—N,N,2,2-Tetramethyl-4-(methylsulfonyl)cyclobutylamine (23 g., 0.11 mole) and methyl *p*-toluenesulfonate (23 g., 0.12 mole) were combined and heated on the steam bath for 2.5 hr. Water (50 ml.) was added, followed by a solution of 10 g. of potassium hydroxide in 10 ml. of water, and the mixture was heated on the steam bath for 1 hr. The water-soluble degradation product was extracted twice with 50-ml. portions of chloroform. The chloroform was removed by evaporation, and the residue was distilled to give 5.5 g. of 2,2-dimethyl-4-(methylsulfonyl)butyraldehyde, b.p. 149–153° at 1 mm., $n^{20}D$ 1.4853.

Anal. Calcd. for $C_7H_{14}O_3S$: C, 47.2; H, 7.9. Found: C, 47.5; H, 8.0.

The 2,4-dinitrophenylhydrazone melted at 153°.

Anal. Calcd. for $C_{13}H_{18}N_4O_6S$: C, 43.6; H, 5.1. Found: C, 43.7; H, 5.3.

2,2-Dimethyl-4-(methylsulfonyl)butyraldehyde.—Methyl vinyl sulfone (15.9 g., 0.15 mole) and N-isobutylideneethylamine (16 g., 0.16 mole) were combined and heated for 1.5 hr. After the first hour, the temperature had risen to 150–160°, where it remained for the last 30 min. of heating. The mixture was cooled, and a solution of concentrated hydrochloric acid (20 ml.) in water (20 ml.) was added. The clear solution was allowed to stand overnight. The mixture was extracted twice with an equal volume of chloroform to remove the heavier-than-water oily layer which had separated. The chloroform was removed by evaporation on the steam bath, and the residue was distilled through a 6-in. Vigreux column to give 17.7 g. (66%) of 2,2-dimethyl-4-(methylsulfonyl)-butyraldehyde, b.p. 126–129° at *ca.* 0.5 mm., $n^{20}D$ 1.4710. The infrared spectrum of this material was identical with that of the aldehyde derived from N,N,2,2-tetramethyl-4-(methylsulfonyl)cyclobutylamine as described above.

The 2,4-dinitrophenylhydrazone melted at 153–154°.

N,N,2,2-Tetramethyl-4-nitro-3-phenylcyclobutylamine (10).—N,N-Dimethylisobutenylamine (33 g., 0.33 mole) was added to β-nitrostyrene (47.5 g., 0.32 mole) in an erlenmeyer flask, and the mixture was stirred manually. The temperature rose to 92° rapidly and then dropped slowly. On standing, crystallization occurred. The solid was stirred in hexane, filtered, and washed with hexane to give 74.5 g. (94%) of crude N,N,2,2-tetramethyl-4-nitro-3-phenylcyclobutylamine, m.p. 86–91°. A sample for analysis was recrystallized from hexane and had m.p. 90–92°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.7; H, 8.1; N, 11.3. Found: C, 67.9; H, 8.3; N, 11.5.

The structure of this material was confirmed by chemical degradation as follows.

N,N,2,2-Tetramethyl-4-nitro-3-phenylcyclobutylamine (167 g., 0.67 mole) and methyl *p*-toluenesulfonate (130 g., 0.7 mole) were combined and heated on a steam bath for 19 hr. Water (400 ml.) was added to the reaction mixture, and it was extracted three times with 150-ml. portions of ether. Evaporation of the ether left 95 g. of nonquaternized material. The remaining aqueous phase was split into two equal portions, A and B.

Sodium bicarbonate (28 g., 0.33 mole) was added to A, and the mixture was heated for 15 min. on a steam bath. The oil which separated was dissolved in ether; the ether was evaporated to leave 26 g. of residue which crystallized to a slush. A good solvent for recrystallization was not found. By dissolving the residue in 150 ml. of ethyl alcohol and chilling the solution in Dry Ice, 4 g. of 2,2-dimethyl-4-nitro-3-phenylbutyraldehyde, m.p. 72°, was obtained.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 64.9; H, 7.1; N, 6.5.

Sodium acetate (28 g., 0.33 mole) was added to B, and the mixture was treated in the same way A was treated to give 27 g.

(27) T. L. Dawson and G. R. Ramage, *J. Chem. Soc.*, 3382 (1957).

of crude aldehyde. Reaction of 1 g. of the crude aldehyde with 2,4-dinitrophenylhydrazine gave 1.3 g. (70%) of the 2,4-dinitrophenylhydrazone of 2,2-dimethyl-4-nitro-3-phenylbutyraldehyde, m.p. 191.5–192.5°.

Anal. Calcd. for $C_{18}H_{19}N_5O_6$: C, 53.9; H, 4.8. Found: C, 53.6; H, 4.9.

Reaction of N,N-Dimethylisobutenylamine with 2-Nitro-1-butene.—N,N-Dimethylisobutenylamine (91 g., 0.92 mole) was added portionwise to 2-nitro-1-butene (91 g., 0.9 mole) with cooling to maintain the temperature at 40–50°. The entire reaction mixture crystallized on cooling, and the product was presumably 2-ethyl-N,N,4,4-tetramethyl-2-nitrocyclobutylamine (11). Pentane was added to the solid, then was removed by filtration. The product began evolving dimethylamine immediately on exposure to air and became gummy. It dissolved in water rapidly with the evolution of dimethylamine, and the solution gave a strong, positive 2,4-dinitrophenylhydrazine test for a carbonyl group. The product was allowed to stand exposed to air for one week, after which time it was completely liquid. Distillation of 83 g. of this material gave 19 g. of a product, b.p. 80–82° at 4 mm., which was apparently impure 2,2-dimethyl-4-nitrohexanal. A satisfactory analysis was not obtained, but it gave a 2,4-dinitrophenylhydrazone, m.p. 116–117°.

Anal. Calcd. for $C_{14}H_{19}N_5O_6$: C, 47.6; H, 5.4. Found: C, 47.4; H, 5.5.

N,N-Dibenzyl-2,2-dimethyl-4-nitro-3-phenylcyclobutylamine.—N-Isobutenyldibenzylamine (12.5 g., 0.05 mole) and β-nitrostyrene (7.4 g., 0.05 mole) were combined. There was a moderate evolution of heat, and the temperature rose to 34°. The mixture was allowed to stand 1 hr., at which time it had partially crystallized. Hexane was added, and the mixture was filtered. The solid was recrystallized from hexane to give 10 g. (50%) of N,N-dibenzyl-2,2-dimethyl-4-nitro-3-phenylcyclobutylamine, m.p. 95–96.5°.

Anal. Calcd. for $C_{26}H_{28}N_2O_2$: C, 78.0; H, 7.1. Found: C, 77.9; H, 7.2.

Cycloadditions of Enamines Containing a β-Hydrogen Atom.—Enamines containing a β-hydrogen atom were found to give cyclobutanes on reaction with electrophilic olefins under mild conditions, that is, standing without external heating in the polar solvent acetonitrile or refluxing in acetonitrile. The cyclobutanes prepared are listed in Table V. The following examples are illustrative.

Methyl 3-Ethyl-2-piperidinocyclobutanecarboxylate (12).—Methyl acrylate (43 g., 0.5 mole), N-(1-butenyl)piperidine (69 g., 0.5 mole), and acetonitrile (150 ml.) containing a pinch of hydroquinone were combined, refluxed for 3 hr., and then allowed to stand overnight. Distillation of the mixture through a 6-in. Vigreux column gave 92 g. (82%) of methyl 3-ethyl-2-piperidinocyclobutanecarboxylate, b.p. 87–89° at *ca.* 0.5 mm., $n^{20}D$ 1.4734.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.3; H, 10.3. Found: C, 69.6; H, 10.3.

This compound was also prepared in 83% yield by allowing the reactants to stand at room temperature in acetonitrile for 3 days.

3-Ethyl-1-cyclobutene-1-carboxylic Acid.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (56 g., 0.25 mole) and methyl *p*-toluenesulfonate (93 g., 0.5 mole) were combined and heated on a steam bath for 16 hr. Water (150 ml.) was added, the mixture was extracted once with ether, and the ether layer then was discarded. Potassium hydroxide (80 g., 1.4 moles) was added to the aqueous layer, and the solution was heated on a steam bath for 4 hr. The mixture was cooled, extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. Distillation of the latter extract gave 20 g. (64%) of 3-ethyl-1-cyclobutene-1-carboxylic acid, b.p. 79–80° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4694.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.3; H, 7.7.

The n.m.r. spectrum showed absorption due to one olefinic proton as a single peak at 7.05 p.p.m.

3-Ethylcyclobutanecarboxylic Acid.—3-Ethyl-1-cyclobutene-1-carboxylic acid (15 g., 0.12 mole) was hydrogenated in pentane (200 ml.) at 25° and 40 p.s.i. over 5% palladium on alumina. Distillation gave 12.4 g. (81%) of 3-ethylcyclobutanecarboxylic acid, b.p. 78–79° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4415.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.5; H, 9.5.

Thermal Decomposition of Methyl 3-Ethyl-2-piperidinocyclobutanecarboxylate.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (22.5 g., 0.1 mole) was heated at atmospheric pressure under a 3-in. Vigreux column. When the temperature reached 170–180°, methyl acrylate began distilling. By continuing the heating and by reducing the pressure in the system slightly, a total of 6 g. (70%) of methyl acrylate was obtained. The system then was evacuated to 5–6 mm., and the heating was continued to give 5 g. (36%) of 1-isobutenylpiperidine, b.p. 60–65° at 5–6 mm., $n^{20}D$ 1.4792. There was 3.5 g. of material in the trap, and the residue weighed 8 g.

Methyl 3-Methyl-2-piperidinocyclobutanecarboxylate.—In a manner analogous to that described above for methyl 3-ethyl-2-piperidinocyclobutanecarboxylate, methyl 3-methyl-2-piperidinocyclobutanecarboxylate was prepared in 67% yield from 1-(1-propenyl)piperidine and methyl acrylate, b.p. 70–75° at 0.5 mm., $n^{20}D$ 1.4741.

Anal. Calcd. for $C_{12}H_{21}NO_2$: N, 6.6. Found: N, 6.6.

3-Methyl-1-cyclobutene-1-carboxylic Acid.—Quaternization of methyl 3-methyl-2-piperidinocyclobutanecarboxylate with methyl *p*-toluenesulfonate and treatment of the resulting salt with aqueous potassium hydroxide, followed by acidification with hydrochloric acid, gave a 55% yield of 3-methyl-1-cyclobutene-1-carboxylic acid, b.p. 68–70° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4682. The infrared and n.m.r. spectra of this compound supported the assigned structure. This compound was unstable and on standing at room temperature for several days changed into a polymer-like material.

Anal. Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.1; H, 7.4.

3-Methylcyclobutanecarboxylic Acid.—Hydrogenation of 3-methyl-1-cyclobutene-1-carboxylic acid at 25° and 40 p.s.i. over 5% palladium on alumina gave an 80% yield of 3-methylcyclobutanecarboxylic acid, b.p. 62.5–63° at 1 mm., $n^{20}D$ 1.4376, lit.[23] $n^{25}D$ 1.4351. The amide derivative melted at 162–163°, lit.[28] m.p. 163–164°, and the anilide melted at 129–131°, lit.[28] m.p. 127–128°.

Diethyl 3-Dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate.—N,N-Dimethyl-1-butenylamine (43 g., 0.434 mole), diethyl maleate (74 g., 0.43 mole), and acetonitrile (100 ml.) were combined and allowed to stand at room tmeperature for 22 hr. Distillation gave 91 g. (78%) of diethyl 3-dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate, b.p. 95–98° at *ca.* 0.8 mm., $n^{20}D$ 1.4482.

Anal. Calcd. for $C_{14}H_{25}NO_4$: N, 5.0. Found: N, 5.2.

4-Ethyl-2-cyclobutene-1,2-dicarboxylic Acid.—Diethyl 3-dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate (27 g., 0.1 mole) and methyl *p*-toluenesulfonate (20 g., 0.11 mole) were combined and heated on the steam bath for 5 hr. and then allowed to stand overnight. A solution of potassium hydroxide (30 g., 0.53 mole) in water (75 ml.) was added, and the resulting mixture was heated for 2 hr. on a steam bath. The mixture was cooled, acidified with concentrated hydrochloric acid, and extracted three times with ether (125 ml.). The ether was evaporated, leaving 15 g. (88%) of crude 4-ethyl-1-cyclobutene-1,2-dicarboxylic acid as an oil which crystallized on standing. A sample recrystallized from ethyl acetate and hexane melted at 128–129.5°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.4; H, 6.2.

1-Ethyl-N,N-dimethylpropenylamine with Methyl Acrylate.—1-Ethyl-N,N-dimethylpropenylamine (33 g., 0.29 mole), methyl acrylate (25 g., 0.29 mole), and acetonitrile (50 ml.) containing a pinch of hydroquinone were combined. A mild exothermic reaction took place, and the temperature was maintained below 30° by intermittent cooling. After the mixture had stood for 3 hr., an infrared spectrum of the material showed only a very weak absorption band in the double bond region (6–6.1 μ). An n.m.r. spectrum of this material showed weak absorption in the olefinic proton regions, apparently due to an unsaturated impurity.

This compound was thermally unstable. Distillation of one-half of the above reaction product gave 21 g. (73%) of what appeared to be methyl 5-dimethylamino-4-methyl-5(and possibly 4)-heptenoate, the Stork-type adduct, b.p. 63–65° at *ca.* 0.3 mm., $n^{20}D$ 1.4598. The infrared spectrum showed increased absorption at 6.1 μ, and the n.m.r. spectrum showed olefinic proton absorption as a quartet centered at 4.6 p.p.m.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.5; N, 7.0. Found: C, 66.0; H, 10.8; N, 6.8.

Methyl 2-Ethyl-3-methyl-1-cyclobutene-1-carboxylate.—Methyl 2-dimethylamino-2-ethyl-3-methylcyclobutanecarboxylate (one-

(28) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 2723 (1959).

half of the product obtained above—*ca.* 28 g., 0.14 mole—in 25 ml. of acetonitrile) was treated with methyl iodide (40 g., 0.28 mole) and allowed to stand for 1.5 hr. The solvent and excess methyl iodide were removed under reduced pressure; the solid residue was dissolved in water (150 ml.) and extracted once with ether. A solution of sodium hydroxide (20 g., 0.5 mole) in water (50 ml.) was added, and the oil layer which separated was removed by extraction with ether. The ether extract on distillation gave 11 g. (49% based on the starting methyl acrylate) of methyl 2-ethyl-3-methyl-1-cyclobutene-1-carboxylate, b.p. 60–61° at 5 mm., $n^{20}D$ 1.4586.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.6; H, 9.1.

1-Ethyl-N,N-dimethylpropenylamine with Diethyl Maleate.—1-Ethyl-N,N-dimethylpropenylamine (20 g., 0.177 mole), diethyl maleate (30.5 g., 0.177 mole), and acetonitrile (50 ml.) containing a pinch of hydroquinone were combined. The temperature of the mixture rose to 54° within 18 min. The mixture was allowed to stand at room temperature for 3 days, after which it was heated to 75° at 0.5 mm. There was left 23 g. (46%) of crude diethyl 3-dimethylamino-3-ethyl-4-methylcyclobutanecarboxylate, $n^{20}D$ 1.4602. The infrared spectrum showed no enamine C=C absorption between 5.9 and 6.5 μ., and no olefinic proton absorption was detected in the n.m.r. spectrum.

3-Ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylic Acid.—Crude diethyl 3-dimethylamino-3-ethyl-4-methyl-1,2-cyclobutanedicarboxylate (20.5 g., 0.072 mole) was combined with methyl *p*-toluenesulfonate (13.5 g., 0.073 mole) and allowed to stand overnight at room temperature. Water (50 ml.) was added, and the solution was extracted once with ether. Potassium hydroxide (25 g., 0.45 mole) was added, and the mixture was heated on a steam bath for 2 hr. It was then cooled, acidified with concentrated hydrochloric acid, and extracted twice with ether (75-ml. portions). Evaporation of the combined extracts on the steam bath left 9 g. (68%) of 3-ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylic acid as an oil which crystallized rapidly. A small sample, recrystallized twice from water, melted at 147.5–149°.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.6; neut. equiv., 92. Found: C, 58.6; H, 6.7; neut. equiv., 91.4.

Diethyl 3-Ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylate.—1-Ethyl-N,N-dimethylpropenylamine (30 g., 0.265 mole) and diethyl maleate (45.5 g., 0.265 mole) were allowed to react as described above to give diethyl 3-dimethylamino-3-ethyl-4-methyl-1,2-cyclobutanedicarboxylate. This crude compound was dissolved in acetonitrile (100 ml.) and treated with methyl iodide (50 g., 0.35 mole), and the mixture was refluxed for 2 hr. at 70°. The solvent and excess methyl iodide were removed under reduced pressure, and the residue was dissolved in 250 ml. of water. The resulting aqueous solution was extracted with ether to remove unquaternized material. Potassium hydroxide (56 g., 1 mole) was added slowly with cooling, and the oil which separated was removed by extraction with ether. Distillation of the extract gave 37 g. (58% yield based on 0.265 mole of starting material) of diethyl 3-ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylate, b.p. 93.5–96° at 0.7–0.8 mm., $n^{20}D$ 1.4581.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.4. Found: C, 65.0; H, 8.4.

Tetraethyl 6-Dimethylamino-5,5-dimethyl-1,1,3,3-cyclohexanetetracarboxylate (16).—N,N-Dimethylisobutenylamine (30 g., 0.3 mole) was combined with diethyl methylenemalonate (96 g., 0.56 mole) which had been inhibited with hydroquinone. The temperature of the mixture rose to 110° after standing for 15 min. The mixture was heated under a reflux condenser, and at 150° the mixture began to reflux. The temperature of the mixture rose rapidly to 168°, and the refluxing virtually stopped. Distillation of the reaction mixture through a 4-in. Vigreux column gave 101 g. (81%) of tetraethyl 6-dimethylamine-5,5-dimethyl-1,1,3,3-cyclohexanetetracarboxylate (16), b.p. 165–173° at 1 mm., $n^{20}D$ 1.4696.

Anal. Calcd. for $C_{22}H_{37}NO_8$: C, 59.7; H, 8.4; mol. wt., 443. Found: C, 59.8; H, 8.8; mol. wt., 446.

The structure assigned to this compound was based on the elemental analysis, the absence of C=C absorption in the infrared spectrum, and the mode of formation.

Tetraethyl 6-Dimethylamino-5-ethyl-1,1,3,3-cyclohexanetetracarboxylate.—To N,N-dimethyl-1-butenylamine (20 g., 0.202 mole) was added diethyl methylenemalonate (64 g., 0.37 mole) portionwise with stirring. The temperature of the mixture rose rapidly to 80–85° during the addition. The mixture was allowed to stand overnight. Distillation of the mixture gave 32 g. (64%) of tetraethyl 6-dimethylamino-5-ethyl-1,1,3,3-cyclohexanetetracarboxylate, b.p. 165–170° at *ca.* 0.8 mm., $n^{20}D$ 1.4644.

Anal. Calcd. for $C_{22}H_{37}NO_8$: C, 59.7; H, 8.4. Found: C, 59.6; H, 8.7.

2-Dimethylamino-3,3-dimethylcyclobutanecarboxylic Acid, N-Oxide (17).—To a solution of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (93 g., 0.5 mole) in methanol (275 ml.) which was chilled to 0° was added dropwise 30% hydrogen peroxide (170 g.). The temperature of the mixture was maintained at 0 ± 5° during the addition; then it was allowed to come to room temperature. After standing overnight, a slurry of 15 ml. of water containing 2 g. of 5% platinum on charcoal was added to destroy the peroxide, and the mixture again was allowed to stand overnight. The mixture was filtered, and the alcohol and water were removed under reduced pressure, keeping the temperature below 40°. The residue, upon treatment with acetone, gave a white solid which was filtered and dried in a vacuum oven. There was obtained 61 g. (65%) of 2-dimethylamino-3,3-dimethylcyclobutanecarboxylic acid, N-oxide, m.p. 168–170°.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.7; H, 9.2; neut. equiv., 187.2. Found: C, 57.8; H, 9.4, neut. equiv., 187.9.

3,3-Dimethyl-4-dimethylamino-1,2-cyclobutanedicarboxylic Acid, 2-Ethyl Ester, N-Oxide (18).—This compound was prepared in a similar manner from diethyl 3-dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarboxylate.

There was obtained from 54.2 g. (0.2 mole) of the diester 23 g. (45%) of the amine oxide, m.p. 157°.

Anal. Calcd. for $C_{12}H_{21}NO_5$: neut. equiv., 259.3. Found: neut. equiv., 258.1.

Hydrolysis of the Cyclobutane Adducts. A. 4,4-Dimethylglutaraldehydic Acid.—A mixture of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (100 g., 0.54 mole) and water (125 ml.) was refluxed for 1.5 hr. The resulting solution was acidified with concentrated hydrochloric acid and then extracted with ether. The extract was distilled to give 48 g. (68%) of 4,4-dimethylglutaraldehydic acid, b.p. 98–105° at *ca.* 1 mm., $n^{20}D$ 1.4457.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.1; H, 8.4.

The 2,4-dinitrophenylhydrazone melted at 151–151.5°, lit.[29] m.p. 147°.

B. Alkaline Hydrolysis of Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate.—Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (97 g., 0.5 mole) was refluxed with a solution of sodium hydroxide (20 g., 0.5 mole) in 150 ml. of water for 4 hr. No dimethylamine was evolved, and the ester had dissolved completely after 1.5 hr. Acidification of the solution with concentrated hydrochloric acid gave no insoluble material, showing that only saponification had occurred.

C. 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylic Acid Hydrochloride (20).—Methyl 3,3-dimethyl-2-dimethylaminocyclobutanecarboxylate (50 g., 0.27 mole) was combined with 250 ml. of 4 *N* hydrochloric acid, and the resulting solution was refluxed for 4 hr. The mixture was evaporated to dryness on a steam bath, 100 ml. of water was added then, and the evaporation was repeated. Ethyl alcohol (100 ml.) was added, and the mixture was evaporated for a third time to dryness. The crystalline residue was triturated with cold 95% ethyl alcohol to give 35 g. of crude product. Recrystallization from ethyl alcohol gave, after drying, 27 g. (49%) of 2-dimethylamino-3,3-dimethylcyclobutanecarboxylic acid hydrochloride, m.p. 196–197°.

Anal. Calcd. for $C_9H_{18}ClNO_2$: neut. equiv., 207.7. Found: neut. equiv., 208.3.

D. Methyl 4,4-Dimethylglutaraldehydate (21).—Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (97 g., 0.5 mole) was combined with a solution of 42 ml. of concentrated hydrochloric acid in 50 ml. of water and refluxed for 3.5 hr. An oil layer began separating soon after the mixture began refluxing. The oil was collected and distilled to give 70.5 g. (89%) of methyl 4,4-dimethylglutaraldehydate, b.p. 40–42° at 0.5 mm., $n^{20}D$ 1.4306.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 61.0; H, 8.9.

E. Acid Hydrolysis of 3,3-Dimethyl-1-cyclobutene-1-carboxylic Acid.—3,3-Dimethyl-1-cyclobutene-1-carboxylic acid (41 g., 0.33 mole) was refluxed, with vigorous stirring, with 33 ml. of concentrated hydrochloric acid and 150 ml. of water for 15 hr. The oil was dissolved in ether and distilled to give 19 g. of mostly

(29) R. H. Wiley and P. Veeravagu, *J. Org. Chem.*, **23**, 297 (1958).

3,3-dimethyl-1-cyclobutene-1-carboxylic acid, b.p. 77–100° at *ca.* 1 mm., which crystallized in the head and receiver, and 11 g. of 4,4-dimethylglutaraldehydic acid, b.p. 103–105° at *ca.* 1 mm., $n^{20}D$ 1.4467, which was identical with that of an authentic sample.

Methyl 4-Ethylglutaraldehydate.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (20 g., 0.089 mole) was combined with a solution of concentrated hydrochloric acid (8 ml.) and water (25 ml.) and refluxed for 2 hr. An oil began separating soon after the mixture began refluxing. The oil was collected and distilled to give 10 g. (72%) of methyl 4-ethylglutaraldehydate, b.p. 57–58° at 1 mm., $n^{20}D$ 1.4321.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.3; H, 9.0.

Attempted Hydrolytic Ring Opening of Diethyl 4-Dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate.—Diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (76 g., 0.28 mole) and water (250 ml.) were combined and refluxed for 23 hr. The mixture then was acidified with hydrochloric acid and extracted twice with 100-ml. portions of ether. Evaporation of the ether left only 5 g. of residue, which gave a weak test for carbonyl groups on treatment with 2,4-dinitrophenylhydrazine reagent.

Refluxing the diester (135 g., 0.5 mole) with 100 ml. of water and 42 ml. of concentrated hydrochloric acid for 18 hr. gave no acid-insoluble material.

3,3-Dimethyl-4-piperidino-1,2-cyclobutanedicarboxylic Acid Hydrochloride.—Diethyl 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate (31 g., 0.1 mole) and 100 ml. of concentrated hydrochloric acid were refluxed for 6 hr. The mixture then was evaporated to dryness on the steam bath. The residue was triturated with hot butyl alcohol to give 17 g. (58%) of 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylic acid hydrochloride, m.p. 234–235°.

Anal. Calcd. for $C_{13}H_{22}ClNO_4$: C, 53.5; H, 7.6. Found: C, 53.2; H, 7.6.

4-Cyano-2,2-dimethylbutyraldehyde (**22**).—2-Dimethylamino-3,3-dimethylcyclobutanecarbonitrile (38 g., 0.25 mole) and water (75 ml.) were refluxed for 5 hr., during which time dimethylamine was evolved through the condenser. The mixture was acidified with concentrated hydrochloric acid, extracted with ether, and the extract was distilled to give 18.5 g. (59%) of 4-cyano-2,2-dimethylbutyraldehyde, b.p. 55–56° at *ca.* 1 mm., $n^{20}D$ 1.4371.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.2; H, 8.9. Found: C, 67.4; H, 9.1.

The 2,4-dinitrophenylhydrazone melted at 140–142°, lit.[30] m.p. 139–140°.

2-Dimethylamino-3,3-dimethylcyclobutanemethylamine.—3,3-Dimethyl-2-dimethylaminocyclobutanecarbonitrile (331 g., 2.2 moles) was dissolved in ethyl alcohol (250 ml.) and hydrogenated in the presence of anhydrous liquid ammonia (125 g.) and alcoholic Raney nickel (36 g.). The catalyst was removed by filtration, and the filtrate was distilled to give 39.5 g. (16%) of 3,3-dimethylpiperidine, b.p. 51–54° at 39–40 mm. The distillation was continued to give 21.9 g. (64%) of 2-dimethylamino-3,3-dimethylcyclobutanemethylamine, b.p. 102.5–104° at 39 mm., $n^{20}D$ 1.4598.

The infrared spectrum of the 3,3-dimethylpiperidine obtained was identical with that of an authentic sample.

Ethyl 3,3-Dimethyl-2-(N-propylacetamido)cyclobutanecarboxylate.—Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate (11.5 g., 0.075 mole) was treated with 9 g. (0.15 mole) of propylamine. After standing overnight at room temperature, the mixture was dissolved in pyridine (50 ml.). The resulting solution was treated with acetyl chloride (12 g., 0.15 mole) with stirring and cooling to keep the temperature below 30°. The reaction mixture was poured into 150 ml. of ice–water, and the resulting mixture was extracted with two 100-ml. portions of ether. The combined extracts were washed with water (25 ml.), and the ether was evaporated on the steam bath. The residue was distilled to give, after removal of a 6-g. forerun boiling from 47–100° at 0.25–0.1 mm., 4.5 g. (24%) of ethyl 3,3-dimethyl-2-(N-propylacetamido)-cyclobutanecarboxylate, b.p. 100–103° at 0.1 mm., $n^{20}D$ 1.4648.

Anal. Calcd. for $C_{14}H_{25}NO_3$: C, 65.8; H, 9.9. Found: C, 65.5; H, 9.9.

Ethyl 4,4-Dimethyl-5-propyliminovalerate.—Crude ethyl 3,3-dimethyl-2-(propylamino)cyclobutanecarboxylate (obtained from 30.4 g. (0.2 mole) of ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate) was distilled to give 25.3 g. (59%) of ethyl 4,4-dimethyl-5-propyliminovalerate (**28**), b.p. 64–65° at 0.2 mm., $n^{20}D$ 1.4407.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.6; H, 10.8. Found: C, 67.6; H, 10.9.

The compound was hydrolyzed by dilute hydrochloric acid to give an aldehyde whose 2,4-dinitrophenylhydrazone (m.p. 105–106°) was identical with that of a derivative of authentic ethyl 4,4-dimethylglutaraldehydate.

Diethyl 3,3-Dimethyl-4-(N-propylacetamido)-1,2-cyclobutanedicarboxylate.—In a manner similar to that described above, the adduct from diethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate (24 g., 0.106 mole) and propylamine gave, upon treatment with acetyl chloride (8.4 g.) in pyridine, 10.0 g. (29%) of diethyl 3,3-dimethyl-4-(N-propylacetamido)-1,2-cyclobutanedicarboxylate, b.p. 123–127° at 0.15–0.2 mm., $n^{20}D$ 1.4655.

Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.4; H, 8.9. Found: C, 62.2; H, 8.9.

Diethyl (1,1-Dimethyl-2-propyliminoethyl)succinate.—The adduct from diethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate (22.6 g., 0.1 mole) and propylamine (6.4 g., 0.11 mole) was distilled to give 20 g. (70%) of diethyl (1,1-dimethyl-2-propyliminoethyl)succinate (**29**), b.p. 110–113° at 0.7–0.8 mm., $n^{20}D$ 1.4493.

Anal. Calcd. for $C_{15}H_{27}NO_4$: C, 63.2; H, 9.5. Found: C, 63.3; H, 9.6.

The compound gave a 2,4-dinitrophenylhydrazone, m.p. 111–112°.

Anal. Calcd. for $C_{18}H_{24}N_4O_8$: C, 50.9; H, 5.6. Found: C, 51.0; H, 5.7.

Methyl 5-Ethylimino-4,4-dimethylvalerate.—Toluene (100 ml.), N-ethylisobutylideneamine (99 g., 1.0 mole), and methyl acrylate (86 g., 1.0 mole) were combined and heated under a reflux condenser. When the temperature reached *ca.* 78°, an exothermic reaction began; the heat source was removed and the mixture refluxed spontaneously for 5 min. at 88–89°. Heating then was resumed and continued for a total of 21 hr. The final temperature was 107°. Distillation gave 66 g. (36%) of methyl 5-ethylimino-4,4-dimethylvalerate, b.p. 52–53° at 1 mm., $n^{20}D$ 1.4379. A polymeric residue (60 g.) was left.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3. Found: C, 64.6; H, 10.3.

Diethyl (2-Ethylimino-1,1-dimethylethyl)succinate.—N-Ethylisobutylideneamine (50 g., 0.5 mole) and diethyl maleate (86 g., 0.5 mole) were combined and heated under reflux for 8 hr., during which time the temperature rose from 109° to 184°. Distillation of the reaction mixture gave 117.5 g. (87%) of diethyl (2-ethylimino-1,1-dimethylethyl)succinate, b.p. 90–92° at 0.5 mm., $n^{20}D$ 1.4478.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3. Found: C, 62.4; H, 9.0.

The 2,4-dinitrophenylhydrazone m.p. 111–112° was identical with that obtained from **29**.

Derivatives of Cyclobutanes Prepared by Standard Methods During This Investigation. A. Alcohols.—The following amino alcohols were prepared by the lithium aluminum hydride reduction of the corresponding esters.

3,3-Dimethyl-2-morpholino-1-cyclobutanemethanol in 76% yield had b.p. 99–103° at 1.5–1.8 mm., $n^{20}D$ 1.4832.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.6. Found: C, 66.1; H, 10.7.

1-Piperidinospiro[3.5]nonane-1-methanol had m.p. 105–106.5°.

Anal. Calcd. for $C_{15}H_{27}NO$: C, 76.0; H, 11.5. Found: C, 76.2; H, 11.4.

3-Dimethylamino-4,4-dimethyl-1,2-cyclobutanedimethanol in 52% yield had b.p. 133–136° at 1 mm., $n^{20}D$ 1.4821.

Anal. Calcd. for $C_{10}H_{21}NO_2$: C, 64.1; H, 11.3. Found: C, 63.7; H, 10.9.

B. Amides.—**3,3-Dimethyl-1-cyclobutanecarboxamide**, m.p. 170–171°, was prepared in 86% yield by treating the corresponding acid chloride with ammonia.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 66.1; H, 10.3. Found: C, 65.9; H, 10.4.

C. Esters.—**Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate**, b.p. 50–54° at 5.5–6.5 mm., $n^{20}D$ 1.4418, was prepared in 77% yield by refluxing the corresponding acid with excess ethyl alcohol and removing the water formed by azeotropic distillation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.8; H, 9.1.

(30) G. Tschudi and H. Schinz, *Helv. Chim. Acta*, **33**, 1879 (1950).

Enamine Chemistry. V. Cycloaddition Reactions of Enamines Derived from Alicyclic Ketones

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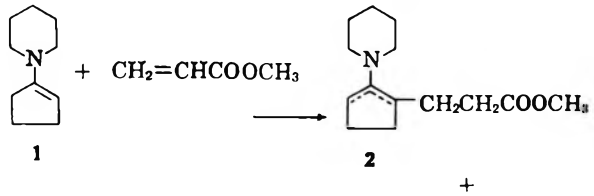
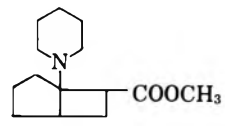
Enamines derived from alicyclic ketones react with methyl acrylate and diethyl maleate under mild conditions to give unstable cyclobutane derivatives. These cyclobutanes may be stabilized by conversion to the corresponding alcohols. Some further transformations of the cyclobutanes along with related simpler cyclobutanes are discussed.

Cycloaddition reactions of enamines derived from aldehydes and acyclic ketones have been reported.[1] We have found that under the proper conditions the reaction can be extended to include enamines derived from alicyclic ketones. These enamines react under mild conditions with methyl acrylate or diethyl maleate to give cyclobutane adducts which are thermally unstable.

When the cyclopentanone–piperidine enamine (**1**) and methyl acrylate are allowed to react in acetonitrile without controlling the temperature, the Stork alkylation product[2] (**2**) is obtained in 68% yield on distillation. When, however, the reaction mixture was maintained below 30°, the undistilled reaction mixture appeared, on the basis of its n.m.r. and infrared spectra, to contain both **2** and the cycloaddition product (**3**).



1 **2**



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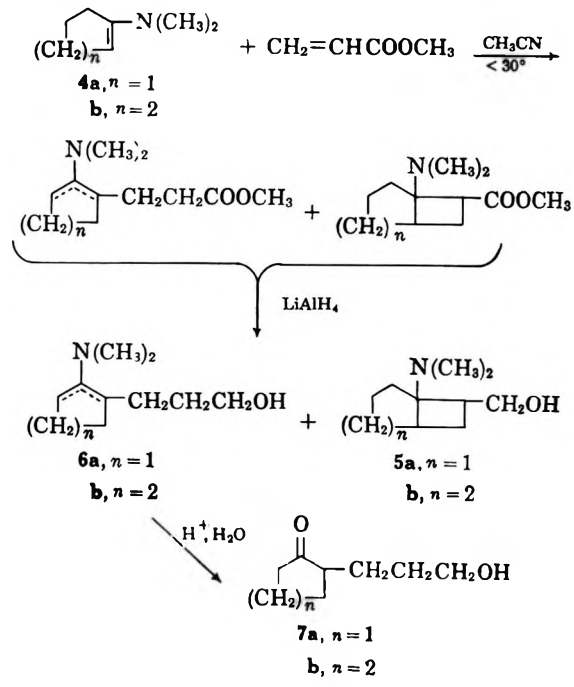
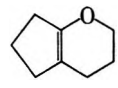
Similar reactions occurred when cyclohexanone enamines were substituted for the cyclopentanone enamine.

In order to demonstrate the presence of cycloaddition products in the enamine–methyl acrylate reaction mixtures, we carried out a sequence of reactions using the dimethylamine enamines of cyclopentanone **4a** and cyclohexanone **4b**.

Crude reaction mixtures from **4a** and **b** with methyl acrylate were stripped of solvent without heating them above 30° and then were subjected to reduction with lithium aluminum hydride under conditions which were shown not to affect the enamine double bond; for example, similar treatment of the cyclohexanone–pyrrolidine enamine gave an 86% recovery of the enamine. This treatment led to a mixture of **5** and **6** from which **5** was separated by means of acid-catalyzed hydrolysis of **6** to the keto alcohol **7**. This sequence afforded **5a** in 15.5% yield and **5b** in 21% yield based on methyl acrylate. The keto alcohol **7a** was converted



largely to pyran derivative **8**; no attempt to isolate **7b** was made.



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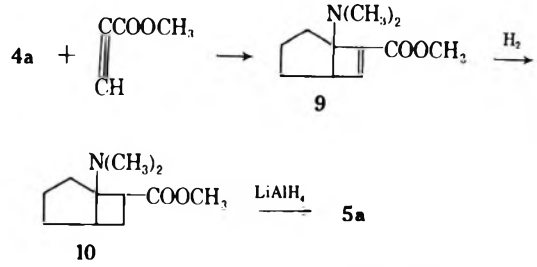
The structures of **5a** and **b** were assigned on the basis of their n.m.r. and infrared spectra as well as the independent synthesis of **5a** *via* another route. The adduct **9** derived from methyl propiolate and **4a**[3] was reduced catalytically at room temperature to the bicycloheptane (**10**) which was converted in 52% over-all yield to **5a** by lithium aluminum hydride.



9 **10**

On very mild warming, **10**, which showed only a weak absorption in the double bond region, was converted to a mixture which contained the Stork adduct

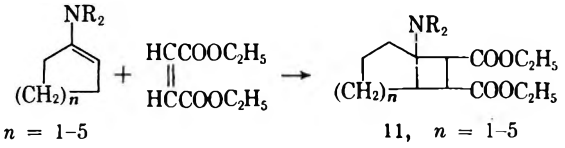
(1) Part IV of this series: K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

(2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(3) Part VI of this series: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

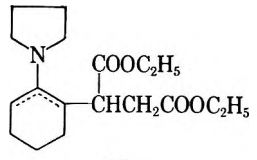
and which gave an infrared spectrum almost identical with that of the crude mixture obtained from **4a** and methyl acrylate.

Diethyl maleate was found to react rapidly and exothermically with a variety of alicyclic ketone enamines in acetonitrile and somewhat less rapidly in the absence of solvent. After the reactions had subsided, the infrared spectra of the reaction mixtures showed virtually no absorption in the double bond region. The reaction products thus appeared to be the cyclobutane adducts (**11**).



n = 1–5 **11**, n = 1–5

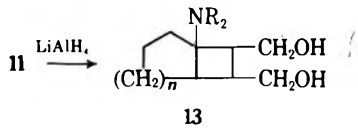
Cook has reported[4] the cyclohexanone–pyrrolidine enamine to react with diethyl maleate under more vigorous conditions, that is, refluxing the reactants alone or in a solvent to give the Stork adduct (**12**).



12

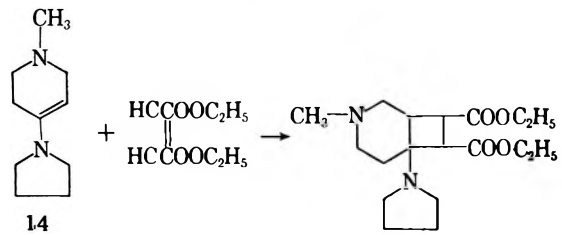
Our adducts (**11**) were, with few exceptions, nondistillable. Even on attempted molecular distillation most of them apparently dissociated into the reactants from which they were prepared, and the reactants recombined in the cold trap to regenerate the adducts (**11**). On heating they were converted more or less rapidly to the Stork products. Indeed, on standing at room temperature for about a year, the cyclopentanone, cyclohexanone, and cycloheptanone enamine adducts (**11**, n = 1, 2, and 3) had been converted largely to the Stork products, as indicated by their infrared spectra. The larger ring compounds (**11**, n = 4 and 5) appeared to be considerably more stable.

The adducts (**11**) could be converted to the stable diols (**13**) by reduction with lithium aluminum hydride.



13

In this case it was not necessary to resort to a hydrolysis step to remove the Stork adduct, since the amount of the latter appeared to be negligible as compared to the methyl acrylate reactions.



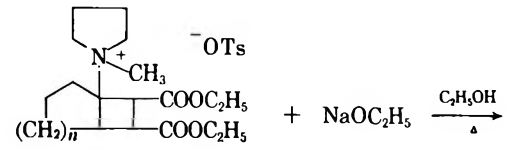
14 **15**

(4) A. G. Cook, Ph.D. thesis, University of Illinois, 1959.

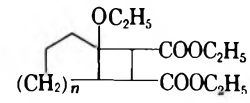
We prepared one cyclobutane derivative (**15**) from an enamine of a heterocyclic ketone (**14**) and diethyl maleate(col. 1, bottom).

Based on spectral data, no cycloaddition occurred when ethyl crotonate was allowed to react with 1-(1-cyclopenten-1-yl)piperidine or 1-(1-cyclohexen-1-yl)-pyrrolidine under mild conditions.

Some Transformations of Cyclobutane Derivatives.—We found that, when the methyl *p*-toluenesulfonate salt (**16**) of the cyclobutane derivatives (**11**, where n = 1 or 2) were treated with alcoholic sodium ethoxide under reflux, the ethoxy substituted derivatives (**17**) were obtained. These presumably were formed by Hofmann-



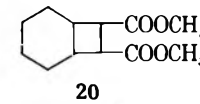
16, n = 1,2



17

type elimination of the salts to give the bicyclo alkenes, followed by the base-catalyzed addition of alcohol.

Dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (**19**) was obtained by the treatment of the methyl *p*-toluenesulfonate salt (**18**) with aqueous sodium hydroxide solution. Hydrogenation of this compound gave the bicyclooctane (**20**), while distillation resulted in a cyclobutene-type rearrangement leading to the unsaturated ester (**21**).



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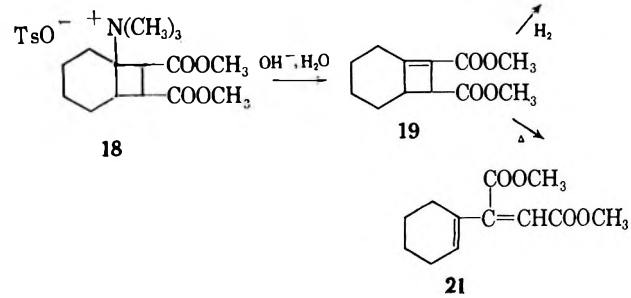
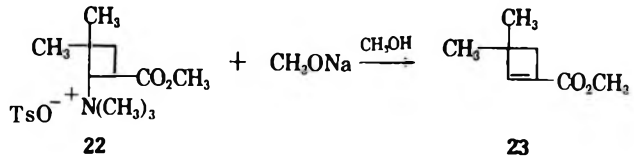


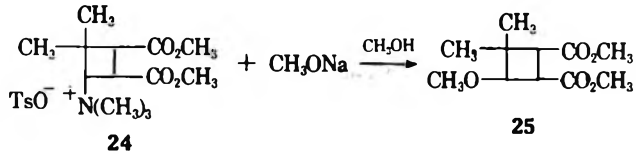
18 **19** **21**

The structures of these products were assigned on the basis of their elemental analyses and their infrared and n.m.r. spectra.

A study of the quaternary salts of simpler model compounds showed marked differences in their behavior. For example, when the methyl tosylate salt of methyl 2-dimethylamino-3,3-dimethyl cyclobutanecarboxylate (**22**) was treated with an equivalent of methanolic sodium methoxide, the elimination product (**23**) was obtained in good yield. In contrast to this result, analogous treatment of the quaternary salt of the corresponding diester (**24**) gave a good yield of dimethyl 3-methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate.

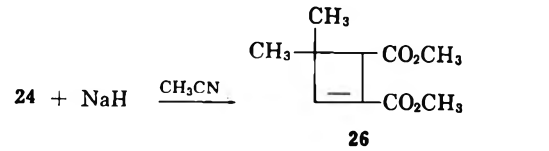


22 23



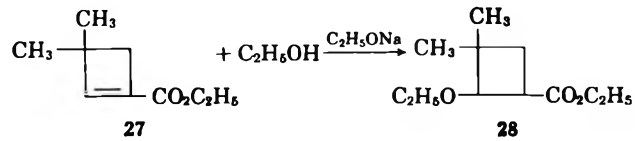
24 25

The cyclobutenedicarboxylate (**26**) could be obtained, however, by treating **24** with an equivalent of sodium hydride in a nonprotonic solvent.



26

A separate experiment showed that base-catalyzed addition of alcohol to the cyclobutene mono ester (**27**) did take place slowly, with ethyl 2-ethoxy-3,3-dimethylcyclobutanecarboxylate (**28**) being obtained in 40% yield after a reaction time of 18 days.



27 28

Experimental[5]

In several cases involving compounds which could not be purified because of their instability, no elemental analyses were obtained. In these cases we relied on n.m.r. and infrared spectral data.

Materials.—All of the enamines used in this investigation were prepared by previously described methods. The following new enamines were prepared.

1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine was prepared in 70% yield by the method of Heyl and Herr,[6] b.p. 73–75° at 0.2 mm., $n^{20}D$ 1.5230.

Anal. Calcd. for $C_{10}H_{18}N_2$: N, 16.8. Found: N, 16.9.

N,N-Dimethyl-1-cyclohexen-1-ylamine was prepared by the method described for N,N-dimethyl-1-cyclopenten-1-ylamine.[3]

Dimethyl 3-dimethylamino-4,4-dimethylcyclobutane-1,2-dicarboxylate was prepared from dimethyl maleate and N,N-dimethylisobutenylamine as has been described for the diethyl ester.[1] It was obtained in 73% yield with b.p. 84–87° at *ca.* 0.5 mm., $n^{20}D$ 1.4559.

Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.3; H, 8.7. Found: C, 59.5; H, 8.6.

Reactions of Alicyclic Ketone Enamines with Electrophilic Olefins. A. 1-(1-Cyclopenten-1-yl)piperidine with Methyl Acrylate.—1-(1-Cyclopenten-1-yl)piperidine (75.5 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (75 ml.) containing a pinch of hydroquinone were combined. An exothermic reaction occurred, and the temperature of the mixture rose to 70° within 11 min. After standing for 5.75 hr. at room temperature, the mixture was distilled to give 80 g. (68%) of methyl 2-piperidino-2-cyclopentene-1-propionate, b.p. 100–104° at *ca.* 0.5 mm., $n^{20}D$ 1.5011. The structure was assigned on the basis of the n.m.r. analysis which showed an olefinic proton resonance, though some of the 1-cyclopentene isomer may have been present.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.9; H, 9.8. Found: C, 71.1; H, 9.8.

This reaction was repeated, and the temperature of the mixture was maintained below 30° by means of intermittent cooling. After the reaction mixture had stood for 4.5 hr. at room temperature, the solvent was removed by distillation under reduced pressure, keeping the temperature below 30°. The infrared spectrum of the undistilled material was different from the spectrum of the distilled compound above. The double bond absorption at 6.1 μ was not strong, as that in the above compound was. This product is apparently a mixture of methyl 2-piperidino-2-(or 1)-cyclopentene-1-propionate and methyl 1-piperidinobicyclo[3.2.0]heptane-7-carboxylate, based on analogy with the subsequently described results.

B. N,N-Dimethyl-1-cyclopenten-1-ylamine with Methyl Acrylate.—N,N-Dimethyl-1-cyclopenten-1-ylamine (55 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (150 ml.) containing a pinch of hydroquinone were allowed to react as described above, keeping the temperature of the mixture below 30°. After the solvent was removed, the residue (94 g.) was dissolved in anhydrous ether (100 ml.) and added dropwise to a slurry of lithium aluminum hydride (13 g., 0.34 mole) in anhydrous ether (300 ml.). The ether refluxed during this addition. The reaction mixture was allowed to stand overnight. Ethyl acetate (10 ml.) and water (75 ml.) were added, and the solids were removed by filtration. Evaporation of the ether from the filtrate on a steam bath left 101 g. of residue. This residue was mixed with water (200 ml.) and concentrated hydrochloric acid (50 g.) and heated on the steam bath for 3 hr. It then was cooled and extracted twice with ether (50 ml.); the aqueous phase was made basic with 10% sodium hydroxide solution, whereupon an oil separated. The oil was separated by extraction with ether and distilled to give 33 g. (39% based on 0.5 mole of methyl acrylate) of crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 96–101° at *ca.* 1 mm., $n^{20}D$ 1.4912. The existence of a weak absorption band at 5.78–5.79 μ in the infrared spectrum of this material suggested the presence of a carbonyl component as an impurity.

The above reaction was repeated, using 0.47-mole quantities of starting materials. There was obtained 30 g. (38%) of crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, which likewise contained a carbonyl impurity.

The crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol from the above two preparations (63 g., 0.37 mole) was dissolved in a solution of water (100 ml.) and concentrated hydrochloric acid (35 ml.), and the resulting solution was extracted seven times with 100-ml. portions of ether. Evaporation of the combined extracts on a steam bath left 23.5 g. of "neutral material."

The acidic aqueous phase was made basic with dilute sodium hydroxide solution, and the oily layer which separated was removed by extraction with ether. Distillation of this ether extract gave 27 g. of 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 96–99° at *ca.* 0.5 mm., $n^{20}D$ 1.4975. The infrared spectrum had OH absorption at 3.1 and no absorption from 5.5 to 6.5 μ. The n.m.r. spectrum had OH absorption at 5.2 (singlet) and OCH_2– absorption at 3.4 p.p.m. (triplet). The infrared spectrum was identical with that of the material obtained from N,N-dimethyl-1-cyclopenten-1-ylamine and methyl propiolate by a series of transformations described subsequently.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.9; H, 11.3. Found: C, 70.8; H, 11.2.

The "neutral material" (23.5 g.) from above was distilled through a 6-in. Vigreux column to give 11.6 g. of distillate, b.p. 38–82° at 1 mm. (mostly 38–40° at 1 mm.). The infrared spectrum of this material indicated the presence of small amounts of hydroxy and carbonyl impurities. The material was redistilled to give 3.5 g of 2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran,[7] b.p. 32.5–33° at 2.5 mm., $n^{20}D$ 1.4872. The infrared spectrum had strong absorption at 5.85 μ. The n.m.r. spectrum contained OCH_2–absorption at 3.8 p.p.m. (triplet) and two broad absorptions due to six (lower field) and four protons.

Anal. Calcd. for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.0; H, 9.0.

This compound gave the 2,4-dinitrophenylhydrazone of 2-(3-hydroxypropyl)cyclopentanone, m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$: C, 52.2; H, 5.6. Found: C, 52.2; H, 5.6.

(5) Melting points were determined using a calibrated Fisher-Johns melting point apparatus. N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane.

(6) F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

(7) See N. D. Zelinskii and N. V. Elagina, *Dokl. Akad. Nauk SSSR*, **86**, 1117 (1952); *Chem. Abstr.*, **47**, 12271 (1953).

C. N,N-Dimethyl-1-cyclopenten-1-ylamine with Methyl Propiolate.—Methyl propiolate (28 g., 0.33 mole) was added slowly to N,N-dimethyl-1-cyclopenten-1-ylamine (38 g., 0.33 mole) in ether (100 ml.) over a 1-hr. period. The temperature was maintained below 35° during this time. The ether was removed by distillation under reduced pressure, keeping the temperature of the mixture below 35° and leaving 65 g. of methyl 1-dimethylaminobicyclo[3.2.0]hept-6-ene-7-carboxylate.[3]

Methyl 1-dimethylaminobicyclo[3.2.0]hept-6-ene-7-carboxylate (65 g., 0.33 mole) was dissolved in pentane (150 ml.) and hydrogenated at room temperature and 40 p.s.i., using 1 g. of 5% palladium-on-alumina catalyst. The catalyst was removed by filtration, and the solvent was removed by distillation (without heating above 30°) under reduced pressure, leaving 71 g. of crude methyl 2-dimethylaminobicyclo[3.2.0]heptane-7-carboxylate, $n^{20}D$ 1.4776.

This product (71 g.) was dissolved in ether, and the resulting solution was added slowly to a slurry of lithium aluminum hydride (11 g., 0.29 mole) in ether (300 ml.). The reaction mixture, after standing overnight at room temperature, was treated with ethyl acetate (to decompose excess hydride) followed by water (100 ml.). The solids were filtered and washed with ether. The filtrate was evaporated on the steam bath, leaving 77 g. of residue. The infrared spectrum of this residue showed the presence of hydroxy (3.0) and carbonyl (5.8) groups and weak unsaturation (6.1 μ). The 77 g. of residue was dissolved in a solution of concentrated hydrochloric acid (40 ml.) and water (200 ml.) and heated for 0.5 hr. on a steam bath. The mixture was cooled and extracted six times with 50-ml. portions of ether. Evaporation of the ether from the combined extracts on the steam bath left 4 g. of residue.

The aqueous layer was made basic with 20% sodium hydroxide solution and extracted twice with 50-ml. portions of ether. Distillation of the combined ether extracts gave, after removal of ether, 29 g. (52% yield, based on 0.3 mole of starting materials) of 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 94–100° at 0.5–0.6 mm., $n^{20}D$ 1.4978. The infrared spectrum of this compound was identical with that of the compound obtained from the lithium aluminum hydride reduction of the adduct from methyl acrylate and N,N-dimethyl-1-cyclopenten-1-ylamine.

D. 1-(1-Cyclohexen-1-yl)pyrrolidine with Methyl Acrylate.—1-(1-Cyclohexen-1-yl)pyrrolidine (76 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (100 ml.) which contained a pinch of hydroquinone were combined. The temperature of the mixture rose to 60° within 20 min. Distillation of the mixture gave, after removal of solvent and 8 g. of forerun, 90 g. (80%) of methyl 2-(1-pyrrolidinyl)-2(or 1)-cyclohexene-1-propionate, b.p. 108–112° at *ca.* 0.5 mm., $n^{20}D$ 1.5072.

E. N,N-Dimethyl-1-cyclohexen-1-ylamine with Methyl Acrylate.—N,N-Dimethyl-1-cyclohexen-1-ylamine (62.5 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (150 ml.) which contained a pinch of hydroquinone were allowed to react, keeping the temperature of the mixture below 30° by means of intermittent cooling. The solvent was removed by distillation under reduced pressure, and the residue (92 g.) was reduced with lithium aluminum hydride (13 g., 0.34 mole) as described above for 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol. The crude alcohol was heated on the steam bath for 2.5 hr. with a mixture of water (250 ml.) and concentrated hydrochloric acid (50 g.). This solution was cooled, extracted twice with 50-ml. portions of ether, and the acidic aqueous phase was made basic with 10% sodium hydroxide solution. The oil which separated was removed by extraction with ether. Distillation of the ether extracts gave, after removal of ether and a 2-g. forerun, 18.5 g. (21% based on starting methyl acrylate) of 1-dimethylaminobicyclo[4.2.0]octane-8-methanol, b.p. 103–107° at 1 mm., $n^{20}D$ 1.5043. The infrared and n.m.r. spectra were consistent with the assigned structure as described above for the homologous bicycloheptane derivative.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.2; H, 11.5. Found: C, 72.1; H, 11.5.

F. 1-(1-Cyclopenten-1-yl)piperidine with Diethyl Maleate.—1-(1-Cyclopenten-1-yl)piperidine (75.5 g., 0.5 mole), diethyl maleate (86 g., 0.5 mole), and acetonitrile (125 ml.) were combined. An exothermic reaction occurred, and the temperature rose to a maximum of 63° within 17 min. After letting the mixture stand for 1 hr., the solvent was removed by distillation under reduced pressure, leaving 170 g. of crude diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate. The infrared spectrum of this material showed no appreciable absorption between 5.9 and 6.5 μ.

Diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate (161 g., 0.5 mole) was dissolved in ether (150 ml.), and the solution was added dropwise with stirring to lithium aluminum hydride (25 g., 0.66 mole) dissolved in ether (700 ml.). The addition, which required 5 hr., was done at such a rate as to maintain gentle refluxing of the ether. The reaction mixture was allowed to stand overnight. Ethyl acetate (50 ml.) was added to decompose excess hydride, then water (200 ml.) was added. The solids were collected and washed with ether; the combined ether filtrate and washings were evaporated on a steam bath. The residue crystallized to give 91 g. (76%) of 1-piperidinobicyclo[3.2.0]heptane-6,7-dimethanol. A sample was purified by dissolving it in 10% hydrochloric acid solution, extracting it with ether to remove neutral impurities, making it basic with dilute sodium hydroxide solution, extracting it with ether, and evaporating it on a steam bath. Recrystallization of the residue from toluene gave white crystals, m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.3; H, 10.5; mol. wt., 239. Found: C, 70.6; H, 10.4; mol. wt., 242.

G. N,N-Dimethyl-1-cyclohexen-1-ylamine with Diethyl Maleate.—N,N-Dimethyl-1-cyclohexen-1-ylamine (75 g., 0.6 mole), diethyl maleate (103 g., 0.6 mole), and acetonitrile (100 ml.) were combined. An exothermic reaction occurred, and the temperature was maintained below 40° by means of intermittent cooling. After standing for 3.5 hr., the mixture was divided into two equal portions, and one portion was reduced as described below.

The other portion was distilled in an alembic-type pot molecular still to give 81 g. (91%) of diethyl 1-dimethylaminobicyclo[4.2.0]-octane-7,8-dicarboxylate, boiling at 65–67° at *ca.* 1–5 μ.

Anal. Calcd. for $C_{18}H_{27}O_4$: C, 64.7; H, 9.2; N, 4.7. Found: C, 64.5; H, 9.0; N, 4.5.

Diethyl 1-dimethylaminobicyclo[4.2.0]octane-7,8-dicarboxylate (90 g., *ca.* 0.3 mole) was reduced with lithium aluminum hydride (30 g., 0.79 mole) as described above for diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate. Distillation of the crude product gave 27.5 g. (43%, based on starting diethyl maleate) of 1-dimethylaminobicyclo[4.2.0]octane-7,8-dimethanol, b.p. 160–165° at 1 mm.

A sample for analysis was redistilled and had b.p. 156–157° at *ca.* 0.5 mm., $n^{20}D$ 1.5140.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.7; H, 10.9. Found: C, 67.6; H, 11.0.

H. 1-(1-Cyclohepten-1-yl)pyrrolidine with Diethyl Maleate.—1-(1-Cyclohepten-1-yl)pyrrolidine (30 g., 0.18 mole), diethyl maleate (31.2 g., 0.18 mole), and acetonitrile (75 ml.) were combined and allowed to stand at room temperature for 1 day. The solvent was removed by distillation under reduced pressure, leaving 61 g. of diethyl 1-(1-pyrrolidinyl)bicyclo[5.2.0]nonane-8,9-dicarboxylate, $n^{20}D$ 1.4932. The infrared spectrum showed strong carbonyl absorption at 5.8, and no absorption at 5.9–6.5 μ.

I. 1-(1-Cycloocten-1-yl)piperidine with Diethyl Maleate.—Similarly, 1-(1-cycloocten-1-yl)piperidine (13 g., 0.067 mole) and diethyl maleate (11.6 g., 0.067 mole) gave 24 g. of diethyl 1-piperidinobicyclo[6.2.0]decane-9,10-dicarboxylate, $n^{20}D$ 1.4918. The infrared spectrum supported the assigned structure as described above.

J. 1,2,3,6-Tetrahydro-1-methyl-4-(1-pyrrolidinyl)pyridine with Diethyl Maleate.—1,2,3,6-Tetrahydro-1-methyl-4-(1-pyrrolidinyl)pyridine (16.6 g., 0.1 mole) and diethyl maleate (17.2 g., 0.1 mole) were combined. The temperature of the mixture rose to a maximum of 66.5° after 5 min. and then dropped back to room temperature. After 3 hr. an infrared spectrum of the product showed no double bond absorption. The yield of diethyl 3-methyl-6-pyrrolidinyl-3-azabicyclo[4.2.0]octane-7,8-dicarboxylate, a viscous liquid with $n^{20}D$ 1.4893, was virtually quantitative.

Some Transformations of Cyclobutane Derivatives. A. Diethyl 1-Ethoxybicyclo[3.2.0]heptane-1,2-dicarboxylate.—1-(1-Cyclopenten-1-yl)pyrrolidine (50 g., 0.365 mole) was added to diethyl maleate (63 g., 0.365 mole) with stirring and cooling to prevent the temperature of the mixture from exceeding 40°, and the mixture was allowed to stand overnight. Upon adding methyl *p*-toluenesulfonate (68 g., 0.365 mole) to the crude diethyl 2-pyrrolidinylbicyclo[3.2.0]heptane-1,2-dicarboxylate, it was necessary to cool the mixture in a cold-water bath to prevent the temperature from rising above 60°. After standing for 2 hr., the reaction mixture had set to a glass. A solution of sodium ethoxide in ethanol was prepared from freshly cut sodium (8.6 g., 0.375 g.-atom) and ethanol (200 ml.). To this solution was

added, dropwise over a 0.5-hr. period, a solution of the quaternary salt in ethanol (200 ml.). The resulting slurry was refluxed for 2.5 hr., cooled, and poured onto ice (500 g.). The pH of the solution was adjusted to 6 with concentrated hydrochloric acid (26 ml.). The solution was extracted with four 250-ml. portions of ether. The combined extracts were dried over sodium sulfate and distilled *in vacuo* to obtain, after removing the ether, alcohol, and a small forerun, 64 g. (61%) of diethyl 1-ethoxybicyclo[3.2.0]heptane-1,2-dicarboxylate, b.p. 106–107° at 0.5 mm., $n^{20}D$ 1.4594.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.4; H, 8.5. Found: C, 63.4; H, 8.5.

B. Diethyl 1-Ethoxybicyclo[4.2.0]octane-1,2-dicarboxylate.—Similarly, the diethyl maleate–cyclohexenylpyrrolidine adduct gave a 57% yield of diethyl 1-ethoxybicyclo[4.2.0]octane-1,2-dicarboxylate, b.p. 127–130° at 0.7 mm., $n^{20}D$ 1.4658.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.5; H, 8.8. Found: C, 64.8; H, 8.8.

C. Dimethyl Bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate.—Dimethyl maleate (72 g., 0.5 mole) was added, all at once, to N,N-dimethyl-1-cyclohexen-1-ylamine (62.5 g., 0.5 mole) in acetonitrile (75 ml.). An exothermic reaction occurred, and the mixture was cooled to maintain the temperature at 40–45°. The mixture then was allowed to stand overnight. The solvent was removed *in vacuo*, and the remaining 132 g. of crude dimethyl 1-dimethylaminobicyclo[4.2.0]octane-7,8-dicarboxylate was treated with methyl *p*-toluenesulfonate (91 g., 0.49 mole), and the mixture was allowed to stand overnight. The resulting quaternary salt was dissolved in water (250 ml.), and the solution was filtered to remove a small quantity of solid (4.2 g.). The solution then was extracted with ether, and the aqueous layer was treated with 200 ml. of 10% sodium hydroxide solution. The oil which separated was removed by extraction with ether, and the extract was dried over magnesium sulfate. The filtered solution was stripped of ether leaving 52.5 g. (48%) of crude dimethyl bicyclo[4.2.0]-oct-8-ene-7,8-dicarboxylate. The n.m.r. spectrum showed two O-methyl absorptions at 3.55 and 3.6, but no other absorption below 3.2 p.p.m. The infrared spectrum showed a double bond absorption at 5.95 μ.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.4; H, 7.3.

D. Dimethyl Bicyclo[4.2.0]octane-7,8-dicarboxylate.—Dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (21.8 g., 0.097 mole) was dissolved in a mixture of ether (25 ml.) and pentane (25 ml.) and hydrogenated at 40 p.s.i. and room temperature over 0.5 g. of 5% palladium-on-alumina catalyst. The catalyst was removed by filtration, and the filtrate was distilled to give, after removal of solvent, 16.4 g. (75%) of dimethylbicyclo[4.2.0]octane-7,8-dicarboxylate, b.p. 100° at 1 mm., $n^{20}D$ 1.4730. The infrared spectrum showed no absorption between 5.8 and 6.0 μ.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0; sapon. equiv., 113.1. Found: C, 63.8; H, 8.0; sapon. equiv., 113.6.

E. Dimethyl (1-Cyclohexen-1-yl)fumarate.—A portion of the crude dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (20 g., 0.089 mole) was distilled at 0.3 mm. to give, after removal of 3 g. of forerun, 13.5 g. (68%) of dimethyl (1-cyclohexen-1-yl)fumarate, b.p. 111–113° at 0.3 mm., $n^{20}D$ 1.5262. The n.m.r. spectrum showed a triplet at 6.2 and a singlet at 9.8 p.p.m. due to the cyclohexene and fumarate protons, respectively.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.4.

F. Methyl 3,3-Dimethyl-1-cyclobutene-1-carboxylate.—Methyl 3,3-dimethyl-2-dimethylaminocyclobutanecarboxylate (1000 g., 5.4 moles) in methanol (1 l.) was treated dropwise with a solution of methyl *p*-toluenesulfonate (1000 g., 5.38 moles) in methanol (100 ml.). The mixture was cooled intermittently with a cold-water bath to keep the temperature from going above 30°. The mixture then was allowed to stand overnight. The resulting solution of quaternary salt was treated with a solution of sodium methoxide (290 g., 5.38 moles) in methanol (850 ml.). After stirring for 1 hr., the mixture was filtered and the alcohol was removed *in vacuo*. Water (500 ml.) and ether (500 ml.) were added to the residue, and the ether layer separated after thorough shaking of the mixture. The aqueous layer was extracted once with 200 ml. of ether, and the combined ether layers were washed with 10% hydrochloric acid and dried over magnesium sulfate. The drying agent was filtered off; the filtrate was distilled to give, after removal of ether, methanol, and a small forerun, 599 g. (79%) of methyl 3,3-dimethyl-1-cyclobutene-1-carboxylate, b.p. 56–62° at 15–17 mm., $n^{20}D$ 1.4440.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.6; H, 8.6. Found: C, 68.6; H, 8.5.

G. Dimethyl 3-Methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate.—To a solution of dimethyl 4,4-dimethyl-3-dimethylaminocyclobutane-1,2-dicarboxylate (243 g., 1.0 mole) in methanol (150 ml.) was added methyl *p*-toluenesulfonate (186 g., 1.0 mole). The temperature of the mixture rose slowly to 35°. The mixture was allowed to stand overnight. A solution of sodium methoxide (54 g., 1.0 mole) in methanol (200 ml.) was added to the solution of quaternary salt. After the slightly exothermic reaction had subsided, the mixture was stirred for 2 hr. and filtered. The filtrate was distilled *in vacuo* to remove the alcohol, and the residue was treated with water (250 ml.) and ether (250 ml.). After thorough shaking, the ether layer was separated, dried over sodium sulfate, and distilled to give 191 g. (83%) of dimethyl 3-methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate, b.p. 62–65° at 0.10–0.15 mm., $n^{20}D$ 1.4483.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.8. Found: C, 57.9; H, 8.0.

H. Dimethyl 4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylate.—Methyl iodide (71 g., 0.5 mole) was added to a solution of dimethyl 4,4-dimethyl-3-dimethylaminocyclobutane-1,2-dicarboxylate (121.5 g., 0.5 mole) in acetonitrile (350 ml.). The reaction mixture was cooled to keep the temperature from exceeding 35°. The mixture then was allowed to stand overnight. This solution of quaternary salt was added to a suspension of sodium hydride (24 g. of a 51% dispersion in mineral oil) in anhydrous acetonitrile (100 ml.). An exothermic reaction occurred with vigorous evolution of gas. When the evolution of gas slowed, the mixture was heated to 60° for 1 hr. and then distilled *in vacuo* to 50° at 80 mm. When the residue was taken up in 400 ml. of water, an oily layer separated. The aqueous solution was extracted with two 300-ml. portions of ether, and the combined ether and organic layers were dried over sodium sulfate. The ether was distilled *in vacuo*, and the distillation was continued to give 65 g. (68%) of dimethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate, b.p. 80–84° at 0.9 mm., $n^{20}D$ 1.4587.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.3; H, 7.3.

I. Ethyl 2-Ethoxy-3,3-dimethylcyclobutanecarboxylate.—To ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate[1] (9.2 g., 0.060 mole) was added ethanol (2.74 g., 0.06 mole) and sodium hydride (0.2 g., 0.004 mole). When all of the sodium hydride had reacted, the mixture was warmed briefly on the steam bath and then allowed to stand for 18 days at room temperature. After filtration to remove a small amount of solid, the filtrate was washed with water and 10% hydrochloric acid solution. The combined aqueous washings were extracted with ether, and the ether was added to the original organic layer. The resulting ethereal solution was dried over Drierite. After filtration, distillation *in vacuo* gave, after removal of ether and a 0.9-g. forerun, 5.5 g. (46%) of ethyl 2-ethoxy-3,3-dimethylcyclobutanecarboxylate, b.p. 35.5–38° at *ca.* 0.5 mm., $n^{20}D$ 1.4290.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.1. Found: C, 66.1; H, 10.0.

Enamine Chemistry. VI. Reactions with Propiolates[1]

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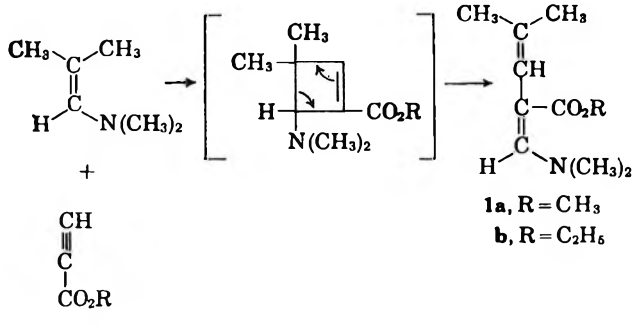
The reaction of a variety of enamines with propiolates was studied. With a few exceptions the reaction products were those derived from the cyclobutene rearrangement of cycloaddition products initially formed. Methods are described for the conversion of several cyclic ketones (with the exception of cyclohexanone) to their higher homologs containing two more carbon atoms in the ring.

Cycloaddition reactions of enamines with electrophilic olefins have been reported previously.[2] Extension of the cycloaddition reaction to include reactions of enamines with acetylenedicarboxylates also has been described.[3,4] The reactions of enamines with propiolates are more complex and will be discussed separately in this paper.

In general, the reactions of propiolates with a number of enamines involved initial cycloadditions to form cyclobutene derivatives. These cyclobutenes rearranged, in most cases spontaneously, to form products whose structures depended on the starting enamine and on the reaction conditions. Since the results differed greatly depending on the enamine used, the reactions of the various enamines will be discussed separately.

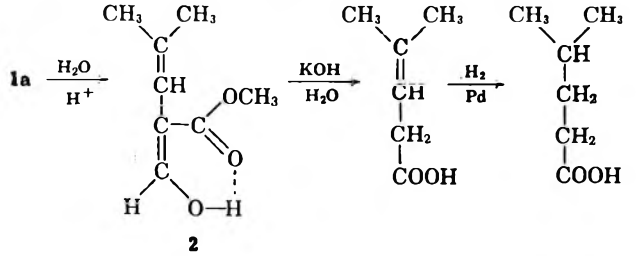
When N,N-dimethylisobutenylamine was allowed to react with methyl or ethyl propiolate, the products expected from cyclobutene rearrangement of the presumed intermediate cycloaddition products were obtained in about 50% yield. When a propiolate was



1a, R = CH_3
b, R = C_2H_5

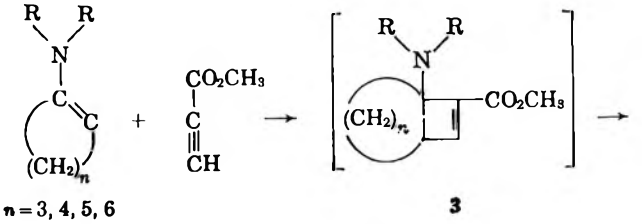
added to the enamine, only a small amount of high-boiling material was formed. Addition of enamine to a propiolate, however, yielded, in addition to the 3-pentenoate (**1**), 29% of an unidentified higher-boiling product formed by reaction of 1 mole of enamine with 2 moles of propiolate.

The structure of **1a** was proved by stepwise hydrolysis to 4-methyl-3-pentenoic acid and hydrogenation of this acid to 4-methylvaleric acid. Both **1a** and the initial hydrolysis product (**2**) had infrared and n.m.r. spectra which supported the assignment of structure.

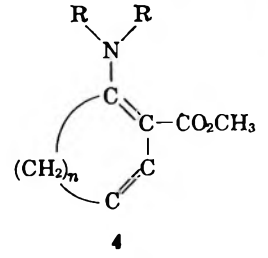


2

The extension of the enamine–propiolate reaction to enamines derived from cyclic ketones was studied then. Reactions of such cyclic enamines with methyl propiolate might be expected by analogy to yield cyclic products with the ring enlarged by two carbon atoms. Ring enlargement products of the type shown were actually obtained in most cases. However, the conditions, yields, and number and types of by-products varied greatly with the ring size of the enamine.

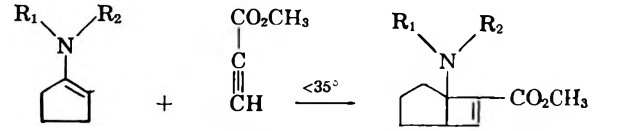


n = 3, 4, 5, 6 **3**



4

When enamines derived from cyclopentanone were allowed to react with methyl propiolate at temperatures below 35°, the products were bicycloheptene derivatives (**5**). The bicycloheptenes were found to undergo rearrangements which depended on the nature of the groups attached to the enamine nitrogen atom.



5a, $R_1 = R_2 = CH_3$
b, $R_1 + R_2 = -(CH_2)_4-$
c, $R_1 + R_2 = -(CH_2)_5-$
d, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$

On standing at room temperature, **5a** isomerized to methyl 2-dimethylamino-1-cyclopentene-1-acrylate (**6**), analogous to the products obtained by Stork and coworkers from cyclopentenylamines and acrylic esters.[5] The structure of **6** was established by hydrolysis and hydrogenation to methyl 2-oxocyclopentanepropio-

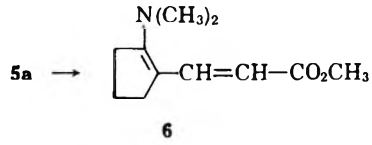
(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(3) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963).

(4) G. A. Berchtold and G. F. Uhlig, *ibid.*, **28**, 1459 (1963).

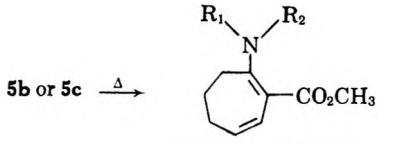
(5) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).



6

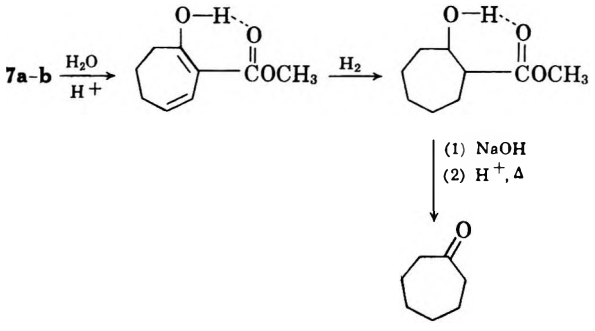
nate. The presence of a small amount of an analogous rearrangement product from **5b** was indicated by the n.m.r. spectra of the crude bicycloheptene and of its crude thermal rearrangement product. It is not clear how the Stork products are formed from the bicycloheptenes. The most plausible explanation is that the initial cycloaddition is reversible and that it competes with a slower but irreversible reaction which leads to the Stork addition product (**6**).

The rearrangement of **5b** and **c** proceeded exothermically when they were heated to about 90°. The products were cycloheptadiene derivatives (**7a** and **b**)

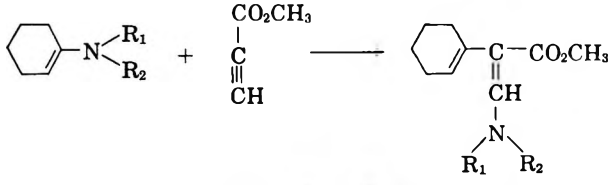


7a, $R_1 + R_2 = -(CH_2)_4-$
b, $R_1 + R_2 = -(CH_2)_5-$

apparently formed by cyclobutene rearrangement. The structure of **7** was established by degradation to cycloheptanone.

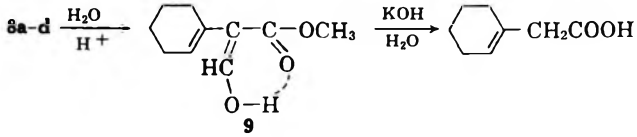


Enamines derived from cyclohexanone reacted with methyl propiolate to form unexpected products.



8a, $R_1 = R_2 = CH_3$
b, $R_1 + R_2 = -(CH_2)_4-$
c, $R_1 + R_2 = -(CH_2)_5-$
d, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$

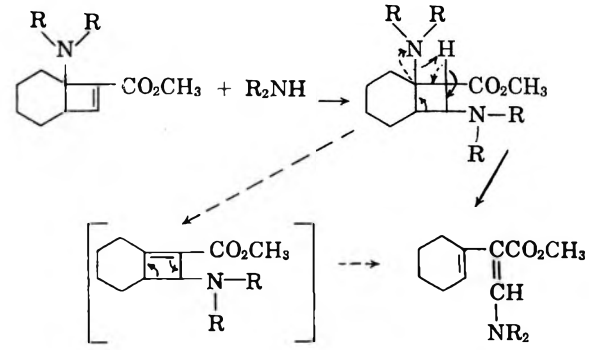
Assignment of structures **8a–d** was based initially on the infrared and n.m.r. spectra of the products. It was supported by acid hydrolysis of the various compounds to a common hydrolysis product (**9**), which could in turn be hydrolyzed by base to 1-cyclohexene-1-acetic acid.



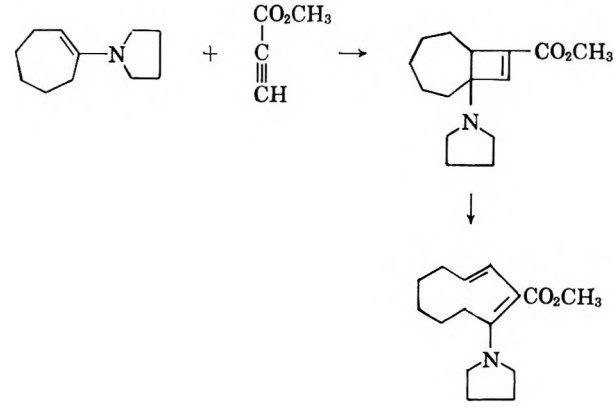
9

It was not possible to detect any products analogous to **6** or **7** in the reaction mixtures of cyclohexanone enamines with methyl propiolate, nor could any bicyclooctene derivatives analogous to **5** be isolated. Apparently the geometry of the bicyclooct-7-ene system is such that cyclobutene rearrangement is not favored, and other reactions occur.[6]

It is possible to rationalize the formation of **8** by assuming the addition of a secondary amine (which would have to be present in only trace amounts) to the intermediate bicyclooctene, followed by loss of the bridgehead amine group with simultaneous or subsequent rearrangement to **8** and regeneration of the secondary amine.



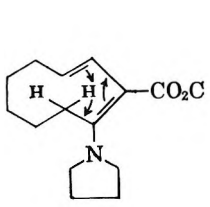
The reaction of 1-(1-cyclohepten-1-yl)pyrrolidine with methyl propiolate proceeded readily. The intermediate bicyclononene rearranged too rapidly for it to be detected, and the product of ring enlargement (**10**) could be isolated in good yield by chilling the reaction mixture. The structure assignment of **10** was based on its infrared and n.m.r. spectra. The compound was quite unstable and rearranged on standing overnight at room temperature or rapidly when it was treated with dilute acid. The product of this rearrangement was a



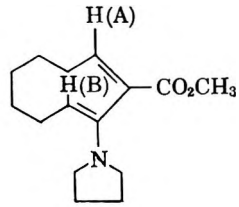
10

basic liquid which no longer showed the characteristic infrared absorptions of the $-C(NR_2)=C(CO_2R)-CH=CH-$ system (maxima at 5.97–6.02 and 6.45–6.6 μ) but showed strong maxima at 5.88 and 6.2 μ. In addition, the n.m.r. spectrum showed a triplet centered at 6.95 p.p.m. (relative to tetramethylsilane) due to one olefinic proton, and an overlapping pair of doublets centered at 4.17 p.p.m. due to one proton. In the light of these spectral data and the chemical transformations to be

(6) *Cf.* ref. 3.



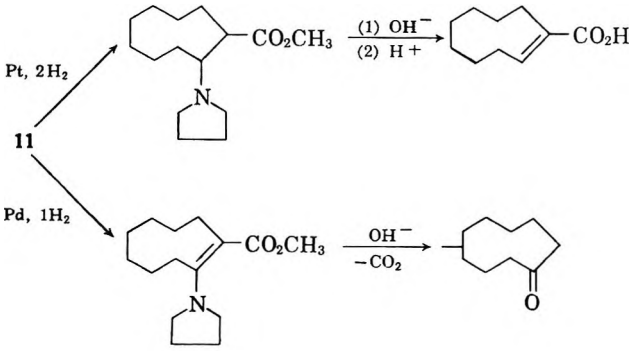
10



11

described, we are assigning structure **11** to the rearrangement product derived from **10**. In **11** the 5.88-μ absorption is due to the α,β-unsaturated ester and the 6.2-μ absorption is due to the enamine C=C. The 6.95-p.p.m. triplet is due to proton A and the 4.17-p.p.m. absorption is due to proton B.[4]

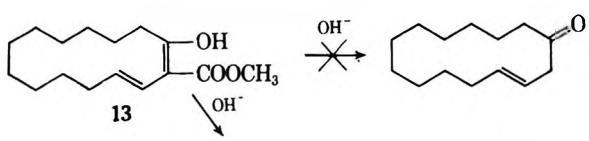
On hydrogenation over platinum in acetic acid, **11** absorbed two equivalents of hydrogen, and the reduction product on digestion with aqueous base gave 1-cyclononene-1-carboxylic acid. Reduction of **11** over palladium in acetic acid gave a break in the rate of hydrogen absorption when one equivalent of hydrogen had been absorbed. Interruption of the hydrogenation at this stage gave **12**, which like **11** did not undergo hydrolysis of the enamine function in dilute acid. Treatment of **12** with dilute base did, however, give cyclononanone in good yield.



12

We can offer no explanation for the failure of **11** and **12** to undergo acid-catalyzed hydrolysis of the enamine function, but can find no other structures which satisfy the available data. Support for the idea that rearrangement of **10** to **11** involves a proton transfer also is found in the fact that the reaction appears to be acid-catalyzed.

Reaction of the pyrrolidine enamines of cyclooctanone and cyclododecanone with methyl propiolate gave products of ring enlargement which were much more stable than the corresponding cyclononadiene. Both the cyclodecadiene and cyclotetradecadiene derivatives underwent acid hydyrolysis of the enamine function. The hydrolysis products on hydrogenation, saponification, and decarboxylation gave cyclodecanone and cyclotetradecanone, respectively, in satisfactory yield. Several attempts to convert the cyclotetradecene keto ester or its enol (**13**) to cyclotetradecenone by basic hydrolysis led only to the ring-opened acid (**14**).



13

$HOOC(CH_2)_{10}CH=CHCH_2COOH$

14

Experimental[7]

Materials.—The pyrrolidine enamines of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone were prepared as described by Kuehne.[8] The morpholine and piperidine enamines of cyclopentanone[9] and cyclohexanone[10] were prepared also by essentially this same method. 1-(1-Cyclododecen-1-yl)-pyrrolidine was prepared as described in a previous paper.[3] The dimethylamine enamine of cyclopentanone was prepared by a modification of the method of Mannich and Davidsen.[11] Linde 13X Molecular Sieve was used as the drying agent instead of potassium carbonate. N,N-Dimethyl-1-cyclopenten-1-ylamine, b.p. 59–60° at 30 mm., $n^{20}D$ 1.4810, was obtained in 63% yield.

Anal. Calcd. for $C_7H_{13}N$: N, 12.6. Found: N, 11.7.

Many of the enamines prepared during this investigation failed to give good analytical results, presumably because of reaction with air and/or atmospheric moisture. Kuehne[8] noted that the refractive indices of enamines which he prepared dropped rapidly on exposure to air, probably for the same reason.

Ethyl 2-(Dimethylaminomethylene)-4-methyl-3-pentenoate (1b).—N,N-Dimethylisobutenylamine (50 g., 0.5 mole) was added over a 15-min. period to ethyl propiolate (50 g., 0.5 mole) with cooling to keep the temperature below 50°. The mixture was allowed to stand for 3 hr. Heat was evolved slowly throughout this period, and the temperature was maintained at 30–45° by cooling the mixture occasionally. After 3 hr. no more heat was evolved, and the mixture was allowed to stand overnight at room temperature. Distillation gave 47 g. (47%) of ethyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (**1b**), b.p. 92–95° at *ca.* 1 mm., a 7.5-g. intermediate cut; and 21.5 g. (29%) of an adduct from 1 mole of N,N-dimethylisobutenylamine and 2 moles of ethyl propiolate, b.p. 135–137° at *ca.* 1 mm., $n^{20}D$ 1.4949.

Anal. Calcd. for **1b**, $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7. Found: C, 66.7; H, 9.7.

Anal. Calcd. for 2:1 adduct, $C_{16}H_{25}NO_4$: C, 65.1; H, 8.5. Found: C, 64.8; H, 8.2.

With 2,4-dinitrophenylhydrazine, **1b** gave the 2,4-dinitrophenylhydrazone of ethyl 2-formyl-4-methyl-3-pentenoate, m.p. 108–109°.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.4; H, 5.2. Found: C, 51.6; H, 5.2.

Methyl 2-(Dimethylaminomethylene)-4-methyl-3-pentenoate (1a).—Methyl propiolate (55 g., 0.65 mole) was added dropwise to N,N-dimethylisobutenylamine (80 g., 0.8 mole) in 50 ml. of ether. The temperature of the reaction mixture rose to 50° after 0.5 hr. and decreased to room temperature over the next 3 hr. Distillation gave, after removal of ether and excess N,N-dimethylisobutenylamine, 61 g. (50%) of methyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (**1a**), b.p. 88–95° at 1–1.5 mm., $n^{20}D$ 1.5297, and 24 g. of higher-boiling material which was not further investigated.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.6; H, 9.4; N, 7.6. Found: C, 65.4; H, 9.3; N, 7.8.

With 2,4-dinitrophenylhydrazine, **1a** gave the 2,4-dinitrophenylhydrazone of methyl 2-formyl-4-methyl-3-pentenoate, m.p. 126–127°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8. Found: C, 49.8; H, 4.9.

Methyl 2-Formyl-4-methyl-3-pentenoate.—Methyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (56 g., 0.31 mole) was dissolved in a solution of concentrated hydrochloric acid (130 ml.) in water (700 ml.). The mixture was allowed to stand with occasional shaking for 3 hr., and an oily layer gradually separated.

The mixture was extracted with ether and the ether layer was distilled to give, after removal of ether, 40 g. (84%) of methyl 2-formyl-4-methyl-3-pentenoate, b.p. 50–53° at 2 mm., $n^{20}D$

(7) Melting points were determined using a calibrated Fisher-Johns melting point apparatus. N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane. All structure assignments were supported by infrared and n.m.r. spectra. Spectral data for specific compounds are included when pertinent.

(8) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

(9) A. Rieche, E. Schmitz, and E. Beyer, *Chem. Ber.*, **92**, 1212 (1959).

(10) S. Hünig, E. Benzing, and E. Lücke, *ibid.*, **90**, 2833 (1957).

(11) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

1.4808. This product gave an intense violet color with iron(III) chloride solution, and its infrared spectrum indicated that it exists largely in the enolic or hydroxymethylene form. This spectrum was compared with those of similar compounds.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.9; H, 8.0.

4-Methyl-3-pentenoic Acid.—Methyl 2-formyl-4-methyl-3-pentenoate (37 g., 0.24 mole) was refluxed with a solution of potassium hydroxide (40 g., 1 mole) in water (150 ml.) for 4 hr. The solution was acidified with concentrated hydrochloric acid and extracted with ether. Distillation of the ether layer gave, after removal of ether, 20 g. (74%) of 4-methyl-3-pentenoic acid, b.p. 85–90° at 4 mm., $n^{20}D$ 1.4464; lit.[12] b.p. 83–84° at 4 mm., $n^{20}D$ 1.4457.

4-Methylvaleric Acid.—4-Methyl-3-pentenoic acid (5 g., 0.044 mole) in 50 ml. of pentane was hydrogenated over 0.5 g. of 5% palladium on alumina at room temperature and 3-atm. pressure. Distillation gave, after removal of pentane, 4.1 g. (80%) of 4-methylvaleric acid, b.p. 69° at 2.5 mm., $n^{20}D$ 1.4144; lit.[12] b.p. 199° at 752 mm., $n^{20}D$ 1.4144. The infrared spectrum was identical with that of authentic 4-methylvaleric acid.

Methyl 5-Piperidinobicyclo[3.2.0]hept-6-ene-6-carboxylate (5c).—Methyl propiolate (57 g., 0.68 mole) was added slowly to 1-(1-cyclopenten-1-yl)piperidine (103 g., 0.68 mole) in ether (200 ml.) over a period of 2 hr. The temperature was maintained below 35° during the addition. The ether was removed by distillation under reduced pressure while the temperature was maintained below 35°. The residue crystallized to give 145 g. (91%) of methyl 5-piperidinobicyclo[3.2.0]hept-6-ene-6-carboxylate, m.p. 41–43°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.5; H, 9.0. Found: C, 71.0; H, 9.1.

The n.m.r. spectrum of this compound showed a single peak at 6.59 p.p.m. assignable to the olefinic proton, and a broad unresolved peak in the region associated with tertiary protons. The failure to observe resolvable splitting between the tertiary and olefinic protons is in agreement with the observed absence of spin–spin splitting in cyclobutene.[14] The infrared spectrum contained a strong absorption at 5.8 and a sharp absorption of medium intensity at 6.1 μ.

When the enamines prepared from cyclopentanone and dimethylamine, pyrrolidine, and morpholine were allowed to react with methyl propiolate under conditions similar to those described for formation of **5c**, the similarity of the infrared and n.m.r. spectra to those of **5c** indicated that the major part of the crude product in each case was the bicycloheptene derivative. Failure to obtain these products as solids, and their thermal instability, precluded complete characterization.

Methyl 2-Dimethylamino-1-cyclopenten-1-acrylate (6).—To N,N-dimethyl-1-cyclopenten-1-ylamine (5.55 g., 0.05 mole) in ether (15 ml.) was added portionwise methyl propiolate (4.2 g., 0.05 mole) over 5 min. with cooling to keep the temperature below 30°. The solvent was distilled under reduced pressure after the mixture had stood at room temperature for 1 hr. The crude product, upon continued standing at room temperature, slowly crystallized. After standing for 11 days, the crystalline mass was triturated with cold ether and filtered to give 7 g. (72%) of methyl 2-dimethylamino-1-cyclopentene-1-acrylate, m.p. 74–75°. The infrared and n.m.r. spectra were different from the spectra of the initial crude product and were consistent with the assigned structure. Characteristics of the spectra were infrared absorptions at 5.95, 6.45, and 8.70 μ and n.m.r. doublets (one proton each) at 7.9 and 5.1 p.p.m.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8; N, 7.2; neut. equiv., 195. Found: C, 67.9; H, 8.8; N, 7.2; neut. equiv., 201.

Methyl 2-Oxocyclopentaneacrylate.—Methyl 2-dimethylamino-1-cyclopentene-1-acrylate (12.5 g., 0.064 mole) was mixed with methanol (50 ml.) and concentrated hydrochloric acid (6.5 ml.), and the mixture was allowed to stand at room temperature for 4 days. Water (40 ml.) was added and the methanol was evaporated on the steam bath until an oil began to separate. Extraction with ether and distillation of the ether extracts gave 4.1 g. (38%) of methyl 2-oxocyclopentaneacrylate, b.p. 104–107° at 1.2 mm., $n^{20}D$ 1.4895.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.1; H, 7.2.

Methyl 2-Oxocyclopentanepropionate.—Methyl 2-oxocyclopentaneacrylate (3.3 g., 0.0196 mole) was hydrogenated in 50 ml. of pentane and 20 ml. of methanol at room temperature and 40 p.s.i. over 0.25 g. of 5% palladium on alumina. The catalyst was removed by filtration and the solvent was removed by distillation *in vacuo* to leave 3.3 g. of residue, $n^{20}D$ 1.4606. An infrared spectrum of this material was identical with that of methyl 2-oxocyclopentanepropionate reported by Terrell.[15] The 2,4-dinitrophenylhydrazone melted at 86.5–87.5°, lit.[16] m.p. 87–88°.

Methyl 2-(1-Pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (7a).—To a solution of 34.3 g. (0.25 mole) of 1-(1-cyclopenten-1-yl)pyrrolidine in 75 ml. of dry ether was added dropwise 21.0 g. (0.25 mole) of methyl propiolate. The temperature of the mixture was maintained at 10–20° during the addition and for 1.5 hr. thereafter by periodic cooling in an ice bath. The solvent was distilled at reduced pressure while the base temperature was kept below 35°. The residue was distilled through an 8-cm. Vigreux column at 0.5-mm. pressure to yield 35.5 g. (65%) of methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (**7a**), b.p. 122–140° (mostly 126–130°), which solidified on cooling. After one recrystallization from hexane, the product melted at 117–119°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.4; H, 8.7; N, 6.8.

The product had infrared maxima at 6.0, 6.25, and 6.60 μ. The n.m.r. spectrum showed olefinic proton resonance at 6.4 (doublet) and 5.6 p.p.m. (multiplet).

In subsequent preparations it was found that **7a** could be obtained without distillation by carrying out the reaction of the enamine and methyl propiolate in ether and evaporating the ether on a steam bath. When the temperature of the residue reached 85–90°, an exothermic reaction occurred. The temperature reached a maximum of about 130° in preparations on a 0.1–0.2-mole scale. The mixture solidified on cooling to about 50°. The cycloheptadiene (**7a**) could be isolated in an average yield of 63% by trituration of the solid residue with ether and filtration to remove the product.

Methyl 2-Oxo-6-cyclohepten-1-carboxylate.—Methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (39 g., 0.18 mole) was dissolved in a mixture of 20 ml. of concentrated hydrochloric acid and 100 ml. of water. After the solution had stood at room temperature for 5 hr., it was extracted with ether to remove an oil which had separated. Evaporation of ether and distillation of the residue yielded 8 g. (27%) of methyl 2-oxo-6-cycloheptene-1-carboxylate, b.p. 71–76° at 1.5 mm., $n^{20}D$ 1.5236.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 65.2; H, 7.4.

Similar results were obtained when the oily crude product from thermal rearrangement of the analogous piperidine compound (**5c**) was hydrolyzed under the same conditions.

Cycloheptanone from Methyl 2-Oxo-6-cycloheptene-1-carboxylate.—Methyl 2-oxo-6-cycloheptene-1-carboxylate (8 g., 0.048 mole) was dissolved in pentane (100 ml.) and hydrogenated at room temperature and 30 p.s.i. over 0.5 g. of 5% palladium-on-alumina catalyst. The mixture absorbed 0.05 mole of hydrogen in 1 hr.

The catalyst was removed by filtration. The filtrate was evaporated on a steam bath to leave 7.5 g. of residue which gave a deep blue color when a small sample was added to alcoholic iron(III) chloride.

Potassium hydroxide (5 g., 0.089 mole) in water (25 ml.) and methanol (10 ml.) was added to the 7.5 g. of residue, and the resulting mixture was heated on the steam bath for 0.5 hr., during which time an oil separated. The solution then was acidified with concentrated hydrochloric acid (gas evolved) and extracted with ether. The ether was evaporated on the steam bath, and 4 g. (74%) of crude cycloheptanone was obtained. The infrared spectrum of this product was identical with that of an authentic sample of cycloheptanone.

The 2,4-dinitrophenylhydrazone, yellow crystals from an ethyl alcohol–ethyl acetate mixture, melted at 147–148°, lit.[17] m.p. 148°.

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(14) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 86.

(15) R. Terrell, Ph. D. thesis, Columbia University, 1954.

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Cycloheptanone from Methyl 2-(1-Pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (7a).—A solution of 22 g. (0.10 mole) of methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate in 100 ml. of acetic acid was hydrogenated over 1.5 g. of 5% palladium on carbon at 40 p.s.i. and room temperature until 0.10 mole of hydrogen had been absorbed. The reaction mixture was filtered, and most of the acetic acid was removed by distillation under reduced pressure. The mixture was then heated with excess sodium hydroxide in 80% aqueous methanol. After most of the methanol had been distilled, the mixture was extracted with ether. The ether solution was washed with dilute hydrochloric acid, and the ether was evaporated to yield 6.0 g. (54%) of cycloheptanone, which was identified by its infrared spectrum.

Methyl α-(Hydroxymethylene)-1-cyclohexene-1-acetate (9).—Methyl propiolate (16.8 g., 0.20 mole) dissolved in 15 ml. of ether was added over a period of 50 min. to a solution of 25 g. (0.20 mole) of N,N-dimethyl-1-cyclohexen-1-ylamine in 50 ml. of ether. The temperature of the reaction mixture was maintained at 25–35° by means of intermittent cooling. The mixture was allowed to stand overnight at room temperature, after which the ether was evaporated on a steam bath. The infrared spectrum of the residue showed a strong absorption at 5.95 and a strong doublet at 6.20–6.26 μ; the n.m.r. spectrum contained a single peak at 7.28 (olefinic proton adjacent to nitrogen) and a closely spaced triplet at 5.28 p.p.m. (cyclohexene olefinic proton). The residue was cooled and added to 100 ml. of 10% hydrochloric acid. An oil began separating almost immediately. After 3 hr., the oil was removed by extraction with ether. Distillation of the ether extract yielded 20.2 g. (55%) of methyl α-(hydroxymethylene)-1-cyclohexene-1-acetate, b.p. 80–82° at 1.5 mm., $n^{20}D$ 1.5003. This compound gave an intense purple color with iron(III) chloride and a positive Fuchsin aldehyde test. Its infrared spectrum had maxima at 5.65, 5.92, and 6.16 μ; its n.m.r. spectrum showed absorptions at 11.3 (bonded O–H, doublet), 6.94 (>C=C(–O)–H, doublet), and 5.28 p.p.m. (ring olefinic proton, unresolved).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 65.4; H, 7.8.

This same product was obtained in approximately the same yield when enamines prepared from cyclohexanone and pyrrolidine, piperidine, and morpholine were treated with methyl propiolate. The nature of the product and the yield were not affected appreciably by the temperature at which the reaction was carried out or by the nature of the solvent. The intermediate aminomethylene esters were all obtained as oils. When attempts were made to purify these compounds by distillation, small amounts of distillates were obtained along with large amounts of tarry residues. The distillates were mixtures in all cases.

1-Cyclohexene-1-acetic Acid.—Methyl α-(hydroxymethylene)-1-cyclohexene-1-acetate (9, 2 g., 0.011 mole) was added to a solution of potassium hydroxide (1 g.) in water (5 ml.). The resulting clear yellow solution was heated on a steam bath for 15 min., cooled, and diluted with 10 ml. of water. This solution was extracted once with 10 ml. of ether and the ether extract was discarded.

Acidification of the aqueous layer with concentrated hydrochloric acid gave an oil which was extracted with ether. Evaporation of the ether on the steam bath gave 1.5 g. of oil, which crystallized on cooling. This solid was recrystallized with considerable loss from pentane to yield 1-cyclohexene-1-acetic acid, m.p. 33–35°. The infrared spectrum was identical with that of a sample of authentic 1-cyclohexene-1-acetic acid obtained from Aldrich Chemical Co.

Anal. Calcd. for $C_8H_{12}O_2$: neut. equiv., 140.2. Found: neut. equiv., 141.8.

Methyl 2-(1-Pyrrolidinyl)-1,8-cyclononadiene-1-carboxylate (10).—To a solution of 49.5 g. (0.30 mole) of 1-(1-cyclohepten-1-yl)pyrrolidine in 100 ml. of ether was added dropwise with stirring 25.2 g. (0.30 mole) of methyl propiolate over a period of 15 min. The temperature of the mixture was maintained at 5–15° during the addition and for 30 min. longer. After part of the solvent was removed at reduced pressure, a white solid separated and was removed by filtration. After being dried in a vacuum oven, the solid weighed 45.5 g. Concentration of the filtrates yielded 5.0 g. of additional solid. The infrared spectrum showed the absorption pattern characteristic of the $-C(NR_2)=C(CO_2R)-CH=CH-$ structure (strong maxima at 5.98 and 6.56 μ). The n.m.r. spectrum showed resonance for single olefinic protons at 6.13 (doublet) and 5.23 p.p.m. (pair of triplets). This solid rearranged on standing overnight at room temperature or immediately on treatment with acid to form an oil, $n^{20}D$ 1.5320, which had strong infrared maxima at 5.88 and 6.2 μ and showed n.m.r. absorption at 6.95 (triplet) and 4.17 p.p.m. (unresolved pair of doublets). Both the infrared and n.m.r. spectra indicated that the oil was a single compound.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3. Found: C, 72.3; H, 9.5.

1-Cyclononene-1-carboxylic Acid.—A solution of 24.9 g. (0.10 mole) of the oil (11) in 100 ml. of acetic acid was hydrogenated at 40 p.s.i. and room temperature over 0.25 g. of platinum oxide with absorption of 0.20 mole of hydrogen. After the catalyst and most of the acetic acid were removed, the residue was treated with 200 ml. of 10% sodium hydroxide and 200 ml. of methanol. The basic mixture was heated overnight on a steam bath in an open beaker. The concentrated solution was diluted to 250 ml. to dissolve the solids and was acidified to precipitate a gummy material. Addition of 150 ml. of ethyl alcohol, warming to 40°, and cooling to 0° precipitated 9.5 g. (57%) of 1-cyclononene-1-carboxylic acid, m.p. 72–77°. An analytical sample, m.p. 77–78°, was prepared by recrystallization from pentane.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.3; H, 9.5. Found: C, 71.5; H, 9.7.

Cyclononanecarboxylic Acid.—1-Cyclononene-1-carboxylic acid (500 mg., 3 mmoles) dissolved in 25 ml. of hexane was hydrogenated at 40 p.s.i and room temperature over 0.5 g. of 5% palladium on alumina. Removal of catalyst and evaporation of solvent yielded an oil which was treated with excess thionyl chloride. The residue, after evaporation of excess thionyl chloride, was divided into two portions and was converted to the amide, m.p. 175.5–177° (lit.[18] m.p. 175–177°), and the anilide, m.p. 140.5–142.5° (lit.[18] m.p. 140.4–141.6°).

Methyl 2-(1-Pyrrolidinyl)-1-cyclononene-1-carboxylate (12).—A solution of 20.0 g. (0.080 mole) of the oil (11) in 90 ml. of acetic acid was hydrogenated at 40 p.s.i. over 3 g. of 5% palladium on carbon until a definite decrease in the rate of hydrogen absorption was observed; 0.076 mole of hydrogen had been absorbed. The mixture was filtered to remove the catalyst, and most of the solvent was removed under reduced pressure. An aqueous solution of the residue was extracted with ether, made basic, and then extracted again with ether. The ether extract from the basic solution was evaporated to yield 13.5 g. of tan solid, m.p. 75–81°. An analytical sample, m.p. 84–85.5°, was prepared by one recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.7; H, 10.0; N, 5.6. Found: C, 71.8; H, 9.7; N, 5.6.

When this compound was dissolved in dilute acid, hydrolysis to the keto ester did not take place to any appreciable extent.

Cyclononanone. A.—Methyl 2-(1-pyrrolidinyl)-1-cyclononene-1-carboxylate (12, 6.0 g., 0.024 mole) dissolved in 25 ml. of methanol was treated with 8 ml. of 25% aqueous sodium hydroxide solution. The methanol was distilled and gradually replaced with water. The resulting two-phase mixture was extracted with ether, and the ether extract was washed with dilute hydrochloric acid. Evaporation of the ether yielded 3.2 g. (95%) of cyclononanone, which was pure according to vapor phase chromatography and which had an infrared spectrum identical with a published spectrum.[19] The 2,4-dinitrophenylhydrazone, m.p. 142–143° (lit. m.p. 139–140°,[20] 146°[21]), and the semicarbazone, m.p. 182–185° (lit.[22] m.p. 183°) were prepared by standard methods.

B.—To a solution of 27 g. (0.16 mole) of 1-(1-cyclohepten-1-yl)-pyrrolidine in 50 ml. of ether was added 14 g. (0.165 mole) of methyl propiolate. The reaction was carried out at 20–28°. The solvent was removed *in vacuo*, and the residue (46 g.) was dissolved in 165 ml. of acetic acid. The acetic acid solution was hydrogenated over 8 g. of 5% palladium on carbon at 40 p.s.i. until 0.16 mole of hydrogen had been absorbed. The mixture was filtered to remove catalyst, and the acetic acid was removed by distillation under reduced pressure until the base temperature reached 50° at 1 mm. The residue (56 g.) was dissolved in 100 ml. of methanol and was treated with 80 g. of 25% aqueous

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(19) A. Blomquist, *et al.*, *ibid.*, **74**, 3639 (1952).
(20) K. Schenker and V. Prelog, *Helv. Chim. Acta*, **36**, 896 (1953).
(21) V. Prelog, K. Schenker, and W. Küng, *ibid.*, **36**, 471 (1953).
(22) L. Ruzicka, Pl. A. Plattner, and H. Wild, *ibid.*, **26**, 1637 (1943).

sodium hydroxide solution. The methanol was distilled over a period of 2 hr., after which the two-phase mixture was cooled and extracted twice with ether. The ether solution was washed with dilute hydrochloric acid and dried over magnesium sulfate. After evaporation of the ether, the residue was distilled to yield 12.5 g. (54% from enamine) of cyclononanone, b.p. 91–95° at 12 mm. Vapor phase chromatography of this material indicated it to be about 91% cyclononanone, with one major and one minor impurity. The infrared spectrum was identical with that of pure cyclononanone except for a weak absorption at 6.06 μ.

Methyl 2-(1-Pyrrolidinyl)-1,9-cyclodecadiene-1-carboxylate.—To a solution of 52.0 g. (0.29 mole) of 1-(1-cycloocten-1-yl)pyrrolidine in 150 ml. of ether was added dropwise a solution of 24.9 g. (0.29 mole) of methyl propiolate in 50 ml. of ether. During the addition, the temperature was maintained at 28–32° by cooling. When most of the methyl propiolate had been added, a white solid began to separate. The mixture was stirred at 25–27° for 1.0 hr., cooled to 0°, and filtered to remove 61.5 g. (80%) of a white solid, m.p. 102–105°. An analytical sample, m.p. 103–105°, was prepared by recrystallization from acetone–ether.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 73.0; H, 9.6. Found: C, 72.9; H, 9.4.

Although this compound was hydrolyzed normally in dilute acid and appeared stable at room temperature, it deteriorated on prolonged storage. The n.m.r. spectrum of a sample which had stood for 40 days at room temperature indicated that only about 20% of the sample had the original structure. When this 40-day-old sample was dissolved in dilute acid and allowed to stand for several hours, only a part of it hydrolyzed. An oil was recovered from the acid solution by making it basic, extracting with ether, and evaporating the ether. This oil appeared to be mainly one component, which had infrared maxima at 5.82 and 6.18 μ and single olefinic proton resonance at 6.80 (pair of doublets) and at 3.90 p.p.m. (triplet) in the n.m.r. spectrum. Thus, this oil appeared to have a structure analogous to that of oil 11 obtained so readily from the cyclononadiene derivative previously described.

Methyl 2-Oxo-9-Cyclodecene-1-carboxylate.—Methyl 2-(1-pyrrolidinyl)-1,9-cyclodecadiene-1-carboxylate, 32.0 g. (0.12 mole), was dissolved in a mixture of 60 ml. of 10% hydrochloric acid and 40 ml. of water; the mixture was warmed at 55–60° on a steam bath. After 0.5 hr. and 1.0 hr., the mixture was cooled and extracted with ether to yield 12.5 g. and 10.5 g., respectively, of colorless oil. Additional heating yielded no more product. The oil was distilled to yield 19.0 g. (74%) of methyl 2-oxo-9-cyclodecene-1-carboxylate, b.p. 109–111° at 0.9 mm., $n^{20}D$ 1.4950.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.4; H, 8.6. Found: C, 68.5; H, 8.7.

Cyclodecanone.—A solution of 18.5 g. (0.088 mole) of methyl 2-oxo-9-cyclodecene-1-carboxylate in 50 ml. of cyclohexane was hydrogenated at 40 p.s.i. over 0.5 g. of 5% palladium on alumina until 0.09 mole of hydrogen had been absorbed. Filtration of the hydrogenation mixture, followed by removal of solvent, yielded 17 g. of residue which was dissolved in 50 ml. of methanol. The methanol solution was treated with 18 g. of 50% aqueous potassium hydroxide solution, and the resulting two-phase mixture was heated at reflux for 0.8 hr. The cooled mixture was extracted with 100 ml. of ether, and the extract was washed with 15 ml. of water. The combined aqueous solutions were extracted with 50 ml. of ether. The combined ether solutions were distilled to remove low-boiling materials, first at atmospheric pressure and finally by heating to a base temperature of 105° at 14 mm. The residue of cyclodecanone weighed 10.0 g. (87%) and contained less than 3% impurities according to vapor phase chromatography. The infrared spectrum was essentially the same as a published spectrum[19] and as a spectrum of commercial cyclodecanone. The 2,4-dinitrophenylhydrazone, m.p. 166° (lit.[23] m.p. 167°), and the semicarbazone, m.p. 205–206° (lit.[19] m.p. 203.5–205.5°), were prepared by standard methods.

Methyl 2-(1-Pyrrolidinyl)-1,13-cyclotetradecadiene-1-carboxylate.—To a solution of 7.33 g. (0.031 mole) of 1-(1-cyclododecen-1-yl)pyrrolidine in 20 ml. of refluxing hexane was added 2.62 g. (0.031 mole) of methyl propiolate. The heat of the reaction maintained the temperature at reflux during the addition although the heating mantle was removed. After addition of the propiolate was complete, heating was resumed for 5 min. The chilled reaction mixture yielded 8.0 g. (81%) of methyl 2-(1-pyrrolidinyl)-1,13-cyclotetradecadiene-1-carboxylate, m.p. 59.5–62°. Attempts to recrystallize this product from several solvents were unsuccessful. In those cases when the material separated from the solvent, the melting point was lowered, sometimes to the extent that only an oil was obtained. Accordingly, an analysis was obtained from the crude product.

Anal. Calcd. for $C_{20}H_{33}NO_2$: C, 75.2; H, 10.4; N, 4.4. Found: C, 75.7; H, 10.8; N, 4.4.

Methyl 2-Oxo-13-cyclotetradecene-1-carboxylate.—Methyl propiolate (136 g., 1.62 moles) was added as rapidly as possible (*ca.* 15 min.) to a refluxing solution of 348 g. (1.63 moles) of 1-(1-cyclododecen-1-yl)pyrrolidine in 500 ml. of hexane. Immediately after the addition was complete, the solvent was removed at reduced pressure, and the residue was added to a well-stirred solution of 200 ml. of concentrated hydrochloric acid in 400 ml. of water. After it was warmed on the steam bath for 30 min., the hydrolysis mixture was cooled and extracted with two 200-ml. portions of ether. Evaporation of the ether yielded an oil, which soon began to crystallize. After being dried overnight *in vacuo*, a small fraction of the product had a melting point of 49–51°. An analytical sample, m.p. 51.5–53.5°, was recrystallized from methanol and from hexane.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.1; H, 9.8. Found: C, 71.3; H, 9.8.

Cyclotetradecanone.—The crude methyl 2-oxo-13-cyclotetradecene-1-carboxylate (see above) in 2 l. of methanol was passed through a 3-cm. bed of activated alumina and then was treated with decolorizing charcoal. The filtered solution was hydrogenated at room temperature and 40 p.s.i. over 10 g. of 5% palladium on alumina. After filtration to remove catalyst, the methanol solution was treated with 348 g. of 50% sodium hydroxide solution and 2.5 l. of water. The resulting mixture was stirred at room temperature for 11 days and the product which separated was removed by filtration every 2–3 days. There was obtained a total of 253 g. (67%) of cyclotetradecanone, m.p. 49–51°, lit.[24] m.p. 52°. The semicarbazone had a melting point of 198.5–199.5°, lit.[24] m.p. 197–198°.

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Some Reactions of Epichlorohydrin with Amines

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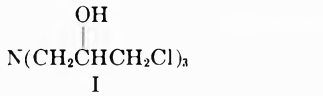
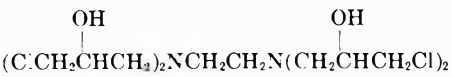
Certain reaction products of epichlorohydrin with ethylenediamine, ammonia, and diethylamine have been isolated and characterized. The chlorohydrin derived from diethylamine and epichlorohydrin is converted to an azetidinium salt on standing.

Because of our interest in epichlorohydrin as a cross-linking agent for polyamines, we undertook a study of the reactions of this versatile reagent with amines of varying functionality. We wish to report some new products derived from these reactions and new physical data and spectra for previously reported compounds.

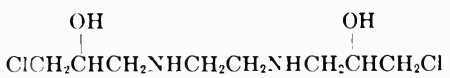
Reaction of Epichlorohydrin with Ethylenediamine.—Since ammonia has been shown to react with three equivalents of epichlorohydrin to give I,[2,3] it was expected that ethylenediamine and four equivalents of epichlorohydrin might afford II under similar conditions. Although II may have been formed to some extent, III separated from the reaction mixture in moderate yield, as a finely divided solid which was insoluble in cold water and cold, neutral organic solvents. Variation in the order of addition of the reactants or in the amount of water or alcoholic solvent did not prevent separation of III before further reaction with epichlorohydrin could occur. The infrared spectrum of III was unusual in that the broad O–H absorption band expected for such an alcohol was not seen, presumably because of strong hydrogen bonding to nitrogen.[4]



I



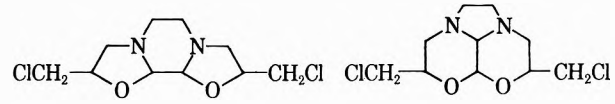
II



III

The reaction of III with nitrous acid gave a solid dinitrosamine. The presence of two secondary amino groups was thus demonstrated, and the possibility that III was an unsymmetrical, N,N-disubstituted ethylenediamine was excluded. The dinitrosamine had typical broad alcoholic OH absorption in the infrared region, and its proton nuclear magnetic resonance (n.m.r.) spectrum was consistent with the expected structure. Since the dinitrosamine was soluble in organic solvents, its molecular weight could be easily determined; the monomeric nature of III thus was confirmed. The possibility that III is a dimer or low polymer which depolymerized in the cold nitrosation mixture is remote. Structures can be written for polymers of the composition of III, joined through dioxane rings or other types of ether linkages, but to agree with the over-all composition, part of the chlorine would need to be ionic, and no significant quantity of ionic chlorine was found.

A tricyclic compound resulted from the reaction of III with aqueous glyoxal. Spectroscopic evidence favored 2,9-bis(chloromethyl)octahydrobisoxazolo[3,2-*a*:2′,3′-*c*]pyrazine (IV) over the isomer (V). Neither ring system has been reported previously.

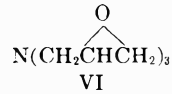


IV V

Reaction of Epichlorohydrin with Ammonia.—Although the reaction of 3 moles of epichlorohydrin with 1 of ammonia undoubtedly gives a mixture of products derived from different reactant ratios,[5] a solid 3:1 product (I) has been reported.[2,3] The solubility properties given for I[2] were similar to those found for III, but the isolation of the solid form apparently has not been reported since 1888.

Our preparations gave sirups, for the most part, but one solution crystallized spontaneously, although very slowly. The solid isolated was apparently identical with that obtained by Fauconnier.[2] Its molecular weight and spectra confirmed the structure I. The low water solubility of the solid, approximately 1%, must be caused by intermolecular hydrogen bonding in the solid.

The tris(epoxide) (VI) previously described as a liquid,[3,6] was obtained in crystalline form. Although the yield of solid directly from the crude product was not so high as might be desired, the pure product was obtained easily without a possibly hazardous[3] distillation.



VI

Reaction of Epichlorohydrin with Diethylamine.—The reaction products of secondary amines with epichlorohydrin, most probably of the structure $R_2NCH_2CHOHCH_2Cl$, have been reported to cyclize to azetidinium salts[7,8] such as VII. Increases in ionic chlorine content of aminochlorohydrins have been noted by others[5,9] and have been attributed to quaternization

(1) To whom communications should be addressed.

(2) A. Fauconnier, *Compt. rend.*, **107**, 115 (1888).

(3) J. B. McKelvey, B. G. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960).

(4) For a discussion of hydrogen bonding in amine–epoxide products and infrared spectra of amino alcohols, see J. F. Harrod, *J. Polymer Sci.*, **1**, 385 (1963). It is possible that the presence of secondary amine groups in III and a 1:1 ratio of –OH groups to N atoms are somehow responsible for the atypical spectrum, especially the lack of a broad absorption band in the vicinity of 3400 cm.$^{-1}$.

(5) J. B. McKelvey, R. R. Benerito, R. J. Berni, and B. G. Burgis, *Textile Res. J.*, **33**, 273 (1963).

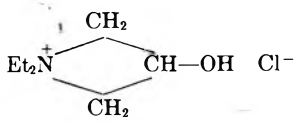
(6) K. Gerzon, J. E. Cochran, Jr., L. A. White, R. Monahan, E. V. Krumkalns, R. E. Scroggs, and J. Mills, *J. Med. Pharm. Chem.*, **1**, 223 (1959).

(7) L. Niemilowicz, *Monatsh.*, **15**, 118 (1894).

(8) R. Rothstein and K. Binovic, *Compt. rend.*, **236**, 1050 (1953).

(9) N. S. Drozdov and O. M. Cherntzov, *Zhur. Obschei Khim.*, **4**, 969 (1934); *Chem. Abstr.*, **29**, 2148 (1935).

reactions.[5] On the other hand, it has been suggested that the ionic chlorine-containing products (presumably including VII) are hydrochlorides of dioxanes,[10] since dioxanes have been obtained by base treatment of the salt reported to be VII.[8]



VII

We have re-examined the reaction of equivalent amounts of epichlorohydrin and diethylamine and found that the crude reaction mixture crystallized on standing. The purified solid product had an apparent molecular weight in water corresponding to the completely ionized salt of VII. In acetonitrile, on the other hand, the molecular weight appeared to be twice as great, corresponding to the unionized salt, as was the Rast molecular weight previously reported.[8]

Infrared and proton n.m.r. spectra clearly show VII to be a secondary alcohol. The infrared spectrum contains no band at 2800 cm.$^{-1}$ attributable to a $-CH_2$ group adjacent to a tertiary amine. A band at about 2600 cm.$^{-1}$, corresponding to a tertiary amine hydrochloride, is absent also. The proton n.m.r. spectrum showed a one-proton doublet (OH attached to a carbon having a single hydrogen), two nonequivalent ethyl groups, and a group of complicated multiplets centered at 5.5 τ and integrating to five protons. The nonequivalence of the ethyl groups is consistent with a four-membered ring having an asymmetric carbon atom opposite the nitrogen. The complex multiplet for the ring hydrogens is not unexpected since the hydrogens form an A_2B_2C system. Therefore, the only reasonable structure for the product appears to be VII.

Our data, then would confirm the azetidinium salt structure proposed by Rothstein and Binovic and fail to support the suggestion made by Heywood and Phillips[10] that these ionic chloride-containing products are simply dioxane dihydrochlorides.

Experimental[11]

1,1'-(Ethylenediimino)bis(3-chloro-2-propanol) (III).—To a mixture of 33 ml. (0.5 mole) of 98% ethylenediamine and 1 ml. of water was added in one portion 167 ml. (2.1 moles) of epichlorohydrin. The mixture was stirred efficiently and cooled in an ice bath to maintain the temperature at 28–32°. After 0.5 hr. the product began to separate. Two hours later the pasty mass was mixed with 1500 ml. of ice–water. The solid was collected on a suction filter and washed with water. After drying in a vacuum desiccator, the product amounted to 80 g. (65%) which melted at 105–112° dec. on further heating. Recrystallization from dimethylformamide raised the melting point to 135°.

In a number of other runs, where the order of addition and mole ratio of ethylenediamine to epichlorohydrin were varied, III was always obtained as a product. In one run where stirring was ineffective, the exothermic reaction was uncontrollable and the mixture decomposed somewhat violently.

Compound III was purified for analysis by recrystallization from dimethylformamide (about 30 ml. per gram, heated to 80°). Recovery was 50% and the melting point was 135–137°.

Anal. Calcd. for $C_8H_{18}Cl_2N_2O_2$: C, 39.19; H, 7.40; Cl, 28.93; N, 11.43; ionic Cl and oxirane oxygen, 0.0. Found: C, 39.27; H, 6.76; Cl, 28.22; N, 11.1; ionic Cl, 0.1; oxirane oxygen, <0.6.

The material is soluble in glacial acetic acid, trifluoroacetic acid, and dilute hydrochloric acid at room temperature; and in water, pyridine, dimethylformamide, dimethyl sulfoxide, and the monomethyl ether of ethylene glycol when heated on a steam bath. The proton n.m.r. spectrum of a trifluoroacetic acid solution was too broad to be useful; no other suitable solvent was found.

The infrared spectrum (mineral oil and halocarbon mulls) showed N–H at 3280 (sharp), OH·····N at 3070 and 2720 (shoulder at 2650), and C–Cl at 733 cm.$^{-1}$.

Titration with perchloric acid in the monomethyl ether of ethylene glycol indicated an equivalent weight of 128. Two breaks at approximately equal volumes of titrant were obtained.

1,1'-[Ethylenebis(nitrosimino)]bis(3-chloro-2-propanol).—To a solution of 25 g. of III (0.1 mole) in a mixture of 50 ml. of concentrated hydrochloric acid and 175 ml. of water, cooled in an ice bath, was added a chilled solution of 21 g. (0.3 mole) of sodium nitrite in 75 ml. of water over a period of 6 min. while the mixture was held below 6°. The solution then was kept in an ice bath for 3.5 hr. The product, collected on a suction filter and washed with water, isopropyl alcohol, and ether, amounted to 3.5 g. and melted at 110–114°. The mother liquor deposited a second crop of 12.2 g. of pale yellow solid which melted at 110–111° (total, 51% yield).

Recrystallization from hot water gave bladed prisms which melted at 114–115°.

Anal. Calcd. for $C_8H_{16}Cl_2N_4O_4$: C, 31.69; H, 5.32; total Cl, 23.39; N, 18.48; mol. wt., 303.15. Found: C, 31.90; H, 4.84; total Cl, 23.34; ionic Cl, 0.6; N, 18.32; mol. wt., 290 (in acetonitrile).

The infrared spectrum showed OH at 3330 (broad), CH_2N–N=O at 1422 and 1390, and C–Cl at 687 cm.$^{-1}$. The n.m.r. spectrum in DMSO-d_6 had peaks at 4.87 (OH), 6.32 (CH_2Cl), and 5.83 τ (N-CH_2CH_2N); the remaining absorption was buried underneath these.

2,9-Bis(chloromethyl)octahydrobisoxazolo[3,2-*a*:2',3'-*c*]pyrazine (IV).[12]—A mixture of 2.5 g. (0.01 mole) of III, 2.0 g. of technical 30% aqueous glyoxal, and 4 ml. of water was stirred until the solid dissolved. An oil began to separate in a few minutes, followed by crystallization of the product, which was collected on a suction filter (after cooling) and washed with water and a small amount of isopropyl alcohol. The 1.8 g. (67%) of nearly colorless crystals melted at 99–101°.

Recrystallization from chloroform–hexane and from acetone gave prisms which melted at 130–132° dec.

Anal. Calcd. for $C_{10}H_{16}Cl_2N_2O_2$: C, 44.95; H, 6.03; Cl, 26.54; N, 10.49; mol. wt., 267.16. Found: C, 45.19; H, 5.77; Cl, 26.20; N, 10.78; mol. wt., 250 (in chloroform).

The infrared sprectrum showed cyclic C–O or C–N at 1040 and C–Cl at 715 cm.$^{-1}$. The 1040-cm.$^{-1}$ absorption is more typical of a five-membered than a six-membered cyclic ether, but this is not conclusive because of the complexity of the structure.

The proton n.m.r. spectrum ($CDCl_3$) had single peaks at 5.35 and 7.28 τ; the remaining absorption formed a complex pattern between 5.4 and 7.2 τ. Detailed analysis was not possible. The material may be a mixture of stereoisomers of IV (or possibly V[12]).

1,1',1''-Nitrilotris(3-chloro-2-propanol) (I).—A mixture of 278 g. (3 moles) of epichlorohydrin, 100 ml. of isopropyl alcohol, and 60 g. (1 mole) of 29% aqueous ammonia (each added in one portion) was stirred and maintained at 31–34° with cooling for 7 hr.

The solution, on storage in a refrigerator, deposited a white solid in 26% yield, which melted at 90–93°. The material was precipitated from dilute hydrochloric acid with potassium carbonate. The product (I) melted at 90–94°, lit.[2] m.p. 92–93°.

Anal. Calcd. for $C_9H_{18}Cl_3NO_3$: C, 36.69; H, 6.16; total Cl, 36.10; N, 4.76; mol. wt., 294.61. Found: C, 36.34; H, 6.01; total Cl, 35.77; ionic Cl, <0.01; N, 5.23; mol. wt., 301 (in acetonitrile).

(10) D. L. Heywood and B. Phillips, *J. Am. Chem. Soc.*, **80**, 1257 (1958).

(11) Melting points were determined on a Fisher-Johns block and are uncorrected. Analyses were performed in these laboratories under the direction of Mr. R. Francel, Mr. J. Deonarine, and Mr. J. Robinson. Molecular weights were determined in a vapor pressure osmometer. Infrared spectra, as mineral oil and halocarbon mulls, were obtained on a Perkin-Elmer spectrophotometer, Model 21. Proton n.m.r. spectra were obtained on a Varian V4300B n.m.r. spectrometer operating at 56.4 Mc.; approximately 10% concentrations were employed in the solvents specified.

(12) Possibly 4,7-bis(chloromethyl)octahydro-5,6-dioxa-2a,8a-diazaacenaphthylene (V).

Although I is soluble in water to only about 1%, it dissolves in acetone to the extent of about 30 g. per 100 ml. of acetone.

The infrared spectrum showed broad OH at 3310, CH_2–N at 2865 (medium), CH–OH at 1050, and C–Cl at 700 cm.$^{-1}$. The n.m.r. spectrum (in DMSO-d_6) had peaks at 4.89 (OH, doublet), near 6.2 (HC<), 6.32 (CH_2Cl), and 7.42 τ (NCH_2, doublet).

One ammonia–epichlorohydrin reaction mixture, prepared as described for I, deposited a very small yield of a different solid which melted at 66–76°. This material has not been analyzed or identified; its infrared spectrum (mineral oil mull) was different from that of I, but showed OH at 3200, CH–OH at 1087 and 1067, and C–Cl at 730 and 695 cm.$^{-1}$.

Tris(2,3-epoxypropyl)amine (VI).—The reaction mixture from one mole of ammonia with three of epichlorohydrin, prepared as described for I, was cooled to 20°. A solution of 140 g. of sodium hydroxide (3.5 moles) in 200 ml. of water was added over a 7-min. period with stirring and cooling to maintain the mixture at 20–25°. After stirring for 50 min. at 20–25°, the layers were separated. The aqueous layer was extracted with ether, with addition of just enough water to dissolve the inorganic salt which had separated, and the combined ether and organic layers were dried with three successive portions of potassium hydroxide pellets and evaporated *in vacuo* from a bath at 45°.

The orange sirup partly crystallized when stored in a refrigerator. Extraction with several portions of boiling hexane gave several crops of a colorless solid (total, 18%) which melted in the vicinity of 45°.

The product was purified by recrystallization from methylcyclohexane (heated to 70°) and melted at 45–46°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; oxirane oxygen, 25.9; mol. wt., 185.22. Found: C, 58.73; H, 7.95; N, 7.0; oxirane oxygen, 24.2; Cl, <0.5; mol. wt., 169.0.

Although the analytical figures are not ideal, they show the chemical identity of the product with the liquids previously reported.[3,6]

The infrared spectrum showed NCH_2 at 2800 and epoxide group at 3600, 3000, and 857 cm.$^{-1}$.

1,1-Diethyl-3-hydroxyazetidinium Chloride (VII).—To a solution of 14.6 g. (0.2 mole) of diethylamine and 0.6 g. of water was added 18.5 g. (0.2 mole) of epichlorohydrin over a period of 10 min. The solution was then maintained at 28–30° with stirring for 6 hr.

The solution crystallized partly upon standing at room temperature or in a refrigerator. The solid was recrystallized from a mixture of acetonitrile (in which it is very soluble) and acetone and had m.p. 154–155°.

Anal. Calcd. for $C_7H_{16}ClNO$: Cl, 21.40; mol. wt., 165.67. Found: ionic chlorine, 21.4; apparent mol. wt., 76 (in water), 162 (in acetonitrile).

The infrared spectrum (mineral oil mull) showed OH absorption at 3200 cm.$^{-1}$ (in addition to that attributed to a small amount of water).

The proton n.m.r. spectrum in DMSO-d_6 showed two ethyl groups whose methylene groups gave two overlapping quartets at 6.4 τ. The remaining spectrum consisted of a five-proton group of complicated multiplets centered at 5.5, and a one-proton doublet (OH) at 2.94 τ, splitting equal to 6.0 c.p.s. The doublet was easily exchanged upon the addition of deuterium oxide, and almost disappeared with sufficient deuterium oxide.

1,1-Diethyl-3-hydroxyazetidinium Picrate (VIII).—A crude diethylamine–epichlorohydrin product was treated with alcoholic picric acid in the hope of stabilizing the chlorohydrin intermediate as a picrate salt. Instead, an azetidinium picrate crystallized slowly from the solution, m.p. 223–226°.

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 43.57; H, 5.06; N, 15.64; Cl, 0.00. Found: C, 43.97; H, 5.07; N, 15.47; Cl (total), none.

Treatment of VII with picric acid gave VIII which melted at 223–227°.

Anal. Found: C, 44.07; H, 5.01; N, 16.12; Beilstein test, negative.

The proton n.m.r. spectrum (DMSO-d_6) was virtually identical with that of the chloride (except, of course, for picrate protons); the OH proton was shifted to ~3.8 τ.

Acknowledgment.—The authors wish to thank Mr. Norman Colthup for interpretation of infrared spectra and Dr. John Lancaster for interpretation of proton n.m.r. spectra. We also wish to thank Professor Gilbert Stork for helpful discussions.

A New Synthesis of β,β-Diarylethylamines[1]

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A number of new β,β-diarylethylamines have been prepared by the reaction between β-phenylethanolamines and aromatic nucleophiles in acid solution. The amines included β-phenylethanolamine, *o*-, *m*-, and *p*-octopamine, *p*-sympatol, norepinephrine, and normetanephrine. The nucleophiles included phenol, catechol, guaiacol, resorcinol, phloroglucinol, β-naphthol, anisole, 4-hydroxycoumarin, and indole.

In the course of work on the biochemistry of octopamine [norsympatol, norsynephrine, α-(aminomethyl)-4-hydroxybenzyl alcohol], it was desirable to seek a synthesis that might allow a convenient laboratory preparation of larger amounts than are practical with the usual methods. Hinsberg[2] had reported a synthesis which involved the Baeyer reaction of phenol and an amino acetal. With 1 mole of acetal for each mole of phenol he claimed that octopamine was formed, (eq. 1), and with 2 moles of phenol, β,β-bis(4-hydroxyphenyl)ethylamine (eq. 2).

$$C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl + H_2O \longrightarrow 4\text{-}HOC_6H_4CHOHCH_2NH_3^+ Cl^- + 2C_2H_5OH \quad (1)$$

$$2C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl \longrightarrow (4\text{-}HOC_6H_4)_2CHCH_2NH_3^+ Cl^- + 2C_2H_5OH \quad (2)$$

Repetition of these reactions in the manner described gave a product which had the reported properties but which was found to contain no octopamine when subjected to analysis by paper chromatography. Furthermore, when authentic octopamine was treated with hydrochloric acid under the conditions used by Hinsberg, it was completely destroyed. The condensation between 2 moles of phenol and 1 mole of amino acetal did yield a product with the properties of the bis(hydroxyphenyl)ethylamine described by Hinsberg. However, paper chromatographic examination of the compound showed that it contained at least three major byproducts which could not be removed completely by recrystallization.

Despite the lack of success in preparing pure β,β-bis(4-hydroxyphenyl)ethylamine from amino acetal and phenol it seemed possible that condensation of octop-

(1) This work was supported in part by Research Grant MH-02278 from the National Institute of Mental Health, U. S. Public Health Service. It was presented at the 143rd National Meeting of the American Chemical Society, Cincinnati, Ohio, Jan., 1963.

(2) O. Hinsberg, German Patent 373,286 (March 5, 1923); *Friedländers Fortschr. Teerfarben fabr.*, **14**, 1278 (1923); *Ber.*, **56**, 852 (1923).

amine and phenol might provide this amine, since the Baeyer reaction is usually considered to proceed *via* the corresponding alcohol as intermediate. If successful, such a procedure would provide a route to symmetrical diarylethylamines, and also could be extended to the preparation of unsymmetrical derivatives that would be difficult to make by other syntheses.[3] The condensation of octopamine and phenol was tried, and was found to proceed smoothly in 2 *N* hydrochloric acid at steam bath temperature to give a 94% yield of the expected product in 2 hr.

$$4\text{-}HOC_6H_4CHOHCH_2NH_2 + C_6H_5OH \xrightarrow{H_3O^+} (4\text{-}HOC_6H_4)_2CHCH_2NH_2 \quad (3)$$

The generality of this reaction (eq. 3) was tested with several β-phenylethanolamines and several phenolic compounds. The amines included the *ortho* and *meta* isomers of octopamine, norepinephrine [arterenol, α-(aminomethyl)-3,4-dihydroxybenzyl alcohol], normetanephrine [α-(aminomethyl)-4-hydroxy-3-methoxybenzyl alcohol], *p*-sympatol [synephrine, α-(methylaminomethyl)-4-hydroxybenzyl alcohol], and β-phenylethanolamine itself. The phenolic compounds tested were catechol, guaiacol, resorcinol, phloroglucinol, β-naphthol, anisole, and 4-hydroxycoumarin in addition to phenol; indole also could be used for the condensation.

The reaction took place with the formation of a minimum amount of side products when an excess (3–5 equiv.) of the phenolic compound was used, the acid was not stronger than 2 *N*, and the total reaction volume was kept relatively small (method A). The excess of phenolic compound could be recovered easily by steam distillation or by extraction from the acid reaction mixture with an organic solvent.

Another successful procedure involved the condensation of the amines with phenols in glacial acetic acid in the presence of *p*-toluenesulfonic acid (method B). The latter method had an advantage in some cases because most of the diarylethylamine toluenesulfonates could be recrystallized readily from water. In general, the toluenesulfonates of the primary amines could be recrystallized more easily than those of secondary amines, while the hydrochlorides of the secondary amines crystallized better than those of the primary amines. Furthermore, method B was more effective when the phenolic compound was less reactive or was insoluble in hot 2 *N* hydrochloric acid, as was the case with anisole or 4-hydroxycoumarin.

The yields, melting points, and analyses for the diarylethylamines which were prepared are summarized in Table I. Excellent yields of products were obtained with all the β-phenylethanolamines tested except *m*-octopamine and β-phenylethanolamine itself. When these two compounds were treated according to method A or B, only traces of the expected diarylethylamines could be detected in the reaction mixture. However, when either *m*-octopamine or β-phenylethanolamine was refluxed for 24 hr. with an excess of phenol in 6 *N* hydrochloric acid, a 65% yield of β-(3-hydroxyphenyl)-β-(4-hydroxyphenyl)ethylamine and a 22% yield of β-(4-hydroxyphenyl)-β-phenylethylamine (β-phenyltyramine), respectively, were obtained. It was interesting and somewhat disturbing that β-phenyltyramine had the same melting point as the previously known α-phenyltyramine.[4] In formulating a reaction path for the formation of the β,β-diarylethylamines, the possibility had been considered that a cyclammonium rearrangement[5] might occur, and that the product might be the α,β-disubstituted ethylamine. The possibility of this rearrangement could be excluded for the more reactive 4-hydroxyphenylethanolamines because the same product (compound 2 in Table I) was obtained by the condensation of octopamine with catechol or by the condensation of norepinephrine with phenol, and the same substance (compound 3 in Table I) was obtained from octopamine and guaiacol as from normetanephrine and phenol. The physical properties of the β-phenyltyramine obtained, however, made it necessary to compare it with an authentic compound prepared by an unambiguous synthesis. Thus, α-phenyltyramine was prepared by the lithium aluminum hydride reduction of 1-(4-hydroxyphenyl)-2-nitro-2-phenylethylene, which was obtained by the condensation of 4-hydroxybenzaldehyde and α-nitrotoluene. In addition to having the same melting point, α- and β-phenyltyramine had nearly identical ultraviolet absorption spectra and showed the same R_f values in several solvent systems. However, the color and speed of development of color of the two compounds with ninhydrin was distinctly different and the mixture melting point of the compounds was markedly depressed; so the product obtained from the condensation reaction must be the β-phenyl derivative.

The failure of *m*-octopamine to form diarylethylamines with the usual reaction conditions occurred because of a self-condensation which took place when it was heated in acid solution. Both *m*-octopamine and its N-methyl derivative, phenylephrine, yielded materials which appeared to be of high molecular weight when they were subjected to these conditions.

Some of these new diarylethylamines might have interesting physiological or pharmacological properties. Hinsberg noted that β,β-bis(3,4,5-trimethoxyphenyl)-ethylamine has a strong action on the surviving uterus. 4-Hydroxycoumarin had already been condensed with primary or secondary benzyl alcohols[6] in chloroform or tetrachloroethane in the presence of hydrogen chloride gas or phosphorus oxychloride, but not with β-phenylethanolamines.

Experimental[7]

Method A. β,β-Bis(4-hydroxyphenyl)ethylmethylamine.—A mixture of 2.04 g. (0.01 mole) of *p*-sympatol hydrochloride [α-(methylaminomethyl)-4-hydroxybenzyl alcohol], 2.8 g. (0.03 mole) of phenol, and 5 ml. of 2 *N* hydrochloric acid was heated for 2 hr. at 100°. The reaction mixture was diluted with 150 ml. of water, extracted with three 100-ml. portions of ether, and then evaporated to dryness *in vacuo*. The residual oil crystallized when it was digested with absolute ether. Recrystallization of the product from 10 ml. of 95% ethanol yielded 2.6 g. of β,β-bis(4-hydroxyphenyl)ethylmethylamine hydrochloride monohydrate, m.p. 136–140°. Addition of 50 ml. of absolute ether to the mother liquor yielded another 0.2 g., total yield 95%.

(3) G. Ehrhart, *Arch. Pharm.*, **295**, 198 (1962).

(4) B. Reichert, and W. Hoffman, *ibid.*, **274**, 153 (1936); J. Tular and L. Lespagnol, *Bull. sci. pharmacol.*, **46**, 305 (1939).

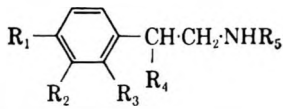
(5) H. Henecka, U. Hörlein, and K. H. Risse, *Angew. Chem.*, **72**, 960 (1960).

(6) E. Ziegler and U. Rossmann, *Monatsh. Chem.*, **88**, 22 (1957); E. Ziegler, U. Rossmann, and F. Litvan, *ibid.*, **88**, 587 (1957).

(7) All melting points were made in open capillary tubes and are corrected.

TABLE I

β,β-DIARYLETHYLAMINES



No.	R_1	R_2	R_3	R_4	R_5	Starting materials: β-(Aryl)-ethanolamine	Starting materials: Phenol	Method[a]	Yield %	M.p., °C.	Formula	Nitrogen: Calcd.	Nitrogen: Found	Salt[b]	M.p., °C.	Nitrogen: Calcd.	Nitrogen: Found
1	OH	H	H	4-Hydroxyphenyl	H	4-Hydroxyphenyl	Phenol	A	94	206–209	$C_{14}H_{15}NO_2$	6.11	5.89	Ts	224–226	3.49	3.42
								B	93								
2	OH	H	H	3,4-Dihydroxyphenyl	H	4-Hydroxyphenyl	Catechol	B	95	160–165[c,d]	$C_{14}H_{15}NO_3$	5.70	5.66	Ts	218–220	3.35	3.27
						3,4-Dihydroxyphenyl	Phenol	B	94						218–220		3.31
3	OH	H	H	4-Hydroxy-3-methoxyphenyl	H	4-Hydroxyphenyl	Guaiacol	B	80	205–209	$C_{15}H_{17}NO_3$	5.40	5.38	Ts	172–175	3.25	3.23
						4-Hydroxy-3-methoxyphenyl	Phenol	B	87						173–176		3.21
4	OH	H	H	2-Hydroxynaphthyl-1	H	4-Hydroxyphenyl	β-Naphthol	B	71	214–218	$C_{18}H_{17}NO_2$	5.02	5.18	Ts	209–211	3.11	3.00
5	OH	H	H	2,4,6-Trihydroxyphenyl	H	4-Hydroxyphenyl	Phloroglucinol	B	88		$C_{14}H_{15}NO_4$			Ts	139–143	3.23	3.14
6	OH	H	H	4-Hydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Phenol	A	95	233–236	$C_{15}H_{17}NO_2$	5.76	5.63	HCl	186–189[c,f]	5.00	4.99
7	OH	H	H	3,4-Dihydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Catechol	A	90		$C_{15}H_{17}NO_3$			HCl	126–128	4.73	4.70
8	OH	H	H	4-Hydroxy-3-methoxyphenyl	CH_3	N Methyl-4-hydroxyphenyl	Guaiacol	A	81	197–198	$C_{16}H_{19}NO_3$	5.12	5.14	HCl	246–249	4.52	4.30
								B	76					Ts	211–215	3.14	3.09
9	OH	H	H	2,4-Dihydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Resorcinol	A	92	142–144[d]	$C_{15}H_{17}NO_3$	5.40	5.23	HCl	116–118	4.73	4.72
10	OH	H	H	2-Hydroxynaphthyl-1	CH_3	N-Methyl-4-hydroxyphenyl	β-Naphthol	A	92	195–198	$C_{19}H_{19}NO_2$	4.77	4.65	HCl	223–224	4.25	4.19
11	OH	OCH_3	H	3,4-Dihydroxyphenyl	H	4-Hydroxy-3-methoxyphenyl	Catechol	B	79		$C_{15}H_{17}NO_4$			Ts	190–192	3.14	3.05
12	OH	OCH_3	H	4-Hydroxy-3-methoxyphenyl	H	4-Hydroxy-3-methoxyphenyl	Guaiacol	B	73		$C_{16}H_{19}NO_4$			Ts	174–179	3.04	2.97
13	OH	OH	H	3,4-Dihydroxyphenyl	H	3,4-Dihydroxyphenyl	Catechol	A	97					HCl	229–231	4.71	4.68
								B	92		$C_{14}H_{15}NO_4$			Ts	222–225	3.23	3.19
14	OH	H	H	4-Methoxyphenyl	H	4-Hydroxyphenyl	Anisole	B	56	165–166	$C_{15}H_{17}NO_2$	5.75	5.58	Ts	191–193	3.37	3.27
15	OH	H	H	4-Methoxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Anisole	B	61	187–188	$C_{16}H_{19}NO_2$	5.44	5.33	Ts	63–65	3.26	3.09
16	H	H	OH	4-Hydroxyphenyl	H	2-Hydroxyphenyl	Phenol	B	98	205–206	$C_{14}H_{15}NO_2$	6.11	6.09	Ts	239–242	3.49	3.46
17	H	OH	H	4-Hydroxyphenyl	H	3-Hydroxyphenyl	Phenol	e	65	95–105[f]	$C_{14}H_{15}NO_2$	6.11	6.00				
18	OH	H	H	4-Hydroxycoumarinyl-(3)	H	4-Hydroxyphenyl	4-Hydroxycoumarin	B[e]	39	155–160	$C_{17}H_{15}NO_4$	4.71	4.64	Ts	230–233[d]	2.98	2.99
19	H	H	H	4-Hydroxyphenyl	H	Phenyl	Phenol	e	22	160–162	$C_{14}H_{15}NO$	6.56	6.54				
20	OH	H	H	Indolyl-3	H	4-Hydroxyphenyl	Indole	B[e]	56	188–194	$C_{16}H_{16}N_2O$	11.10	11.25				

[a] For the preparation of the compounds the same molar quantities and reaction conditions were used as described in the Experimental section of the paper. Different amounts of solvents were required for the recrystallization of the different products. [b] Ts is *p*-toluenesulfonate. [c] See ref. 8. [d] Melts with decomposition. [e] See Experimental. [f] See ref. 9.

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HCl \cdot H_2O$: N, 4.70. Found: N, 4.61.

The compound lost 6.0% by weight when dried for 1 day at 100° (2 mm.) over phosphorus pentoxide (calcd.: 6.05%). The anhydrous compound melted at 130–135°, solidified between 150–170°, and remelted at 186–189°.

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HCl$: N, 5.76. Found: N, 5.63.

Method B. β,β-Bis(4-hydroxyphenyl)ethylamine.—A mixture of 1.53 g. (0.01 mole) of octopamine [α-(aminomethyl)-4-hydroxybenzyl alcohol], 2.8 g. (0.03 mole) of phenol, 2.3 g. (0.012 mole) of *p*-toluenesulfonic acid monohydrate, and 4 ml. of glacial acetic acid was heated for 1.5 hr. at 100°. The acetic acid was removed *in vacuo*, the residue was diluted with 200 ml. of water, and the excess of phenol was extracted with three 100-ml. portions of ether. When the aqueous solution was concentrated to about 50 ml. and kept in a refrigerator for 2 hr., 3.4 g. of β,β-bis(4-hydroxyphenyl)ethylamine *p*-toluenesulfonate, m.p. 224–226°, separated; 0.35 g. of less pure product, m.p. 210–220°, was obtained from the mother liquor.

The free amine was precipitated from an aqueous solution of the salt by the addition of dilute ammonium hydroxide.[8] It contains 1 to 2 moles of water if it is dried in a vacuum desiccator at room temperature (12 mm.) and melts at 100–110°. However, the water can be removed completely by drying over phosphorus pentoxide at 100° (2 mm.). The amine obtained in this manner sintered at 125–130° and melted at 206–209°.[9]

β-(3-Hydroxyphenyl)-β-(4-hydroxyphenyl)ethylamine.—A mixture of 5 g. (0.0264 mole) of *m*-octopamine hydrochloride [α-(aminomethyl)-3-hydroxybenzyl alcohol], 25 g. (0.266 mole) of phenol, and 100 ml. of 6 *N* hydrochloric acid was refluxed for 24 hr. The reaction mixture was diluted with 100 ml. of water and the excess of phenol was extracted with four 100-ml. portions of ether. The aqueous solution was concentrated to a volume of about 50 ml. and dilute ammonium hydroxide was added. When a precipitate first appeared, charcoal was added and the solution was filtered. More dilute ammonium hydroxide was then added to the filtrate until no further precipitate formed. The resulting β-(3-hydroxyphenyl)-β-(4-hydroxyphenyl ethylamine (compound 17 in Table I) was collected, recrystallized from ethanol–water, and dried at 80° (2 mm.). The yield was 3.9 g. (64.5%) and the melting point was 95–105°. Several attempts to obtain a product with a higher melting point were unsuccessful, and even when the compound was kept for 24 hr. at 120–130° it did not resolidify (see ref. 9). Chromatographic examination of the heated amine showed that it had not undergone alteration or decomposition.

β-Phenyltyramine.—A solution of 12 g. (0.069 mole) of β-phenylethanolamine hydrochloride and 7 g. (0.0745 mole) of phenol in 50 ml. of 6 *N* hydrochloric acid was refluxed for 24 hr. The mixture was cooled, diluted with 80 ml. of water, and extracted with four 100-ml. portions of ether. The aqueous solution was made alkaline (pH 12) by the addition of 50% sodium hydroxide solution (some ammonia was liberated), and the remaining β-phenylethanolamine (less than 1 g.) was extracted with two 100-ml. portions of ether. The aqueous layer was neutralized to pH 8.5 by the addition of hydrochloric acid and β-phenyltyramine was extracted with five 100-ml. portions of ether. The solvent was evaporated *in vacuo* and the crystalline residue was digested with a little dry benzene. The yield was 3.2 g. (22%), m.p. 158–160.5°. One recrystallization of this material from aqueous ethanol yielded a product melting at 160–162°; λ_{max}^{MeOH} 279 mμ (ε 1850), 233 (6900).

1-(4′-Hydroxyphenyl)-2-nitro-2-phenylethylene.—A mixture of 9.5 g. (0.07 mole) of α-nitrotoluene, 10 g. (0.082 mole) of 4-hydroxybenzaldehyde, 4 g. (0.052 mole) of ammonium acetate, and 50 ml. of glacial acetic acid was refluxed for 2 hr. and then poured into 500 ml. of cold water. The resulting oil, which crystallized slowly, was separated, dried, washed with petroleum ether (b.p. 30–60°), and dissolved in 50 ml. of absolute ether. A small amount of insoluble material was removed by filtration, the ethereal solution was evaporated to dryness, and the residue was recrystallized from ethanol–water; 2.9 g. (17%) of yellow prisms, m.p. 147–149°, was obtained.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.80; H, 4.60; N, 5.80. Found: C, 69.93; H, 4.83; N, 5.47.

α-Phenyltyramine.—A solution of 2 g. (0.0083 mole) of 1-(4′-hydroxyphenyl)-2-nitro-2-phenylethylene in 100 ml. of absolute ether was added to the refluxing ether of a well-stirred and boiling mixture of 2 g. (0.064 mole) of lithium aluminum hydride and 250 ml. of absolute ether during a period of about 1 hr. Stirring and refluxing was continued for another 4 hr. The excess of lithium aluminum hydride was decomposed by the addition of 400 ml. of water, and concentrated hydrochloric acid was added until all inorganic material had dissolved. The aqueous layer was then separated and passed through a 7 × 10 cm. column of Amberlite CG-120 (H^+) (100–200 mesh). α-Phenyltyramine was eluted from the resin with a mixture of concentrated ammonium hydroxide and ethanol (1:2). The first 350 ml. of alkaline eluate was collected and evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol–water to yield 1.1 g. (63%) of α-phenyltyramine, m.p. 157–159°. After two more recrystallizations from 95% ethanol the product melted at 160–162°, lit.[4] m.p. 159°. A mixture with β-phenyltyramine softened at 143° and melted at 146–148°; λ_{max}^{MeOH} 279 mμ (ε 1750), 231 (6300).

β-(4-Hydroxycoumarinyl-3)-*p*-tyramine.—A mixture of 1.53 g. (0.01 mole) of octopamine [α-(aminomethyl)-4-hydroxybenzyl alcohol], 1.70 g. (0.0105 mole) of 4-hydroxycoumarin, 2.3 g. (0.012 mole) of *p*-toluenesulfonic acid monohydrate, and 6 ml. of glacial acetic acid was heated at 100° for 2 hr. The acetic acid was removed at 70° (12 mm.), the residue was digested two times with a mixture of 8 ml. of ethanol, and 12 ml. of benzene, and was then recrystallized from methanol. The yield[10] was 1.94 g. (39%) of the *p*-toluenesulfonate, m.p. 230–233° dec.

β-(Indolyl-3)-*p*-tyramine.—A mixture of 1.53 g. (0.01 mole) of octopamine, [α-(aminomethyl)-4-hydroxybenzyl alcohol], 4 g. (0.034 mole) of indole, 3.8 g. (0.02 mole) of *p*-toluenesulfonic acid monohydrate, and 5 ml. of glacial acetic acid was heated on a boiling water bath for 4 hr. The acetic acid was removed *in vacuo* and the remaining brown oil was taken up into 200 ml. of methanol and passed through a 4 × 4 cm. column of Amberlite CG-120 (H^+). The column was washed with 1 l. of methanol to remove most of the colored impurity. β-(Indolyl-3)-*p*-tyramine was eluted from the column with a mixture of one part of concentrated ammonium hydroxide with two parts of methanol. The first 1.2 l. of alkaline eluate was collected and evaporated to dryness. The residue was washed with 25 ml. of ether and was recrystallized from ethanol to yield 1.4 g. (56%) of product, m.p. 188–194°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.22; H, 6.41; N, 11.10. Found: C, 76.20; H, 6.81; N, 11.25.

Acknowledgment.—Mrs. Kerin N. Yates performed the nitrogen analyses of these compounds. The other analyses were made by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(8) All the free amines listed in Table I were obtained in this manner. They were usually insoluble in water (except for the phloroglucinol derivative) and could be recrystallized from dilute ethanol. However, in solution the catechol derivatives were quite unstable in the presence of oxygen, and even in the solid state they darkened within a few weeks; hence, only one free catecholamine (compound 2 in Table I) was prepared.

(9) Hinsberg (see ref. 2) first reported a melting point of 95°, and then later 105°, but did not give an analysis; this melting point probably is for the hydrate. However, the anhydrous form also melted at about 100–120° if it was quickly heated, and then solidified and melted again at 206–209°. Even if it was heated very slowly a sintering could be observed at about 125–130°. This phenomenon occurred with many of the compounds listed in Table I, and also with some of the hydrochlorides (compounds 6, 7, and 9 in Table I). The phenomenon could be observed especially well with the condensation product of octopamine and β-naphthol (compound 4 in Table I) which melted at 95–105° to a glass-like substance even when it was heated very slowly, crystallized at 120–130°, and melted again at 214–218°. The melting and resolidifying was not connected with a structural change, since compound 1 was recovered unchanged after it had been heated at 200° for 10 min. A possible explanation for this behavior is that the anhydrous compounds might have retained the crystal structure of the hydrates after the water had been removed.

(10) Only one run was made with equal amounts of *p*-sympatol and of 4-hydroxycoumarin. The yield might well be improved by a variation of the reaction conditions, in particular by the use of an excess of 4-hydroxycoumarin.

Correlation of Base Strengths of Aliphatic and N-Substituted Anilines

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The base strengths of secondary and tertiary aromatic amines of the type $C_6H_5NR_1R_2$ are plotted against the Taft σ^* values. Each class of amine lies on a different line. All of the aliphatic amines reported by Hall[1] and all of the aromatic amines reported herein are approximately correlated to a single line each by the equation $\log K/K_0 = \rho^*\Sigma\sigma^* + H(n)$. The quantity, $\Sigma\sigma^*$, is the sum of the polar substituent constants of the groups attached to the amino nitrogen, n is the number of hydrated $\overset{+}{N}$–H groups in the ammonium ion, and H is an empirical constant measuring the base-strengthening effects of each hydrated $\overset{+}{N}$–H group. The values of the reaction series constant, ρ^*, and the hydration constant, H, are the same for both the aliphatic and aromatic series. The equation attributes the effect of structure on base strength to the sum of independent polar, solvation, and resonance effects and provides an approximate evaluation of hydration effects in amines.

Attempts to explain basic strength of amines in water in terms of structure have met with varying degrees of success. Discrepancies in correlation have been related to various factors including hydration,[1-3] proximity,[4] steric,[1,5] and polarization effects.[6] By far the most successful attempt to correlate basicities was made by Hall[1] who showed that a large number of primary, secondary, and tertiary aliphatic amines could be satisfactorily correlated with the Taft equation, $\log K/K_0 = \rho^*\Sigma\sigma^*$, where $\Sigma\sigma^*$ was the sum of the polar substituent constants of groups attached to the amino nitrogen; each class of amines fell on a different line. Because tertiary amines correlated better by the Taft equation than did the primary and secondary amines, Hall discounted the B-strain theory as an explanation of the base weakening that generally occurs in going from primary to secondary to tertiary amines. He concluded that (1) polar effects were primarily responsible for relative base strengths within a given class of amines, (2) solvation effects were responsible for the separation of amines into four groups (NH_3, 1°, 2°, 3°), and (3) steric hindrance of solvation was responsible for deviations from the correlation lines noted for primary and secondary amines containing bulky groups. To account for the insensitivity of the tertiary ammonium ions to steric effects, Hall postulated that these ions might not be hydrated.

This paper reports the correlation of secondary and tertiary aromatic amines of the type $C_6H_5NR_1R_2$ by the Taft equation and the further correlation of the pK_a values reported by Hall[1] and the pK_a values for aromatic amines by a single equation. While Hall drew correlation lines through amines of minimum steric requirements, the correlations described here include all data in a least-squares fitting process and all slopes and intercepts were determined in this manner.

Results and Discussion

In Table I have been assembled the pK_a and $\Sigma\sigma^*$ values for aromatic amines which have been found in the literature or determined in our laboratories. Plots of the data are given in Fig. 1. Figure 1 reveals that for each class of aromatic amine a linear correlation exists between pK_a and $\Sigma\sigma^*$ with the exception of benzoquinuclidine and the N-*t*-butylanilines which will be discussed later. Table II lists the ρ^* and intercept values of the lines shown in Fig. 1 and for the data given by Hall[1]; although the ρ^* values are nearly identical, the intercepts are distinctly different.

All of the data in Table I (with the exception of compounds 13, 24, and 26) and all of the data given by

TABLE I

pK^a OF AROMATIC AMINES, $C_6H_5NR_1R_2$, IN WATER AT 25°

No.	R_1	R_2	$\Sigma\sigma^*$	pK_a	Ref.
1	H	$CH{\equiv}CCH_2$	1.85	3.07	*a, b*
2	H	$C_6H_5CH_2$	1.31	4.04	*c*
3	H	$HOCH_2CH_2$	1.29	4.06	*c, d*
4	H	$CH_2{=}CHCH_2$	1.23	4.18	*b, e*
5	H	CH_3	1.09	4.89	*f*
6	H	CH_3CH_2	0.99	5.10	*f*
7	H	$CH_3CH{=}CHCH_2$	1.22	5.12	*b*
8	H	*sec*-C_4H_9	0.87	5.24	*b*
9	H	*n*-C_3H_8	0.88	5.24	*b*
10	H	*i*-C_3H_8	0.89	5.30	*c*
11	H	*n*-C_4H_9	0.96	5.44	*c*
12	H	*t*-C_5H_{11}	0.77	6.35	*b, g*
13	H	*t*-C_4H_9	0.77	7.10	*h*
14	N-Morpholine		1.27	3.20	*a, c*
15	$C_6H_5CH_2$	$C_6H_5CH_2$	1.05	4.00	*i*
16	$HOCH_2CH_2$	$HOCH_2CH_2$	1.00	4.07	*c*
17	CH_3	CH_3	0.60	5.07	*c, f*
18	N-Piperidine		0.46	5.20	*a*
19	*n*-C_3H_8	*n*-C_3H_8	0.37	5.63	*f*
20	CH_3	*n*-C_3H_8	0.49	5.68	*f*
21	CH_3	CH_3CH_2	0.50	5.99	*j*
22	CH_3CH_2	*n*-C_3H_8	0.39	6.40	*c, f*
23	CH_3CH_2	CH_3CH_2	0.40	6.52	*c, j*
24	Benzoquinuclidine		0.64	7.79	*k, l*
25	H	H	1.58	4.65	*j*
26	CH_3	*t*-C_4H_9	0.3	7.25	*h*

[a] The σ^* values were those given by Hall.[1] [b] V. Wolf and D. Ramin, *Ann.*, **626**, 47 (1959). [c] These values were determined by us using the Hammett spectrophotometric method. [d] R. Miguel, A. Lattes, and P. Maraval, *Bull. soc. chim. France*, 303 (1962). [e] The σ^* values of the crotyl group were used. [f] N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932). [g] The σ^* values of the *t*-butyl group was used. [h] N-*t*-Butylaniline value is for 19° while the value for N-methyl-N-*t*-butylaniline is at 31° [G. Verlearschi and P. Rumpf, *Compt. rend.*, **229**, 1152 (1949)]. [i] These values were determined by us by potentiometric titrations in nitromethane after the method of C. A. Streuli, *Anal. Chem.*, **31**, 1652 (1959). [j] N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5124 (1930). [k] For this compound we considered $\Sigma\sigma^* = \sigma_{C_6H_5}{}^* + 2\sigma_{C_6H_5(CH_2)_3}{}^*$. [l] B. M. Wepster, *Rec. trav. chim.*, **71**, 1171 (1952).

(1) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).
(2) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1299 (1949).
(3) T. S. Moore and T. F. Winmill, *ibid.*, 1635 (1912).
(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 225.
(5)(a) H. C. Brown, *Science*, **103**, 385 (1946); (b) G. Vexlearschi and P. Rumpf, *Compt. rend.*, **229**, 1152 (1949); **228**, 1655 (1949).
(6) S. R. Palit, *J. Phys. Colloid Chem.*, **51**, 1028 (1947).

TABLE II

AND INTERCEPT VALUES FOR TAFT PLOTS OF AMINE BASICITIES

Amine type		Intercept (pK_a)	r	Std. dev.
C_6H_5NRH	2.96	8.19	0.897	0.52
$C_6H_5NR_2$	3.15[a]	7.25[a]	0.939[a]	0.40[a]
Av. for aromatic amines	3.06 ± 0.09			
RNH_2	3.07 ± 0.09[b]	13.06[b]	0.990	0.23
R_2NH	2.94 ± 0.10[b]	11.66[b]	0.985	0.33
R_3N	3.23 ± 0.05[b]	9.55[b]	0.997	0.15
Av. for aliphatic amines	3.08 ± 0.10			

[a] Value does not include data for benzoquinuclidine. [b] From data given by Hall (see ref. 1) using a least-square fitting process.

Hall can be satisfactorily correlated to single lines by use of eq. 1. This equation attributes the effect of structure on the relative basicity of amines to the sum of independent polar and hydration effects and assumes constant resonance effects within the aromatic series.[7]

$$\log K/K_0 = \rho^*\Sigma\sigma^* + H(n) \qquad (1)$$

In eq. 1, n is the number of hydrated $\overset{+}{N}$–H groups in the ammonium ion. The empirical constant, H (−1.12 ± 0.14), is attributed to the base-strengthening effect of hydrating a single $\overset{+}{N}$–H group. The reaction series constant ρ^* (3.23 ± 0.05) used is the ρ^* value for the tertiary aliphatic amines. The best fit of the data is obtained when the following values of n are used: NH_4^+, $n = 4$; RNH_3^+ and $C_6H_5NH_3^+$, $n = 3$; $R_2NH_2^+$ and $C_6H_5NRH_2^+$, $n = 2$; $C_6H_5NR_2H^+$, $n = 1$; R_3NH^+, $n = 0$.

The correlations by eq. 1 shown in Fig. 2 include the 77 amines listed by Hall[1] and the 26 aromatic amines listed in Table I; the aliphatic series covers eight powers of 10 and the aromatic series covers nearly six powers of 10. The correlation coefficients for the aliphatic and aromatic series are 0.988 and 0.939, respectively.

The success of eq. 1 in correlating the pK_a values of both aliphatic and aromatic amines by using the parameters indicated supports the following hypotheses: (a) relative polar effects in both the aliphatic and aromatic amines are proportional to the substituent constants σ^* and are additive; (b) the relative polar effects are equal in each class of amines; (c) polar, resonance, and solvation effects are separate and independent variables; (d) solvation effects are directly proportional to the number of $\overset{+}{N}$–H groups in the ammonium ions with the exception of the tertiary ammonium ions, which have no water of hydration associated with the $\overset{+}{N}$–H group; (e) the difference in the intercepts of the two lines in Fig. 2 represents the base-weakening effect of a single aromatic ring conjugated with the amine nitrogen; and (f) in comparison to polar, resonance, and solvation effects, steric effects are of secondary importance (however, see below).

Condition b, that relative polar effects are equal in each class of amines, is supported by the similarities of re-

(7) A more general equation of the form $\log K/K_0 = \rho^*\Sigma\sigma^* + H(n) + R$ when R accounts for the resonance effect of a single phenyl group on the base strength of amines would allow correlation of all the aliphatic and aromatic amines to a single line. For the data given the value of the resonance effect R would be 3.61 pK units. (Referee's comment: "The independent estimate of R from the pK_a of benzoquinuclidine is in good agreement with this value.")

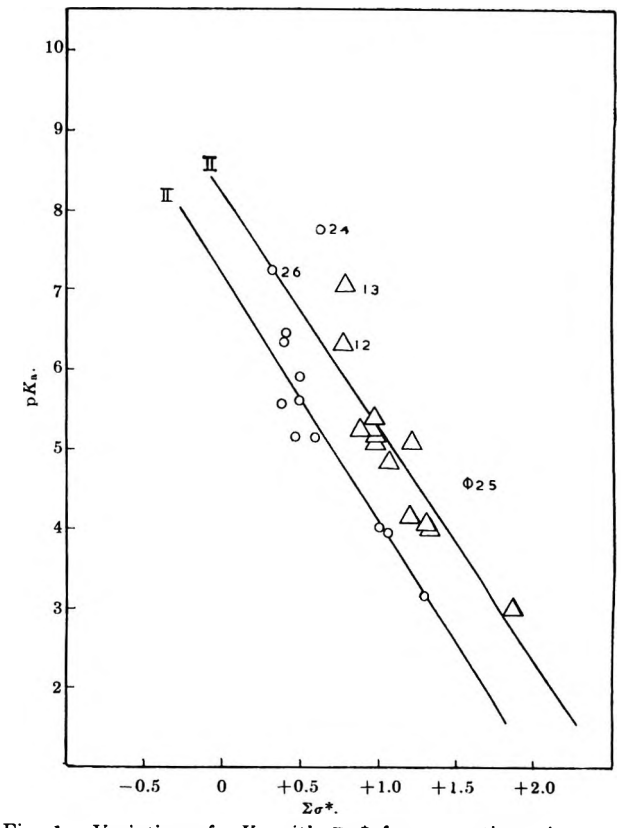

Fig. 1.—Variation of pK_a with $\Sigma\sigma^*$ for aromatic amines: ○, $C_6H_5NR_1R_2$; △, C_6H_5NHR; ϕ, $C_6H_5NH_2$.

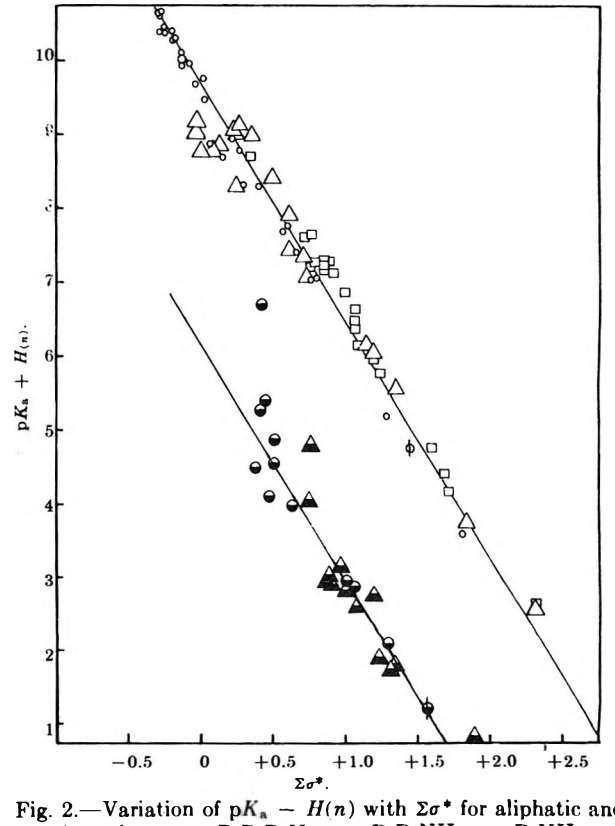

Fig. 2.—Variation of $pK_a - H(n)$ with $\Sigma\sigma^*$ for aliphatic and aromatic amines: ○, $R_1R_2R_3N$; △, R_1R_2NH; □, R_1NH_2; ϕ, NH_3; ◒, $C_6H_5NR_1R_2$; ▲, $C_6H_5NR_1H$; ◒, $C_6H_5NH_2$.

action series constants ρ^* listed in Table II. Others[1-3,8] have postulated that hydration is proportional to the number of hydrated $\overset{+}{N}$–H groups in the ammonium ion. That hydration is directly proportional to the number of $\overset{+}{N}$–H groups (condition d) is supported by the fact that a single hydration constant, H, is applicable to all classes of amines; the use of a single constant H for both the aliphatic and aromatic amines also implies that the hydration of a single $\overset{+}{N}$–H group is little affected by the electron density on the amino nitrogen.

The effect of steric hindrance on base strength of aliphatic amines has been discussed by Hall.[1,9] For aromatic amines, steric hindrance to solvation (base weakening) may occur as in the aliphatic series; in addition, steric inhibition of resonance (base strengthening) may take place. Benzoquinuclidine appears to be a clear example of this latter effect.[10] In fact, if this compound is considered an "aliphatic" tertiary amine ($n = 0$), the correlation with eq. 1 is good (pK_a 7.79; pK_a 7.60, calcd. from eq. 1).

(8) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **82**, 2965 (1960).
(9) H. K. Hall, Jr., *ibid.*, **79**, 5444 (1957).
(10) B. M. Wepster, *Rec. trav. chim.*, **71**, 1171 (1952).

The deviation of the *t*-butylanilines (compounds 13 and 26) can be abscribed to steric inhibition of resonance, however, neither pK_a value was determined at 25°. In view of the deviation of N-*t*-amylaniline (compound 12) it would seem that steric factors alone cannot explain the deviation of the N-*t*-butylanilines.

In order to obtain the correlation of the data by eq. 1 using a single adjustable parameter, H, the value of ρ^* (3.23 ± 0.05) for the 3° aliphatic amines was used. It was then assumed that the correlation line for the aliphatic amines would pass through the trimethylamine point. This method permits the evaluation of H by eq. 2 and gives the value of -1.12 ± 0.14.

$$H = \frac{\Sigma[\log K/K_0 - 3.23(\Sigma\sigma^*)]}{\Sigma(n)} \qquad (2)$$

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A New Synthesis of Amino Phosphonic Acids[1]

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A new synthesis of amino phosphonic acids has been developed, involving the Curtius degradation of substituted diethyl phosphonoacetylhydrazides. This appears to be a general synthesis for 1-aminoalkylphosphonic acids since aminomethylphosphonic (glycine analog), 1-aminoethylphosphonic (alanine analog), and 1-amino-2-phenylethylphosphonic (phenylalanine analog) acids were synthesized in this manner successfully. Two additional phosphonic acid analogs of the naturally occurring amino carboxylic acids also were synthesized by special methods. These were 2-amino-4-phosphonobutyric acid (a glutamic acid analog) and 2-amino-3-phosphonopropionic acid (an aspartic acid analog). An improved isolation procedure for amino phosphonic acids is described and the over-all yields of the three amino acids produced by the Curtius degradation were 56–80%, based on the parent phosphonoacetic esters.

Kabachnik and Medved[3] have described what appears to be a general method for producing 1-aminoalkylphosphonic acids. They condensed both aldehydes and ketones with ammonia and a dialkyl phosphonate to give dialkyl esters of 1-aminoalkylphosphonic acids. Hydrolysis of the esters produced the free amino acids. Kabachnik and Medved did not prepare any phosphonic acid analog of a naturally occurring amino acid and their method gave over-all yields of 40% or less. Chalmers and Kosolapoff[4] used the same method for preparing 1-amino-2-phenylethylphosphonic acid (phenylalanine analog) and 1-aminoethylphosphonic acid (α-alanine analog) as well as a number of additional similar products. Their over-all yields were never greater than 41.5%. Aminomethylphosphonic acid (glycine analog) has been prepared by the ammonolysis of halomethylphosphonic acid esters[5] and by condensing N-(bromomethyl)phthalimide with dibutyl sodiophosphonate, followed by the hydrolysis of the resulting product.[4,6]

Since so few phosphonic acid analogs of the naturally occurring amino carboxylic acids have been prepared, it seemed desirable to consider the synthesis of additional ones. However, Kabachnik and Medved's method suffers from serious deficiencies—many of the aldehydes necessary for the synthesis of additional 1-aminoalkylphosphonic acids are not available readily and the yields of the phosphonic acids prepared by this method have been relatively poor. We report the first use of the Curtius reaction[7] for the preparation of 1-amino-

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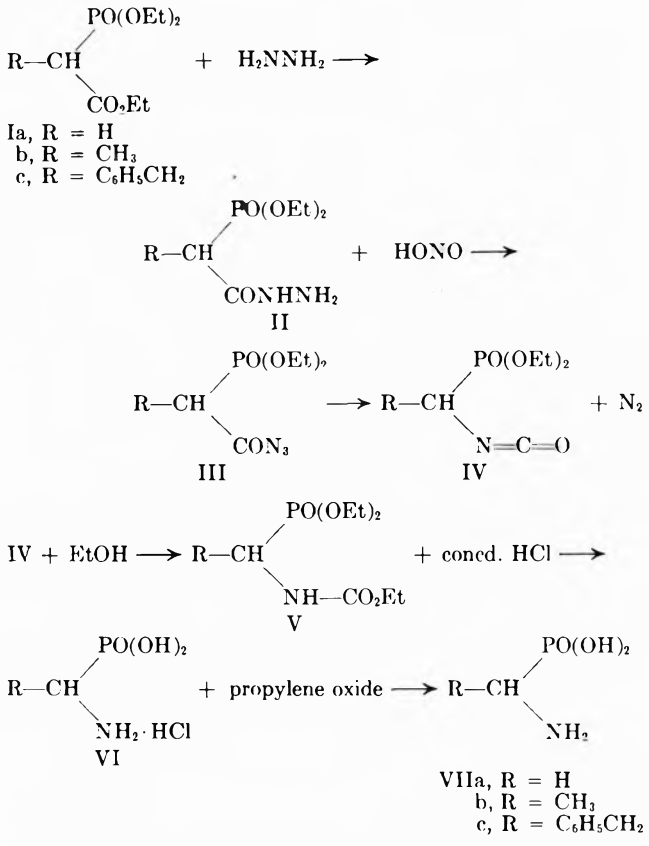
(2) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the A. and M. College of Texas, Aug., 1958; Department of Chemistry, Walla Walla College, College Place, Wash.
(3) (a) M. I. Kabachnik and T. Ya. Medved, *Dokl. Akad. Nauk SSSR*, **83**, 689 (1952); (b) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 868 (1953); (c) T. Ya. Medved and M. I. Kabachnik, *ibid.*, 314 (1954).
(4) M. E. Chalmers and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 5278 (1953).
(5) (a) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 635 (1950); (b) M. I. Kabachnik and T. Ya. Medved, *ibid.*, 95 (1951).
(6) V. Chavane, *Bull. soc. chim. France*, 774 (1948).
(7) P. A. S. Smith, "Organic Reactions," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337.



alkylphosphonic acids, thus avoiding some of the limitations of the earlier syntheses.

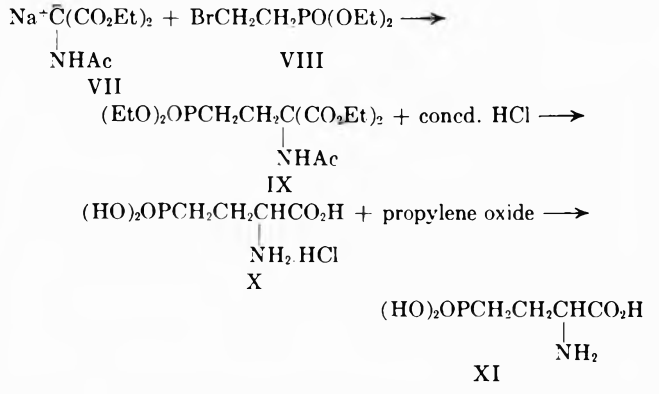
Apparently the key step in this synthesis was the condensation of hydrazine with the phosphonoacetic esters (I). This reaction usually was mildly exothermic, but for the less reactive esters it appeared desirable to heat the mixture at 40–50°. For reasons not yet determined, heating the mixture to 100° usually resulted in the isolation of none of the desired product. No attempt was made to isolate intermediates II–VI. Hydrolysis of crude V gave a viscous residue believed to be VI. It was noted that continued heating of this viscous residue *in vacuo* resulted in the liberation of hydrogen chloride and the production of the free amino acid (VII). This is not surprising since the phosphonic acid group is a relatively strong acid. However, the preferred method of isolating the amino acid (VII) was to leave sufficient hydrochloric acid in the crude residue so that the residue dissolved completely in 95% ethanol. To this ethanolic solution was added propylene oxide or butylene oxide slowly until no chloride ion remained. The amino acid (VII) separated from solution occasionally as an oil which quickly solidified, and the solid was of sufficient purity that it often required only one recrystallization to produce an analytically pure product.

From Ia, VIIa has been recovered in an over-all yield of 54%, VIIb has been produced from Ib in an over-all yield of 80%, and VIIc has been produced from Ic in an over-all yield of 56%. It is believed that further studies of these reactions may result in additional increases in yields.

The phosphonoacetic esters (I) can be produced readily by two routes. One involves the Arbuzov reaction between triethyl phosphite and ethyl chloroacetate to give Ia,[8] followed by the alkylation of Ia by the method of Kosolapoff and Powell.[9] This method gave approximately a 40% yield of the monoalkylated product, plus a small amount of what appeared to be the dialkylated product when benzyl chloride was employed as the alkylating agent.

The second and preferred synthesis of Ib was that of Ackerman and co-workers.[10] Ib was obtained in 83% yield from ethyl 2-bromopropionate and triethyl phosphite. Ib cannot be produced satisfactorily by the alkylation method of Kosolapoff and Powell[9] because a mixture of the unalkylated, the monoalkylated, and the dialkylated phosphonoacetic esters results, and all three of these compounds have virtually identical boiling points.

The synthesis of 2-amino-4-phosphonobutyric acid was accomplished by first condensing diethyl 2-bromoethylphosphonate with the sodium derivative of diethyl acetamidomalonate to give what was undoubtedly the desired substituted malonate (IX). Without attempting to isolate IX, the crude product from the first step was hydrolyzed by heating with concentrated hydrochloridic acid, and, after removal of the excess acid, the crude X, dissolved in 95% alcohol, was treated with an excess of propylene oxide. XI was recovered in an over-all yield of 46% from diethyl acetamidomalonate.



At times, recrystallization of XI from alcohol–water and other purification procedures failed to give pure XI. Finally an excellent chromatographic method was devised, involving the use of an ion-exchange resin. This method also worked well for purifying 2-amino-3-phosphonopropionic acid (XV).

Kamai and Kukhtin[11] described the esterification of carboxylic acids with trialkyl phosphites; with acrylic acid, simultaneous esterification and addition of the resulting dialkyl phosphonate to the C to C double bond occurred, forming trialkyl 3-phosphonopropionate. Thus, it appeared that a trialkyl phosphite might react with 2-acetamidoacrylic acid[12] (XII) to give a derivative of a phosphonic acid analog of aspartic acid. Such a reaction occurred when XII was heated with a mixture of trimethyl phosphite and dimethyl phosphonate. It is believed that the first reaction produced methyl 2-acetamidoacrylate (XIII) and this compound in turn condensed with dimethyl phosphonate to produce trimethyl 2-acetamido-3-phosphonopropionate (XIV). The hydrolysis of crude XIV gave 2-amino-3-

(8) (a) B. A. Arbuzov and V. S. Vinogradova, *Dokl. Akad. Nauk, SSSR*, **99**, 85 (1954); (b) R. H. Wiley, U. S. Patent 2,478,441 (1949).

(9) G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, **72**, 4198 (1950).

(10) B. Ackerman, R. M. Chladek, and D. Swern, *ibid.*, **79**, 6524 (1957).

(11) G. Kamai and V. A. Kukhtin, *Khim. i Primenenie Fosfororgan. Soedin. Akad. Nauk SSSR Kazansk. Filial Tr. 1-Konf.*, 91 (1955).

(12) T. Wieland, G. Ohnancker, and W. Ziegler, *Ber.*, **90**, 194 (1957).

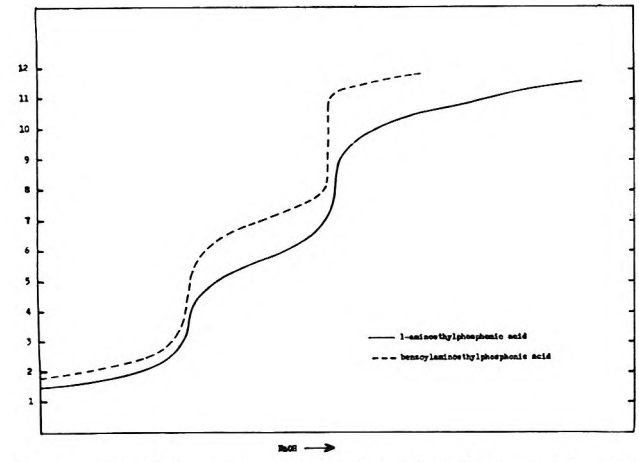


Fig. 1.—Titration curves for amino phosphonic acids and derivatives.

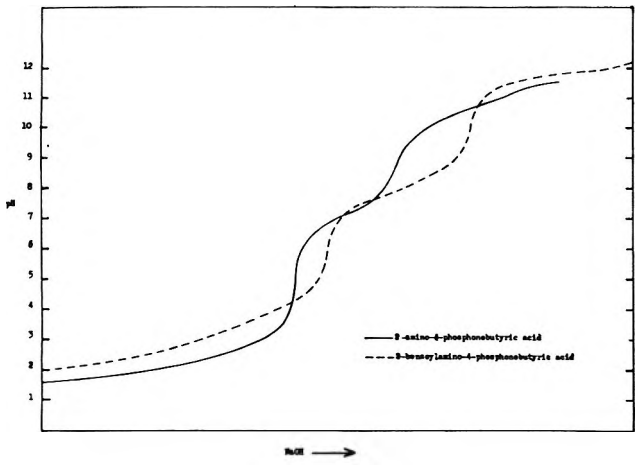
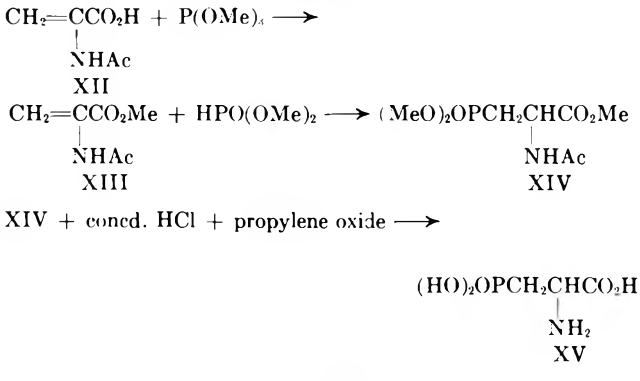


Fig. 2.—Titration curves for amino carboxy phosphonic acids and derivatives.



phosphonopropionic acid (XV) in a 50% over-all yield from XII.

Since our melting points for 1-aminoethylphosphonic acid and 1-amino-2-phenylethylphosphonic acid were in serious disagreement with values reported earlier,[4] all five of the amino acids were converted into the N-benzoyl derivatives. The benzoyl derivative of XV was an amorphous solid for which no suitable solvent could be found for recrystallization. The remaining derivatives were thoroughly purified and then hydrolyzed back to the parent amino acids.

Potentiometric titrations were carried out with the amino phosphonic acids and the N-benzoyl derivatives. All five amino acids gave two sharp breaks in the titration curves and one very weak break, as illustrated by the curves for 1-aminoethylphosphonic acid and 2-amino-4-phosphonobutyric acid in Fig. 1 and 2. The N-benzoyl derivatives of VIIa, b, c, and XI gave two sharp breaks in the titration curve (Fig. 1 and 2). It should be noted that in the titration curve of the N-benzoyl derivative of XI, the first break corresponded to the neutralization of two acid groups.

Since XI and XV are 2-amino carboxylic acids, it was not surprising that they gave positive ninhydrin tests. However, the ninhydrin tests on the remaining three amino acids were also positive. The intense characteristic violet color was produced only after adding a small amount of sodium bicarbonate to neutralize the excess acidity. Since the formation of free ammonia is believed to be one step in the production of the color in the ninhydrin test, the requirement of a slightly basic solution to produce an intense color seems reasonable. That a more or less normal ninhydrin reaction was taking place with VIIc was indicated by the fact that the characteristic odor of phenylacetaldehyde was noted soon after the reaction started. This surprising cleavage of the C to P bond was further confirmed by the positive identification of phosphate ion in the solution following the ninhydrin test on VIIa.

Experimental

All melting points were determined with a Hershberg apparatus and are corrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All reagents were the best grade available and were used generally without further purification.

Determination of Neutralization Equivalents.—Potentiometric titrations of the amino phosphonic acids and their N-benzoyl derivatives were carried out with a Beckman Zeromatic pH meter and with a Model D Sargent automatic titrator.

The amino acid, dissolved in water containing 1 mole of hydrochloric acid per mole of amino acid, was titrated with 0.1 *N* sodium hydroxide. The N-benzoyl derivatives were dissolved in water or 50% alcohol and titrated with 0.1 *N* sodium hydroxide. Curves similar to those shown in Fig. 1 and 2 resulted.

Since the amino phosphonic acids gave only two sharp breaks after the addition of excess hydrochloric acid, the neutralization equivalents were calculated from the amount of base required to go from the first to the second break. The first break corresponded to the isoelectric points for Ia, Ib, and Ic but not for XI and XV. Thus, these neutralization equivalents are actually molecular weights.

The neutralization equivalents of the N-benzoyl derivatives were determined from the amount of base required to go to the second sharp break. Since this corresponded to 2 equiv. of base for the Ia, Ib, and Ic derivatives and 3 equiv. of base for the derivative of XI, these were conventional neutralization equivalents.

Aminomethylphosphonic Acid (VIIa).—A mixture of 22.4 g. (0.1 mole) of triethyl phosphonoacetate,[8] b.p. 121–123° (4 mm.), $n^{30}D$ 1.4280, and 3.7 g. (0.11 mole) of 95+% hydrazine was stirred vigorously in a flask protected from moisture. The temperature of the mixture rose spontaneously to 48°. The homogeneous solution was heated to 75° and then allowed to cool to room temperature over a 24-hr. period. The suspension which resulted when 100 ml. of anhydrous ether was added with vigorous stirring was cooled to 0° and 20.5 ml. of 6 *N* hydrochloric acid was added dropwise at 0°. A white solid separated. The temperature was decreased to −10° and a solution of 8.3 g. (0.12 mole) of sodium nitrite in 15 ml. of water was added dropwise. After stirring for 10 min. longer at −10°, the resulting two layers were separated rapidly and the water layer was extracted with four 50-ml. portions of ether. To the combined ether extracts was added 50 ml. of absolute ethanol. This solution slowly evolved gas as it warmed to room temperature. Standing over night usually resulted in the separation of a small amount of white solid which was removed by filtration. The ether and excess alcohol were removed by distillation, leaving a somewhat viscous residue. To this residue was added 100 ml. of concentrated

hydrochloric acid and the resulting solution was heated under reflux for 2 days. The hydrolysate was treated with carbon to remove a small amount of dark-colored oil and was evaporated nearly to dryness on a steam bath under vacuum. A small excess of hydrochloric acid should remain in this viscous residue as this point in order for it to be completely soluble in 95% ethanol. If the residue were heated at reduced pressure for a prolonged period of time, increasing quantities of the residue failed to dissolve in alcohol. Aminomethylphosphonic acid and the other related amino phosphonic acids appeared to give hydrochloride salts in solution, but all attempts to isolate dry hydrochloride salts have given only the free amino acid.

The hydrolysate residue, containing excess hydrochloric acid, was dissolved in 100 ml. of 95% ethanol, and to this solution was added propylene oxide[13] or butylene oxide[13] dropwise with good stirring until there was no further precipitation of the amino acid. At times the precipitate was at first gummy but became granular on standing. This solid was collected on a filter, washed with ethyl alcohol, and dried in a vacuum oven. It was purified further by dissolution in a small quantity of hot water, filtration to remove any insoluble solid, followed by the addition of ethyl alcohol to the hot filtrate with good stirring until the separation of crystalline solid ceased. After chilling, the mixture was filtered and the solid was washed with ethyl alcohol and dried; it weighed 6.0 g. (54% over-all yield from triethyl phosphonoacetate). The titration curve showed two sharp breaks, the first at pH 3.45 (isoelectric point) and the second at pH 7.85. The neutralization equivalent found was 114 (calcd. 111) and this compound melted at 286.5° dec., lit.[5a] m.p. 310°.

A 3-g. portion of the amino acid was converted into the N-benzoyl derivative by the method of Staiger[14] utilizing 4.2 g. of benzoyl chloride and 29 ml. of 2 *N* sodium hydroxide. The resulting solution was brought to pH 2 with dilute hydrochloric acid and was extracted with ether, and the water layer was evaporated to dryness on a steam bath under vacuum. The product was extracted from the residue with 100 ml. of hot ethyl alcohol, but it was found that the extract contained sodium ions which could not be removed by recrystallizations. Therefore, the alcohol solution was evaporated to dryness, the residue was dissolved in 20 ml. of water, and this solution was passed through Dowex 50 resin in the H^+ form. The eluate was evaporated to dryness *in vacuo*, and the residue was recrystallized several times from glacial acetic acid and finally from ethyl alcohol. The white crystals melted at 179–180°, lit.[15] m.p. 182°; the neutralization equivalent found was 109 (calcd. 107.5).

A portion of the benzoylaminomethylphosphonic acid was hydrolyzed by heating with concentrated hydrochloric acid for 48 hr. After removing the benzoic acid by extraction with ether, the water layer was evaporated almost to dryness and the free amino acid was recovered by solution in ethyl alcohol, followed by treatment with propylene oxide. The melting point of this recovered amino acid was 286.5° dec.

1-Amino-2-phenylethylphosphonic Acid (VIIc).—This compound was synthesized by essentially the same method as compound VIIa When 31.4 g. of triethyl β-phenyl-α-phosphonopropionate[9] was mixed with 3.7 g. of hydrazine, there was only about a 3° rise in temperature, and the mixture did not become completely homogeneous for a number of hours. Since VIIb was only slightly soluble in water, the crude amino acid was dissolved in approximately 1 l. of boiling water, the solution was filtered, and the filtrate was diluted with alcohol until crystallization started and then was chilled. There was recovered 11.3 g. of white crystals (56% yield from Ic), m.p. 281° dec., lit.[4] m.p. 225–227°. The titration curve produced two sharp breaks, one at pH 3.8 (isoelectric point) and the second at pH 7.5; the neutralization equivalent found was 192 (calcd. 201).

The N-benzoyl derivative, prepared as described for compound VIIa, was only slightly soluble in water. In order to remove sodium ions completely, an alcoholic solution was passed through the Dowex 50 resin. The product was purified further by recrystallization from water, producing a white solid, m.p. 207–208°. When this derivative was titrated in a 50% alcohol solution, there was a sharp break at pH 5 and a less distinct one at approximately pH 10.

Anal. Calcd. for $C_{15}H_{16}NO_4P$: C, 59.01; H, 5.28; P, 10.15; neut. equiv., 152.5. Found: C, 58.99, 59.15; H, 5.44, 5.45; P, 10.27, 10.36; neut. equiv., 156.5.

When this benzoyl derivative was hydrolyzed, the parent amino acid was recovered, m.p. 281° dec.

Anal. Calcd. for $C_8H_{12}NO_3P$: C, 47.76; H, 6.01; P, 15.40. Found: C, 47.83, 47.65; H, 6.02, 6.24; P, 15.48, 15.42.

1-Aminoethylphosphonic Acid (VIIb).—A study was made of the conditions required to produce the best yield of this compound. The following is the procedure which gave consistently good results. To 32 g. (1 mole) of 95+% hydrazine, contained in a 250-ml. three-necked flask fitted with a good stirrer, dropping funnel, and drying tube, was added 119 g. (0.5 mole) of triethyl α-phosphonopropionate[8a,10] dropwise. The reaction temperature increased rapidly to 40° and was controlled at this point by the rate of addition of the ester After standing overnight, a 1-mm. vacuum was applied, while the mixture was heated to 50°. The clear, viscous residue was dissolved in 56 ml. of water, 500 ml. of absolute ether was added, and the mixture was cooled to −10°. At this temperature, 56 ml. of concentrated hydrochloric acid was added, followed by a solution of 46.7 g. of sodium nitrite dissolved in 88 ml. of water. After stirring for 5 min. longer, the layers were separated and the cold water was extracted twice with 100-ml. portions of ether. The ether extracts were added to 250 ml. of absolute ethanol and this solution was allowed to stand overnight. After filtration, the filtrate was concentrated to dryness under vacuum. There remained 106.1 g. of viscous residue. To this residue was added 100 ml. of water and 300 ml. of concentrated hydrochloric acid, and the solution was heated under reflux for 36 hr. After treating the hydrolysate with carbon, the filtrate was evaporated almost to dryness at reduced pressure and the residue was dissolved in 95% ethanol. The amino acid was recovered by treatment with propylene oxide, yielding 50 g. of solid (80% from Ib) which was in a high state of purity without additional recrystallization. A quantity of this product was purified further by dissolution in a small quantity of water, followed by the addition of alcohol. The pure compound had a melting point of 283–285° dec. and has been reported[4] to melt above 340°. A potentiometric titration produced two sharp breaks at pH 3.6 (isoelectric point) and pH 8.2 (Fig. 1).

Anal. Calcd. for $C_2H_8NO_3P$: C, 19.20; H, 6.44, P, 24.77; neut. equiv., 125. Found: C, 19.28; 19.08; H, 6.57, 6.31; P, 24.65, 24.83; neut. equiv., 123.

The N-benzoyl derivative was prepared as described for compound VIIa. The deionized product was recrystallized from ethyl acetate containing a trace of acetic acid. The derivative melted at 183° dec.

Anal. Calcd. for $C_9H_{12}NO_4P$: C, 47.16; H, 5.28; P, 13.52; neut. equiv., 114.5. Found: C, 47.15, 47.35; H, 5.33, 5.19; P, 13.70, 13.59; neut. equiv., 115.5.

Hydrolysis of this benzoyl derivative produced 1-aminoethylphosphonic acid m.p. 283–285° dec.

2-Amino-4-phosphonobutyric Acid (XI).—The sodium derivative of diethyl acetamidomalonate was prepared from 120 ml. of absolute ethanol, 6.9 g. of sodium metal, and 65.1 g. of diethyl acetamidomalonate. About 115 ml. of ethanol was distilled from this solution, 150 ml. of dry toluene was added, and the distillation was continued. When the last of the ethanol was removed, a tan solid separated and broke into small particles by the action of the Hershberg stirrer. An additional 100 ml. of dry toluene was added and the distillation was continued until approximately 150 ml. of toluene had distilled. To the suspension, 125 ml. of diethyl carbonate was added, causing the tan solid to form a well-dispersed suspension. To this finely divided suspension was added 80 g. of diethyl β-bromoethylphosphonate[16] and the stirring was continued for 2 hr. at 115°. The reaction temperature was lowered to 85° and the suspension was held at this temperature for an additional 11 hr. The mixture was filtered hot to remove sodium bromide, the solvent was removed from the filtrate at 30-mm. pressure, and distillation was then continued at 1 mm. until the temperature of the distilling vapors reached 145°. Since the viscous distillation residue showed no tendency to distil or to crystallize, it was heated under reflux with 200 ml. of 6 *N* hydrochloric acid for 22 hr. After concentrating this solution nearly to dryness under vacuum, 150 ml. of water was added, and the dark color was removed by treating the solution

(13) Supplied through the courtesy of The Dow Chemical Co.

(14) R. E. Staiger, *J. Org. Chem.*, **9**, 396 (1944).

(15) M. Engelmann and J. Pikl, U. S. Patent 2,304,156 (1942).

(16) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

with activated charcoal.[17] The decolorized solution was evaporated almost to dryness and the residue was dissolved in 200 ml. of 80% ethanol. If necessary, a few drops of hydrochloric acid was added to make the residue completely soluble in the alcohol solution. Addition of propylene oxide precipitated 28 g. (46% from diethyl acetamidomalonate) of product, which at times could not be purified completely by recrystallization from water. Preferably the crude solid was dissolved in a minimum of water, and the solution was passed through 400 ml. of Dowex 50W-X8 resin (H^+ form). A strongly acidic impurity passed through rapidly, washing with distilled water caused the eluate to become neutral, and more water caused XI to be eluated as a mildly acidic eluate. Finally, washing the column with 3 *N* hydrochloric acid removed a small amount of an amino acid impurity that was not identified. Evaporation of the XI eluate to a small volume, adding alcohol until the hot solution began to cloud, followed by chilling produced highly purified XI as a white solid, m.p. 226° dec. Titration of this compound gave no break at the isoelectric point, pH 2.1, but gave moderately strong breaks at pH 4.8 and 8.7 and a weak break at pH 11 (Fig. 2).

Anal. Calcd. for $C_4H_{10}NO_5P$: C, 26.24; H, 5.50; P, 16.92; neut. equiv., 183. Found: C, 26.30, 26.23; H, 5.63, 5.58; P, 16.78, 16.82; neut. equiv., 185.

For some reason, the first preparation of the N-benzoyl derivative gave a solid, m.p. 205.5°, from water, but subsequent preparations, after alternate recrystallizations from water and from dioxane, melted at 197°. A potentiometric titration of this compound produced the first sharp break at pH 6.0, the amount of base consumed being twice that required for attaining the second break in the titration curve at pH 10.2. Thus, the first end point included the neutralization of two acidic hydrogens (Fig. 2).

Anal. Calcd. for $C_{11}H_{14}NO_6P$: C, 46.00; H, 4.91; P, 10.79; neut. equiv., 95.7. Found: C, 45.77, 45.83; H, 4.45, 4.98; P, 10.73, 10.65; neut. equiv., 95.7.

Hydrolysis of the benzoyl derivative produced XI, m.p. 226° dec.

2-Amino-3-phosphonopropionic Acid (XV).—A mixture of 12.9 g. (0.10 mole) of N-acetyl-α-aminoacrylic acid[12] (XII), 12.4 g. (0.10 mole) of trimethyl phosphite, and 14 ml. of dimethyl phosphonate was heated on a steam bath until XII had dissolved. This required 10–15 min. The solution was heated for an additional 60 min. on the steam bath and then was allowed to stand at room temperature for 36 hr. Volatile materials were removed by heating the mixture to 130° in a dibutyl phthalate bath at a pressure of 0.7 mm. The residue was hydrolyzed by refluxing with 130 ml. of concentrated hydrochloric acid for 55 hr. The hydrolysate was filtered to remove a small amount of dark, insoluble material and the filtrate was evaporated almost to dryness *in vacuo*. The residue was dissolved in 200 ml. of water and the hot solution was treated with carbon and filtered, producing a colorless filtrate. This filtrate was concentrated to about 20 ml., 100 ml. of ethyl alcohol was added, followed by butylene oxide dropwise until no more solid separated from solution. This compound also was purified best by the Dowex 50 treatment described for XI. The yield of XV was 8.45 g. (50% from XII), m.p. 228° dec. The titration curve was very similar to that of XI, giving no break at the isoelectric point (pH 2.2), moderate breaks at pH 4.5 and 8.8, and a very weak break at pH 11.

Anal. Calcd. for $C_3H_8NO_5P$: C, 21.32; H, 4.77; P, 18.33; neut. equiv., 169. Found: C, 21.09, 21.17; H, 4.59, 4.88; P, 18.26, 18.26; neut. equiv., 172.

An attempt was made to prepare the N-benzoyl derivative of XV, but this was not entirely satisfactory, since no good method was found to purify the product.

General Properties and Reactions with Ninhydrin.—Compounds VIIa, VIIb, and XV were soluble in cold water, but VIIc and XI were appreciably soluble only in hot water. They were all insoluble in the usual organic solvents.

Dilute solutions of VIIa, VIIb, VIIc, XI, and XV were mixed with a 0.1% aqueous solution of ninhydrin and were heated to boiling. All produced pale blue to red colors. When the same tests were carried out after the acidic solutions of the amino acids had been neutralized with sodium bicarbonate, intense violet solutions resulted.[18] It was further noted that the characteristic odor of phenylacetaldehyde was produced during the ninhydrin reaction with VIIc.

To the lavender solution from the ninhydrin reaction with VIIa, excess 6 *N* nitric acid was added, followed by a solution of ammonium molybdate. There resulted the characteristic positive test for the phosphate ion. When the same procedure was employed with VIIa with the exception that no ninhydrin was added, the resulting phosphate test was negative.

Acknowledgment.—We wish to express our appreciation to the Robert A. Welch Foundation and to the National Institutes of Health (GM 09014–02) for grants which supported this work.

(17) If much hydrochloric acid were left in this solution, the charcoal would not remove the color. However, if all the hydrochloric acid were removed, the solid residue had a low solubility in water.

(18) D. A. MacFadyen [*J. Biol. Chem.*, **153**, 507 (1944)] has shown that α-amino carboxylic acids react with ninhydrin at pH 5–7 to give the characteristic purple-colored solution, whereas at pH 2.5 or less no colored product results.

Synthesis of 3-Phospholenes by Reduction of Diene–Phosphonous Dichloride Adducts[1]

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Received August 29, 1963

Seven 3-phospholenes were prepared in moderate yield by reduction with magnesium of the cyclic chlorophosphoranes resulting from addition of phosphonous dichlorides to 1,3-dienes. This class of compounds has not been characterized previously. They react rapidly with air but readily form stable quaternary salts. Infrared and n.m.r. spectra confirm the 3-phospholene structure.

Cyclic chlorophosphoranes (I) are formed by a Diels–Alder reaction between 1,3-dienes and phosphonous dichlorides.[3] The reaction generally is conducted at room temperature without a solvent, in the presence of a polymerization inhibitor. The adducts, which are probably ionic as are other trialkyldichlorophosphoranes,[4] are hydrolyzed readily to 3-phospholene oxides; and over-all yields of 60–70% are, in fact, common. The reaction constitutes one of the simplest methods of constructing a phosphorus-containing ring system. It has the additional valuable feature of providing a system

(1) From a portion of the Ph.D. dissertation of D. A. M., Duke University, 1963. Presented in part before the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962. Support of some of this work by the Research Corporation, through a Frederick Gardner Cottrell grant, is gratefully acknowledged.

(2) Philip Morris Research Assistant, 1961–1962.

(3)(a) W. B. McCormack, U. S. Patents 2,663,736 and 2,663,737 (Dec. 22, 1953); (b) B. A. Arbuzov and L. A. Shapshinskaya, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 65 (1962); (c) I. G. M. Campbell, R. C. Cookson, and M. B. Hocking, *Chem. Ind.* (London), 359 (1962); (d) T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Am. Chem. Soc.*, **84**, 3673 (1962).

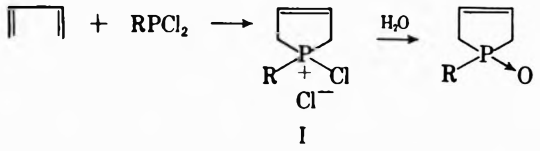
(4) K. Issleib and W. Seidel, *Z. anorg. allgem. Chem.*, **288**, 201 (1956); J. Goubeau and R. Baumgärtner, *Z. Elektrochem.*, **64**, 598 (1960).

Table I

3-Phospholenes and Their Quaternary Salts

Compound	Yield %	B.p., °C. (mm.)	M.p., °C.	Formula	Quaternary salt —Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Phosphorus, %— Calcd.	Found
IIa	39[a]	135–138 (760)	142–143[b]	$C_{13}H_{18}BrP$	54.75	54.71	6.36	6.65	10.86	10.63
IIb	38[c]	135–136 (760)	158–159[b]	$C_{13}H_{18}BrP$	54.75	54.70	6.36	6.72	10.86	11.27
IIc	20[a]	159–160 (760)	153–154[b]	$C_{12}H_{15}BrClP$	47.16	46.86	4.95	4.67	10.14	10.00
IId[d]	39[c]	133–134 (16)[e]	84–85.5[f]	$C_{11}H_{18}IP$	47.00	47.08	5.46	5.56	9.33	9.16
IIe	28[c]	158–160 (20)	220–221[b]	$C_{19}H_{22}BrP$	63.17	62.91	6.14	6.16	8.57	8.63
IIf	20[a]	179–180 (22)	168–170[b]	$C_{17}H_{17}BrClP$	55.53	55.20	4.66	4.60	8.42	8.32
IIg	16[c]	165–166 (20)	181–182.5[b]	$C_{19}H_{22}BrP$	63.17	63.36	6.14	6.65	8.57	8.76

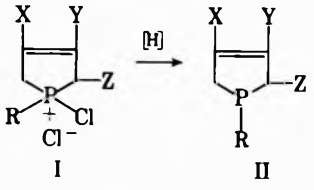
[a] Based on weight of adduct charged. [b] Benzyl bromide salt. [c] Based on phosphonous dichloride used for adduct preparation. [d] *Anal.* Calcd. for $C_{11}H_{13}P$: C, 74.98; H, 7.44; P, 17.58. Found: C, 74.71; H, 7.17; P, 17.72. [e] Lit.[7] b.p. 150–151° (30 mm.). [f] Ethiodide.



I

with the functionality of the double bond, which should permit access to numerous derivatives. Advantage has already been taken of this reactivity to produce 3,4-dibromophospholane 1-oxides, and, from these, phosphole 1-oxides by dehydrohalogenation.[5]

We have devised a method for the reduction of the adducts (I) to the phosphines (II) and have demonstrated the generality of the method by the preparation of seven representative compounds. The dual functionality of the tricovalent phosphorus and the double bond should make these compounds valuable intermediates.



I II

	R	X	Y	Z
a,	CH_3	CH_3	H	H
b,	CH_3	H	H	CH_3
c,	CH_3	Cl	H	H
d,	C_6H_5	CH_3	H	H
e,	C_6H_5	CH_3	CH_3	H
f,	C_6H_5	Cl	H	H
g,	p-$CH_3C_6H_4$	CH_3	H	H

The reduction[6] of I has been accomplished by treating a suspension of I in tetrahydrofuran (THF) with magnesium turnings, which was suggested by its efficacy in another chlorophosphorane reduction.[8] The mixtures were worked up in an appropriate manner, and the phosphines (II) were obtained by distillation. A successful analysis was obtained on one phosphine (IId); the rapid uptake of oxygen, however, made it difficult to obtain good values for these compounds, and the expedient of converting the phosphines to the stable quaternary salt form for analysis (Table I) was adopted. Benzyl bromide was particularly useful for forming crystalline salts.

Granular aluminum, also effective for certain chlorophosphorane reductions,[9] failed to reduce Id or f in THF. Some aluminum was consumed, but no product was obtained. Another reducing agent, methyl phosphorodichloridite (CH_3OPCl_2),[10] likewise failed to reduce Ic or d in THF. Although a smooth reaction occurred in converting the slurry to a solution, no phosphine was obtained on distillation. The reaction was not examined further. On the other hand, lithium aluminum hydride[7] did effect the reduction when tried on Ia. The yield (28%) was somewhat lower than that (39%) obtained on magnesium reduction of another portion of the same batch of Ia. However, the isolation procedure is simpler, and this agent is worthy of consideration for this reduction.

Tetrahydrofuran is the preferred medium for the magnesium reduction, although it dissolves little I. Methylene chloride, a good solvent for I, permitted no reduction. Other solvents investigated included benzene, chlorobenzene, ether, dioxane, diglyme, and ethyl and isopropyl acetates, all tried in the reduction of Ia. None was a good solvent, and in no case was reduction observed.

The yields (Table I) of 3-phospholenes from reduction of I appear to run below those reported[3a] for 3-phospholene 1-oxides from hydrolysis of I. However, the reduction reaction itself appears largely complete, judging visually from the amount of magnesium consumed. Some loss undoubtedly occurs in the isolation of the 3-phospholenes, as these are oxidized very rapidly. Most of the yields in Table I are from single runs, and it is felt that improvements can be made with further study of the process. The reductions of adducts Ic and f, both vinylic chlorides, were performed at lower temperatures to prevent Grignard reagent formation, which might have occurred in refluxing THF. The yields may be particularly low in these cases due to incomplete reduction.

In conventional Diels–Alder reactions, steric prevention of the diene from attaining a planar cisoid conformation hinders the addition of the dienophile.[11] McCormack[3a] cited certain structural features, which offer this hindrance, as being important also where a phosphonous dichloride is the dienophile. Unreactive dienes were stated to include (A) those containing two substituents on one or both of the 1 and 4 positions, (B) those having a *cis* arrangement of one vinyl group with respect to a 1 or 4 substituent, when present, and (C) those having three carbons of the diene system incorporated in an alicyclic structure. We attempted to treat two dienes of type A (hexachloro-1,3-butadiene and 2,5-dimethyl-2,4-hexadiene) with the strongly

(5) E. Howard, Jr., and R. E. Donadio, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1959, p. 100P.

(6) After much of this work was complete, we found that Balon[7] had effected the reduction of Id with lithium aluminum hydride. However, the yield was not given, and no product analysis or characterization was provided.

(7) W. J. Balon, U. S. Patent 2,853,518 (Sept. 23, 1958).

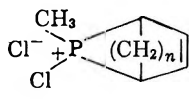
(8) L. D. Quin and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **83**, 4124 (1961).

(9) L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **27**, 4120 (1962).

(10) L. D. Quin and C. H. Rolston, *ibid.*, **23**, 1693 (1958).

(11) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

dienophilic methylphosphonous dichloride, but, as predicted, no reaction was observed on prolonged standing. We also exposed two alicyclic dienes to the same dichloride, hoping to form the interesting bicyclic compounds, III (from cyclopentadiene) and IV (from 1,3-



III, $n=1$

IV, $n=4$

cyclooctadiene). Neither adduct formed after several days at room temperature. Cyclopentadiene is, of course, well-known to participate in Diels–Alder reactions; its failure to react here may be due to the strain involved in constructing the four-membered ring component of III. 1,3-Cyclooctadiene is not known to react with dienophiles,[11] and its inactivity here was not unexpected. The requisite planar cisoid conformation can only be achieved with considerable ring strain.[12]

The infrared spectra of IIa, c, and d showed C=C stretching peaks (weak but sharp) as expected[13a] at 1656, 1639, and 1623 cm.$^{-1}$, respectively. Compound IIe, a tetrasubstituted ethylene, had very weak, ill-defined absorption[13a] in the same general region. The stretching vibration of the vinyl hydrogen in IIa was detectable at 3020 cm.$^{-1}$; this absorption was poorly defined in the spectrum of IIc, and in IId could not be distinguished from aromatic hydrogen absorption. Trisubstituted ethylenes show C–H out-of-plane deformation[13a] in the region 800–840 cm.$^{-1}$, and in IIa, a peak of medium intensity was located at 839 cm.$^{-1}$. However, IIc had two peaks in this region (819 and 845 cm.$^{-1}$), while IId had a peak at 812 cm.$^{-1}$. Compound IIe, with no vinyl hydrogen, also absorbed at 817 cm.$^{-1}$. Until additional structures have been examined, it does not appear possible to associate confidently absorption in the 800–840-cm.$^{-1}$ region with this vibrational mode. Compounds IId and e showed strong absorption at 1437 and 1439 cm.$^{-1}$, respectively. This frequency has been associated with the P-phenyl grouping.[13b] Characteristic phenyl absorptions appeared at 694 and 741 cm.$^{-1}$ in both compounds.

In one case (IIe), the 60-Mc. n.m.r. spectrum was obtained and found to be in accord with the assigned structure. A sharp singlet at τ 8.43 was assigned to hydrogens of the two equivalent methyls, a broad symmetrical singlet at τ 7.51 to the ring methylene hydrogens, and a complex centered at τ 2.73 to the phenyl hydrogens. Splitting of the methylene hydrogen peak by phosphorus–hydrogen coupling was not apparent under the conditions used.

Experimental

General.—Melting and boiling points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All preparations and manipulations of chlorophosphorane adducts and phosphines were conducted in a nitrogen atmosphere.

Phenylphosphonous dichloride was obtained from Eastman. Methylphosphonous dichloride was kindly supplied by U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Md. *p*-Tolylphosphonous dichloride was prepared according to *Organic Syntheses*.[14] Dienes were obtained from commercial sources, and, except for chloroprene, used as received. Chloroprene was received in xylene solution; the pure diene was recovered by vacuum distillation and was used immediately. Tetrahydrofuran was purified by distillation from lithium aluminum hydride.

Formation of Diene–Phosphonous Dichloride Adducts.—An equimolar amount of phosphonous dichloride was added to the diene containing about 2–4 wt. % of cupric stearate. The flask was stoppered and allowed to stand until solidification of the mixture was complete, or until no further solid seemed to be forming. In general, reactions with methylphosphonous dichloride were complete in a few days, while with arylphosphonous dichlorides, reaction periods of 1–2 weeks were required. The adduct then was broken up in the flask and washed with pentane. Some of the adducts were recovered by filtration in a drybox and the yield was determined as follows: Ia, 0.21 mole run, 84% after 5 days; Ic, 0.36 mole run, 82% after 1 week; If, 0.85 mole run, 39% after 2 weeks.

Preparation of P-Methyl-3-Phospholenes. A. Magnesium Reduction.—The adduct was suspended in THF in a ratio of about 25 g./150 ml. and stirred vigorously while 1 molar equiv.[15] of dry, ether-washed magnesium turnings was added in small portions. Reductions of Ia and b were generally exothermic, and some moderation with an ice bath was required during magnesium addition to maintain gentle reflux. The mixtures were refluxed 1 hr. after the reaction subsided. However, occasional reductions were only mildly exothermic and required several hours at reflux. The reduction of Ic was performed at low temperatures to prevent Grignard formation; magnesium was added over a 4-hr. period with ice-bath cooling, and the mixture then was stirred 14 hr. at room temperature. Final reaction mixtures were generally cloudy solutions or thin slurries containing some residual magnesium and occasionally a gummy deposit.

The mixtures were treated slowly with cold water to destroy remaining phosphorus chlorides. The solutions were made strongly acidic with 8 *N* hydrochloric acid and then distilled until all THF was removed. The residual solutions were made basic with concentrated sodium hydroxide and then steam distilled. The products were removed from the distillates by ether extraction. The ether extracts were dried with sodium sulfate and distilled at atmospheric pressure. By this procedure, **1,3-dimethyl-3-phospholene (IIa), 1,2-dimethyl-3-phospholene (IIb), and 3-chloro-1-methyl-3-phospholene (IIc)** were prepared. Additional data appear in Table I.

Attempts to separate a mixture of IIa and THF by distillation with a Vigreux column were unsuccessful, even though there is a 70° range in boiling point. These two compounds may form an azeotrope, but this has not been established. To overcome this difficulty, the above isolation procedure, utilizing the basic character of phosphines, was devised for IIa and then was applied to all P-methyl compounds. (The higher boiling P-aryl compounds were easily fractionated from THF).

B. Lithium Aluminum Hydride Reduction.—An 18.5-g. (0.10 mole) sample of Ia was dispersed in 100 ml. of ether and treated with 0.2 g. (0.053 mole) of lithium aluminum hydride. A gentle reaction occurred. After 2 hr., the mixture was hydrolyzed carefully and treated with dilute sodium hydroxide. Ether extraction was performed and the extracts then were distilled to give 3.2 g. (0.028 mole, 28% yield) of IIa, identical with that prepared by magnesium reduction.

Preparation of P-Aryl-3-phospholenes.—The reduction of adducts Id, e, and g was carried out in essentially the same manner used for Ia and b. However, it was usually necessary to heat the mixture after the first addition of magnesium to start the reaction. At reflux, however, consumption of magnesium proceeded briskly. The mixture was refluxed 1–2 hr. after the reaction had subsided. The temperature during reduction of If was held below 35°, and the mixture was stirred an additional 18 hr. after no further reaction was apparent.

About one-half of the solvent was removed by distillation, and then cold water was added slowly. The mixtures were made basic with 10 *N* sodium hydroxide, and the resulting slurries were extracted several times with benzene or ether. After drying over sodium sulfate, the extracts were stripped of solvent and distilled

(12) A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.*, **77**, 998 (1955).

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, (a) Chapter 3, (b) Chapter 18.

(14) B. Buchner and L. B. Lockhart, Jr., *Org. Syn.*, **31**, 88 (1951).

(15) Based on the weight of adduct when isolated, otherwise on the starting material in the adduct preparation. In the latter case, 100% yield of adduct was assumed; some excess magnesium was used therefore.

in vacuo. Thus were obtained **3-methyl-1-phenyl-3-phospholene** (IId), **3,4-dimethyl-1-phenyl-3-phospholene** (IIe), **3-chloro-1-phenyl-3-phospholene** (IIf), and **3-methyl-1-(*p*-tolyl)-3-phospholene** (IIg). Additional information is given in Table I.

Preparation of Quaternary Salts from 3-Phospholenes.—About 1 g. of the 3-phospholene was treated in ether with about 2 g. of benzyl bromide. The salt slowly deposited on standing as either a crystalline solid or an oil that later crystallized. All salts were recrystallized readily from a mixture of methanol and ethyl acetate. Melting point and analytical data appear in Table I.

The ethiodide of IId was prepared in the same manner. It developed a yellow color on standing, but gave a satisfactory analysis. Color formation occurred more rapidly with the ethiodide of IIa; ethiodides were concluded, therefore, to be less satisfactory derivatives than the benzyl bromide salts.

Spectra.—The infrared spectra of IIa, c, d, and e were taken on films of the liquids. A Perkin-Elmer Model 21 spectrophotometer was used. The n.m.r. spectrum of IIe was prepared on the neat liquid, with tetramethylsilane as internal reference. This spectrum was kindly prepared by Dr. James P. Collman, University of North Carolina, using a Varian A-60 spectrometer.

The Synthesis of Some 2,3-Diarylcyclopropane-1-carboxylic Acids

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Received July 10, 1963

The three possible stereoisomeric 2,3-diphenylcyclopropane-1-carboxylic acids were prepared and their structure assignments were corroborated by n.m.r. spectra and pK_a measurements. As expected, the all-*cis* isomer, prepared by the catalytic hydrogenation of 2,3-diphenylcyclopropene-1-carboxylic acid, was the weakest acid in the series. The three possible stereoisomeric bis(*p*-methoxyphenyl)- and the four 2-(*p*-methoxyphenyl)-3-phenylcyclopropane-1-carboxylic acids also were prepared (two as an inseparable mixture), and structure assignments were made.

There is considerable recent literature dealing with 2-aryl- and 2,2-diarylcyclopropane-1-carboxylic acids,[1] but little information is available concerning 2,3-diarylcyclopropane-1-carboxylic acids; in fact, only three such compounds have been reported.[2] The compounds were desired for contemplated studies of the cyclopropylcarbinyl rearrangements of 2,3-diarylcyclopropylmethanols[1] as a possible route to the synthesis of biologically active α,α'-disubstituted stilbenes. Since published procedures[2a-c] for the preparation of 2,3-diarylcyclopropanecarboxylic acids from stilbenes indicated disappointingly low yields, better preparative techniques were sought.

Of the three possible isomers of 2,3-diphenylcyclopropane-1-carboxylic acid,[3] only two have been prepared, namely, those derived from *cis*- and *trans*-stilbene. The third possible isomer in the series, the all-*cis* compound has not been isolated previously. Preparation of it by catalytic hydrogenation of the known 2,3-diphenyl-2-cyclopropene-1-carboxylic acid appeared feasible, because *cis* hydrogen addition should occur on the side opposite the carboxyl group.

Accordingly, syntheses of the 2,3-diarylcyclopropane-1-carboxylic acids were undertaken to provide all the stereoisomers in a given series both for structure and property characterization and as possible starting materials of interest for further transformations.

Results and Discussion

Repetition of previous work[2a,b] confirmed that the reaction of *cis*- and *trans*-stilbene with ethyl diazoacetate in the absence of solvent gave 2,3-diphenylcyclopropane-1-carboxylic acids in yields of only about 20%. The principal difficulty was that, at the temperature (125°) necessary for the thermal decomposition of ethyl diazoacetate, *trans*-stilbene sublimed to the upper surfaces of the reaction flask out of contact with the liquid diazo compound. However, when the reaction mixture was diluted with benzene, anhydrous copper sulfate was added, and the reaction was conducted at reflux temperature, the reaction proceeded smoothly and in high yield. A recent report[4] indicates that refluxing cyclohexane also achieves the improved results.

After considerable preliminary work, optimum conditions involving the use of freshly dehydrated copper sulfate as the catalyst and benzene as the solvent were achieved, whereby all the *cis*- and *trans*-stilbenes were converted to the corresponding 2,3-diarylcyclopropane-1-carboxylic acids in good yield. From the *cis*-stilbenes were obtained the *trans,trans* isomers, and from the *trans*-stilbenes the *cis,trans* isomers. Only where *trans*-4-methoxystilbene was the starting material, was a mixture of isomers obtained. Attempts to separate the two isomers, *cis*-2-(*p*-methoxyphenyl)-*trans*-3-phenylcyclopropane-1-carboxylic acid and *trans*-2-(*p*-methoxyphenyl)-*cis*-3-phenylcyclopropane-1-carboxylic acid as the free acids, or methyl esters, were unsuccessful. Thin layer chromatography of the methyl esters on a silica gel plate showed the two expected isomers as overlapping spots. In acetone and in carbon tetrachloride, the n.m.r. spectrum of the mixture showed splitting of the peaks due to the arylmethoxy group and the carbomethoxy group, indicating that these groups are in different environments and hence the two isomers are present.

Catalytic reduction of 2,3-diphenyl-2-cyclopropene-1-carboxylic acid gave a product, m.p. 170–172°, different

(1) H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.*, **77**, 6026, 6396 (1955); F. J. Impastato, L. Barash, H. M. Walborsky, *ibid.*, **81**, 1516 (1959); H. M. Walborsky and J. F. Pendleton, *ibid.*, **82**, 1405 (1960); H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *ibid.*, **83**, 2517 (1961); F. J. Impastato and H. M. Walborsky, *ibid.*, **84**, 4839 (1962).

(2) (a) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *ibid.*, **71**, 3307 (1949); (b) G. P. Hager and C. I. Smith, *J. Am. Pharm. Assoc.*, **41**, 193 (1952); (c) W. M. Jones, *J. Am. Chem. Soc.*, **81**, 3776 (1959); (d) V. Biro, W. Voegtli, and P. Lauger, *Helv. Chim. Acta*, **37**, 2230 (1954).

(3) The designations of *cis* and *trans* isomers used in this paper are based on the relationships of the aryl groups to the carboxylic acid group. Thus *trans,trans*-2,3-diphenylcyclopropane-1-carboxylic acid refers to the isomer in which both phenyl groups, although *cis* to each other, are *trans* to the carboxyl.

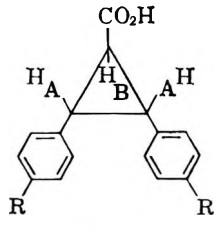
(4) I. A. D'yakanov, M. I. Komendantev, Fu Gui-siya, and G. L. Korichev, *J. Gen. Chem. USSR*, **32**, 928 (1962); I. A. D'yakanov, Fu Gui-siya, G. L. Korichev, and M. I. Komendantev, *ibid.*, **31**, 681 (1961).

from the starting material as well as from the two known 2,3-diphenylcyclopropane-1-carboxylic acids. However, the melting point reported[5] for the isomeric 3,4-diphenyl-3-butenoic acid, which can conceivably be obtained by opening of the cyclopropene ring, is 172–173°. The n.m.r. spectrum, however, showed peaks consistent with cyclopropane ring protons and no peaks which would be characteristic of the open-chain compound; hence, the compound was the desired *cis,cis*-2,3-diphenylcyclopropane-1-carboxylic acid.

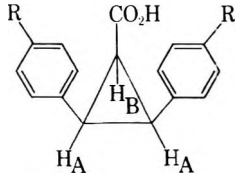
The acidity constants of the three 2,3-diphenylcyclopropane-1-carboxylic acids in aqueous ethanol are *trans,trans* acid, $K_a = 21.0 \times 10^{-7}$; *cis,trans* acid, $K_a = 9.3 \times 10^{-7}$; *cis,cis* acid, $K_a = 2.0 \times 10^{-7}$. These differences in acidity confirm the previously reported[4] order for the first two in the series, and the complete order can be accommodated best on the basis of steric hindrance to solvation of the carboxylate anion; hindrance to solvation by one phenyl group in the *cis,trans* acid and by two phenyl groups in the *cis,cis* acid is consistent with the observed results.[6]

Attempts to hydrogenate 2-(*p*-methoxyphenyl)-3-phenyl-2-cyclopropene-1-carboxylic acid in the Parr apparatus with palladium on calcium carbonate in glacial acetic acid were unsuccessful. However, with the use of a more active palladium-on-carbon catalyst,[7] both 2-(*p*-methoxyphenyl)-3-phenyl- and 2,3-bis(*p*-methoxyphenyl)-2-cyclopropene-1-carboxylic acids were reduced successfully to the corresponding *cis,cis*-2,3-diarylcyclopropane-1-carboxylic acids. Both of these *cis,cis* acids showed cyclopropane absorptions in their n.m.r. spectra corresponding to those obtained from *cis,cis*-diphenylcyclopropane-1-carboxylic acid.

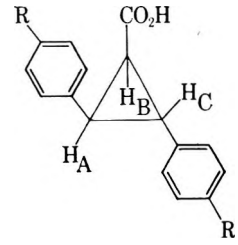
The n.m.r. spectra of the three series of 2,3-diarylcyclopropane-1-carboxylic acids correlate well with the spectra which would be predicted for such acids.[8] Thus, the spectra for *trans, trans*-2,3-diarylcyclopropane 1-carboxylic acids showed five peaks characteristic of an A_2B system.



The spectra of the *cis,cis*-2,3-diarylcyclopropane-1-carboxylic acids showed eight peaks, again typical of an A_2B system.



The difference between the spectra of the above two compounds arises from the smaller ratio of chemical shift to coupling constant in the latter A_2B system. The *cis,trans*-2,3-diarylcyclopropane-1-carboxylic acids showed twelve peaks, consistent with spectra for an ABC system.



Further evidence of correct assignment of the structures of the 2,3-diarylcyclopropane-1-carboxylic acids can be seen in n.m.r. spectra of the aromatic protons. The peaks due to the aromatic protons in both the *cis,cis*- and *trans,trans*-diphenyl- and bis(*p*-methoxyphenyl) acids are symmetrical about a common center; those peaks due to the aromatic protons of the *cis,trans* acids are unsymmetrical, as are the peaks due to the aromatic protons of the three 2-(*p*-methoxyphenyl)-3-phenyl acids.

Experimental[9]

Starting Materials.—*trans*-**Stilbene**, m.p. 123–125°, was prepared by the method in "Organic Syntheses."[10] *trans*-4-Methoxystilbene, m.p. 135–136°, was prepared by two methods: the first was adapted from that of Spatz,[11] which was a modification of a method developed by Anschutz,[12] and the second involved the thermal dehydration of the secondary alcohol formed by the reaction of anisaldehyde with the Grignard reagent prepared from benzyl chloride.[13] *trans*-4,4′-Dimethoxystilbene, m.p. 214–215°, was prepared by the method of Spatz[11]; all-*cis*-stilbenes were prepared by extension to appropriate starting materials of the procedures outlined in *Organic Syntheses*.[14,15]

Diphenylacetylene, m.p. 59–60°, was prepared by the method outlined in *Organic Syntheses*.[16]

(*p*-**Methoxyphenyl**)**phenylacetylene** was prepared from *trans*-4-methoxystilbene.[17,18] The material apparently exists in two polymorphic forms, m.p. 58.5–59.5° and 88–89° (lit. m.p. 56–57°[17] and 89–90°[16]). **Bis**(*p*-**methoxyphenyl**)**acetylene** was prepared from anisil *via* the dihydrazone in a manner analogous to the preparation of diphenylacetylene, m.p. 143–145°, lit.[19] m.p. 145°. The copper sulfate used was freshly dehydrated by heating Mallinckrodt reagent grade anhydrous copper sulfate in a casserole over a free flame. Baker technical copper powder was used in all experiments leading to the formation of diarylcyclopropenecarboxylic acids.

Ethyl diazoacetate was prepared by a modification of the method outlined in *Organic Syntheses*[20] which consisted principally of carrying out the reaction in an externally cooled separatory funnel, thus permitting rapid extraction of the ester. Final

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(9) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. N.m.r. spectra were obtained at 60 Mc. with a Varian A-60 instrument in the solvent indicated. The peaks are recorded in parts per million (p.p.m.) τ values, with tetramethylsilane as an internal reference (τ 10).

(10) R. L. Shriner and A. Berger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 786.

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solvent evaporation is best achieved in a rotatory evaporator using a water aspirator.

cis,trans **2,3-Diphenylcyclopropane-1-carboxylic Acid.**—*trans*-Stilbene (35 g.), 2 g. of freshly dehydrated copper sulfate, and 75 ml. of reagent grade benzene were placed in a special reaction vessel. The reaction vessel was a 500-ml. four-necked standard taper round-bottomed flask. The center neck was fitted with a sealed mechanical stirrer having a Teflon blade. A thermometer was mounted in one neck of the flask and the two remaining openings were fitted with condensers. On top of one of the condensers was mounted a pressure-equalizing dropping funnel, and the top of the other condenser was connected to a bubbler filled with toluene for monitoring the evolution of nitrogen.

The mixture was heated to 75° with stirring, and 45 ml. of ethyl diazoacetate was added over a period of 6.75 hr. The mixture was stirred for an additional 0.5 hr. and then allowed to stand overnight. Sodium hydroxide (25 g.), and 200 ml. of 95% ethanol were added, and the mixture was refluxed with stirring for 6 hr. The ethanol and the benzene were removed by distillation, and 200 ml. of water was added. The aqueous mixture was heated to 90° and filtered. On cooling overnight, the crystals of the insoluble sodium salt[2b] which separated were filtered and redissolved in hot water, the solution was filtered again, and the filtrate was acidified with 10% hydrochloric acid. The recovered *trans*-stilbene, extracted with dichloromethane from the water-insoluble copper–stilbene mixture, weighed 14.5 g. The precipitate of *cis,trans*-2,3-diphenylcyclopropane-1-carboxylic acid obtained from the filtrate weighed 22.0 g. (81% conversion), m.p. 157–158°, lit.[2b] m.p. 157–158.5°. Recrystallization from methanol–water gave pure white acid, m.p. 157–158°.

The acid was esterified with diazomethane in ethyl ether and recrystallized twice from methanol to give methyl *cis,trans*-2,3-diphenylcyclopropane-1-carboxylate, m.p. 67–67.5°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.66; H, 6.41.

The n.m.r. spectrum, determined in carbon tetrachloride, showed a split peak at 2.78–2.82 (two different sets of phenyl protons), a single peak at 6.59 (carbomethoxy protons), and a multiplet of twelve peaks at 6.73–7.82 τ (cyclopropane protons of an ABC system). The acyclic and cyclopropane protons were in the ratio of 1:1, respectively.

trans,trans-**2,3-Diphenylcyclopropane-1-carboxylic Acid.**—*cis*-Stilbene (36 g.), 75 ml. of reagent grade benzene, and 2 g. of freshly dehydrated copper sulfate were heated to 75° with stirring in the reaction vessel previously described; 40 ml. of ethyl diazoacetate was added over a period of 5.25 hr., and the mixture was allowed to stand overnight. Sodium hydroxide (25 g.) and 200 ml. of 95% ethanol were added, and the mixture was refluxed with stirring for 4 hr. Ethanol and benzene were removed by distillation and 200 ml. of water was added; after being heated to 80°, the aqueous mixture was filtered, and the flask and filter were rinsed with hot water. Unchanged *cis*-stilbene (20.8 g.) was removed by petroleum ether (b.p. 40–60°) extraction. Acidification of the aqueous solution precipitated free acid, which was filtered, washed with water, and air-dried to yield 15.3 g. (76% conversion) of crude *trans,trans*-2,3-diphenylcyclopropane-1-carboxylic acid. Two recrystallizations from ethanol–water (Norit A) gave pure acid, m.p. 154.4–155.5°, lit.[2c] m.p. 152.5–154.5°.

The acid was esterified with diazomethane in ethyl ether and recrystallized from methanol to give pure methyl *trans,trans*-2,3-diphenylcyclopropane-1-carboxylate, m.p. 71.5–72°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.89; H, 6.53.

The n.m.r. spectrum, determined in carbon tetrachloride, showed a peak at 2.98 (phenyl protons), at 6.27 (carbomethoxy protons), a doublet centered at 6.98 (J = 5.3 c.p.s., protons adjacent to phenyl groups), and a triplet centered at 7.52 τ (proton adjacent to carbomethoxy group). The acyclic and the two sets of cyclopropane protons were in the ratio of approximately 3:2:1, respectively.

Mixture of *cis*-**2-(***p*-**Methoxyphenyl)-***trans*-**3-phenylcyclopropane-1-carboxylic Acid and** *trans*-**2-(***p*-**Methoxyphenyl)-***cis*-**3-phenylcyclopropane-1-carboxylic Acid.**—*trans*-4-Methoxystilbene (27 g.) and 1.5 g. of copper sulfate were treated in the manner described previously to give 5.5 g. of recovered *trans*-4-methoxystilbene and 23.0 g. of crude acids (83% conversion), m.p. 129–150°. Recrystallization of portions of the crude acids from ethanol–water gave material with m.p. 130–150°. Chromatography on acidic alumina failed to separate the mixture.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; neut. equiv., 268.3. Found: C, 76.02; H, 5.73; neut. equiv. 267.

Approximately 15 g. of the crude acids was refluxed overnight with 56 ml. of methanol, 17 ml. of dichloromethane, and 2 drops of concentrated sulfuric acid. The esterification mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane solutions were washed with 5% sodium carbonate, dried over anhydrous sodium sulfate and filtered. Removal of the solvent and recrystallization from acetone gave the methyl esters, m.p. 74–88°. Repeated attempts to separate the methyl esters by fractional crystallization were unsuccessful. Two attempts at separation by zone melting were likewise unsuccessful. Chromatography of the methyl esters on silica gel gave no separation. All attempted separations gave fractions which differed by only a few degrees from the range, m.p. 74–88°, obtained by the first recrystallization.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.23; H, 6.71.

The n.m.r. spectrum was determined on the mixed methyl esters in carbon tetrachloride. The spectrum showed a multiplet at 2.70–3.40 (aromatic protons), a singlet at 6.35 and a slightly split peak at 6.60 (methoxy and carbomethoxy protons), and a multiplet of peaks at 6.75–7.87 τ (cyclopropane protons of an ABC system). Available data do not permit unambiguous assignment of the methoxy and carbomethoxy peaks. The two sets of acyclic protons and cyclopropane protons were in the ratio of approximately 1:1:1, respectively. The n.m.r. spectrum determined in acetone clearly revealed the presence of two carbomethoxy peaks and two methoxy peaks separated by 1.4 and 0.6 c.p.s.

Although one isomer was clearly present as the major component of the mixture, its structure could not be differentiated.

trans-**2-(***p*-**Methoxyphenyl)-***trans*-**3-phenylcyclopropane-1-carboxylic Acid.**—To 32.4 g. of *cis*-4-methoxystilbene and 1.2 g. of freshly dehydrated copper sulfate in 75 ml. of reagent grade benzene was added 39 ml. of ethyl diazoacetate over a period of 4.25 hr. There was obtained, in the manner previously described, 20 g. of crude gummy acid (83% yield based on 18.8 g. of *cis*-4-methoxystilbene not recovered). The crystalline acid was obtained by saponification of the purified methyl ester (see below), and, after several recrystallizations of the acid from methanol and then a final crystallization from benzene, pure *trans*-2-(*p*-methoxyphenyl)-*trans*-3-phenylcyclopropane-1-carboxylic acid, m.p. 111–112°, was obtained.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; neut. equiv., 268.3. Found: C, 75.84; H, 5.70; neut. equiv., 269.

The crude acid was esterified by refluxing overnight 20 g. of acid in 60 ml. of methanol, 22 ml. of dichloromethane, and 3 drops of concentrated sulfuric acid. Repeated recrystallizations of the ester from benzene–petroleum ether gave pure methyl *trans*-2-(*p*-methoxyphenyl)-*trans*-3-phenylcyclopropanecarboxylate, m.p. 64.5–65°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.66; H, 6.37.

The n.m.r. spectrum, determined in carbon tetrachloride, showed a multiplet at 2.90–3.60 (two different types of aromatic protons), singlets at 6.52 and 6.39 (carbomethoxy and aromatic methoxy protons), a doublet centered at 7.04 (J = 5.0 c.p.s., protons adjacent to aromatic rings), and a triplet centered at 7.56 τ (protons adjacent to carbomethoxy group). The two sets of aliphatic and the two sets of cyclopropane protons were in the ratio of approximately 3:3:2:1, respectively.

cis,trans-**2,3-Bis(***p*-**methoxyphenyl)cyclopropane-1-carboxylic Acid.**—To 15.2 g. of *trans*-4,4′-dimethoxystilbene and 1.2 g. of anhydrous copper sulfate in 50 ml. of benzene at a temperature of 75–80° was added 30 ml. of ethyl diazoacetate over a period of 6 hr. Isolation of the acid in the manner previously described gave 11.25 g. (84% yield based on unrecovered starting material) of crude brown acid. Seven recrystallizations from ethanol–water gave pure *cis,trans*-2,3-bis(*p*-methoxyphenyl)cyclopropane-1-carboxylic acid, m.p. 164–165°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08; neut. equiv., 298.3. Found: C, 72.44; H, 5.95; neut. equiv., 297.

The acid was esterified with diazomethane in ethyl ether. After three recrystallizations from methanol, pure methyl *cis,trans*-2,3-bis(*p*-methoxyphenyl)cyclopropane-1-carboxylate was obtained, m.p. 104.5–105.0°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.87; H, 6.43.

The n.m.r. spectrum determined in chloroform showed an unsymmetric multiplet at 2.60–3.30 (aromatic protons and chloroform), a peak at 6.23 (aromatic methoxy protons), a peak at 6.49 (carbomethoxy protons), and a multiplet of twelve peaks at 6.69–7.85 τ (cyclopropane protons of an ABC system). The two sets of acyclic and cyclopropane protons were in the ratio of approximately 2:1:1, respectively.

trans,trans-**2,3-Bis(*p*-methoxyphenyl)cyclopropane-1-carboxylic Acid.**—To 31.8 g. of *cis*-4,4′-dimethoxystilbene and 2 g. of freshly dehydrated copper sulfate in 75 ml. of reagent grade benzene at 40° was added, over a period of 4 hr., 30 ml. of ethyl diazoacetate. Isolation of the crude acid in the manner previously described gave 12.6 g. (88% yield based on 11.3 g. of unrecovered stilbene) of crude acid. Recrystallization from methanol–benzene, benzene, and finally from methanol–water gave pure *trans,trans*-2,3-bis(*p*-methoxyphenyl)cyclopropane-1-carboxylic acid, m.p. 119.5–121°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08; neut. equiv., 298.3. Found: C, 72.43; H, 6.07; neut. equiv., 296.

Esterification of the acid with diazomethane in ethyl ether gave a liquid methyl ester which was not purified further.

The n.m.r. spectrum determined in carbon tetrachloride showed a symmetrical multiplet centered at 3.32 (two equivalent sets of aromatic protons), a peak at 6.33 (carbomethoxy protons), a peak at 6.44 (aromatic methoxy protons), a doublet centered at 7.13 (J = 5.5 c.p.s., two protons adjacent to aromatic groups), and a triplet at 7.68 τ (protons adjacent to carbomethoxy group). There were three other small peaks, probably due to impurities in the liquid methyl ester. The two sets of aliphatic protons and two sets of cyclopropane protons were in ratios of approximately 3:6:2:1, respectively.

2,3-Diphenyl-2-cyclopropene-1-carboxylic Acid.—This acid was prepared according to the literature method.[21] To 40 g. of diphenylacetylene and 2 g. of copper powder at *ca* 125° was added 60 ml. of ethyl diazoacetate, over a period of 2.75 hr. Isolation in the usual manner gave 17.4 g. of crude acidic material. Several recrystallizations from ethanol–water gave 8.0 g. of pure 2,3-diphenyl-2-cyclopropene-1-carboxylic acid, m.p. 207–210° dec., lit.[20] m.p. 209–210° dec., in 31% yield based on 18 g. of diphenylacetylene not recovered. The ultraviolet spectrum (log ϵ) had λ_{max} 225 mμ (log ϵ 4.54), 333 (4.48), 307 (4.71), and 323 (4.61).

2-(*p*-Methoxyphenyl)-3-phenyl-2-cyclopropene-1-carboxylic Acid.—This acid was prepared according to the method previously described.[22] To 25.5 g. of (*p*-methoxyphenyl)phenylacetylene and 2.3 g. of copper powder at *ca* 125° was added, over a period of 2.75 hr., 25 ml. of ethyl diazoacetate. Isolation in the usual manner gave 8.8 g. of crude acid, which was recrystallized once from acetone–water and three times from methanol to give 2.0 g. of 2-(*p*-methoxyphenyl)-3-phenyl-2-cyclopropene-1-carboxylic acid, m.p. 177–177.5° dec., lit.[22] m.p. 179.5–181.5°, in 18% yield based on 8.6 g. of unrecovered (*p*-methoxyphenyl)phenylacetylene. The ultraviolet spectrum had λ_{max} 236 mμ (log ϵ 4.70), 317 (4.23), and 334 (4.49).

The n.m.r. spectrum of the methyl ester determined in carbon tetrachloride showed a multiplet at 2.30–3.25 (aromatic protons), singlets at 6.25 and 6.38 (carbomethoxy and aromatic methoxy protons), and a peak at 7.32 τ (cyclopropene proton). The two sets of acyclic protons and the cyclopropene proton were in the ratio of approximately 3:3:1, respectively.

2,3-Bis(*p*-methoxyphenyl)-2-cyclopropene-1-carboxylic acid was prepared in a manner analogous to that of the preceding two 2,3-diaryl-2-cyclopropene-1-carboxylic acids. To 8 g. of 4,4′-bis(*p*-methoxyphenyl)acetylene and 1 g. of copper powder there was added, over a period of 4 hr., 8 ml. of ethyl diazoacetate. Sodium hydroxide (10 g.) and 100 ml. of 95% ethanol were added, and the mixture was refluxed for 3 hr. After the ethanol was distilled, 100 ml. of water was added, and the mixture was heated to 90° and filtered. The flask and filtrate were rinsed with hot water. The filtrate was acidified, and there was precipitated the free crude acid. The air-dried crude acid weighed 7.8 g.; 2.3 g. of 4,4′-bis(*p*-methoxyphenyl)acetylene was recovered. Recrystallization of the crude acid from ethanol–water gave dark brown acid, m.p. 206.5–207.5° dec. Recrystallization from glacial acetic acid gave the acid as brown crystals. Recrystallization from 95% ethanol gave 2.10 g. of yellow crystals, m.p. 206.8–207.5° dec., in 29% yield based on unrecovered bis(*p*-methoxyphenyl)acetylene. Recrystallization from acetone–water gave a powder with a slight yellow tint, m.p. 203–203.5° dec. The ultraviolet spectrum had λ_{max} 238 mμ (log ϵ 4.11), 243 (4.10), 321 (4.62), and 339 (4.57).

This acid, as did the other 2,3-diaryl-2-cyclopropene-1-carboxylic acids, appeared to decompose slightly on repeated recrystallizations.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; neut. equiv., 296.3. Found: C, 72.63; H, 5.54; neut. equiv., 293.

cis-cis-**2,3-Diphenylcyclopropane-1-carboxylic Acid.**—In a Parr hydrogenation flask were placed 4.72 g. (0.02 mole) of 2,3-diphenyl-2-cyclopropene-1-carboxylic acid, 150 mg. of palladium on calcium carbonate (Baker), and 100 ml. of glacial acetic acid. The acid was hydrogenated in the Parr apparatus at 40 p.s.i. for 19 hr. The mixture was filtered; the catalyst, residue, and flask were rinsed with glacial acetic acid; and the acetic acid was removed under vacuum on a rotary evaporator at the temperature of a hot water bath. Methanol (50 ml.) was added and the evaporation was repeated. One recrystallization from methanol using Norit A gave yellow material with m.p. 170–173°. Two additional recrystallizations from methanol gave 1.2 g. (25% yield) of slightly yellow *cis,cis*-2,3-diphenylcyclopropane-1-carboxylic acid, m.p. 172.5–174.5°. Recrystallization from benzene–hexane gave pure white crystals with m.p. 174.5–175.0°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92; neut. equiv., 238.3. Found: C, 80.65; H, 5.86; neut. equiv., 239.

The acid was esterified with diazomethane in ethyl ether to give, after two recrystallizations from methanol, methyl *cis,cis*-diphenylcyclopropane-1-carboxylate, m.p. 81.5–82.5°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.69; H, 6.42.

The n.m.r. spectrum determined in carbon tetrachloride showed a peak at 2.93 (aromatic protons), a peak at 6.55 (carbomethoxy protons), and a multiplet of seven peaks at 7.05–7.80 τ (cyclopropane protons of an A_2B system). The aromatic, acyclic, and cyclopropane protons were in ratio of approximately 10:3:3, respectively.

cis-**2-(*p*-Methoxyphenyl)-*cis*-3-phenylcyclopropane-1-carboxylic Acid.**—Repeated attempts to hydrogenate 2-(*p*-methoxyphenyl)-3-phenyl-2-cyclopropene-1-carboxylic acid using several different catalysts in either ethanol or glacial acetic acid gave only unchanged starting material. Successful hydrogenation was finally achieved by the method recently reported by the Browns.[7] In the flask of the Brown apparatus was placed 300 mg. of Norit A in 50 ml. of absolute ethanol. One milliliter of 1.0 M sodium borohydride solution (3.7 g. of sodium borohydride in 100 ml. of a solution prepared by diluting 5 ml. of aqueous 2.0 N sodium hydroxide to 100 ml. with absolute ethanol) was added to the flask and then 0.5 ml. of 0.2 M aqueous palladium chloride was injected to form a palladium-on-carbon catalyst. After 1 min., 5 ml. of glacial acetic acid was added to decompose the sodium borohydride and to form an atmosphere of hydrogen. A warm solution of 1.2 g. (0.0045 mole) of 2-(*p*-methoxyphenyl)-3-phenyl-2-cyclopropene-1-carboxylic acid in 25 ml. of 10% acetic acid in absolute ethanol was added. Over a period of 0.75 hr., about 7 ml. of the 1.0 M sodium borohydride solution was added to the flask to maintain the hydrogen atmosphere

The mixture was filtered, the flask and filter were rinsed with 95% ethanol, the filtrate was evaporated to one-fifth of its original volume, and the concentrated solution was poured into water. The aqueous mixture was extracted with dichloromethane; the dichloromethane extract was washed once with water and dried over anhydrous sodium sulfate. The dried solution was filtered, and the solvent was evaporated to give a thick oil, which was crystallized from benzene–hexane. Three additional recrystallizations from benzene–hexane gave 438 mg. (37% yield) of pure *cis*-2-(*p*-methoxyphenyl)-*cis*-3-phenylcyclopropane-1-carboxylic acid, m.p. 129.8–130.2°.

Anal. Cal. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; neut. equiv., 268.3. Found: C, 76.09; H, 5.93; neut. equiv., 266.

The n.m.r. spectrum determined in deuteriochloroform showed a multiplet at 2.78–3.42 (aromatic protons), a peak at 6.30 (aromatic methoxy protons), and a multiplet of eight peaks at 6.73–7.83 τ (cyclopropane protons of an A_2B system). The acyclic and cyclopropane protons were in the ratio of 1:1, respectively.

cis,cis-**2,3-Bis(*p*-methoxyphenyl)cyclopropane-1-carboxylic Acid.**—This acid was prepared in a manner similar to the preceding acid, except that 1.2 g. (0.004 mole) of 2,3-bis(*p*-methoxyphenyl)-2-cyclopropene-1-carboxylic acid was added to the

(21) R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).

(22) R. Breslow, J. Lockhart, and A. Small, *J. Am. Chem. Soc.*, **84**, 2793 (1962).

flask of the Brown hydrogenator along with the solvent and Norit A. Reduction was carried out for 1 hr. Isolation of the product in the manner described above gave crystalline material, which after three recrystallizations from benzene–hexane and one recrystallization from ethanol gave 232 mg. (19% yield) of pure white *cis,cis*-2,3-bis(*p*-methoxyphenyl)cyclopropane-1-carboxylic acid, m.p. 157–158°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08; neut. equiv., 298.3. Found: C, 72.14; H, 6.45; neut. equiv., 298.

The n.m.r. spectrum determined in deuteriochloroform showed a symmetric multiplet at 2.88–3.40 (two sets of equivalent aromatic protons), a peak at 6.27 (aromatic methoxy protons), and a multiplet of eight peaks at 6.68–7.84 τ (cyclopropane protons of an A_2B system). The acyclic and cyclopropane protons were in the ratio of approximately 2:1, respectively.

Potentiometric Titrations of the 2,3-Diphenylcyclopropane-1-carboxylic Acids.—Identical weights, 100-mg. (0.42-mole) each, of *cis,cis*-, *cis,trans*-, and *trans,trans*-diphenylcyclopropane-1-carboxylic acids were dissolved in 25 ml. of absolute ethanol, and 25 ml. of distilled water was added. Each solution was titrated potentiometrically with 0.05 *N* sodium hydroxide in 50% by volume aqueous ethanol. The pH meter used was standardized against an aqueous buffer at pH 7.

From the curves obtained by plotting the pH of the solution *vs.* the volume of titrant, the pH at half-neutralization (4.20 ml. of titrant) was determined. Calculations gave the pK_a and K_a of the acids. The values were as follows.

cis,cis isomer: $pK_a = 6.69$; $K_a = 2.0 \times 10^{-7}$
cis,trans isomer: $pK_a = 6.03$; $K_a = 9.3 \times 10^{-7}$
trans,trans isomer: $pK_a = 5.68$; $K_a = 21.0 \times 10^{-7}$

The values given in the literature[4] are for the *trans,trans* isomer, $K_a = 17.1 \times 10^{-7}$; and for the *cis,trans* isomer, $K_a = 0.91 \times 10^{-7}$. We can offer no explanation for the discrepancy between the literature and our value in the latter case.

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Synthesis and Transformation Products of Compounds in the 1,3,4,5-Tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic Acid Series

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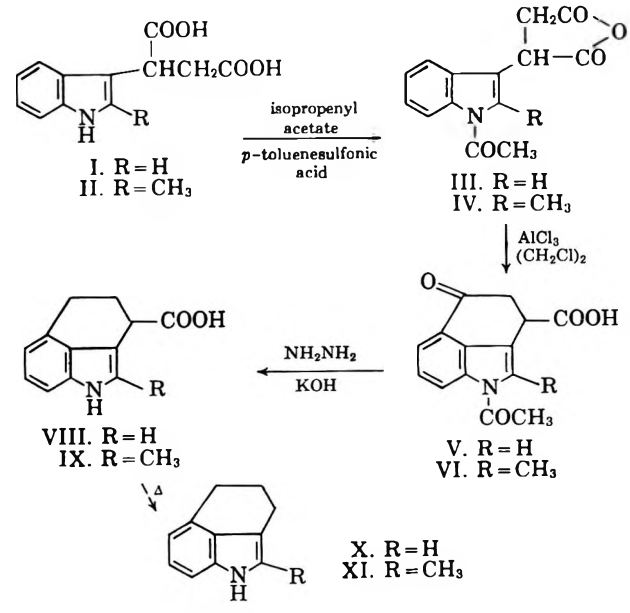
1-Acetyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic acid (V) was synthesized from 3-indolesuccinic acid (I) *via* 1-acetyl-3-indolesuccinic anhydride (III). The corresponding 2-methyl compound (VI) was prepared analogously from 2-methyl-3-indolesuccinic acid (II) *via* the anhydride IV. 1,3,4,5-Tetrahydrobenz[*cd*]-indole-3-carboxylic acid (VIII) and the corresponding 2-methyl compound (IX) were prepared by the Wolff–Kischner reduction of V and VI, respectively. Compound VIII was decarboxylated to the known 1,3,4,5-tetrahydrobenz[*cd*]indole (X), and IX to the corresponding 2-methyl derivative (XI). In the 2-methyl series, acid IX was converted to amides XV and XVI, which were reduced to amines XVII and XVIII, respectively. Acid IX afforded methyl ketone XIX which was converted to two isomers of 3-(1-aminoethyl)-1,3,4,5-tetrahydro-2-methylbenz[*cd*]indole (XXII) *via* reduction of oxime XX. An interesting fragmentation followed by reduction was observed in the case of oxime XX and also was applied to the oxime of indole-3-acetone.

Interest in the tetracyclic ergoline[1] system has been stimulated over the years by the potent physiological activity of compounds in this series. In the present paper we describe a method for the synthesis of 2-unsubstituted and 2-methyl-substituted tricyclic compounds in the 1,3,4,5-tetrahydrobenz[*cd*]indole series which is relatively simple, and which made possible the introduction of a carboxylic acid function in the hitherto inaccessible 3-position.

The synthesis of 1-acetyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic acid (V) was accomplished in two steps starting from 3-indolesuccinic acid (I). Reaction of I with isopropenyl acetate and *p*-toluenesulfonic acid brought about concomitant acetylation and anhydride formation, and led to 1-acetyl-3-indolesuccinic anhydride (III). Compound III underwent a facile cyclization in 1,2-dichloroethane with aluminum chloride to give the tricyclic N-acetyl keto acid V.

The ring structure of this cyclization product was proved by deacetylation and reduction of V with hydrazine[2] under mild conditions, followed by thermal



decarboxylation of the resulting acid VIII to 1,3,4,5-tetrahydrobenz[*cd*]indole (X),[3] which was identical with an authentic sample.[4]

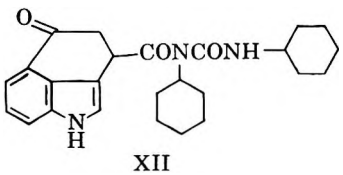
(1) For recent reviews on this subject, see D. F. Downing, *Quart. Rev.*, **16**, 133 (1962); R. Voigt, *Pharmazie*, **17**, 318 (1962); V. Erspamer in "Progress in Drug Research," Vol. 3, E. Jucker, Ed., Interscience, New York, N. Y., 1961, p. 269; J. H. Birkinshaw and C. E. Stickings in "Progress in the Chemistry of Organic Natural Products," Vol. 20, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1962, p. 17. Subsequent papers include G. N. Walker and B. N. Weaver, *J. Org. Chem.*, **26**, 4441 (1961); J. A. Moore and M. Rahm, *ibid.*, **26**, 1109 (1961); C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, **44**, 1736 (1961).

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

(3) F. C. Uhle *ibid.*, **71**, 761 (1949); J. A. Barltrop and D. A. H. Taylor, *J. Chem. Soc.*, 3403 (1954); F. C. Uhle, C. G. Vernick, and G. L. Schmir, *J. Am. Chem. Soc.*, **77**, 3334 (1955).

(4) We thank Dr. F. C. Uhle for sending us a sample of this material for comparison.

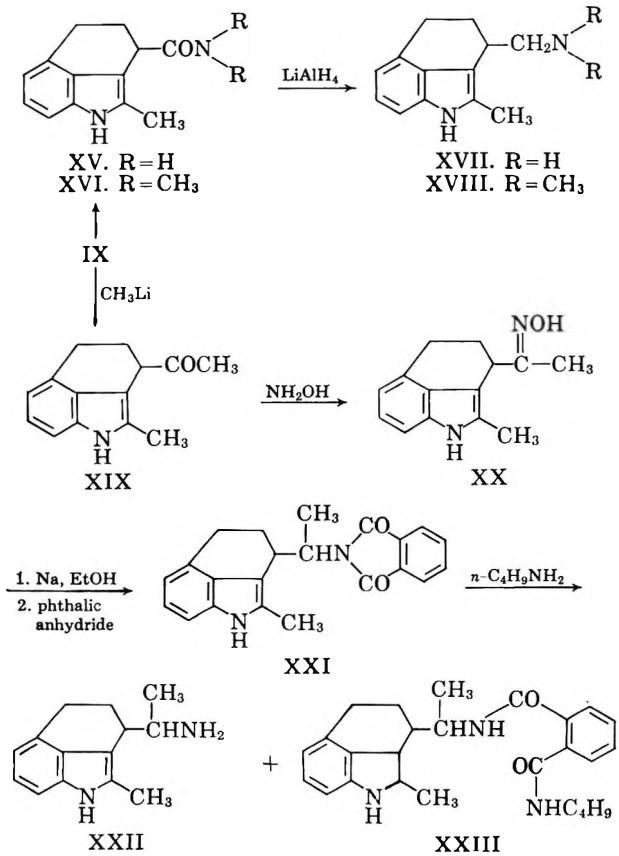
Acid V was best converted to the corresponding methyl ester VII by the oxalyl chloride procedure (see Experimental). An attempted esterification with methanol in presence of N,N′-dicyclohexylcarbodiimide led to addition product XII.[5,6]



XII

In the 2-methyl-1,3,4,5-tetrahydrobenz[*cd*]indole series the required starting material, 2-methyl-3-indolesuccinic acid (II), was prepared by condensation of 2-methylindole with maleic acid. The last two steps were analogous to those described above and led *via* anhydride IV to 1-acetyl-2-methyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic acid (VI). The assignment of structure to this compound is supported by the ultraviolet and infrared spectra (see Experimental). Additional evidence was provided by isolation of 2-methyl-1,3,4,5-tetrahydrobenz[*cd*]indole (XI) from the decarboxylation of acid IX, which in turn was obtained from VI by treatment with hydrazine. The ultraviolet and infrared spectra of XI were similar to those of the known compound X.

Several transformations of acid IX were carried out. Lithium aluminum hydride ($LiAlH_4$) reduction of



XV. R=H
XVI. R=CH_3

XVII. R=H
XVIII. R=CH_3

XIX

XX

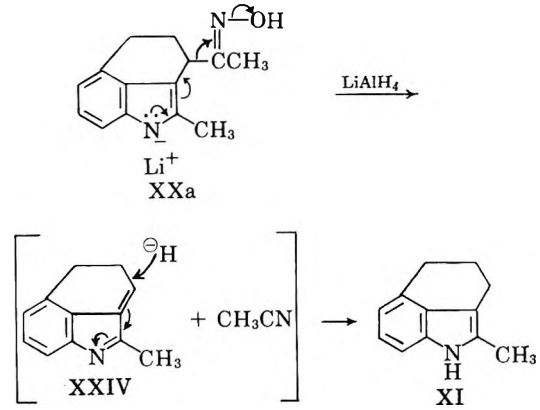
XXI

XXII

XXIII

methyl ester XIII, prepared from IX by the oxalyl chloride procedure, led to carbinol XIV. Compound IX also was converted *via* its acid chloride to amide XV and dimethyl amide XVI, which were in turn reduced with $LiAlH_4$ to amines XVII and XVIII, respectively.

Reaction of acid IX with methyllithium led to methyl ketone XIX which was converted to oxime XX. Reduction of XX with $LiAlH_4$ afforded a basic product, which appeared to be the hydroxylamine derived from XX, and a neutral compound (XI) which was identical with the decarboxylation product of acid IX. The formation of XI from XX can be rationalized in terms of a second-order Beckmann rearrangement,[7] and likely proceeds *via* the indolenine XXIV. The driving force for this reaction probably derives from negative charge on the indolic nitrogen in salt XXa. This type of



XXa

XXIV

XI

cleavage followed by reduction also was demonstrated to occur with the model oxime of indole-3-acetone, which on treatment with $LiAlH_4$ afforded a small yield of skatole along with the product of simple reduction, α-methyltryptamine.

The above fragmentation was circumvented by reduction of oxime XX with sodium and ethanol to give a mixture of two diastereoisomeric amines, which were separated by chromatography of their phthalimido derivatives (XXI). Treatment of each diastereoisomeric phthalimido compound (XXI) with butylamine produced the corresponding amines (XXII). The product of partial aminolysis (XXIII) was also isolated from the reaction of one of the phthalimido derivatives, and it was readily converted to the corresponding amine.

Experimental[8,9]

3-Indolesuccinic acid (I) was prepared as described previously[10] by condensation of indole-3-carboxaldehyde with ethyl cyanoace-

(5) The same type of adduct, namely phthaloyl-L-threonyl-N,N′-dicyclohexylurea, was isolated in addition to the desired peptide derivative from the reaction of phthaloyl-L-threonine with amino acid esters and N,N′-dicyclohexylcarbodiimide in dioxane or tetrahydrofuran by J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).

(6) The ultraviolet spectrum of XII (see Experimental) is similar to that of 1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole reported by C. A. Grob and J. Voltz, *Helv. Chim. Acta*, **33**, 1796 (1950).

(7) For leading references on the second-order Beckmann rearrangement, see R. K. Hill, *J. Org. Chem.*, **27**, 29 (1962); J. P. Freeman, *J. Org. Chem.*, **26**, 3507 (1961).

(8) Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol (unless otherwise specified) using a Cary spectrophotometer Model 14. Infrared spectra (recorded in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is a magnesia-silica gel adsorbent manufactured by Floridin Co., Tallahassee, Fla.

(9) The author is indebted to Dr. R. W. Rinehart and his associates for microanalyses, to Betty F. Zimmer and Miss L. M. Pschigoda for ultraviolet and infrared spectra, and to Mr. L. G. Laurian for laboratory assistance.

(10) Y. G. Perron and W. F. Minor, *J. Org. Chem.*, **24**, 1165 (1959).

tate, followed by reaction with potassium cyanide, and then hydrolysis with potassium hydroxide.

1-Acetyl-3-indolesuccinic Anhydride (III).—A mixture of 3-indolesuccinic acid (I, 187 g., 0.8 mole), 1500 ml. of isopropenyl acetate, and 15 g. of *p*-toluenesulfonic acid was refluxed for 10 min. The condenser was then replaced by a 1 in. × 8 in. column packed with glass helices attached to a condenser set for distillation. The mixture was heated for 3 hr., and 300 ml. of distillate was collected. During the last 0.5 hr. the temperature of the oil bath was raised from 120 to 128°, and the boiling point of the distillate rose from 55–65 to 90°. The dark reaction mixture was evaporated at 40–50° *in vacuo* to dryness. The residue was dissolved in 400 ml. of acetic acid and 50 ml. of acetic anhydride and allowed to crystallize overnight. The resulting solid was filtered and washed with acetic acid followed by ether. This solid was refluxed with 2 l. of benzene and filtered. The insoluble product III amounted to 21.5 g. melting at 169–170° (first crop). The benzene filtrate was evaporated to *ca.* 1500 ml. and was allowed to crystallize overnight; this gave 62.7 g., m.p. 170–171° (second crop). The third crop of the same melting point amounted to 4.84 g. The total yield was 89.04 g. (44%). The analytical sample was prepared by recrystallization from benzene containing a little acetic anhydride (Darco-G-60) as pale yellow needles, m.p. 170–171°. Ultraviolet spectrum showed λ_{max} 239 mμ (ε 19,450); 260 (8800); sh 270 (7750); sh 280 (4700); 290 (7200); 298 (7700). Infrared spectrum showed 3120 (=CH) 1860, 1825, 1783, 1750 (anhydride); 1688 (acetyl); 1610, 1600, 1577, 1503, 1480 (C=C); 1395, 1360, 1260, 1217, 1065, 1010 (C–O/C–N); 767, 758, 728, 672 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.42; H, 4.17; N, 5.56.

1-Acetyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic Acid (V).—Aluminum chloride (136 g., 1.02 moles) was added in portions over a 10-min. period to a stirred solution of 1-acetyl-3-indolesuccinic anhydride (III, 88 g., 0.342 mole) in 1370 ml. of 1,2-dichloroethane. The mixture became warm and an oily complex separated. The mixture was refluxed on a steam bath for 15 min. It was then cooled in an ice bath; 300 g. of ice was added followed by a solution of concentrated hydrochloric acid (260 ml.) in 1370 ml. of water. The resulting suspension was stirred in the cold for at least 1 hr. until a precipitate resulted. It was then filtered, and the solid was dissolved in 1 l. of acetone. The solution was treated with 10 g. of Darco-G-60, filtered, and evaporated to *ca.* 100 ml. Methylene chloride (250 ml.) was added; the solution was evaporated to *ca.* 100 ml. and allowed to crystallize; 59.5 g. (68% yield), m.p. 172–173°, unchanged on recrystallization from water. Ultraviolet spectrum showed λ_{max} 226 mμ (ε 15,100); 257 (16,800); sh 292 (8700); 302.5 (10,750); 326 (3800). Infrared spectrum showed 3080, 2720, 2600 (acid OH); 1725, 1715, 1680, 1670, sh 1655 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45; $COCH_3$, 16.73. Found: C, 65.64; H, 4.48; N, 5.53; $COCH_3$, 17.47.

1,3,4,5-Tetrahydrobenz[*cd*]indole-3-carboxylic Acid (VIII).—Potassium hydroxide (8.18 g., 0.146 mole) was dissolved in 73.5 ml. of diethylene glycol by heating. The solution was cooled and 7.53 g. (0.0293 mole) of N-acetylketo acid V and 7.3 g. (0.146 mole) of 85% aqueous hydrazine hydrate were added. The solution was refluxed for 10 min. The condenser was then removed and the solution was evaporated until the inside temperature reached 190° and was then heated for 10 min. It was cooled and 200 ml. of water was added. The solution was extracted with ether (5 × 100 ml.). The aqueous layer was cooled in ice and acidified with 40 ml. of concentrated hydrochloric acid. The acidic solution was extracted with ether (5 × 200 ml.), the extracts were washed with water and treated with Nuchar C-190-N, and the resulting pale yellow solution was dried over sodium sulfate and evaporated to give 1.8 g. of a crude VIII as a yellow solid. Crystallization from chloroform afforded 0.45 g. (7.6% yield), m.p. 203° dec., unchanged on recrystallization from chloroform. Ultraviolet spectrum showed λ_{max} 223 mμ (ε 33,400); 274 (5750); 280 (5900); 291 (4560). Infrared spectrum showed 3390 (NH); 3000, 2700, 2620 (OH); 1688 (C=O); 1608, 1512 (C=C); 930–915 (OH deformation); 795, 785, 770, 765, 750, 710 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.66; H, 5.66; N, 7.22.

1,3,4,5-Tetrahydrobenz[*cd*]indole (X).—One hundred milligrams of acid VIII was heated at 210° for 5 min. The resulting brown oily distillate solidified. On sublimation at 60° (0.01 mm.) colorless crystals of X were obtained; 58 mg. (74% yield), m.p. 57–58,[3] unchanged after crystallization from petroleum ether (b.p. 30–60°). Ultraviolet spectrum showed λ_{max} 225 mμ (ε 34,450); 275 (5500); 281 (5700); 291 (4400). Infrared spectrum showed 3380 (NH); 3040 (=CH); 1613, 1602, 1552, 1506 (C=C); 800, 773, 750 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.72; H, 7.15; N, 8.93.

This compound was found to be identical with an authentic sample[4] as determined by mixture melting point and comparison of ultraviolet and infrared spectra.

Methyl 1-Acetyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylate (VII). A. With Diazomethane.—A solution of acid V (5.14 g., 0.02 mole) in methanol was added to an ethereal solution of diazomethane prepared from 11 g. (0.072 mole) of N-methyl-N-nitroso-N′-nitroguanidine while cooling in ice. The solution was evaporated to *ca.* 30 ml. and allowed to crystallize overnight. The crystals were filtered and washed with ether, 2.26 g., m.p. 121–123°. A second crop was collected from the filtrate to bring the total yield to 55%. A sample was recrystallized for analysis from methanol, m.p. 123–124°. Ultraviolet spectrum showed λ_{max} 226 mμ (ε 15,650); 256 (17,350); sh 292 (9250); 302 (11,200) sh 328 (3900). Infrared spectrum showed 1727, 1707, 1678 (C=O); 1606, 1576, 1498, 1483 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.15; H, 4.39; N, 4.84.

B. With Oxalyl Chloride.—Oxalyl chloride (40 ml., 0.47 mole) was added during 15 min. to a suspension of acid V (10.30 g., 0.04 mole) in 400 ml. of benzene while stirring and refluxing. The mixture was refluxed for an additional 15 min., and the solution was allowed to stand at room temperature for 2 hr. It was then evaporated to dryness *in vacuo* at 50–60°. The residue was flushed twice with 50-ml. portions of benzene. The residue was suspended in 600 ml. of methanol, the suspension was refluxed for 15 min., and the resulting solution was evaporated to *ca.* 50 ml. *in vacuo*. The suspension was filtered and the product washed with cold methanol; 7.1 g., m.p. 121–122°. The second crop amounted to 1.09 g., m.p. 120–121°, yield 76%.

C. Attempted Esterification of V in Presence of N,N′-Dicyclohexylcarbodiimide.—N,N′-Dicyclohexylcarbodiimide (2.32 g., 0.0106 mole) was added to a solution of V in 50 ml. of methanol. The resulting suspension was stirred overnight after adding 25 ml. of methanol. The suspension was filtered to separate some N,N′-dicyclohexylurea. The filtrate was evaporated to dryness, and the residue was refluxed with 100 ml. of ether and filtered to separate a further crop of N,N′-dicyclohexylurea. The ethereal filtrate was evaporated to dryness, and the residue was crystallized from 10 ml. of methanol to give 1,3-dicyclohexyl-1-(1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-ylcarbonyl)urea (XII)[5] in two crops; 1.2 g., m.p. 219–221°. Recrystallization from methanol afforded needles melting at 219.5–220°. Ultraviolet spectrum showed λ_{max} 242 mμ (ε 16,800); 320 (4800); 360 (4250).[6] Infrared spectrum showed 3340, 3260 (NH); 3110; 3060 (=CH); 1680, 1650 (C=O) 1622; 1600, 1495 (C=C) 1525 (amide II) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 70.77; H, 7.47; N, 9.87; CH_3CO, 0.

2-Methyl-3-indolesuccinic Acid (II).—A mixture of 2-methylindole (131.17 g., 1.0 mole) and maleic acid (116.07 g., 1.0 mole) was well mixed and then heated on the steam bath. After 10 min. it melted and then started to solidify. The flask was quickly removed from the bath and a vigorous reaction ensued. It was allowed to stand for 0.5 hr. A solution of potassium hydroxide (113 g.) in 1800 ml. of water was added and the mixture heated on the steam bath with stirring for 40 min. The solution was cooled, decanted, and extracted with ether (4 × 200 ml., discarded). It was then treated with Nuchar C-190-N (10 g.) in the hot, filtered, cooled, acidified with concentrated hydrochloric acid (250 ml.) and allowed to crystallize overnight in the refrigerator. The precipitate was filtered and washed with cold water to give 126.3 g. of material melting at 210–211° dec. The filtrate was extracted with ether (4 × 500 ml.). The ethereal extracts were washed with saturated salt solution and evaporated to give a brown solid (10.5 g., m.p. 183–200°) which was crystallized from 175 ml. of acetonitrile to give 5.0 g. of material melting at 210–211° dec. The total yield was 53%. This compound was previously prepared by hydrolysis of the adduct obtained from 2-

methylindole and maleic anhydride, lit.[11a] m.p. 212° dec.; *cf.* also ref. 11b.

1-Acetyl-2-methyl-3-indolesuccinic Anhydride (IV).—A mixture of 233 g. (0.945 mole) of 2-methyl-3-indolesuccinic acid (II), isopropenyl acetate (1880 ml.), and *p*-toluenesulfonic acid monohydrate (18.8 g.) was refluxed for 20 min. The acetone was then distilled slowly over a period of 6 hr. through a glass helices-packed column. The distillation was allowed to proceed until the boiling point reached 95°. The solution was then evaporated to dryness and the resulting dark solid crystallized from 660 ml. of acetic acid and 130 ml. of acetic anhydride. After 2 days the dark crystals were filtered, washed with acetic acid and then with ether; 123.9 g. (52%), m.p. 185–186° dec.. This material was suitable for cyclization with aluminum chloride.

A sample was dissolved in benzene, filtered from the dark pigment, and allowed to crystallize; pale yellow plates, m.p. 189–191.5°. This material (0.8 g.) was recrystallized from 2.5 ml. of acetic acid and 0.5 ml. of acetic anhydride, m.p. 192–193° (sint. 189°). Ultraviolet spectrum showed λ_{max} 244 mμ (ε 15,450); f 264 (9750); f 272 (8700); f 276 (7950); 290 (5250); 298.5 (5250). Infrared spectrum showed 1858, 1775 (anhydride); 1687 (acetyl); 1605, 1580, 1475 sh (C=C); 1305, 1260, 1242, 1220, 1210, 1060, 1035, 1025, 1005, 995 (C–O/C–N); 842, 763, 750, 727, 680 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.67; H, 4.77; N, 5.26.

1-Acetyl-2-methyl-1,3,4,5-tetrahydro-5-oxobenz[*cd*]indole-3-carboxylic Acid (VI).—Anhydride IV (9.57 g., 0.035 mole) was dissolved in 176 ml. of hot 1,2-dichloroethane. The solution was cooled to room temperature with stirring to give a fine suspension. Aluminum chloride (23.5 g., 0.177 mole) was added all at once. The mixture warmed up slightly and after 5 min. was heated on the steam bath for 2 hr. It was cooled in ice; ice was added and then a solution of 27 ml. of concentrated hydrochloric acid in 142 ml. of water. The mixture was filtered and the precipitate was washed well with water. It was crystallized from acetone (Nuchar C-190-N) to give 5.6 g. of yellow needles, m.p. 215–217° dec. The second crop amounted to 1.6 g., m.p. 205–207° (75%). A sample was recrystallized for analysis from acetone, m.p. 212–216° dec. (sint. 207°). Ultraviolet spectrum showed λ_{max} 226.5 mμ (ε 17,850); 259 (15,250); f 292 (8700); f 303 (10,800); 341 (4150); in base: f 220 (16,500); 251 (17,500); f 272 (3300); 309 (4500); 360 (4050). Infrared spectrum showed 3090 sh, 3020 sh, 2700, 2690, 2510, 2340 (OH, acid); 1715, 1700, 1680 (C=O); 1655 sh, 1647, 1608, 1587, 1483 (C=C); 1320 (C–O); 790, 756 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16; neut. equiv., 271. Found: C, 66.37; H, 4.74; N, 5.00; neut. equiv., 263.

The dinitrophenylhydrazone was crystallized from ethanol in the form of orange needles, m.p. 243–244° dec. (sint. 240°). Ultraviolet spectrum showed $\lambda_{max}^{CHCl_3}$ 264.5 mμ (ε 20,950); 307 (10,600); 394 (30,250).

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.87; H, 3.80; N, 15.52. Found: C, 55.65; H, 3.74; N, 15.73.

2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-3-carboxylic Acid (IX).—Potassium hydroxide (35.8 g., 0.64 mole) was dissolved in diethylene glycol (320 ml.). The solution was cooled to room temperature and 34.8 g. (0.128 mole) of VI was added followed by 38.4 g. (0.64 mole) of hydrazine hydrate (85%). The mixture was refluxed for 10 min. The inside temperature was then raised to 190° and the solution refluxed at that temperature for 10 min. The solution was cooled, 500 ml. of water was added, and the mixture extracted with ether (3 × 200 ml., discarded). The aqueous solution was cooled in ice and acidified with 140 ml. of concentrated hydrochloric acid. It was then extracted with ether (10 × 300 ml.). The ether extracts were washed with water, saturated salt solution, dried by passage through sodium sulfate, and evaporated to give a dark oil. The oil was dissolved in chloroform and treated with Nuchar C-190-N, and the solution was evaporated down to about 100 ml. and allowed to crystallize; yellow plates, 12.7 g., m.p. 173–174°. The second crop amounted to 1.45 g., m.p. 171–173° (51%). A sample was recrystallized for analysis from chloroform, m.p. 174–174.5°. Ultraviolet spectrum showed λ_{max} 226 mμ (ε 34,200); f 275 (7250); 279 (7350); f 290 (5350). Infrared spectrum showed 3340 (NH); 3100 sh, 3010 sh, 2720, 2630, 2600, 2540 (OH, acid); 1690 (C=O); 1620, 1608, 1573, 1505 (C=C); 1330, 1305, 1240, 1233 (C–O/C–N), 932 (OH, deformation); 785, 780, 763, 755, 747, 688 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.96; H, 6.04; N, 6.38.

Decarboxylation of IX to 2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]-indole (XI).—Acid IX (0.3 g.) was heated in an oil bath at 220° for 5 min. The product was sublimed at 75–140° (0.1 mm.). The sublimate (0.2 g.) was dissolved in methylene chloride, and the solution was washed with 5% sodium hydroxide (2 × 10 ml.), water, and salt solution. The solution was dried by passage through sodium sulfate and evaporated. The product (60 mg.) was crystallized from Skellysolve B to give colorless crystals of XI melting at 74–75°. This compound was identical with the sample obtained by treatment of oxime XX with $LiAlH_4$ as shown by mixture melting point and comparison of ultraviolet and infrared spectra.

The basic extracts were acidified with 10% hydrochloric acid, extracted with methylene chloride, and worked up as usual. The product (0.13 g.) was crystallized from chloroform and melted at 171–172°. Mixture melting point with the starting material IX showed no depression.

2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-3-carboxylic Acid Chloride.—Acid IX (4.3 g., 0.02 mole) was dissolved in 200 ml. of hot benzene. The solution was cooled in ice, and oxalyl chloride (20 ml.) was added during 5 min. while swirling. The dark solution was allowed to stand at room temperature; gas evolution started after a few minutes. After 2 hr. the solution was evaporated at 40–45° *in vacuo*. Benzene (50 ml.) was added and the solution evaporated again to give the oily brown acid chloride which was used directly.

Methyl Ester of 2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-3-carboxylic Acid (XIII).—The acid chloride was prepared from 0.09 mole of the acid with oxalyl chloride in benzene as described above. The benzene solution was evaporated to dryness and 300 ml. of methanol was added. After the reaction subsided, the suspension was refluxed for 45 min. The mixture was allowed to crystallize overnight and afforded 17.34 g. in two crops. It was recrystallized from methanol (Darco G-60) to give 13.1 g. melting at 157–158°. The second crop amounted to 1.54 g., m.p. 156–157°, total yield 71%. The analytical sample melted at 156.5–157.5°. Ultraviolet spectrum showed λ_{max} 225 mμ (ε 35,450); f 274 (7300); 279 (7450); f 289 (5300). Infrared spectrum showed 3340 (NH); 1705 (C=O); 1627, 1612, 1582, 1510 (C=C); 1225 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.29; H, 6.57; N, 6.06.

2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-3-methanol (XIV).—A solution of methyl ester XIII (6.9 g., 0.03 mole) in 100 ml. of tetrahydrofuran was added during 0.5 hr. to a solution of $LiAlH_4$ (7 g.) in 500 ml. of ether. The mixture was then refluxed for 3 hr. It was cooled in ice and decomposed with dilute sulfuric acid. The aqueous layer was extracted twice with ether and the combined ether layer was washed with sodium bicarbonate solution, and then with saturated salt solution, dried by passage through sodium sulfate, and evaporated to give 6.5 g. of a pale green oil. A sample was evaporatively distilled at 120–140° (0.05 mm.). Attempts to achieve crystallization were unsuccessful. Ultraviolet spectrum showed λ_{max} 227 mμ (ε 35,000); f 274 (7000); 279 (7100); f 290 (5200). Infrared spectrum showed ($CHCl_3$ mull) 3520, 3380, 3300 sh (OH/NH); 1625, 1610, 1580, 1505 (C=C); 1075, 1050, 1028 sh, 1022 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.81; H, 7.21; N, 7.26.

2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-3-carboxamide (XV).—Fifty milliliters of aqueous ammonium hydroxide (29%) was added to the oily acid chloride (cooled in ice) prepared from 2.15 g. of acid IX (0.01 mole) by the oxalyl chloride procedure. An oily product separated which afforded a precipitate after it was scratched. The suspension was cooled in ice and filtered, and the solid was washed with cold water; 1.25 g. (59%), m.p. 210–212°. Crystallization from methanol–benzene (Nuchar C-190-N) afforded pale yellow leaflets melting at 213–215°. A sample was recrystallized for analysis from benzene containing a trace of methanol, m.p. 214–215.5°. Ultraviolet spectrum showed λ_{max} 224.5 mμ (ε 33,900); 274 (7200); 278 (7300); f 289 (5150). Infrared spectrum showed 3410, 3320, 3180 (NH); 1665 (C=O); 1642 (amide II); 1587 (C=C); 775, 752 (ring) cm.$^{-1}$.

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Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.86; H, 6.67; N, 12.73.

2-Methyl-1,3,4,5-tetrahydro-3-aminomethylbenz[*cd*]indole Acetic Acid Salt (XVII).—A solution of amide XV (0.86 g., 4 mmoles) in 35 ml. of warm tetrahydrofuran (freshly distilled from $LiAlH_4$) was added during 5 min. with stirring to a solution of $LiAlH_4$ (1 g.) in 100 ml. of ether. The mixture was then refluxed for 5 hr. and allowed to stand for 2 days. It was cooled in ice and decomposed in succession with 1 ml. of water, 1 ml. of 15% sodium hydroxide solution, and 3 ml. of water. The suspension was filtered, the precipitate was washed well with ether, and the filtrate was evaporated to dryness at room temperature to give 0.83 g. of a yellow oil. It showed only a trace of residual amide band at 1670 $cm.^{-1}$. The oil (0.794 g.) was dissolved in 25 ml. of warm ether, and the solution was decanted from a small amount of undissolved amorphous material. A solution of acetic acid (0.36 g.) in 3 ml. of ether was added. The resulting precipitate was filtered and washed with ether; 0.9 g., m.p. 190–192.5° dec. (sint. 189°). It was dissolved in about 10 ml. of methanol, 40 ml. of ether was added, and crystallization allowed to proceed in the cold overnight; clusters of needles, 0.75 g., melting at 195–198° dec., darkening at 185°. Ultraviolet spectrum showed λ_{max} 226 mμ (ϵ 34,900); 274 (7250); 279 (7300); f 290 (5150). Infrared spectrum showed 3260 (NH); 3000, 2770, 2700, 2640, 2560, 2460, 2190 (salt); 1635, 1575 sh, 1560 sh, 1538, 1415 (COO^-/C=C); 735, 680 (ring) $cm.^{-1}$.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.89; H, 7.44; N, 10.49.

2-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole-N,N-dimethyl-3-carboxamide (XVI).—Fifty milliliters of aqueous dimethylamine (40%) was added to the oily acid chloride (cooled in ice) prepared from 2.15 g. of acid IX (0.01 mole) by the oxalyl chloride procedure. The resulting suspension was stirred for a few minutes. It was then cooled in ice and filtered, and the precipitate was washed with cold water; 2.15 g. (89%), m.p. 231–233°. Crystallization from methanol (Nuchar C-190-N) gave pale yellow plates, m.p. 232.5–234° (darkening at 220°), unchanged on added recrystallization. Ultraviolet spectrum showed λ_{max} 227 mμ (ϵ 62,800); f 274 (6750); 280 (6950); f 290 (5100). Infrared spectrum showed 3190 (NH); 1620 sh, 1612 (C=O); 1578, 1500 (C=C); 757, 745, 723 (ring) $cm.^{-1}$.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 73.96; H, 7.73; N, 11.83.

2-Methyl-1,3,4,5-tetrahydro-N,N-dimethyl-3-aminomethylbenz[*cd*]indole (XVIII).—A solution of dimethylamide XVI (1.55 g.; 6.4 mmoles) in 100 ml. of hot tetrahydrofuran (freshly distilled from $LiAlH_4$) was added to a solution of $LiAlH_4$ (2 g.) in 150 ml. of ether so that mild reflux resulted. The mixture was then refluxed for 6 hr. and allowed to stand overnight. It was decomposed in succession with 2 ml. of water, 2 ml. of 15% sodium hydroxide solution, and 6 ml. of water. The suspension was filtered, the cake washed with ether, and the filtrate evaporated to dryness *in vacuo* to give 1.48 g. (quantitative yield) of a solid melting at 111.5–113.5° (it showed no residual amide band in the infrared). A sample was crystallized for analysis from Skellysolve B; prisms, m.p. 113.5–115°. Ultraviolet spectrum showed λ_{max} 227 mμ (ϵ 32,150); f 274 (6900); 280 (6950); f 290 (5100). Infrared spectrum showed 3140 (NH); 2780, 2740 sh, 2700 (tert. amine); 1623, 1606, 1575, 1507, 1495 sh (C=C); 860, 846, 800, 780, 738 (ring) $cm.^{-1}$.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.59; H, 8.57; N, 12.43.

2-Methyl-3-acetyl-1,3,4,5-tetrahydrobenz[*cd*]indole (XIX).—A solution of methyllithium[12] containing 0.015 equiv. of the reagent in 23 ml. of ether was added during 10 min. to a solution of acid IX (1.08 g., 5 mmoles) dissolved in 50 ml. of ether under nitrogen at room temperature. Immediate precipitation occurred accompanied by mild reflux. The mixture was then refluxed for 35 min. It was cooled in ice, 50 ml. of water was added, and the ether layer was separated. The aqueous solution was extracted twice with ether. The combined ether solution was washed twice with saturated salt solution, dried by passage through sodium sulfate, and evaporated to give 0.34 g. of a viscous oil. Crystallization from ether–Skellysolve B afforded 0.24 g. (22%) of prisms, m.p. 96.5–97.5°. Recrystallization (Nuchar C-190-N) gave raised m.p. 97–98°. Ultraviolet spectrum showed λ_{max} 225 mμ (ϵ 35,200); 274 (7450); f 280 (7400); f 289 (5300). Infrared spectrum showed 3320 (NH); 1688 (C=O); 1620, 1608, 1575 (C=C) $cm.^{-1}$.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.20; H, 7.00; N, 6.66.

The aqueous solution was cooled in ice, acidified with concentrated hydrochloric acid, and extracted with ether. Work-up in the usual way afforded 0.8 g. (73% recovery) of the starting acid which melted at 170–173°.

Oxime of 2-Methyl-3-acetyl-1,3,4,5-tetrahydrobenz[*cd*]indole (XX).—A solution of ketone XIX (6.3 g., 0.0296 mole) in 40 ml. of 95% ethanol was added to a solution of hydroxylamine hydrochloride (10.4 g., 0.15 mole) and sodium acetate (18.5 g., 0.225 mole) in 40 ml. of water. The mixture was refluxed for 1 hr., and the resulting yellow solution was evaporated until an oily product separated. Water (50 ml.) was added and the mixture was cooled and filtered to give 6.38 g. (94.5%) of oxime mixture, m.p. 163–171° (sint. 145°). One crystallization from benzene–petroleum ether (b.p. 30–60°) gave clusters melting at 167–174° (sint. 154°). Ultraviolet spectrum showed λ_{max} 227 (mμ ϵ 36,150); 274 (7100); 280 (7200); f 290 (5100). Infrared spectrum showed 3350 (NH); 3200 (OH); 1660 (w) (C=N); 1605, 1570, 1505 (C=C); 963, 940, 906, 860 (=N—OH) $cm.^{-1}$.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.55; H, 7.36; N, 12.63.

Reduction of Oxime XX with $LiAlH_4$.—A solution of oxime XX (5.88 g., 0.0258 mole) in 175 ml. of ether was added during 15 min. to $LiAlH_4$ (9.8 g., 0.258 mole) in 500 ml. of ether. The suspension was stirred and refluxed for 7.5 hr. and allowed to stand for 2 days. The mixture was worked up as described below and separated into basic and neutral fractions. Analytical results and ultraviolet spectrum indicated that the basic fraction (2.15 g.) was impure hydroxylamine derivative of the starting material. Papergram analysis of the neutral fraction (2.51 g.) showed the presence of the starting oxime. A solution of the two fractions (4.06 g.) in 100 ml. of tetrahydrofuran was added during 15 min. to a solution of $LiAlH_4$ (10 g.) in 500 ml. of tetrahydrofuran under nitrogen. The resulting cloudy solution was stirred and refluxed for 16 hr. It was then decomposed in succession with 10 ml. of water, 10 ml. of 15% sodium hydroxide, and 30 ml. of water. The mixture was filtered, and the filtrate was evaporated to *ca.* 10 ml. and diluted with 100 ml. of ether. The ethereal solution was extracted three times with 10% hydrochloric acid (total, 75 ml.). The acidic extracts were washed once with ether, and then treated with 15% sodium hydroxide. The resulting yellow oil was extracted with ether. The ether layer was washed with water, saturated salt solution, dried by passage through sodium sulfate, and evaporated to give a 2.78 g. of a foamy powder, m.p. 85–95° (efferv.). Ultraviolet spectrum showed λ_{max} 225 mμ (ϵ 30,200); f 275 (6070); 280 (6170); f 289 (4520).

Anal. Calcd. for the hydroxylamine, $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.40; H, 8.35; N, 11.74.

The neutral ethereal fraction was worked up as usual to give a greenish oil (0.78 g.) which slowly crystallized. It was dissolved in 10 ml. of ether and treated twice with Nuchar C-190-N to give a pale yellow solution. It was evaporated to a small volume; Skellysolve B was added and the solution evaporated to about 5 ml. and cooled in Dry Ice to give oily crystals. On warming cautiously in Skellysolve B the crystals dissolved leaving the impure gum behind. The solution was allowed to crystallize to give pale yellow plates of XI (0.33 g.), m.p. 74.5–75.5°. It was sublimed at 70° (0.05 mm.) to give prisms melting at 73–74°, unchanged on recrystallization from Skellysolve B. Ultraviolet spectrum showed λ_{max} 230 mμ (ϵ 33,100); f 275 (6500); 281.5 (6800); f 291 (5050). Infrared spectrum showed 3350 (NH); 1602, 1575, 1502 (C=C) $cm.^{-1}$.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.13; H, 7.64; N, 7.90.

Oxime of Indole-3-acetone.—A solution of 10.6 g. (0.0614 mole) of indole-3-acetone[13] and hydroxylamine (prepared from 21.6 g. or 0.31 mole of hydroxylamine hydrochloride and 37.7 g. or 0.46 mole of sodium acetate) in 50 ml. of 95% ethanol and 83 ml. of water was refluxed for 45 min. The initial yellow solution turned brown. The solution was evaporated until it became cloudy, 150 ml of water was added, and the brown oil was extracted with ether and chloroform. The organic layer was washed with water, sodium bicarbonate solution, then with

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(13) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

water, and saturated salt solution, dried over sodium sulfate, and evaporated to give 11.6 g. (quantitative yield) of a brown oil which could not be crystallized. Infrared showed no residual carbonyl absorption. Ultraviolet spectrum showed λ_{max} 221 mμ (ε 33,950); 274 (6000); 280 (6300); 289 (5400).

Reduction of the Oxime of Indole-3-acetone with $LiAlH_4$.—A solution of the oxime (11.5 g., 0.061 mole) in 100 ml. of tetrahydrofuran was added at room temperature during 5 min. to a solution of $LiAlH_4$ (23.2 g., 0.61 mole) in 1 l. of tetrahydrofuran. The mixture was then refluxed under nitrogen for 20 hr. It was cooled in ice and decomposed in succession with 23 ml. of water, 23 ml. of 15% sodium hydroxide, and 70 ml. of water. The suspension was filtered, the cake was washed with ether, and the combined filtrate was evaporated to about 20 ml. and diluted with 250 ml. of ether. The ether solution was extracted five times with 10% hydrochloric acid (total 125 ml.). The acid extracts were washed once with ether and then treated in the cold with 15% sodium hydroxide. The product was extracted with ether and worked up as usual to give 7.92 g. of a brown oil which solidified overnight. Direct crystallization proved difficult. Therefore, 1 g. of the crude solid was distilled from an oil-jacketed flask at 140–170° (outside *T*., 0.1 mm.) to give 0.5 g. of a yellow oil which solidified, m.p. 99–102°. It was crystallized from benzene–petroleum ether (b.p. 30–60°) to give clusters of needles, m.p. 104–105.5°. This product was identical with an authentic sample of α-methyltryptamine[14] (by infrared and mixture melting point).

The neutral ether solution was worked up to give 0.7 g. of a brown solid. It was sublimed at 70–75° (0.1 mm.) and afforded 0.5 g. of a white crystalline sublimate, m.p. 98.5–99°, which was identical with skatole (by infrared and ultraviolet spectra and mixture melting point).

Reduction of Oxime XX with Sodium and Ethanol.—Sodium (78 g.) was added during 20 min. to a refluxing solution of the oxime (12.1 g., 0.053 mole) in 800 ml. of absolute ethanol without external heating. The solution was then refluxed for 1 hr. The resulting brown solution was cooled in ice, 800 ml. of water was added, and the solution was evaporated *in vacuo* until about 800 ml. of distillate was collected and an oil separated. The mixture was extracted with ether and the ethereal layer washed with water and then extracted six times with a total of 175 ml. of 10% hydrochloric acid. The acidic extracts were washed once with ether and treated with 15% sodium hydroxide. The resulting oil was extracted with ether and worked up as usual to give 9.88 g. of crude amine XXII as an oily brown solid. The neutral ethereal solution was worked up in the usual way to give 1.873 g. of brown residue which was shown by papergram to be the impure oxime.

Phthalimido Derivatives XXI.—A mixture of phthalic anhydride (7.8 g., 0.0526 mole) and the crude amine from sodium–ethanol reduction (7.53 g., 0.0352 mole) was heated in an oil bath. The temperature was raised to 210° during 15 min. and then kept at 210–220° for 15 min. The mixture was allowed to cool, 350 ml. of absolute ethanol was added, and the mixture was refluxed for 1 hr. and 40 min. It was evaporated *in vacuo* to a small volume, diluted with 250 ml. of ethyl acetate, and washed three times with dilute sodium bicarbonate solution. The bicarbonate washes were re-extracted once with ethyl acetate and the combined organic layer was filtered, washed with water, then twice with 10% hydrochloric acid followed by saturated salt solution. It was dried over sodium sulfate and evaporated to give 11.5 g. of a brown solid.

The solid was dissolved in 100 ml. of benzene and chromatographed on 1,150 g. of Florisil. Elution with 6% acetone–Skellysolve B (8 l.) gave 124.3 mg. (discarded). Further elution (10 l.) gave a total of 7.07 g. of product with varying m.p. 184 to 187°. It was crystallized from methanol (Darco G-60) to give isomer A of XXI; 3.32 g. of yellow clusters, m.p. 180–181°. The second crop amounted to 0.48 g., m.p. 179–180°. The analytical sample melted at 182–182.5° (from methanol). Ultraviolet spectrum showed λ_{max} 222 mμ (ε 71,850); f 242 (11,400); 275 (9150); 279 (9250); 290 (7250). Infrared spectrum showed 3400, 3360 (NH); 1768, 1700 (C=O); 1622 sh, 1615, 1575, 1508 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 77.01; H, 5.94; N, 8.10.

Further elution (18 l.) gave 5.3-g. total of product melting from 166 to 170°. Crystallization from methanol afforded isomer B of XXI; 2.08 g. of yellow rods, m.p. 169–170°. The second crop (0.46 g.) melted at 167–168°. Ultraviolet spectrum showed λ_{max} 225 mμ (ε 71,250); f 240 (12,800); 275 (8050); 280 (8150); f 289 (6600). Infrared spectrum showed 3350 (NH); 1771, 1695 (C=O); 1615, 1605 sh, 1579, 1510 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.92; H, 5.98; N, 8.17.

Cleavage of XXI Isomer A to XXII Isomer A.—A solution of XXI (isomer A, m.p. 180–181°, 3.8 g., 0.011 mole) in 100 ml. methanol and 11 ml. of butylamine[15] was refluxed for 20.5 hr. under nitrogen. It was evaporated to dryness *in vacuo* to give a pale yellow gum. Water (50 ml.) and ether (50 ml.) were added, and the mixture was stirred until a fine suspension resulted. Filtration (filtrate worked up below) gave 2.65 g. of a colorless precipitate, m.p. 209–213° (sint. 155°). Crystallization from aqueous methanol afforded colorless needles of partial product of aminolysis, N-butyl-N′-[1-(1,3,4,5-tetrahydro-2-methylbenz[*cd*]-indole-3-yl)ethyl]phthalamide (XXIII), m.p. 217–218°, unchanged on further crystallization. Ultraviolet spectrum showed λ_{max} 227 mμ (ε 45,950); 273.5 (8400); f 278 (8200); f 290 (5550). Infrared spectrum showed 3350, 3260, 3180 (NH); 3030 (=CH); 1625 (C=O); 1600, 1580, 1507 sh, 1480 sh (C=C); 1560 sh (amide II) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{31}N_3O_2$: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.68; H, 7.59; N, 10.15.

The above filtrate was separated into layers, and the aqueous layer was extracted once with ether. The ether extracts were washed four times with 10% hydrochloric acid (85 ml.) and treated with 15% sodium hydroxide. The product was extracted three times with ether and worked up as usual to give 1.05 g. (45% yield) of a pale yellow oil. Crystallization from benzene–petroleum ether (b.p. 30–60°) gave XXII isomer A, m.p. 123–125° (0.91 g.). Recrystallization from ether–Skellysolve B gave raised m.p. 126–127°. Ultraviolet spectrum showed λ_{max} 228 mμ (ε 35,050); f 275 (7050); 280 (7150); f 290 (5200). Infrared spectrum showed 3130, 3020 (NH); 1620, 1597, 1575 (C=C/NH def.) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.23; H, 8.45; N, 13.03.

The neutral ether fraction was worked up to give 1.19 g. of a gummy solid which was crystallized from benzene to give solvated N,N′-dibutyl phthalamide, m.p. 92–96°[15,16] (by C, H, N analyses) identical by infrared with the sample obtained below.

Cleavage of XXIII to XXII Isomer A.—A solution of XXIII (2.45 g., 5.9 mmoles) in 50 ml. of ethanol and 17 ml. of butylamine was refluxed under nitrogen for 22.5 hr. The solution was evaporated to dryness *in vacuo* to give a gum. Water and ether were added (50 ml. of each) and the mixture was stirred. A solution resulted at first and then a white precipitate separated. The suspension was filtered to give 0.9 g. of solid, m.p. 105–110°, which was not investigated further. The filtrate was separated into layers, and the ether layer was washed four times with 10% hydrochloric acid (total 100 ml.). The acidic extract was washed with ether and then treated with potassium hydroxide. The product was extracted with ether and worked up as usual to give 0.81 g. of crude XXII isomer A. It was triturated with ether–petroleum ether (b.p. 30–60°) to give 0.588 g., m.p. 126–127°.

Cleavage of XXI Isomer B to XXII Isomer B.—A solution of XXI (isomer B, m.p. 169–170°, 2.54 g. or 7.4 mmoles) in 63 ml. of ethanol and 22 ml. of butylamine was refluxed for 72 hr. under nitrogen. The pale yellow solution was evaporated to dryness *in vacuo*. Ether (100 ml.) and 10% hydrochloric acid (100 ml.) was added, and the mixture was stirred for about 1 hr. to give an almost complete solution. The layers were separated and the aqueous was extracted with ether. The acidic solution was cooled and treated with 30% potassium hydroxide. The resulting product was extracted with benzene and worked up as usual to give 1.58 g. of a pale yellow oil. It was crystallized from benzene–petroleum ether (b.p. 30–60°) to give 0.13 g. of N,N′-dibutylphthalamide melting at 115–116°[15,16] identical by infrared with the sample obtained previously. The filtrate was evaporated to dryness, the residue was dissolved in ether, and the same acid extraction procedure was followed as above, the only difference being that ethyl acetate was used to extract neutral material from the acidic layer. The product amounted to 1.04 g.

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(15) R. E. Schaub and M. J. Weiss, *J. Am. Chem. Soc.*, **80**, 4683 (1958).

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and showed no residual amide in the infrared. It was crystallized from ether–Skellysolve B to give 0.82 g. of XXII isomer B, m.p. 101–102.5°, unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} 227 mμ (ε 35,400); 274 (6950); 279 (7050); f 289 (5000). Infrared spectrum showed 3160, 3100, 3050 (NH); 1623, 1603, 1585, 1510 (C=C/NH def.) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.52; H, 8.69; N, 12.87.

Copper-Catalyzed Reactions of Benzoyl Peroxide with Norbornadiene Derivatives[1,2]

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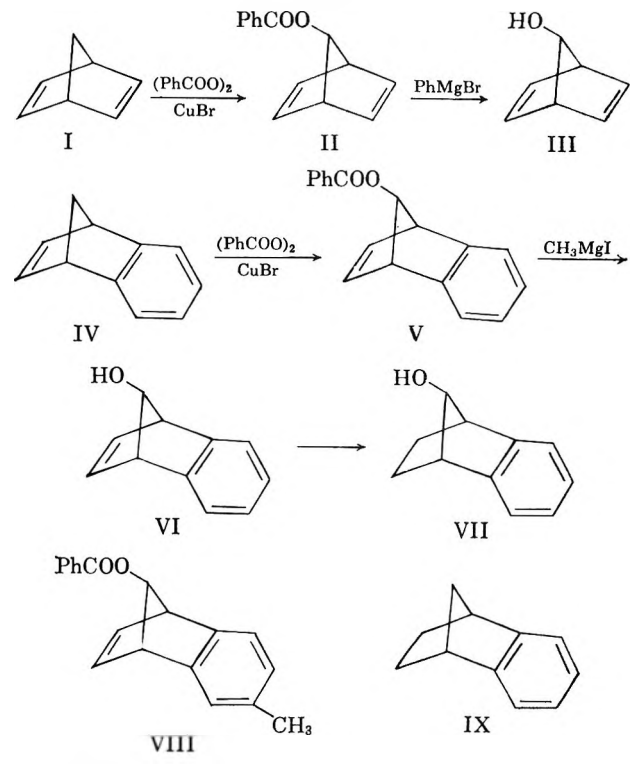
The copper-catalyzed reactions of benzoyl peroxide with norbornadiene or benzonorbornadiene derivatives have been shown to give the stereospecific 7-benzoyloxy derivatives. It has proved to be a much improved method for use in syntheses than others reported hitherto. A rational mechanism involves addition of PhCOO· to the olefinic double bond, oxidation of the adduct radical into the carbonium ion intermediate, the Wagner–Meerwein rearrangement, and proton loss to form a double bond. In addition, bis(*p*-chlorobenzoyl) peroxide has proved to give the best yield of the desired esters.

The chemistry of 7-substituted bicyclo[2.2.1]heptanes has been of considerable interest in recent years, particularly in connection with the behavior in solvolytic displacement reactions. Aside from the saturated parent compounds many unsaturated and aromatic variants have been investigated.[3] Until very recently, however, the preparations of these compounds required a long and arduous route. The formation of 7-*t*-butoxynorbornadiene by the reaction of *t*-butyl perbenzoate and norbornadiene found by Story[4] has provided a facile path to this series of compounds. However, a weak point in this reaction may be that one can not control the stereochemistry of the 7-alcohol or other derivatives which are obtained from the replacement of *t*-butyloxy group *via* 7-norbornadienyl cation.[4]

In connection with another investigation,[5] it became necessary to prepare these kinds of alcohols which had a desired stereochemistry. In a previous communication,[6] we reported that the copper-catalyzed reaction of benzoyl peroxide with norbornadiene derivatives had proved to be a much improved method for use in syntheses and also satisfactory for the above requirement. This paper deals with further improvements of our method and with detailed investigations of the reaction mechanism.

CHART I



Results and Discussion

The reaction of norbornadiene (I) with benzoyl peroxide in the presence of cuprous bromide gave a 35% yield of 7-benzoyloxynorbornadiene (II) from the peroxide as the sole substitution product. The hydrolysis of II with phenylmagnesium bromide[7] yielded 7-norbornadienol (III) almost quantitatively, whose structure was identified by independent synthesis.[4] In order to elucidate the stereochemistry of this reaction, the same procedure was applied for benzonorbornadiene (IV), which is readily obtainable by the cycloaddition of benzyne with cyclopentadiene.[8] *anti*-7-Benzoyloxybenzonorbornadiene (V) was obtained in about 40% yield. The structure of V was established by hydrolysis with methylmagnesium iodide to *anti*-7-benzonorbornadienol (VI), then catalytic reduction to *anti*-7-benzonorborneol (VII), which was confirmed by independent synthesis.[3b] The *syn*-benzoyloxy-substituted product has not been obtained under a variety of reaction conditions. Applications of the above reaction to some benzonorbornadienes having substituents on the benzene ring were also successful,

(1) Part IV of a series on bicyclic systems; Part III, *Bull. Chem. Soc. Japan*, **37**, 40 (1964).

(2) Presented, in part, at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1963.

(3) (a) S. Winstein and C. Ordronneau, *J. Am. Chem. Soc.*, **82**, 2084 (1960), and references therein; (b) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960); (c) E. E. van Tamelen and C. I. Judd, *ibid.*, **80**, 6305 (1958).

(4) P. R. Story, *ibid.*, **82**, 2085 (1960); P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

(5) H. Tanida, *J. Am. Chem. Soc.*, **85**, 1703 (1963).

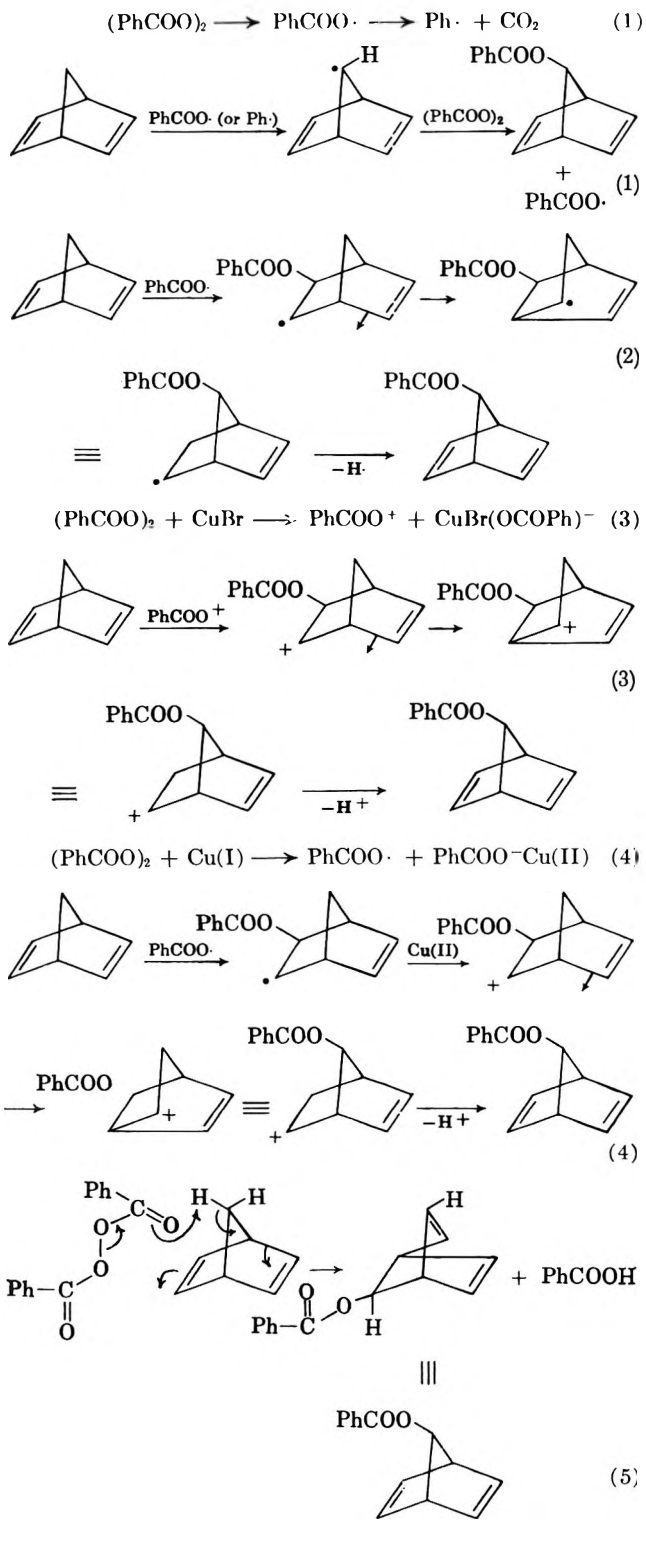
(6) H. Tanida and T. Tsuji, *Chem. Ind.* (London), 211 (1963).

(7) Phenylmagnesium bromide was better than methylmagnesium iodide previously used (refer to ref. 6), because III was more easily distilled, leaving trityl alcohol.

(8) G. Wittig and E. Knauss, *Ber.*, **91**, 895 (1958).

giving approximately same yields.[5] Even in the case of 4′-methylbenzonorbornadiene,[3] the product isolated was *anti*-7-benzoyloxy-4′-methylbenzonorbornadiene (VIII) without any attack of the benzoxy radical on the 4′-methyl group which was located in the benzyl position. None of the desired product was obtained in the case of benzonorbornene (IX), which suggested that the presence of an olefinic double bond was necessary for this reaction. (See Chart I.)

CHART II



On the basis of these results, we considered that the mechanism of this reaction would be one of the following five alternatives, which may be pictured and illustrated as shown in Chart II.

(1) A hydrogen abstraction from the homoconjugated bridge methylene (C-7) in the initial step of the reaction by the benzoyloxy or phenyl radical, which was formed by the decomposition of benzoyl peroxide. If this mechanism operates, the Wagner–Meerwein rearrangement will not occur.

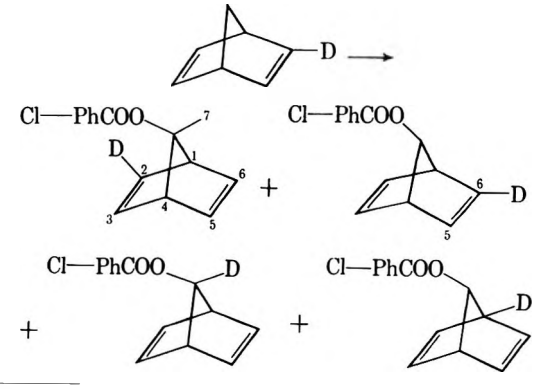
(2) An all-radical mechanism, which would involve the addition of a benzoyloxy radical to the double bond, followed by a radical type of Wagner–Meerwein rearrangement, and then elimination of a hydrogen radical.

(3) An all-ionic mechanism, which would be initiated by the addition of a benzoyloxy cation formed by a copper salt-catalyzed ionic decomposition of benzoyl peroxide,[10] followed by the Wagner–Meerwein rearrangement, and proton loss to form a double bond.

(4) A mechanism, which, initially radical and becoming ionic in mid-course, starts as the addition of a benzoyloxy radical like mechanism 2, but involves the change of the resulting radical into a carbonium ion intermediate by the oxidative action of copper ions, followed by the Wagner–Meerwein rearrangement, and finally proton loss to form a double bond. It is substantially a modification of the general olefin–benzoyl peroxide mechanism proposed by Kochi.[11]

(5) A concerted cyclic mechanism, which might be attractive, but does not appear to assign any function to the cuprous bromide. Perhaps cuprous bromide may coordinate loosely with the olefinic bond and with the peroxide and thus may serve to bring the reagents together.

Deuterium-Labeling Experiment.—Occurrence of a rearrangement in the reaction path was evidenced by deuterium-labeling experiments carried out by essentially the same methods as Story used in the case of the *t*-butyl perbenzoate reaction.[12] 2-Deuterionorbornadiene was prepared by the method of Streitweiser.[13] Analysis by n.m.r. spectra showed that 25.0% of the olefinic hydrogens were replaced by deuterium. The deuterated norbornadiene was treated with bis(*p*-chlorobenzoyl) peroxide, which gave the product in the best yield as mentioned below, in the presence of



(9) For the preparation of this compound refer to H. Tanida, R. Muneyuki, and T. Tsuji, *Bull. Chem. Soc. Japan*, **37**, 40 (1964).

(10) Ionic mechanisms involving peroxide are well-known, for example, in the 9-decalyl perbenzoate solvolysis (E. S. Gould, "Mechanism and Structure in Organic Chemistry" Henry Holt and Co., New York, N. Y., 1959, p. 633).

(11) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 1572 (1962).

(12) P. R. Story, *Tetrahedron Letters* **No. 9**, 401 (1962).

(13) A. Streitweiser and R. A. Caldwell, *J. Org. Chem.*, **27**, 3360 (1962).

cuprous bromide to yield deuterated 7-*p*-chlorobenzoyloxynorbornadiene which was examined by n.m.r. Careful investigation of the peak areas and comparison with an authentic undeuterated sample showed deuterium at all skeletal positions in an approximately statistical distribution as shown in Table I. These data and the formation of the stereospecific product from benzonorbornadiene (IV) will rule out mechanism 1.

TABLE I

DISTRIBUTION OF THE DEUTERIUM IN 7-*p*-CHLOROBENZOYLOXYNORBORNADIENE PREPARED FROM 2-DEUTERIONORBORNADIENE

Position of hydrogen	Distribution of D	Calcd. value[a]
C-2 and C-3	0.32	0.25
C-5 and C-6	0.20	0.25
C-7	0.23	0.25
C-1 and C-4	0.32	0.25

[a] Calculated on the assumption that the Wagner–Meerwein rearrangement would occur.

order to investigate whether the decomposition of benzoyl peroxide is heterolytic or homolytic, some experiments were carried out using *p*-monosubstituted benzoyl peroxide (X). As shown in Table II, the product ratio of *p*-substituted and unsubstituted benzoyloxynorbornadienes and of *p*-substituted and unsubstituted

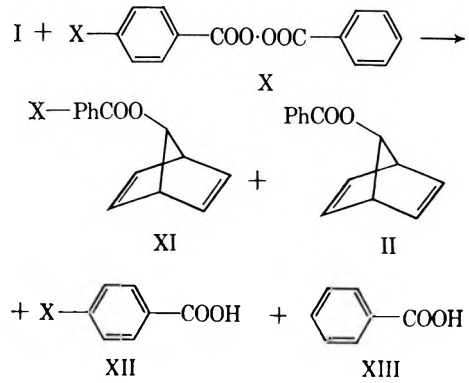


TABLE II

SUBSTITUENT EFFECTS

Substituent[a]	Reaction time required, hr.	Products, %[b] XI	II	XII	XIII	Ratio XI:II	XII:XIII
CN	11.5	12.8	13.0	21.3	23.7	0.98	0.90
Cl	9	26.5	24.6	24.3	31.0	1.08	0.78
H	9		25.4		62.8		
MeO	8	17.3	19.9	34.1	30.9	0.87	1.10

[a] In the case of *p*-NO_2, a very low yield was obtained with a large amount of tarry products. [b] Calculated from the peroxide used.

TABLE III

EFFECTS OF COPPER ION AND SOLVENTS

(with 7.11 g. of IV and 3.03 g. of benzoyl peroxide)

Runs	CuBr, mg.	Solvents	Temp., °C.	Time, hr.	Ph-COOH, %	V, %[a]	High mol. products, g.
1	0	Benzene	Reflux	25	22.3	0	
2	5	Benzene	Reflux	6.33	78.2	29.7	2.75
3	10	Benzene	Reflux	5.33	87.3	37.7	1.89
4	25	Benzene	Reflux	5.66	92.4	48.0	1.78
5	25	Chlorobenzene	100°	4.0	84.6	44.8	2.20
6	40	Chlorobenzene	110°	4.0	84.0	47.9	1.85
7	25	CH_3CN	Reflux	11.0	62.8	*b*	2.61
8	25	CH_3COOH (1) Benzene (3)	Reflux	5.0		*c*	2.83

[a] Yields of crude V from the peroxide. [b] Vapor phase chromatography showed a mixture of two products. [c] Besides the 7-benzoyloxy derivative, other kinds of compounds having carbonyl were found by infrared.

The possibility that all paths are radical would be rejected by the following considerations. Berson and his co-workers[14] reported that the thermal decomposition of 2-azobornane at temperatures above 250° gave a mixture of hydrocarbons, among which is 2,3,3-trimethylnorbornane, resulting from a free-radical Wagner–Meerwein rearrangement. However, the yield of the rearranged product in his experiments was lower than 2%, under a variety of reaction conditions, and his conditions were very drastic. To the best of our knowledge, there is no other example of a free-radical Wagner–Meerwein rearrangement reported in the literature. Thus we can reasonably assume that such a high yield of the substitution product as ours would not be obtained under milder conditions from a reaction involving a radical rearrangement.

Reactions with Substituted Benzoyl Peroxides.—In benzoic acid (XI : II and XII : XIII in Table II) was approximately unity within experimental errors, although their total yields were dependent upon the kind of benzoyl peroxides used. The heterolytic decomposition of benzoyl peroxide would not be preferred owing to the lack of substituent effects observed here. Thus mechanism 3 would be eliminated. In addition, the variation of total yields (XI + II) of the esters suggests the usefulness of *p*-substituted benzoyl peroxides in this reaction.

Effects of the amounts of cuprous bromide added and of the solvents were investigated in order to decide whether or not a concerted cyclic mechanism operated. As clearly shown in Table III, increasing the amount of the added copper salt increased the yield. None of the desired product was obtained in the absence of copper salt. Employment of such a nucleophilic solvent as acetic acid or acetonitrile gave some by-products, indicating solvolysis participation in a kind of ionic

(14) J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Am. Chem. Soc.*, **84**, 3337 (1962).

intermediate in this reaction. The important role of copper catalyst would not be explained by the idea of a cyclic mechanism.

Thus, all our observations, indicating the homolytic cleavage of benzoyl peroxide, the radical addition of the olefinic double bond, the significant role of copper ion, and the evidence of a carbonium ion Wagner–Meerwein rearrangement, are most satisfactorily interpreted by mechanism 4.

Finally, we wish to state that the use of bis(*p*-chlorobenzoyl) peroxide gives the best yield of the desired benzoyl esters, as expected from the above-described experiments of substituted benzoyl peroxides.

Experimental[15]

7-Benzoyloxynorbornadiene (II).—To a stirred mixture of 101 g. (1.10 moles) of norbornadiene (I) and 1.6 g. of freshly prepared cuprous bromide in 500 ml. of benzene, there was added, in a nitrogen atmosphere, a solution of 203 g. (0.84 mole) of benzoyl peroxide in 600 ml. of benzene over a period of 2 hr. at 40°. After the addition was completed, the reaction mixture was heated gradually to boiling and then refluxed for 3 days. Qualitative analysis by potassium iodide–starch paper indicated that no benzoyl peroxide remained after this period. During the course of the reaction, the color of the solution changed gradually from blue to green. After cooling to room temperature, the reaction mixture was extracted with 10% aqueous sodium carbonate to remove 70 g. of benzoic acid, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent left 185 g. of an oily residue. Vacuum distillation of this residue gave 78.0 g. of crude II, b.p. 100–102° (0.6 mm.), which was further purified by column chromatography on 1 kg. of Merck standard alumina using hexane to give 64.5 g. (36.2% from the peroxide) of pure II as colorless prisms, m.p. 53–54°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.22; H, 5.78.

7-Norbornadienol (III).—To a solution of phenylmagnesium bromide in ether, which was prepared from 76.0 g. of bromobenzene and 11.7 g. of magnesium turnings in 300 ml. of anhydrous ether, there was added slowly a solution of 41.0 g. of the benzoyl ester (II) in 200 ml. of anhydrous ether in a nitrogen atmosphere. After refluxing for 2 hr., the mixture was poured into a saturated aqueous solution of ammonium chloride. The ether layer which separated was dried over anhydrous sodium sulfate. After removal of the solvent, the triphenylcarbinol was filtered as it precipitated by an addition of *n*-pentane. The filtrate was concentrated, and the residue was distilled to give 17.0 g. (83.2%) of 7-norbornadienol (III), b.p. 78–80° (56 mm.), $n^{26}D$ 1.5097, which was identified with an authentic sample.[4]

anti-**7-Benzoyloxybenzonorbornadiene** (**V**).—Essentially the same procedure as above was applied for the reaction of 7.11 g. (0.05 mole) of benzonorbornadiene (IV) with 3.03 g. (0.013 mole) of benzoyl peroxide and 25 mg. of cuprous bromide in 50 ml. of benzene. The reaction required 6 hr., and the color of the solution was blue. After removal of 1.41 g. (92.4%) of benzoic acid, 4.46 g. (62.8%) of IV was recovered by distillation under reduced pressure leaving 3.11 g. of an oily residue. High vacuum distillation of the residue gave 1.57 g. (48.0% from the peroxide) of crude V, b.p. 150° (0.25 mm.), and left 1.78 g. of viscous high molecular products. Crude V was purified by recrystallization from hexane to yield 1.10 g. (33.6%) of pure V as colorless needles with m.p. 95–96°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.56; H, 5.50.

anti-**7-Benzonorbornadienol** (**VI**).—A solution of 262 mg. (0.001 mole) of the benzoyl ester (V) in 10 ml. of anhydrous ether was added dropwise to an ether solution of methylmagnesium iodide which was prepared from 852 mg. of methyl iodide and 146 mg. of magnesium turnings in 20 ml. of anhydrous ether. After refluxing for 2.5 hr., the mixture was poured into a saturated aqueous solution of ammonium chloride, washed with 10% aqueous sodium thiosulfate, and dried over anhydrous sodium sulfate. After removal of phenyldimethylcarbinol by vacuum distillation at about 110–120° (5 mm.), the residue (200 mg.) was recrystallized from hexane to yield 120 mg. (76.3%) of VI as colorless prisms with m.p. 105–106°, lit.[3b] m.p. 106.3–108.2°.

anti-**7-Benzonorborneol** (**VII**).—A catalytic reduction of the dienol (VI) with palladium on charcoal yielded colorless prisms, m.p. 104–105°, lit.[3b] m.p. 104.1–105.7°, which were recrystallized from hexane and identified with an authentic sample.[3b]

7-*p*-Chlorobenzoyloxynorbornadiene (**XIV**).—With 35.9 g. (0.39 mole) of norbornadiene (I), 41.3 g. (0.13 mole) of bis(*p*-chlorobenzoyl) peroxide (97.5% of purity), and 300 mg. of cuprous bromide in 650 ml. of benzene, the above procedure was carried out. A color change in the reaction mixture was from green to blue. After removal of 9.8 g. (48.1%) of *p*-chlorobenzoic acid and the solvent, 46.7 g. of the oily residue was chromatographed on 200 g. of Merck standard alumina using hexane. The hexane eluate (29 g.) was vacuum distilled to give 14.4 g. (44.1% from the peroxide) of XIV at b.p. 108° (0.1 mm.), which was immediately crystallized forming colorless needles with m.p. 82–83°.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.18; H, 4.46. Found: C, 68.39; H, 4.76.

anti-**7-*p*-Chlorobenzoyloxybenzonorbornadiene** (**XV**).—With 100 g. (0.703 mole) of benzonorbornadiene (IV), 75 g. (0.234 mole) of bis(*p*-chlorobenzoyl) peroxide, and 745 mg. of cuprous bromide in 1600 ml. of benzene, the above procedure was carried out. The reaction mixture was washed with 10% aqueous sodium carbonate to remove *p*-chlorobenzoic acid. After removal of the solvent, *n*-hexane was added to the residue to precipitate 16.3 g. of crystals as the first crop of crude XV, m.p. 115–127°. After removal of the solvent, the mother liquor was chromatographed on alumina using 15% benzene–hexane to yield 10.7 g. of crystals. Both sets of crystals collected (39.1% yield) were recrystallized from hexane to give 24.7 g. of pure XV as colorless needles with m.p. 126–127°. The yield of the pure crystals was 35.8% from the peroxide.

Anal. Calcd. for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.15. Found: C, 73.13; H, 4.52.

Reaction in the Absence of Cuprous Bromide.—To a stirred solution of 13.8 g. (0.15 mole) of benzonorbornadiene (IV) in 100 ml. of benzene was added 12.1 g. (0.05 mole) of benzoyl peroxide in 100 ml. of benzene during 2.5 hr. under reflux. The mixture was refluxed with stirring for an additional 25 hr. until the peroxide disappeared. After removal of 1.36 g. (22.3%) of benzoic acid, nonacidic products were distilled to yield 790 mg. of an oil at b.p. 70–75° (0.22 mm.), which was chromatographed on 30 g. of alumina using hexane. None of the desired 7-benzoyloxynorbornadiene was obtained.

Reactions with *p*-Monosubstituted Benzoyl Peroxide.—*p*-Methoxy-, *p*-chloro-, *p*-cyano-, and *p*-nitrobenzoyl peroxides were prepared from the corresponding *p*-substituted benzoyl chloride, perbenzoic acid, and potassium hydroxide, according to the method of Wieland and Rasuwajew.[16]

The standard procedure was carried out with 12.8 g. (0.139 mole) of norbornadiene (I), *p*-monosubstituted benzoyl peroxide (0.035 mole), and 75 mg. of cuprous bromide. The work-up procedure yielded the acidic and nonacidic products. The former were methylated by absolute methanol containing 5% dry hydrogen chloride and were separated into methyl benzoate and methyl *p*-substituted benzoate by distillation or vapor phase chromatography. The latter nonacidic products were chromatographed on 200 g. of alumina using 10% benzene–hexane to remove the high molecular products. The eluate was distilled again. The distillate obtained was chromatographed on alumina using hexane, 10% benzene–hexane, and finally 30% benzene–hexane. By careful separation, biphenyl and 7-benzoyloxynorbornadiene were obtained.

7-*p*-Methoxybenzoyloxynorbornadiene had m.p. 82–83°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.52; H, 5.81.

7-*p*-Cyanobenzoyloxynorbornadiene had m.p. 120°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 75.97; H, 4.74; N, 5.79.

Acknowledgment.—We wish to thank Prof. J. F. Bunnett and Prof. H. Hart for helpful discussions and Prof. E. Ochiai and Dr. K. Takeda for their encouragement. Our thanks go also to Dr. S. Sumimoto for the preparation of a deuterio compound.

(15) All melting points and boiling points are uncorrected.

(16) H. Wieland and G. Rasuwajew, *Ann.*, **480**, 168 (1930).

Metalation of N-Methylbenzamide with Excess *n*-Butyllithium. Condensations with Electrophilic Compounds to Form *ortho* Derivatives. Cyclizations[1]

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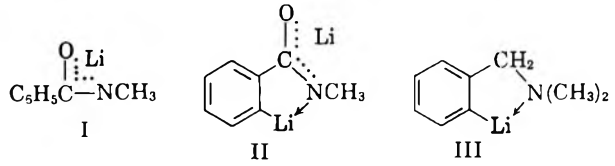
Received October 21, 1963

In contrast to N,N-dimethylbenzamide, N-methylbenzamide underwent *ortho* metalation as well as N-metalation with excess *n*-butyllithium to form dilithioamide II, which was condensed with benzophenone, acetophenone, *p*-chlorobenzophenone, and benzonitrile to form the corresponding *ortho*-substituted amides. The carbinol amides from the first two ketones were cyclized to phthalides. II was condensed with fluorenone, benzaldehyde, cyclohexanone, and cyclohexene oxide, and the resulting intermediate carbinol amides were cyclized to afford the corresponding lactones. These reactions furnish useful methods for the synthesis of such compounds. Attempts to effect *ortho* metalation of benzamide were unsuccessful.

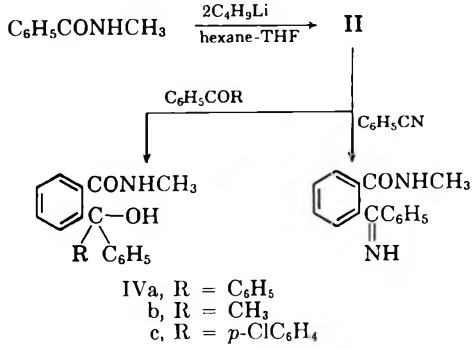
It is well-known that N,N-dialkylamides undergo addition reactions with Grignard[3] and lithium[4] reagents leading to the formation of ketones. We have observed such an addition reaction of N,N-dimethylbenzamide with *n*-butyllithium in tetrahydrofuran–hexane to form valerophenone (70%).

It seemed possible, however, that N-methylbenzamide, which would undergo an initial N-metalation with *n*-butyllithium to form monolithioamide I, might exhibit *ortho* metalation with excess of this reagent to give dilithioamide II, since the carbonyl group in I should be deactivated towards an addition reaction. This was realized. The somewhat related *ortho* metalation of benzyldimtheylamine with *n*-butyllithium in hexane–ether to form lithioamine III has been achieved recently.[5]



The formation of *o*,N-dilithioamide II was established by condensations with electrophilic compounds. Thus, II was condensed with benzophenone, acetophenone, *p*-chlorobenzophenone, and benzonitrile to form IVa–c and V in yields of 81, 43, 51, and 53%, respectively (Scheme A).

SCHEME A



IVa, R = C_6H_5
b, R = CH_3
c, R = *p*-ClC_6H_4

The metalation of N-methylbenzamide was generally effected with 2.5 molecular equivalents of *n*-butyllithium in refluxing hexane–tetrahydrofuran (15 min.). The condensations were usually carried out at the reflux temperature of the solvent mixture, but that with acetophenone was realized in much better yield at 0° (see Experimental). The general conditions were chosen on the basis of preliminary experiments with benzophenone (Table I).

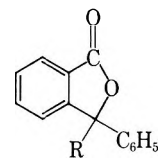
TABLE I

METALATION OF N-METHYLBENZAMIDE (A) WITH *n*-BUTYLLITHIUM (B) IN MIXTURE OF HEXANE AND ANOTHER SOLVENT. CONDENSATION WITH BENZOPHENONE (C)

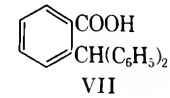
Mole ratio, B:A[a]	Other solvent[b]	Metalation time, hr.[c]	Mole ratio, C:A[d]	Condensation time, hr.[c]	IVa, yield %
2:1	Ether	5	2.2:1	3	45
2:1	Monoglyme	0.25	2.2:1	3	0
2:1	THF[e]	4[f]	2.2:1	3	42
2:1	THF	1	2.2:1	3	33
2:1	THF	0.25	2.2:1	3	57
3:1	THF	0.25	3.2:1	3	77
3:1	THF	0.25	3.2:1	0.5	81
2.5:1	THF	0.25	1.6:1	0.5	81

[a] *n*-Butyllithium (1.5 *M*) in hexane and 0.05 mole of A were used. [b] Volume equal to that of hexane. [c] At refluxing temperature of the solvent mixture. [d] Dissolved in volume of ether equal to that of hexane. [e] Tetrahydrofuran. [f] At room temperature.

The structures of the carbinol amides IVa–c and of the imine amide V were supported by analyses and by their infrared spectra, which showed peaks at 3350–3280 cm.$^{-1}$ for a secondary amide,[6] and at 1650–1620 cm.$^{-1}$ for an amide carbonyl group.[7] Structures IVa and b were confirmed by cyclization in refluxing toluene or xylene to evolve methylamine and give the known phthalides VIa and b. Moreover, VIa was



VIa R = C_6H_5
b R = C_6H_5



VII

(1) Supported in part by a National Institutes of Health grant.

(2) National Science Foundation Science Faculty Fellow, on leave from Thiel College.

(3) See E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1954, p. 582.

(4) An example of the use of a lithium reagent for ketone synthesis has involved metalation of 2-phenyl-5-methylpyrrocoline with *n*-butyllithium, followed by condensation with N,N-dimethylbenzamide: V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.*, **80**, 2020 (1958).

(5) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

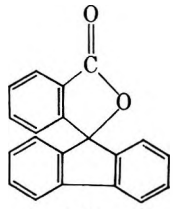
(6) See L. H. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 207.

(7) Ref. 6, p. 209.

hydrolyzed and reduced to form the known acid VII. The structure of imine amide V was confirmed by hydrolysis to *o*-benzoylbenzoic acid.

It should be pointed out that carbinol amides IVa–c cyclize so readily that methylamine was evolved on attempted recrystallization from refluxing ethanol. However, they were recrystallized satisfactorily at lower temperatures (see Experimental). Baeyer[8] reported that the carbinol acid corresponding to IVa could not be isolated because of its tendency to cyclize to the phthalide.

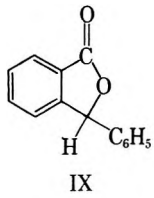
Likewise dilithioamide II was condensed with fluorenone, but the resulting carbinol amide underwent cyclization even at room temperature to form spirophthalide VIII in 58% yield (based on I).



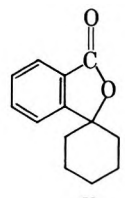
VIII

Structure VIII was supported by analysis, by agreement of its melting point with the reported value, and by its infrared spectrum, which showed a peak at 1760 cm.$^{-1}$ for the five-membered lactone,[9] but no absorption between 3000–2500 cm.$^{-1}$, indicating the absence of aliphatic hydrogen.[10]

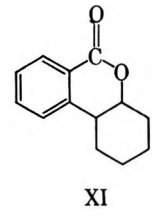
Similarly, dilithioamide II was condensed with benzaldehyde, cyclohexanone, and cyclohexene oxide to form presumably the corresponding carbinol amides, which were isolated as their lactones, IX, X, and XI, in yields of 42, 27, and 11%, respectively. The intermediate carbinol amides were not isolated since, in contrast to carbinol amides IVa–c, they did not precipitate on decomposing the reaction mixtures with water. Their isolation was not attempted because of their tendency to cyclize. As in the condensation with acetophenone, those with benzaldehyde and cyclohexanone were best effected at relatively low temperatures. Apparently the lower temperature minimized ionization of α-hydrogen of the ketones and hydride ion reduction of the aldehyde (see Experimental).



IX



X



XI

The melting point of phthalide IX agreed with the reported value. Structures X and XI, which are isomeric, were supported by their analyses and by their infrared spectra, which in X showed a peak at 1760 cm.$^{-1}$ for the five-membered lactone,[9] and in XI exhibited absorption at 1720 cm.$^{-1}$ for the six-membered lactone.[11]

(8) A. Baeyer, *Ann.*, **202**, 36 (1880).
(9) Ref. 6, p. 186.
(10) Ref. 6, p. 14.
(11) Ref. 6, p. 185.

The condensations of N-methylbenzamide through metalation furnishes a convenient method for the synthesis of such *ortho*-substituted derivatives as IVa–c and V, all of which appear to be new. This direct method generally should be preferable to the possible indirect route involving the ring opening of an appropriate phthalide with methylamine, a type of reaction employed previously with phthalide itself.[12]

The present reactions appear useful for the synthesis of certain phthalides such as VIa, and especially the spirophthalides VIII and X and the isocoumarin derivative XI. This route seems preferable to that employed earlier for VIII involving oxidation of 9-hydroxy-9-(*o*-tolyl)fluorene.[13] However, other methods are more convenient for phthalides VIb[14] and IX.[15]

In contrast to N-methylbenzamide, benzamide failed to undergo *ortho* metalation with excess *n*-butyllithium under similar conditions. Possibly the N-lithiobenzamide formed initially was too insoluble in the solvents employed. However, precipitation of N-lithio-N-methylbenzamide (I) did not prevent *ortho* metalation. Incidentally, benzamide is known to react with excess Grignard reagents to form ketones.[16]

Experimental[17]

Metalation of N-Methylbenzamide with *n*-Butyllithium to Form Dilithioamide II.—To a solution of 6.76 g. (0.05 mole) of N-methylbenzamide[18] in 80 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) in a dry flask under nitrogen was added, during 10 min., 80 ml. (0.125 mole) of 1.56 *M* *n*-butyllithium in hexane. During the addition the mixture refluxed and deposited a white precipitate which turned orange as the last of the *n*-butyllithium was added. The resultant mixture was then refluxed for 15 min. to give a dark red solution containing a tacky red precipitate. Heating was stopped and the mixture, containing dilithioamide II, was then employed as described below.

Condensation of II with Certain Ketones and Benzonitrile (Scheme A).—These reactions were effected under nitrogen as described below. The results are summarized in Table II.

(A) **With Benzophenone.**—To the stirred mixture containing II was added, during 8 min., a solution of 14.6 (0.08 mole) of benzophenone in 80 ml. of dry ether. The resulting mixture was refluxed for 0.5 hr. to give a clear red solution. This solution was cooled in an ice bath, and 100 ml. of water was added. The resulting precipitate was collected on a funnel and rinsed with water and ether. After drying *in vacuo*, a portion was dissolved in tetrahydrofuran at room temperature and cooled in the refrigerator to give an analytical sample of IVa.

Presumably because of its ease of cyclization, the melting point of IVa was not necessarily indicative of its purity. Thus, in certain experiments, product IVa obtained after drying *in vacuo* but not recrystallized exhibited a melting point from 133–136° dec. to 161–164° dec., yet the infrared spectra of these materials were essentially identical with that of the analytical sample. Moreover, the crude product was converted in 90% yield to pure phthalide VIa (see below). Similar observations were made also with IVb and IVc.

(B) **With Acetophenone.**—The mixture containing II was cooled in an ice bath for 5 min., and a solution of 9.6 g. (0.08 mole) of acetophenone in 80 ml. of ether was added during 20 min. The ice bath was removed, and the mixture was stirred for 30 min. and then poured into a mixture of 70 ml. of 2 *M* hydro-

(12) A. Thielacker and H. Kolenda, *Ann.*, **584**, 87 (1953).
(13) H. D. Tubbs and S. H. Tucker, *J. Chem. Soc.*, 2939 (1951).
(14) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3364 (1962).
(15) F. Ullman, *Ann.*, **291**, 23 (1896).
(16) S. S. Jenkins, *J. Am. Chem. Soc.*, **55**, 703 (1933).
(17) Melting points were taken on a Fisher-Johns melting point stage which had been calibrated with standard samples. Analyses were by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 237 Infracord in potassium bromide pellets.
(18) P. van Romburgh, *Rec. trav. chim.*, **4**, 388 (1885).

TABLE II

CONDENSATIONS OF DILITHIOAMIDE II WITH KETONES AND NITRILES

Ketone or nitrile	Product	Yield %	M.p., °C.[a]	Empirical formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Benzophenone	α,α-Diphenyl-α-hydroxy-N-methyl-*o*-toluamide (IVa)	81	162.5–163	$C_{21}H_{19}NO_2$	79.47	6.03	4.41	79.27	6.03	4.60
Acetophenone	*o*-(1-Hydroxy-1-phenylethyl)-N-methylbenzamide (IVb)	43[b]	157–159	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.14	6.69	5.35
p-Chlorobenzophenane	α-(4-Chlorophenyl)-α-hydroxy-α-phenyl-N-methyl-*o*-toluamide (IVc)	51	177–177.5	$C_{21}H_{18}ClNO_2$[c]	71.69	5.16	3.98	71.75	5.09	3.74
Benzonitrile	*o*-Benzimidoyl-N-methylbenzamide (V)	53	183–185[d]	$C_{15}H_{14}N_2O$	75.60	5.92	11.76	75.45	6.01	11.67

[a] Of the analytical sample. Melted with decomposition unless otherwise noted. [b] Condensation effected at 0° (see Experimental). [c] *Anal.* Calcd.: Cl, 10.08. Found: Cl, 9.92. [d] Melted without decomposition.

chloric acid and 50 g. of ice. The layers were separated and the organic layer (which contained a suspension of some of the product) was washed with 60 ml. of water and combined with an ether extract of the aqueous layers. After washing with saturated sodium chloride solution, the organic layer was filtered to remove the first crop of IVb. The solvents were removed from the filtrate under reduced pressure (rotary evaporator). The residue was triturated with 25 ml. of ether, and the mixture cooled and filtered to give more IVb. A sample of the combined product was recrystallized from hot methanol with rapid cooling to afford the analytical sample of IVb.

When the condensation of II with acetophenone was effected at the reflux temperature (0.5 hr.), there was obtained much polymeric material along with a 46% recovery of N-methylbenzamide and a 53% recovery of acetophenone.

(C) **With *p*-Chlorobenzophenone.**—This condensation was effected as described under A employing 17.3 g. (0.08 mole) of *p*-chlorobenzophenone. After filtering the product IVc that had precipitated on adding water, a second crop of IVc was obtained by the evaporation of solvents and addition of ether to the residue as described under B. The product was recrystallized as described under A.

(D) **With Benzonitrile.**—This condensation was effected as described under A employing 17.0 g. (0.165 mole) of benzonitrile, except that the reaction mixture was decomposed by pouring it into a solution of 8.6 g. (0.16 mole) of ammonium chloride in 120 ml. of ice–water. The resultant mixture was cooled and scratched to induce crystallization. The solid was collected on a funnel and recrystallized from benzene to give V.

Cyclization of IVa and b to Form Phthalides VIa and b. (A) **Cyclization of IVa.**—A mixture of 12.6 g. (0.04 mole) of crude IVa, m.p. 144–148° dec., and 75 ml. of toluene was heated at reflux for 30 min. A vigorous evolution of methylamine took place and all material eventually dissolved. The toluene was evaporated under reduced pressure and the residue was recrystallized from hexane–ethanol to give 10.2 g. (90%) of 3,3-diphenylphthalide (VIa), m.p. 116–117° (lit.[14] m.p. 116–116.5°). The melting point was not depressed on admixture with an authentic sample.[14] The infrared spectra were identical.

(B) **Cyclization of IVb.**—Similarly, 1.1 g. (0.0043 mole) of crude IVb, m.p. 151–152° dec., was refluxed for 30 min. in 25 ml. of xylene. The xylene was removed under reduced pressure and the residue was recrystallized from hexane–ethanol to give 0.7 g. (73%) of 3-methyl-3-phenylphthalide (VIb), m.p. 76.5–77° (lit.[19] m.p. 76.8–78°).

Hydrolysis and Reduction of VIa to VII.—This was effected essentially as described previously[8] by refluxing a mixture of 3.5 g. (0.012 mole) of VIa and a solution of 13.4 g. (0.24 mole) of potassium hydroxide in 30 ml. of water and 50 ml. of ethanol for 7 hr. The ethanol was evaporated from the resulting solution and 1.6 g. (0.072 mole) of zinc dust was added. After refluxing for 17 hr. the mixture was cooled, washed with ether, and the aqueous layer acidified to yield 1.3 g. (37%) of 2-benzhydrylbenzoic acid, m.p. 155–159°, and 159–160.5° after recrystallization from 95% ethanol (lit. m.p. 155–157°,[8] 158–162°[20]).

Condensation of II with Fluorenone to Form Phthalide VIII.—A solution of 14.4 g. (0.08 mole) of fluorenone in 80 ml. of ether was added during 10 min. to the mixture containing II. After stirring for 15 min. without heating, the reaction mixture was cooled in an ice bath and then poured into 70 ml. of 2 *M* hydrochloric acid and 30 g. of ice. The layers were separated and the organic layer was washed with water and combined with an ether extract of the aqueous layers. The organic layer was washed with saturated sodium chloride solution, and the solvents were then evaporated under reduced pressure at room temperature to leave a semisolid residue. This was triturated with 35 ml. of methanol, then cooled, and filtered to give 8.3 g. (58%) of spiro-[fluorene-9,1′-phthalan]-3′-one (VIII), m.p. 222.5–224°. Recrystallization from methanol–benzene gave VIII, m.p. 224–224.5° (lit. m.p. 226°,[13] 219–220°[21]).

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 84.15; H, 4.11. Found: C, 84.49; H, 4.25.

Partial evaporation of the first filtrate above yielded 4.3 g. of recovered fluorenone, m.p. 80–82.5°.

When the condensation of II with fluorenone was effected in the usual manner (refluxed 0.5 hr.), the reaction mixture darkened and the yield of VIII was slightly lower (49%).

Condensation of II with Other Electrophilic Compounds to Form Lactones. (A) **With Benzaldehyde.**—The mixture containing II was cooled in an ice bath and a solution of 8.4 g. (0.08 mole) of benzaldehyde in 80 ml. of ether was added during 30 min. The mixture was stirred for 20 min., then for 45 min. with the cooling bath removed, and poured into 80 ml. of 2 *M* hydrochloric acid and 40 g. of ice. The layers were separated and the organic layer was washed with water and combined with an ether extract of the aqueous layers. After washing with saturated sodium chloride solution and drying over sodium sulfate, the solvents were evaporated and the residue was distilled *in vacuo*. There was obtained 1.6 g. (19%) of benzyl alcohol, b.p. 82–86° (10 mm.) (identified by v.p.c., enhancement technique), 2.0 g. (30%) of recovered N-methylbenzamide, b.p. 114–118° (0.3 mm.) (m.p. 76–79°, undepressed on mixture with an authentic sample), and 5.1 g. (49%) of 3-phenylphthalide (IX), b.p. 158–164° (0.3 mm.). Recrystallization of this product from hexane–ethanol gave 4.3 g. (42%) of IX, m.p. 114.5–116.5° (lit.[15] m.p. 115°). The infrared spectrum showed a strong peak at 1750 cm.$^{-1}$ indicative of a five-membered lactone.

When the above condensation was effected under the conditions employed with benzophenone (0.5 hr. at reflux), there was obtained only a 26% yield of IX along with a 35% yield of benzyl alcohol.

(B) **With Cyclohexanone.**—The mixture containing II prepared from 8.44 g. (0.0625 mole) of N-methylbenzamide was cooled in a Dry Ice–acetone bath (rapid stream of dry nitrogen) while a solution of 9.8 g. (0.10 mole) of cyclohexanone in 100 ml. of ether was added during 10 min. The mixture was stirred 35 min. at −80°, then 30 min. with the bath removed. After pouring into 90 ml. of 2 *M* hydrochloric acid and 50 g. of ice, the layers were separated and the organic layer was washed with water and combined with an ether extract of the aqueous layers. The solvents were evaporated and a solution of 35 g. (0.625 mole)

(19) M. S. Newman, *J. Org. Chem.*, **27**, 323 (1962).

(20) A. Drory, *Ber.*, **24**, 2563 (1891).

(21) C. F. Koelsch, *J. Am. Chem. Soc.*, **55**, 3394 (1933).

of potassium hydroxide in 125 ml. of water and 95 ml. of 95% ethanol was added to the residue. The resulting solution was refluxed for 10 hr., and the ethanol was evaporated. The cooled mixture was washed with ether and combined with a 3 *M* sodium hydroxide extract of the ether washing. The aqueous layer was acidified with concentrated hydrochloric acid without cooling. After coming to room temperature, the resulting mixture was taken up in ether. The ether solution was extracted with several portions of saturated sodium bicarbonate solution and dried over sodium sulfate. Removal of the solvent left 5.6 g. of solid residue which was recrystallized from 40 ml. of hexane and a little ethanol. There was obtained 3.4 g. (27%) of spiro[cyclohexane-1,1′-phthalan]-3′-one (X), m.p. 78–81°. Recrystallization from hexane afforded an analytical sample, m.p. 81.5–82.5°.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.02; H, 6.79.

Acidification of the bicarbonate extracts above yielded 2.1 g. (28% based on starting N-methylbenzamide) of benzoic acid, m.p. 120.5–121.5°, undepressed on admixture with an authentic sample.

When the above condensation was effected by refluxing for 0.5 hr., there was obtained an 83% recovery of N-methylbenzamide (isolated by distillation). When the condensation was effected by stirring for 20 min. at 0°, and 45 min. at room temperature, there was obtained 18% of X and 33% of benzoic acid.

(C) With Cyclohexene Oxide.—The mixture containing II was heated at reflux while a solution of 7.84 g. (0.08 mole) of cyclohexene oxide in 80 ml. of ether was added during 12 min. The mixture was refluxed an additional 20 min. and then poured into 65 ml. of 2 *M* hydrochloric acid and 35 g. of ice. From this point the reaction mixture was worked up as described above under B for cyclohexanone. There was obtained 1.4 g. (23%) of benzoic acid and 2.3 g. of crude lactone which was recrystallized from hexane and a little ethanol to give 1.1 g. (11%) of 1,2,3,4,4a,-10b-hexahydro-6H-dibenzo[*b*,*d*]pyran-6-one (XI), m.p. 93–94°. A second recrystallization from hexane gave an analytical sample, m.p. 94–94.5°.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.92; H, 6.91.

Attempted Metalation of Benzamide.—A mixture of 0.05 mole of benzamide and 0.156 mole of *n*-butyllithium in 100 ml. each of tetrahydrofuran and hexane was refluxed for 15 min., and the resulting mixture was treated with 0.16 mole of benzophenone in 100 ml. of ether essentially as described above for the metalation of N-methylbenzamide and condensation with this ketone. On addition of water to the cooled reaction mixture, no precipitate formed. On working up the organic layer 65% of the benzamide was recovered. No *ortho* product was found. A similar result was obtained when monoglyme was used instead of tetrahydrofuran.

When the mixture of benzamide and butyllithium in tetrahydrofuran and hexane was refluxed for 17 hr. and water then added, a black oily material insoluble in the organic and water layers was produced.

Diazoniapentaphene Salts

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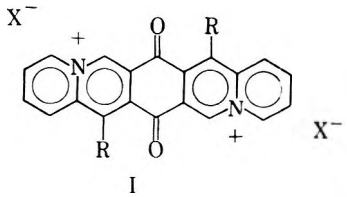
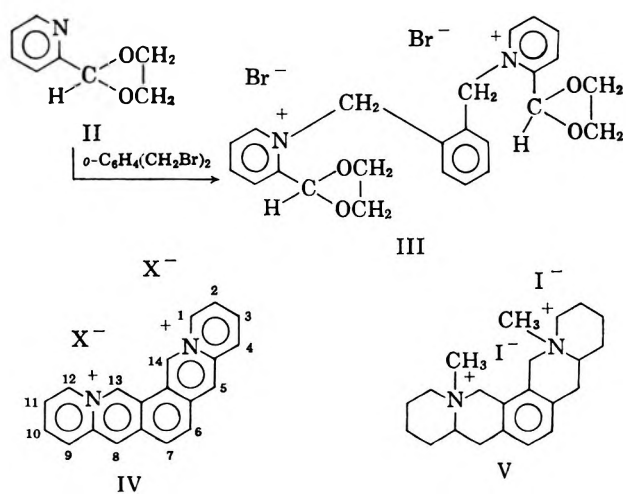
Through use of a recently developed technique, 12a,14a-, 4a,12a-, and 4a,8a-diazoniapentaphene salts have been prepared. These are believed to be the first completely aromatic condensed benzenoid compounds which contain two quaternary nitrogen atoms at bridgehead positions.

In earlier studies it was shown that diaryls could be synthesized with a quinolizinium nucleus in each moiety,[2] and that, as in 4a,11a-diazoniapentacene-6,13-quinone[3] (I), two quinolizinium nuclei may exist in a single fused ring system, separated by a quinone nucleus. The present communciation is concerned with the synthesis of the previously unknown class of compounds in which two quinolizinium nuclei are united through a fused benzenoid ring.



I

The problem involved in the synthesis of such a derivative is that a double cyclization must occur, the second step involving a cyclization into the greatly deactivated acridizinium nucleus. The recently demonstrated[4] ability of salts of 2-(1,3-dioxolan-2-yl)pyridine (II) to undergo cyclization, even in the presence of strongly deactivating groups, recommended the acetal (II) as a starting material.



II III IV V

Reaction of the acetal (II) with α,α'-dibromo-*o*-xylene in dimethylformamide (DMF) or tetramethylene sulfone (TMS) produced the crystalline bisquaternary salt (III) in good yield. Cyclization of the salt in polyphosphoric acid at 145° followed by addition of perchloric acid to the diluted solution afforded what is presumably the perchlorate salt, but which detonated at 350° with such vigor that combustion analysis was out of the question. Anion-exchange resins, the usual recourse in such a situation, proved useless, in that the salt was attacked by the resin with the formation

(1) This research was supported by a research grant (CA-05509) of the National Cancer Institute of the National Institutes of Health. A preliminary report of this work appeared as a Letter to the Editor, *Chem. Ind.* (London), 1247 (1963).

(2) C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 78 (1963).

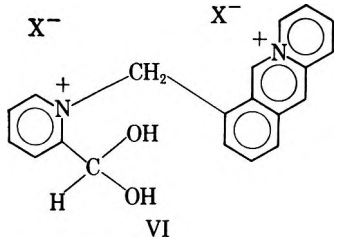
(3) C. K. Bradsher and M. W. Barker, *ibid.*, **29**, 61 (1964).

(4) C. K. Bradsher and J. C. Parham, *ibid.*, **28**, 83 (1963); J. C. Parham, Ph.D. dissertation, Duke University, 1963.

of a dark purple color. Like the diazoniapentacenequinone (I) salts,[3] the perchlorate of IV was attacked by polar solvents and could be recrystallized satisfactorily only from acidified solutions. As an alternative to the perchloric acid method, precipitation with potassium iodide was tried. The resulting "iodide," which may well have been the triodide, was too insoluble to purify for analysis, but when stirred with silver sulfate, it gave a low yield of the bisulfate (IV. X = HSO_4), the first pure diazoniapentaphene salt. The only successful method found for isolation of the diazoniapentaphene ion (IV) from phosphoric acid solution involved precipitation as the bistribromide (Br_3^-).[4] The extremely insoluble precipitate is easily converted to the bromide by heating in methanol–acetone, and provides a 47% over-all yield of the bromide (IV, X = Br) from the quaternary salt (III).

Although there existed only a single way in which dicyclization into the aromatic nucleus could occur, and both spectral and analytical data indicated dicyclization, it was felt that confirmatory chemical proof would be desirable. When the new ring system was hydrogenated, it absorbed the 8 moles of hydrogen necessary to saturate the two quinolizinium nuclei. The reduction product was converted to the methiodide (V) which had the expected composition but was probably a mixture of stereoisomers. Oxidation of the methiodide V yielded 1,2,3,4-benzenetetracarboxylic acid, confirming that dicyclization had occurred in the expected way.

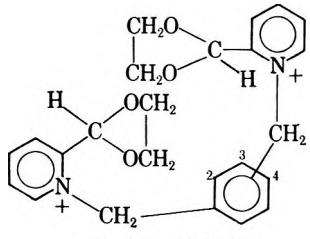
One other observation of note was that under mild cyclization conditions (90°) an acridizinium derivative (VI) could be isolated. The absence of infrared



VI

absorption in the carbonyl region and strong absorption in the hydroxyl region suggest that the compound forms a stable hydrate, a common phenomenon among 2-formylpyridinium salts.[5]

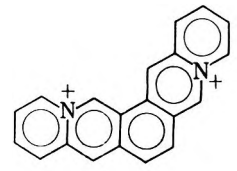
The diazoniapentaphene synthesis was repeated starting with the quaternary salts VII and VIII pre-



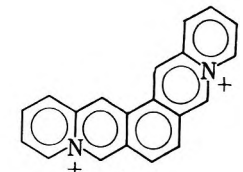
Position 3 VII
Position 4 VIII

pared from α,α'-dibromo-*m*-xylene and α,α'-dibromo-*p*-xylene and yielded 4a,12a-diazoniapentaphene (IX) and 4a,8a-diazoniapentaphene(X), respectively. Both

(5) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, *J. Org. Chem.*, **26**, 368 (1961).

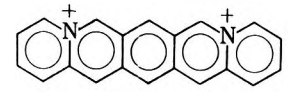


IX

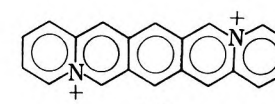


X

were obtained from the dibromoxylene in over 50% over-all yield. The cyclization of the intermediate quaternary salts VII and VIII differs from that of the salt III (obtained from α,α'-dibromo-*o*-xylene) in that linear dicyclization products IXA and XA might be formed. These alternative formulas may be eliminated on the basis of ultraviolet spectral evidence



IXA



XA

(Table I). The spectra of IX and X show marked similarity to that of IV, about which no such uncertainty exists, and all three spectra resemble the spectrum of pentaphene much more closely than that of pentacene. Further evidence that IX and X are correctly formulated as diazoniapentaphenes instead of diazoniapentacenes (IXA and XA) lies in the yellow color of the products. Every analogy suggests that the compounds represented by IXA and XA should be blue since the linear hydrocarbon pentacene is deep violet blue.[6]

TABLE

ULTRAVIOLET ABSORPTION MAXIMA (mμ) OF DIAZONIAPENTAPHENES (BROMIDES)

12a,14a- (IV)		4a,12a- (IX)		4a,8a- (X)	
λ_{max}	Log ε	λ_{max}	Log ε	λ_{max}	Log ε
231	4.48	235	4.51	232[a]	4.32
242	4.47	258	4.59	255	4.44
263	4.63	286	4.39	274[a]	4.18
296	4.26	296	4.36	285.5	4.29
323[a]	4.20	347[a]	4.65	297.5	4.35
340	4.47	357	4.79	325[a]	4.30
348[a]	4.31	375	4.51	341	4.67
369	4.49	404	3.82	354.5	4.68
389	4.54	427	3.70	362	4.51
395[a]	4.45			384	4.59
415	3.60			422	3.73
				447	3.72

[a] Shoulder.

Experimental

Unless otherwise indicated, all analyses were by Dr. Ing. A. Schoeller, Kronach, Germany. Melting points were determined in capillaries on a Mel-Temp apparatus and are uncorrected. All ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. quartz cells with the Cary Model 14 spectrophotometer.

1,2-Bis(1-methylene-2-[1,3-dioxolan-2-yl]pyridinium bromide)-benzene (III).—A solution containing 13.40 g. of α,α'-dibromo-*o*-xylene and 15.1 g. of 2-(1,3-dioxolan-2-yl)pyridine[4] (II) in 12 ml. of dimethylformamide was allowed to stand for 2 days in a stoppered flask. The solid mass of salt was broken up and washed thoroughly with ethyl acetate, then crystallized from methanol–ethyl acetate; yield 24.28 g. (81%), m.p. 177–180°.

An analytical sample was obtained from the same solvents as large white prisms, m.p. 185–186° dec.

Anal. Calcd. for $C_{24}H_{26}Br_2N_2O_4$: C, 50.88, H, 4.59; N, 4.94. Found: C, 51.06; H, 4.59; N, 5.18.

(6) E. Clar and Fr. John, *Ber.*, **62**, 3021 (1929); **63**, 2967 (1930).

The **perchlorate** crystallized from methanol as small colorless prisms, m.p. 220–221°.

Anal. Calcd. for $C_{24}H_{26}Cl_2N_2O_{12}$: C, 47.61; H, 4.33; N, 4.63. Found: C, 47.45; H, 4.13; N, 4.97.

12a,14a-Diazoniapentaphene Bromide (IV, X = Br).—A solution containing 5.66 g. of the quaternary salt (III, X = Br) in 82 g. of polyphosphoric acid was stirred on the steam bath for 2 hr. to assure homogeneity. It was then maintained at 150–160° for 17 hr. with vigorous stirring. After cooling the solution, 100 g. of ice was added with stirring. The diluted reaction mixture was stirred on the steam bath for 2 hr. to assure complete hydrolysis of the polyphosphoric acid and prevent precipitation of polyphosphate salts. The cooled solution was stirred rapidly while the "tribromide reagent" (three volumes of hydrobromic acid to one volume of bromine) was added dropwise until precipitation was complete. The orange-yellow tribromide (IV, X = Br_3) was collected and washed well with cold water.

The tribromide was suspended in a mixture containing 250 ml. of acetone and 250 ml. of methanol and heated on the steam bath with stirring until the salt dissolved. The solution was treated with charcoal, concentrated, and ethyl acetate added. From the chilled solution, 2.13 g. (48%) of the bromide was obtained as yellow needles. Recrystallization from acidified (HBr) methanol–ethyl acetate gave 2.07 g., (47%), m.p. >400°. The analytical sample consisted of tiny bright yellow needles, m.p. >400°, with darkening above 300°.

Anal. Calcd. for $C_{20}H_{14}Br_2N_2$: C, 54.32; H, 3.19; N, 6.33. Found: C, 54.35; H, 3.11; N, 6.25.

The **2-anthraquinone sulfonate** was prepared by addition of a saturated aqueous solution of sodium 2-anthraquinone sulfonate to an aqueous solution of the bromide. The analytical sample was recrystallized from acidified (HCl) methanol–ethyl acetate as small yellow prisms, m.p. 318° dec. and gas evolution.

Anal. Calcd. for $C_{48}H_{28}N_2O_{10}S_2 \cdot H_2O$: C, 65.89; H, 3.46; N, 3.20. Found: C, 66.05; H, 3.46; N, 3.35.

The **bisulfate** (IV, X = HSO_4) was obtained from the crude "iodide" by stirring a suspension of the salt and silver sulfate (10 molar excess) in very dilute sulfuric acid. The insoluble salts were removed by repeated filtration of the solution through a sintered glass funnel. The salts were washed with methanol and the washing combined with the filtrate. Vacuum evaporation of the solvents and crystallization of the residue repeatedly from methanol–ethyl acetate (acidified with sulfuric acid) afforded the product as blunt brownish yellow needles, m.p. >400°, with gradual charring above 270°.

Anal. Calcd. for $C_{20}H_{16}N_2O_8S_2$: C, 50.41; H, 3.38; N, 5.88. Found: C, 50.09; H, 3.38; N, 6.01.

Di(1,4,6,7,8,9-hexahydro-9a*H*-quinolizino)[2,3-*a*:3,2-*b*]benzene Dimethiodide (V).—Hydrogenation at room temperature and atmospheric pressure of a methanolic solution (100 ml.) containing 1.06 g. of 12a,14a-diazoniapentaphene chloride (obtained by stirring the "iodide" with silver chloride) resulted in an uptake of 95% of the calculated 8 moles of hydrogen. The solution was filtered and concentrated, and ethyl acetate was added. The fluffy white salt which precipitated, presumably the dihydrochloride, m.p. 339–340° (1.03 g.), was converted to the free base and methylated with methyl iodide affording the dimethiodide (V). This was crystallized from methanol–ethyl acetate affording crystals which decomposed gradually above 225°; yield 1.31 g. (81%). The analytical sample consisted of colorless prisms, m.p. 230–240°, and may have been a mixture of stereoisomers.

Anal. Calcd. for $C_{22}H_{34}I_2N_2$: C, 45.53; H, 5.90; N, 4.83. Found: C, 45.19; H, 5.93; N, 5.03.

Oxidation of the Dimethiodide (V).—To a solution containing 0.58 g. of the methiodide (V) in 20 ml. of water at 100°, 6.3 g. of potassium permanganate dissolved in 100 ml. of water was added, along with 10 ml. of 10% sodium hydroxide solution. After the addition period (2 hr.), heating was continued overnight. Excess permanganate was destroyed by addition of isopropyl alcohol, and the manganese dioxide was removed by filtration. The clear filtrate was acidified with concentrated hydrochloric acid and heated on the steam bath for 2 hr. Inorganic salts were removed by percolating the solution through a Dowex 50-X cation-exchange resin column loaded with hydrogen ion. The eluate and washings were evaporated to dryness *in vacuo* (aspirator) and the residue sublimed *in vacuo*. The sublimate (probably 1,2,3,4-benzenetetracarboxylic acid anhydride) was heated in 5 ml. of water and concentrated to dryness *in vacuo*; yield 45 mg. (17%) of crude 1,2,3,4-benzenetetracarboxylic acid, m.p. 228–231° (lit.[7,8] m.p. 236–238°). Methylation with diazomethane gave the tetramethyl ester of 1,2,3,4-benzenetetracarboxylic acid as colorless needles from ether–ligroin, m.p. 128–129° (lit.[8] m.p. 131.1–131.8 cor.).

Anal. Calcd. for $C_{14}H_{14}O_8$: C, 54.19; H, 4.54. Found: C, 54.32; H, 4.50.

7-(1-Methylene-2-dihydroxymethylpyridinium perchlorate)-acridizinium Perchlorate (VI).—A solution containing 8.5 g. of the quaternary salt (III) in 104 g. of polyphosphoric acid was stirred for 8 hr. on the steam bath. The mixture was diluted, heated, and finally treated with the "tribromide reagent." The red gummy precipitate first formed turned to an orange solid after standing for 2 hr. in ice. When this solid was suspended in 200 ml. of acetone, a yellow solid identified as 12a,14a-diazoniapentaphene separated.

The oily residue obtained by concentration of the filtrate was dissolved in water and converted to the perchlorate by addition of 35% perchloric acid. The pale yellow perchlorate (VI) was recrystallized from methanol–ethyl acetate; yield 1.77 g. (23%), m.p. 237–238° dec. The analytical sample consisted of short yellow-tan needles, m.p. 253–254°; λ_{max} (log ϵ), 211[9] (4.12), 245[9] (4.53), 250 (4.54), 363 (3.87), 381 (4.03), and 400.5 mμ (3.99).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_2O_{10}$: C, 46.44; H, 3.51; N, 5.42. Found: C, 46.97; H, 3.66; N, 5.43.

1,3-Bis(1-methylene-2-[1,3-dioxolan-2-yl]pyridinium bromide)-benzene (VII).—The quaternization reaction with 13.40 g. of α,α'-dibromo-*m*-xylene was carried out as in the case of the *ortho* isomer yielding 26.83 g. (95%) of the bisquaternary salt (VII).

The analytical sample was obtained from methanol–ethyl acetate as colorless rhombohedral prisms, m.p. 95.5–97°.

Anal. Calcd. for $C_{24}H_{26}Br_2N_2O_4$: C, 50.88; H, 4.59; N, 4.94. Found: C, 50.84; H, 4.70; N, 5.14.

The **perchlorate** formed colorless platelets from methanol–ethyl acetate, m.p. 155.5–156.5°.

Anal. Calcd. for $C_{24}H_{26}Cl_2N_2O_{12}$: C, 47.61; H, 4.33; N, 4.63. Found: C, 47.98; H, 4.29; N, 4.98.

4a,12a-Diazoniapentaphene (IX) Bromide.—The cyclization of the bisquaternary salt (VII) was carried out essentially as in the case of the *ortho* isomer, except that at no time was all of the tribromide completely dissolved in the acetone–methanol mixture; yield 54%.

The analytical sample was obtained from acidified (hydrobromic acid) methanol–ethyl acetate, m.p. >400° (charring above 380°).

Anal. Calcd. for $C_{20}H_{14}Br_2N_2$: C, 54.32; H, 3.19; N, 6.33. Found: C, 54.32; H, 3.13; N, 6.38.

1,4-Bis(1-methylene-2-[1,3-dioxolane-2-yl]pyridinium bromide)-benzene (VIII).—A solution of 10.5 g. of α,α'-dibromo-*p*-xylene in 20 ml. of dimethylformamide was allowed to react with 12.1 g. of 2-(1,3-dioxolan-2-yl)pyridine (II) as in the formation of the isomeric salts (III and VII); yield 13.87 g. (61%), m.p. 195–199°. The analytical sample crystallized from methanol–ethyl acetate as small white needles, m.p. 201–202° dec., and previous shrinkage.

Anal. Calcd. for $C_{24}H_{26}Br_2N_2O_4$: C, 50.88; H, 4.59; N, 4.94. Found: C, 50.82; H, 4.34; N, 4.94.

The **perchlorate** formed colorless irregular prisms from methanol, m.p. 244–244 5°.

Anal. Calcd. for $C_{24}H_{26}Cl_2N_2O_{12}$: C, 47.61; H, 4.33; N, 4.63. Found: C, 47.93; H, 4.56; N, 4.74.

4a,8a-Diazoniapentaphene (X) Bromide.—The cyclization of 11.32 g. of the quaternary salt (VIII) was carried out as in the case of the isomers, except that 1 l. of acetone–methanol was used for conversion of the tribromide salt (X, X = Br_3) to the bromide (X, X = Br). The total recrystallized yield was equivalent to 5.75 g. (65%), m.p. >400°. The analytical sample was obtained from acidified methanol as a yellow microcrystalline powder, m.p. >400°, with charring above 390°.

Anal. Calcd. for $C_{20}H_{14}Br_2N_2$: C, 54.32; H, 3.19; N, 6.33. Found: C, 54.00; H, 3.31; N, 6.35.

The **2-anthraquinone sulfonate** salt was crystallized from acidified (hydrochloric acid) methanol–ethyl acetate as a yellow microcrystalline powder, m.p. 282° dec., and previous shrinkage.

Anal. Calcd. for $C_{48}H_{28}N_2O_{10}S_2 \cdot {}^1/_2H_2O$: C, 66.58; H, 3.38; N, 3.57. Found: C, 66.21; H, 2.95; N, 3.24.

(7) L. I. Smith and E. J. Carlson, *J. Am. Chem. Soc.*, **61**, 291 (1939).
(8) F. Gonzalez-Sanchez, *Tetrahedron*, **1**, 231 (1957).
(9) Shoulder.

17-Azasteroids. I[1]

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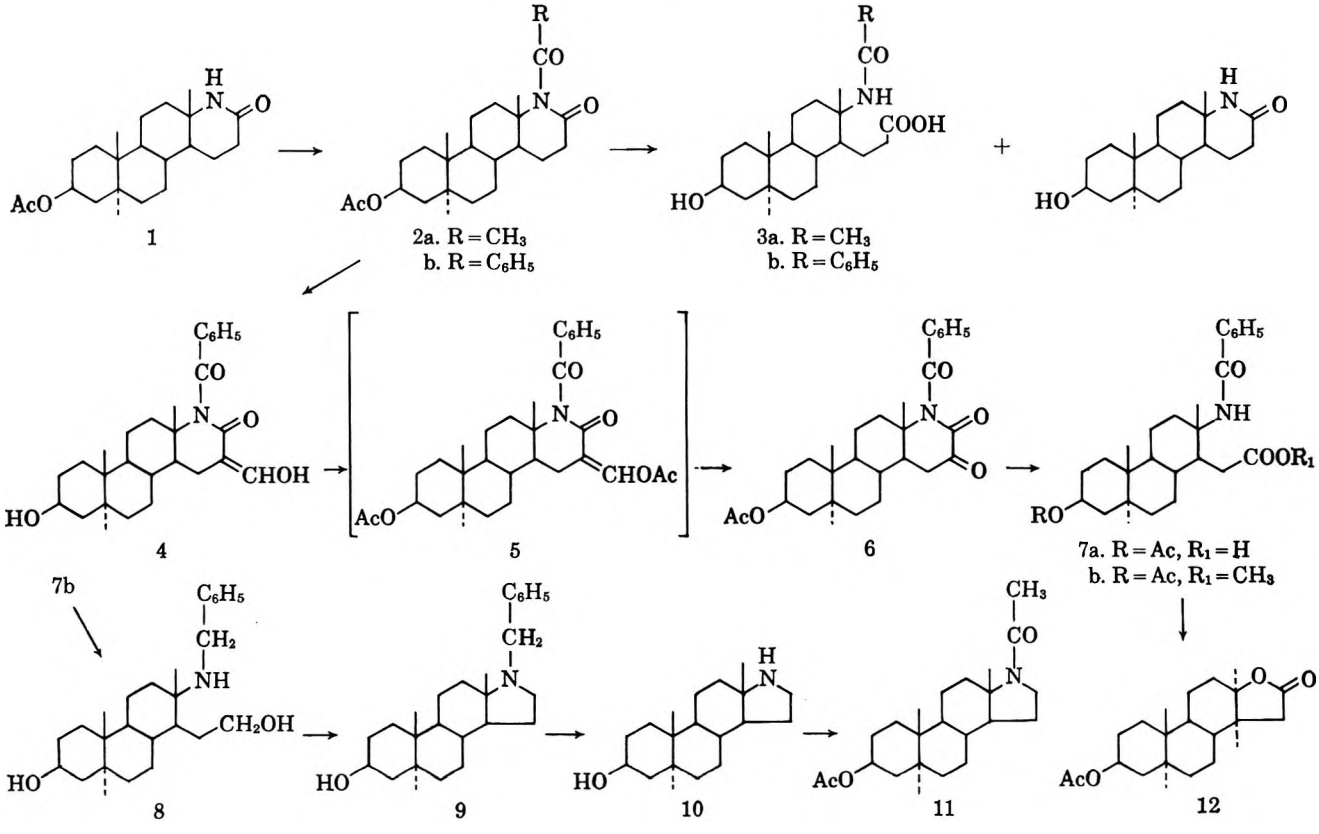
The elimination of C-17 from a known 17a-aza-D-homosteroid gave 13α-benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol which could be cyclized to produce a 17-azasteroid. This paper describes the synthesis of 3β-acetoxy-5α-17-azapregnan-20-one.

Structural modifications of naturally occurring steroids have produced changes in their biological activities which usually cannot be predicted. In this connection a recently published synthesis of 17-oxa-5α-androstan-3-one[2] noted that a modification of that procedure could lead to 17-azasteroids.

Although several publications[3-5] have appeared recently in which a total synthesis was used for the preparation of azasteroids, it was decided that a partial synthesis might yield the desired product more readily, and this paper describes the elimination of C-17 from a 17a-aza-D-homolactam, followed by reduction and ring closure to a five-membered amine. (See Chart I.)

CHART I



The known 3β-acetoxy-17a-aza-5α-D-homoandrostan-17-one[6] (1), prepared by the Beckmann rearrangement of the oxime of 3β-acetoxy-5α-androstan-17-one, served as starting material. The first step in the degradation of ring D was the introduction of a carbonyl function on C-16 which, by virtue of the α-dicarbonyl grouping, would make possible the elimination of C-17.

Originally, it was planned to formylate the six-membered lactam (in close analogy[7] to the formylation of the corresponding lactone), which then could be degraded to the desired α-keto lactam. Attempts employing conventional procedures for the formylation of C-16 failed. Acetylation or benzoylation of the lactam 1 rendered the 17-carbonyl of the resulting imide more "ketonic," evidenced by the preferential cleavage of the bond between the nitrogen and C-17 on alkaline treatment. This could be explained by the release of I-strain[8] or the generally greater reactivity of trigonal carbons (*e.g.*, >C=O) in a cyclohexyl *vs.* acyclic systems. This greater ketonic character led to preferential hydroxy methylation of the imides 2a and 2b in the 16 position. However, condensation also occurred on the methyl carbon of the acetate groups of 2a. The

(1) This work was supported, in part, by a National Institutes of Health grant H-5266.

(2) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(3) G. R. Clemo and L. K. Mishra, *J. Chem. Soc.*, 192 (1953).

(4) J. H. Burckhalter and H. Watanabe, Abstracts, 143rd National Meeting of the American Chemical Society, Cincinnati, Ohio, Jan., 1963, p. 14A.

(5) R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback, and R. E. Brown, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 39M.

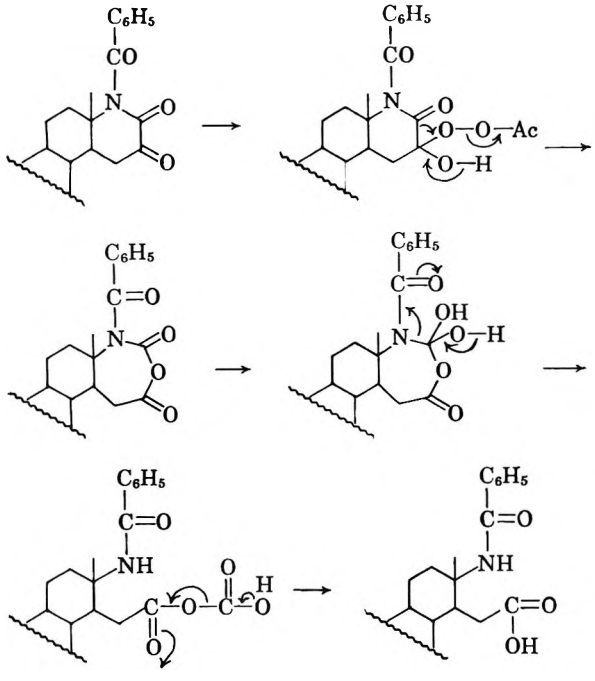
(6) R. Anliker, M. Müller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **38**, 1404 (1955).

(7) L. H. Knox, R. Villotti, F. A. Kincl, and H. J. Ringold, *J. Org. Chem.*, **26**, 501 (1961).

(8) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

imide **2b**, upon treatment with ethyl formate and sodium hydride in dry benzene, yielded in excellent yield the desired hydroxy methylene product **4**. Acetylation of **4** gave the diacetate **5**, which was directly ozonized without purification. The ozonolysis yielded a neutral product, which was identified as the desired 16-keto-N-benzoyl lactam, and as main product an acid which was first esterified with diazomethane, then acetylated, and finally chromatographed to give ester **7b** in excellent yield. The neutral α-keto benzoylamide (**6**) could be degraded to **7b** with peracetic acid. (See Chart II.)

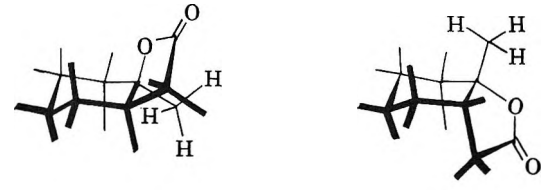
CHART II



A plausible mechanism for this degradation is a Baeyer–Villiger type attack on the carbonyl at C-16 followed by rearrangement to the anhydride. Hydration of the carbonyl at C-17 would then be followed by ring opening to a hydrogen carbonate which readily hydrolyzes with a concomitant loss of the original C-17. However, the same over-all change could have been effected by attack on the C-17 carbonyl. The over-all yield in the sequence from **1** to **7b** was approximately 37%. At this point, the first objective (the elimination of C-17) had been reached.

Possessing a satisfactory method for the preparation of a 17-nor compound, there remained for the completion of the synthesis the ring closure to the five-membered amine. The N-benzoyl ester (**7b**) was reduced with excess lithium aluminum hydride which gave the N-benzyl diol (**8**). The benzylamine (**9**) was obtained in good yield by treatment of **8** with thionyl chloride at room temperature. The hydrogenolysis of the N-benzyl compound (**9**) in ethanol containing a few drops of acetic acid over a platinum oxide catalyst gave a crystalline but very hygroscopic product (**10**), which was acetylated without any further purification to yield 3β-acetoxy-17-aza-5α-pregnan-20-one.[9]

Treatment of the acid **7a** with concentrated hydrochloric acid in acetic acid, instead of producing the desired five-membered lactam, yielded exclusively a nonnitrogenous compound identified as 3β-acetoxy-5α,13α-17-oxaandrostan-16-one (**12**). The structural assignment of **12** is based on its elemental analysis, its infrared absorption spectrum, its n.m.r spectrum,[10] and finally its nonidentity with the known 3β-acetoxy-17-oxa-5α-androstan-16-one.[2] This isolactone **12**, which has a C–D *cis* ring fusion, is the thermodynamically more stable product because it can be produced from 3β-acetoxy-17-oxa-5α-androstan-16-one under identical conditions. Inspection of models of the two possible isolactones **12** reveals that in the case of the 14β isomer (B) there are more severe 1,3-diaxial nonbonding interactions than in the case of the 13α isomer (A). A number of plausible mechanisms, *e.g.*, elimination of the benzamido group, formation of a carbonium ion at C-13, or assisted solvolysis, can be suggested to explain the over-all change.



A B

Experimental[12]

3β,N-Diacetoxy-17a-aza-5α-D-homoandrostan-17-one (2a$_B$ from 1.—A solution of 900 mg. of the lactam **1** in 10 ml. of pyridine and 5 ml. of acetic anhydride was heated on a steam bath for 5 hr. The solution was cooled, the excess acetic anhydride was decomposed with methanol and then poured into ice–water. The resulting precipitate was collected, washed thoroughly with water, and dried to yield 1.05 g. of crude diacetate. Crystallization from ether gave 880 mg. of pure **2a**, m.p. 134–136°. A portion was recrystallized for analysis from ether–hexane, m.p. 136–138°; $[\alpha]_D$ −14° (*c* 0.8); infrared absorption, ν_{max} 1730 (3-acetoxy), 1650 (N-acetyl lactam), and 1250 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.19; H, 9.01; N, 3.74.

3β-Hydroxy-13,17-seco-17α-acetylamino-5α-androstan-17-oic Acid (3a) from 2a.—To a solution of 360 mg. of the N-acetyl D-lactam (**2a**) in 50 ml. of methanol was added 200 mg. of potassium hydroxide in 5 ml. of water, and the mixture was refluxed for 2.5 hr., after which most of the methanol was removed *in vacuo*. Dilution with water was followed by extraction with ether. The ether layer was washed with 2 *N* potassium hydroxide and water, and then dried over sodium sulfate. Removal of solvent yielded 60 mg. of a neutral substance, m.p. 295–297°, which was identical in all respects with the known 3β-hydroxy-17a-aza-5α-D-homoandrostan-17-one.[6] The alkaline solution and the aqueous washings were mixed and acidified with 2 *N* hydrochloric acid to

(9) The conformation of the side chain is being investigated.

(10) In the case of the isolactone **12**, the C-15 protons are shifted downfield compared to the C-15 protons of the normal lactone,[2] probably owing to different stereochemical relationship with the rest of the molecule. They appear as two doublets centered at τ 7.17 (15α-H) and 7.79 (15β-H) with J_{AB} = 17 c.p.s., and are further split by the 15α proton with J_{AX} = 6 c.p.s. and J_{BX} ~ 0 c.p.s. (where A is 15α-H and B is 15β-H). The calculated values from the Karplus equation[11] are θ_1 (14α–15α) ~33° and θ_2 (14α–15β) ~87°. Inspection of a model of lactone **12** reveals that the dihedral angles between 14α and 15α is 30° and between 14α and 15β is 90°, comparing well with the values obtained from the Karplus equation.

(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(12) The microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points were taken on a Fisher-Jones hot stage and are corrected. Rotations were taken, unless noted otherwise, in chloroform. The infrared spectra were recorded from a pressed potassium bromide pellet on a Perkin-Elmer infracord spectrophotometer. Davison Type 923, 100–200-mesh silica gel was used for all chromatographic separations. The ultraviolet absorption spectrum was taken in methanol solution on a Cary 14 spectrophotometer. The n.m.r. spectra were recorded on a Varian V-4300B spectrometer using 20% solutions in deuteriochloroform and tetramethylsilane as an internal standard.

congo red. The flocculent precipitate was extracted with dichloromethane; the extract was washed with water, dried over sodium sulfate, and taken to dryness to give 290 mg. of acid **3a**, m.p. 223–226°. An analytical sample was prepared by recrystallization from acetone–hexane and had m.p. 226–227°; $[\alpha]_D$ +33° (*c* 0.85); ν_{max} 3350 (–OH), 3200 (N–H), 1698 (C=O of acid), 1630 (C=O of amide), and 1570 (N–H deformation and C–N stretching of amide) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.95; H, 9.61; N, 3.90.

3β-Acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostan-17-one (2b) from 1.—To a solution of 1.42 g. of the lactam in 10 ml. of dichloromethane was added 60 ml. of a 15% aqueous solution of sodium hydroxide. The mixture was stirred vigorously with cooling (0–5°) while 7 ml. of benzoyl chloride in 10 ml. of dichloromethane was added within a period of 45 min. The mixture was stirred at room temperature for another 1 hr. Then the dichloromethane layer was separated and washed twice with a cold 2 *N* sodium hydroxide solution and then washed free of alkali with ice–water and dried over sodium sulfate. Removal of solvent yielded 1.52 g. of an oil which was crystallized from ether to give 1.25 g. of the N-benzoyl derivative (**2b**), m.p. 215–217°. The analytical sample was prepared by recrystallization from ether and had m.p. 216.5–217.5°; $[\alpha]$ +5° (*c* 0.75); infrared absorption maxima, ν_{max} 1740 (3-acetate), 1720 (N-benzoate), 1680 (C=O of lactam), 1625 (C=C aromatic), and 1250 (acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.16; H, 8.62; N, 3.17.

3β-Hydroxy-13,17-seco-13a-benzoylamino-5a-androstan-17-oic Acid (3b) from 2b.—Alkaline treatment of the N-benzoyl lactam (**2b**) according to the procedure described for the N-acetyl lactam gave in 70% yield the N-benzoyl seco acid (**3b**), m.p. 223–225°. The neutral material was identified as the known 3β-hydroxy-17a-aza-5α-D-homoandrostan-17-one.[6] An analytical sample of the acid was prepared by recrystallization from dichloromethane ether, m.p. 225–227°; $[\alpha]_D$ +10° (c, 1.0, methanol); infrared absorption maxima, ν_{max} 3350 (OH), 3250 (N–H), 1700 (C=O), 1680 (C=O of N benzoate), 1575 (C=C, aromatic), and 1550 (N–H deformation) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.18; H, 8.85; N, 3.51.

3β-Hydroxy-N-benzoyl-16-hydroxymethylene-17a-aza-5α-D-homoandrostan-17-one (4) from 2b.—To a solution of 2 g. of N-benzoyl lactam (**2b**) in 150 ml. of dry thiophene-free benzene was added 1.5 g. of sodium hydride. While the mixture was being stirred under nitrogen, 8 ml. of dry ethyl formate was added within 5 min., and the mixture was stirred for another 4.5 hr. at room temperature under nitrogen. The excess hydride carefully was decomposed by adding methanol and then water. The aqueous layer was separated, and the benzene layer was washed with water. The aqueous alkaline solution and the first washing were combined and acidified with cold hydrochloric acid, thereby precipitating the hydroxy methylene derivative (**4**). The precipitate was filtered off, washed thoroughly with water, and dried to give 2.1 g. of **4**. This product did not crystallize well and gave a poor analysis (probably due to some water of crystallization); it had m.p. 135–138°; $[\alpha]^{22}_D$ –49° (*c* 1.0, methanol); infrared absorption maxima, ν_{max} 3500 (–OH), 1690, 1650 (Ph–C(=O)–N–C(=O)–), and 1600 (hydroxymethylene C=C) cm.$^{-1}$; λ_{max} 245 mμ (log ε 3.90).

3β-Acetoxy-N-benzoyl-16-acetoxymethylene-17a-aza-5α-D-homoandrostan-17-one (5) from 4.—To a solution of 1.5 g. of the hydroxymethylene compound (**4**) in 10 ml. of pyridine, 5 ml. of acetic anhydride was added and stored at room temperature for 18 hr. Decomposition of excess acetic anhydride with methanol and usual work-up yielded 1.6 g. of oily diacetate **5** (no hydroxyl band in the infrared spectrum).

3β-Acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostane-16,17-dione (6) and Methyl 3β-Acetoxy-13α-benzoylamino-13,16-seco-5α-17-norandrostan-16-oic Acid (7b) from 5.—A stream of ozone was passed through a solution cooled to –10° of 1.5 g. of the oily diacetate **5** in 60 ml. of a 1:1 mixture of ethyl acetate and acetic acid for 1 hr. After that, 10 ml. of 30% hydrogen peroxide and 10 ml. of water were added, and the mixture was stored at room temperature for 18 hr. After extraction with a large volume of ether, the ether solution was washed with water, then with five 50-ml. portions of cold 2 *N* sodium hydroxide solution, and then again with water. The solution was dried over sodium sulfate and the ether was evaporated, yielding 295 mg. of a neutral product—3β-acetoxy-N-benzoyl-17a-aza-5α-D-homoandrostane-16,17-dione (**6**), m.p. 212–215°. A sample was prepared for analysis by recrystallization from methanol–ether and had m.p. 216–218°; $[\alpha]^{22}_D$ +32° (*c* 0.85); ν_{max} 1745 (3-acetoxy), 1700 (N-benzoate and 16-ketone), 1675 (C=O lactam), 1625 (C=C aromatic), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{33}NO_5$: C, 71.49; H, 7.78; N, 3.09. Found: C, 71.37; H, 7.43; N, 3.35.

The alkaline solution and the first aqueous washing were combined, acidified to congo blue with cold 2 *N* hydrochloric acid, and extracted with dichloromethane. The organic extract was washed several times with water and dried over sodium sulfate. Removal of solvent gave 1.05 g. of the oily acid **7a**. Since attempts to crystallize the acid failed, it was methylated in ethereal solution with diazomethane. Evaporation of the solvent left 1.18 g. of an oil, the infrared spectrum of which showed the presence of a small hydroxyl band and a low intensity acetoxy band. The oil then was acetylated in pyridine solution with acetic anhydride at 0° for 16 hr. Usual work-up yielded 1.12 g. of an oil which was chromatographed on a column of 100 g. of silica gel. Elution with ethyl acetate–benzene mixtures (8:92) yielded crystalline fractions melting between 124–128°, which were combined to give 850 mg. of the crystalline ester **7b**. Two recrystallizations from hexane yielded an analytical sample, m.p. 126–127°; $[\alpha]^{22}_D$ –7° (*c* 1.0); ν_{max} 3400 (N–H of amide), 1735 (3-acetate), 1675 (C=O of benzamide), 1600 (C=C aromatic), 1530 (N–H deformation of amide), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{39}NO_5$: C, 71.61; H, 8.37; N, 2.98. Found: C, 71.73; H, 8.39; N, 3.07.

Methyl-3β-Acetoxy-13α-benzoylamino-13,16-seco-5α-17-norandrostan-16-oic Acid (7b) from 6.—To a solution of 150 mg. of the 16-keto-N-benzoyl lactam (**6**) in 5 ml. of acetic acid and 5 ml. of ethyl acetate was added 1 ml. of 40% peracetic acid, and the mixture was stored at room temperture for 24 hr. Then it was diluted with ethyl acetate and washed several times with water and then extracted with a cold 2 *N* sodium hydroxide solution and water. Drying over sodium sulfate and subsequent removal of the solvent yielded 5 mg. of a neutral product identified as starting material **6**. The alkaline extract was acidified with cold 2 *N* hydrochloric acid, and the acidic material was extracted with dichloromethane. The dichloromethane extract was washed with water and dried over sodium sulfate. Upon removal of the solvent, 120 mg. of an oily residue was left, which was esterified in ethereal solution with diazomethane to give 120 mg. of a crystalline ester, m.p. 125–127°, identical in all respects with the ester **7b** obtained previously.

13α-Benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol (8) from 7b.—To a slurry of 600 mg. of lithium aluminum hydride in 200 ml. of purified tetrahydrofuran was added a solution of 450 mg. of the ester **7b** in 20 ml. of absolute tetrahydrofuran, and the mixture was refluxed for 72 hr. After cooling, the excess reagent was decomposed with ethyl acetate and a saturated solution of sodium sulfate was added to coagulate the inorganic materials. The precipitate was filtered off and the residue was washed thoroughly with tetrahydrofuran. The washings and the filtrate were combined and dried over sodium sulfate. Removal of solvent *in vacuo* yielded 380 mg. of an oil, the infrared spectrum of which did not show any carbonyl band and which was chromatographed on a column of 40 g. of silica gel. Elution with ethyl acetate–benzene mixtures (35 to 50%) gave material melting between 150–155°. These fractions were combined to give 300 mg. of 13α-benzylamino-13,16-seco-5α-17-norandrostane-3β,16-diol (**8**). A sample was recrystallized from dichloromethane–hexane for analysis, m.p. 159–161°; $[\alpha]^{22}_D$ –26° (*c* 0.75); ν_{max} 3400 (OH), and 3200 (N–H) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.20; N, 3.63. Found: C, 77.64; H, 10.40; N, 3.50.

N-Benzyl-5α-17-azaandrostan-3β-ol (9) from 8.—To a solution of 400 mg. of the diol **8** in 15 ml. of dioxane, 1.0 ml. of freshly distilled thionyl chloride was added, and the solution was left at room temperature for 1 hr. Ice was added and the solution was neutralized with sodium hydrogen carbonate. The resulting precipitate was extracted with ethyl acetate, and the extract was washed several times with water and then dried over sodium sulfate. Removal of solvent yielded 370 mg. of an oil which was chromatographed on a column of 35 g. of silica gel. Elution with 25% ethyl acetate in benzene yielded 300 mg. of crystalline **9**,

m.p. 143–146°. A sample was recrystallized from ether–hexane for analysis and had m.p. 147–148°; $[\alpha]^{22}D$ +37° (*c* 1.0); ν_{max} 3450 (OH) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}NO$: C, 81.69; H, 10.15; N, 3.81. Found: C, 81.81; H, 10.15; N, 4.01.

3β-Acetoxy-5α-17-azapregnan-20-one (11) from 9.—The solution of 300 mg. of the N-benzyl compound (9) in 10 ml. of methanol containing a few drops of acetic acid was added to 50 mg. of platinum oxide, and the mixture was reduced with hydrogen for 18 hr. at 40 p.s.i. The catalyst was filtered off and washed with some ethanol. Evaporation of solvent gave 250 mg. of an oil which crystallized from ether. The crystals were too hygroscopic for isolation and the amine, therefore, was acetylated at room temperature with 2 ml. of acetic anhydride in 5 ml. of pyridine for 18 hr. Usual work-up yielded 270 mg. of an oil which was chromatographed on a silica gel column. Elution with 30–35% ethyl acetate in benzene yielded 200 mg. of crystalline 17-azapregnanolone acetate (11), m.p. 175–176°. A portion was recrystallized from ether for analysis and had m.p. 180–182°; $[\alpha]^{22}D$ +24° (*c* 0.63); ν_{max} 1740 (3-acetate), 1660 (C=O of N-acetate), and 1245 (3-acetate) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.11; H, 9.82; H, 3.90.

3β-Acetoxy-5α,13α-17-oxaandrostan-16-one (12) from 7a.—To a solution of 200 mg. of benzamido acid (**7a**) in 10 ml. of glacial acetic acid was added 2.2 ml. of concentrated hydrochloric acid, and the mixture was refluxed under nitrogen for 20 hr. The acids were removed *in vacuo*, water was added, and the residue was extracted with dichloromethane. The extract was washed with a 2 *N* sodium carbonate solution and water and dried over sodium sulfate. Removal of solvent yielded 130 mg. of neutral material which was chromatographed on a column of 15 g. of silica gel. Elution with 5% ethyl acetate in benzene yielded 110 mg. of the lactone 12, m.p. 140–143°. A portion of it was recrystallized from ether for analysis and had m.p. 145–146°; $[\alpha]^{22}D$ −23° (c 1.00 in dioxane); ν_{max} 1754 (γ-lactone), 1725 (3-acetate), and 1235 (3-acetate) cm.$^{-1}$; τ 7.17 (15α-H, $J_{15\alpha,15\beta}$ = 17 c.p.s. and $J_{15\alpha,14\alpha}$ = 6 c.p.s.), 7.79 (15β-H, $J_{15\beta,25\alpha}$ = 17 c.p.s. and $J_{15\beta,14\alpha}$ = 0 c.p.s.), 8.68 (18-CH_3), and 9.27 (19-CH_3).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.58; H, 9.04.

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The Ionization Constants of Some Imidazoles

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The basic and the acidic ionization constants of some imidazole derivatives have been determined spectrophotometrically or potentiometrically. For the nitroimidazoles, the spectrophotometric method has been used in concentrated sulfuric acid solutions for which the Hammett acidity function, H_0, has been adopted. Tautomeric equilibrium constants of the imidazoles containing an imino hydrogen have been calculated. The ionization constants have been correlated to the substituents and their position in the imidazole ring. The usefulness of pK_a measurements in assigning structures of these compounds is pointed out.

The chemistry of imidazoles has been studied[1] extensively and attention has been paid to their ionization constants. The pK_a values of some imidazoles have been determined[1,2] and useful observations have been made recently for some nitro derivatives, whose basicity is diminished strongly by the electronegative nitro group.[3] We then have considered of interest a further study of the basicity of the imidazole derivatives of this type. The potentiometric method was used for the derivatives whose basic dissociation constants were still measurable in this way. For the nitro derivatives we adopted the spectrophotometric method in concentrated acid solutions, which provides a suitable way for obtaining correct values. The acidic ionization constants also were determined potentiometrically. All the results obtained, together with data referred to in literature, have been correlated and evaluations useful for structure determination have been found.

Results and Discussion

The absorption spectra of the nitroimidazoles studied are reported in Table I. The introduction of a nitro group in the imidazole ring markedly changes the ultraviolet spectrum: the imidazole band at 207–208 mμ (ϵ_{mol} 5010)[4] is shifted to about 300 mμ in the nitro derivatives. This latter band is affected by the pH of the medium, and it shifts to longer wave lengths by acidic ionization and to shorter ones by protonation (see Table I). The ultraviolet absorption then allowed us to calculate the basic pK_a values of nitroimidazoles. The electron withdrawing effect of the nitro group strongly diminishes the basicity of the nitroimidazoles, and those containing an imino hydrogen behave as acids in water solution. The protonation takes place only in solutions of concentrated acids, and the pK_{BH^+} values become very low or even negative. The acidity of the solutions used was expressed with the Hammett function, H_0.[5] A number of solutions of sulfuric acid in water were prepared, and, from the tables reported by Paul and Long,[6] the corresponding H_0 values were derived, some of them having been confirmed using *p*-nitroaniline, *o*-nitroaniline, and 2,4-dinitroaniline as indicators.[7] The H_0 function already has been adopted for substituted imidazoles[3] even though these compounds are very different in structure from the aniline derivatives used in establishing the H_0 scale. The similarity in slopes found for the nitroimidazoles and the indicators indicates that the H_0 values of sulfuric acid solutions may be used for

(1) K. Hofmann, "Imidazole and Its Derivatives," Part I, Interscience Publishers, Inc., New York, N. Y., 1953.

(2) A. Albert, "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p. 97.

(3) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1352 (1960).

(4) G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. chim. ital.*, **85**, 769 (1955).

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 267.

(6) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(7) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 1096 (1959).

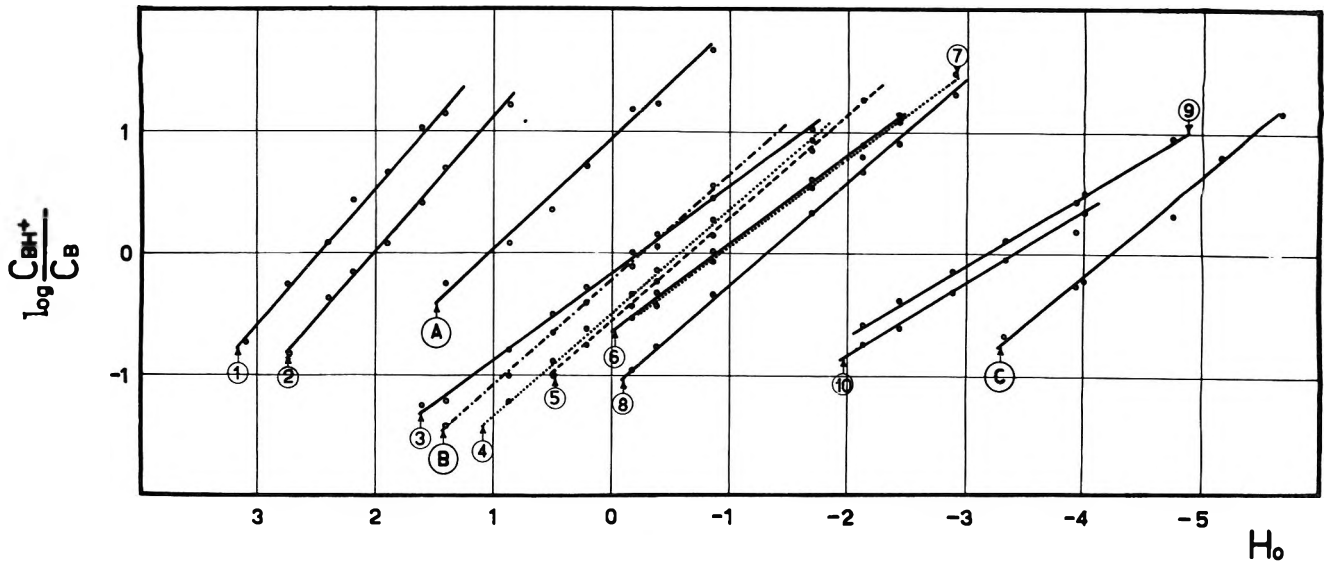


Fig. 1.—Plot of the logarithm of ionization ratios of indicators and imidazole derivatives against H_0. Indicators are A, *p*-nitroaniline; B, *o*-nitroaniline; and C, 2,4-dinitroaniline. Imidazole derivatives are 1, 1-(β-hydroxyethyl)-2-methyl-5-nitro; 2, 1-methyl-5-nitro; 3, 4(5)-nitro; 4, 1-methyl-2-nitro; 5, 1-methyl-4-nitro; 6, 2-nitro; 7, 1-(β-hydroxyethyl)-2-nitro; 8, 1-methyl-4-chloro-5-nitro; 9, 1-methyl-4-nitro-5-chloro; and 10, 4(5)-nitro-5(4)-chloro.

Table I

The Main Absorption Band of Nitroimidazoles

Imidazole derivatives	Medium	Form[a]	$\lambda_{max.}$ mμ	log ε
2-Nitro-	0.1 *M* NaOH	CB	372	4.13
	5×10^{-1} *M* H_2SO_4	N	325	3.95
	8.25 *M* H_2SO_4	CA	298	3.91
4(5)-Nitro	0.1 *M* NaOH	CB	350	4.01
	pH 7.38	N	298	3.86
	8.25 *M* H_2SO_4	CA	264	3.90
1-Methyl-2-nitro-	pH 4.63	N	325	3.93
	5 *M* H_2SO_4	CA	300	3.89
1-Methyl-4-nitro-	pH 4.63	N	300	3.90
	8.25 *M* H_2SO_4	CA	266	3.87
1-Methyl-5-nitro-	pH 7.38	N	305	3.81
	2 *M* H_2SO_4	CA	266	3.70
1-(β-Hydroxyethyl)-2-nitro-	5×10^{-3} *M* H_2SO_4	N	326	3.93
	8.25 *M* H_2SO_4	CA	300	3.90
4(5)-Nitro-5(4)-chloro-	0.1 *M* NaOH	CB	356	4.01
	10^{-4} *M* H_2SO_4	N	304	3.82
	17 *M* H_2SO_4	CA	267	3.86
1-Methyl-4-nitro-5-chloro-	*M* H_2SO_4	N	308	3.85
	14 *M* H_2SO_4	CA	272	3.88
1-Methyl-4-chloro-5-nitro-	5×10^{-3} *M* H_2SO_4	N	312	3.93
	14 *M* H_2SO_4	CA	272	3.82
1-(β-Hydroxyethyl)-2-methyl-5-nitro	pH 6.24	N	319	3.97
	2 *M* H_2SO_4	CA	277	3.81
2-4(5)-Dinitro	0.1 *M* NaOH	CB	354	4.09
	5×10^{-3} *M* H_2SO_4	N	304	4.05
1-Methyl-2,4-dinitro-	5 *M* H_2SO_4	N	305	4.06

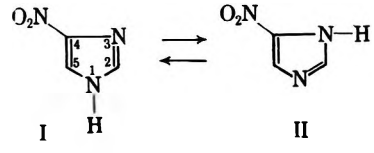
[a] CB, conjugate base; N, the neutral molecule; CA, conjugate acid.

these compounds. All the nitro derivatives were dissolved in the appropriate acidic solutions and, from the spectra recorded, the pK_{BH^+} values were calculated by the following equation.[6,7]

$$pK_{BH^+} = H_0 + \log \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

In the strongest acid solutions we have found also the absence of isosbestic points, attributed to the change of medium over the range of sulfuric acid concentrations used.[6,8] In these cases we obtained accurate pK_{BH^+} values by adopting two methods: (a) assuming that medium effects involve mainly lateral spectral shifts, we shifted the curves laterally until they intersected at a common isosbestic point[6]; (b) following the proposal by Davis and Geissman,[8] we plotted the differences of extinctions at two suitable wave lengths against H_0, minimizing in this way the effect of medium on the absorption. For the weakest bases investigated, *e.g.*, dinitroimidazoles, the protonation was still incomplete in the strongest sulfuric acid solution used. In these cases we adopted the method of least squares.[9] In the chloroimidazoles studied, the position of the absorption band is not suitable for a spectrophotometric determination, but their basicity allowed potentiometric measurements of the ionization constant. All the data obtained with the spectrophotometric or the potentiometric methods and also the pK_a values of interest for the present study reported by other authors are summarized in Table II.

Imidazoles containing an imino hydrogen can exist in two tautomeric forms which, for 4(5)-nitroimidazole, are I and II. We calculated the tautomer ratio of the



compounds studied of this type in the manner proposed by Mason[10] for N-heteroaromatic hydroxy compounds. The K_t values reported in the seventh column of Table II were derived from the pK_{BH^+} values of the two N-methyl isomers by the equation that follows.

(8) C. T. Davis and T. A. Geissman, *J. Am. Chem. Soc.*, **76**, 3507 (1954).
(9) J. C. D. Brand, W. C. Horning, and M. B. Thornley, *J. Chem. Soc.*, 1374 (1952).
(10) S. F. Mason, *ibid.*, 674 (1958).

TABLE II

THE ACIDIC AND BASIC IONIZATION CONSTANTS, THE TAUTOMERIC [K_t = (4-SUBST.)/(5-SUBST.)] CONSTANTS, AND THE CALCULATED pK_{BH^+} OF IMIDAZOLE DERIVATIVES

Imidazole derivative	Proton lost, potentiometry	Proton gained: Potentiometry	Proton gained: Spectrophotometry, Literature	Proton gained: Spectrophotometry, Difference at two wave lengths[a]	Proton gained: Spectrophotometry, $pK = H_0 + \log \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$	log K_t	Calcd. pK_{BH^+}
None		6.95[b]					
1-Methyl-		7.25[c]					
2-Methyl-		7.86[b, c]					
2-Nitro-	7.15[d]			−0.80	−0.81		
4(5)-Nitro-	9.20[e]		−0.05[b]	−0.23	−0.16	2.70	
1-Methyl-2-nitro-				−0.40	−0.48		
1-Methyl-4-nitro-			−0.53[b]	−0.61	−0.58		
1-Methyl-5-nitro-			2.13[b]	2.03	2.12		
4(5)-Chloro-[f]						1.65	
1-Methyl-4-chloro-		3.10[g, h]					
1-Methyl-5-chloro-		4.75[h, i]					
1-(β-Hydroxyethyl)-2-nitro-				−1.15	−0.86		
4(5)-Nitro-5(4)-chloro-	5.85[d]				−3.62	2.27[j]	
1-Methyl-4-nitro-5-chloro					−3.49		−3.08
1-Methyl-4-chloro-5-nitro-					−1.42		−2.03
1-(β-Hydroxyethyl)-2-methyl-5-nitro				2.40	2.55		2.68
2,4(5)-Dinitro-	2.85[d]				−7.33	Not calculated	−7.92
1-Methyl-2,4-dinitro-					−7.47		−8.34

[a] Ref. 8. [b] Ref. 2. [c] Ref. 1. [d] In CH_3OH–H_2O, 1:1 with 0.1 *N* NaOH. [e] In DMF–H_2O, 1:2 with 0.1 *N* NaOH. [f] Unknown. [g] As hydrochloride in water with 0.1 *N* NaOH. [h] A value of 6.23 for 1-methyl-4-chloroimidazole is reported[b] for the product synthesized by G. Dedichen [*Ber. deut. chem. Ges.*, **39**, 1831 (1906)] and later demonstrated by Sarasin[21] to be 1-methyl-5-chloroimidazole. It differs from our value possibly because of the different method used. [i] In CH_3OH–H_2O, 1:3 with 0.1 *N* HCl. [j] (4-nitro-5-chloro)/(4-chloro-5-nitro).

$$K_t = \frac{K_{N(1)-Me}}{K_{N(3)-Me}}$$

The K_t of 2,4(5)-dinitroimidazole, of which one methyl derivative is known, could be calculated by equation[11]

$$K_t = \frac{K_1}{K_{N(1)-Me}} - 1$$

but it gives a negative value, as the parent compound is a stronger base than its N(1)-methyl derivative.[10] From the K_t values it can be deduced that the less acidic tautomer is preponderant over the other. This behavior can be interpreted by considering the strength of the N–H bond in the two tautomeric forms. It appears evident that, as the hydrogen atom can migrate from one nitrogen to the other, the tautomeric system will predominantly assume the form in which the N–H bond is stronger.

It seems pertinent to emphasize some features of imidazole derivatives that can be deduced from an inspection of the data reported in Table II. We obtained the effect of each substituent on the basic ionization constant, calculating it as the difference between the pK_{BH^+} of the substituted imidazole and that of the parent compound. The calculated effects are reported in Table III as a function of the position in the imidazole ring, and the following considerations can be derived. The introduction of a methyl group increases the basic strength,[12a] while the hydroxyethyl group produces an opposite effect, even if very small, due to the presence of the electronegative hydroxyl.[12b] Concerning electronegative substituents, chlorine appears to affect the basicity much less than the nitro group. The influence of these substituents is stronger when they are in close proximity to the basic nitrogen, and the 2- and 4-positions are equivalent in this respect. It is noteworthy that, for the polysubstituted imidazoles, the effect of each substituent is in a fair approximation additive. In fact the values calculated in this way are in satisfactory accordance with the experimental ones, as can be observed in the eighth column of Table II. From these results it follows that the ionization constant of an imidazole derivative of uncertain molecular structure assists in establishing the position of the substituents. The structure of 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole,[13a] whose demonstration has not been published, can be confirmed by the fact that the experimental pK_{BH^+} is in agreement with the calculated one. Similarly, the structure of the methyldinitroimidazole, obtained from 2,4(5)-dinitroimidazole and diazomethane, could be established as 1-methyl-

TABLE III

EFFECT OF SUBSTITUENTS ON THE pK_{BH^+} OF THE IMIDAZOLE

Position	1	2	4	5	4(5)
CH_3—	+0.30	+0.91			
NO_2—		−7.76	−7.83	−5.13	−7.11
Cl—			−4.15	−2.50	
CH_2—OH					
CH_2—	−0.05				

(11) The two equations (4 and 5) reported by Mason[10] are misprinted and should be corrected as follows.

$$K_t = \frac{K_1}{K_{O-Me}} - 1 \quad (4)$$

$$K_t = \frac{1}{\frac{K_1}{K_{N-Me}} - 1} \quad (5)$$

(12) H. C. Brown, B. H. McDaniel and O. Häfliger, "Determination of Organic Structures by Physical Methods," Vol. I, E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, (a) p. 573, (b) p. 578.

(13) (a) C. Cosar and L. Joulou, *Ann. Inst. Pasteur*, **96**, 238 (1959); (b) British Patent, 836,854 (1960).

2,4-dinitroimidazole. This structure was confirmed by its transformation into 1-methyl-4-nitro-5-chloroimidazole with 2-chloroethanol.[14]

Experimental

Apparatus.—The potentiometric titrations were carried out with a Jonosis Q3 potentiometer. The spectrometric measurements were carried out on a Beckman DK2 spectrometer.

Materials.—The following imidazole derivatives had the melting points and properties reported in the literature and were prepared according to the cited references: **2-Nitro**, m.p. 284° dec.[14]; **4(5)-nitro**, m.p. 308°[3,15]; **1-methyl-4-nitro**, m.p. 133°[16]; **1-methyl-5-nitro**, m.p. 55°[17]; **1-methyl-4-chloro**, b.p. 252°,[18] purified by gas chromatography; **1-methyl-5-chloro**, b.p. 205°[19]; **4(5)-nitro-5(4)-chloro**, m.p. 216°[14]; **1-methyl-4-nitro-5-chloro**, m.p. 148°[14]; **1-methyl-4-chloro-5-nitro**, m.p. 78°[14]; **1-(β-hydroxyethyl)-2-methyl-5-nitro**, m.p. 160°[13b]; and **2,4(5)-dinitro**, m.p. 268°.[14]

1-Methyl-2-nitroimidazole.—To a 4% solution of diazomethane in ethyl ether, 200 mg. of 2-nitroimidazole was added, and the mixture was allowed to react at room temperature overnight. Evaporation of the solvent yielded 130 mg. of a light yellow product, which, after recrystallization from ethanol, melted at 101–102°.

Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.91; H, 4.08; N, 32.95.

1-(β-Hydroxyethyl)-2-nitroimidazole.—A mixture of 2 g. of 2-nitroimidazole silver salt[20] and 8 ml. of 2-bromoethanol in 85 ml. of toluene was refluxed for 14 hr. then evaporated to dryness under reduced pressure. The residue was extracted three times with 50 ml. of boiling water each time, and the collected extracts were evaporated to dryness. The residue, recrystallized from ethyl acetate, yielded 800 mg. of light yellow crystals melting at 157°.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.13; H, 4.63; N, 26.95.

1-Methyl-2,4-dinitroimidazole.—2,4(5)-Dinitroimidazole (200 mg.) was treated with diazomethane as described above for the mononitro derivative. By concentration of the solvent, 140 mg. of crystals was obtained, which, after two crystallizations from ethanol, melted at 172°.

Anal. Calcd. for $C_4H_4N_4O_4$: C, 27.92; H, 2.34; N, 32.56. Found: C, 27.87; H, 2.47; N, 32.64.

No traces of the isomeric 1-methyl-2,5-dinitroimidazole could be found in the mother liquor of the crystallization.

1-Methyl-4-nitro-5-chloroimidazole.—A mixture of 680 mg. of 1-methyl-2,4-dinitroimidazole and 10 ml. of 2-chloroethanol was refluxed for 2 hr. The resulting solution was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol, yielding 400 mg. of product with m.p. 148° and infrared spectrum identical with that of 1-methyl-4-nitro-5-chloroimidazole obtained as described by Sarasin.[21] No traces of the isomeric 1-methyl-4-chloro-5-nitroimidazole could be detected in the mother liquor of the crystallization.

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Derivatives of 3-Methylthiazolo[3,2-*a*]benzimidazole[1,2]

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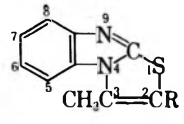
Depending upon reaction conditions, 3-(2-benzimidazolylthio)-2,4-pentanedione (I) or ethyl 2-(2-benzimidazolylthio)acetoacetate (II) when treated with acetic anhydride in pyridine either undergo cyclization or form enol acetates; however, 1-(2-benzimidazolylthio)-2-propanone (III) gives only the enol acetate. A possible mechanism and supporting infrared data are discussed.

As thiazolethiols and 2-mercaptobenzimidazole are known accelerators for the vulcanization of rubber with sulfur and antidegradants for rubber, respectively, it was desirable to prepare a novel heterocyclic compound containing both the thiazolyl and benzimidazolyl moieties. Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one has been prepared by the dehydration of 2-benzimidazolylthioacetic acid[3,4]; the purpose of this investigation was to prepare compounds having the following structure.



R = H, $COCH_3$, $COOC_2H_5$, COOH, $CHOHCH_3$, $CONHC_6H_5$, CCH_3 (‖ NOH)

The preparation of these new compounds was realized as illustrated in Fig. 1.

The key intermediates, 3-(2-benzimidazolylthio)-2,4-pentanedione (I), ethyl 2-(2-benzimidazolylthio)-acetoacetate (II), and 1-(2-benzimidazolylthio)-2-propanone (III), required for the synthesis of the new compounds, were prepared by the reaction of the potassium salt of 2-mercaptobenzimidazole with 3-chloro-2,4-pentanedione, ethyl α-chloroacetoacetate, and chloroacetone, respectively. The data are summarized in Table I.

When the mixture containing I, acetic anhydride, and pyridine was heated for only 10 min. at 90–100°, the product isolated in 96% yield was 3-(2-benzimidazolylthio)-4-hydroxy-3-penten-2-one acetate (IV). We had anticipated that acetylation would have occurred on the amino group. However, our postulate was not substantiated since the infrared spectrum revealed that the hydroxyl group was acetylated. However, when this mixture was heated at 90–100° for 3 hr., methyl 3-methylthiazolo[3,2-*a*]benzimidazolyl ketone (V) which contained no ester bonds in the infrared spectrum was obtained in 99% yield. When the mixture was heated at 90–100° for 1 hr., IV and V were ob-

(1) The *Chemical Abstracts*' preferred name for all compounds was kindly furnished by Dr. L. T. Capell of the *Chemical Abstracts*' service.
(2) Presented at the 146th National Meeting of the American Chemical Society, Denver, Colo., January, 1964.
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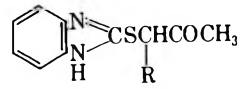
Table I

3-(2-Benzimidazolylthio)-2,4-pentanedione (I), Ethyl 2-(2-Benzimidazolylthio)acetoacetate (II), and 1-(2-Benzimidazolylthio)-2-propanone (III)



No.	R	% yield, crude	M.p., °C.	Empirical formula	% N Calcd.	% N Found	% S Calcd.	% S Found
I	$-COCH_3$	88.5	185–186[a]	$C_{12}H_{12}N_2O_2S$	11.28	11.19	12.91	12.56
II	$-COOC_2H_5$	71.8	149–150[a]	$C_{13}H_{14}N_2O_3S$	10.07	10.38	11.52	11.26
III	$-H$	82.2	114–115[a]	$C_{11}H_{10}N_2OS$	13.58	13.66	15.52	15.30

[a] Recrystallization from ethyl alcohol.

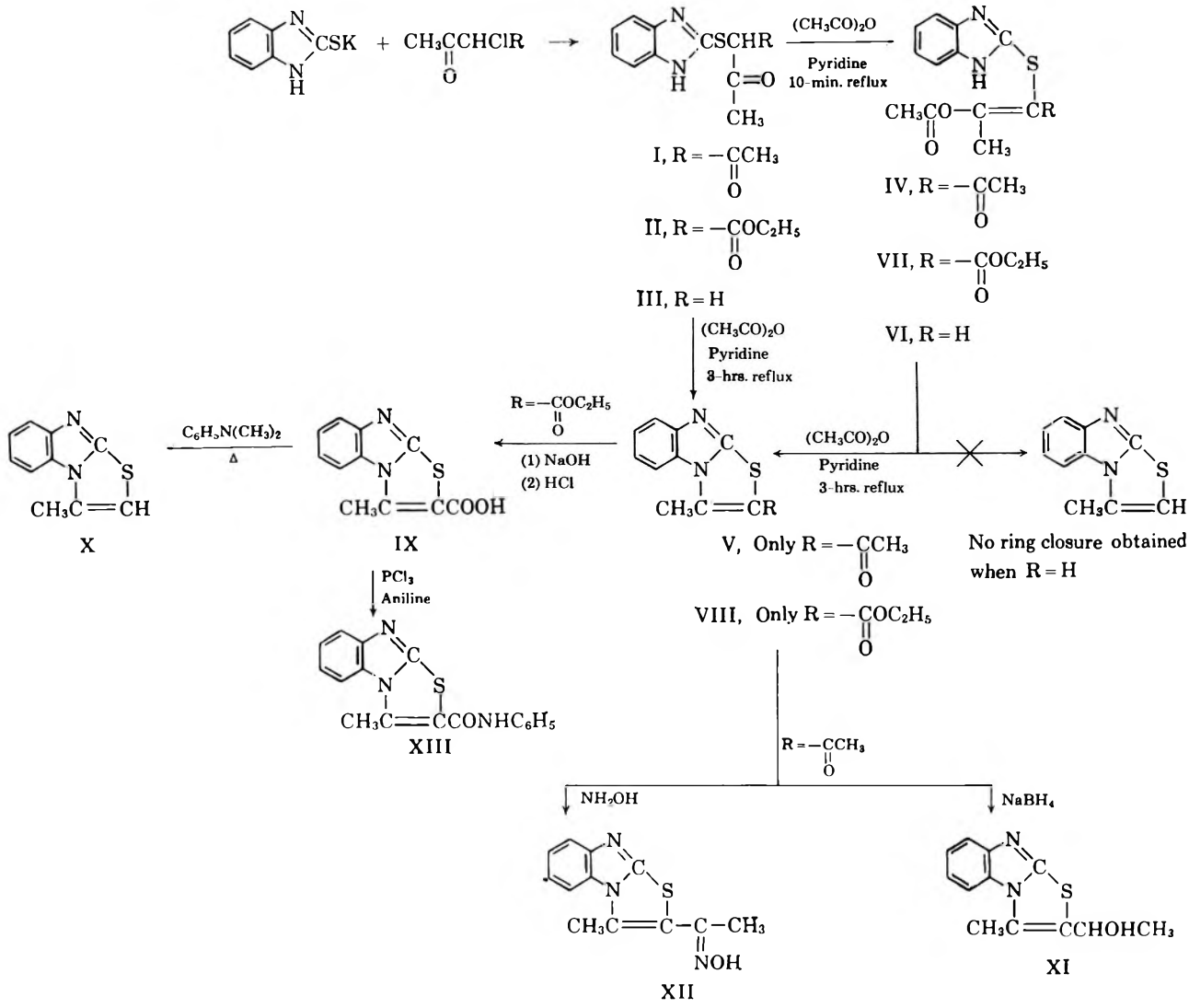


Figure 1

tained in 27.4 and 69.5% yields, respectively. The separation of IV from V was accomplished by cooling the reaction mixture to 0° and collecting V by filtration. Upon the addition of cold water to the filtrate, IV precipitated and was collected by filtration. An attempt to prepare V by heating IV with pyridine alone at 90–100° for 3 hr. failed. However, when pyridine, acetic anhydride, and IV were heated under the same conditions, V was obtained in 97.5% yield.

It was anticipated that the reaction of III with acetic anhydride and pyridine at 90–100° for a period of 4 hr. would yield the desired 3-methylthiazolo[3,2-*a*]benzimidazole (X) but instead 1-(2-benzimidazolylthio)-1-propen-2-ol acetate (VI) was obtained in 99% yield. The infrared spectrum and elemental analysis confirm that no ring closure occurred under these conditions.

The treatment of II with acetic anhydride and pyridine at 90–100° for 10 min. furnished ethyl 2-(2-benzimidazolylthio)-3-hydroxycrotonate acetate (VII) in 99% yield. Because of the great similarity of the infrared spectrum of VII with that of VIII, with only a slight increase in carbonyl and ester absorbance, it was likely that this intermediate was unstable and underwent some ring closure during work-up. Further

Table II

Infrared Data of I–XIII

Compound	ν, cm.$^{-1a}$	Assignment
I	3200–2600 (br)	N–H st. and O–H st. (enol)
	1550 (br)	C=O st. (conjugate chelation)
	1393 (s)	Unassigned
II	3340 (w)	N–H st.
	3200 (br)	O–H st. (enolic)
	1730 (m)	C=O st. (ester)
	1590 (s)	C=O st. (conjugate chelation)
	1448 (s)	C–H deformation
	1389 (m)	CH_3 def. (sym.)
	1250 (vs)	C–O st. (ester)
III	3400–2500 (br)	N–H st.
	1712 (m)	C=O st.
	1449 (s)	CH_2 + CH_3 def.
	1361 (s)	CH_3 def. (sym.)
IV	3350 (w)	N–H st.
	1720 (s)	C=O st. (ester)
	1680 (s)	C=O st. (conj. to double bond)
	1610 (s)	C=C st.
	1560 (s)	Unassigned
	1455 (s)	CH_3 def. (asym.)
	1370 (s)	CH_3 def. (sym.)
	1250 (s)	C–O st. (ester)
V	1674 (s)	C=O st. (conj. to double bond)
	1610 (m)	C=C st.
	1560 (s)	Unassigned
	1455 (s)	CH_3 def. (asym.)
	1370 (s)	CH_3 def. (sym.)
	1310 (s)	Unassigned
VI	3400 (w)	N–H st.
	1650 (s)	C=O st. (hydrogen bonded)
	1620 (w)	C=C st.
	1255 (s)	C–O st. (ester)
VIII	1708 (s)	C=O st. (conj. to double bond)
	1612 (m)	C=C st. (conj. to carbonyl)
	1595 (s)	Unassigned
	1455 (m)	CH_2 + CH_3 def.
	1380 (m)	CH_3 def. (sym.)
	1250 (s)	C–O st. (ester)
IX	2353 (m)	O–H st. (H-bonded carboxylic acid)
	1675 (m)	C=O st. (conj. to double bond)
	1315 (m)	Unassigned
X	3110 (w)	C–H st. (fused ring olefin)
	1616 (w)	C=C st.
	1448 (s)	CH_3 def. (asym.) and other unassigned
	1382 (w)	CH_3 def. (sym.)
	1308 (m)	Unassigned
XI	3200 (m)	O–H st. (hydrogen bonded)
	1624 (m)	C=C st.
	1290 (m)	Unassigned
	1087 (s)	O–H def.
XII	2800–2600 (br)	N–O–H associated
	1600 (m)	C=C st. (conj.)
	1400 (s)	Unassigned
XIII	3300 (br)	N–H st. (secondary amide)
	1670 (m)	C=O st. (amide I)
	1610 (w)	C=C (conj. to carbonyl)
	1455 (w)	CH_3 def. (asym.)
	1440 (s)	Unassigned
	1377 (w)	CH_3 def. (sym.)
	694 (m)	C–H out-of-plane def. of monosubstituted phenyl group

[a] br = broad, w = weak, m = medium, s = strong, v = very.

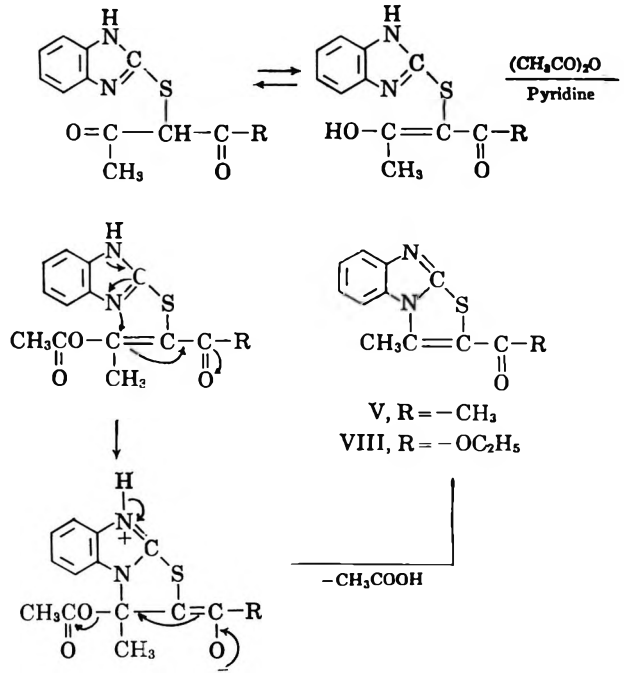


Fig. 2.—Mechanism for V and VIII.

evidence of instability was the evolution of an acetic acid odor upon standing. As expected, the reaction of VII or II in an acetic anhydride–pyridine solution at 90–100° for 3 hr. gave ethyl 3-methylthiazolo[3,2-*a*]-benzimidazole-2-carboxylate (VIII) in 98 and 96.5% yields, respectively.

The saponification of VIII with aqueous sodium hydroxide furnished 3-methylthiazolo[3,2-*a*]benzimidazole-2-carboxylic acid (IX) in 90.5% yield.

The decarboxylation of IX in a dimethylaniline solution at 190–200° furnished 3-methylthiazolo[3,2-*a*]-benzimidazole (X) in 45.3% yield.

The reduction of V with sodium borohydride gave the expected α,3-dimethylthiazolo[3,2-*a*]benzimidazole-2-methanol (XI) in 86.5% yield.

2-Acetyl-3-methylthiazolo[3,2-*a*]benzimidazole oxime (XII) was obtained in 77% yield by the reaction of V with hydroxylamine.

The treatment of IX with phosphorus trichloride and aniline furnished 3-methylthiazolo[3,2-*a*]benzimidazole-2-carboxanilide (XIII) in 64.2% yield.

The mechanism as illustrated in Fig. 2 is offered for the cyclization reactions. The presence of the acetyl of ethoxycarbonyl group in the 2-position facilitated ring closure because of increased resonance stabilization. However, when the above groups were replaced by hydrogen, this phenomenon was not a contributing factor and thus no ring closure occurred.

The infrared spectra of compounds I, VI, IX, XI, and XII were determined from suspensions in Nujol and halocarbon oil. The infrared spectra of compounds II, III, IV, V, VIII, X, and XIII were determined in chloroform (5000 to 830 cm.$^{-1}$) and dimethylformamide solutions (830 to 600 cm.$^{-1}$). A Perkin-Elmer Model 21 spectrophotometer with a sodium chloride prism was used. In all cases the C–H st. (aromatic) and C–H st. (aliphatic) bands were consistent with the proposed structures. Other significant infrared absorption bands of the compounds and assignments where possible are given in Table II.

A medium intensity band in the region 1490 cm.$^{-1}$ consistently appeared in all benzimidazole derivatives and is attributed to skeletal in-plane vibrations of the benzimidazole ring. The C–H out-of-plane deformation bands (region of 750 cm.$^{-1}$) characteristic of *ortho*-substituted phenyl groups were present in all spectra of benzimidazole derivatives. In compound X of Table II the assignment of the higher than normal frequency of 3110 cm.$^{-1}$ was made to the C–H st. of the olefinic group. This was based upon the assumption that the additional strain due to the fused rings induced more s character which resulted in a shorter C–H bond. For the purpose of comparison several frequencies of unassigned absorption bands are given in Table II.

Experimental[5]

3-(2-Benzimidazolylthio)-2,4-pentanedione (I), Ethyl 2-(2-benzimidazolylthio)acetoacetate (II), and 1-(2-Benzimidazolylthio)-2-propanone (III).—A stirred mixture containing 150.2 g. (1.0 mole) of 2-mercaptobenzimidazole, 2000 ml. of ethyl alcohol, and 66 g. (1.0 mole) of 85% potassium hydroxide was heated at 78–80° for 10 min. After cooling the resulting solution to 30°, 1 mole of 3-chloro-2,4-pentanedione, ethyl α-chloroacetoacetate, or chloroacetone was added in one portion. An exothermic reaction set in causing a temperature rise from 30 to 40°. After stirring at 25–30° for 18 hr., the reaction mixture was added to 2000 g. of ice–water. After stirring for 30 min. at 0–10°, the precipitate was collected by filtration, washed with water until free of chloride, and air-dried at 50°. The data are summarized in Table I.

3-(2-Benzimidazolylthio)-4-hydroxy-3-penten-2-one Acetate (IV).—A stirred slurry containing 32 g. (0.129 mole) of I, 65 ml. of pyridine, and 33 ml. of acetic anhydride was heated from 25 to 90° over a 3-min. period. The stirred solution was maintained at 90–100° for only 10 min. and immediately cooled to 0°. To this solution, 1 l. of cold water was added and stirring was continued at 0–5° for 1 hr. The resulting precipitate was collected by filtration, washed with water until neutral to litmus, and air-dried at 25–30°. The product, m.p. 130–132°, was obtained in 96% yield. After recrystallization from ethyl alcohol, it melted at 136–137°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: N, 9.65; S, 11.04. Found: N, 9.64, S, 10.76.

Methyl 3-Methylthiazolo[3,2-*a*]benzimidazolyl Ketone (V). Method 1.—A stirred slurry containing 49.2 g. (0.2 mole) of I, 50 ml. of acetic anhydride, and 100 ml. of pyridine was heated at 95–100° for 3 hr. The solution was cooled to 0° and held at 0–5° for 1 hr. The resulting precipitate was collected by filtration, washed with water until neutral to litmus, and air-dried at 25–30°. The product, m.p. 167–168°, was obtained in 99% yield. After recrystallization from ethyl alcohol the melting point remained unchanged.

Anal. Calcd. for $C_{12}H_{10}N_2OS$: N, 12.17; S, 13.92. Found: N, 12.51; S, 13.70.

Method 2.—A stirred solution containing 22 g. (0.076 mole) of IV, 50 ml. of pyridine, and 25 ml. of acetic anhydride was heated at 95–100° for 3 hr. The product was isolated as described in method 1. The product, m.p. 164–166°, was obtained in 97.5% yield. After recrystallization from ethyl alcohol, it melted at 167–168°. A mixture melting point with the product obtained from method 1 was not depressed and the infrared spectra of the two were superimposable.

Anal. Calcd. for $C_{12}H_{10}N_2OS$: N, 12.17; S, 13.92. Found: N, 12.51; S, 13.92.

3-(2-Benzimidazolylthio)-4-hydroxy-3-penten-2-one Acetate (IV) and Methyl 3-Methylthiazolo[3,2-*a*]benzimidazolyl Ketone (V).—A stirred solution containing 24.9 g. (0.1 mole) of I, 25 ml. of acetic anhydride, and 50 ml. of pyridine was heated at 90–100° for 1 hr. After cooling to 5°, the resulting solid was collected by filtration, washed with 1 l. of water, and air-dried at 25–30°. The product V, m.p. 163–167°, was obtained in 69.5% yield. After recrystallization from ethyl alcohol, it melted at 167–168°. A mixture melting point with product obtained from method 1 or 2 was not depressed, and the infrared spectra of the three products were superimposable. The combined filtrate was filtered and the product was air-dried at 25–30°. The product IV, m.p. 120–126°, was obtained in 27.4% yield. After recrystallization from ethyl alcohol, it melted at 136–137°. A mixture melting point with the product obtained by heating I for only 10 min. was not depressed, and the infrared spectra of the two were superimposable.

1-(2-Benzimidazolylthio)-1-propen-2-ol Acetate (VI).—A stirred solution containing 41.3 g. (0.2 mole) of III, 50 ml. of acetic anhydride, and 100 ml. of pyridine was heated at 90–100° for 4 hr. After cooling to 25°, 1000 ml. of water was added and stirring was continued at 25–30° for an additional 30 min. The precipitate was collected by filtration, washed with water until neutral to litmus, and air-dried at 25–30°. The product, m.p. 155–158°, was obtained in 99% yield. After recrystallization from ethyl alcohol, it melted at 171–172°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: N, 11.28; S, 12.91. Found: N, 11.29; S, 13.30.

Ethyl 2-(2-Benzimidazolylthio)-3-hydroxycrotonate Acetate (VII).—A stirred solution containing 27.9 g. (0.1 mole) of II, 50 ml. of pyridine, and 25 ml. of acetic anhydride was heated from 25 to 90° over a 3-min. period and then maintained at 90–100° for only 10 min. After immediately cooling the stirred solution to 0°, 500 ml. of water and 600 ml. of ethyl ether were added. After stirring for 15 min., the ether solution was separated, washed with water until the washings were neutral to litmus, and dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 30° at 1–2 mm. The resulting semi-solid was air-dried on a porous plate at 25–30°. The product, m.p. 68–71°, was obtained in 99% yield. After recrystallization from ethyl alcohol, it melted at 88–90°. Upon standing the compound was unstable and liberated acetic acid.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: N, 8.75; S, 10.01. Found: N, 9.15; S, 10.10.

Ethyl 3-Methylthiazolo[3,2-*a*]benzimidazole-2-carboxylate (VIII). Method 1.—A stirred solution containing 55.7 g. (0.2 mole) of II, 50 ml. of acetic anhydride, and 100 ml. of pyridine was heated at 90–100° for 3 hr. After cooling to 0°, 1000 g. of ice–water was added and stirring was continued at 0–5° for 30 min. The precipitate was collected by filtration, washed with water until neutral to litmus, and air-dried at 25–30°. The product, m.p. 106–109°, was obtained in 96.5% yield. After recrystallization from ethyl alcohol, it melted at 122–123°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: N, 10.76; S, 12.32. Found: N, 10.67; S, 12.37.

Method 2.—A stirred solution containing 15 g. (0.047 mole) of VII, 25 ml. of acetic anhydride, and 50 ml. of pyridine was heated at 90–100° for 3 hr. After cooling to 0°, 400 g. of ice–water was added and stirring was continued at 0–5° for 30 min. The solid was collected by filtration, washed with water until neutral to litmus, and air-dried at 25–30°. The product, m.p. 115–118°, was obtained in 98% yield. After recrystallization from ethyl alcohol, it melted at 122–123°. A mixture melting point with the product obtained from method 1 was not depressed, and the infrared spectra of the two were superimposable.

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: N, 10.76; S, 12.32. Found: N, 10.74; S, 12.21.

3-Methylthiazolo[3,2-*a*]benzimidazole-2-carboxylic Acid (IX).—A solution containing 182 g. (0.7 mole) of VIII, 224 g. (1.4 moles) of 25% aqueous sodium hydroxide, and 1600 ml. of ethyl alcohol was stirred at 75–80° for 4 hr. After cooling to 25°, the reaction mixture was added to 4000 g. of ice–water. The stirred solution was made acidic with 220 g. (2.2 moles) of concentrated hydrochloric acid. The resulting precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 50°. The product, m.p. 249–252° dec., was obtained in 90.5% yield. The melting point remained unchanged upon dissolving IX in dilute sodium hydroxide and then reprecipitating from concentrated hydrochloric acid.

Anal. Calcd. for $C_{11}H_8N_2O_2S$: N, 12.06; S, 13.81. Found: N, 12.25; S, 13.75.

3-Methylthiazolo[3,2-*a*]benzimidazole (X).—A stirred solution containing 38 g. (0.17 mole) of IX and 150 ml. of dimethylaniline was heated at 190–200° for 5 hr. After cooling to 25°, 500 ml. of water containing 125 g. (1.25 moles) of concentrated hydrochloric acid was added. A small amount of impurities was removed by filtration. To the stirred filtrate, concentrated ammonium hydroxide was added dropwise until pH 9 was obtained. To this

(5) All melting points were taken upon a Fisher-Johns block and are uncorrected.

stirred slurry, 300 ml. of ethyl ether was added and stirring continued for 15 min. The precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The product, m.p. 162–164°, was obtained in 45.3% yield. After recrystallization from ethyl alcohol, it melted at 165–166°.

Anal. Calcd. for $C_{10}H_8N_2S$: N, 14.88; S, 17.03. Found: N, 14.42; S, 16.93.

α,3-Dimethylthiazolo[3,2-*a*]benzimidazole-2-methanol (XI).—To a stirred solution containing 46.1 g. (0.2 mole) of V in 500 ml. of ethyl alcohol was added dropwise at 65–70° a solution containing 7.6 g. (0.2 mole) of sodium borohydride in 200 ml. of ethyl alcohol over a 30-min. period. The stirred reaction mixture was heated at 75–80° for 2 hr. After cooling to 25°, the reaction mixture was added to 2000 g. of ice–water and stirred at 0–10° for 1 hr. The solid was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The product, m.p. 222–228°, was obtained in 86.5% yield. After recrystallization from dimethylformamide, it melted at 227–228°.

Anal. Calcd. for $C_{12}H_{12}N_2OS$: N, 12.06; S, 13.80. Found: N, 12.06, S, 14.12.

2-Acetyl-3-methylthiazolo[3,2-*a*]benzimidazole Oxime (XII).—A stirred slurry containing 46.1 g. (0.2 mole) of V and 500 ml. of ethyl alcohol was heated to 75°. To the cooled stirred solution at 25° was added in one portion 16.4 g. (0.25 mole) of hydroxylamine hydrochloride in 50 ml. of water. A solution containing 17.4 g. (0.125 mole) of potassium carbonate in 60 ml. of water was added dropwise at 25–30° over a 15-min. period. The stirred reaction mixture was heated at 75–80° for 2.5 hr. After cooling to 5°, the precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air-dried at 25–30°. The product, m.p. 230–234° dec., was obtained in 77% yield. After recrystallization from ethyl alcohol, it melted at 246–247° dec.

Anal. Calcd. for $C_{12}H_{11}N_3OS$: N, 17.13; S, 13.07. Found: N, 16.95; S, 13.16.

3-Methylthiazolo[3,2-*a*]benzimidazole-2-carboxanilide (XIII).—To a stirred slurry containing 34.9 g. (0.15 mole) of IX, 14.1 g. (0.15 mole) of aniline, and 200 ml. of chlorobenzene, 6.9 g. (0.05 mole) of phosphorus trichloride was added dropwise at 80–90° over a 5-min. period. The stirred reaction mixture was heated at 120–130° for 6 hr. After cooling to 25°, 500 ml. of water containing 40 g. (0.25 mole) of 25% aqueous sodium hydroxide was added and stirring was continued for 1 hr. The precipitate was collected by filtration, washed with water until the wash water was neutral to litmus, and air-dried at 25–30°. The product, m.p. 232–233° dec., was obtained in 64.2% yield. The melting point remained unchanged after recrystallization from dimethylformamide.

Anal. Calcd. for $C_{17}H_{13}N_3OS$: N, 13.67. Found: N, 13.40.

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The 1,4-Anhydrohexitols. Synthesis and Periodate Oxidation[1]

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The 1,4-anhydrohexitols are prepared from the pentoses by application of the nitromethane synthesis followed by reduction and deamination. The rate of "overoxidation" of the 1,4-anhydrohexitols by sodium metaperiodate depends on the rearrangement of the initially formed trialdehyde to a rapidly oxidized form which absorbs at 272 mμ.

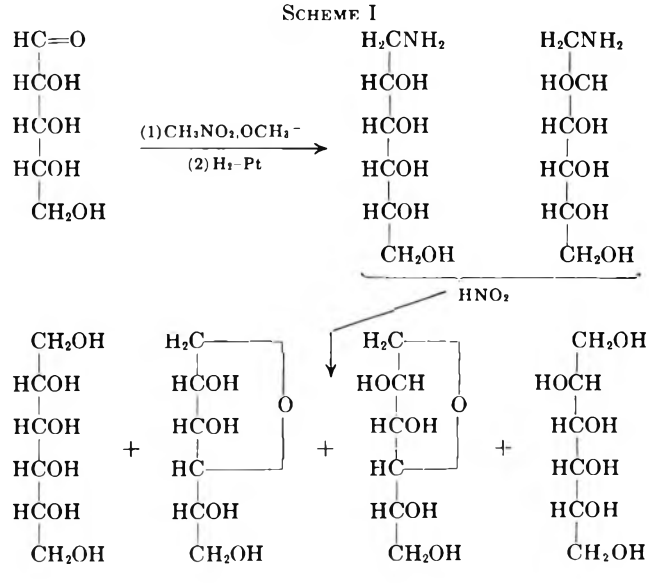
In connection with an investigation of the acid-catalyzed anhydrization of the alditols it was necessary to synthesize those 1,4-anhydrohexitols which are not described in the literature. Most methods of synthesis require the hexose, or a derivative thereof, as starting material and these are not all readily available.[2,3]

In the synthesis reported here, the pentoses, which are readily available, were used as starting materials and the following sequence of reactions was applied to them: pentose → 2-epimeric sodio *aci*-nitro alcohols[4] → 2-epimeric hexitylamines → 2-epimeric hexitols + 2-epimeric 1,4-anhydrohexitols.

The reactions were carried out on D-ribose, D-arabinose, D-lyxose, and D-xylose. In Scheme I the sequence is illustrated using D-ribose as an example.

Paper column chromatography[5] using butanone–water as solvent in all cases gave a fractionation of the products into at least three components. The fastest moving component was an impurity identified as a 1-deoxy-1-(methylnitrosoamino)pentitol.[6] The second and third fractions were the two epimeric 1,4-anhydrohexitols, and the slowest moving component was a mixture of the two epimeric alditols. The 1,4-anhydroalditols from lyxose and xylose were not well-resolved on the column and were separated *via* the isopropylidene derivatives. In all cases one of the pair had *cis* hydroxyl groups in the tetrahydrofuran ring and, therefore, formed a diisopropylidene derivative, whereas the other, having *trans* hydroxyl groups in the ring, could form only a monoisopropylidene deriva-

SCHEME I



(1) This investigation was supported in part by a grant from the Atlas Powder Co., Wilmington, Del., and in part by Public Health Service Research Grant GM 09021 from the National Institute of General Medical Sciences.

(2) L. F. Wiggins, *Adran. Carbohydrate Chem.*, **5**, 191 (1950).

(3) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 3742 (1951).

(4) J. C. Sowden and H. O. L. Fischer, *ibid.*, **67**, 1713 (1945).

(5) LKB, Chro Max Column, Stockholm, Sweden.

(6) R. Barker, in preparation.

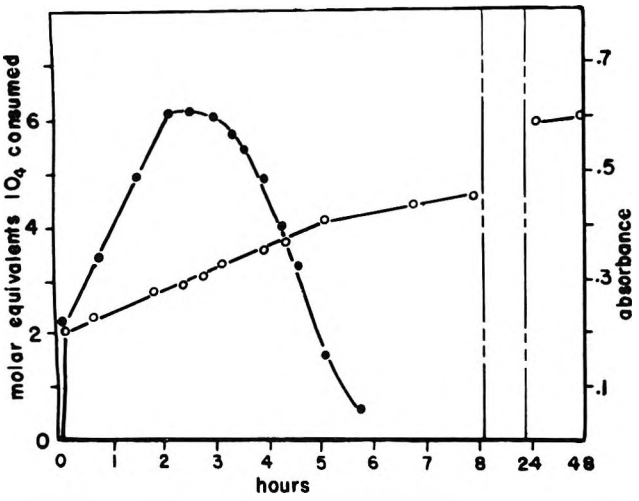


Fig. 1.—Uninterrupted oxidation of 1,4-anhydro-DL-allitol. Periodate consumption, 3 m*M* alditol and 20 m*M* sodium metaperiodate. Absorbance of a 25-fold dilution of the oxidation mixture.

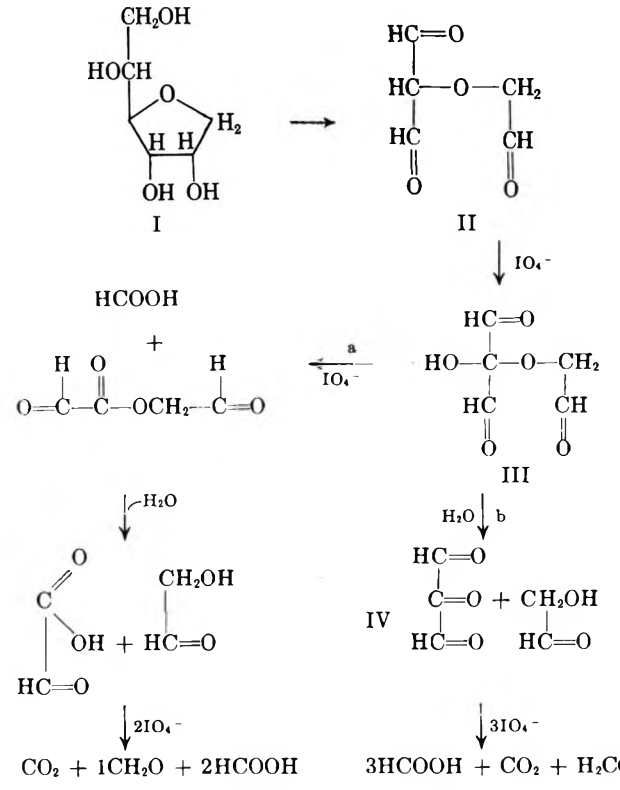
tive. The two types of isopropylidene derivatives can be separated readily by adsorption chromatography on Florisil.[7]

All of the 1,4-anhydrohexitols consumed 6 molar equivalents of periodate and gave 2 molar equivalents of formaldehyde and 3 molar equivalents of formic acid.[8] It was of interest to study the kinetics of the periodate reaction to ascertain whether configuration or internal hemiacetal formation of the intermediates affected the rate. To expedite this a more rapid spectrophotometric method of measuring periodate consumption was sought. The methods currently in the literature use very dilute solutions and give very low rates.[9] To this end the oxidation of D-mannitol was investigated. An excellent agreement between decrease in absorbance and molar equivalents of periodate consumed was obtained when the reaction was followed at 270 mμ. Using 3 ml. of 3.1 m*M* sodium metaperiodate and 1.0 μmole of mannitol, the oxidation was complete in 7 min., at which time 5.00 ± 0.02 molar equivalents of oxidant had been consumed.

When the same molar proportions of oxidant and 1,4-anhydroalditol were employed, the absorbance of the sample fell during the first 3 min. and then increased to a maximum at approximately 5 hr. and again decreased until a steady value was reached after 4 days. Total periodate consumption was then 6.05 molar equivalents.

The 1,4-anhydrohexitols (I) give rise, on consumption of 2 molar equivalents of periodate, to a "trialdehyde" (II). This compound has been postulated[8] to undergo oxidation to the mesoxaldehyde derivative (III) which undergoes further oxidation *via* pathways a or b[10] (Scheme II). The only component of this scheme which would be expected to have a strong absorption band at 270 mμ is the reductone (IV). Since it is unlikely that IV could occur in sufficient quantities to account for the observed absorbance early in the course of the oxidation (*cf.* Fig. 1), an attempt was

SCHEME II



made to elucidate the structure of the absorbing substance.

1,4-Anhydro-DL-allitol (I) was oxidized with sodium metaperiodate so that 2 molar equivalents of oxidant were consumed in 10 min. The dilute solution containing II and iodate was kept at room temperature and the amount of oxidizing material (iodate) and absorbance were assayed at intervals. No decrease in titer was observed over a period of 3 days, and no iodine[11,12] was formed. The absorbance increased steadily for a period of 24 hr. at which time it was stable at a value corresponding to a molar absorbance of 1.4×10^4 at 272 mμ. No other absorption maxima were observed. The rate of appearance of the absorbing substance is first order for approximately 90% of the reaction period, indicating that the reaction being observed probably involves only the rearrangement of the trialdehyde (II). Initial first-order kinetics are consistent also with an equilibrium in which the absorbing species predominates. The rearrangement is essentially instantaneous in neutral solution and is inhibited by acidic conditions. It procedes as shown in Fig. 2 in unbuffered iodate solution (pH 4–5). No alteration in the carbon skeleton of II occurs during the rearrangement, since reduction of II and its rearrangement product, followed by acetylation, yield the same material as analyzed by gas chromatography. The rearranged product behaves as a weak acid with a pK_a of 5.5, and when placed in basic solution it reacts with base in a nonstoichiometric fashion to yield a product, the molar extinction coefficient of which is 2.4×10^4 (λ_{max} 277 mμ).

When the rearranged product is treated with an excess of sodium metaperiodate, the optical density

(7) Floridin Co., Tallahassee, Fla.

(8) C. F. Huebner, S. R. Ames, and E. D. Bubl, *J. Am. Chem. Soc.*, **68**, 1621 (1946).

(9) J. S. Dixon and D. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).

(10) M. Cantley, L. Hough, and A. P. Pittet, *J. Chem. Soc.*, 2527 (1963).

(11) T. G. Halsall, E. L. Hirst, and J. K. N. Jones, *ibid.*, 1427 (1947).

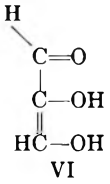
(12) H. G. Fletcher, Jr., H. W. Diehl, and R. K. Ness, *J. Am. Chem. Soc.*, **76**, 3029 (1954).

falls rapidly to a value corresponding to a molar extinction of 1.15×10^4. During the same interval (1 min.) 1 molar equivalent of periodate is consumed, and no formaldehyde, formic acid, or carbon dioxide is evolved. The subsequent uptake of periodate (3 molar equivalents) is slow and follows second-order kinetics as shown in Fig. 2. The appearance of formic acid and formaldehyde parallel the consumption of periodate. These findings are interpreted as indicating that, in the consumption of the last 3 moles of oxidant, the rate is limited by the consumption of the first of these 3 moles. The finding that the process is second order indicates that a hydrolysis does not limit the rate of the reaction since a hydrolysis would be expected to show first-order kinetics.[13]

The sequence of events outlined above is represented in Fig. 2.

The same series of events appears to occur in the uninterrupted oxidation of I. This hypothesis is borne out by the finding that the initial rate of increase in absorbance at 270 mμ in the uninterrupted oxidation (Fig. 1) is essentially the same as the rate of rearrangement of II to the absorbing substance (III) in the absence of oxidation. These rates would concur if III is instantaneously oxidized, and if the product of that oxidation (IV) also absorbs at 270 mμ and is itself much more slowly oxidized. The rate of destruction of the absorbing substance (IV) in the uninterrupted oxidation would reflect a balance between rate of formation and rate of breakdown and would be expected to appear lower than when only breakdown is being observed. The observed change in absorbance with time (Fig. 1) is as predicted by these considerations.

The structure of the rearranged product has not been elucidated. It is probable that it is a hemialdal or hemiacetal,[14] and it must contain a conjugated system to have ϵ 1.4×10^4 at 272 mμ. According to Evans and Gillam,[15] an acyclic α,β-unsaturated aldehyde substituted at both the α- and β-position should have λ_{max} 230 $\pm$ 5 mμ. However, triose reductone (VI) has been reported to have λ_{max} 266 mμ,[16] and a number of other endiols conjugated with carbonyls have absorptions



VI

in the range of 260–290 mμ with molar absorbancies of the order of 10^4 l. mole^{-1} cm.$^{-1}$.[17]

The very rapid oxidation of the absorbing material is reminiscent of the finding of Wolfrom and Bobbitt that cyclic 1,3-diketones oxidize considerably faster than do their acyclic counterparts.[18] It has been suggested by Bose, Foster, and Stephens[19] that a cyclic enol may be the reactive species in the oxidation of

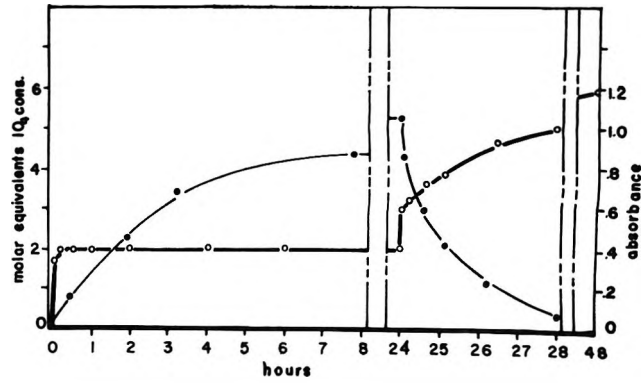
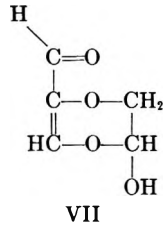


Fig. 2.—Interrupted oxidation of 1,4-anhydro-DL-allitol. Periodate consumption, 50 mM alditol and 2 molar equivalents of periodate at time 0; diluted to give 2 mM alditol after 30 min.; added 16 mmoles of periodate at 24 hr. Absorbance of a 50-fold dilution of the oxidation mixture.

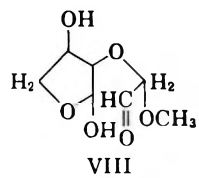
cyclic 1,3-diketones. A possible structure for the reactive species which is formed by the rearrangement of II based on the above considerations is VII which may oxidize rapidly to yield III or one of the many forms of III which would be present in aqueous solution.



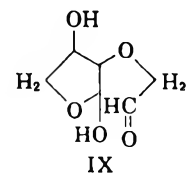
VII

It is also possible that to some extent the variations in rate of oxidation of active methylene compounds with pH which have been observed[20] are a function of the rate of formation of a rapidly oxidizeable form of the malondialdehyde derivative analogous to VII.

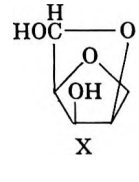
The rate of the uninterrupted periodate oxidation of 1,4-anhydroalditols can be used to determine whether the hydroxyls in the tetrahydrofuran ring are *cis* or *trans* to each other when sufficiently dilute solutions are used.[21] The oxidation of *cis* hydroxyls is essentially instantaneous and the oxidation of *trans* hydroxyls requires approximately 5 hr. when solutions 2 mM with respect to glycol and 16 mM with respect to periodate are used. That the difference in rates is not due to internal hemiacetal formation is shown by comparison with the rates of oxidation of 1,4-anhydroerythritol and 1,4-anhydro-DL-threitol which contain, respectively, *cis* and *trans* glycol structures in a tetrahydrofuran ring as the only oxidizable groups. In contrast to the findings by Criegee,[22] that methyl D-mannofuranoside is oxidized by lead tetraacetate preferentially at the *cis*-ring hydroxyls,



VIII



IX



X

(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 11.
(14) R. D. Guthrie, *Advan. Carbohydrate Chem.*, **16**, 105 (1961).
(15) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).
(16) H. V. Euler, H. Hasselquist, and G. Hanshoff, *Arkiv Kemi*, **6**, 471 (1953).
(17) E. F. Hartree, *J. Am. Chem. Soc.*, **73**, 6244 (1953).
(18) M. L. Wolfrom and J. M. Bobbitt, *ibid.*, **78**, 2489 (1956).
(19) J. L. Bose, A. B. Foster, and R. W. Stephens, *J. Chem. Soc.*, 3314 (1959).
(20) M. Cantley and L. Hough, *ibid.*, 2711 (1963), and earlier papers by the latter author.
(21) H. Klosterman and F. Smith, *J. Am. Chem. Soc.*, **74**, 5336 (1952).
(22) R. Criegee, *Ann.*, **495**, 211 (1932).

with the formation of a cyclic hemiacetal (VIII) which impedes further oxidation, no indication of a difference in the rate of consumption of the first 2 molar equivalents of periodate was observed in the oxidation of the 1,4-anhydrides of mannitol, allitol, gulitol, or talitol. It is, therefore, unlikely that structures such as IX or X occur to an appreciable extent during the oxidation.

In all cases the R_f of the 1,4-anhydro alditol having a *trans* glycol grouping in the tetrahydrofuran ring was slightly higher than that of its epimer having a *cis* glycol.

Experimental[23]

(1) **1,4-Anhydro-D-allitol and 1,4-Anhydro-D-altritol. A. Mixed Sodio-*aci*-nitro Alcohols from D-Ribose.**[4]—To a solution of 50 g. of D-ribose in 250 ml. of dry methanol and 250 ml. of nitromethane at room temperature was added during 30 min. 250 ml. of dry methanol containing 10 g. of sodium. The heavy precipitate which formed was collected after 2 hr. and thoroughly washed with dry methanol to remove nitromethane and ribose,[24] and then with ether. After drying *in vacuo* it weighed 52 g.

B. Mixed 1-amino-1-deoxy-D-allitol and D-altritol.—The mixed sodio-*aci*-nitro alditols from A (52 g.) in 500 ml. of 25% aqueous acetic acid were hydrogenated over platinum oxide (1 g.) in a Parr[25] pressure reaction apparatus at pressures between 10 and 30 lb. Hydrogen uptake was measured by decrease in pressure and ceased after 18 hr. when approximately 15 l. (3 molar equiv.) had been consumed. After removal of the catalyst by filtration, the solution was concentrated to a sirup which was redissolved in water and percolated through a column containing 350 ml. of IR 120[26] cation-exchange resin in the H^+ form. The column was washed with water until the eluate was no longer acidic,[27] and then eluted with approximately 6% aqueous ammonia slowly so that the reaction between the eluent and the resin did not cause the column to overheat. The first 300 ml. of basic eluate was collected and concentrated to give 56 g. of amber sirup. The product gave one zone on paper chromatography in butanone–water (100:8 v./v.), R_f 0.1, which reacted with ninhydrin and periodate–benzidine sprays.[28]

C. Mixed 1,4-Anhydro-D-allitol, 1,4-Anhydro-D-altritol, Allitol, and D-Altritol (D-Talitol) and Their Separation.—To a solution of 56 g. of mixed 1-amino-1-deoxy alditols from B in 250 ml. of 25% aqueous acetic acid was added 20 g. of sodium nitrite in small batches during 30 min. The temperature rose to 40° and nitrogen was evolved rapidly. After 18 hr. the reaction mixture was boiled for 1 hr. and then concentrated to yield 80 g. of a pale yellow sirup. This sirup was dissolved in 200 ml. of water and passed over columns containing 500 ml. of IR 120 (H^+) and 500 ml. of IR 45 in the free base form. The neutral eluate was concentrated and dried at 0.1 mm. overnight to yield a thick yellow sirup weighing 26 g. Paper chromatography in butanone–water showed that the sirup contained at least four components. The fastest moving (R_f 0.4) was shown to be 1-deoxy-1-(methyl nitrosoamino)-D-ribitol which was present in small amounts (*ca.* 5%). The next two zones which constituted more than 50% of the mixture had R_f values of 0.17 and 0.11. The fourth zone did not move from the point of application.

This separation also was accomplished on a Chro Max[5] paper column (size 4). When 8 ml. of an aqueous solution containing 4.3 g. of the mixture was applied to a dry column, the column was eluted with 60 ml. of butanone followed by butanone–water (100:8 v./v.), and 25-ml. fractions of the eluate were collected, the fast moving components (214 mg.) was found in tubes 70–120. Fractions 161–255 contained 954 mg. of material which was crystallized and recrystallized from isopropyl alcohol and had m. p. 106.5–107.5° and $[\alpha]_D$ +13.9 (*c* 3.7, water). The compound was identified as 1,4-anhydro-D-altritol on the basis of (i) the consumption of 6 molar equiv. of periodate, (ii) the slow rate of consumption of the second mole of oxidant, (iii) higher R_f on paper chromatography, and (iv) the transformation to a monoisopropylidene derivative which consumed 1 molar equiv. of periodate.

Anal. Calcd. for $C_6H_{12}O_5$ (164.16): C, 43.90; H, 7.37. Found: C, 44.11; H, 7.45.

Fractions 285–420 contained 1.20 g. of material which was crystallized from ethyl alcohol to give m.p. 83–85°, $[\alpha]^{25}_D$ +46.1 (*c* 5.5, water). The compound has an infrared spectrum essentially identical with that of the known 1,4-anhydro-DL-allitol,[29] and the spectra of the acetates taken as smears of the pure compounds are identical.

Anal. Calcd. for $C_6H_{12}O_5$ (164.16): C, 43.90; H, 7.37. Found: C, 44.05; H, 7.54.

The column then was washed with water. The eluate contained 1.6 g. of material which by electrophoresis in 0.2 *M* arsenite buffer pH 9.6[30] appeared to consist of equal parts of allitol and talitol.

(2) **1,4-Anhydro-D-iditol and 1,4-Anhydro-D-gulitol. A. B.**[31]—D-Xylose (50 g.) was dissolved in 35 ml. of water with warming. To this solution was added 500 ml. of an equivolume mixture of methanol and nitromethane and then a solution of 10 g. of sodium in 500 ml. of methanol slowly with constant, vigorous stirring. The precipitate was collected after 8 hr. by centrifugation in the cold and washed with several small volumes of ice-cold methanol. The washed precipitate was dissolved in 250 ml. of 50% aqueous acetic acid and hydrogenated over platinum oxide. The product which was isolated as described for the ribose derivatives weighed 36 g.

C.—The 1-amino-1-deoxyalditols (36 g.) were deaminated and the product was purified as described under 1 C.

Paper column chromatography of 7.6 g. of the product gave three fractions. The first fraction representing 6% of the mixture was an *N*-nitroso compound.[6] The second fraction representing 60% of the mixture was itself a mixture of 1,4-anhydro-D-iditol and 1,4-anhydro-D-gulitol in approximately equal amounts. The third fraction, representing 30% of the mixture, contained the alditols, iditol and glucitol, and was obtained by eluting the column with water.

D. Separation of 1,4-Anhydro-D-iditol and 1,4-Anhydro-D-gulitol *via* Their Isopropylidene Derivatives.—The mixture of 1,4-anhydro-D-glucitol and 1,4-anhydro-D-iditol (4.0 g.) was dissolved in 200 ml. of dry acetone containing 0.5 ml. of concentrated sulfuric acid. After 24 hr. the solution was passed over a column containing 50 ml. of IR 45 which had been washed previously with acetone. The neutral eluate was concentrated to give 5.3 g. (97%) of a sirup. An ethereal solution of this sirup was passed over a column containing 70 g. of Florisil[7]; the column was eluted with 500 ml. of dry ether and then with 500 ml. of methanol.

The ether eluate contained 2.3 g. of material which deposited crystals from solution in ether–petroleum ether (b.p. 60–90°); the melting point after two recrystallizations from the same solvent was 83–83.5°, $[\alpha]_D$ +30.4 (*c* 3.34, toluene). This is the diisopropylidene derivative of 1,4-anhydro-D-gulitol.

Anal. Calcd. for $C_{12}H_{20}O_5$ (244.29): C, 59.00; H, 8.25. Found: C, 58.86; H, 8.38.

1,4-Anhydro-D-gulitol.—The diisopropylidene derivative (1.4 g.) was hydrolyzed by heating at 100° in 50% aqueous acetic acid for 2 hr. After removal of the solvent and repeated concentration from water to remove acid, a neutral sirup was obtained which showed a strong absorption at 5.8 μ which was interpreted and indicated the presence of a considerable proportion of an acetate in the material. Saponification, followed by removal of the cations on IR120 (H^+) and removal of the water, gave a sirup which deposited 600 mg. of crystals from solution in 100 ml. of ethyl acetate. Recrystallization from ethyl acetate gave a material with m.p. 109–110° and $[\alpha]^{25}_D$ +9° (c 8.6, water). Montgomery and Wiggins reported m.p. 113° and $[\alpha]_D$ −7.5 for the L isomer (3,6-anhydro-D-glucitol).

(23) Melting points are corrected. Evaporations were performed at water aspirator pressure on a rotary evaporator. Descending paper chromatography was carried out on Whatman 31 paper at room temperature. This paper gives similar separations to Whatman 1 but is twice as fast.

(24) Removal of nitromethane is essential to avoid the later formation of 1-deoxy-1-(methylnitrosoamino)pentitols.[8]

(25) Parr Instrument Co. Moline, Ill., U. S. A.

(26) Rohm and Haas Co., Phildelphia 5, Pa.

(27) Concentration of this eluate gave 2.7 g. of a sirup which was slightly reducing.

(28) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(29) R. Barker, K. O. Lloyd, R. R. Thompson, and J. C. Sowden, in preparation.

(30) J. L. Frahn and J. A. Mills, *Australian J. Chem.*, **12**, 65 (1959).

(31) Letters indicate the steps in the synthesis corresponding to the designation given under 1,4-anhydro-D-allitol and 1,4-anhydro-D-altritol.

1,4-Anhydro-D-iditol.—The material eluted from Florisil with methanol (2.13 g.) was hydrolyzed in aqueous acetic acid and then in aqueous base. After deionization, 1.6 g. of material was obtained which was crystallized twice from isopropyl alcohol to give 800 mg. of material with m.p. 94–95°, $[\alpha]^{25}D$ +17.9° (*c* 3.5, water). Le Maistre[32] has reported m.p. 95–96° and $[\alpha]^{25}D$ −17.7° for the L compound.

Anal. Calcd. for $C_6H_{12}O_5$ (164.16): C, 43.90; H, 7.37. Found: C, 44.00; H, 7.60.

1,4-Anhydro-D-galactitol and 1,4-Anhydro-D-talitol.—These were prepared from D-lyxose and isolated as described for the products from D-xylose. 1,4-Anhydro-D-galactitol had m.p. 95–96°, $[\alpha]^{25}D$ −18° (*c* 2, water), and an infrared spectrum identical with that of an authentic sample.[3]

2,3:5,6-Diisopropylidene-1,4-anhydro-D-talitol was shown to have an infrared spectrum in chloroform identical with that of the known racemic compound,[29] melted at 45°, and had $[\alpha]^{25}D$ −19.4° (*c* 2.9, toluene).

Anal. Calcd. for $C_{12}H_{20}O_5$ (244.29): C, 59.00; H, 8.25. Found: C, 59.31; H, 8.46.

Hydrolysis of the isopropylidene derivative gave a sirup which has not crystallized in more than a year and which has not given a crystalline acetate, benzoate, or *p*-nitrobenzoate. The sirup shows only one component on chromatography in a variety of solvents and has $[\alpha]D$ −57.8° (*c* 2.2, water).

Periodate Oxidations.—All oxidations were carried out in unbuffered sodium metaperiodate at room temperature (22–25°). Utilization of oxidant was followed by titration of iodine released from a suitable aliquot on addition of 5 ml. each of 2 *N* sulfuric acid and 20% aqueous potassium iodide with either 0.1 *N* or 0.01 *N* thiosulfate. The possibility of iodine consumption by the products of the oxidation was checked by the addition of a standard iodine solution, sulfuric acid, and iodide to a sample of the oxidation mixture and titration of the iodine present with standard thiosulfate. No consumption of iodine was observed.

Formaldehyde was determined with chromotropic acid by an adaptation of the method of Frisell, Meech, and Mackenzie.[33] Formic acid was determined by addition of an excess of ethylene glycol to an aliquot of the reaction mixture and titration with 0.01 *N* sodium hydroxide to the methyl orange end point, after 30 min.

The Preparation of Trialdehyde from 1,4-Anhydro-DL-allitol.—To an ice-cold solution of 492 mg. (3 mmoles) of 1,4-anhydro-DL-allitol in 50 ml. of water was added 11.5 ml. (6.1 mmoles) of 0.53 *M* sodium metaperiodate. After 0.5 hr. at room temperature, the reaction was essentially complete and the volume was made up to 1500 ml. with water. If this dilution was not made, iodine was produced in the reaction mixture in about 1 hr. No iodine was observed in the diluted solution even after 5 days at 25°. The dilute solution was used to follow the increase in absorbancy and to follow the oxidation of the absorbant compound. Absorbancy was measured in a Zeiss PM II spectrophotometer using 0.2-ml aliquots of the diluted reaction mixture diluted with 5.0 ml. of water.

When the absorbancy had reached a maximum value (24 hr.), 10 ml. of 0.53 *M* sodium metaperiodate was added to 500 ml. of the solution. The consumption of oxidant and the appearance of acid and formaldehyde were followed as outlined above.

Immediately after dilution to 1.5 l., a 500-ml. aliquot was treated with 1 g. of sodium borohydride. After standing overnight, the excess hydride was destroyed with acetic acid and the solution was concentrated to a small volume. After deionizing, the residue was acetylated in pyridine. Examination of the product by vapor phase chromatography using Dow-Corning high vacuum grease on Chromosorb W at 220° showed one component with a retention time greater than that for arabitol pentaacetate.

A second 500-ml. aliquot was similarly treated when the absorbancy had reached a maximum value. The same yield of the same acetate was obtained.

(32) J. W. Le Maistre, private communication.

(33) W. R. Frisell, L. A. Meech, and C. G. Mackenzie, *J. Biol. Chem.*, **207**, 709 (1954).

The Route of Cyclic Anhydride Formation from Mono-*O*-tolylsulfonyl Glycols[1]

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In the intramolecular displacement of *p*-tolylsulfonate anions by an oxide ion it is shown that a tolylsulfonyl ester on a primary hydroxyl function is displaced by oxide ions derived from hydroxyl groups in the following order of reactivity: primary γ-OH > secondary γ-OH = secondary α-OH > primary δ-OH. A tolylsulfonyl ester on a secondary hydroxyl function is displaced most readily by an oxide ion derived from a primary α-OH; reactions with competing oxide ions derived from primary γ-hydroxyls and secondary α-hydroxyls have not been observed.

It previously has been shown[2] that, under basic conditions in a system containing a primary hydroxyl group γ to a *p*-tolylsulfonyl ester function and a secondary hydroxyl group α to the function, intramolecular *p*-tolylsulfonate anion displacement proceeds preferentially by attack of the oxide ion in the γ-position.

The purpose of the present investigation was to elucidate the route of base-catalyzed tolylsulfonate anion displacement in each of the following three situations involving unbranched glycols: (1) primary hydroxyl group α and γ to the ester, (2) a primary hydroxyl δ and a secondary hydroxyl α to the ester, and (3) secondary hydroxyl groups α and δ to the ester.

To examine the first two situations, the products formed when the 2- and 1-*O*-*p*-tolylsulfonyl esters of L-1,2,5-pentanetriol (I)[3] were treated with alkali were investigated.

1,5-Di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol (II) was prepared from L-glutamic acid by the following series of reactions: L-glutamic acid → L-α-hydroxyglutaric acid → dimethyl L-α-hydroxyglutarate → methyl L-α-hydroxyglutarolactonate → L-1,2,5-pentanetriol (I) → 1,5-di-*O*-benzoyl-L-1,2,5-pentanetriol → II.

Treatment of II with aqueous sodium hydroxide gave tetrahydrofurfuryl alcohol, $[\alpha]^{24}D$ +14.9 ± 0.3° (*c* 5.0, nitromethane), as the only isolable product. Kenyon, *et al.*,[4] reported $[\alpha]^{20}_{6893}$ −17.5° (c 5.0, nitromethane) for the levorotatory enantiomer. Since Gagnaire and Butt[5] found that the tetrahydrofurfuryl alcohol having a positive rotation is the L isomer, it is

(1) This investigation was supported in whole by Public Health Service Research Grant GM 09021 from the National Institute of General Medical Sciences.

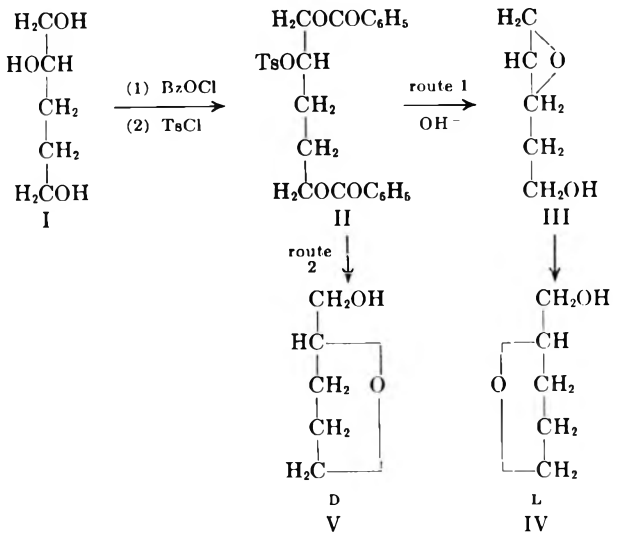
(2) F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).

(3) H. Katsura, *Nippon Kagaku Zasshi*, **77**, 1789 (1956); *Chem. Abstr.*, **53**, 5126 (1959).

(4) M. P. Balfe, M. Irwin, and J. Kenyon, *J. Chem. Soc.*, 313 (1951).

(5) D. Gagnaire and A. Butt, *Bull. soc. chim. France*, 312 (1961).

SCHEME I



concluded that the tetrahydrofurfuryl alcohol obtained is predominantly the L isomer, whose formation can be explained only by a double inversion of configuration (route 1), indicating preferential participation of the α-hydroxyl group in displacement of the tolylsulfonyl ester. Based on the previously reported rotation of tetrahydrofurfuryl alcohol, the maximum per cent of II reacting *via* route 2 is 7.5%.

An attempt was made to determine whether the difference between the observed rotation and the reported[4] rotation of tetrahydrofurfuryl alcohol is due to partial racemization resulting from initial displacement by the γ-hydroxyl group (route 2) or to the presence of optically inert impurities in the isolated product. It was felt that the rotation of the tetrahydrofurfuryl alcohol that would result if only route 1 was operative would be identical with that of the tetrahydrofurfuryl alcohol obtained by the acid-catalyzed dehydration of L-1,2,5-pentanetriol, since the acid-catalyzed reaction usually proceeds without inversion of configuration.[6] However, the tetrahydrofurfuryl alcohol obtained from L-1,2,5-pentanetriol by treating it with 2 *N* hydrochloric acid at 100° for 36 hr. had $[\alpha]^{24}D$ +10.2 (*c* 5.0, nitromethane), which indicated appreciable racemization. Gagnaire and Butt[5] have reported also racemization in the acid-catalyzed dehydration of 1,2,5-pentanetriol using more drastic conditions.

In a further effort to determine whether route 2 is operative, the tetrahydrofurfuryl alcohol ($[\alpha]^{25}D$ + 14.9°) obtained from II was converted to its 3,5-dinitrobenzoyl ester which was recrystallized to constant melting point and rotation and then converted back to the alcohol. The alcohol obtained in this fashion had $[\alpha]^{25}D$ +15.5 ± 0.3° (c 5.0, nitromethane), a value only slightly different from the rotation of the starting alcohol. Examination of the alcohol preparations by gas chromatography indicated the presence of a small proportion of material with a very short retention time relative to tetrahydrofurfuryl alcohol which we feel is a contaminant due to the method of isolating the alcohol. On this basis we conclude that, in the base-catalyzed displacement of the tolylsulfonyl group from II, route 2 is followed by less than 5% of the sample.

(6) L. F. Wiggins, *Advan. Carbohydrate Chem.*, **5**, 191 (1950).

The initial formation of III is substantiated by the demonstration that treatment of II with sodium methoxide results in the formation of an epoxide in 95% yield. Unless the method used to determine the presence of an epoxide in the reaction mixture[7] gives positive results with *ortho* esters, this finding rules out anchimeric assistance by the benzoyloxy group with the intermediate formation of an *ortho* ester, as Baker and Haines[8] demonstrated in the displacement of mesyloxy groups in the alditols. Since both benzoyl groups are primary, they should be removed at approximately the same rate, thereby allowing approximately equal opportunity for the two hydroxyl groups to assist in the displacement. The electron-withdrawing tendency of the neighboring sulfonate ester might potentiate the release of the α-hydroxyl group, although this effect would be counteracted by steric hindrance due to the same group.

1-*O*-*p*-Tolylsulfonyl-L-1,2,5-pentanetriol (X) was prepared as follows: I → 1,2-*O*-isopropylidene-L-1,2,5-pentanetriol (VI) → 5-*O*-benzyl-1,2-*O*-isopropylidene-L-1,2,5-pentanetriol (VII) → 5-*O*-benzyl-L-1,2,5-pentanetriol (VIII) → 5-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol (IX) → X. (See Scheme II.)

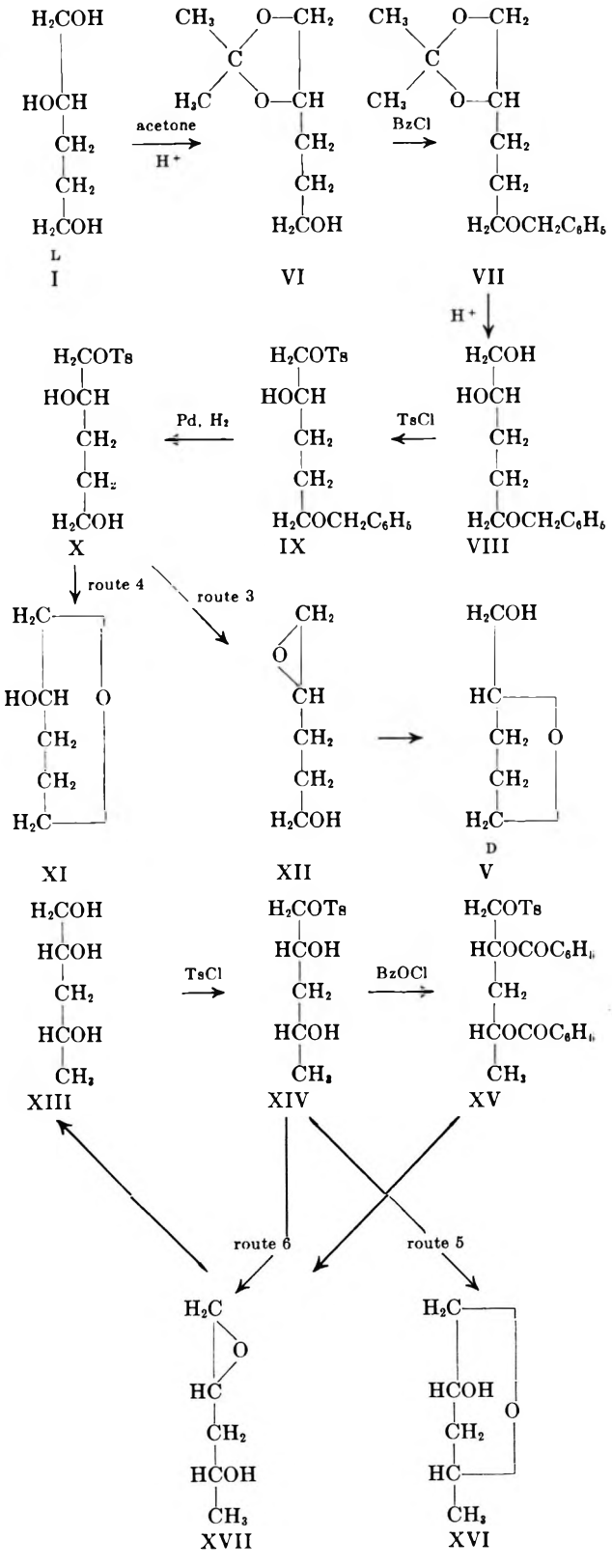
Treatment of X with aqueous base results in a mixture which was shown by gas chromatography to be 92.5% tetrahydrofurfuryl alcohol (V) and 7.5% 3-hydroxytetrahydropyran (XI). The tetrahydrofurfuryl alcohol is the D isomer (V) since the specific rotation of its 3,5-dinitrobenzoyl ester is equal in magnitude and opposite in direction to the corresponding derivative obtained from IV. The possibility of the formation of XI by rearrangement of the epoxide (XII) is excluded on the basis that no XI results from the rearrangement of epoxide III, which is formed when II is treated with base. Thus, the formation of V and XI from X on treatment with base shows that routes 3 and 4 are operative.

The route of displacement when the third situation exists was demonstrated by examination of the products formed when the 1-*O*-*p*-tolylsulfonyl ester of 1,2,4-pentanetriol (XIV) was treated with alkali. The tolylsulfonyl ester was not isolated from the reaction in which it was formed. An excess of aqueous base was added to the reaction mixture and the amount of triol (XIII) formed was determined by periodate oxidation. The amount of triol formed was 42% of the theoretical, indicating that 58% of the ester had been converted to 2-methyl-4 hydroxytetrahydrofuran (XVI). These findings indicate that secondary α- and γ-hydroxyl functions participate with approximately equal ease in the displacement of a primary tolylsulfonate anion. The amount of triol formed is a measure of the amount of 1,2-epoxy-4-hydroxypentane (XVII) formed (route 6), since previous work has shown that a 4-hydroxyl group cannot attack the 1-position of a 1,2-epoxide.[2] The amount of XVI formed is a measure of the extent of γ-hydroxyl group participation (route 5).

The assumption that the tolylsulfonyl ester utilized in the above experiments was 1-*O*-*p*-tolylsulfonyl-1,2,4-pentanetriol (XIV) was validated by converting a sample of it to the dibenzoyl ester (XV) and refluxing

(7) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).
(8) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

SCHEME II



the latter in acetone containing potassium iodide for 2 hr.; 95% of the theoretical amount of sodium *p*-tolylsulfonylate was obtained indicating that XV was a primary tolylsulfonyl ester.[9]

Upon treating XV with aqueous base, 38% of the tolysulfonyloxy function is displaced by the γ-hydroxyl group giving rise to 2-methyl-4-hydroxytetrahydrofuran (XVI), and 62% is displaced by the α-hydroxyl group forming the epoxide (XVII) which rearranges to give the triol (XIII). The amount of XVI formed was determined by isolation. The amount of XIII formed was measured by periodate oxidation of the aqueous solution after XVI had been extracted. These findings indicate that, although the rate of removal of the benzoyl groups may influence the proportion of reaction which occurs *via* route 5 or 6, it does not exercise complete control over the route taken.

Our results are in accord with the finding that treatment of 6-*O*-*p*-tolylsulfonyl-D-fructose phenylosotriazole with sodium methylate yields 60% of the corresponding 5,6-epoxide.[10]

The base-catalyzed displacement of a *p*-tolylsulfonate anion is described as follows.

(1) In a secondary *p*-tolylsulfonyl ester containing primary hydroxyl groups α and γ to the ester function, the oxide ion derived from the α-hydroxyl group is involved. The epoxide which is formed rearranges to the more stable tetrahydrofuran ring.

(2) In a primary *p*-tolylsulfonyl ester containing a secondary hydroxyl group α and a primary hydroxyl group δ to the ester, the ion from the α-hydroxyl group is involved primarily. Displacement by the δ-oxide occurs to only a slight degree. The epoxide ring formed by displacement by the α-hydroxyl group rearranges to a five-membered ring.

(3) In a primary tolylsulfonyl ester with secondary hydroxyl groups α and γ to the ester, the displacement proceeds with approximately equal participation of the two hydroxyl groups. The epoxide formed by attack of the α-hydroxyl group is opened to the *vic* glycol.

These findings indicate that the extent to which various hydroxyl groups participate in the displacement of tolylsulfonate anions depends upon their position and on whether they are primary or secondary. As would be expected from their greater acidity,[11] primary hydroxyl groups are more reactive than secondary. It is also probable that a hydroxyl group α to the ester function is more acidic due to electron withdrawal by the sulfonic ester group.[12]

The ratio of products found in the various cases examined is dependent then upon the specific rate of cyclization, which is probably greatest for the five-membered ring, and upon the acidity of the hydroxyl function, which is greater for primary hydroxyl functions and which is enhanced when the hydroxyl is adjacent to the ester being displaced.

Experimental[13]

Dimethyl L-α-Hydroxyglutarate.[3]—Nitrogen trioxide[14] was bubbled intermittently into a gently stirred suspension of 500 g. of L-glutamic acid in 1200 ml. of water. The temperature was maintained between 10–15° with an ice bath. When the evolution of nitrogen became vigorous, the addition of nitrogen trioxide was stopped until the evolution of nitrogen subsided. The

(9) R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

(10) E. Hardegger and E. Schreier, *Helv. Chim. Acta*, **35**, 623 (1952).

(11) J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).

(12) H. W. Heine and W. Seigfried, *ibid.*, **76**, 489 (1954).

(13) Melting points are corrected. Evaporations were carried out at water-aspirator pressure on a rotary evaporator. Aerograph gas chromatographic apparatus, Model A90-S, was used for the vapor phase separations on a 10% Carbowax 20M on Chromosorb W column. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(14) P. R. Shildneck, U. S. Patent 2,461,701 (1949); *Chem. Abstr.*, **43**, 3841 (1949).

process was continued until a homogeneous solution was obtained (approximately 7 hr.). Filtration of the solution through a layer of Celite and concentration of the filtrate at 50° gave 519 g. of α-hydroxy-L-glutaric acid as a thick, slightly yellow sirup. After drying the acid at 50° under 1-mm. pressure for 25 hr., a 100-g. portion was converted to the dimethyl ester by refluxing for 12 hr. with 500 ml. of methanol containing 10 ml. of concentrated sulfuric acid. The solution was cooled to 0°, neutralized with 120 ml. of cold 3 *N* methanolic potassium hydroxide, and concentrated at 40° to remove the methanol. The residue was taken up in 300 ml. of water and extracted with six 200-ml. portions of chloroform. Concentration of the chloroform extracts gave 82 g. of material which on vacuum distillation gave 73 g. (61%) of product, b.p. 85–92° (0.1 mm.). Katsura[3] reported b.p. 82–90° (0.13 mm.).

Methyl L-α-Hydroxyglutarolactonate.—Dimethyl L-α-hydroxyglutarate (30 g.) was heated in an open beaker for 16 hr. at 200°. Crystallization from 50 ml. of isopropyl alcohol gave 19.2 g. (78%) of crystals, m.p. 48–50°. Four recrystallizations from the same solvent gave a material with m.p. 58–60° and $[\alpha]^{24}D$ +3.1° (*c* 4.5, water).

Anal. Calcd. for $C_6H_8O_4$ (144.1): C, 50.01; H, 5.59. Found: C, 50.15; H, 5.46.

L-1,2,5-Pentanetriol.[3]—To a well-stirred, refluxing suspension of 5 g. of powdered lithium aluminum hydride in 150 ml. of dioxane was added dropwise during 1 hr. a solution of 10 g. of L-α-hydroxyglutarolactone in 100 ml. of dioxane. After the addition was complete, the mixture was refluxed for 1 hr. and then cooled to 0°. The excess lithium aluminum hydride was destroyed by the dropwise addition of ethyl acetate. Isolation of the product was accomplished in the following manner.[15] Hydrolysis of the alcoholate was effected by the addition of 20 ml. of saturated aqueous sodium sulfate solution followed by boiling for 15 min. After removal of the water with anhydrous magnesium sulfate (35 g.), the mixture was filtered and the residue was washed thoroughly with dioxane. Concentration of the combined filtrate and washings gave 7.7 g. (93%) of the triol with $[\alpha]^{24}D$ −19.6° (*c* 5.0, ethanol). Katsura[3] reported $[\alpha]^{29}D$ −11.6° (94% ethanol). The triol gave an 84% yield of a tri-*O*-*p*-nitrobenzoyl ester, which after two recrystallizations from ethanol–acetone (1:1) melted at 130–132° and had $[\alpha]^{24}D$ +8.6 (*c* 5.0, methylene chloride).

Anal. Calcd. for $C_{26}H_{21}N_3O_{12}$ (567.47): C, 55.03; H, 3.73. Found: C, 55.29; H, 3.95.

1,5-Di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol.—To a solution of 10.8 g. of L-1,2,5-pentanetriol in 150 ml. of pyridine was added dropwise with stirring 22 ml. of benzoyl chloride. The temperature was maintained below −10° with a Dry Ice bath. After the addition of the benzoyl chloride was complete, the reaction mixture was left at room temperature for 3 hr., and then 200 ml. of methylene chloride was added. The methylene chloride solution was extracted successively with cold water, 1 *N* sulfuric acid, saturated sodium bicarbonate solution, and water; it was dried over sodium sulfate and concentrated to give 29 g. (100%) of a slightly viscous sirup. The sirup was dissolved in 200 ml. of pyridine and 25 g. of *p*-toluenesulfonyl chloride was added. After remaining 48 hr. at room temperature, the reaction mixture was washed as described above. Crystallization of the product from 200 ml. of ethanol gave 23 g. (53%) of crystals which after two recrystallizations melted at 85–87° and had $[\alpha]^{24}D$ +6.2 (*c* 9.0, methylene chloride).

Anal. Calcd. for $C_{26}H_{26}O_7S$ (482.49): C, 64.72; H, 5.43. Found: C, 64.58; H, 5.42.

L-Tetrahydrofurfuryl Alcohol.—A solution of 1 g. of L-1,2,5-pentanetriol in 10 ml. of 2 *N* hydrochloric acid was heated in a stoppered tube at 100° for 36 hr. and then continuously extracted with ether for 12 hr. The ether extract was concentrated, and the residue was taken up in methylene chloride, dried over sodium sulfate, and filtered. Concentration of the filtrate gave 0.77 g. (90%) of product with $[\alpha]^{24}D$ +10.2 (*c* 5.0, nitromethane). Conversion of 0.42 g. of this alcohol to the 3,5-dinitrobenzoyl ester gave 1.0 g. (82%) of sirup which from solution in 20 ml. ethanol gave 0.62 g. (51%) of crystals, m.p. 74–76°. After three recrystallizations, the material melted at 74–76° and had $[\alpha]^{24}D$ +16.4 (*c* 2.0, methylene chloride).

Anal. Calcd. for $C_{12}H_{12}N_2O_7$ (296.2): C, 48.65; H, 4.08. Found: C, 48.43; H, 4.17.

(15) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLemore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

Action of Aqueous Alkali on 1,5-Di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol.—To a solution of 5.29 g. of 1,5-di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol in 100 ml. of acetone was added 40 ml. of 1 *N* sodium hydroxide. After the reaction mixture had remained at room temperature for 24 hr., the acetone was removed by concentration and the remaining aqueous solution continuously was extracted with ether for 12 hr. The ether extract contained 1.01 g. (92%) of material, $[\alpha]^{24}D$ +14.9° (*c* 5.0, nitromethane), which was demonstrated by gas chromatography to be predominantly a compound whose retention time was identical with that of tetrahydrofurfuryl alcohol.

3,5-Dinitrobenzoyl-L-tetrahydrofurfuryl Alcohol and Its Saponification.—A portion of the tetrahydrofurfuryl alcohol (0.6 g.) was converted to the 3,5-dinitrobenzoyl ester in the usual manner to give 1.46 g. (84%) of sirup, $[\alpha]^{24}D$ +18.6° (*c* 4.0, methylene chloride), from which was obtained by crystallization from 28 ml. of ethanol 1.05 g. of crystals, m.p. 76–77°, $[\alpha]^{24}D$ +20.5 (*c* 5.0, methylene chloride). Three recrystallizations from 25 ml. of ethanol gave 0.5 g. of crystals whose melting point was raised to 77.5–78.5° and specific rotation was unchanged. The ester (0.5 g.) was dissolved in 20 ml. of acetone and 4 ml. of 1 *N* sodium hydroxide was added. After leaving the reaction mixture at room temperature for 24 hr., the acetone was removed by evaporation and 20 ml. of water was added. The reaction mixture was left at room temperature for 3 additional days at which time the tetrahydrofurfuryl alcohol was extracted from the aqueous mixture with ether as described previously. The tetrahydrofurfuryl alcohol (120 mg., 65%) obtained had $[\alpha]^{24}D$ +15.5° (*c* 5.0, nitromethane).

Action of Sodium Methoxide on 1,5-Di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2-5-pentanetriol.—To a solution of 4.82 g. of 1,5-di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol was added 10 ml. of 1.92 *N* sodium methoxide, and the resulting solution was diluted to 50 ml. with chloroform. A 5-ml. aliquot of the reaction mixture was removed 10 min. after the sodium methoxide had been added. The aliquot was immediately neutralized to the phenolphthalein end point with 2 *N* acetic acid and its epoxide content was determined by the thiosulfate method.[7] To the neutralized aliquot was added 10 ml. of acetone and 10 ml. of 0.2 *M* sodium thiosulfate. The solution was heated at 60° with constant stirring and the pH was maintained at the phenolphthalein end point with 0.17 *N* acetic acid. After 25 min., the reaction was complete and 0.95 mequiv. (95%) of hydroxyl ions had been released, demonstrating the presence of 0.95 mequiv. (95%) of epoxide in the original aliquot. Subsequent samples showed the presence of decreasing amounts of epoxide.

5-*O*-Benzyl-1,2,-*O*-isopropylidene-L-1,2,5-pentanetriol.—A solution of 15 g. of L-1,2,5-pentanetriol in 500 ml. of dry acetone containing 1.2 ml. of concentrated sulfuric acid was stirred at room temperature for 15 hr. and then passed through a column of 50 ml. of IR 45 (OH^-).[16] Concentration of the eluent gave 25.0 g. of a sirup from which, on distillation at atmospheric pressure, was obtained 9 g. of acetone condensation products (b.p. 95–100°) and 15 g. (75%) of 1,2,-*O*-isopropylidene-D-1,2,5-pentanetriol (b.p. 225–228°). To a solution of 7.0 g. of this compounds in 100 ml. of benzene were added 11.5 g. of powdered potassium hydroxide and 12.5 ml. of benzyl chloride. After refluxing the mixture for 3.5 hr., the solids were removed by filtering through a layer of Celite and the filtrate was concentrated. Distillation of the residue gave 5.8 g. of dibenzyl ether (b.p. 80–110° at 15 mm.) and 10.3 g. (99%) of the desired product, b.p. 176–185° (15 mm.). Redistillation gave 9.7 g. of colorless, nonviscous liquid, b.p. 180–184° (15 mm.), $[\alpha]^{24}D$ +8.5° (c 3.0, dioxane).

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.3): C, 71.98; H, 8.85. Found: C, 72.28; H, 8.94.

5-*O*-Benzyl-D-1,2,5-pentanetriol.—To a solution of 9 g. of 5-*O*-benzyl-1,2-*O*-isopropylidene-L-1,2,5-pentanetriol in 200 ml. of dioxane was added 50 ml. of 0.1 *N* hydrochloric acid, and the resulting solution was boiled (approximately 1 hr.) until no acetone could be detected in the distillate with 2,4-dinitrophenylhydrazine reagent. After concentration, the residue was dissolved in 50 ml. of ethanol and the resulting solution was passed through a column containing 10 ml. of IR 45 (OH^-).[16] Concentration of the eluent gave 7.3 g. of a slightly yellow viscous sirup which was distilled at 1 mm. The product (6.1 g., 81%) was obtained as a colorless viscous sirup, b.p. 158–163°, $[\alpha]^{24}D$ −11.3° (*c* 2.3, ethanol).

(16) Rohm and Haas Co., Philadelphia, Pa.

Anal. Calcd. for $C_{12}H_{18}O_3$ (210.3): C, 68.54; H, 8.63. Found: C, 68.38; H, 8.41.

5-O-Benzyl-1-O-p-tolylsulfonyl-L-1,2,5-pentanetriol.—A solution of 3.4 g. of *p*-toluenesulfonylchloride in 20 ml. of pyridine was added to a solution of 3.6 g. of 5-*O*-benzyl-L-1,2,5-pentanetriol in 20 ml. of pyridine, with both solutions at 0°. The reaction mixture was left at 0° for 24 hr. and then the product was isolated by taking up the reaction mixture in methylene chloride and washing as described previously. The sirup (5.7 g., 90%) obtained was characterized as the 2-*O*-*p*-nitrobenzoyl ester (78% from the sirup) which melted at 54.5–55.5°, $[\alpha]^{24}D$ +3.5 (c 2.0, methylene chloride).

Anal. Calcd. for $C_{26}H_{27}NO_8S$ (513.5): C, 60.81; H, 5.30. Found: C, 60.56; H, 5.45.

1-O-p-Tolylsulfonyl-L-1,2,5-pentanetriol.—Palladium chloride (2 g. of 10% palladium chloride on charcoal) in 25 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 1 hr. at which time it was filtered and thoroughly washed with ethyl acetate to remove hydrogen chloride. The catalyst then was rehydrogenated in 25 ml. of ethyl acetate, and 2.6 g. of 5-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol in 25 ml. of ethyl acetate was added. After 10 min. the hydrogenation was complete with the consumption of 151 ml. of hydrogen (95%). The catalyst was removed by filtering the mixture through Celite, and the filtrate was concentrated to give 1.9 g. (100%) of the product as a sirup, from which an 88% yield of the crystalline 2,5-di-*O*-*p*-nitrobenzoyl ester, m.p. 133–135°, $[\alpha]^{24}D$ +3.6° (*c* 4.5, methylene chloride), could be obtained.

Anal. Calcd. for $C_{26}H_{24}N_2O_{11}S$ (572.4): C, 54.55; H, 4.22. Found: C, 54.44; H, 4.20.

Action of Aqueous Alkali on 1-O-p-Tolylsulfonyl-L-1,2,5-pentanetriol.—To a solution of 1.9 g. of 1-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol in 10 ml. of methanol was added 10 ml. of aqueous 1 *N* sodium hydroxide. After heating the solution at 50° for 0.5 hr., it was neutralized with 2 *N* hydrochloric acid, concentrated until no methanol remained, decolorized with charcoal, and filtered through Celite. The filtrate was extracted continuously with ether for 24 hr. and the ether extract was concentrated. The residue was taken up in 20 ml. of methylene chloride and the solution was dried with sodium sulfate, filtered, and concentrated. Analysis of the product (0.56 g., 79%) by gas chromatography showed it to be approximately 7.5% of a compound with the same retention time as 3-hydroxytetrahydrofuran,[17] in addition to tetrahydrofurfuryl alcohol. The tetrahydrofurfuryl alcohol was the D isomer as was shown by $[\alpha]^{24}D$ −20.7 ± 0.8° (*c* 1.0, methylene chloride) of the 3,5-dinitrobenzoyl ester obtained in 41% yield from the mixture.

1,2,4-Pentanetriol.—To a well-stirred solution of 43 g. of 1-penten-4-ol in 453 g. of 90% formic acid was added during a 30-min. period 59 g. of 30% hydrogen perioxide, the temperature being maintained below 40° with an ice bath. After the addition was complete, the reaction mixture was left at room temperature for 24 hr. and then concentrated at 50°. To remove the formic acid, the residue was taken up in 200 ml. of water and concentrated; this process was repeated three times. The formate ester was saponified then by boiling with 300 ml. of 2 *N* sodium hydroxide for 1 hr., at which time the solution was passed successively through columns containing 500 ml. of IR 120 (H^+)[16] and 500 ml. of IR 45 (OH^-).[16] The eluent was concentrated and the residue was distilled to give 41 g. (68%) of product, b.p. 149–153° (0.03 mm.), which after redistillation appeared pure by paper chromatography and gas chromatography and which consumed 1 molar equiv. of sodium metaperiodate.

Anal. Calcd. for $C_5H_{12}O_3$ (120.1): C, 49.98; H, 10.06. Found: C, 48.71; H, 10.08.

2,4-Di-O-benzoyl-1-O-p-tolylsulfonyl-1,2,4-pentanetriol.—A solution of 8.0 g. of *p*-toluenesulfonyl chloride in 25 ml. of pyridine was added to a solution of 4.8 g. of 1,2,4-pentanetriol in 25 ml. of pyridine, both solutions at 0°. The resulting mixture was left for 2 hr. at 0°, then warmed to room temperature, and left for 4 hr. The reaction mixture was then cooled to 0°, and 13 ml. of benzoyl chloride was added dropwise to keep the temperature below 20°. Two hours after the addition was complete the reaction mixture was worked up in the usual fashion and 19 g. (95%) of product was obtained as a thick slightly yellow sirup.

Action of Sodium Iodide on 2,4-Di-O-benzoyl-1-O-p-tolylsulfonyl-1,2,4-pentanetriol.—A solution of the tolylsulfonyl ester (3.57 g.) in 25 ml. of acetone containing 4.3 g. of sodium iodide was refluxed for 2 hr. and then cooled to 0°. The sodium *p*-toluenesulfonate (1.23 g., 95%) was removed by filtration. No sodium *p*-toluenesulfonate was formed when 1,5-di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-1,2,5-pentanetriol was treated with sodium iodide under the same conditions.

2-Methyl-4-hydroxytetrahydrofuran.—A solution of 1. g. of 1,2,4-pentanetriol in 10 ml. of 2 *N* hydrochloric acid was heated in a stoppered tube for 36 hr. at 100°. The product (0.81 g., 95%) was isolated in the manner described for the isolation of L-tetrahydrofurfuryl alcohol prepared by the anhydrization of L-1,2,5-pentanetriol.

Action of Sodium Methoxide on 2,4-Di-O-benzoyl-1-O-p-tolylsulfonyl-1,2,4-pentanetriol.—Freshly prepared sodium methoxide (1 ml., 2.3 *N*) was added to a solution of 4.26 g. (0.88 mequiv.) of the *p*-tolylsulfonyl ester in 75 ml. of chloroform at 0°, and the resulting mixture was diluted to 100 ml. with cold chloroform. After 30 min., a 10-ml. aliquot was removed and its epoxide content, determined as described previously, was found to be 0.38 mequiv. (43%). The epoxide content was the same after 70 min.

Action of Aqueous Alkali on 2,4-Di-O-benzoyl-1-O-p-tolylsulfonyl-1,2,4-pentanetriol.—To a solution of 2,4-di-*O*-benzoyl-1-*O*-*p*-tolylsulfonyl-1,2,4-pentanetriol in 100 ml. of acetone was added 40 ml. of aqueous 1 *N* sodium hydroxide. After remaining at room temperature for 3 days, the reaction mixture was titrated with 1 *N* hydrochloric acid; 32.8 mequiv. (97%) of base had been consumed. The neutral solution was extracted continuously with ether for 24 hr. From this ether solution 0.43 g. (38%) of material was isolated which by gas chromatography could not be separated from the 3-methyl-3-hydroxytetrahydrofuran obtained from the dehydration of 1,2,4-pentanetriol. The aqueous solution was diluted to 100 ml. Periodate consumption of aliquots indicated the presence of 840 mg. (62%) of triol in the aqueous layer.

Action of Aqueous Alkali on 1-O-p-Tolylsulfonyl-1,2,4-pentanetriol.—To a solution of 0.75 g. of 1,2,4-pentanetriol in 25 ml. of pyridine at 0° was added a solution of 1.2 g. of *p*-toluenesulfonyl chloride in 15 ml. of pyridine at 0°. After the reaction mixture had remained for 12 hr. at 0°, 20 ml. of 1 *N* sodium hydroxide was added and the solution was left at room temperature for 3 days at which time it was neutralized with 2 *N* sulfuric acid. By periodate oxidation it was determined that the solution contained 0.32 g. (42%) of 1,2,4-pentanetriol.

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Elimination of the Exocyclic Secondary *p*-Tolylsulfonyloxy Group in a D-Glucofuranose Structure[1,2]

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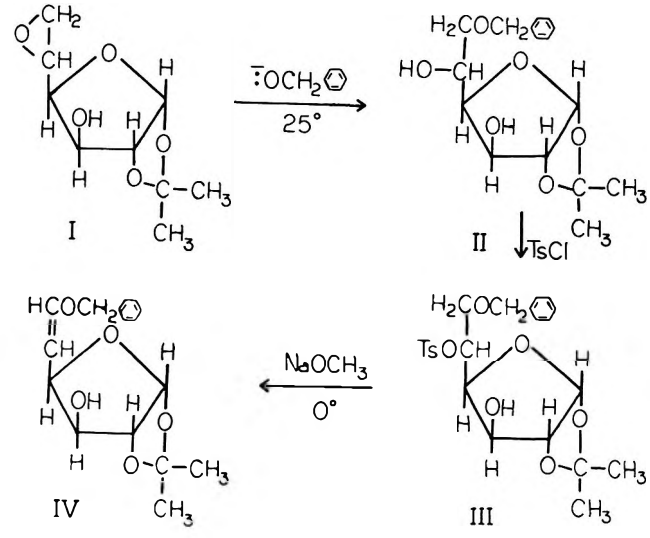
Although the stereochemical configuration of 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose would seem to permit formation of a 3,5-anhydro (oxetane) ring under experimental conditions usually adopted for anhydro ring formation, the olefin, 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose is nevertheless obtained in 95% yield by a desulfonyloxylation and β-elimination of the tosylated D-glucofuranose derivative. Reductive ozonolysis and n.m.r. indicate that the double bond in the olefin is between carbons 5 and 6. Mild catalytic hydrogenation of the vinylene sugar derivative affords crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.

Formation of an oxetane ring by base-catalyzed elimination of a suitably located tosyloxy group in the sugar molecule has been described previously in the literature.[3-5] A specific example wherein an exocyclic primary tosyloxy group in 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose is eliminated in the presence of sodium methoxide to give 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose was demonstrated by Levene and Raymond.[6]

In this work an attempt to introduce an oxetane ring into a D-glucofuranose derivative, by anionic elimination of the exocyclic secondary tosyloxy group, gives an unsaturated D-glucofuranose derivative in 95% yield rather than the expected anhydro sugar.

5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (I) prepared from 1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose serves as the starting compound for this synthesis. Compound I is treated with sodium benzyl alkoxide to give crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (II) in 80% yield. The benzyl group is stable in alkali and is removed conveniently by catalytic hydrogenolysis. Since the steric and electrical effects of the 6-*O*-benzyl group in II are closely analogous to the 6-*O*-benzoyl group as in 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose,[7] and selective tosylation of the more reactive C-5 hydroxyl group of the latter compound has been reported,[7,8] it is expected that monotosylation of II also would give a C-5 tosylated derivative. Crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III) is obtained in 50% yield by selective tosylation of III. Crystalline 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose obtained by catalytic hydrogenolysis of III is treated with sodium methoxide to give 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose. Isolation and identification of the known[9] anhydro derivative proves the structure of III. One product isolated after reductive desulfonyloxylation[10,11] of III with lithium aluminum hydride and subsequent hydrogenolysis with palladium on carbon is identified as 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.[12]

A crystalline product (IV) obtained from the reaction of III with sodium methoxide absorbs bromine from a bromine–carbon tetrachloride solution and decolorizes an aqueous potassium permanganate solution. Since the product obtained from a reductive ozonolysis of the crystalline olefinic sugar derivative is identified as 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[13] (V) on paper chromatography, and the latter is converted to 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose phenylhydrazone[13,14]



(VI), the olefinic sugar is concluded to be 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IV). Acetylation of IV gives 3-*O*-acetyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose.

Two different melting points of IV are observed. One crystalline form shows a constant melting point of 113° on recrystallization. However, when the crystals are melted and cooled, the melting point increases to 119.5° and remains at this value on subsequent remelts. The lower melting crystalline form exhibits birefringence and is obtained as long needles. The higher melting form is amorphous in appearance

(1) Journal Paper No. 2224 of the Purdue University Agricultural Experiment Station.

(2) Presented before the Division of Carbohydrate Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

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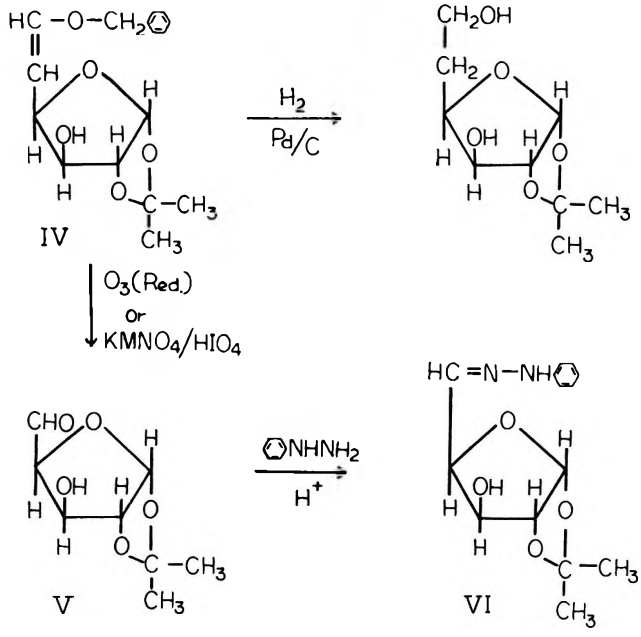

but has a crystalline X-ray pattern. Both forms have the same absorption spectra in infrared.

The n.m.r. spectrum of II obtained in deuterated chloroform shows a specific proton coupling at τ 3.1 to 3.8 due to the hydrogens on the C-6 position. A proton coupling of this nature which is not observed in the spectrum of IV reveals that there is one hydrogen on C-6 and, therefore, suggests that a double bond is located between C-5 and C-6.

Examination of the infrared spectrum of IV reveals specific absorptions at 1310 and 975 cm.$^{-1}$, indicative of a *trans* arrangement of hydrogens.

Crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose is obtained in about 90% yield by a simultaneous catalytic hydrogenation and hydrogenolysis of IV with palladium on carbon.

This observed phenomena wherein an exocyclic secondary tosyloxy group is eliminated with an accompanying β-proton elimination in a D-glucofuranose structure is interesting, since the vinylene sugar obtained contains an activated double bond due to the electron-withdrawing effect of the adjacent benzyl ether group. Vinylene sugar derivatives of this type are not known and, therefore, synthetic possibilities of similar compounds are now under investigation in our laboratory to determine their potential usefulness as either dienophiles for the synthesis of Diels–Alder type addition compounds and as activated monomers for polymerization.

Experimental

Analytical Methods.—Chromatographic identifications of sugar derivatives were made at 25° on Whatman No. 1 filter paper and developed in irrigants A, 1-butanol–ethanol–water (40:11:19 v./v.), or B, ethyl acetate–pyridine–water (10:4:3 v./v.). Spray indicators employed were C, potassium permanganate–periodate, and D, an acetone solution of silver nitrate, followed by an ethanolic sodium hydroxide solution.[15] Purity of crystalline products were determined by thin layer chromatography on 1 × 3 in. silica gel G[16]-coated microscope slides irrigated with E, 1-butanol saturated with water, or F, chloroform–acetone (1:1 v./v.). Plates were sprayed with a dilute ethanolic solution containing 5% sulfuric acid and charred at 110° until permanent spots were visible. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were done at reduced pressure.

5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (I).—Compound I was prepared by the method described in "Methods in Carbohydrate Chemistry," Vol. II.[17] However, the starting material, namely 1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose, for the preparation of I was scaled up by a modified procedure. The chloroform solution containing the 6-*O*-tosyl derivative was extracted with an aqueous solution of copper sulfate until the color of the extract changed from a prussian blue to an azure blue. The chloroform phase was washed successively with two portions of water, a dilute chilled solution of acetic acid, and finally with water, after which it was dried over anhydrous sodium sulfate, filtered, and evaporated below 40°. The 6-*O*-tosyl derivative crystallized from a solution of ether and petroleum ether (b.p. 40–60°) in 63% yield and had a melting point of 108°.

6-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (II).—Compound I (36 g.) was added slowly to 400 ml. of a cooled, continuously stirred solution of benzyl alcohol which contained 4 g. sodium. The solution was maintained at 25° for 3 days and then slowly neutralized with a chilled dilute solution of sulfuric acid. Sodium sulfate was filtered from solution and washed with two 20-ml. portions of benzyl alcohol. Combined washings and filtrate were extracted with two 50-ml. portions of water. The aqueous phase was made alkaline with a 40% solution of potassium hydroxide and extracted with diethyl ether. Both ether extracts and benzyl alcohol filtrates were combined and dried over anhydrous sodium sulfate. After filtration, ether was removed under reduced pressure and the remaining benzyl alcohol was removed by high vacuum distillation. Compound II, contained in the residue, crystallized from a mixture of ether–petroleum ether to yield 45 g. (80%), m.p. 74–75°. Compound II was recrystallized from ethyl acetate and petroleum ether to give m.p. 79°, $[\alpha]^{25}D$ −3.5° (*c* 0.97, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.14. Found: C, 61.74; H, 7.12.

6-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III).—A solution containing 30 g. of II dissolved in 100 ml. of pyridine was cooled with stirring to −5°. A one-half portion of 18.42 g. of tosyl chloride (*p*-toluenesulfonyl chloride) was added to the solution over a period of 2 hr. The solution was maintained at 25° for 5 hr., cooled again to −5°, and the remaining half portion of tosyl chloride was added as before. After 10 hr. at 25°, the reaction mixture was treated with ice and stirred for 0.5 hr., after which 100 ml. of chloroform was added, and the total mixture was poured into ice–water. The chloroform layer was washed sequentially with water, an ice-cold solution of aqueous hydrochloric acid until slightly acidic (pH 4.0), and an aqueous solution of sodium bicarbonate until neutral. After several washings with water, the chloroform layer was dried over sodium sulfate, filtered, and evaporated below 40° to a sirup which crystallized from a benzene–petroleum ether mixture. Compound III was obtained as long needles; the yield was 23 g. (50%), m.p. 130–131°, $[\alpha]^{25}D$ −10.1° (*c* 1.15, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_8S$ (464.53): C, 59.47; H, 6.07; S, 6.90. Found: C, 59.56; H, 6.09; S, 7.06.

1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose.—Compound III (1 g.) was dissolved in 25 ml. of absolute ethanol containing 5 g. of 5% palladium on carbon. The mixture was subjected to 50 p.s.i. of hydrogen in a Parr hydrogenation apparatus and shaken at 25° for 10 hr. Filtration and evaporation of the solution gave a sirup which readily crystallized from benzene–petroleum ether to yield 716 mg. (88%) of product, m.p. 124°, $[\alpha]^{25}D$ +8.0° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_8S$ (374.4): C, 51.33; H, 5.92; S, 8.56. Found: C, 51.38; H, 5.86; S, 8.41.

5,6-Anhydro-1,2-*O*-isopropylidene-β-L-idofuranose.—A solution containing 500 mg. of 1,2,-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose dissolved in 0.5 ml. of alcohol-free chloroform was chilled to −15° and a 0.25-ml. portion of methanol containing 60 mg. of sodium was added. After the reaction mixture was maintained at 0° for 3 hr., 0.2 ml. of a saturated solution of potassium bicarbonate was added. The mixture was evaporated at 0° to remove methanol, extracted with three portions of chloroform, and dried over anhydrous magnesium

(15) W. E. Trevelyan, P. D. Proctor, and S. J. Harrison, *Nature*, **166**, 444 (1950).

(16) Brinkman Instruments, Inc., Great Neck, L. I., N. Y.

(17) R. L. Whistler and M. L. Wolfrom, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p. 190.

sulfate. After filtration and evaporation of solution, a crystalline product obtained from a benzene–petroleum ether mixture was identical with 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose,[9] since the melting point of 74° remained undepressed when admixed with an authentic sample.

Reduction of Compound III.—After 2 g. of III was dissolved in 25 ml. of anhydrous tetrahydrofuran and cooled to 0°, 1 g. of lithium aluminum hydride was added. Within 0.5 hr. the mixture was warmed to 25°, then stirred for 2 hr., and refluxed an additional 48 hr. Excess hydride was destroyed carefully by a slow addition of water. After 100 ml. of a saturated aqueous sodium sulfate solution was added, the mixture was poured into a separatory funnel and mixed with a dilute chilled hydrochloric acid solution until the solids were dissolved. The tetrahydrofuran layer was drawn off, and the remaining aqueous phase was extracted with four 20-ml. portions of chloroform. The chloroform extracts were combined with the tetrahydrofuran layer, washed three times with water, and dried over anhydrous magnesium sulfate. A sirupy product obtained after filtration and evaporation of solvent was dissolved in 25 ml. of absolute ethanol and hydrogenated at 50 p.s.i. for 10 hr. at 25° with palladium on carbon. A portion of the sirupy product obtained after hydrogenation crystallized from a benzene–petroleum ether mxiture as long needles; the yield was 150 mg., m.p. 95°, $[\alpha]^{25}D$ −9.0 (*c* 0.50, chloroform).

A mixture melting point of this product and an authentic sample of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose remained undepressed.

Anal. Calcd. for $C_9H_{16}O_5$ (204.22): C, 52.94; H, 7.89. Found: C, 53.14; H, 7.79.

6-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IV).—Compound III (2 g.) was dissolved in 15 ml. of alcohol-free chloroform. The mixture was cooled to −5° and 8 ml. of methanol containing 12.5% sodium methylate was added. The solution was stirred for 1 hr. at 0° and then at 25° for an additional 16 hr. A saturated solution of potassium bicarbonate was added, and the mixture was evaporated to remove methanol. The residue was extracted four times with 25-ml. portions of chloroform and dried over anhydrous magnesium sulfate. The solution was filtered and evaporated under reduced pressure to a sirup which crystallized from a mixture of benzene–petroleum ether in long fine needles to yield 1.25 g. (95%) of product with m.p. 113°, $[\alpha]^{25}D$ −47.3° (*c* 1.15, chloroform). Paper chromatograms of IV in irrigants A and B when sprayed with indicator C revealed a single component. Thin layer chromatograms in irrigants E and F indicated that IV was not contaminated with any foreign organic material. It absorbed bromine from a bromine–carbon tetrachloride solution and instantaneously decolorized a potassium permanganate solution indicating unsaturation; ν_{max}^{KBr} 1310 (m) and 975 (s), *trans* double bond; and 810 and 948 cm.$^{-1}$, vinyl ether.

Anal. Calcd. for $C_{16}H_{20}O_5$ (292.33): C, 65.74; H, 6.89. Found: C, 65.92; H, 6.82.

Reductive Ozonolysis of IV.—A 20-ml. portion of purified ethyl acetate was cooled to −70° in a Dry Ice–acetone bath and ozone was bubbled through the solution until a permanent blue color was maintained. A solution containing 30 mg. of IV, dissolved in 1 ml. of cold ethyl acetate, was added to the ozone-saturated ethyl acetate solution. Excess ozone was immediately evaporated and the remaining ethyl acetate solution containing the respective ozonide was concentrated nearly to dryness. After a 10-ml. portion of methylene chloride and 50 mg. of Lindlar catalyst[18] were added to the ozonide, the mixture was agitated for 0.5 hr. in a hydrogen atmosphere. Filtration and evaporation of the hydrogenated solution gave a sirupy product which, on paper chromotography in irrigants A and B, developed with indicator D, migrated identically with 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[13] (V). The latter was converted to 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose phenylhydrazone[13,14] (VI), m.p. 140°, $[\alpha]^{25}D$ −42.0° (*c* 2.0, chloroform).

3-*O*-Acetyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose.—A 300-mg. portion of IV was dissolved in 3 ml. of pyridine, cooled to 0°, and 1 ml. of acetic anhydride was added. After 10 hr. at 0°, the reaction mixture was warmed to 25° for an additional 9 hr., then poured into ice–water, and stirred until the gummy acetate settled. A chloroform solution containing the acetyl derivative was washed with water and dried over anhydrous sodium sulfate. After filtration and evaporation of solution, the acetyl derivative, obtained as a semisolid, crystallized from benzene–petroleum ether to give a product with m.p. 78°, $[\alpha]^{25}D$ −34.5° (*c* 1.05, chloroform).

Anal. Calcd. for $C_{18}H_{22}O_6$ (334.36): C, 64.66; H, 6.63; CH_3CO, 12.87. Found: C, 64.83; H, 6.72; CH_3CO, 12.63.

5-Deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.—Compound IV (200 mg.) was dissolved in 20 ml. of absolute ethanol containing 1 g. of palladium on carbon. The mixture was subjected to 50 p.s.i. of hydrogen pressure in a Parr hydrogenation apparatus and shaken at 25° for 8 hr. Filtration of the reaction mixture and evaporation of solvent gave a sirup, which spontaneously crystallized from a mixture of benzene–petroleum ether to yield 130 mg. (90%) of product with m.p. 95°, $[\alpha]^{25}D$ −10.0° (*c* 0.71, in chloroform). An X-ray powder diffraction pattern of the crystalline product was identical with an authentic sample of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.

Anal. Calcd. for $C_9H_{16}O_5$ (204.22): C, 52.94; H, 7.89. Found: C, 53.05; H, 7.98.

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6-Deoxy-6-hydrazinoamylitol and 6-Deoxy-6-hydrazinocellulose[1]

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Direct tosylation of amylitol and cellulose to (degree of substitution) 0.65 and 0.64, respectively, and reaction with hydrazine leads to 6-deoxy-6-hydrazinoamylitol of D.S. 0.40 and 6-deoxy-6-hydrazinocellulose of D.S. 0.50. Different oxidants remove the hydrazino groups with formation of 6-deoxyglycans which on hydrolysis produce D-glucose and D-quinovose. Reaction of the 6-deoxy-6-hydrazinoglycans with D-glucose or D-glucono-1,4-lactone produces the appropriate derivatives in quantitative yields.

Introduction of hydrazino groups into the linear polysaccharides amylose and cellulose is undertaken to make available reactive groups that may be used as attachment points for sugars or sugar derivatives. In this way it is possible to construct molecules with sugar size chains of controlled lengths. By insertion of the hydrazino groups, used for coupling, at the C-6 position, side chains are uniformly located. Such definite compounds are of value in establishing the relationship between molecular architecture and physical properties of high polymeric hydrophilic molecules. Previously, this laboratory[2] made 6-amino-6-deoxy-

(1) Journal Paper No. 2222 of the Purdue Agricultural Experiment Station, Lafayette, Ind.

(2) R. L. Whistler and D. G. Medcalf, presented in part before the Carbohydrate Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; *Arch. Biochem. Biophys.*, **104**, 150 (1964).

amylose by nucleophilic displacement of *p*-tolylsulfonyloxy (tosyloxy) groups specifically located at carbons C-6 in 2,3-di-*O*-phenylcarbamoylamylose with azide ions, and then subsequent reduction. For degrees of substitution (D.S.) less than 1.0, initial blocking of secondary hydroxyl groups is unnecessary and direct tosylation of the polysaccharide may be used. As shown in previous work,[3] direct tosylation up to a D.S. of about 0.7 introduces tosyl groups almost entirely on primary positions with attachment of very few at secondary positions. Therefore, in this work tosyl groups were introduced to a D.S. of 0.65 and 0.64 in amylitol and cellulose, respectively. Secondary substitution did not exceed a D.S. of 0.05. While reaction of 6-*O*-tosylcellulose with hydrazine at 100° for 30 min. suffices to remove all tosyl groups, reaction of tosylamylitol in pyridine with hydrazine at 100° for 1 hr. does not completely remove the tosyl groups. However, a second treatment with hydrazine alone, at 17° for 34 hr., suffices. Direct treatment of 6-*O*-tosylamylitol with hydrazine at 17° for 48 hr. removes all tosyl groups, but gives a product with only a low hydrazino content.

Hydrazinolysis of polysaccharides occurs when they are heated with hydrazine,[4] particularly for extended times. Since amylose is especially susceptible to alkaline degradation, it was hydrogenated to amylitol before treatment. Hydrogenated chondroitin sulfate has been found[5] to be more resistant to hydrazinolysis than the reducing polysaccharide. Viscosity measurements indicated that, under the conditions used here, hydrazinolysis is not extensive. The results appear to confirm previous[4] observations.

Reaction with hydrazine does not lead to complete replacement of tosyloxy groups by hydrazino groups. Even those tosyloxy groups on primary positions are not fully replaced, being 83% replaced in the cellulose derivative and 67% replaced in the amylitol derivative. Since the hydrazinoglycans are free of tosyl groups, some tosyl groups must be removed by hydrolysis, a conclusion substantiated by the isolation of hydrazinium tosylate in expected yield from the reaction mixture. The hydrochloric acid salts of 6-deoxy-6-hydrazinocellulose and 6-deoxy-6-hydrazinoamylitol are stable and water soluble, producing clear, nonretrograding solutions. Addition of acetic acid to pH 5 causes a solution of 6-deoxy-6-hydrazinoamylitol to form a stiff gel. The free 6-deoxy-6-hydrazinoglycans are fairly stable under nitrogen at low temperatures. However, at 25° in the presence of air, the white solids change to a light yellow color and the nitrogen content decreases progressively. Hydrolysis of this product yields D-glucose and 6-deoxy-D-glucose, D-quinovose. Various oxidants attack and remove the hydrazine groups from the C-6 position leaving 6-deoxy units. Oxidants which attack the free base in this way are oxygen, hydrogen peroxide, nitrous acid, iodine, and potassium iodate. Iodate ion reacts rapidly and quantitatively with hydrazinoamylitol with completion of the reaction in 15 min.

The 6-deoxy-6-hydrazinoglycans react readily with a concentrated solution of D-glucose to attach one D-glucose unit to each hydrazino group, probably as the hydrazone. These derivatives do not hydrolyze in dilute aqueous solution. Likewise the 6-deoxy-6-hydrazinoglycans react with D-glucono-1,4-lactone to form D-gluconohydrazines in quantitative yields. These hydrazides are stable in neutral aqueous solution but hydrolyze readily on addition of dilute base.

(3) R. L. Whistler and S. Hirase, *J. Org. Chem.*, **26**, 4600 (1961).
(4) Z. Yosizawa and T. Sato, *Biochim. Biophys. Acta*, **52**, 591 (1961).
(5) M. L. Wolfrom and B. O. Juliano, *J. Am. Chem. Soc.*, **82**, 2588 (1960).

Experimental

Chromatography.—Chromatographic separations were on Whatman No. 1 paper at 20° with the following irrigants: A, ethyl acetate–acetic acid–formic acid–water (18:3:1:4 v./v.); B, ethyl acetate–pyridine–water (10:4:3 v./v.); C, 1-butanol–ethanol–water (40:11:19 v./v.). For location of components, papers were sprayed with silver nitrate–sodium hydroxide solution.[6]

Amylitol was prepared from corn amylose isolated as the 1-butanol complex.[7] After three recrystallizations, the 1-butanol–amylose complex from 120 g. of starch was dissolved in 1 l. of previously boiled 0.2 *N* sodium hydroxide solution. Ten grams of sodium borohydride[8] was added, and the mixture was allowed to stand at 17° for 24 hr. The solution was acidified with acetic acid, and the amylitol precipitated by addition of 1.5 l. of methanol. The precipitate was suspended in 1 l. of water, precipitated with 1.5 l. of methanol, and dried by washing with three successively fresh portions of absolute ethanol in a Waring Blendor followed with dry ether. The remaining ether was removed under reduced pressure over calcium chloride.

6-*O*-Tosylamylitol.—Ten grams of this fluffy powder was stirred in 100 ml. of dry pyridine for 10 min. at 100°. The thick suspension was cooled to 5° and 17.54 g. of tosyl chloride was added with vigorous stirring. After 1 hr. at 5°, the pink mixture was heated to 30° for 1 hr. It then was poured slowly, with stirring, into 2 l. of 80% methanol. On decantation of the methanol and washing the precipitate with water in a Waring Blendor, a powder resulted which was washed free of chloride ion with water and was dried in a vacuum desiccator containing calcium chloride. Sulfur analysis indicated a D.S. of 0.65. Primary tosyl groups were determined[9] by displacement of the primary groups with iodine in 2,5-hexanedione at 120° for 2 hr. Organic iodine was converted[10] to iodine ion by displacement with hydroxyl using potassium hydroxide in ethanol to indicate a D.S. of 0.60, tosyl groups in the amylitol. Tosyl groups located at secondary positions were estimated from sulfur analysis to correspond to a D.S. of 0.05.

6-Deoxy-6-hydrazinoamylitol.—To establish improved conditions for tosyl displacement, 1-g. portions of the derivative were dissolved in 20-ml. portions of dry pyridine and treated at 100° with 0.2, 0.5, 1.0, 2.0, 4.0, and 8.0 ml. of anhydrous hydrazine. Products were precipitated by addition of 150 ml. of methanol, centrifuged, washed through several portions of fresh methanol in a Waring Blendor, washed with diethyl ether in a beaker, filtered, and dried over calcium chloride in a vacuum desiccator. Bound hydrazine estimated by nitrogen analysis[11] indicated D.S. of 0.14, 0.20, 0.25, 0.31, 0.38, and 0.38. Sulfur determinations indicated tosyl contents corresponding to D.S. of 0.36, 0.28, 0.20, 0.14, 0.10, and 0.09.

Since complete elimination of tosyl groups was not obtained, the above products were reacted with anhydrous hydrazine a second time. This effected complete removal of tosyl groups. For example, 0.5 g. of the product having a D.S. of 0.38 in hydrazino groups and 0.10 in tosyl groups when treated with 5 ml. of hydrazine at 17° in oxygen-free nitrogen[12] for 34 hr. was devoid of sulfur and possessed a hydrazino content equivalent to a D.S. of 0.40.

When 5 g. of 6-*O*-tosylamylitol of D.S. 0.65 was treated with 50 ml. of hydrazine at 17° for 48 hr. in an oxygen-free atmos-

(6) W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950).
(7) T. J. Schoch, *J. Am. Chem. Soc.*, **64**, 2957 (1942).
(8) M. Abdel-Akher, J. K. Hamilton, and F. Smith, *ibid.*, **73**, 4691 (1951).
(9) F. B. Cramer and C. B. Purves, *ibid.*, **61**, 3458 (1939); T. S. Gardner and C. B. Purves, *ibid.*, **64**, 1539 (1942); C. J. Malm, L. J. Tanghe, and B. C. Laird, *ibid.*, **70**, 2740 (1948).
(10) J. F. Mahoney and C. B. Purves, *ibid.*, **64**, 9 (1942).
(11) S. J. Clark, "Quantitative Methods of Organic Microanalysis," Butterworth and Co., London, 1956, p. 91.
(12) L. F. Fieser, *J. Am. Chem. Soc.*, **46**, 2639 (1924).

phere, the product was free of sulfur and had a hydrazine content equivalent to a D.S. of 0.15.

After removal of the polysaccharide derivative, the reaction mixture from the detosylation and the methanol washings, were concentrated to dryness under reduced pressure and the residue was dissolved in ethanol. After filtration, the solution was concentrated to about 10 ml., and 3 ml. of dry ether was added. On standing at 25° for 1 hr., white crystals appeared which were filtered and washed with dry ether. Further concentration of the mother liquor to about 2 ml., addition of ether to slight turbidity, and cooling in a refrigerator gave a second crop of crystals. The total yield was 2.2 g., with m.p. 122°, undepressed on mixture with hydrazinium tosylate.

Anal. Calcd. for $C_7H_8N_2H_4SO_3$: C, 41.13; H, 5.87; N, 13.75. Found: C, 40.99; H, 5.45; N, 13.62.

Authentic hydrazinium tosylate was prepared from 200 mg. of toluenesulfonic acid by reaction with 2.0 ml. of hydrazine hydrate. After heating for a few minutes on the steam bath, the mixture was concentrated to dryness. Upon standing at 25° for 1 hr., a white crystalline material appeared which was filtered and washed with dry ether and had a melting point of 122°.

Oxidation with Hydrogen Peroxide.—To 0.5 g. of 6-deoxy-6-hydrazinoamylitol of D.S. 0.40, 15 ml. of 10% hydrogen peroxide solution was added. The temperature increased from 25 to 35°, and some foaming occurred. The mixture was cooled to 25° and a solution of 1 *N* sodium hydroxide was added to adjust the pH to 11. After 15 min. the solution was poured into 50 ml. of methanol, filtered, washed with methanol, and then washed with dry diethyl ether. The product was soluble in cold water, gave a blue color with iodine, and reduced Fehling's solution which indicated that some depolymerization had occurred also.

Oxidation with Potassium Iodate.—6-Deoxy-6-hydrazinoamylitol (6 g.) of D.S. 0.4 was dissolved in 100 ml. of 2% acetic acid solution by stirring and heating at 100° for several minutes. The solution was cooled to 25° and 5 ml. of 98% formic acid solution was added with 20 ml. of a water solution containing 1.1 g. of potassium iodate. An immediate reduction of the iodate to iodine was indicated by the development of a dark blue color. The temperature increased to 35° and some foam appeared. After 15 min., 10 g. of potassium iodide was added, followed by enough sodium thiosulfate to remove the color of the iodine complex. After 2 days of dialysis against distilled water, the solution was concentrated to 50 ml., and the polysaccharide was precipitated and washed as before.

The yellowish nitrogen-free product was soluble in water, gave a blue color with iodine, a negative test with Fehling's solution, and did not gelatinize with acetic acid.

Determination of the Hydrazino Groups by Oxidation with Potassium Iodate.—6-Deoxy-6-hydrazinoamylitol (26.6 mg.) of D.S. 0.40 was dissolved in 10 ml. of 1% acetic acid solution, and 10.0 ml. of a solution of 0.01 *M* potassium iodate was added with 1 ml. of concentrated formic acid. After 15 min., 200 mg. of potassium iodide was added and the excess of iodine was titrated with 0.05 *N* sodium thiosulfate solution. Under these conditions 1 mole unit of hydrazinoamylitol was oxidized by 0.35 mole of potassium iodate.

Oxidation with Iodine.—6-Deoxy-6-hydrazinoamylitol (241 mg.) of D.S. 0.40 was dissolved in 50 ml. of 1% acetic acid solution and titrated with 0.12 *M* iodine solution. The pH was brought to 7.4 and kept constant throughout the titration by addition of sodium bicarbonate solution. A total of 14.7 ml. of iodine solution was added. One mole of 6-deoxy-6-hydrazinoamylitol was oxidized by each 1.34 moles of iodine. The oxidized solution was dialyzed, concentrated, and precipitated as before. The product was soluble in water, reduced Fehling's solution slightly, and did not gelatinize with acetic acid.

Reaction with Nitrous Acid.—6-Deoxy-6-hydrazinoamylitol (1 g.) of D.S. 0.4 was dissolved in 60 ml. of 2% aqueous acetic acid, and 2 g. of sodium nitrite was added at 30°. After 5 min., during which time gas evolved, the solution was neutralized with 1 *N* sodium hydroxide and the polysaccharide was precipitated with methanol. After centrifugation, the yellowish precipitate was washed with methanol followed by dry ether. The product was soluble in water, reduced Fehling's solution slightly, and did not gelatinize with acetic acid.

Isolation and Identification of Quinovose.—Acid hydrolysates from the oxidized products, after neutralization with barium carbonate and filtration, were concentrated to dryness. Each was examined as follows. Absolute methanol (10 ml.) was added and any colored precipitate was discarded. The clear methanolic solution was concentrated under reduced pressure and chromatographed on Whatman No. 3 MM paper, using either irrigant A or B. The zone corresponding to D-quinovose was eluted with water, and the extract was concentrated and heated with 200 mg. of *p*-nitrophenylhydrazine in 20 ml. of 1 *N* hydrochloric acid. The red precipitate was recrystallized from 50% ethanol and the melting point and mixture melting point with authentic *p*-nitrophenyl-D-quinovosazone[13] was 222°. The number of D-quinovose units produced by oxidation of the hydrazoamylitol was estimated by acid hydrolysis, oxidation of the product with periodate, and quantitative determination of the acetaldehyde produced.[14] For the iodate oxidized hydrazinoamylitol of D.S. 0.40, the resulting 6-deoxy content was 0.16.

Retrogradation.—A 250-mg. portion of 6-deoxy-6-hydrazinoamylitol of D.S. 0.4 was dissolved in 50 ml. of 1% hydrochloric acid solution, the pH was adjusted to 5, and the mixture was held at 4° for 8 days. Likewise, a solution of 250 mg. of amylitol in 25 ml. of 1 *M* potassium hydroxide solution was neutralized with an equal volume of 1 *M* hydrochloric acid solution, the pH was adjusted to 5, and the solution was held at 4° for 8 days. The solution of 6-deoxy-6-hydrazinoamylitol remained clear, but the amylitol solution quickly clouded and developed a precipitate.

Hydrazinocellulose.—Cut cotton linters (230 g.) were stirred with 4 l. of acetic acid in a Waring Blendor. Then 1.5 ml. of concentrated sulfuric acid was added and the reaction mixture was kept at 25° for 2 hr. Acetic anhydride (1 l.) was added and the mixture was stirred frequently for 5 hr. The thick solution was poured in a small stream into about 20 volumes of water. After standing at 25° for 2 hr. with frequent change of water, the filamentous precipitate was stirred in a Waring Blendor and washed with an excess of water. The acetyl content was 44.5%.

The cellulose acetate was deacetylated by placing it in an 8-l. solution of 0.5 *N* sodium hydroxide in ethanol at 25° for 2 days. The product was filtered through cheese cloth, washed with water until neutral, and air-dried for 4 days. Drying this product to constant weight under reduced pressure at 60° gave a yield of 225 g. Ten grams of the regenerated cellulose was activated[15] in a mixture of 50 ml. of water and 150 ml. of pyridine. It was then washed three times with anhydrous pyridine, filtered, and 23.5 g. of tosyl chloride (2 moles of tosyl chloride per mole of D-glucose unit) was added in 200 ml. of anhydrous pyridine. After shaking the mixture at 25° for 24 hr., the mixture was poured into a 2 l. of methanol, filtered, and stirred with methanol in a Waring Blendor. After filtration, the tosyl derivative was washed with methanol until the filtrate gave a negative test for chlorine. The product was light brown and the yield was 15.5 g. of D.S. 0.64 (of which 0.60 was primary). Under the same conditions used for the preparation of 6-deoxy-6-hydrazinoamylitol, cellulose gave a white fluffy compound which was insoluble in water or dilute acid solutions. A soluble 6-deoxy-6-hydrazinocellulose was obtained by a slightly different procedure. For this 1 g. of 6-*O*-tosylcellulose (D.S. 0.64, 40 mesh) was heated and stirred at 100° with 10 ml. of anhydrous hydrazine in the absence of oxygen for 25 min. It then was poured into 200 ml. of methanol. The 6-deoxy-6-hydrazinocellulose precipitated as a white fibrous mass which was broken up by stirring for 1 min. in a Waring Blendor. It was filtered and washed again in a Waring Blendor for 1 min. with 80% aqueous methanol. The product was filtered then and washed with dry methanol. All excess hydrazine must be washed out as soon as possible. The 0.5 g. of final product was soluble in dilute acids as long as it was not subjected to prior drying. The D.S. was 0.50 and sulfur was absent.

Reaction with D-Glucose.—Both 6-deoxy-6-hydrazinoamylitol and 6-deoxy-6-hydrazinocellulose reacted similarly when subjected to reactions involving hydrazino groups. 6-Deoxy-6-hydrazinocellulose (D.S. 0.50), freshly prepared from 1.0 g. of 6-*O*-tosylcellulose while still wet with methanol, was transferred to a 2.3 × 20 cm. test tube which contained 4 g. of D-glucose dissolved in 15 ml. of water. Glacial acetic acid (1 ml.) was added, and the mixture was shaken thoroughly and heated at 45° for 30 min. No change in color was observed but higher temperatures for longer times produced a brown color. After addition of 20 ml. of 1 *N* sodium hydroxide solution, the mixture was poured into 200 ml. of methanol stirred in a Waring Blendor. A fine white

(13) F. Feist, *Ber.*, **33**, 2098 (1900).
(14) B. H. Nicolet and L. A. Shim, *J. Am. Chem. Soc.*, **63**, 1456 (1941).
(15) C. Malm, L. Tanghe, and B. Laird, *ibid.*, **70**, 2747 (1948).

precipitate developed. The mixture was heated to boiling for 10 min. and centrifuged. The precipitate was suspended twice in 100-ml. portions of hot 80% aqueous methanol and centrifuged to remove traces of D-glucose. The polysaccharide was washed with methanol and dried over calcium chloride to yield 0.7 g.

The amount of D-glucose combined with the polymer was determined by periodate oxidation. An 18.3-mg. portion was mixed with 80 ml. of 5% potassium chloride solution and 20 ml. of 0.3 *M* sodium metaperiodate. The mixture was shaken in the dark at 18°. Aliquots were taken every 12 hr., and the formic acid present was titrated by 0.01 *N* sodium hydroxide solution using methyl red–methylene blue as indicator. 6-Deoxy-6-hydrazinocellulose was used in a blank determination. The oxidation was complete in about 2 days. The amount of formic acid obtained indicated that the number of D-glucose units which had become attached were equivalent to the number of hydrazino groups present.

The product formed by treating D-glucose with the 6-deoxy-6-hydrazinocellulose of D.S. 0.5, when freshly prepared, was readily soluble in water. When 100 mg. of the polymer was shaken in 10 ml. of water for 48 hr., no free D-glucose was evident on paper chromatography of solution aliquots.

Reaction with D-Glucono-1,4-lactone.—6-Deoxy-6-hydrazinocellulose of D. S. 0.50, freshly prepared from 1.0 g. of 6-*O*-tosylcellulose, was placed in a 2.3 × 20 cm. test tube which contained 4 g. of D-glucono-1,4-lactone dissolved in 15 ml. of water. The mixture was shaken thoroughly and heated at 45° for 30 min. After centrifugal removal of a small amount of insoluble material, the centrifugate was mixed with 30 ml. of 1 *N* sodium hydroxide solution. The mixture, when poured into 200 ml. of methanol and stirred in a Waring Blendor, produced a fine white precipitate. The methanol suspension was heated, centrifuged, and the precipitate was washed twice with 100-ml. portions of 60% aqueous methanol. It then was washed with methanol and dried over calcium chloride to yield 0.7 g. The amount of combined D-gluconic acid was estimated by periodate oxidation of the product and measurement of the amount of formaldehyde released. The amount found corresponded to the attachment of one D-gluconic acid unit to each hydrazino group.

The product was alkaline hydrolyzed by suspending 200 mg. in 15 ml. of hot ethanol, adding 5 ml. of 0.1 *N* sodium hydroxide solution, and heating at 100° for 5 min. The mixture was filtered while hot, and the filtrate was neutralized with diluted acid and chromatographed using irrigants A, B, and C. On spraying with silver nitrate solution a single strong spot appeared, corresponding to D-gluconate.

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2,2′:5′,2″-Terpyrrole[1a]

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The synthesis of 2,2′:5′,2″-terpyrrole has been accomplished by dehydrogenation of pyrrole trimer and decarboxylation of a terpyrrole dicarboxylic acid. The properties found for this compound differ appreciably from those reported previously for material assigned the terpyrrole structure. A general procedure has been developed for the synthesis of terpyrroles from the condensation of a 2,2′-bipyrrole and a 2-pyrrolidinone to give a pyrrolinylbipyrrole, and dehydrogenation of the latter.

It has been suggested that pyrrole is an intermediate in the formation of naturally occurring melanins and that pyrrole black, generated when pyrrole is oxidized in acetic acid, is structurally similar to melanins.[2] Because of the polymeric character of pyrrole black, Chierici and co-workers attempted to synthesize 2,2′:5′,2″-terpyrrole (I) to determine if this compound is an intermediate in the formation of pyrrole black and of possible significance in relation to melanin.[3] From the reaction of 1,4-di-2′-pyrrylbutane-1,4-dione and ammonia, they reported the isolation of a compound assigned structure I, m.p. 100° dec., too unstable for further characterization. These properties were quite unexpected in view of our experience with 2,2′-bipyrroles.[4] Therefore, we have investigated the synthesis of terpyrroles and describe here several representatives of this system.

Pyrrole, treated with acid, undergoes trimerization[5] to form pyrrole trimer, 2,5-di-2′-pyrrylpyrrolidine (II).[6] When II was subjected to catalytic dehydrogenation, the product obtained had the molecular formula of the desired terpyrrole but was clearly not the same material as previously reported[3b] since it melted at 242°. The following spectral evidence established the structure of this compound as terpyrrole (I). (a) The n.m.r. spectrum showed six β-protons (δ 6.2) and two α-protons (δ 6.7) as complex signals, while integration established the approximate location of the three protons attached to nitrogen (δ ~10). (b) The ultraviolet spectrum retained the same fine structure as found in 2,2′-bipyrrole (III)[4] and exhibited the anticipated bathochromic shift (~45 mμ) relative to bipyrrole. A methanolic solution of terpyrrole exposed

II I

to air and light slowly turns green and, after 24 hr., a black precipitate forms. These changes occur instantaneously when hydrogen peroxide is added to a solution of I in acetic acid. However, crystalline material is stable for long periods when stored in the cold in the absence of air and light. From a comparison of these properties with those reported by Chierici and Serventi,[3b] it is clear that the material they had isolated was not terpyrrole.

A more general synthesis of terpyrroles was effected by condensation of a 2,2′-bipyrrole with a 2-pyrroli-

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(2) (a) A. Angeli and A. Pieroni, *Atti accad. Lincei*, **30**, 241 (1921); (b) A. Pieroni and A. Maggi, *Gazz. chim. ital.*, **53**, 120 (1923).

(3) (a) L. Chierici and A. Cella, *Ann. chim.* (Rome), **43**, 141 (1953); (b) L. Chierici and G. Serventi, *Gazz. chim. ital.*, **90**, 23 (1960).

(4) (a) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962); (b) H. Rapoport and N. Castagnoli, *ibid.*, **84**, 2178 (1962).

(5) M. Dennstedt and J. Zimmermann, *Ber.*, **20**, 850 (1887).

(6) H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).

TABLE I

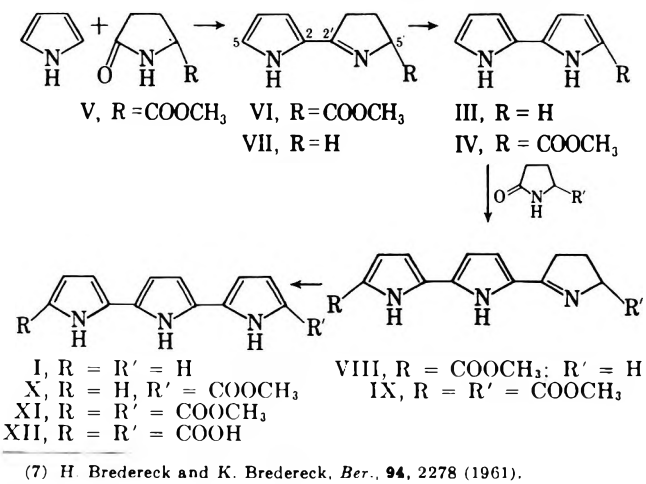
NUCLEAR MAGNETIC RESONANCE ABSORPTION[a] OF TERPYRROLE AND RELATED COMPOUNDS

Compound	Structural element					
	$H_{5',5''}$	$H_{4',4''}$	$H_{3',3''}$	OCH_3	$H\alpha$[b]	$H\beta$[b]
VI[b]	4.8(t)[f][g]	2.3(m)[2]	3.1(m)[2]	3.7(s)[3]	6.9(m)[1]	6.2(m)[1]
						6.6(m)[1]
						6.8(m)[2]
						6.6(m)[1]
IV[c]				3.8(s)[3]		6.4(m)[1]
						6.1(m)[1]
VIII[d]	3.9(m)[2]	2.2(m)[2]	3.2(t)[2]	3.8(s)[3]		6.7–7.1(m)[4]
IX[d]	4.9(t)[1]	2.4(m)[2]	3.3–3.8(m)[8]			6.7–7.2(m)[4]
XI[c]				3.8(s)[6]		6.4–7.1(m)[6]
I[e]					6.7(m)[2]	6.2(m)[6]

[a] As δ-values referred to internal tetramethylsilane (δ = 0). [b] In deuteriochloroform. [c] In acetone. [d] In liquid sulfur dioxide. [e] In methanol. [f] Letters in parentheses refer to singlet (s), triplet (t), multiplet (m). [g] Numbers in brackets refer to number of protons obtained by integration. [h] α- or β-pyrrole hydrogens.

dinone in the presence of phosphorus oxychloride to form a pyrrolinylbipyrrole. Dehydrogenation of the pyrroline then led to the terpyrrole. With the unsubstituted 2,2′-bipyrrole and 2-pyrrolidinone, polymeric material was formed rapidly and neither starting material nor product could be isolated from the reaction mixture. The difficulty appeared to be due to the instability of bipyrrole to acidic conditions and the self-condensation of 2-pyrrolidinone in the presence of phosphorus oxychloride.[7]

To overcome this difficulty, the corresponding reaction was considered with 5-methoxycarbonyl-2,2′-bipyrrole (IV) since the ester group should increase the stability of the bipyrrole significantly. Two methods were examined for the preparation of IV, *viz.*, the condensation of methyl 2-pyrrolecarboxylate with 2-pyrrolidinone, and the condensation of methyl 2-pyrrolidinone-5-carboxylate (methyl pyroglutamate, V) with pyrrole, followed by dehydrogenation in each case. The first procedure failed because of the low reactivity of the carbomethoxypyrrole toward electrophilic attack, over 90% of the starting pyrrole ester being recovered. However, the second method gave the required 2,2′-(5′-methoxycarbonyl-1′-pyrrolinyl)pyrrole (VI) in reasonable yield. As in the case of the unsubstituted pyrrolinylpyrrole (VII) previously reported,[4b] VI shows a reversible acid shift in its ultraviolet absorption, a consequence of the extended resonating system of the protonated form, and a strong band at 1630 cm.$^{-1}$ attributed to C=N stretching. The carbonyl band appeared at 1725 cm.$^{-1}$. The position of the double bond was unambiguously established by n.m.r. (Table I), the low field triplet (δ 4.8) from the methine proton clearly eliminating any other possible isomer. Dehydrogenation of VI proceeded smoothly to yield the desired carbomethoxybipyrrole (IV).



Condensation of IV with 2-pyrrolidinone gave the pyrrolinylbipyrrole (VIII), the structure of which was established by analysis and spectral data similar to that given above. This reaction was complicated by the ease with which 2-pyrrolidinone undergoes self-condensation[4b,7] and the deactivating influence of the ester group on the nucleophilic character of the bipyrrole. The greater stability of methyl pyroglutamate in the presence of phosphorus oxychloride, however, led to an improved yield of the dicarbomethoxy pyrrolinylbipyrrole (IX).

Catalytic dehydrogenation of the two pyrrolinylbipyrroles (VIII and IX) gave the desired terpyrroles (X and XI). It is of interest to note the greater ease with which IX undergoes dehydrogenation (84% of the theoretical volume of hydrogen evolved in 45 min.) compared with VIII under the same conditions (50% of theory in 100 min.). Presumably, this difference is due to the increased lability of the pyrroline α-hydrogen in IX.

The above two routes to terpyrroles were related by saponification of the diester (XI) to the diacid (XII) which, when heated to 200° (20 μ), underwent decarboxylation to give pure terpyrrole, identical with that obtained by the dehydrogenation of pyrrole trimer.

Experimental[8]

2,2′:5′,2″-Terpyrrole (I).—A mixture of 561 mg. (2.79 mmoles) of pyrrole trimer II,[6] 575 mg. of 5% palladium on carbon, and 15 ml. of *p*-cymene was boiled under a slow nitrogen sweep with magnetic stirring. After 30 min., the reaction mixture was cooled to about 80° and 20 ml. of benzene (oxygen-free) was introduced. The warm mixture was filtered under a nitrogen atmosphere and the filtrate was reduced to about one-half its original volume *in vacuo*. Cooling of the residual solution caused crystallization of the product (76 mg., 0.39 mmole, 14%). Sublimation at 130° (20 μ) gave pure terpyrrole, m.p. 242°; $\lambda_{max}^{CH_3OH}$ 345 mμ (sh) (ϵ 13,000), 327 (25,900), 319 (26,000).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.1; H, 5.6; N, 21.3. Found: C, 73.2; H, 5.7; N, 21.1.

Methyl 2-Pyrrolidinone-5-carboxylate (Methyl Pyroglutamate, V).—Sublimed, commercial pyroglutamic acid (m.p. 179–183°, 300 g., 2.32 moles) was added to 3 l. of anhydrous methanol

(7) H. Bredereck and K. Bredereck, *Ber.*, **94**, 2278 (1961).

(8) Microanalyses were performed by the Microchemical Laboratory University of California, Berkeley, Calif.. Ultraviolet spectra were determined in methanol.

which previously had been saturated with anhydrous hydrogen chloride. The heterogeneous mixture was stirred for 72 hr. during which time all of the solid had gone into solution. An n.m.r. spectrum taken at this time showed that over 98% of the acid had undergone esterification. The methanol was removed by distillation at room temperature *in vacuo* and the residue was dissolved in chloroform (500 ml.). The chloroform solution was extracted with two 50-ml. portions of aqueous bicarbonate, dried over magnesium sulfate, concentrated on a rotary evaporator, and distilled to give 280 g. (1.96 moles, 85%) of the pure ester, b.p. 101–103° (0.15 mm.), lit.[9] b.p. 160° (8 mm.).

2,2′-(5′-Methoxycarbonyl-1′-pyrrolinyl)pyrrole (VI).—To a mixture of 10 g. (70 mmoles) of methyl pyroglutamate, 5 g. (75 mmoles) of pyrrole, and 50 ml. of anhydrous methylene chloride was added, at a temperature of 0° with stirring and under a nitrogen atmosphere, 10.5 g. (69 mmoles) of phosphorus oxychloride over a 1-hr. period. After stirring at 0° for 19 hr. more, the slightly pink solution was added with vigorous swirling to 100 ml. of 7.5 *N* potassium hydroxide with an adequate amount of ice to maintain the temperature at 0°. The resulting mixture was extracted with three 100-ml. portions of chloroform, each extract being washed with water. The combined organic phase was then dried over potassium carbonate and the solvent was removed *in vacuo* to yield a nearly colorless solid which, on crystallization from benzene–hexane (1:1), gave 6.9 g. (35.5 mmoles, 51%) of 2,2′-(5′-methoxycarbonyl-1′-pyrrolinyl)pyrrole, m.p. 101–102°; $\lambda_{max}^{0.1\ N\ KOH-CH_3OH}$ 279 mμ (ε 16,900); $\lambda_{max}^{0.1\ N\ HCl-CH_3OH}$ 324 mμ (ε 29,800), 270 sh (3900).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6; OCH_3, 16.1. Found: C, 62.6; H, 6.4; N, 14.6; OCH_3, 16.0.

5-Methoxycarbonyl-2,2′-bipyrrole (IV).—A suspension of carbomethoxypyrrolinylpyrrole VI (1.9 g., 10 mmoles) and 30% palladium on carbon (3.56 g., 100 mole % Pd) in 50 ml. of di-*n*-hexyl ether was stirred vigorously for 45 min. at 200°. The hot reaction mixture was then filtered under an atmosphere of nitrogen and cooling gave 1.5 g. (79%) of 5-methoxycarbonyl-2,2′-bipyrrole. Sublimation at 120° (10 μ) provided an analytical sample, m.p. 231–232°; λ_{max} 325 mμ (ε 26,900), 220 (13,600).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7; OCH_3, 16.3. Found: C, 63.4; H, 5.5; N, 14.5; OCH_3, 15.9.

5-Methoxycarbonyl-5′-(2″Δ¹″pyrrolinyl)-2,2′-bipyrrole (VIII).—To a mixture of 2.9 g. (19.2 mmoles) of 5-methoxycarbonyl-2,2′-bipyrrole (IV), 22 g. (260 mmoles) of 2-pyrrolidinone, and 25 ml. of dioxane was added at room temperature, with stirring, under nitrogen, 16.5 g. (110 mmoles) of phosphorus oxychloride over a 20-min. period. The reaction mixture was stirred an additional 100 min. at room temperature. The dark, blue-green contents of the flask were then added to an ice-cold solution of sodium acetate (85 g. of trihydrate, 600 mmoles) with vigorous stirring. While maintaining the temperature at 0° by the addition of ice, the pH of the solution was raised to 9 by the slow addition of 10 *N* sodium hydroxide. Extraction of this heterogeneous mixture with ether gave a dark red ether solution which was washed several times with water, dried over anhydrous potassium carbonate, and evaporated to give 2.7 g. of a glass.

This material was chromatographed on 60 g. of activity IV alumina, using methylene chloride to develop the column. The first 100 ml. gave 400 mg. of the 2-pyrrolidinone self-condensation material[7] followed by 2 g. of a mixture of three compounds (detected by thin layer chromatography) with the next 400 ml. of methylene chloride. This material was crystallized from benzene–acetone to give 1.2 g. (4.7 mmoles, 24.5%) of 5-methoxycarbonyl-5′-(2″-Δ¹″-pyrrolinyl)-2,2′-bipyrrole, m.p. 210–212° dec.; $\lambda_{max}^{0.1\ N\ KOH-CH_3OH}$ 363 mμ (ε 31,000), 350 sh (28,000), 300 sh (11,200); $\lambda_{max}^{0.1\ N\ HCl-CH_3OH}$ 389 mμ (ε 42,300), 384 sh (38,400), 258 (10,500).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.4; H, 5.9; N, 16.3. Found: C, 65.1; H, 6.0; N, 16.1.

5-Methoxycarbonyl-5′-(5″-methoxycarbonyl-2″-Δ¹″-pyrrolinyl)-2,2′-bipyrrole (IX).—The carbomethoxybipyrrole (IV, 3.35 g., 17.6 mmoles), methyl pyroglutamate (35 g., 244 mmoles), 50 ml. of dioxane, and 50 ml. of methylene chloride were mixed and cooled to 0° under a nitrogen atmosphere. Then, over a 30-min. period, phosphorus oxychloride (5.5 g., 36 mmoles) was added with stirring. The reaction mixture was stirred an additional hour at 0° and poured with rapid stirring into an ice-cold aqueous solution of sodium acetate (31 g. of trihydrate, 216 mmoles). With temperature maintained at 0°, 10 *N* sodium hydroxide was added slowly to pH 9, the heterogeneous, aqueous mixture was extracted several times with ether, and the combined ether extracts were washed with water. Drying over potassium carbonate and removing the solvent gave 5.65 g. of an oil. Upon warming with 25 ml. of benzene, the oil crystallized, and sublimation of the crystalline mass at 150° (10^{-5} mm.) gave 4.2 g. (133 mmoles, 76%) of 5-methoxycarbonyl-5′-(5″-methoxycarbonyl-2″-Δ¹″-pyrrolinyl)-2,2′-bipyrrole, m.p. 176–178°; $\lambda_{max}^{0.1\ N\ KOH-CH_3OH}$ 360 sh mμ (ε 30,300), 345 (36,000); $\lambda_{max}^{0.1\ N\ HCl-CH_3OH}$ 402 mμ (ε 45,300).

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.9; H, 5.4; N, 13.3. Found: C, 60.8; H, 5.31; N, 13.1.

5-Methoxycarbonyl-2,2′:5′,2″-terpyrrole (X).—A mixture of the pyrroline (VIII, 600 mg., 2.44 mmoles), 30% palladium on carbon (830 mg., 100 mole % Pd), and 35 ml. of hexyl ether was heated at 200° with vigorous stirring for 100 min. The hot reaction mixture was then filtered under a nitrogen atmosphere and the cooled filtrate was diluted with 400 ml. of hexane and kept at −80° for 6 hr. The precipitate that formed was collected and combined with material obtained from acetone digestion (three 25-ml. portions) of the catalyst. Chromatography on 15 g. of activity IV alumina and elution with methylene chloride gave first a complex mixture (100 ml.) that contained none of the desired product followed by 20 mg. (0.08 mmole, 3.2%) of the terpyrrole (X), which was sublimed at 140° (5×10^{-5} mm.), m.p. 191–193° dec., λ_{max} 358 mμ (ε 28,800).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.9; H, 5.1; N, 16.5. Found: C, 65.9; H, 5.3; N, 16.3.

5,5″-Bismethoxycarbonyl-2,2′:5′,2″-terpyrrole (XI).—A mixture of the pyrroline (IX, 2.5 g., 7.94 mmoles), 30% palladium on carbon (2.82 g., 100 mole % Pd), and 100 ml. of hexyl ether was heated at 200° for 45 min. with vigorous stirring and a slow nitrogen sweep. The hot reaction mixture was then filtered under a nitrogen atmosphere and hexane (900 ml.) was added to the cooled filtrate causing precipitation. After further cooling, 800 mg. (2.54 mmoles, 32%) of terpyrrole XI was obtained. Material obtained from catalyst digests (three 50-ml. portions of acetone) was chromatographed on 30 g. of activity IV alumina and eluted with methylene chloride to give another 150 mg. (0.47 mmoles, 6.0%) of the desired terpyrrole. Crystallization of the combined 950 mg. from benzene–acetone gave 380 mg. (1.2 mmoles, 15.4%) of pure biscarbomethoxyterpyrrole XI, m.p. 279–280°; λ_{max} 385 sh mμ (ε 34,100), 367 (43,500), 226 (19,400).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.3; H, 4.8; N, 13.4. Found: C, 61.7; H, 5.1; N, 13.0.

2,2′:5′,2″-Terpyrrole-5,5″-dicarboxylic Acid (XII).—A solution of 200 mg. (0.64 mmole) of diester XI in 50 ml. of methanol, 25 ml. of water, and 10 ml. of 10 *N* sodium hydroxide was boiled for 1 hr (the initial red color that formed faded during the course of the reaction). The cooled solution was concentrated to one-half volume *in vacuo* on a rotary evaporator. Then, 100 ml. of water was added, and the solution was washed with three 50-ml. portions of ether. The pH was carefully lowered to 2 with dilute phosphoric acid, the mixture was extracted with three 50-ml. portions of ether, and the combined ether extracts were washed with water and then extracted with two 50-ml. portions of aqueous bicarbonate. Re-extraction into ether after acidifying to pH 2 and evaporation of the dried ether extracts left 156 mg. (0.53 mmole, 82.5%) of the yellowish diacid (XII) which was too unstable for further purification.

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.9; H, 3.9; N, 14.7. Found: C, 58.0; H, 4.5; N, 14.0.

Decarboxylation of Diacid XII to 2,2′:5′,2″-Terpyrrole (I).—A solution of the diacid (150 mg., 0.52 mmole) in acetone was coated onto the bottom surface of a sublimer. The sublimer was then evacuated to 20 μ and heated in an oil bath maintained at 200°. After about 30 sec., a white solid started to collect on the cold finger and the pressure increased to about 400 μ. After 15 min., the pressure had returned to 20 μ. The sublimate (75 mg., 38 mmoles, 73%) was found by comparison of ultraviolet and n.m.r. absorption and melting point to be identical with the terpyrrole obtained by dehydrogenation of pyrrole trimer.

(9) T. Weiland and H. Fritz, *Ber.*, **86**, 1186 (1953).

Kothe's Hydrocarbon. 1,2-Bis(β-phenylethyl)benzene[1a]

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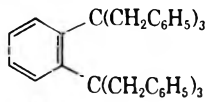
A hydrocarbon reported by Kothe in 1888 is shown, by several physical methods, to be 1,2-bis(β-phenylethyl)benzene. Several routes to prepare other similar hydrocarbons were attempted. It is suggested that the Kothe reaction may be a general one for obtaining various *o*-dialkylbenzenes.

In 1888 Kothe[2] reported obtaining a hydrocarbon, m.p. 72–73°, by the interaction of phthalic anhydride, benzyl chloride, and zinc dust, for which he proposed structure **1**.

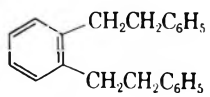


1

Since such a product presumably would form by the multiple addition of a benzylzinc reagent to phthalic anhydride followed by a reduction, we were greatly interested in repeating the synthesis to examine the product of this unprecedented series of transformations.

Initial attempts to obtain Kothe's hydrocarbon were unsuccessful when the reagents were allowed to interact only briefly. By carrying out the reaction in refluxing benzene for 24 hr., however, there was obtained a mixture of at least three products: a hydrocarbon, m.p. 83–85°, believed to be identical with that of Kothe, phthalide, and a higher melting solid, as yet unidentified. Kothe's hydrocarbon was finally separated from the other products by chromatography on alumina and fractional distillation of the ligroin eluate.

Molecular weight determinations by two methods indicated that Kothe's hydrocarbon contains two benzyl units, contrary to the structure originally proposed, which contains six benzyl units. Thus the problem of structure determination was reduced to distinguishing between two possibilities, **2** and **3**.



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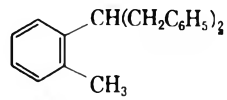
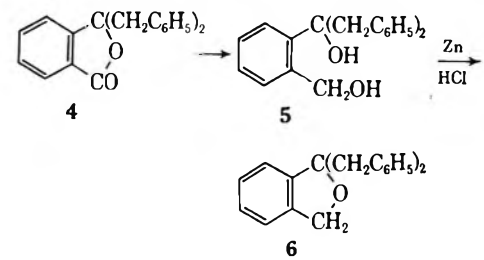


3

The ultraviolet spectrum is consistent with both **2** and **3**, since it resembles those of toluene and xylene. The infrared spectrum contains no band at 1380 cm.$^{-1}$ assignable to a C–CH_3 and thus is suggestive of structure **2**. Compelling evidence for **2** came from the n.m.r. spectrum, which exhibits only one peak assignable to aliphatic protons. Clearly the n.m.r. spectrum of **3** would be expected to contain several multiplet peaks as well as a singlet methyl peak. From the combined evidence of composition, molecular weight, and spectral properties, it is concluded that Kothe's hydrocarbon is 1,2-bis(β-phenylethyl)benzene (**2**). Although, to our knowledge, this compound has not been reported previously, three references have appeared to its *para* isomer, whose melting point has been variously reported as 89°,[3] 91°,[4] and 47–48.5°.[5] Since the first two melting points correspond closely to the hydrocarbon described here, it is possible their structure was incorrectly assigned. Alternatively the low melting compound,[5] believed to be the *para* isomer, may be bibenzyl (m.p. 52°). Certainly the identity of the *para* isomer remains in question.

Attempts to synthesize the alternative dibenzylated structure led to some significant failures although not to **3**. Reduction of 3,3-dibenzylphthalide (**4**) with lithium aluminum hydride gave diol **5**, which was subjected to treatment with zinc dust and hydrochloric acid. Instead of reduction product **3**, however, the product was 1,1-dibenzylphthalan (**6**) formed by dehydration.



4 **5** **6**

In view of Pettit's recent observation[6] that benzyl–oxygen bonds are particularly susceptible to hydrogenolysis with mixed hydrides, we attempted the direct synthesis of **3** from 3,3-dibenzylphthalide (**4**) by using a lithium aluminum hydride–aluminum chloride reagent described by Nystrom.[7] The result, however, was a mixture of **5** and **6**, which could be converted entirely to **6** by treatment with zinc dust and acid.

The formation of a hydrocarbon by Kothe's method seems most likely a sequence of additions by benzylzinc reagent and one or more reduction steps. The appearance of phthalide as a product indicates the reducing power of the medium. A likely intermediate would be 1,3-dibenzylidenephthalan (**7**), which, however, was not found among the products. It is difficult to obtain by synthesis,[8] but a closely related phthalan (**8**) can be prepared in satisfactory yield by treatment of 3,3-dibenzylphthalide with benzylmagnesium chloride. We subjected this phthalan (**8**) to the action of zinc dust in boiling benzene to determine whether it would undergo

(1)(a) Presented in part before the Organic Division at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961; (b) participant in National Science Foundation Summer Institute for Secondary School Teachers of Chemistry, University of New Hampshire, 1960; (c) National Science Foundation Undergraduate Research Fellow, 1959–1960.

(2) R. Kothe, *Ann.*, **248**, 56 (1888).

(3) K. Shishido and O. Odajima, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding 222 (1942); *Chem. Abstr.*, **45**, 588 (1951).

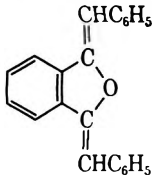
(4) Ng. Ph. Buu-Hoi, Ng. Hoan, and P. Jacquignon, *J. Chem. Soc.*, 1381 (1951).

(5) A. F. Dobryanskii and Y. I. Kornilova, *Sb. Statei Obshch. Khim. Akad. Nauk SSSR*, **1**, 315 (1953); *Chem. Abstr.*, **49**, 851 (1955).

(6) G. R. Pettit, B. Green, P. Hofer, D. C. Ayres, and P. J. S. Pauwels, *Proc. Chem. Soc.*, 357 (1962).

(7) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(8) R. Weiss, K. Grobstein, and R. Sauermann, *Ber.*, **59B**, 301 (1926).



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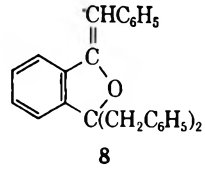
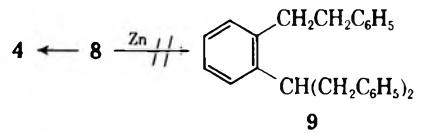


8

reduction to hydrocarbon **9**. Instead lactone **4**—a reverse aldol product—was the only compound isolated besides starting material. The phthalan is very susceptible to hydrolysis, as shown by its decomposition to **4** simply when heated in benzene, a property which had been observed before.[8]



9

In view of current widespread interest in the synthesis and properties of *o*-dialkylbenzenes,[9,10] the reaction originally described by Kothe warrants further attention as a possible alternative to more classical synthetic methods for obtaining various dialkylbenzenes.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 21 double-beam spectrophotometer with sodium chloride optics. The ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer 4000 Spectracord. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

Preparation of Kothe's Hydrocarbon. Action of Benzyl Chloride and Zinc Dust on Phthalic Anhydride.[2]—A mixture of 37 g. of phthalic anhydride, 70 g. of zinc dust, and 100 ml. of benzene (previously dried over sodium) was heated to reflux temperature. Stirring was started, and a solution of 100 g. of benzyl chloride dissolved in 80 ml. of dry benzene was added over a period of 1 hr. while refluxing was maintained. During this time hydrogen chloride was evolved continually, and the reaction mixture became caked, so that stirring could not be continued. An additional 20 g. of benzyl chloride in 10 ml. of dry benzene was added in a few portions, and the mixture was heated under reflux without stirring for 15.5 hr. Then a solution of 10 g. of benzyl chloride in 10 ml. of dry benzene was added in three portions, and refluxing was continued for 8 hr. The flask was cooled in an ice bath and the mixture decomposed cautiously with 30 ml. of dilute hydrochloric acid. The yellow, supernatant organic layer was removed by decantation and combined with two ether washings and three benzene washings of the residue; the solution was steam distilled until the distillate was clear. When the residue was taken up in ether–benzene, and the solution allowed to stand for a day, diluted with ligroin (b.p. 60–90°), allowed to stand overnight, and then cooled in ice for 4 hr., a light yellow solid separated, m.p. 155–185° dec., yield 5.0 g. About 50 ml. of the filtrate was subjected to chromatography on a 2 cm. × 48 cm. column packed with basic alumina. Elution with 700 ml. of ligroin yielded oils. When the eluent was enriched with 1–5% benzene in ligroin, a crystalline substance was obtained, subsequently shown to be phthalide, m.p. 73–74.5°, mixture melting point with an authentic sample 72.5–75.0°. The remainder of the original filtrate, about 110 ml., was separated on a 3 cm. × 60 cm. chromatographic column of basic alumina by elution with 1.1 l. of ligroin. When the residue from the ligroin solutions was fractionally distilled at aspirator pressure, the portion of b.p. 240–250° solidified in the receiver. Additional amounts of slightly colored solid were obtained by repeated fractionation of the forerun and residue. The yield of colorless product, m.p. 73–83°, was 13.5 g. (19%). It was recrystallized several times from 95% ethanol to m.p. 83–85°; λ_{max} 262 mμ (log ε 2.34), 266 (2.31), 269 (2.29), 275 (1.96). The n.m.r. spectrum (carbon tetrachloride) contains one peak assignable to methylene protons (τ 6.16) and two peaks assignable to aromatic C–H (τ 3.03, 2.92).[11]

Anal. Calcd. for $C_{22}H_{22}$: C, 92.26; H, 7.74; mol. wt., 286. Found: C, 92.88; H, 7.36; mol. wt. (Rast, sealed, immersed tubes), 297, 283, 255; mol. wt. (osmometer), 292.

1,1-Dibenzyl-3-benzylidenephthalan (8).—To a solution of benzylmagnesium chloride, prepared in 100 ml. of ether from 9.3 ml. of benzyl chloride and 1.98 g. of magnesium, was added 6 g. of 3,3-dibenzylphthalide[12] in several portions during 5 min. The orange-brown solution was heated under reflux for 2 hr. and then decomposed with dilute hydrochloric acid. The ether layer was combined with ether washings of the aqueous layer and dried over anhydrous magnesium sulfate. By removal of the solvent a light orange, amorphous material was obtained, which was converted to solid by the addition of ethanol, m.p. 144–148°, yield 4.8 g. (65%). Three recrystallizations from ethanol–benzene changed the melting point to 143.5–146°, lit.[8] m.p. 139–149°; λ_{max} 232 mμ (log ε 4.01), 240 (3.99), 250 sh (3.81), 307 sh (4.27), 3.18 (4.40), 333 (4.44), 350 (4.20).

Anal. Calcd. for $C_{29}H_{24}O$: C, 89.65; H, 6.23. Found: C, 90.03; H, 6.89.

Attempted Reduction of 1,1-Dibenzyl-3-benzylidenephthalan with Zinc Dust.—A mixture of 1.0 g. of the phthalan, 2 g. of zinc dust, and 20 ml. of dry benzene was stirred and heated under reflux for 24 hr., an additional 20 ml. of dry benzene being added after the first 23 hr. The hot mixture was filtered and the filtrate concentrated to about 10 ml. and set aside. The first crop of crystalline material consisted of 3,3-dibenzylphthalide, m.p. 203–207°, yield 0.17 g. (21%). By dilution of the filtrate with ethanol, concentration, and cooling, there were recovered two fractions of the starting material: 0.24 g. (24%), of m.p. 145–148°, and 0.27 g. (27%) of m.p. 138–144°. Heated 28 hr. in benzene alone, the phthalan was converted to 3,3-dibenzylphthalide in 60% yield.

Dibenzyl(*o*-hydroxymethylphenyl)carbinol (5).—To a suspension of 0.3 g. of lithium aluminum hydride in dry ether was added 1.0 g. of 3,3-dibenzylphthalide in small portions with intermittent stirring. The mixture was stirred at room temperature for 1 hr., then at reflux temperature for 45 min., and decomposed slowly with ordinary ether. Cold, dilute sulfuric acid was added to the flask, surrounded by an ice–salt bath, so that the temperature of the mixture was maintained at 3–8°. When it was strongly acid, ether and benzene were added to dissolve the white solid at the interface; the organic layer was separated and combined with ether and benzene washings of the water layer. After the solution had been dried over anhydrous magnesium sulfate, filtered, concentrated to 5 ml., and let stand, the colorless, crystalline alcohol appeared, m.p. 132–133.5°, yield 0.50 g. Recrystallized three times from benzene–petroleum ether (b.p. 40–60°), the alcohol melted at 133.5–134.0°, lit.[13] m.p. 133–134.5°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 82.74; H, 6.72.

A second crop, m.p. 128–130°, weighed 0.14 g. (total yield 64%). The infrared spectrum (10% chloroform) contains alcohol bands at 3535 and 3375 $cm.^{-1}$.

1,1-Dibenzylphthalan (6).—To a mixture of 0.5 g. of the above alcohol, 1 g. of zinc dust, and 10 ml. of benzene was added 1 ml. of concentrated hydrochloric acid dropwise during a few minutes. Addition of each drop of acid caused a vigorous reaction to ensue. The mixture was heated under reflux for 6.5 hr., let stand overnight, heated to boiling, and filtered. The filtrate, which was combined with benzene washings of the residue, was washed successively with saturated sodium sulfate, 5% sodium carbonate, and saturated sodium sulfate, and then dried over anhydrous magnesium sulfate. The solution was filtered and concentrated, and a few drops of ligroin were added to the residue after 2 days. Large colorless prisms were deposited, m.p. 81.5–84.5°, yield 0.20 g. (42%). It was recrystallized repeatedly from ligroin, m.p. 88.0–88.7°, lit.[12] m.p. 88–89°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.87; H, 6.91.

(8) C. Hoogzand and W. Hübel, *Tetrahedron Letters*, No. 18, 637 (1961).

(9) L. R. C. Barclay, C. E. Milligan, and N. D. Hall, *Can. J. Chem.*, **40**, 1664 (1962).

(11) We are very grateful to Dr. Glenn Berchtold, Massachusetts Institute of Technology, for determination of this n.m.r. spectrum.

(12) W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 1447 (1952).

(13) A. Ludwig, *Ber.*, **40**, 3060 (1907).

The infrared spectrum (chloroform) indicates the absence of alcohol bands. The n.m.r. spectrum (carbon tetrachloride) contains two sharp peaks at τ 6.81 and 5.56, and an unresolved multiplet centered at about τ 3.0. The relative integrated intensities are 1.9, 1.0 and 7.8, respectively.[14]

(14) This spectrum was measured at the University of New Hampshire with a Varian Model A-60 instrument.

Reduction of 3,3-dibenzylphthalide with a 1:1 molar mixture of lithium aluminum hydride–aluminum chloride in ether[7] led to a mixture of 1,1-dibenzylphthalan (6) and dibenzyl-*o*-(hydroxymethylphenyl)carbinol (5). A 0.73-g. sample of this mixture was converted by treatment with zinc dust and hydrochloric acid to 0.20 g. of 6 (m.p. 87.5–89.0°) whose infrared spectrum (chloroform) was identical with that of the phthalan obtained above.

Mercaptan Oxidations. VII. Oxidative Desulfurization of Benzyl Mercaptan, Benzyl Disulfide, and Related Species

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The base-catalyzed oxidation of benzyl mercaptan and benzyl disulfide was studied in dimethyl sulfoxide (80%)–*t*-butyl alcohol (20%) at 23.5° and 80° in the presence of potassium *t*-butoxide, sodium methoxide, and potassium hydroxide. Oxidative desulfurization of the mercaptan and disulfide to benzoic acid was the predominant reaction observed in the presence of the alkoxide bases. The reaction path proposed involves the formation of peroxide ions which can rearrange to alkoxide ions that are unstable and decompose to benzaldehyde and α-toluenethiosulfinate ions ($C_6H_5CH_2S(O)S^-$). Apparently, the aldehyde and acid salt are oxidized rapidly to benzoic acid. The latter is substantiated by the fact that potassium α-toluenesulfonate could be oxidized rapidly to benzoic acid in quantitative yields. In the presence of potassium hydroxide, the main oxidation product was potassium α-toluenesulfonate. This is due apparently to the decreased basicity and increased sulfur nucleophilicity of the hydroxide ion. The oxidation of α,α'-dimercapto-*p*-xylene also was investigated. This compound was oxidized to terephthalic acid in 30 to 84% yield depending on the particular reaction conditions employed.

Previous studies in these laboratories have established that dipolar solvents markedly accelerate the base-catalyzed oxidation of mercaptans (thiols) by molecular oxygen.[1] If these reactions are allowed to proceed to completion, both alkyl and aryl mercaptans can be oxidized to their corresponding sulfonic acid salts.[2,3] The latter finding represents a new base-catalyzed oxidation reaction since the predominant product from the base-catalyzed oxidation of a mercaptan is usually the disulfide.[4] The present investigation is an extension of our previous studies on solvent effects in the base-catalyzed oxidation of sulfur compounds and is concerned with the oxidation of benzyl mercaptan, benzyl disulfide, and some related species. These compounds contain benzylic hydrogens which should be fairly acidic in a polar medium. Thus, it seemed worthwhile to determine if oxidation to the sulfonic acid or oxidative desulfurization to carboxylic acids would be the predominant course of reaction in mercaptans and disulfides of this general type.

Results

The base-catalyzed oxidation of benzyl mercaptan, benzyl disulfide, potassium α-toluenesulfonate, and α,α'-dimercapto-*p*-xylene has been studied at a constant oxygen partial pressure of one atmosphere at 23.5° and 80°. Reactions were carried out in dimethyl sulfoxide (DMSO, 80%)–*t*-butyl alcohol (20%)[5] using potassium hydroxide, sodium methoxide (NaOMe), and potassium *t*-butoxide (KO-*t*-Bu) as the bases. The ratio of base to reactant varied from 3 to 6 depending on the particular benzyl compound oxidized. Specific reaction conditions employed and product yields obtained under these conditions are summarized in Table I. In the presence of KO-*t*-Bu at 80°, benzyl mercaptan, benzyl disulfide, and potassium α-toluenesulfonate were converted to benzoic acid in 74 to 100 mole % yields. The mercaptan also formed benzyl disulfide and stilbene, the disulfide apparently being oxidized as it was formed. Stilbene was also a by-product of the disulfide oxidation. The initial rates of oxidation are shown in Fig. 1 for the system KO-*t*-Bu–DMSO–*t*-C_4H_9OH at 80°. All rates of oxygen consumption were extremely rapid. The acid salt consumed 2 moles oxygen/mole acid in 25 min. The mercaptan and disulfide were less reactive than the acid, consuming 0.75 and 0.45 mole oxygen/mole reactant, respectively, in 25 min. All rates of oxidation decreased in the latter stages of reaction since water and alcohols are formed, and the base is consumed by the acid products that are formed.

Under less vigorous conditions of oxidation (NaOMe at 23.5°) benzyl mercaptan and benzyl disulfide were still oxidized readily to benzoic acid, but the yield of disulfide from the mercaptan was increased by a factor of 2.5. Both reactions yielded a small quantity of stilbene. When the weak base, potassium hydroxide, was used, the mercaptan and disulfide yielded potassium α-toluenesulfonate as the main oxidation product at 23.5°. In the protic solvent methanol, oxidation of the mercaptan beyond the disulfide stage did not occur

(1) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, **28**, 1311 (1963), and references therein.

(2) T. J. Wallace and A. Schriesheim, *Tetrahedron Letters*, 1131 (1963).

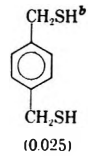
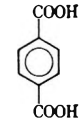
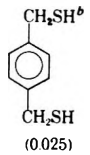
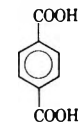
(3) T. J. Wallace and A. Schriesheim, paper to be submitted for publication.

(4) For a recent review of this area, see A. A. Oswald and T. J. Wallace, "The Anionic Oxidation of Mercaptans and the Co-Oxidation of Mercaptans with Olefins," Organic Sulfur Compounds, Vol. II, N. Kharasch, Ed., Pergamon Press, New York, N. Y., in press.

(5) This mixture has been employed as a solvent medium for the anionic oxidation of acidic hydrocarbons by Russell and co-workers [see Preprints 17th National Organic Chemistry Symposium, Bloomington, Ind., June 25, 1961].

TABLE I

SUMMARY OF BENZYL MERCAPTAN AND α,α'-DIMERCAPTO-*p*-XYLENE OXIDATION STUDIES IN DMSO-*t*-BUTYL ALCOHOL

Reactant (mole)	Base (mole)	Temp., °C.	Product	Yield, mole %[a]	% conversion of reactant	Time, hr.
$C_6H_5CH_2SH$ (0.05)	KO-*t*-Bu (0.15)	80	$(C_6H_5CH_2)_2S_2$	10.0	100	23
			C_6H_5COOH	85		
			$C_6H_5CH{=}CHC_6H_5$	3.4		
$(C_6H_5CH_2)_2S_2$ (0.025)	KO-*t*-Bu (0.15)	80	C_6H_5COOH	70	90	18
			$C_6H_5CH{=}CHC_6H_5$	18.4		
$C_6H_5CH_2SO_3K$ (0.05)	KO-*t*-Bu (0.15)	80	C_6H_5COOH	~100	100	25
$C_6H_5CH_2SH$ (0.05)	NaOMe (0.15)	23.5	$(C_6H_5CH_2)_2S_2$	26.2	90	23
			C_6H_5COOH	60.4		
			$C_6H_5CH{=}CHC_6H_5$	1.8		
$(C_6H_5CH_2)_2S_2$ (0.025)	NaOMe (0.15)	23.5	C_6H_5COOH	90	99	28
			$C_6H_5CH{=}CHC_6H_5$	3.0		
$C_6H_5CH_2SH$ (0.05)	KOH (0.15)	23.5	$(C_6H_5CH_2)_2S_2$	8.0	92	14.5
			C_6H_5COOH	29.5		
			$C_6H_5CH_2SO_3H$	50		
$(C_6H_5CH_2)_2S_2$ (0.025)	KOH (0.15)	23.5	C_6H_5COOH	31	99	19
			$C_6H_5CH_2SO_3H$	61		
			$C_6H_5CH{=}CHC_6H_5$	0.5		
 (.05)	KO-*t*-Bu (0.20)	80		84	100	29
 (0.025)	NaOMe (0.10)	23.5		84	99	23
 (0.025)	KOH (0.10)	23.5		30	71	21
$C_6H_5CH_2SH$ (0.05)	NaOMe[c] (0.20)		$(C_6H_5CH_2)_2S_2$	84	90	23

[a] Moles of product produced/theoretical moles × 100. [b] A polymeric disulfide of undetermined structure was produced also. [c] NaOMe–MeOH was employed as the base–solvent system.

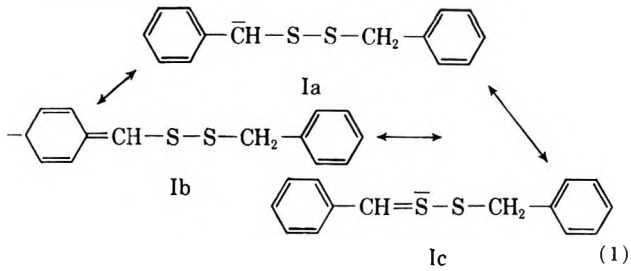
at room temperature and the disulfide showed no tendency to oxidize over a 20-hr. period.

The last phase of these oxidation studies were carried out with α,α'-dimercapto-*p*-xylene. This compound was oxidized rapidly under all conditions employed. As shown in Fig. 1, 2 moles oxygen/mole dimercaptan was consumed in 21 min. using potassium hydroxide in DMSO–*t*-C_4H_9OH at 23.5°. This is comparable to the rate observed with potassium benzyl sulfonate in the presence of KO-*t*-Bu at 80°. Terephthalic acid was the acidic product identified in all reactions, the yield varying from 30 to 84 mole % depending on the base and temperature used. Polymeric disulfides also were found, but no attempt to elucidate the structure of these disulfides or any other intermediates was made. Further, no attempt to determine the final fate of the sulfur moiety in any of these reactions was made.

Discussion

The results obtained in the present study indicate that benzyl mercaptan is initially oxidized to benzyl disulfide which, in the presence of excess base, is unstable and decomposes by several competing reaction paths to give ultimately benzoic acid and stilbene. Possible mechanistic paths by which these transformations proceed are of interest since they represent the first examples in which a mercaptan and disulfide of this general type are oxidatively desulfurized in the presence of base and oxygen at such a rapid rate.

The initial oxidation of the mercaptide ion ($C_6H_5CH_2S^-$) to the disulfide proceeds rapidly. In the presence of excess base, the resulting disulfide apparently undergoes α-proton abstraction to form a resonance-stabilized carbanion (Ia, b, and c). The resulting carbanion can rearrange to a 1,2-diphenylethyl mercaptide ion which in the presence of base is unstable and eliminates sulfide ion (S_2^{-2}) to give stilbene. This reaction previously was observed in the absence of oxygen with



(1)

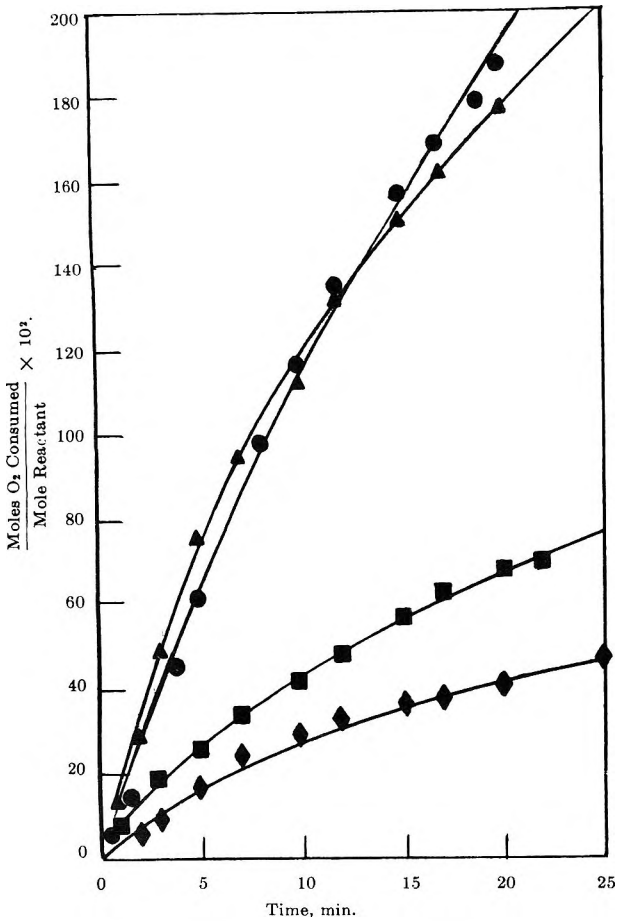


Fig. 1.—Rates of oxygen consumption for anionic oxidation in DMSO-*t*-C_4H_9OH: ●, $C_6H_5CH_2SO_3K$ (KO-*t*-Bu, 80°); ▲, *p*-$HSCH_2C_6H_4CH_2SH$ (KOH, 23.5); ■, $C_6H_5CH_2SH$ (KO-*t*-Bu, 80°); ◆, $(C_6H_5CH_2)_2S_2$ (KO-*t*-Bu, 80°).

several benzyl-type sulfur compounds.[6,7] Since oxygen is present in a large excess, it is not surprising that this reaction proceeds in low yield. Thus, the main reaction path involves oxidation of the α-carbanion. As shown in Table I, benzoic acid is formed in high yields in the presence of KO-*t*-Bu and NaOMe. Even at 23.5°, the yield of benzoic acid from benzyl mercaptan and benzyl disulfide varied from 60 to 90%. Thus, the intermediate products must be highly unstable in the presence of base and oxygen.

$$PhCH(-)S-S-CH_2Ph + O_2 \longrightarrow PhCH(-)S-S-CH_2Ph + O_2 \quad (2)$$

II

$$II + O_2 \longrightarrow PhCH(OO\cdot)-S-S-CH_2Ph \quad (3)$$

III

$$III + RH \longrightarrow PhCH(OOH)-S-S-CH_2Ph + R\cdot \quad (4)$$

IV

$$IV + B^- \longrightarrow PhCH(O-O^-)-S-S-CH_2Ph + BH \quad 5)$$

V

$$III + Ia \longrightarrow V + II \quad (6)$$

(6) T. J. Wallace, *et al.*, *Proc. Chem. Soc.*, 137 (1963).

(7) It also has been determined that $C_6H_5CH_2SH$ and $C_6H_5CH_2SO_3K$ do not α-eliminate in these base–solvent systems.

Intuitively, we feel that the carbanion is first oxidized to an unstable hydroperoxide ion (V) as shown. This species is analogous to the hydroperoxides formed during the co-oxidation of mercaptans with olefins. These intermediates are highly unstable and rearrange to β-hydroxy sulfoxides as shown.[4] In the present case,

$$R-S-CH_2CH(OOH)-R \longrightarrow R-S(=O)-CH_2CHR(OH) \quad (7)$$

a similar rearrangement of V would yield, presumably, an unstable alkoxide ion (VI) that could readily de-

$$V \longrightarrow [Ph-C(H)(O^-)-S-S(=O)-CH_2Ph] \longrightarrow PhCHO + PhCH_2S(=O)-S^- \quad (8)$$

VI

compose to benzaldehyde and a thiosulfinate ion ($C_6H_5CH_2S(O)S^-$). The aldehyde would form benzoic acid readily. The acid could oxidize further to the thiosulfonate ($C_6H_5CH_2SO_2S^-$) or undergo concommitant proton abstraction at the α-benzyl position. The thiosulfonate also would form the anion readily. Based on our results with the α-toluenesulfonate ion, both carbanions should oxidize readily to another unstable peroxide ion that eliminates the sulfur moiety and ultimately gives benzoic acid.

$$Ph-CH(-)S(=O)-O^- \longrightarrow PhCH=O + SO_4^{-2} \quad (9)$$

Initial electron transfer between the carbanion and oxygen (eq. 2) is most reasonable since detailed studies by Russell[8] on the base-catalyzed autoxidation of acidic hydrocarbons indicate that this reaction does occur. The proposed intermediacy of benzaldehyde in these reactions is also reasonable since benzaldehyde and benzyl alcohol are highly unstable under the present reaction conditions.[9] Based on the results of our recent elimination studies on aliphatic sulfones and sulfoxides,[10,11] instability of intermediate VI under the present reaction conditions also would be expected. Rate studies have established that sulfinate ion (RSO_2^-) elimination from isopropyl sulfone in KO-*t*-Bu–DMSO is so rapid that accurate rate measurements cannot be obtained even at room temperature.

In the presence of potassium hydroxide at 23.5° both the mercaptan and disulfide react rapidly, but this base alters the reaction path to some extent since potassium α-toluenesulfonate is the predominant product. Our previous studies on the oxidation of mercaptide ions to sulfonic acids indicated that hydroxide

(8) For a discussion see G. A. Russell, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 107, *et seq.*

(9) In the present system and in DMF, we have found benzaldehyde and benzyl alcohol are rapidly autoxidized at room temperature to benzoic acid in the presence of KOH, NaOMe, and KO-*t*-Bu; this is also true for acetophenone, see ref. 5.

(10) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963).

(11) J. E. Hofmann, T. J. Wallace, and A. Schriesheim, *ibid.*, in press.

ion was highly nucleophilic toward the disulfide linkage.[2,12] Thus, in addition to the above possible reaction path, preferential displacement on the disulfide linkage to form the mercaptide ion and a sulfenate ion (RSO^-) must occur. The sulfenate ion would, of course, be unstable[12] and could either disproportionate to the disulfide and sulfonic acid or be oxidized directly by oxygen. Since potassium hydroxide is a relatively

$$3\ PhCH_2SO^- \longrightarrow (PhCH_2)_2S_2 + PhCH_2SO_3^- \quad (10)$$

$$PhCH_2SO^- \xrightarrow{O_2} PhCH_2SO_3^- \quad (11)$$

weak base, proton abstraction from the α-toluenesulfonate ion does not occur as readily as with the alkoxide bases, hence the decreased yield of benzoic acid in the presence of this base.

The oxidation of α,α'-dimercapto-*p*-xylene to terephthalic acid undoubtedly occurs by the above paths. Formation of the monocarboxylic acid should facilitate further oxidation at the α'-position. Since the intermediates were complex and their structures were not determined, further discussion is not warranted. However, the results demonstrate the generality of these reactions with mercaptans of this type.

Experimental

Reagent.—Benzyl mercaptan (Aldrich Chemical Co.) was purified by distillation through an 18-in. silvered column equipped with a tantalum wire spiral (b.p. 90° at 5 mm.). α,α'-Dimercapto-*p*-xylene (Evans Chemetics) was obtained as the reagent grade material (98% pure) and used without further purification. Both mercaptans were stored under nitrogen and handled in a nitrogen drybox. Benzyl disulfide (m.p. 70°) was prepared from the reaction of benzyl mercaptan with iodine according to the procedure outlined in Vogel.[13] Potassium α-toluenesulfonate was prepared from the reaction of benzyl bromide with potassium sulfite according to the method of Fromm.[14] Potassium *t*-butoxide was obtained from the Mine Safety Appliance Co. as the sublimed material and stored in a nitrogen drybox.

Purification of Solvents.—*t*-Butyl alcohol (Matheson Coleman and Bell) and DMSO (Crown Zellerbach) were purified by distillation over Linde 13-X Molecular Sieves to remove any water that was present. The sieves were conditioned previously by calcination at 400° for 4 hr. All solvents were stored under a nitrogen atmosphere.

Oxidation Experiments.—All base–solvent systems were made up to the appropriate molarity under nitrogen in a heavy walled Pyrex flask equipped with a side arm. The reactant was added to the reaction flask, the flask was sealed under nitrogen, removed from the drybox, and transferred to the oxidation apparatus. Oxygen was stored in a polyethylene balloon under 1-atm. pressure and was passed through a wet-test meter, into a calcium chloride drying tower, through a water-cooled Friedrichs condenser, and into the reaction flask containing the reaction mixture. The system was flushed with oxygen through the flask side arm, the side arm was sealed, and an equilibrium pressure was established. The reaction was initiated by stirring at 1300 r.p.m. The volume of oxygen consumed as a function of time was determined from the wet-test meter which allows an estimation of the volume of gas consumed to within ±1 ml. With this method, a constant oxygen pressure of 1 atm. was maintained above the system. All reactions were allowed to proceed to completion. This oxidation technique has been described in greater detail elsewhere.[15]

Quantitative Determination of Reactants and Products.—Unchanged mercaptan was determined by potentiometric titration with standard silver nitrate solution. Unchanged disulfide or disulfide produced as an oxidation product was determined by reduction to the mercaptan in zinc–acetic acid and subsequent titration with silver nitrate. Blank samples containing mercaptan, disulfide, and a mixture of mercaptan and disulfide were subjected to these techniques, and the results indicated that the method was essentially quantitative (±1%). Analysis for the aromatic acids and stilbene was carried out according to the method of Pobiner, Wallace, and Hofmann.[16] Two methods can be employed. One involves an extraction–ion-exchange–infrared procedure and the other an extraction–ultraviolet procedure. Both rely on initial homogenization with water and subsequent extraction with cyclohexane to remove the starting material and nonacidic products. This removes any spectral interference during the determination of acidic products. The acidic products remain as their acid salts in the aqueous DMSO phase and are liberated subsequently by acidification with hydrochloric acid. If the acid is aromatic, it can be quantitatively determined directly by ultraviolet spectroscopy from standard curves. If the acidic material is aliphatic or presents a weak ultraviolet absorption, it is determined by the ion-exchange–infrared method. This involves treating the aqueous phase with Amberlite LA-2 anion-exchange resin. The free acid is extracted with carbon tetrachloride and quantitatively determined by infrared spectroscopy. These methods were accurate to within 95–99% for all products identified.

Other Methods of Identification.—In addition to the infrared and ultraviolet comparison to authentic samples, the products were isolated and identified by melting point at least once when separation was feasible. Thus, benzoic acid (m.p. 121–122°) and stilbene (m.p. 124°) were further substantiated. Terephthalic acid, which sublimes, had an infrared spectrum which was identical with an authentic sample. In the oxidation of α,α'-dimercapto-*p*-xylene, polymeric disulfides were formed but no attempt to determine the structures was made owing to the complexity of the material.

Acknowledgment.—We thank Mr. J. I. Haberman and Mr. F. T. Fitzsimmons for experimental assistance and the Esso Research and Engineering Co., especially the Process Research Division, for the privilege of publishing this research.

(12) See also A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(13) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans Green and Co., London, England, 1959.

(14) E. Fromm and J. S. Palma, *Ber.*, **39**, 3312 (1906).

(15) T. J. Wallace, W. Bartok, and A. Schriesheim, *J. Chem. Educ.*, **40**, 39 (1963).

(16) H. Pobiner, T. J. Wallace, and J. E. Hofmann, *Anal. Chem.*, **35**, 680 (1963).

The *ortho*-Claisen Rearrangement of 2-Alloxypyridine. *ortho*-Claisen Rearrangement to Nitrogen[1]

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Unsymmetrically substituted allylic 2-pyridyl ethers give normal Claisen products on rearrangement to the N-1 and the C-3 atoms when heated in a tertiary amine solvent. Neat rearrangement of a γ-substituted 2-pyridyl ether results in the formation of an abnormal 1-substituted 2-pyridone.

ortho-Claisen rearrangement of 2-substituted 4-alloxypyrimidines was shown recently to give the corresponding 2-substituted 4-hydroxy-5-allylpyrimidines.[3] A subsequent investigation[4] of this reaction showed it to possess the characteristics normally associated with the *ortho*-Claisen rearrangement[5] and established that simultaneous rearrangement to the N-3 atom occurs to nearly the same extent, forming the isomeric 2-substituted 3-allyl-4-pyrimidone. While no investigation of the mechanism of the rearrangement to the N-3 atom was conducted, the lack of formation of the corresponding 1-allyl-4-pyrimidone indicated this rearrangement to be intramolecular.

A number of studies have established that a great deal of specificity is observed in the direction of Claisen rearrangement. Holton[6] recently pointed out that, when two dissimilar *ortho* positions are available, Claisen rearrangement normally takes place predominantly to the position having the higher electron density, the position at which the greater amount of nitration occurs in the corresponding phenol.

In view of these observations, it seems surprising that Claisen rearrangement of a 4-alloxypyrimidine should take place indiscriminately to the markedly different N-3 and C-5 atoms.[7]

Rearrangement of the 2-substituted 4-alloxypyrimidines was accompanied by the formation of considerable amounts of decomposition products. For this reason, and because of the greater simplicity of the system, 2-alloxypyridines were chosen to investigate the *ortho*-Claisen rearrangement to nitrogen.

Mikhant'ev[8] previously had synthesized 2-alloxypyridine (I) by treatment of 2-chloropyridine with sodium alloxide. In our hands, however, this procedure afforded 2-alloxypyridine which was contaminated with a substantial amount of unchanged 2-chloropyridine. A modification of this procedure gave I in higher purity. Rearrangement of I at 255° in dimethylaniline gave two isomeric products, 3-allyl-2-pyridone (II), recovered by crystallization from the reaction mixture, and 1-allyl-2-pyridone (III), obtained by chromatography of the residue (see Scheme I).

Two additional ethers, 2-crotoxypyridine (IV) and 2-(1-methylalloxy)pyridine (V), were prepared. The method by which these compounds were synthesized, nucleophilic substitution of 2-chloropyridine by the sodium salts of the corresponding alcohols, rules out any possible allylic rearrangement. When the crotoxy ether (IV) was heated in dimethylaniline, 3-(1-methylallyl)-2-pyridone (VI) and 1-(1-methylallyl)-2-pyridone (VII) were obtained. The 1-methylallyl ether (V) gave 3-crotyl-2-pyridone (VIII) and 1-crotyl-2-pyridone (IX) on rearrangement in dimethylaniline. In each case the products obtained under these conditions resulted from inversion of the allylic group, indicating that the rearrangements to the N-1 and C-3 atoms are normal intramolecular Claisen rearrangements.

Determination of the Structure of Rearrangement Products.—The n.m.r. spectrum[9] of 2-pyridone was determined and found to show two low-field signals at 2.67 and 2.77 τ due to the 4 and 6 protons. Two additional signals, a doublet at 3.40 (J = 9 c.p.s., relative area = 1) and a triplet at 3.80 τ (J = 7 c.p.s., relative area = 1), can be assigned unequivocally to the 3 and 5 protons, respectively, based on their multiplicity.[10]

The n.m.r. spectra of the 3-substituted 2-pyridones (II, VI, and VIII) all show the presence of the two low-field 4 and 6 protons and the triplet signal assigned to the 5 proton. However, in the three spectra no doublets corresponding to that of the 3 proton of 2-pyridone are present, indicating that the allylic groups of pyridones II, VI, and VIII are attached to the 3 position of the ring.[11] The 1-substituted 2-pyridones (III, VII, and IX) show the presence of four ring protons, thereby indicating that the allylic groups are attached to the ring nitrogen atom.

The spectra of the crotyl pyridones (VIII and IX) show a high-field quartet at 8.37 (J = 3.0, 1.1 c.p.s., relative area = 3) and 8.28 τ (J = 3.3, 1.0 c.p.s., relative area = 3), respectively, due to independent splitting of the methyl signals by the two vinylic protons.[12a] The methyl groups of pyridones VI and VII which are split by a single proton appear as doublets

(1) This investigation was supported in part by Grant CA-02857 from the National Institutes of Health, U. S. Public Health Service.

(2) Allied Chemical Corp. Research Fellow, 1963–1964.

(3) H. J. Minnemeyer, J. A. Egger, J. F. Holland, and H. Tieckelmann, *J. Org. Chem.*, **26**, 4425 (1961).

(4) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *ibid.*, **28**, 1015 (1963).

(5) For an excellent recent review of the Claisen rearrangement, see S. J. Rhoads, "Molecular Rearrangements," P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp. 655–683.

(6) P. G. Holton, *J. Org. Chem.*, **27**, 357 (1962).

(7) For a discussion of the characteristics of the pyrimidine ring positions, see D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp. 5–8.

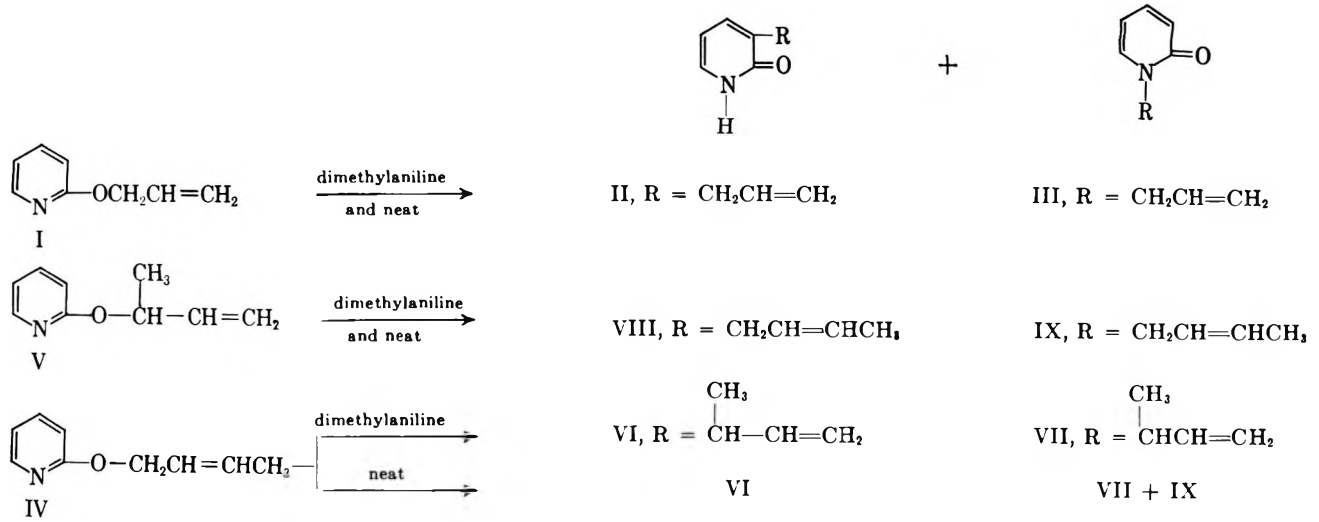
(8) B. I. Mikhant'ev, E. I. Federov, A. I. Kucherova, and V. P. Potapova, *Zh. Obshch. Khim.*, **29**, 1874 (1959).

(9) All n.m.r. spectra were determined using a Varian A-60 spectrometer. Measurements were made in deuteriochloroform solution using tetramethylsilane as an internal standard.

(10) These assignments are consistent with the findings of Elvidge and Jackman who determined the n.m.r. spectrum of 1-methyl-2-pyridone and report a range of 2.69–2.74 for the 4 and 6 protons, 3.43 for the 3 proton, and 3.85 τ for the 5 protons [see J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961)].

(11) It should be mentioned that no signal is observed for the 1 proton in any of the 2-pyridones which are potentially tautomeric. This is not unusual as signals from N–H protons are often broad and able from background [see A. R. Katritzky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 223 (1962)].

SCHEME I



at 8.69 (J = 7.0 c.p.s., relative area = 3) and 8.55 τ (J = 7.0 c.p.s., relative area = 3), respectively.[12b]

Additionally, the 1-allyl isomer (III) obtained by rearrangement of the alloxy ether (I) is identical with an authentic sample of III prepared by the procedure of Mikhant'ev.[8] The 1-crotyl rearrangement product (IX) was identical with the product obtained when the sodium salt of 2-pyridone was alkylated with crotyl chloride.[13]

Neat Rearrangement of Ethers.—Neat rearrangement of the ethers (I, IV, and V) took place only if these materials were distilled, chromatographed, then redistilled, and rearranged while fresh. Material of lesser purity underwent polymerization when subjected to rearrangement conditions in the absence of solvent.

The composition of the reaction mixtures resulting from the neat rearrangements was investigated by gas chromatography. Neat rearrangement of the allyl ether (I) and the 1-methylallyl ether (V) afforded the same products as were obtained upon rearrangement in dimethylaniline. The amounts of 1 and 3 isomers afforded by the neat rearrangement of I and V were somewhat variable but were comparable to those obtained when these ethers were rearranged in dimethylaniline.

Neat rearrangement of the crotyl ether (IV) at 245° gave the expected 1-methylallyl isomers (VI and VII), and, in addition, afforded the 1-crotyl isomer (IX) but none of the 3-crotyl isomer (VIII). In rearrangements under these conditions, formation of a crotyl product from a crotyl ether is, to our knowledge, previously unreported.[14]

The formation of the 1-substituted products by rearrangement of the crotyl ether (IV) was investigated as a function of time and showed that the normal 1-substituted isomer (VII) is initially formed in greater amount. The ratio of the abnormal 1-crotyl isomer (IX) to the normal isomer (VII) increased as the reaction proceeded and IX accounted for 40–60% of the combined 1-substituted isomers when rearrangement was complete.

Formation of the 1-crotyl isomer (IX) by rearrangement of the crotyl ether (IV) is somewhat analogous to the results observed in the abnormal Claisen rearrangement of 3-ethylallyl phenyl ether. This rearrangement afforded a mixture of the normal product, *o*-(1-ethylallyl)phenol, and an abnormal rearrangement product, *o*-(1,3-dimethylallyl)phenol. The abnormal product has been demonstrated recently to result from isomerization of the initially formed normal product.[15,16]

In the present case, however, isomerization of the normal product (VII) to the abnormal product (IX) does not take place. When a pure sample of the 1-methylallyl isomer (VII) was subjected to rearrangement conditions, none of the abnormal 1-crotyl isomer (IX) formed. Moreover, no reverse rearrangement of VII to form either of the ethers (IV or V) occurred.

Formation of the 1-crotyl isomer (IX) from the crotyl ether (IV) also could result from isomerization of IV to the 1-methylallyl ether (V) prior to rearrangement. However, none of the branched chain ether (V) could be detected by gas chromatography in samples withdrawn during the course of a neat rearrangement of the crotyl ether (IV). The lack of formation of the 3-crotyl isomer (VIII) when the crotyl ether (IV) is rearranged may be taken as additional evidence that no isomerization of IV to V occurs prior to rearrangement, since any V present would form VIII as well as IX on rearrangement.

In summary, ethers I, IV, and V undergo normal Claisen rearrangement when heated in dimethylaniline. The γ-carbon atom of the allylic chain becomes attached to the N-1 and C-3 atoms of the ring. The allyl ether (I) and the 1-methylallyl ether (V) also undergo normal Claisen rearrangement to both the 1 and 3 positions

(12) (a) In the n.m.r. spectra of crotyl alcohol and the crotyl ether (IV), the signals due to the methyl groups have the same general contour as those observed for the 1- and 3-crotyl pyridones (VIII and IX); (b) the same doublet pattern for the methyl groups is observed in the n.m.r. spectra of 1-methylallyl alcohol and the 1-methylallyl ether (V).

(13) An attempt to synthesize the 1-(1-methylallyl) isomer (VII) by alkylating the sodium salt of 2-pyridone with 3-chloro-1-butene also led to the formation of the 1-crotyl isomer (IX). This apparently occurs *via* an S$_N$2′ mechanism.

(14) It should be noted that a similar mixture of crotyl and 1-methylallyl products has been obtained from the acid-catalyzed rearrangement of aliphatic N-phenylformimidates. However, when these rearrangements were run without acid catalysis, only the normal inversion products were obtained [see R. M. Roberts and F. A. Hussein, *J. Am. Chem. Soc.*, **82**, 1950 (1960)].

(15) E. N. Marvell, D. R. Anderson, and J. Ong, *J. Org. Chem.*, **27**, 1109 (1962).

(16) W. van Philipsborn, *Angew. Chem., Intern. Ed. Engl.*, **2**, 487 (1963).

when rearranged neat. When the crotyl ether (IV) is rearranged neat, normal Claisen rearrangement takes place to the C-3 atom to form the 1-methylallyl isomer (VI). Rearrangement to the nitrogen atom, however, gives both the normal 1-methylallyl isomer (VII) and the abnormal 1-crotyl product (IX).

The formation of a mixture of normal and abnormal products on neat rearrangement of the crotyl ether (IV) could take place by several mechanistic pathways. At present insufficient experimental data is at hand to decide on one of these possibilities. This will be the subject of a forthcoming investigation.

Experimental[17]

2-Alloxypyridine (I).—This material was prepared by a modification of the method of Mikhant'ev.[8] Sodium (4.1 g., 0.18 g.-atom) was dissolved in 40 ml. of allyl alcohol. To this was added 10.2 g. (0.090 mole) of 2-chloropyridine. The mixture was heated on an oil bath at 115° for 8 hr., poured into 50 ml. of water, and extracted with ether. After drying, the solvent was removed under reduced pressure to give crude product which distilled at 62° (12 mm.) to yield 7.9 g. (65%).

This material was shown by infrared analysis to be identical with a sample which had been prepared by the method of Mikhant'ev and was chromatographed to remove the unchanged 2-chloropyridine.

2-Crotoxypyridine (IV).—2-Chloropyridine (10.2 g., 0.090 mole) was added to a solution of 2.30 g. (0.10 g.-atom) of sodium dissolved in 50 ml. of crotyl alcohol. The mixture was heated on an oil bath for 8 hr. at 120°. Work-up of the reaction mixture as for the preparation of I gave 9.2 g. (78%) of IV, b.p. 94° (12 mm.).

Anal. Calcd. for $C_8H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 71.99; H, 7.38; N, 9.79.

2-(1-Methylalloxy)pyridine (V) was prepared in 55% yield by the procedure used for the preparation of IV and had b.p. 86° (20 mm.).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.39; H, 7.45; N, 9.17.

Rearrangement of 2-Alloxypyridine (I) in Dimethylaniline.—A solution of 11.2 g. of I in 22 ml. of dimethylaniline was heated in a sealed tube for 12 hr. at 255°.

A. 3-Allyl-2-pyridone (II).—Upon cooling, 2.0 g. of II precipitated from solution and was separated by filtration. Removal of the solvent at reduced pressure and addition of a seed crystal precipitated an additional 1.2 g. of II. The combined solids, 3.2 g. (29%), were recrystallized from petroleum ether–chloroform to give a product with m.p. 124–126°.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.13; H, 6.86; N, 10.10.

B. 1-Allyl-2-pyridone (III).—The filtrate from above was chromatographed on alumina. Initial elution with ligroin removed a mixture of unaltered I and some dimethylaniline. Elution with benzene afforded 2.9 g. (26%) of III which was found to be identical by infrared with an authentic sample of III prepared by the method of Mikhant'ev.[8]

Rearrangement of 2-(1-methylalloxy)pyridine (V) in Dimethylaniline.—V (4.4 g.) in 9 ml. of dimethylaniline was heated in a sealed tube for 4 hr. at 245°.

A. 3-Crotyl-2-pyridone (VIII).—Crystals of VIII separated from solution on cooling and were collected as described for 3-allyl-2-pyridone (II). Combination of the initially precipitated crystals and those obtained after removal of the solvent gave 1.5 g. (34%) of VIII, m.p. 114–116°, after recrystallization from ligroin–chloroform.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.31; H, 7.46; N, 9.17.

B. 1-Crotyl-2-pyridone (IX).—The filtrate from A was chromatographed on alumina as described for 1-allyl-2-pyridone (III) and afforded 1.3 g. (30%) of IX. This material was further purified by preparative scale gas chromatography to obtain an analytical sample.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.43; H, 7.59; N, 9.53.

1-Crotyl-2-pyridone (IX) by Alkylation of 2-Pyridone.—The procedure used was essentially that of Mikhant'ev.[8] The sodium salt of 2-pyridone (15.3 g., 0.15 mole) was added to a solution of 62.5 g. (0.69 mole) of crotyl chloride in 60 ml. of absolute ethanol. The mixture was refluxed for 2.5 hr. Precipitated sodium chloride was removed by filtration, and the solvent and excess crotyl chloride were removed under reduced pressure to give a light brown oil which distilled to give 7.6 g. (34%) of product, b.p. 94° (0.1 mm.). This was shown by infrared analysis to be identical with IX obtained by rearrangement of the ether V.

Rearrangement of 2-Crotoxypyridine (IV) in Dimethylaniline.—A solution of 3.0 g. of 2-crotoxypyridine in 6 ml. of dimethylaniline was heated in a sealed tube at 250° for 7 hr.

A. 3-(1-Methylallyl)-2-pyridone (VI).—After cooling, the solvent was removed at reduced pressure; the residue was dissolved in 50 ml. of ether and extracted with 10% sodium hydroxide solution. The aqueous layer was made weakly acidic with 6 *N* hydrochloric acid, and, after filtration, was extracted with chloroform. Evaporation of the chloroform after drying gave 1.1 g. (37%) of crude VI as a light tan oil. This was purified by gradient elution chromatography on alumina but could not be crystallized. Chloroform, ether, ethyl acetate, and methyl alcohol were used with VI being eluted by ethyl acetate–methyl alcohol. This material was further purified by preparative scale gas chromatography to obtain an analytical sample.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.11; H, 7.46; N, 9.61.

B. 1-(1-Methylallyl)-2-pyridone (VII).—Evaporation of the ether fraction from A gave 1.8 g. of light brown oil which was chromatographed as described for 1-allyl-2-pyridone (III) and gave 0.9 g. (30%) of VII which was further purified by preparative scale gas chromatography to obtain an analytical sample.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39 Found: C, 72.21; H, 7.58; N, 9.62.

Neat Rearrangement of 2-Alloxypyridine (I), 2-(1-Methylalloxy)pyridine (V), and 2-Crotoxypyridine (IV).—Distilled samples of the ethers were chromatographed on alumina, redistilled, and rearranged while fresh. The rearrangements were conducted at 245° in sealed tubes.

The composition of the reaction mixtures was investigated by gas chromatography.[18] Peak areas were measured using a K & E 4236 planimeter. Synthetic mixtures were used to obtain correction factors. Positive identifications were established by trapping components, determining their infrared spectra, and comparing these with the spectra of authentic materials.

Neat rearrangement of ethers I and V was shown by this procedure to give the same 1-substituted 2-pyridones (40–55% yield) and 3-substituted 2-pyridones (35–45% yield) as were obtained by rearrangement in dimethylaniline.[19] Relative amounts of 1- and 3-substituted 2-pyridones were found to vary somewhat from batch to batch.

The crotyl ether (IV) gave 3-(1-methylallyl)-2-pyridone (VI) in 30–40% yield. No 3-crotyl-2-pyridone (VIII) was observed at the correct retention time for authentic VIII. Two 1-substituted isomers, 1-(1-methylallyl)-2-pyridone (VII) and 1-crotyl-2-pyridone (IX), were formed when IV was rearranged. The normal isomer (VII) formed in greater amount initially. The amount of abnormal product (IX) increased with respect to VII as the reaction proceeded. The combined yield of the 1-substituted isomers (VII and IX) ranged from 50–60%. The amount of IX formed unaccountably varied from batch to batch but was generally 40–60% of the total yield of 1-substituted isomers when rearrangement was complete.[19]

Attempted Isomerization of 1-(1-Methylallyl)-2-pyridone (VII).—Several sealed tubes containing neat 1-(1-methylallyl)-2-pyridone were heated on an oil bath at 245°. Seven samples were removed at 0.5-hr. intervals and investigated by gas chromatography.[18]

The chromatograms obtained showed that no direct isomerization of VII to the 1-crotyl isomer (IX) takes place. Ethers IV

(17) All melting points are corrected. Microanalyses were performed by Alfred Bernhardt, Mulheim, Germany.

(18) A 2-ft., 20% General Electric XF-1150 on Chromosorb-W column was used. The temperature was programmed from 100–230° at 11°/min. with a helium flow rate of 60 ml./min.

(19) Several unidentified minor components were observed these chromatograms. These components were present also in samples which were rearranged in dimethylaniline.

and V and the 3-substituted 2-pyridones (VI and VIII) also were shown not to form when neat 1-(1-methylallyl)-2-pyridone (VII) is heated under rearrangement conditions.

Attempted Isomerization of 2-Crotoxypyridine (IV) to 2-(1-Methylalloxy)pyridine (V).—Neat IV was heated in sealed tubes at 245°. Samples were withdrawn at 0.5-hr. intervals for 5 hr. and examined for the presence of the isomerized ether (V) by gas chromatography.[18] The column temperature was maintained at 100° for 8 min. before programming began.

No peak due to V was observed in any of the samples. It was determined that no more than 0.5% of V could be present at any time during the rearrangement.

Aryl Fluoroalkyl Sulfides. I. Preparation by Reaction of Grignard Reagents with Trifluoromethanesulfenyl Chloride[1]

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The reaction of arylmagnesium halides with trifluoromethanesulfenyl chloride provides a new and convenient synthesis of aryl trifluoromethyl sulfides. The scope and mechanism of this reaction is discussed, and the chemical and physical properties of aryl fluoroalkyl sulfides are described.

Aryl trifluoromethyl sulfides have been synthesized by reaction of antimony trifluoride with aryl trichloromethyl sulfides which were in turn prepared by photo-

$$ArSCH_3 \xrightarrow[h\nu]{Cl_2} ArSCCl_3 \xrightarrow{SbF_3} ArSCF_3$$

initiated chlorination of aryl methyl sulfides.[2] This method is only of moderate utility since the aromatic substituents are limited to inert groups such as nitro or halogens, and the aryl methyl sulfides are not readily available.

Phenyl tetrafluoroethyl sulfide has been prepared by base-catalyzed addition of thiophenol to tetrafluoroethylene.[3] However, this reaction has not been ex-

$$C_6H_5SH + CF_2{=}CF_2 \xrightarrow{base} C_6H_5SCF_2CF_2H$$

tended to substituted thiophenols, and the properties of the tetrafluoroethylthio group have not been studied.

The aryl trifluoromethyl sulfides have been oxidized to the corresponding sulfones by chromic anhydride in sulfuric acid,[2,4] but otherwise the trifluoromethylthio group appears to be inert to normal chemical transformations of the aromatic ring such as reduction of nitro groups,[2] nitration (*ortho–para* orientation),[5] diazotization of amino groups, and hydrolysis of nitriles.[2] Potential dyes[2a,6] and pharmaceutical chemicals[7] containing the SCF_3 and SO_2CF_3 groups have been reported.

Results and Discussion

Synthesis.—The reaction of arylsulfenyl chlorides with Grignard reagents has been reported as a method for preparation of aryl sulfides.[8] This reaction has now been extended to provide a new direct method for preparation of aryl trifluoromethyl sulfides by reaction of aryl Grignard reagents with trifluoromethanesulfenyl chloride (see Table I).[9]

$$ArMgX + CF_3SCl \longrightarrow ArSCF_3 (+ ArCl + ArX)$$

The sulfide is obtained in a yield of about 50% by bubbling CF_3SCl into a solution of the Grignard reagent at 0°. In addition, aryl chloride and aryl halide are formed as by-products (5 to 15%) from the Grignard reagent (if X is not Cl). In a search for optimum conditions, it was found that, if CF_3SCl was added to a solution of phenylmagnesium bromide chilled to −40° or if an inverse addition procedure was used (maintaining the reaction mixture at −60° to −80°), the yield of phenyl trifluoromethyl sulfide decreased but that of bromobenzene increased proportionately. The purification of the product by distillation (C_6H_5Cl, b.p. 132°; $C_6H_5SCF_3$, b.p. 142°; C_6H_5Br, b.p. 155°) was simplified by use of arylmagnesium chloride,[10] and yields of products were comparable to yield from reaction of the bromide. Purification also was simplified when arylmagnesium iodide was used, but the yield of aryl trifluoromethyl sulfide was significantly lower.

In order to rationalize the results, consideration was given to the mechanism of the reaction. Although mechanism studies have not been reported on the reaction of arylsulfenyl chlorides with Grignard reagents, a mechanism has been proposed for the reaction of Grignard reagents with alkyl halides.[11] The mechanism suggested is a S_N2 or a "push–pull" type which involves

(1) This work was presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) (a) French Patent 820,796 (1937); J. Dickey, U. S. Patent 2,436,100 (1948); British Patents 503,920 (1939) and 479,774 (1938); (b) L. M. Yagupolsky and A. I. Kiprianov, *J. Gen. Chem. USSR*, **22**, 2273 (1952); (c) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **24**, 885 (1954).

(3) D. C. England, L. R. Melby, M. A. Dietrich, and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **82**, 5166 (1960).

(4) L. M. Yagupolsky and B. E. Gruz, *J. Gen. Chem. USSR*, **31**, 1219 (1961).

(5) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **26**, 99 (1956).

(6) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **25**, 1725 (1955).

(7) (a) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960); (b) French Patent 1,245,552 (1960).

(8) H. Lecher, *Ber.*, **58**, 409 (1925); G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1526 (1929); G. Sanna, *Gazz. chim. ital.*, **72**, 305 (1942).

(9) Trifluoromethanesulfenyl chloride was originally reported by R. N. Haszeldine and J. M. Kidd [*J. Chem. Soc.*, 3219 (1953)], who prepared it by reaction of CF_3SSCF_3 or $(CF_3S)_2Hg$ with Cl_2. A convenient synthesis of large quantities of CF_3SCl is the reaction of CCl_3SCl with NaF in tetramethylene sulfone [C. W. Tullock, U. S. Patent 2,884,453 (1959); and C. W. Tullock and D. D. Coffman, *J. Org. Chem.*, **25**, 2016 (1960)].

(10) Arylmagnesium chlorides are readily prepared in tetrahydrofuran as solvent from aryl chloride and magnesium with isopropyl alcohol or aluminum isopropoxide as initiator [E. T. Blues and D. Bryce-Smith, *Chem. Ind.* (London), 1533 (1960)].

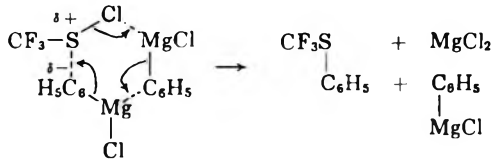
(11) (a) For a general discussion, see M. S. Kharasch and O. Reinmuth "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1048; (b) C. G. Swain, *J. Am. Chem. Soc.*, **70**, 1119 (1948).

TABLE I

PREPARATION OF ARYL TRIFLUOROMETHYL SULFIDES, $ArMgX + CF_3SY \rightarrow ArSCF_3$

ArX, g. (mole) for Grignard reagent[a]	Solvent (ml.) and reaction temperature, °C.[b]	CF_3SCl, g. (mole)	Products	Yield,[c] %
C_6H_5Br 78.5 (0.50)	Ether (500), 0–20	70 (0.50)	$C_6H_5SCF_3$[d]	52
			C_6H_5Cl	11
			C_6H_5Br	6
C_6H_5Br[e] 39.2 (0.25)	Ether (250), −40 to −30	35 (0.25)	$C_6H_5SCF_3$	40
			C_6H_5Cl	3
			C_6H_5Br	24
C_6H_5Br[e] 39.2 (0.25)	Ether (250 ml) Inverse addition to CF_3SCl in 150 ml. of ether at −80°	40 (0.28)	$C_6H_5SCF_3$	31
			C_6H_5Cl	4
			C_6H_5Br	43
C_6H_5Cl 22.5 (0.20)	Tetrahydrofuran (150), −10–0	30 (0.21)	$C_6H_5SCF_3$	54
			C_6H_5Cl	9
C_6H_5I 51.0 (0.20)	Ether (150), −10–0	41 (0.29)	$C_6H_5SCF_3$	23
			C_6H_5Cl	3
			C_6H_5I	12
m-$ClC_6H_4CH_3$ 50.4 (0.40)	Tetrahydrofuran (200), 0–10	55 (0.40)	m-$CH_3C_6H_4SCF_3$	32
			m-$CH_3C_6H_4Cl$	3
p-$ClC_6H_4CH_3$ 50.4 (0.40)	Tetrahydrofuran (200), 0–10	55 (0.40)	p-$CH_3C_6H_4SCF_3$	34
			p-$CH_3C_6H_4Cl$	7
C_6H_5Cl 7.85 (0.07)	Tetrahydrofuran (40), 0–10	CF_3SBr 11 (0.061) in 20 ml. of tetrahydrofuran	$C_6H_5SCF_3$	8
			C_6H_5Br	3
			C_6H_5Cl	Trace

[a] Grignard reagent prepared in normal manner (see "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 550 and ref. 10) using a slight molar excess of magnesium. [b] Unless indicated otherwise, CF_3SCl was bubbled slowly into a solution of Grignard reagent at reaction temperature indicated. [c] Yields determined on total crude product (distilled) by vapor phase chromatographic analysis. [d] B.p. 141–142°, $n^{25}D$ 1.4633, lit.[2c] b.p. 141–142°. [e] Grignard reagent from same preparation.



1

a transition state such as **1** (not necessarily a cyclic intermediate).

A similar mechanism is suggested for the sulfenyl halide reaction; like the carbon in alkyl halides, the sulfur of CF_3SCl is slightly more positive in character than the chlorine, and attack by the carbanion species is directed chiefly to sulfur. However, the difference in electron density between Cl and S is sufficiently small that some attack occurs on the chlorine to displace CF_3S^-. At low temperatures or under inverse addition conditions employing arylmagnesium bromide, the reaction is sufficiently slow so that CF_3SBr can form through exchange of CF_3SCl with magnesium bromide or aryl magnesium bromide.[12] Bromine is more electronegative and polarizable (the strong electron-withdrawing power of the CF_3 group enhances this electronegativity) than chlorine; thus the results described here are explained by competing Br^- or CF_3S^- displacement. Evidence in support of this hypothesis was obtained by treating CF_3SBr, prepared by a literature procedure,[13] with phenylmagnesium chloride. Although the over-all yield of isolable products was lowered, the yield of phenyl trifluoromethyl sulfide relative to bromobenzene decreased compared to that of sulfide to bromo- or chlorobenzenes in the CF_3SCl reactions. A similar result has been reported for the reaction of Grignard reagents with cyanogen halides; cyanogen chloride gives benzonitrile but cyanogen bromide gives chiefly bromobenzene.[14] Another example of the different reaction course resulting from differences in electronegativity of halogen has been reported by Kohrich.[15] The reaction of *o*-lithiophenyl phenyl sulfone with benzenesulfonyl fluoride gave *o*-phenylsulfonylphenyl phenyl sulfone, whereas, with benzenesulfonyl chloride, *o*-chlorophenyl phenyl sulfone was the only product.

This synthesis was extended to reaction of *m*- and *p*-tolyl Grignard reagents with CF_3SCl and may be general for any Grignard reagent with a perfluoroalkylsulfenyl chloride. Phenyllithium with CF_3SCl gave a very low yield of product, and mainly tar was formed. The reaction of CF_3SSCF_3 with a Grignard reagent would have the advantage of eliminating the aryl halide by-products, but again tar was the principal product.

Properties.—The physical and chemical properties of aryl trifluoromethyl sulfides (Table II) have been compared to those of aryl tetrafluoroethyl sulfides and aryl perfluoroalkyl ethers. These sulfides also have been employed in measurements of the electronic effect of fluorine substitution and in study of mechanisms of transmission of inductive and resonance effects.[16]

As generally recognized, the replacement of aliphatic hydrogen by fluorine causes a decrease in boiling point ($C_6H_5SCF_3$, b.p. 142°; $C_6H_5SCH_2CF_2H$, 180° (approx.); and $C_6H_5SCH_3$, 190°). The ultraviolet and infrared

(12) Sulfenyl halides undergo exchange reactions with metallic salts, for example, KCN and KSCN. However, no reference to studies on exchange with salts of bromides has been found: see (a) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 298 (1946); (b) A. Schoberl and A. Wagner in Houben-Weyl "Methoden der Organischen Chemi Schwefel-, Selen-, Tellur-Verbingdungen, Vol. IX, E. Muller, Ed., Georg Thieme, Stuttgart, 1955, Chapter on sulfenic derivatives.

(13) Difluorobromomethanesulfenyl bromide, obtained from addition of bromine to thiocarbonyl fluoride, was treated with antimony trifluoride [N. N. Yarovenko and A. S. Vasilena, *J. Gen. Chem. USSR*, **29**, 3749 and 3754 (1959)].

(14) Ref. 11a, p. 787.

(15) G. Kohrich, *Ber.*, **92**, 2981 (1959).

(16) (a) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963); (b) Eaton and W. A. Sheppard, *ibid.*, **85**, 1310 (1963).

TABLE II.—ARYL FLUOROALKYL SULFIDES. PHYSICAL AND ANALYTICAL DATA

Compound	B.p. (mm.), °C.	M.p., °C., or $n^{25}D$	Method of preparation (% yield)[a]	Formula	Analyses,[b] % Carbon[c] Calcd.	Carbon[c] Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Sulfur Calcd.	Sulfur Found	Other Calcd.	Other Found
$H_2NC_6H_4SCF_3$, *meta*	163–164	1.4683	A	$C_7H_7F_3S$	50.0	50.1	3.68	3.52	29.7	29.8	16.7	17.1		
para	167–168	1.4700	A	$C_7H_7F_3S$	50.0	50.6	3.68	4.03	29.7	29.2	16.7	16.3		
$HO_2CC_6H_4SCF_3$, *meta*[d]		75.4–75.9	C (59)	$C_8H_5F_3O_2S$	43.3	43.0	2.27	2.44	25.7	25.1	14.4	14.0	Neut. equiv. 222	221
														221
para[e]		161–162.4	C (93)	$C_8H_5F_3O_2S$	43.3	43.4	2.27	2.41	25.7	25.5	14.4	14.0	Neut. equiv. 222	221
										25.7		13.9		222
m-$HOC_6H_4SCF_3$	91 (11)	65.4–66.4	*f* (37)	$C_7H_5F_3OS$					29.4	29.8	16.5	16.7		
m-$O_2NC_6H_4SCF_2CF_2H$	80 (0.50)	1.5060	B (64)	$C_8H_5F_4NO_2S$					27.8	29.1	12.6	12.6	N 5.6	5.5
														5.7
$H_2NC_6H_4SCF_2CF_2H$, *meta*	80 (1.0)	1.5148	E (100)	$C_8H_7F_4NS$					33.8	33.5	14.2	13.7	N 6.2	6.6
para	76 (0.50)	1.5219	B (78)	$C_8H_7F_4NS$					33.8	33.9	14.2	14.0	N 6.2	6.3
$H_3CC_6H_4SCF_2CF_2H$, *meta*	95–97 (23–24)	1.4706	B (63)	$C_9H_8F_4S$					33.9	33.3	14.3	14.0		
para	79 (8.5)	1.4715	B (59)	$C_9H_8F_4S$	48.2	48.9	3.60	3.69	33.9	33.5	14.3	14.3		
$HO_2CC_6H_4SCF_2CF_2H$, *meta*		74.6–75.2	C (40)	$C_9H_6F_4O_2S$	42.6	43.2	2.38	2.57	29.9	29.6	12.6	12.3	Neut. equiv. 254	252
														257
para		171.2–172.4	C (52)	$C_9H_6F_4O_2S$	42.6	42.4	2.38	2.48	29.9	29.8	12.6	13.0	Neut. equiv. 254	254
														256

[a] Letter refers to procedure given in Experimental section. Yield only given for compounds prepared by methods other than reported in Table I. [b] All compounds were characterized also by infrared, ultraviolet, and H^1 and F^{19} n.m.r. spectra. [c] For compounds containing fluorine and sulfur, carbon analyses are often 0.4 to 0.7% high but not reproducibly so. [d] Lit.[4] m.p. 75–76°. [e] Lit.[2c] m.p. 160–161°. [f] Prepared by diazotization of corresponding aniline followed by hydrolysis (method given by R. H. F. Manske, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 404).

spectra of these derivatives show no unexpected characteristics. The F^{19} n.m.r. spectra have been reported previously.[16b]

The inert character of SCF_3 when attached to the aromatic nucleus was indicated in earlier reports.[2,4,7] The SCF_2CF_2H group has been found to be similarly inert, and a series of chemical transformations have been carried out on the aromatic nucleus of the aryl perfluoroalkyl sulfides to prepare a series of anilines, benzoic acids, and phenols for pK_a and F^{19} chemical shift studies. For example, tolyl fluoroalkyl sulfides were oxidized to the corresponding benzoic acids by light-catalyzed bromination to benzal bromide followed by hydrolysis–oxidation with concentrated nitric acid. The thermal stability of the aryl fluoroalkyl sulfides is poorer than that of the corresponding ethers.[17] The sulfides decompose extensively at approximately 500° in a sealed stainless steel tube, whereas the ethers are stable to nearly 600°.

Nitration of phenyl trifluoromethyl sulfide was repeated,[5] and the product composition determined by F^{19} n.m.r. and infrared spectral methods. Gas chromatographic analysis for isomers composition was not a satisfactory method. In agreement with the literature report (where only a chemical analysis method was employed), the product was found to be a mixture of *para* (chiefly) and *ortho* isomers. No *meta* isomer was detected, but nitrophenyl trifluoromethyl sulfones and sulfoxides were by-products arising from oxidation by the nitric acid.[2a] Catalytic hydrogenation of the nitro derivatives was found to be a suitable method for preparation of the anilines.

Experimental

Materials.—The aryl halides and mercaptans were obtained from chemical supply houses. The trifluoromethanesulfenyl chloride, b.p. −2–0°, was prepared from trichloromethanesulfenyl chloride and sodium fluoride in tetramethylene sulfone by the method of Tullock.[8] Bis(trifluoromethyl) disulfide is a by-product in this preparation. Trifluoromethanesulfenyl bromide, b.p. 34–35°, was prepared by the method of Yarovenko and Vasilena[13] by reaction of CF_2BrSBr with a mixture of antimony trifluoride and pentachloride; CF_2BrSBr was prepared by addition of bromine to thiocarbonyl difluoride. *m*-Nitrophenylthiophenol was prepared by dextrose–base reduction of nitrophenyl disulfide.[18] Samples of *m*- and *p*-nitrophenyl trifluoromethyl sulfides were prepared by the literature procedure.[2] Sodium hydride, as a 57% dispersion in mineral oil, was obtained from Metal Hydrides Inc., Beverly, Mass.

A. Reaction of Grignard Reagents with CF_3SCl.—The following procedure is typical. A solution of 50.4 g. (0.40 mole) of *p*-chlorotoluene in 200 ml. of anhydrous tetrahydrofuran was mixed with 11.0 g. (0.46 g.-atom) of magnesium turnings and 2.0 g. of aluminum isopropoxide in a 500-ml., three-necked flask under nitrogen.[10] The stirred mixture was heated at reflux overnight until the magnesium had reacted. The solution was cooled to −10° in an ice–acetone bath, and 55 g. (0.40 mole) of CF_3SCl was bubbled slowly into the solution at a rate such that the reaction temperature was maintained at 0 to 5°. The exothermic reaction ceased after approximately 50 g. of CF_3SCl had been added. The solution was allowed to warm to room temperature over several hours, then cooled to 0°, and 500 ml. of 0.25 *N* sulfuric acid added in portions. The reaction mixture was poured into 500 ml. of water, and the product was extracted with two 100-ml. portions of pentane. The combined pentane extracts were washed with water, 10% sodium carbonate solution, and dried over anhydrous $MgSO_4$. The pentane was distilled through a 45-cm. glass helices-packed column, and the crude product distilled through a 45-cm. spinning-band column. A

(17) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964).

(18) G. M. Bennet and W. A. Berry, *J. Chem. Soc.*, 1669 (1927).

fraction of 29.7 g., b.p. 70–100° (chiefly 95–100°) (90 mm.), was collected. The product yield was determined by gas chromatographic analysis of this sample; pure (95–99%) *p*-tolyl trifluoromethyl sulfide was obtained by careful fractionation through a 45-cm. spinning-band column or a glass helices-packed column.

B. Addition of Thiophenols to Tetrafluoroethylene.—The procedure described previously[3] was employed with the following modifications.[19] The thiophenol (0.25–0.50 mole) was dissolved in 150 ml. of dimethoxyethane (glyme), and 10–20 molar % of 53% sodium hydride dispersion in mineral oil was added. When the reaction was complete, the solution was diluted with 150 ml. of dimethylformamide and transferred to the reactor. The tetrafluoroethylene reaction was carried out as previously described,[3] and the product worked up in the normal manner.

C. Oxidation to Benzoic Acids.—A solution of 9.60 g. (0.05 mole) of *p*-tolyl trifluoromethyl sulfide and 16.0 g. (0.10 mole) of bromine in 100 ml. of carbon tetrachloride was radiated under reflux overnight with a General Electric sun lamp. At the end of this time, the bromine color had disappeared, and considerable HBr had evolved. The carbon tetrachloride was evaporated at room temperature under a nitrogen stream, and 50 ml. of concentrated nitric acid was added. The mixture was stirred vigorously overnight; bromine gradually evolved, and finally the product separated from the aqueous phase as a solid. The mixture was poured into several hundred milliliters of ice–water, and the solid product was separated by suction filtration and washed thoroughly with water. The yield of crude *p*-(trifluoromethylthio)benzoic acid, m.p. 157–158.5°, was 10.3 g. The product was purified to constant m.p. 161.0–162.4° by recrystallizations from approximately 125 ml. of 60% hexane–40% benzene, followed by sublimation at approximately 100° (5 mm.).

D. Nitration.—A solution of 5.0 g. (0.028 mole) of phenyl trifluoromethyl sulfide and 15 g. of concentrated sulfuric acid was cooled to 0°, and 3.2 g. (0.035 mole) of nitric acid (70%) was added dropwise while keeping the reaction temperature at 0°. After addition was completed, the reaction mixture was stirred for 40 min. at 0° and then poured into 200 ml. of ice–water. The oil was extracted in methylene chloride and after drying, the extracts were distilled through a 30-cm. spinning-band column. A total of 4.13 g. of pale yellow liquid, b.p. 90–91° (5.0 mm.), $n^{26}D$ 1.5125–1.5165, was identified by infrared and F^{19} n.m.r. analysis as chiefly *p*-nitrophenyl trifluoromethyl sulfide containing 20–30% of a second component with spectral properties characteristic for an *ortho* isomer. No *meta* isomer was detected. Gas chromatographic analysis on a column of 20% Dow Corning high vacuum grease on 60–80-mesh Celite also indicated 20% of a second component, but complete separation was not accomplished on a selection of columns usually suitable for fluorocarbons or aromatic isomer mixtures. A control reference mixture of *meta* and *para* isomers could not be separated under any of the conditions employed. A higher boiling fraction [93–105° (1.5 mm.), $n^{26}D$ 1.5515] was shown by spectral analysis (comparison with an authentic sample) to contain some nitrophenyl trifluoromethyl sulfone.

E. Reduction.—Chemical reduction of nitrophenyl trifluoromethyl sulfide with stannic chloride has been reported in the literature.[2] In this work, catalytic hydrogenation, as described by the following procedure, was found to be more convenient. A solution of 19.7 g. (0.077 mole) of *m*-nitrophenyl tetrafluoroethyl ether in 150 ml. of absolute ethanol containing 0.08 mole of hydrogen chloride was hydrogenated at approximately 3 atm. of pressure in a Parr apparatus using 0.30 g. of platinum oxide as catalyst. The theoretical amount of hydrogen was absorbed in a few minutes. The catalyst was removed by filtration, and the alcohol solution evaporated under nitrogen. The residual solid was triturated with 100 ml. of ether and filtered. The *m*-(tetrafluoroethylthio)aniline hydrochloride was obtained as white platelets in an approximately quantitative yield of 21 g. The free aniline was obtained by adding the hydrochloride to an excess of a stirred 10% solution of sodium carbonate layered with ether. The aniline obtained from the dried ether extract distilled at 80° (1.0 mm.).

(19) We wish to thank Dr. D. C. England of this laboratory for suggesting these modifications.

Aryl Fluoroalkyl Sulfides. II. Preparation by Condensation of Trifluoromethanesulfenyl Chloride with Aromatic Systems

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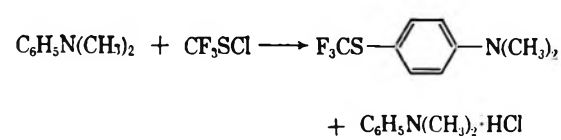
The condensation of trifluoromethanesulfenyl chloride with aromatic compounds provides a convenient new synthesis of aryl trifluoromethyl sulfides. Activated aromatic derivatives, such as phenols or dimethylaniline, react at room temperature without a catalyst to give high yields of the corresponding *p*-substituted aryl trifluoromethyl sulfide. Benzene, toluene, and halobenzenes require higher temperatures and Lewis acid catalysts, such as hydrogen fluoride or boron trifluoride.

In the previous paper,[1] the literature on aryl fluoroalkyl sulfides was reviewed, and the reaction of Grignard reagents with CF_3SCl was described as a new synthetic route to aryl trifluoromethyl sulfides. The condensation of alkyl- or arylsulfenyl chlorides with aromatic compounds has been reported as a method for preparation of aryl sulfides.[2] As an extension of this reaction, we wish to report the convenient preparation of aryl trifluoromethyl sulfides by substitution of aromatic derivatives with CF_3SCl. The method is particularly advantageous for aromatic systems with electron-donating substituents.

Introduction of gaseous CF_3SCl into dimethylaniline in ether or phenol in chloroform–pyridine at room temperature gave the corresponding aryl trifluoromethyl sulfide in yields of 58 to 75%. As normally observed in electrophilic, aromatic-type substitutions in aromatic rings highly activated by groups such as $N(CH_3)_2$ or OH, substitution was almost exclusively in the *para* position.



$$C_6H_5N(CH_3)_2 + CF_3SCl \longrightarrow F_3CS\text{–}C_6H_4\text{–}N(CH_3)_2 + C_6H_5N(CH_3)_2\cdot HCl$$

Benzene did not react with CF_3SCl at room temperature even in the presence of a Lewis acid. By carrying out the reaction in a stainless steel autoclave at 100° in the presence of boron trifluoride, phenyl trifluoromethyl sulfide was obtained in a yield of 57%. Similar conditions were needed for reaction with toluene. The over-

(1) W. A. Sheppard, *J. Org. Chem.*, **29**, 895 (1964).

(2) (a) C. M. Buess and N. Kharasch, *J. Am. Chem. Soc.*, **72**, 3530 (1950); (b) H. Brintzinger and M. Langheck, *Ber.*, **86**, 557 (1953); H. Brintzinger and H. Ellwanger, *ibid.*, **87**, 300 (1953).

all yield of tolyl trifluoromethyl sulfides was higher, and the product was a mixture of *ortho* and *para* isomers with a trace of *meta*. Chloro- and bromobenzene required a catalyst (anhydrous hydrogen fluoride) and a temperature of 200°; total yield of the resulting *ortho*, *meta*, and *para* isomer mixture of haloaryl trifluoromethyl sulfides was approximately 25%. The yield of *meta* isomer was low, as expected, and the products were contaminated with dihalobenzenes from disproportionation or chlorination as a result of the drastic conditions required. Disubstitution of benzene with CF_3SCl did not occur to any detectable extent even under forcing conditions. It previously has been shown that the deactivating effect of an SCF_3 group in withdrawing electrons is significantly greater than that of a halogen.[3]

Thiophenol gave only phenyl trifluoromethyl disulfide ($C_6H_5SSCF_3$). In the reaction of phenols with CF_3SCl, substitution occurs in the ring, but it is possible that the sulfenate ester ($ArOSCF_3$)[4] may form initially and rearrange rapidly into the ring.

No study was made of the mechanism of this reaction, but it is considered to be an ionic reaction that proceeds as a typical electrophilic aromatic substitution. The attacking species is probably CF_3S^+, formed by coordination of CF_3SCl with a Lewis acid.

Experimental

Materials.—The trifluoromethanesulfenyl chloride, b.p. −2–0°, was prepared from trichloromethanesulfenyl chloride and sodium fluoride in tetramethylene sulfone by the method of Tullock.[5] All other reagents were obtained from chemical supply houses.

A. Trifluoromethyl *p*-(N,N-Dimethylamino)phenyl Sulfide.—To a solution of 63 g. of trifluoromethanesulfenyl chloride dissolved in 700 ml. of anhydrous ether was added 110 g. of dimethylaniline over a period of 30 min. The mixture was filtered and the precipitate rinsed with ether on the filter. The washings and filtrate were combined and evaporated *in vacuo*. Upon distillation of the residue through a 45-cm. spinning-band still, there was obtained 59.2 g. (58%) of *p*-(N,N-dimethylamino)phenyl trifluoromethyl sulfide, b.p. 43–74° (0.9 mm.), $n^{25}D$ 1.5297–1.5301. This material was shaken once with aqueous sodium bicarbonate, once with water, dried over anhydrous magnesium sulfate, and redistilled. The product was obtained as a colorless liquid distilling at 54° (0.15 mm.), $n^{24}D$ 1.5309.

Anal. Calcd. for $C_9H_{10}F_3NS$: C, 48.9; H, 4.6; S, 14.5. Found: C, 49.0; H, 4.5; S, 14.5.

The proton n.m.r. spectrum (neat) showed a single sharp resonance at τ 7.63 assigned to the methyl groups and a typical AB pattern centered at 3.43 (J_{AB} = 9 c.p.s.), as usually observed with *p*-substituted aromatic compounds.

B. Trifluoromethyl Hydroxyaryl Sulfides.—A mixture of 18.8 g. (0.2 mole) of phenol, 16.0 g. (0.20 mole) of pyridine, and 100 ml. of chloroform was cooled to 0° while 32.0 g. (0.23 mole) of trifluoromethanesulfenyl chloride was added. After addition was complete, approximately 75 ml. of chloroform was removed by distillation, and 150 ml. of ether was added to the viscous mixture. Pyridine hydrochloride precipitate was removed by pressure filtration. The filtrate was distilled to give 30.0 g. (72.5%) of *p*-(trifluoromethylthio)phenol as a colorless liquid, b.p. 71–75° (3 mm.).[6] This phenol slowly crystallized on standing.

Anal. Calcd. for $C_7H_5F_3SO$: C, 43.3; H, 2.6; F, 29.4. Found: C, 43.4; H, 2.6; F, 29.6.

The proton n.m.r. spectrum in chloroform-*d* displayed an AB pattern for the aromatic hydrogens centered at τ 2.9 (J_{AB} = 9 c.p.s.) and a single phenolic OH resonance at 3.7 which disappeared when methanol-O-*d* was added. The relative integrated intensity ratio was 4:1, respectively. The infrared spectrum of the product was also consistent with the *para* isomer assignment. In addition to the strong O–H absorption at 3400 cm.$^{-1}$, bands in the 2000–1660-cm.$^{-1}$ region and a strong band at 840 cm.$^{-1}$ were consistent with a *p*-disubstituted benzene.

From the reaction of CF_3SCl with *o*-cresol under the conditions described above, 2-methyl-4-(trifluoromethylthio)phenol, b.p. 70–76° (0.4–0.5 mm.), was obtained in 75% yield.

Anal. Calcd. for $C_8F_7OF_3S$: F, 27.4; S, 15.4. Found: F, 26.8; S, 14.8.

The isomer assignment in this case was based on infrared data. The 2000–1650-cm.$^{-1}$ region was indicative of only 1,2,4 substitution, and additional bands at 1210, 1040, 995, and 885 cm.$^{-1}$ were consistent with this assignment. By gas chromatographic analysis, this product was noted to contain small amounts of impurities, one of which was probably the 1,2,3 isomer.

C. Phenyl Trifluoromethyl Disulfide.—When the above reaction was repeated with thiophenol, the product was a liquid, b.p. 35.5–37.5° (0.48 mm.), which was characterized as phenyl trifluoromethyl disulfide (yield 67%).

Anal. Calcd. for $C_7H_5F_3S_2$: C, 40.0; H, 2.4; F, 27.1; S, 30.5. Found: C, 40.4; H, 2.6; F, 27.1; S, 30.0.

The characterization was confirmed by infrared data (monosubstituted benzene, no SH absorption), and by comparison of infrared and ultraviolet spectral properties to those of the known compound, phenyl trichloromethyl disulfide. The ultraviolet spectrum in 95% ethyl alcohol showed a λ_{max} at 271 mμ (ϵ 1318) and a shoulder at 230 mμ (ϵ 7980). No product resulting from electrophilic substitution on the ring was found.

D. Phenyl Trifluoromethyl Sulfide.—An evacuated 240-ml. "Hastelloy"-lined bomb was charged with 50 g. of benzene, 27 g. (0.20 mole) of CF_3SCl, and 5 g. of boron trifluoride. The mixture was heated at 50° for 2 hr. and 100° for 4 hr. The resulting solution was distilled through a spinning-band column. After stripping the excess benzene, 20.0 g. (57%) of phenyl trifluoromethyl sulfide,[1] b.p. 141–142°, was obtained. Slightly higher yields were obtained in larger scale reactions in a 1-l. autoclave. No disubstituted product was obtained when an excess of CF_3SCl was employed. Also, no reaction occurred between CF_3SCl and benzene with boron trifluoride etherate as catalyst at atmospheric pressure and temperatures up to 80°.

E. Tolyl Trifluoromethyl Sulfides.—The conditions described above for the benzene reaction were employed. Tolyl trifluoromethyl sulfide, b.p. 98–100° (100 mm.) [lit.[1] b.p. 95° (23 mm.) and 79° (8.5 mm.) of *m*- and *p*-tolyl trifluoromethyl sulfide, respectively], was obtained in a yield of 75%. Gas chromatographic and spectral analyses were employed to determine the isomer ratio of a fractionated sample of a portion of the product, b.p. 103–105° (112 mm.) and $n^{26}D$ 1.4741–1.4720.

Gas chromatographic analyses were carried out on a 2-m. column packed with 20% diglyceride on 60–80-mesh firebrick at 123° using helium as carrier gas. The retention time of authentic sample mixtures of the tolyl trifluoromethyl sulfide was *meta*, 10.3 min., and *para*, 11.6 min. (an authentic sample of *ortho* isomer was not available). The main product fractions eluted at 10.2–10.6 min. and 11.5–11.8 min. From infrared analysis of fractions collected from elution, the 10.2–10.6-min. peak was identified as chiefly *ortho* and the 11.5–11.8-min. peak as *para*. The small amount of *meta* product was apparently eluted with the large *ortho* fraction.

F^{19} n.m.r. analysis of fractions showed resonances at −24.15 (*para*), −24.63 (*meta*), and −24.93 p.p.m. (assigned to *ortho*), with the solvent carbon tetrachloride (internally referenced from $CFCl_2CFCl_2$). The *meta* and *para* were assigned by comparison to

TABLE I

		Isomer, %				
		ortho		*para*		*meta*,
Fraction	Weight, g.	G.c.	N.m.r.	G.c.	N.m.r.	N.m.r.
2	1.57	67	72	32	28	Trace
3	3.65	64	64	36	34	3
4	3.59	51	45	49	53	2
5	2.68	34	33	66	66	2

(3) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963).

(4) S. Andreades [U. S. Patent 3,081,350 (1963)] reports the preparation of sulfenate esters, $ROSCF_3$, by reaction of aliphatic alcohols with CF_3SCl in the presence of a base.

(5) C. W. Tullock, U. S. Patent 2,884,453 (1959); C. W. Tullock and D. D. Coffman, *J. Org. Chem.*, **28**, 2016 (1960).

agupolsky and M. S. Marenets [*J. Gen. Chem. USSR*, **24**, have reported *p*-(trifluoromethylthio)phenol, b.p. 77–78° (7 mm.) and m.p. 57–58°, prepared by hydrolysis of *p*-(trifluoromethylthio)benzenediazonium sulfate.

authentic samples, and the relative intensities were measured from integrated spectra.

Isomer assignments were confirmed by infrared comparison of the spectrum of each fraction with authentic spectra of *m*- and *p*-tolyl trifluoromethyl sulfides: *para*, 812 (s), 755 (w), and 705 cm.$^{-1}$; *meta*, 782 (s), 690 (m), and 685 cm.$^{-1}$. In particular, a comparison was made of the CH out-of-plane deformation bands. In the spectrum of each fraction, the strong band at 815 cm.$^{-1}$ was assigned to *para* and was noted to increase in relative intensity in going from fraction 2–5. In accord with the other analysis, a strong band at 760 cm.$^{-1}$ was assigned to the *ortho* isomer and decreased in relative intensity from fraction 2–5. Weak absorption at 685 and 785 cm.$^{-1}$ was assigned to the *meta* isomer. A weak absorption at 715 cm.$^{-1}$ may be associated with the *para* isomer but was not definitely assigned.

On the basis of the above analyses, the approximate isomer composition of the product was *ortho*, 52%; *para*, 47%; and *meta*, 1–2%.

F. Halobenzenes.—Twenty-seven grams of CF_3SCl was treated with 40 g. of chlorobenzene in the presence of 10 g. of anhydrous hydrogen fluoride in a 240-ml. "Hastelloy" bomb heated at 100° for 2 hr., 150° for 2 hr., 175° for 2 hr., and 200° for 2 hr. A total of 10.5 g. of product, b.p. 171–177°, $n^{23}D$ 1.509–1.497, was obtained. From gas phase chromatographic analyses, confirmed with infrared and proton n.m.r. studies as described for the tolyl derivative, the product was shown to contain relative isomer ratios of *ortho*, 24%; *meta*, 2–3%; and *para*, 74%. In this case, the *ortho* isomer concentrated in the higher boiling fraction and was eluted at longer times in gas chromatographic analysis on the same column as above. Identification of product was made on an eluted sample by mass spectrometric, infrared, and n.m.r. analyses. Dichlorobenzenes also are believed to be present as impurities in reaction mixtures.

The above reaction was repeated using 50 g. of bromobenzene instead of chlorobenzene. A total of 20.3 g. of product, b.p. 105–118° (50 mm.), was collected. This material partially crystallized; the crystals were removed by filtration and were found not to contain fluorine. The liquid fraction, 13.1 g., was analyzed by gas chromatography as described above. It was shown to contain the *ortho*, *meta*, and *para* isomers in approximately the same relative amounts as from chlorobenzene but with approximately 30% impurity of a mixture of dibromo- and bromochlorobenzenes, tentatively characterized by mass spectrometric analysis of fractions eluted by gas chromatography. The crystallized fraction also was characterized tentatively by spectral analysis as a mixture of dihalobenzenes.

Catalytic Hydrogenation of Some Naphthyl Alkenes[1-3]

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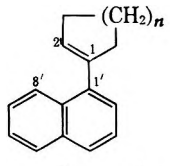
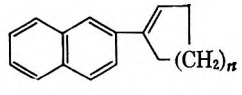
Rates of catalytic hydrogenation of twelve naphthyl alkenes and two cycloalkyl naphthalenes have been studied using acetic and propionic acids as solvents, Adams' platinum as catalyst, both constant volume and constant temperature (5–40°), and 1–2-atm. pressure. For most of the naphthyl alkenes, first-order rate plots (with respect to the pressure of hydrogen) showed two linear portions corresponding to (1) more rapid reduction of the alkenyl double bond (accompanied by some reduction of the naphthalene ring) and to (2) slower reduction of the resultant alkyl naphthalene, respectively. In general, rate constants for hydrogenation increased with increasing temperature, with change from acetic acid to propionic acid, and (for process 1) with decrease in number of substituents on the carbon atoms of the alkenyl double bond. There was no evidence of preliminary double bond migration.

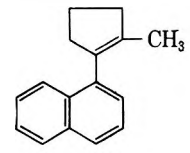
In an earlier publication Klemm and Hodes[4] found that 1-(1-naphthyl)cyclohexene (III) hydrogenated at a slower rate (for reduction of the alkenyl double bond) than that found for its analogs, 1-(1-naphthyl)cyclopentene (I), 1-(2-naphthyl)cyclopentene (II), and 1-(2-naphthyl)cyclohexene (IV), which hydrogenated at essentially identical rates. These results, obtained at 25° with Adams' platinum catalyst in glacial acetic acid, were interpreted in terms of steric hindrance to the attainment of coplanarity in III (but not in the others) during the complex-forming phase of the reaction owing to the fact that collision between hydrogen atoms on C-2 and -8′ would occur. The present investigation is an extension of the previous work. Compounds studied were I–X, 1-vinylnaphthalene (XI), 2-vinylnaphthalene (XII), 1-cyclopentylnaphthalene (XIII), and 1-cyclohexylnaphthalene (XIV).



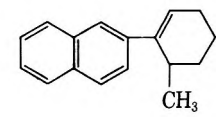
I, $n = 1$
III, $n = 2$
V, $n = 3$



II, $n = 1$
IV, $n = 2$
VI, $n = 3$



VII



VIII

Experimental

Compounds I–XIII were available or prepared in the purified forms previously described[4-9] and were stored as the narrow-melting polynitro aromatic molecular compounds indicated. Immediately before use each complex was dissociated by adding

(1) Abstracted (in part) from the Ph.D. thesis of R. Mann, University of Oregon, June, 1959. A detailed description of the construction and manipulation of the apparatus used in this research as well as plots of many kinetic runs may be found in this thesis.

(2) Part XIII, in the series on Chemical Reactivities of Arylcycloalkenes. For part XII, see L. H. Klemm, W. C. Solomon, and A. J. Kohlik, *J. Org. Chem.*, **27**, 2777 (1962).

(3) This research was supported (in part) through sponsorship by the Office of Ordnance Research, U. S. Army, Contract No. DA-04-200-ORD-176; by the U. S. Air Force under Contract No. AF 49(638)-473, monitored by the Air Force Office of Scientific Research of the Air Research and Development Command; and (in part) by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to these donors.

(4) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, **73**, 5181 (1951).

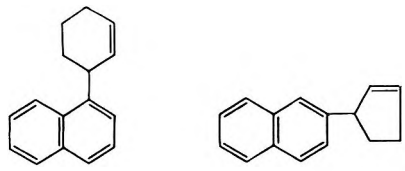
(5) L. H. Klemm and H. Ziffer, *J. Org. Chem.*, **20**, 182 (1955).

(6) For the revised structure of VII, see footnote 7 in ref. 25 and the discussion in the present paper.

(7) L. H. Klemm, J. W. Sprague, and H. Ziffer, *J. Org. Chem.*, **20**, 200 (1955).

(8) L. H. Klemm, B. T. Ho, C. D. Lind, B. I. MacGow and E. Y. K. Mak, *ibid.*, **24**, 949 (1959).

(9) W. E. Bachmann and L. H. Klemm, *J. Am. Chem. Soc.*, **72**, 4911 (1950).



IX X

a concentrated benzene solution of it to a column of alumina–Celite (1:1 by vol.) and eluting with reagent grade petroleum ether (30–60°). The residue from evaporation of the effluent was distilled under nitrogen *in vacuo*. In the case of a liquid product, a center fraction of 1–2° boiling range was selected for use. For a solid product, the distillate was recrystallized to constant melting point from absolute ethanol or methanol. Perbenzoic acid titration[5] showed the presence of 98.8 mole % unsaturation in the sample of VII used.

For preparation of XIV, a solution of 223 g. (0.88 mole) of cyclohexyl *p*-toluenesulfonate[10] (prepared in 88% yield, m.p. 42–44°, from purified[11] *p*-toluenesulfonyl chloride) in 500 ml. of anhydrous ether was added dropwise to the Grignard reagent prepared from 21.1 g. (0.87 g.-atom) of magnesium turnings, 180 g. (0.87 mole) of 1-bromonaphthalene, and 250 ml. of ether. The mixture was stirred for 2 days at room temperature, treated with ice-cold aqueous ammonium chloride, and extracted with ether. Fractional distillation of the dried ethereal layer produced 14.8 g. (8%) of pale yellow XIV, b.p. 118–123° (0.4 mm.). It was purified further by three recrystallizations of its monopicrate (m.p. 125–126°)[12] from absolute ethanol, chromatographic dissociation of the picrate, and distillation of the effluent, obtained as a colorless liquid, b.p. 121–123° (0.7 mm.).

Except for one run, the catalyst, Adams' platinum oxide American Platinum Works), was taken from the same thoroughly premixed batch in every case. Hydrogen (electrolytic grade) was used from one tank only. Mass spectral analysis[13] of this gas indicated the probable presence of 0.7% nitrogen and 0.1% oxygen therein. In a few runs, the hydrogen was deoxygenated before use but this procedure was discontinued since it showed no significant effect on the values of the rate constants obtained. Solvent A_1 was Baker and Adamson glacial acetic acid (99.7%), used directly from the bottle. Batch A_2 acetic acid (anhydrous, b.p. 116°) was prepared by treating the foregoing solvent with chromium trioxide according to the directions of Eichelberger and LaMer[14] and then distilling it through a 2 × 120 cm. column packed with glass helices. Batch P_1 propionic acid (b.p. 138–139°) was prepared from practical grade (Distillation Products Industries) material by refluxing with potassium permanganate, distilling therefrom, and then carefully fractionating by means of the aforementioned column. It gave negative tests with bromine in carbon tetrachloride and aqueous permanganate. Batch P_2 propionic acid resulted from the same practical grade material, but was purified according to the method of Vogel.[15]

Rate studies were made in an all-glass (except for one ground-glass joint lubricated with Dow Corning silicone high vacuum grease and the contact with the column of mercury in the attached manometer) system completely bathed in water thermostated to ±0.1°. Stirring (150 cycles/min.) was accomplished by means of a stomping device (similar to one described by Castille)[16] consisting of a Teflon disk attached to a long glass rod containing a soft iron core, activated by means of water-cooled solenoids surrounding the narrow upper portion of the water-jacketed reaction vessel. During a run, the volume of the system (V) was maintained constant (0.256 l.) to within a fraction of a milliliter, and the decreasing pressure was measured to ±0.3 cm. in the manner described previously.[4] In a typical experiment, the reaction vessel (a flat-bottomed cylindrical cell) was charged with 50 ml. of solvent, 5.00 mmoles of hydrocarbon) and 75.0 mg. of catalyst. The initial pressure of hydrogen was 2

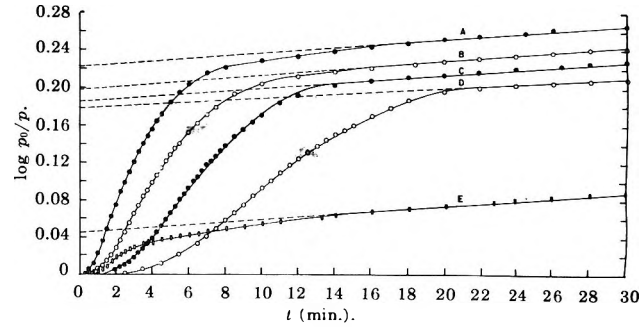


Fig. 1.—Hydrogenation kinetic runs in P_2 propionic acid. Curves A–D for 1-(2-naphthyl)cyclohexene (IV) at temperatures of 39.9, 29.9, 19.9, and 9.9°, respectively, curve E for 2-methyl-1-(1-naphthyl)cyclopentene (VII) at 29.9°.

atm. and the final pressure (after 40 min. when measurements were terminated) was 1 atm. or more. Observed manometric pressures were corrected for barometric reading and vapor pressure of the solvent. The logarithm of the ratio of the initial pressure, p_0, to the instantaneous pressure, p, was plotted against reaction time, t, in minutes (see Fig. 1 and 2) and (except in a few cases such as curve E in Fig. 1 and curve D in Fig. 2 where one considers that a *bona fide* first linearity is missing) the slopes (k_1' and k_2') of the first and second linear portions of the resulting curve were determined graphically. The corresponding specific reaction rates, k_1 and k_2, were calculated from the relationships[17a] $k_1 = 2.303\ k_1'V/RTW$ and $k_2 = 2.303\ k_2'V/RTW$, where R is the molar gas constant, T is the reaction temperature in °K.,[17b] and W is weight of catalyst used in grams. The second linear portion of the curve was extrapolated to $t = 0$ in order to obtain the intercept on the $\log(p_0/p)$ axis. Values (for single trials or averages for duplicate or multiple trials made under identical conditions of temperature, solvent, and substrate) for the rate constants and the intercepts are given in Table I. With only a few exceptions, variation of results from individual trials was $< \pm 5\%$ of the average value for k_1 and $< \pm 10\%$, for k_2. Periodic checks on the activity of the catalyst were made using I, 29.9°, and A_1 solvent (run 27). Variations in values of k_1 and k_2 from duplicate trials made over the period of 18 months which elapsed during collection of the kinetic data in Table I were no greater than those from consecutive duplicate trials.

Discussion

Examination of Table I shows that, in general in the same solvent, k_1 and k_2 increase with increasing temperature over the range of temperatures studied (5–40° in propionic acid, 20–40° in acetic acid). This phenomenon readily is observable for k_1' in curves A–D in Fig. 1, where the increase in induction period with decreasing temperature is apparent also. Since reduction of the platinum oxide catalyst was conducted *in situ* and no special precautions were taken to protect the solvent from absorption of moisture from the air while it was being transferred to the reaction chamber, all solvents used contained at least small amounts of water. Comparison of runs 3 and 5 shows that the deliberate addition of water to the solvent served to decrease k_1 somewhat but scarcely affected k_2 beyond experimental error. The gross change of solvent from acetic acid to propionic acid, on the other hand, brought about a consistent increase (up to 46% at 29.9°) in k_1, but gave variable effects on k_2 (*cf.* runs 27, 3; 30, 4; 35, 9; 36, 10; 40, 13).[18]

Comparison of data for intercepts on the log axis shows that in only three cases (compounds VII, XIII,

(10) W. J. Hickinbottom and N. W. Rogers, *J. Chem. Soc.*, 4131 (1957).

(11) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 380.

(12) Reported m.p. 126.7–127.4°, M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, **69**, 505 (1947).

(13) We are indebted to Dr. Thomas A. Whatley and Dr. D. F. Swinehart for this analysis.

(14) W. Eichelberger and V. K. LaMer, *J. Am. Chem. Soc.*, **55**, 3633 (1933).

(15) A. I. Vogel, *J. Chem. Soc.*, 1814 (1948).

(16) A. Castille, *Bull. soc. chim. Belges*, **46**, 5 (1937).

(17) (a) R. D. Schuetz, L. R. Caswell, and J. C. Sternberg, *J. Org. Chem.*, **24**, 1080 (1959); (b) temperature was converted from °C.

(18) The effect of varying solvent on the kinetics of hydrogenation of nitro compounds has been investigated by H. C. Yao and P. H. Emmett, *J. Am. Chem. Soc.*, **81**, 4125 (1959); **83**, 796, 799 (1961).

TABLE I

RATES OF HYDROGENATION OF SOME NAPHTHYL ALKENES[a]

Run no.[d]	Compound	t, °C.	No. of trials[e]	k_1, mmoles min.$^{-1}$ atm.$^{-1}$ g.$^{-1}$	k_2 mmoles min.$^{-1}$ atm.$^{-1}$ g.$^{-1}$	Intercept on log p_0/p axis
			In propionic acid[b]			
1	I	4.9	2	3.71	0.27	0.15
2	I	14.9	2	5.9	0.42	0.15
3	I	29.9	3	10.4	0.71	0.18
4	I	39.9	1	16.5	0.96	0.16
5[h]	I	30.1	1	9.1	0.81	0.17
6	II	5.0	1	3.98	0.37	0.14
7	II	6.9	1	4.54	0.36	0.15
8	II	17.9	1	6.99	0.73	0.16
9	II	29.9	2	11.5	0.80	0.17
10	II	39.9	2	15.9	1.2	0.19
11*	IV	9.9	1	4.61	0.23	0.19
12*	IV	19.9	1	6.59	0.36[j]	0.19
13*	IV	29.9	1	9.58	0.33[j]	0.20
14*	IV	39.9	1	12.7	0.37[j]	0.23
15	IV	29.9	2	10.4	1.19	0.18
16*	VI	29.9	2	9.79	0.74	0.20
17*[l]	VII	29.9	2	*m*	0.38	0.04
18	VIII	4.9	2	2.63	0.26	0.15
19	VIII	29.9	2	7.43	0.68	0.14
20	VIII	40.1	1	9.70	1.16	0.16
21*	XIII	29.9	2	*m*	0.48	0.05
			In propionic acid[b]			
22	XI	29.9	2	25.3	1.32	0.19
23	XII	19.9	1	19.0	0.48	0.18
24	XII	29.9	1	21.0	0.72	0.20
			In acetic acid[c]			
25	I	19.7	2	5.64	0.31	0.15
26	I	24.9	2	6.39	0.48	0.16
27	I	29.9	6[f]	7.11	0.53	0.17
28[g]	I	32.5	2	8.90	0.75	0.18
29[g]	I	35.0	3	8.86	0.72	0.17
30	I	39.7	3	9.54	0.75	0.17
31*	I	29.9	2	9.98	0.85	0.18
32*	II	29.9	2	9.01	1.15	0.17
33[i]	II	29.9	1	10.3	0.75	0.18
34	II	19.9	2	6.3	0.50	0.15
35	II	29.9	2	9.07	0.75	0.16
36	II	39.9	2	10.4	0.95	0.17
37	III	19.9	1	3.47	0.39	0.16
38	III	29.9	2	5.08	0.73	0.14
39	III	40.1	1	6.37	0.90	0.16
40*	IV	29.9	2	7.98	1.07	0.16
41	V	29.9	1	3.8[k]	0.53	0.14
42*	X	29.9	2	12.9	1.16	0.17
43	IX	19.9	1	10.9	0.33	0.18
44	IX	29.9	2	13.3	0.55	0.19
45	IX	39.9	1	17.3	0.62	0.20
46	XIV	29.9	2	*m*	0.48	0.03
			In propionic acid[b]			
47*	XII	9.9	1	10.8	0.18	0.18
48*	XII	19.9	2	13.5	0.31	0.19
49*	XII	29.9	2	19.1	0.23	0.20

[a] Unless otherwise designated, reactions were run using 50 ml. of solvent, 75.0 mg. of platinum oxide from the same premixed batch, and 5 mmoles of hydrocarbon. [b] Unstarred runs in this solvent were made in batch P_1 propionic acid; starred runs, in batch P_2 propionic acid. [c] Unstarred runs in this solvent were made in batch A_1 acetic acid; starred runs, in batch A_2 acetic acid. [d] Not listed chronologically. [e] Where two trials are reported, they were made in succession; where three or more trials are reported, only two were made consecutively. [f] This series of trials was made over a period of 18 months in order to check the retention of activity of the catalyst. It includes runs from two different bottles of A_1 acetic acid and one run using 2.58 mmoles of hydrocarbon. [g] From the nearly identical rate constants found in runs 28 and 29, it appears that some irregularity may occur in the hydrogenation of I between 29.9° and 35.0° in A_1 acetic acid. [h] Using P_1 propionic acid to which 1% of water was added. [i] Using a fresh batch of catalyst. [j] k_2 appears to be insensitive to changes in temperature in runs 12–14. [k] This represents a maximum value, inasmuch as the earlier part of the short linear portion coincides with the log plot for reduction of the catalyst (as noted from run 46). [l] See ref. 6. [m] No *bona fide* first linear portions ascribable to hydrogenation of the substrate were present in the log plots of these runs. However, preliminary reduction and sorption of hydrogen by the catalyst is observed.

and XIV) were particularly low values (0.04 ± 0.01 at 29.9°) obtained. Moreover, of all the compounds studied, only these three absorbed less than an equimolar amount (compared to the size of hydrocarbon sample used) of hydrogen during a 40-min. run. The intercept values compare favorably with that of 0.02–0.04 obtained as a blank for reduction–saturation of the catalyst–solvent combination alone. However, in the absence of hydrocarbon substrate, the catalyst readily was observed to coagulate after only a few minutes of reaction time. In contrast, during any regular run, no coagulation was visually apparent until near the termination of the run, if at all. Since XIII and XIV can give only reduction of the naphthalene moiety, we have used the intercept of 0.04 ± 0.01 as an operative value representing the appropriate blank (at 29.9°) for the regular runs. At this temperature an intercept of 0.18 ± 0.03 would correspond to absorption of 1 mole of hydrogen per mole of hydrocarbon (plus blank). Intercepts found were 0.17 ± 0.03 for all compounds except the aforementioned three.

As suggested previously[4] and in accordance with the results noted in the preceding paragraph, the second linear portion of the curve is considered generally to represent only a first-order reduction process[19] for the naphthalene moiety. Consistent with this assignment are the facts that, for runs made under the same conditions, k_2 values are nearly identical for the conjugated and unconjugated pair of 2-cyclopentenylnaphthalenes II and X (runs 32 and 42), as well as for (runs 44 and 46) 1-cyclohexylnaphthalene (XIV) and the unconjugated 1-cyclohexenylnaphthalene (IX). The slightly higher value of k_2 (run 38) for the conjugated 1-cyclohexenylnaphthalene (III) as compared to values for the latter pair may be ascribed to some overlapping of the first and second linearities in the curve for this compound.[20] The curve for VII is nearly superimposable on those for XIII and XIV, despite the fact that VII is a *bona fide* naphthyl alkene.[21] Though lack of material

(19) Since studies with varying amounts of catalyst and investigations of the time dependence of concentrations of hydrocarbons were not made, this really must be considered a pseudo first-order process.

(20) J. W. Cook and C. A. Lawrence [*J. Chem. Soc.*, 1431 (1936)] reported simultaneous reduction of the cyclohexenyl double bond and the naphthalene ring in preparative studies.

(21) This was the first indication that VII has the structure shown rather than that of 5-methyl-1-(1-naphthyl)cyclopentene assigned previously.[5]

prevented checking this point, it seems likely that preferential hydrogenation of the naphthalene ring (rather than of the cycloalkenyl double bond) occurs in VII.

With assignment of the second linearity to exclusive reduction of the naphthalene moiety, one thence must ascribe the first linearity (where present) to reduction of the alkenyl double bond plus, in general, some simultaneous reduction of the naphthalene moiety. Except for the initial portion of the curve where reduction–activation of the platinum oxide catalyst occurs, one may represent the slope of the kinetic curve at any point by the semiempirical equation (1) that follows

$$\frac{d \log(p_0/p)}{dt} = k_A g_A + k_N g_N \qquad (1)$$

where k_A is an inherent partial rate constant referring to reduction of the alkenyl double bond only, k_N is an inherent partial rate constant referring to reduction of the naphthalene ring only, and g_A and g_N are parameters which vary with t and with the hydrocarbon used. g_A and g_N may take values ≥ 0. Interest and simplicity are attached to those periods of time when both g_A and g_N remain effectively constant, for then one obtains a simple integral equation (2) for a first-order reaction.

$$\log(p_0/p) = (k_A g_A + k_N g_N)t \qquad (2)$$

Thus, during the second linearity we take $g_A = 0$ and $g_N = 1$, *i.e.*, $k_N = k_2'$. The case corresponding to $g_A = g_N = 1$ for the first linearity has been discussed by Klemm and Hodes,[4] who noted that under such circumstances extrapolation of the second linearity to $t = 0$ would give an intercept corresponding precisely to that amount of hydrogen required for the blank plus reduction of the alkenyl double bond, *i.e.*, $k_A + k_N = k_1'$. In such case the naphthyl and alkenyl moieties appear to act independently. For the case where $0 < g_A < 1$ and $g_N > 1$, the naphthyl moiety may be considered to usurp some of the catalytic sites otherwise open to the alkenyl moiety. Generally one would expect this situation to lead to the result $k_1' < k_A + k_N$ and to a low value for the intercept. On the other hand, for $g_A > 1$ and $0 < g_N < 1$, the alkenyl moiety may be considered to usurp catalytic sites otherwise open to the naphthyl moiety. Again such situation should lead to the result $k_1' > k_A + k_N$ and to a high value for the intercept. Examination of Table I shows that, as expected (except in a few cases), large values for the intercept (at 29.9°) are associated with large values of k_1, and vice versa.

Examination of Table I also shows the effects of structural factors in the hydrocarbon on k_1. Using only data for the reaction temperature 29.9°, it is apparent that k_1 decreases with increasing substitution on the alkenyl double bond.[22,23] Thus (for values of k_1), in solvent P_1, monosubstituted alkenes (k_1 = 21–25.3; runs 22, 24) > trisubstituted alkenes (7.4–11.5; runs 3, 9, 15, 19); in P_2, mono- (19.1; run 49) > tri- (9.5–9.8; runs 13, 16) > tetra- (0; run 17); in A_1, di- (13.3; run 44) > tri- ($\leq$9.1; runs 27, 35, 38, 41); and in A_2, di- (12.9; run 42) > tri- (7.9–10; runs 31, 32, 40). Comparing values of k_1 for the same alkene run in two different solvents, both at 29.9°, one can get an estimate of the relative effect on k_1 of the solvent. Taking P_1 as the standard solvent for comparison one gets k_1 (in P_1) = 1.1 k_1 (in P_2); *cf.* runs 13, 15; 24, 49 = 1.27–1.46 k_1 (in A_1); *cf.* runs 3, 27; 9, 35 = 1.04–1.30 k_1 (in A_2); *cf.* runs 3, 31; 9, 32; 15, 40. On this basis one obtains for our compounds the relative specific rates k_1 in solvent P_1 of monosubstituted alkenes (21–25) > disubstituted alkenes (13–20) > trisubstituted alkenes (up to 12) > tetrasubstituted alkenes (0).

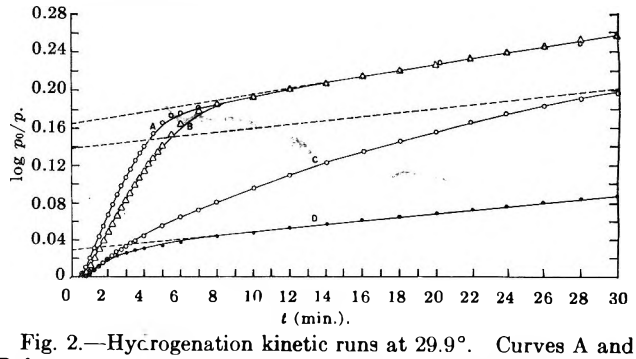


Fig. 2.—Hydrogenation kinetic runs at 29.9°. Curves A and B for 1-(2-naphthyl)cyclopentene (II) in P_1 propionic acid and in A_1 acetic acid, respectively; curve C for 1-(1-naphthyl)cycloheptene in A_1 acetic acid; curve D for 1-cyclohexylnaphthalene in A_1 acetic acid.

Double bond migration to form more stable alkenes has been reported[22] to occur on various catalysts in the presence of hydrogen. Comparison of runs 32 and 42 shows that in the 2-cyclopentenylnaphthalene system (where the conjugated isomer II should be considerably more stable[24] than the nonconjugated one X) k_1 for X is greater than for II. Although these data do not militate against any bond migration of the type X → II prior to hydrogenation, it is clear that if such migration does occur its rate cannot be enormously faster than that for hydrogenation of X directly. The situation is even clearer in the 1-cyclohexenylnaphthalene system (IX, III; compare runs 43–45 with 37–39, respectively) where k_1 is nearly three times as large for the unconjugated arrangement as for the conjugated one. In this case, however, because of appreciable twisting around the pivotal bond[24] there may be little, if any, increase in stability to be gained by the transformation of IX → III.

In solvent P_1 at 29.9° (runs 9, 15, 16, and 24), one observes the order of reactivity, as based on conjugated alkenyl substituents in the 2-naphthyl position, vinyl >> cyclopentenyl $\geq$ cyclohexenyl $\geq$ cycloheptenyl (estimated). Also in A_1 at 29.9° (runs 22, 27, 38, and 41) one obtains the order, for substituents in the 1-naphthyl position, vinyl (estimated) >> cyclopentenyl > cyclohexenyl > cycloheptenyl. These orders are consistent with bulkiness of the groups, but apparently not with conjugative powers of the groups as measured by polarographic reduction and ultraviolet spectra.[25] In addition, for P_1 solvent one estimates, for the isomeric conjugated 1- and 2-alkenyl naphthalenes, the order cycloheptenyl (>2.5) > cyclohexenyl (1.6–2.2) > cyclopentenyl (1.1) > vinyl (0.83) for the ratio k_1 (2 isomer) to k_1 (1 isomer). The values near 1.0 for the vinyl

(22) G. C. Bond, "Catalysis by Metals," Academic Press, New York, N. Y., 1962, Chapter 11.

(23) B. B. Corson in "Catalysis," Vol. III, P. H. Emmett, Ed., Reinhold Publishing Corp., New York, N. Y., 1955, pp. 89–90.

(24) Compare ultraviolet absorption spectra as reported by L. H. Klemm, H. Ziffer, J. W. Sprague, and W. Hodes, *J. Org. Chem.*, **20**, 190 (1955), and in ref. 8.

(25) See discussion in L. H. Klemm, C. D. Lind, and J. T. Spence, *ibid.*, **25**, 611 (1960).

and cyclopentenyl cases are consistent with the postulation that in these compounds there is little energetic difference to the attainment of coplanarity (assumed to be desirable for most facile adsorption)[4] onto the catalytic surface between the corresponding 1 and 2 isomers. Steric hindrance to attainment of coplanarity in the 2 isomers should be less than in the 1 isomers for the cyclohexenyl and cycloheptenyl pairs, however. The slower rate of hydrogenation of VIII as compared to IV (runs 15 and 19) seems to be ascribable to steric hindrance effects only (either greater hindrance to the attainment of coplanarity in VIII or hindrance to adsorption due to the sidewise projecting methyl group in this compound, or both).[24]

Syntheses of Jasmone and the Related Compounds. I. Preparation of Dihydrojasmone and the Homologs from γ,γ-Dialkylparaconic Acids[1]

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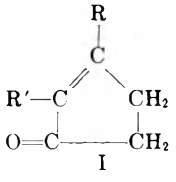
Received October 7, 1963

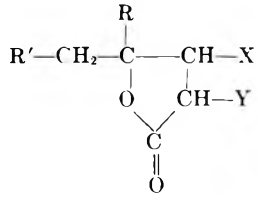
γ,γ-Dialkylparaconic acids (III) were synthesized by hydrolysis of γ,γ-dialkyl-α,β-dicarbethoxybutyrolactones (IV), or by means of lactonization of the Stobbe half-esters (IX). The butyrolactones (IV) were obtained by the condensation of ethyl β,β-dialkylglycidates (V) with sodiomalonate. Treatment of the paraconic acids (III) with polyphosphoric acid gave the corresponding 2,3-dialkyl-2-cyclopenten-1-ones (I), including dihydrojasmone. As by-products, unsaturated dibasic acids (VII) and acid anhydrides (VIII) were separated.

A new route to dihydrojasmone (I, R = CH_3 and R′ = C_5H_{11}) and its homologs from lactonic intermediates (III and IV) was studied. The cyclopentenones (I) previously have been obtained by dehydration of γ-butyrolactones (II),[2-8] but lactonic acids (III) or esters (IV), which can be prepared more readily than II, were found also to be converted into I in good yields. A number of cyclopentenones (I) were synthesized by this procedure.

The paraconic acids (III) were obtained in two ways. The first route involves the reaction of ethyl γ,γ-dialkylglycidates (V) with sodiomalonate.[9]

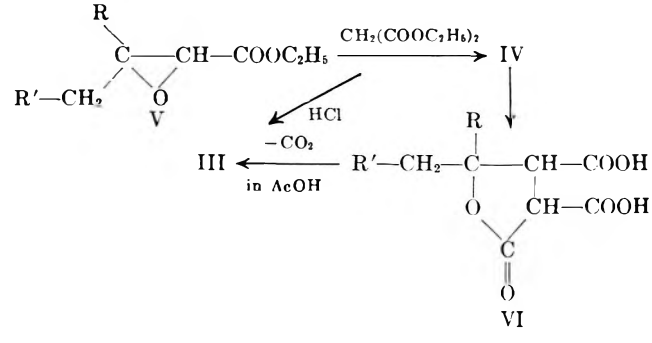


I



II, X = Y = H
III, X = COOH, Y = H
IV, X = Y = $COOC_2H_5$

In this reaction 70–80% yields of γ-methyl-γ-alkyl-α,β-dicarbethoxybutyrolactones (IV) were obtained. The new lactone diesters (IV) are listed in Table II. The lactone diesters (IV) were converted into the paraconic acids (III) by means of hydrolysis to VI followed by decarboxylation.[10] Pyridine[10] or 20% sulfuric acid,[11] when used as a decarboxylating agent, afforded the paraconic acids (III) in yields of 40–60%. Glacial



acetic acid was found to give much better yields of 70–80%. The paraconic acids[12] (III) were obtained, however, in one step from the lactone diesters (IV) by the action of concentrated hydrochloric acid in 78% yield.

Hydrolysis of the lactone diesters (IV) in the presence of excess of 5 *N* sodium hydroxide followed by decarboxylation gave unsaturated dibasic acids (VII) through the fission of the lactone ring.

(1) Presented at the 14th Annual Meeting of the Chemical Society of Japan, Tôkyô, April, 1961.

(2) R. L. Frank, P. G. Arvan, J. W. Richter, and C. R. Vanneman, *J. Am. Chem. Soc.*, **66**, 4 (1944).

(3) F. B. LaForge and W. F. Barthel, *J. Org. Chem.*, **10**, 222 (1945).

(4) R. L. Frank, R. Armstrong, J. Kwiatek, and J. A. Price, *J. Am. Chem. Soc.*, **70**, 1379 (1948).

(5) M. Elliott, *J. Chem. Soc.*, 2231 (1956).

(6) C. Rai and S. Dev, *Experientia*, **11**, 114 (1955); *J. Indian Chem. Soc.*, **34**, 266 (1957).

(7) E. Demole, E. Lederer, and D. Mercier, *Helv. Chem. Acta*, **45**, 685 (1962).

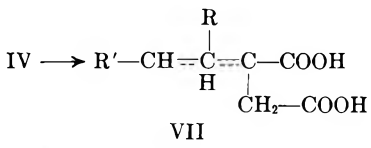
(8) L. Givaudan, German Patent 639,455 (1936); *Chem. Abstr.*, **31**, 1434 (1937).

(9) The reaction of β,β-dimethylglycidate with sodiomalonate has been recorded. See A. Haller and G. Blanc, *Compt. rend.*, **142**, 1471 (1906); G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem. USSR*, **7**, 2373 (1937); *Chem. Abstr.*, **32**, 2099 (1938). The reaction by the carbanion of malonate occurred at the α-position of glycidate. However, R. E. Parker, *Chem. Rev.*, **59**, 737 (1959), described that anions from amines combined with the β-carbon, while Y. Liwschitz, Y. Rabinsohn, and D. Perera, *J. Chem. Soc.*, 1116 (1962), showed the α-attack by ammonia. The present results of the reaction sequences confirmed the α-attack by malonate.

(10) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(11) S. F. Birch and J. F. Thorpe, *J. Chem. Soc.*, 1821 (1922).

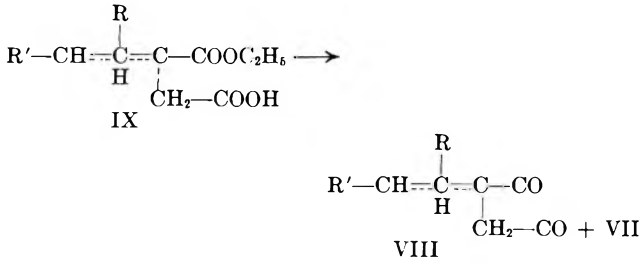
(12) Infrared spectra of the neat paraconic acids (III) have a single carbonyl band at about 1735 $cm.^{-1}$. Absorption in chloroform showed two bands at 1780–1755 $cm.^{-1}$ for lactone carbonyl and at 1720–1700 $cm.^{-1}$ for carboxylic acid carbonyl, respectively. Ethyl γ-methyl-γ-hexylparaconate have a lactone carbonyl band at 1776 $cm.^{-1}$ and an ester carbonyl band at 1729 $cm.^{-1}$. The lowering of the lactone carbonyl frequency of neat γ,γ-dialkylparaconic acids (III) may be due to intermolecular hydrogen bonding. See C. Katsuta and N. Sugiyama, *Bull. Chem. Soc. Japan*, **35**, 1194 (1962).



VII

The second route to the paraconic acids (III) is a lactonization of β,γ- or γ,δ-unsaturated acids (IX) which were readily prepared by the Stobbe condensation[5,13] of dialkyl ketones with diethyl succinate. This lactonization was effected by the action of hydrochloric acid[11] or hydrogen bromide in aqueous acetic acid.[14]

When the Stobbe half-esters (IX)[15] were distilled, corresponding acid anhydrides (VIII) were produced in varying amounts. Under more drastic conditions of distillation, the half-esters (IX, R = CH_3 and R′ = C_4H_9) were completely converted into a mixture of 64%



IX

VIII

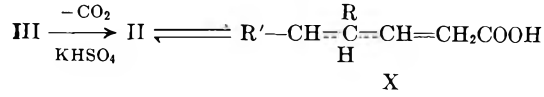
of the acid anhydrides (VIII) and 35% of unsaturated dibasic acids (VII). VII and VIII also could be converted into the paraconic acids (III) by the action of concentrated hydrochloric acid or hydrogen bromide in acetic acid.

Cyclopentenones (I) were obtained in high yields by the treatment of the paraconic acids (III) with polyphosphoric acid.[16] Reaction of γ-methyl-γ-hexylparaconic acid (III, R = CH_3 and R′ = C_5H_{11}) gave a mixture containing 65% of dihydrojasmone (I, R = CH_3 and R′ = C_5H_{11}),[5,6,13,17,18] 28% of dibasic acid (VII, R = CH_3 and R′ = C_5H_{11}), and 4% of acid anhydride (VIII, R = CH_3 and R′ = C_5H_{11}). Both recovered dibasic acid and acid anhydride were again lactonized to give γ-methyl-γ-hexylparaconic acid and subsequently subjected to cyclization. Such treatment, when repeated, gave after all 80% of dihydro jasmone.

It appeared that the decarboxylation preceded the cyclization. When the reaction was stopped at the early stage, γ-methyl-γ-decanolactone (II, R = CH_3 and R′ = C_5H_{11}) was isolated in fair yields along with the cyclopentenone (I).

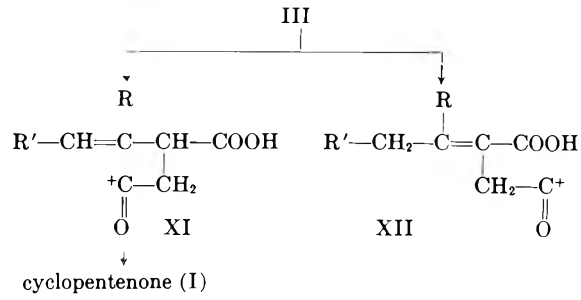
Other cyclopentenones (I) were prepared similarly. The physical constants together with yields of these compounds are listed in Table I.

The decarboxylation of γ-methyl-γ-hexylparaconic acid (III, R = CH_3 and R′ = C_5H_{11}) to γ-methyl-γ-decanolactone (II, R = CH_3 and R′ = C_5H_{11}) and the lacto–enoic tautomerism[19] of the γ-butyrolactone and 4-methyldec-3(or 4)-enoic acid (X, R = CH_3 and R′ = C_5H_{11}) were observed also in this case.



X

As to the mechanism for the cyclodehydration[20] of γ,γ-dialkylparaconic acid (III) with polyphosphoric acid, lactone ring opening and simultaneous elimination of water might be included as one of the possibilities. Thus the acyl cations (XI) undergo intramolecular condensation by a Friedel–Crafts type reaction to give cyclopentenone (I) with the elimination of carbon dioxide. As a side reaction, XI and XII gave unsaturated dibasic acids (VII), which could be separated from the cyclodehydration products by an alkali extraction.



cyclopentenone (I)

TABLE I

2,3-DIALKYL-2-CYCLOPENTENONES (*I*)

R	R′	B.p., °C. (mm.)	Yield, %	$n^{20}D$
CH_3	CH_3	110 (35)	78.2	1.4830
CH_3	C_2H_5	96 (35)	63.1	1.4830
CH_3	C_3H_7	98 (14)	80.9	1.4811
CH_3	C_4H_9	123 (18)	78.7	1.4817
CH_3	C_5H_{11}	91 (2)	80.4	1.4807
CH_3	C_6H_{13}	143 (18)	81.2	1.4847
CH_3	*i*-C_3H_7	100 (26)	85.2	1.4812
CH_3	*i*-C_4H_9	112 (18)	85.2	1.4807
C_2H_5	CH_3	95 (16)	81.2	1.4850

Experimental[21]

Ethyl β-Methyl-β-alkylglycidates (V).—Following Johnson's method,[22] a mixture of 22.8 g. (0.2 mole) of 2-heptanone, 24.5 g. (0.2 mole) of ethyl chloroacetate, and 22.4 g. of potassium *t*-butoxide in 160 ml. of dry *t*-butyl alcohol was stirred at 10–15° for 1 hr., and after addition of ice–water the reaction mixture was extracted with ether. The products obtained on evaporation of the ethereal solution were distilled under reduced pressure to give 30 g. (75%) of ethyl β-methyl-β-pentylglycidate (V, R = CH_3 and R′ = C_4H_9), b.p. 142° (28 mm.), $n^{23}D$ 1.4339; infrared: 1755 and 1730 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.11; H, 10.19.

In a similar way, 75% (based on 5-methyl-2-pentanone) of ethyl β-methyl-β-isobutylglycidate was obtained, b.p. 119° (28 mm.), $n^{23}D$ 1.4302.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.71; H, 9.71.

(13) W. S. Johnson and G. H. Daub, "Organic Reaction," Coll. Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 26. The product of the condensation is a mixture of the β,γ- and γ,δ-unsaturated acids (see ref. 5).

(14) J. H. Amin and S. C. Bhattacharyya, Indian Patent 64,959 (August 3, 1960); *Chem. Abstr.*, **55**, 2521 (1961).

(15) Ultraviolet spectra (ref. 5) of the Stobbe half-esters revealed that at the first step of the Stobbe condensation half-esters rich in the α,β-unsaturated type were produced, but during the distillation course their content decreased.

(16) R. F. Jameson, *J. Chem. Soc.*, 752 (1959).

(17) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IIA, Elsevier Publishing Co., Amsterdam, 1953, pp. 96, 101.

(18) J. H. Amin, R. K. Razden, and S. C. Bhattachryya, *Perfum. Essent. Oil Record*, **49**, 502 (1958).

(19) W. S. Johnson and R. H. Hunt, *J. Am. Chem. Soc.*, **72**, 935 (1950).

(20) *Cf.* S. Dev, *Chem. Ind.* (London), 1071 (1954).

(21) Microelemental analyses were carried out by Miss Kenko Ogawa of this laboratory.

(22) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4395 (1953).

From 2-pentanone and 2-octanone the corresponding glycidates were obtained in 81% (lit.[23] 57%) and 76% (lit.[24] 41%) yields, respectively.

Reaction of Ethyl β-Methyl-β-pentylglycidate with Malonic Ester.—A mixture of 13.6 g. (0.2 mole) of sodium ethoxide, 37.5 g. (0.25 mole) of diethyl malonate in 120 ml. of anhydrous ethanol, and 20 g. (0.1 mole) of ethyl β-methyl-β-pentylglycidate (V, R = CH_3 and R′ = C_4H_9) was refluxed for 25 hr. The mixture was acidified and taken up in ether. The ether layer was washed with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated. Distillation of the residue yielded 12 g. (38% based on the glycidate) of γ-methyl-γ-pentyl-α,β-dicarbethoxybutyrolactone (IV, R = CH_3 and R′ = C_4H_9), b.p. 172° (2 mm.); infrared: 1785 cm.$^{-1}$ (lactone C=O), 1740 and 1725 cm.$^{-1}$. (ester C=O). Also yielded was the unchanged glycidate (11g.), which was treated again with the freshly prepared sodiomalonate solution. Thus in total, 23.3 g. (74%) of the lactone diesters were obtained.

Other lactone diesters (IV), obtained similarly, are given in Table II.

TABLE II

γ-METHYL-γ-ALKYL-α,β-DICARBETHOXYBUTYROLACTONES (IV) (R = CH_3)

R′	B.p., °C. (2 mm.)	$n^{25}D$	Yield,[a] %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_2H_5	152	1.4534	81	58.73	7.75	58.84	7.76
i-C_3H_7	153	1.4520	66	59.98	8.05	60.33	8.12
C_4H_9	172	1.4531	72	61.16	8.35	61.47	8.44
C_5H_{11}	180	1.4542	70	62.17	8.59	62.57	8.77

[a] These yields are the total of the repeated reaction products.

Saponification of Lactone Diesters (IV) with 1 *N* Sodium Hydroxide. Paraconic Acids (III) *via* Lactonedicarboxylic Acids (VI).—A mixture of 100 ml. of a 1 *N* sodium hydroxide solution and 15.7 g. (0.05 mole) of γ-methyl-γ-pentyl-α,β-dicarbethoxybutylrolactone (IV, R = CH_3 and R′ = C_4H_9) was refluxed for 4–5 hr. and neutralized to pH 7–6.5 with dilute sulfuric acid. When the solvent was removed *in vacuo*, there was obtained in oily state the lactonedicarboxylic acid (VI), which could not be crystallized. A solution of this oil in 50 ml. of glacial acetic acid was boiled for 30 min. when vigorous evolution of carbon dioxide was observed. Acetic acid was removed and to the residue 150 ml. of water was added. The precipitated light brown material was recrystallized from a mixture of water and ethanol (9:1) to give 4.6 g. (43% based on the lactone diesters) of γ-methyl-γ-γ-pentylparaconic acid (III, R = CH_3 and R′ = C_4H_9), m.p. 177°.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.86; H, 8.53.

The evaporated residue of the mother liquor formed a tarry brown oil, which was hydrolyzed repeatedly with 1 *N* sodium hydroxide to afford 3.5 g. (33.5%) of the paraconic acid. In total, 8.1 g. (76.5%) of γ-methyl-γ-pentylparaconic acid was obtained.

Hydrolysis of Lactone Diesters (IV) with Concentrated Hydrochloric Acid. Paraconic Acids (III).—A mixture of 15.7 g. (0.05 mole) of γ-methyl-γ-pentyl-α,β-dicarbethoxybutyrolactone (IV, R = CH_3 and R′ = C_4H_9) and 70 ml. of concentrated hydrochloric acid was vigorously refluxed for 5 hr. Upon cooling to room temperature, the mixture solidified in a dark brown material, which, recrystallized from water–ethanol (9:1), gave 8.4 g. (78%) of α-methyl-γ-pentylparaconic acid (II, R = CH_3 and R′ = C_4H_9), m.p. and m.m.p. 177°. The infrared spectra also showed identity with the compound described in the preceding paragraph.

Hydrolysis of Lactone Diesters (IV) with an Excess Alkali. Unsaturated Dibasic Acids (VII).—A mixture of 100 ml. of 5 *N* sodium hydroxide and 15 g. (0.05 mole) of γ-methyl-γ-isobutyl-α,β-dicarbethoxybutyrolactone (IV, R = CH_3 and R′ = i-C_3H_7) was refluxed for 4–5 hr. and then acidified to pH 7–6.5 with dilute sulfuric acid. After most of the solvent was evaporated *in vacuo*, the residue was taken up in ether.

(23) V. F. Martynov and Ua. A. Kastrom, *J. Gen. Chem. USSR*, **26**, 61 (1956); *Chem. Abstr.*, **49**, 9606 (1955).

(24) E. Fourneau and J. R. Billeter, *Bull. soc. chim. France*, [5]**6**, 1616 (1939).

Evaporation of the solvent left 7.3 g. of a pale yellow cake. The solid, dissolved in 50 ml. of pyridine, was refluxed for 2 hr. for the sake of decarboxylation, and the solution was evaporated. The residue was taken up in ether and washed with dilute hydrochloric acid and water. After removing the solvent *in vacuo*, the residue was recrystallized from water to give 4.4 g. [42% based on the lactone diesters (IV)] of 3-carboxyl-4,6-dimethyl-3(or 4)-hexenonic acid (VII, R = CH_3 and R′ = C_4H_9), m.p. 158°; infrared: 1680 cm.$^{-1}$ (C=O); 1610 cm.$^{-1}$ (C=C).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.21; H, 8.13.

Stobbe Half-Esters (IX).—These compounds were prepared by the condensation of dialkyl ketones with diethyl succinate in the presence of potassium *t*-butoxide as described in the literature.[13] From 11.4 g. of 2-heptanone and 26.1 g. of diethyl succinate, 21.8 g. (90%) of crude Stobbe half-esters (IX, R = CH_3 and R′ = C_4H_9) were obtained. Other half-esters were prepared similarly.

Distillation of the Half-Esters (IX).—Distillation of 8.0 g. of the half-esters (IX, R = CH_3 and R′ = C_4H_9) under 2.5 mm. at 145–155° gave 7.9 g. of a mixture of the half-esters (IX) and acid anhydrides (VIII). The mixture was dissolved in 50 ml. of ether and extracted with a 6% potassium carbonate solution. The ether layer was washed with water, dried, and evaporated. Distillation of the residue yielded 1.5 g. (18.7%) of acid anhydride (VIII, R = CH_3 and R′ = C_4H_9), b.p. 145° (2.5 mm.), $n^{21}D$ 1.4836; infrared: 1828 (m) and 1760 (s) cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.52; H, 8.21.

The combined alkaline extracts were acidified. The half-esters were taken up in ether, dried over anhydrous sodium sulfate, and evaporated. Distillation of the residue afforded 6.4 g. (80%) of half-esters (IX, R = CH_3 and R′ = C_4H_9), b.p. 142° (0.8 mm.), $n^{21}D$ 1.4639. The infrared spectrum of this material was identical with that of an authentic sample.[5] The ultraviolet measurement[5] showed that the half-esters contained 77% of an alkylidene compound.

When the distillation was carried out at 210° under 70 mm. in the course of 2 hr., 8.0 g. of the half-esters gave 5.2 g. (64%) of acid anhydride (VIII), 58% of which consisted of an alkylidene compound. The residue gave, on recrystallization from a mixture of water and ethanol (1:5), an isomeric mixture of dibasic acids (VII, R = CH_3 and R′ = C_4H_9), m.p. 117°.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.71; H, 8.40.

Hydrolysis of the Half-Esters (IX) with an Aqueous Potassium Hydroxide Solution. Unsaturated Dibasic Acids (VII).—A mixture of 12.1 g. (0.05 mole) of half-esters (IX, R = CH_3 and R′ = C_4H_9) and 10 g. (0.18 mole) of potassium hydroxide in 300 ml. of water was heated for 3 hr. at 70–80°. White precipitates separated on acidification with hydrochloric acid were recrystallized from water to give 9.7 g. (90%) of dicarboxylic acids (VII, R = CH_3 and R′ = C_4H_9), m.p. 123°; infrared: 1700 and 1686 cm.$^{-1}$ (C=O); ultraviolet: λ_{max} 223 mμ (ε 8100) [lit.[5] for VII, R = CH_3 and R′ = H: λ_{max} 221 mμ (ε 9350) in ethanol]. The alkylidene and alkenyl type compounds were calculated[5] as to exist in a ratio of 86:14.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.80; H, 8.56.

Lactonization of the Stobbe Half-Esters (IX) into Paraconic Acids (III).—Refluxing of half-esters with concentrated hydrochloric acid[13] or with hydrobromic acid in aqueous acetic acid[14] gave the corresponding paraconic acids in good yields. New γ,γ-dialkylparaconic acids prepared in this way are shown in Table III.

TABLE III

γ,γ-DIALKYLPARACONIC ACIDS (III) (R = CH_3)

R′	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_2H_5	144	66	58.05	7.58	58.23	7.55
C_3H_7	132	88	59.98	8.05	60.26	8.05
C_4H_9	177	84	61.66	8.47	61.86	8.53
C_5H_{11}[11]	167	85	...	...	...	...
C_6H_{13}	183	82	64.44	9.15	64.79	9.19
t-C_3H_7	170	95	59.98	8.05	60.22	8.09
t-C_4H_9	156.5	95	61.66	8.47	61.93	8.63

Lactonization of the Acid Anhydrides (VIII) or the Dibasic Acids (VII) into the Paraconic Acids (III).—The refluxing of the acid anhydrides (VIII) or the dibasic acids (VII) with concentrated acid or with hydrobromic acid in aqueous acetic acid afforded the paraconic acids (III) in quantitative yield.

Ethyl γ-Methyl-γ-hexylparaconate.—Refluxing of 4.6 g. of γ-methyl-γ-hexylparaconic acid with 30 ml. of benzene and 10 ml. of ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate gave the ester in a quantitative yield, b.p. 148–149° (1.5 mm.), $n^{21}D$ 1.4578.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.70; H, 9.49.

Decarboxylation of Paraconic Acids (III).—The decarboxylation was carried out following the procedure of Johnson and Hunt.[19] A mixture of 6 g. (0.028 mole) of γ-methyl-γ-pentylparaconic acid (III, R = CH_3 and R′ = C_4H_9) and 0.5 g. of potassium hydrogen sulfate was treated at 220–235° for 2 hr. and there were obtained 2.4 g. of γ-methyl-γ-nonanolactone (II, R = CH_3 and R′ = C_4H_9), b.p. 143° (18 mm.) [reported b.p.[25] 129–131° (13 mm.)], $n^{18}D$ 1.4527, and 0.8 g. of 4-methyl-3(or 4)-nonenoic acid (X, R = CH_3 and R′ = C_4H_9), b.p. 145° (3 mm.), $n^{18}D$ 1.4537; infrared: 1695 cm.$^{-1}$ (C=O) and 1625 cm.$^{-1}$ (C=C).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.61; H, 10.51.

The lacto-enoic tautomerism was observed with these compounds as in the literature.[19]

Cyclodehydration of γ-Methyl-γ-hexylparaconic Acid.—To 6 ml. of polyphosphoric acid warmed on an oil bath at 100–120° was added portionwise 11.4 g. (0.05 mole) of γ-methyl-γ-hexylparaconic acid (III, R = CH_3 and R′ = C_4H_9). After all of the solid had dissolved, the mixture was heated gradually for about 30 min. under reduced pressure to a final temperature of 150°. During this period vigorous evolution of carbon dioxide was observed. After the decomposition reaction subsided, the temperature was raised gradually during about 4 hr. to 190°, when crude cyclopentenone was distilled. From the ethereal solution of this crude cyclopentenone, acidic material was removed with a 5% potassium carbonate solution. The ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. On redistillation of the crude cyclopentenone 5.6 g. (67%) of 2-pentyl-3-methyl-2-cyclopentenone-1 (dihydrojasmone) (I, R = CH_3 and R′ = C_5H_{11}) was obtained, b.p. 90–91° (2 mm.) [reported[2] b.p. 91° (2 mm.)], $n^{20}D$ 1.4855 (reported[5] $n^{20}D$ 1.4851); semicarbazone, m.p. 173° (lit.[5] m.p. 174°); 2,4-dinitrophenylhydrazone, m.p. 121.5 (lit.[6] m.p. 123°). This ketone, semicarbazone, and 2,4-dinitrophenylhydrazone gave correct analyses. Infrared spectra of this ketone was identical with that of the authentic sample. The higher boiling fraction gave 4 g. of the acid anhydride, b.p. 143° (2 mm.), $n^{21}D$ 1.4856 (lit.[5] $n^{20}D$ 1.4851); infrared: 1830 (m) and 1780 (s) cm.$^{-1}$ (C=O).

The combined alkaline extracts were acidified with dilute hydrochloric acid, and the precipitated crystals were recrystallized from water–ethanol (5:1) to give 3.2 g. (28%) of dibasic acids (VII, R = CH_3 and R′ = C_5H_{11}), m.p. 153°; infrared: 1698 cm.$^{-1}$ (C=O); ultraviolet: λ_{max} 223 mμ (ε 3000). The alkylidene and alkenyl compounds were calculated[5] as to exist in a ratio of 30:70.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 61.66; H, 8.47. Found: C, 61.79; H, 8.56.

Both recovered dibasic acid and acid anhydride were repeatedly lactonized by means of hydrogen bromide in acetic acid to γ-methyl-γ-hexylparaconic acid which was subjected to cyclodehydration to give 1.1 g. of the cyclopentenone. After all, 6.7 g. (80%) of 2-pentyl-3-methyl-2-cyclopentenone-1 was obtained.

Other cyclopentenone derivatives are listed in Table II.

Similar treatment of 9.2 g. of γ-methyl-γ-decanolactone (II, R = CH_3, R′ = C_5H_{11}, X = H, and Y = H) with polyphosphoric acid[6] afforded 7.5 g. (90%) of dihydrojasmone. The corresponding ethyl paraconate and Stobbe half-esters gave inferior yields, *i.e.*, 43 and 29%, respectively.

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Formation of an Organotin–Nitrogen Bond. II.[1] Syntheses of Tris(trialkyltin)amines

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Tris(trialkyltin)amines, $(R_3Sn)_3N$, were prepared by the reaction of lithium amide or sodium amide with trialkyltin halide. Infrared absorption of these compounds at 728–712 cm.$^{-1}$ was assigned to an antisymmetric stretching vibration of an Sn–N–Sn linkage. The decomposition of these compounds in air revealed that tris(trimethyltin)amine was converted to trimethyltin hydroxide, while tris(triethyltin)- and tris(tri-*n*-propyltin)-amines were converted to trialkyltin carbonate *via* bis(trialkyltin) oxide. Except for bis(trimethyltin) oxide, bis(trialkyltin) oxides absorb atmospheric carbon dioxide to afford trialkyltin carbonates.

Bullard, *et al.*,[2] reported a product they assumed to be tris(trimethyltin)amine, $[(CH_3)_3Sn]_3N$, being produced by the reaction of (trimethylstannyl)sodium and bromobenzene in liquid ammonia, but they did not isolate nor characterize the compound.

Recently it has been noted in a short communication that tris(trimethyltin)amine was produced by treatment of trimethyl(dimethylamino)tin with ammonia, but experimental details were not described.[3]

These compounds have now been prepared by the reaction of the corresponding trialkyltin halide with lithium or sodium amide in liquid ammonia or ether and were isolated analytically pure by vacuum distillation in nitrogen atmosphere.

Lithium amide reacts with trialkyltin chloride in liquid ammonia, diethyl ether, and tetrahydrofuran, while sodium amide reacts only in liquid ammonia but not in diethyl ether, tetrahydrofuran, or pyridine at the respective refluxing temperatures.

It is known that the formation of a silicon compound having the structure of $(R_3Si)_3N$ type[3b] is very difficult owing to steric hindrance. In the case of tin compounds, however, owing presumably to the greater radius of the tin atom, the nitrogen atom could find a vacancy among the three tin atoms so that $(R_3Sn)_3N$ type compounds were obtained readily.

Evidence for the $(R_3Sn)_3N$ structure of these compounds is based upon, besides the coincidence of analyses and the absence of an infrared absorption of an N–H bond, the fact that these compounds liberate

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(3) (a) K ones and M. F. Lappert, *Proc. Chem. Soc.*, 358 (1963); (b) NOTE ADDED IN PROOF.—A silicone compound of the $(R_3Si)_3N$ type was reported by U. Wannagat and O. Brandstätter, *Angew. Chem.*, **75**, 345 (1963); *Angew., Chem. Intern. Ed. Engl.*, **2**, 263 (1963).

ammonia and the respective nitrogen-free organotin compounds on exposure to air, or give trialkyltin chloride and ammonium chloride with hydrochloric acid.

As soon as tris(trimethyltin)amine was exposed to air, ammonia gas was evolved and white crystals of trimethyltin hydroxide were obtained quantitatively. A similar change was noticed in trimethyl(diethylamino)tin to afford diethylamine and trimethyltin hydroxide. The same air exposure of tris(triethyltin)-amine, tris(tri-*n*-propyltin)amine, and trialkyl(diethylamino)tin (where alkyl groups are ethyl, *n*-propyl, or *n*-butyl), however, resulted in the formation of ammonia or amine and trialkyltin carbonates.

The formation and decomposition of trialkyltin carbonate have not been described precisely. On exposure of bis(triethyltin) oxide to air or dry carbon dioxide, white crystals of triethyltin carbonate were formed as traced by the quantitative weight increase as well as by the infrared observation following the change. Among the mentioned bis(trialkyltin) oxides, however, only the trimethyltin derivative does not react with atmospheric carbon dioxide.

As to the decomposition of the carbonate,[4] it was found that trialkyltin carbonate gives bis(trialkyltin) oxide almost quantitatively on heating at 140–150° for 5 hr. *in vacuo*.

The tris(trialkyltin)amines had a volatility which showed their monomeric structures, and had higher boiling points compared with the corresponding bis-(trialkyltin) oxides supporting their higher molecular weights.

In the spectra of tris(trimethyltin)-, tris(triethyltin), and tris(tri-*n*-propyltin)amine, strong bands which may be associated with an antisymmetric stretching vibration of an Sn–N–Sn linkage were observed at 728, 712, and 712 cm.$^{-1}$, respectively, but no band at 3300–3500 cm.$^{-1}$ characteristic of N–H stretching was present. In silicon compounds, the band at 934 cm.$^{-1}$ is assigned to the antisymmetric stretching vibration of Si–N–Si for hexamethyldisilazane. This is observed at a frequency lower than that of Si–O–Si for hexamethyldisiloxane at 1055 cm.$^{-1}$.[5] The spectra of bis(trialkyltin) oxide have an intense band at about 775 cm.$^{-1}$ which is assigned to the antisymmetric stretching vibration of Sn–O–Sn link.[6,7] Assuming that antisymmetric stretching vibrations of Sn–N–Sn and Sn–O–Sn linkages for trialkyltin derivatives have a similar relation to these of Si–N–Si and Si–O–Si linkages, and, considering the hydrolytic observations, it may be possible to assign the strong band at 728–712 cm.$^{-1}$ in the spectra of tris(trialkyltin) amines to an antisymmetric stretching vibration of an Sn–N–Sn linkage.

No vibration connected with the symmetric stretching of an Sn–N–Sn linkage was detected in a potassium bromide region. This vibration may be expected to occur at a frequency below 400 cm.$^{-1}$, since a symmetric stretching vibration of Si–N–Si occurs at 566 cm.$^{-1}$.[5]

Existence of C–Sn–C symmetric stretching vibrations[8] in the spectrum of tris(trimethyltin)amine at 503 cm.$^{-1}$ showed that trimethyltin group is not planar[9] in this compound. This fact and their volatility may support the covalent character of organotin–nitrogen bonding.

The air decomposition of tris(trialkyltin)amine was also studied by the infrared spectra. Upon exposure of tris(trialkyltin)amine to air, the strong band at 728–712 cm.$^{-1}$ disappeared, in accordance with the progress of the hydrolysis by the atmospheric moisture. At last, tris(trimethyltin)amine was converted into trimethyltin hydroxide whose spectrum had an Sn–O–H deformation vibration at 917 cm.$^{-1}$,[6,10] while tris(triethyltin)- and tris(tri-*n*-propyltin)amine were converted into the corresponding trialkyltin carbonates having characteristic bands of carbonate.[11] In the course of the air decomposition of trialkyltinamino derivatives which give carbonates, only an antisymmetric stretching band of Sn–O–Sn, but no band of an Sn–O–H, was observed during any stage of the reaction. The carbonates are formed apparently *via* the oxides, which in turn seemed to be produced by the hydrolysis of the starting materials with atmospheric moisture. Presumably the transformation of the hydroxide grouping (Sn–O–H) was so fast that the spectra were not observed.

Experimental

Infrared.—The infrared spectra of the liquid samples which were very sensitive to air were measured in a sealed sodium chloride plate (or potassium bromide plate) by dropping the sample from an injector. The decomposition of the compounds in air was performed by exposing them to air on a sodium chloride or potassium bromide plate.

Tris(trimethyltin)amine, $[(CH_3)_3Sn]_3N$. **A.**—To a suspension of 2.3 g. (0.06 mole) of sodium amide powder in 40 ml. of liquid ammonia at about −50°, 11.0 g. (0.045 mole) of trimethyltin bromide[12] (b.p. 160–163°) in 30 ml. of anhydrous ether was added dropwise. After stirring for 2 hr. at about −50°, both ammonia and ether were evaporated. The reaction product was distilled *in vacuo* yielding 4.0 g. (53%) of tris(trimethyltin)amine, b.p. 133–134° (20 mm.), m.p. 22–24°, as white crystalline needles which showed a negative Beilstein test for halogen. All procedures were carried out in a nitrogen atmosphere. The product was stored in sealed ampoules under nitrogen. Infrared absorptions (liquid) appeared at 2980 (m), 2910 (m), 1430 (w), 1295 (w), 1285 (m), 760 (sh), 728 (vs), 674 (sh), 524 (s), and 503 (m) cm.$^{-1}$. On exposure to air, the very strong band at 728 cm.$^{-1}$ disappeared and after 30 sec. new bands came out at 917 and 760 cm.$^{-1}$ instead.

Anal.[1] Calcd. for $C_9H_{27}NSn_3$: N, 2.77; Sn, 70.45. Found: N, 2.77; Sn, 70.53.

As soon as 2.53 g. (0.050 mole) of the substance was exposed to air on a watch glass, ammonia gas was evolved, and 2.70 g. (0.149 mole) of white crystals were obtained. These crystals were identified as trimethyltin hydroxide[10,13] by identical infrared spectra and a mixture melting point. On addition of dilute hydrochloric acid to an ethereal solution of the methyltinamine, trimethyltin chloride and ammonium chloride were obtained from ethereal and aqueous layer, respectively.

B.—A lithium amide suspension prepared from 0.56 g. (0.08 g. atom) of lithium metal and 0.01 g. of ferric nitrate in 50 ml. of liquid ammonia was diluted with 50 ml. of anhydrous ether. The

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suspension was kept at room temperature to evaporate the ammonia and finally was refluxed for 1 hr. to remove a trace of ammonia. To this lithium amide suspension in ether 12.1 g. (0.05 mole) of trimethyltin bromide in 30 ml. of anhydrous ether was added. Refluxing for 3 hr. followed by vacuum distillation gave 7.0 g. (83%) of white crystals, b.p. 130° (14 mm.), m.p. 22–24°.

Tris(triethyltin)amine and **Tris(tri-*n*-propyltin)amine** were prepared also in about 70% yields by an analogous method.

Tris(triethyltin)amine was obtained from triethyltin chloride,[14] b.p. 86–88° (9 mm.), as white crystalline needles, b.p. 192–194° (4 mm.), redistillation, m.p. 21–22°.

Anal. Calcd. for $C_{18}H_{45}NSn_3$: N, 2.22; Sn, 56.38. Found: N, 2.23; Sn, 56.48.

As soon as 2.52 g. (0.0400 mole) of the substance was exposed to air, ammonia was evolved and 2.81 g. (0.0596 mole) of white crystals were obtained. These crystals were identified as triethyltin carbonate by the infrared spectra (1540, 1370, 1070, and 833 cm.$^{-1}$ [11]) and analyses. During air decomposition, a strong band at 775 cm.$^{-1}$ (Sn–O–Sn) appeared, but this disappeared in several minutes.

Tris(tri-*n*-propyltin)amine, prepared from tri-*n*-propyltin chloride,[14] b.p. 122–123° (10 mm.), was a colorless liquid, b.p. 143–145° (0.6 mm.), on redistillation.

Anal. Calcd. for $C_{27}H_{63}NSn_3$: N, 1.85; Sn, 46.98. Found: N, 1.94; Sn, 46.79.

On similar air exposure, from 1.06 g. (0.0140 mole) of the substance, 1.15 g. (0.0207 mole) of pasty viscous oil was obtained. This was identified as tri-*n*-propyltin carbonate by an analogous method.

Trimethyl(diethylamino)tin.[15]—An ether solution of diethylaminolithium prepared from 0.76 g. (0.11 g.-atom) of lithium metal and 6.9 g. (0.05 mole) of *n*-butyl bromide and 4.0 g. (0.055 mole) of diethylamine in 30 ml. of anhydrous ether was added dropwise to a solution of 7.3 g. (0.03 mole) of trimethyltin bromide[12] in 30 ml. of ether. After refluxing for 3 hr., the solvent was distilled and the reaction product was fractionated under atmospheric pressure. A fraction boiling at 156–162°, lit.[15] b.p. 162°, was collected, yielding 4.3 g. (61%). The infrared spectrum of this compound had the characteristic absorptions of the diethylaminotin grouping at 1455, 1372, 1290, 1185, 1170, 1150, 1116, 1075, 1048, 1007, and 872 cm.$^{-1}$. All these bands immediately disappeared on exposure to air and a characteristic band of trimethyltin hydroxide at 917 cm.$^{-1}$ appeared.

Decomposition of Bis(triethyltin) Oxide by Exposure to Air.—On exposing 2.97 g. (0.00694 mole) of bis(triethyltin) oxide[16] (b.p. 142–143° at 13 mm., n^{20}D 1.5005) to air for 12 hr., 3.26 g. of white crystals were obtained. The weight increase of 0.29 g. corresponds to the 0.0066 mole of carbon dioxide. These crystals were identified also as triethyltin carbonate by infrared spectrum, analysis, and decomposition point.

Bis(triethyltin) Oxide from Triethyltin Carbonate.—Upon heating 3.2 g. of triethyltin carbonate at 140–150° *in vacuo*, the white crystals melted with evolution of carbon dioxide. After an additional heating for 5 hr., the product was distilled at 155–156° (20 mm.) to obtain 2.7 g. (93%) of bis(triethyltin) oxide, n^{20}D 1.4990. The infrared spectrum had a strong band at 775 cm.$^{-1}$, but no bands at 1540, 1370, 1070, and 833 cm.$^{-1}$.

Decomposition of Bis(tri-*n*-propyltin) Oxide by Exposure to Air.—On exposing 1.45 g. (0.00283 mole) of bis(tri-*n*-propyltin) oxide[17] (b.p. 151–166° at 5 mm., n^{20}D 1.4917) to air for 12 hr., 1.56 g. of viscous pasty oil was obtained. The weight increase of 0.11 g. corresponds to 0.0025 mole of carbon dioxide. This was identified as tri-*n*-propyltin carbonate by infrared spectrum.

Bis(tri-*n*-propyltin) Oxide from Tri-*n*-propyltin Carbonate.—A 2.9-g. sample of tri-*n*-propyltin carbonate was heated for 5 hr. at about 150° under diminished pressure and the content was distilled at 161–165° (5 mm.) when bis(tri-*n*-propyltin) oxide, n^{20}D 1.4911, was obtained, yielding 2.4 g. (90%). The infrared spectrum had a strong band at 775 cm.$^{-1}$, but no bands at 1540, 1370, and 833 cm.$^{-1}$.

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Condensation of Halophenols with Formaldehyde and Primary Amines[1]

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The reaction of *o*- and *p*-halogen-substituted phenols with formaldehyde and representative primary aliphatic amines was studied. The number of halogen substituents on the phenol and the specific amine used were found to be important factors in determining both the course of the condensation and the stability of the benzoxazines, which were obtained with substituted N,N-bis(hydroxybenzyl)amines and substituted 2-aminomethylphenols.

The Mannich reaction involving phenols, formaldehyde, and primary amines has been used as a convenient source of a variety of compounds. The course of this generally facile condensation is, however, greatly influenced by a number of reaction variables.[4,5] In particular, the size of the *ortho* substituent on the phenol has been shown to play an important role. For example, by merely utilizing the calculated quantities of reactants in the condensation of 2,4-dimethylphenol with formaldehyde and cyclohexylamine, high yields (70–90%) of either 2-cyclohexylaminomethyl-4,6-dimethylphenol (Ia), or 3-cyclohexyl-3,4-dihydro-6,8-dimethyl-2*H*-1,3-benzoxazine (IIa), or bis(3,5-dimethyl-2-hydroxybenzyl)cyclohexylamine (IIIa) can be obtained.[4] Use of 4-*t*-butylphenol in place of 2,4-dimethylphenol, however, resulted in a high yield of a benzoxazine (II) even when the molar ratio of reactants was that calculated for the formation of a bis(hydroxybenzyl)amine (III). In contrast, efforts to prepare benzoxazines (II) from a phenol having an *o*-*t*-butyl substituent were unsuccessful, and only the bis(hydroxybenzyl)amine (III) was obtained.[4]

In view of the striking manner in which the course of the condensation can be shifted by steric factors, it was of interest to determine the effect of varying the electrophilic character of substituents on the phenol. A comparison of *o*-chloro- and *o*-methylphenols in such studies appeared to have attractive possibilities for substantially eliminating steric factors since the chloro and methyl groups are approximately equivalent in size.

(1) This investigation was supported in part by Research Grant CY-5211 from the National Cancer Institute of the Public Health Service. We are also indebted to the University of Utah Research Committee for a research fellowship to E. L. Mortenson.

(2) Department of Chemistry, Arizona State University, Tempe, Ariz.

(3) This paper was abstracted in part from a dissertation presented to the faculty of the University of Utah by E. L. Mortenson in partial fulfillment of the requirements for the Ph.D. degree.

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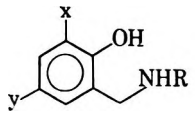
TABLE I

SUBSTITUTED 2-AMINOMETHYLPHENOLS AND N,N-BIS(2-HYDROXYBENZYL)AMINES



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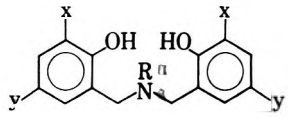


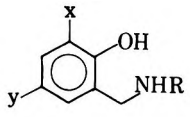
III

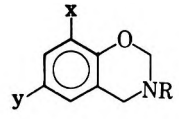
Structure	R	x	y	Yield,[a] %	Recrystn. solvent	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	CH_3	Cl	Cl	61	CH_3OH	191–192	$C_8H_9Cl_2NO$[b]	46.62	46.86	4.40	4.17		
I	C_6H_{11}	Cl	Cl	67	CH_3OH	157–158	$C_{13}H_{17}Cl_2NO$	56.96	57.45	6.25	6.50	5.11	4.70
I	CH_3	Br	Br	73[c]	C_6H_6	194–195	$C_8H_9Br_2NO$	32.57	33.01	3.08	3.39	4.75	4.66
I	C_6H_{11}	Br	Br	90	C_2H_5OH	168–169	$C_{13}H_{17}Br_2NO$	43.00	43.01	4.72	4.75	3.86	3.57
I	$C_6H_5CH_2$	Cl	Cl	72	C_2H_5OH	112–113	$C_{14}H_{13}Cl_2NO$[d]	59.59	59.74	4.64	4.49		
III	CH_3	Cl	Cl	18	CH_3OH	118–119	$C_{15}H_{13}Cl_4NO_2$[e]	47.27	47.45	3.44	3.48		
III	CH_3	Br	Br	88[f]	C_6H_6	129–130	$C_{15}H_{13}Br_4NO_2$	32.23	32.33	2.34	2.68	2.56	2.51
III	CH_3	CH_3	Cl	66	CH_3OH	104–105	$C_{17}H_{19}Cl_2NO_2$	60.02	60.34	5.63	5.97	4.12	4.36
III	C_6H_{11}	CH_3	Cl	53	ligroin	140–141	$C_{22}H_{27}Cl_2NO_2$	64.70	64.55	6.67	6.76		
III	C_6H_{11}	Cl	CH_3	48	ligroin	124–125	$C_{22}H_{27}Cl_2NO_2$	64.70	64.54	6.67	7.09		
III	CH_3	Br	$C(CH_3)_3$	50	C_2H_5OH	122–123	$C_{23}H_{31}Br_2NO_2$	53.82	53.83	6.09	6.12		
III	C_6H_{11}	Br	$C(CH_3)_3$	43	ligroin	167–168	$C_{28}H_{39}Br_2NO_2$[g]	57.84	58.49	6.76	6.70		

[a] In all instances the reactant ratio of phenol–formaldehyde–amine was 2:2:1, that calculated for structure III. The yields given for compounds of structure I were based on this amine. [b] The **hydrochloride** melted at 193–194° after recrystallization from methanol. *Anal.* Calcd. for $C_8H_{10}Cl_3NO$: Cl^-, 14.62. Found: Cl^-, 14.56. [c] A 93% yield was obtained by the condensation of equimolar condensation of reactants. [d] **Hydrochloride,** m.p. 207–208°, from methanol. *Anal.* Calcd. for $C_{14}H_{14}Cl_3NO$: Cl^-, 11.13. Found: Cl^-, 11.04. [e] **Hydrochloride,** m.p. 164–166°, from methanol. *Anal.* Calcd. for $C_{15}H_{14}Cl_5NO_2$: Cl^-, 8.49. Found: Cl^-, 8.43. [f] Yield in 2 weeks; yield was 13% after 3 days. [g] **Hydrochloride,** m.p. 170–173°, from methanol. *Anal.* Calcd. for $C_{28}H_{40}Br_2ClNO_2$: Cl^-, 5.72. Found: Cl^-, 5.62.

A further variation in electronegative effects was visualized through use of di- as well as monohalophenols (see Table I).

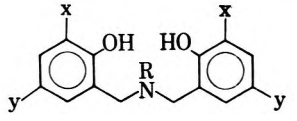
Condensation of 2,4-dichlorophenol with formaldehyde and cyclohexylamine in the proportions required for the formation of a bis(hydroxybenzyl)amine (IIIb) resulted in the isolation of only the corresponding Mannich base (Ib, 67% yield). However, replacement of cyclohexylamine with methylamine in this reaction led to the isolation of both the Mannich base (Ic, 61% yield) and the bis(hydroxybenzyl)amine (IIIc, 18% yield). Use of benzylamine in this reaction led to the isolation of a high yield of Mannich base (Id) along with some benzoxazine (IIc) but no bis(hydroxybenzyl)amine.





Ia, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = CH_3; x = y = Cl
d, R = $C_6H_5CH_2$; x = y = Cl
e, R = CH_3; x = y = Br
f, R = C_6H_{11}; x = y = Br

IIa, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = $C_6H_5CH_2$; x = y = Cl
d, R = CH_3; x = y = Br



IIIa, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = CH_3; x = y = Cl
d, R = CH_3; x = y = Br

Efforts to convert the Mannich base from cyclohexylamine (Ib) to the corresponding bis(hydroxybenzyl)amine (IIIb) by reaction with equimolar quantities of formaldehyde and 2,4-dichlorophenol at room temperature gave a 60% yield of the corresponding benzoxazine (IIb). In contrast, reaction of 2-cyclohexylaminomethyl-4,6-dimethylphenol (Ia) with formaldehyde and 2,4-dimethylphenol was shown earlier to form bis(3,5-dimethyl-2-hydroxybenzyl)methylamine (IIIa) readily.[4] The benzoxazine (IIb) also was obtained directly from the reaction of 2,4-dichlorophenol with formaldehyde and cyclohexylamine in the calculated proportions at 85°. The analogous benzoxazines (II) were obtained when cyclohexylamine was replaced with methyl- or benzylamine. The new benzoxazines prepared in this work are listed in Table II.

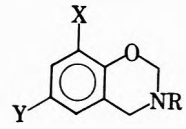
Reaction of 2,4-dibromophenol with formaldehyde and methylamine in a 2:2:1 molar ratio at room temperature for 3 days gave a 73% yield of Mannich base (Ie) along with a 13% yield of the bis(2-hydroxybenzyl)-amine (IIId). However, when the reaction time was 2 weeks, a much higher yield (88%) of the bis compound (IIId) was obtained. These results suggest that the Mannich base may be an intermediate in the formation of IIId. This is of particular interest in view of earlier indications that the Mannich base is not an intermediate in the synthesis of naphthoxazines from 2-naphthol, formaldehyde, and primary aromatic amines.[6] When 2,4-dibromophenol reacted with formaldehyde and cyclohexylamine in a molar ratio of 2:2:1, only the Mannich base (If) was isolated. High yields of the benzoxazine (IId) were obtained directly from 2,4-dibromophenol, formaldehyde, and methylamine in a 1:2:1 molar ratio, and also from 2,4-dibromo-6-methylaminomethylphenol and formaldehyde in equimolar proportions.

Replacement of the 4-methyl group in 2,4-dimethylphenol with chlorine did not lead to significantly dif-

(6) W. J. Burke, K. C. Murdock, and G. Ek, *J. Am. Chem. Soc.*, **76**, 1077 (1954).

TABLE II

SUBSTITUTED 3,4-DIHYDRO-2*H*-1,3-BENZOXAZINES



R	x	y	Yield,[a] %	Recrystn. solvent	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	Cl	Cl	69	ligroin	56–57	$C_9H_9Cl_2NO$	49.56	49.58	4.16	4.25
C_6H_{11}	Cl	Cl	36[b]	ligroin	56–57	$C_{14}H_{17}Cl_2NO$	58.75	58.48	5.99	5.87
$C_6H_5CH_2$	Cl	Cl	39[c]	CH_3OH	62–63	$C_{15}H_{13}Cl_2NO$	61.24	61.47	4.45	4.56
CH_3	Br	Br	68	ligroin	78–79	$C_9H_9Br_2NO$	35.21	35.44	2.95	2.95
$C_6H_5CH_2$	Br	Br	78	CH_3OH	77–78	$C_{15}H_{13}Br_2NO$	47.02	47.36	3.42	3.61
CH_3	CH_3	Cl	69	C_2H_5OH	55–56	$C_{10}H_{12}ClNO$	60.76	60.42	6.12	6.11
C_6H_{11}	CH_3	Cl	44	CH_3OH	48–49	$C_{15}H_{20}ClNO$	67.78	68.18	7.59	7.81
$C_6H_5CH_2$	CH_3	Cl	73	CH_3OH	77–78	$C_{16}H_{16}ClNO$	70.19	69.99	5.89	5.95

[a] Based on the reaction of the phenol with formaldehyde and the amine in a 1:2:1 molar ratio. [b] Obtained in 60% yield from Mannich base. [c] Obtained in 83% yield from Mannich base.

ferent results in most of the condensations studied. Reaction of 4-chloro-2-methylphenol and formaldehyde with methylamine, cyclohexylamine, or benzylamine in a 1:2:1 molar ratio at 85° gave the expected benzoxazines. Similarly, N,N-bis(5-chloro-2-hydroxy-3-methylbenzyl)amines (III) were obtained by condensation of the calculated quantities of 4-chloro-2-methylphenol and formaldehyde with methyl- or cyclohexylamine. However, reaction with benzylamine under these conditions led to the isolation of only the corresponding benzoxazine. It was shown earlier[4] that 4-*t*-butyl-2-chlorophenol and formaldehyde reacted with methylamine and with cyclohexylamine in a 2:2:1 molar ratio to give the corresponding bis(hydroxybenzyl)amines.

If an N-methylol Mannich base is considered as an intermediate, the competitive reactions then involve either ring closure with the phenolic hydroxyl (benzoxazine formation), or an electrophilic attack on the *ortho* position of another molecule of the phenol to yield a bis(hydroxybenzyl)amine. Any lowering of the electron density at the free *ortho* position would, accordingly, be expected to be unfavorable to the latter reaction. This is consistent with the results of the present study which show that replacement of both methyl groups in 2,4-dimethylphenol with chloro or bromo substituents results in a marked reduction in the tendency to form bis(hydroxybenzyl)amines. The replacement of the 4-methyl group in 2,4-dimethylphenol with chlorine apparently did not bring about a sufficient reduction in the electron density at the free *ortho* position to produce any significant changes in the condensations investigated except with benzylamine.

The stability of the benzoxazines in alcohols was shown to be dependent upon the particular phenol and primary amine used in the synthesis. For example in a comparison of benzoxazines derived from cyclohexylamine, those from 2,4-dimethylphenol and 4-chloro-2-methylphenol were stable in hot ethanol. However, the analogous benzoxazine from 2,4-dichlorophenol was readily converted to the corresponding Mannich base (Ib) in 89% yield by treatment of the benzoxazine in refluxing 95% ethanol for 10 min. Benzoxazines from methylamine and either 2,4-dichloro- or 2,4-dibromophenols were sufficiently unstable in methanol that the transformation to the Mannich base occurred even at room temperature. It was possible, however, to convert the Mannich base, 2,4-dibromo-6-methylaminomethylphenol, to the benzoxazine (IId) by heating with excess formaldehyde in methanol. In condensations employing the molar proportions calculated for bis(hydroxybenzyl)amine formation, the products were commonly recrystallized from alcohols. Under such conditions any benzoxazines formed from 2,4-dihalophenols and methyl- or cyclohexylamine would be expected to convert to the corresponding Mannich bases.

In contrast to the results with methyl- or cyclohexylamine, the benzoxazines from benzylamine and either 2,4-dichloro- or 2,4-dibromophenol were stable in hot methanol and could be recrystallized readily from this solvent. However, the benzoxazines from 4-chloro-2-methylphenol and both methyl- and benzylamine were stable in hot methanol.

Compounds representative of those prepared in this study are being screened for antitumor activity by the Cancer Chemotherapy Center of the National Institutes of Health.

Experimental[7]

2-Cyclohexylaminomethyl-4,6-dichlorophenol.—The molar reactant ratio is that calculated for the formation of N,N-bis(3,5-dichloro-2-hydroxybenzyl)cyclohexylamine. Cyclohexylamine (4.95 g., 0.05 mole) in 15 ml. of dioxane was added dropwise to a solution of 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) in 10 ml. of dioxane. 2,4-Dichlorophenol (16.4 g., 0.1 mole) in 25 ml. of dioxane was added, and the resulting solution was shaken thoroughly, stoppered, and kept at room temperature for 5 days. The solvents were removed under reduced pressure and the yellow liquid residue dissolved in 20 ml. of warm methanol. Upon cooling, a solid (9 g., 67% yield) precipitated and was removed by filtration, m.p. 157–158° after recrystallization from methanol.

In another run under comparable conditions the product was isolated as the **hydrochloride**, 11.5 g., 74% yield, m.p. 237–238°, after recrystallization from ethanol–water (1:1).

Anal. Calcd. for $C_{13}H_{18}Cl_3NO$: Cl^-, 11.41. Found: Cl^-, 11.35.

Only the Mannich base (28% yield) was isolated when the above reaction was repeated at room temperature.

Reaction of 2,4-Dichlorophenol with Methylamine and Formaldehyde.—Aqueous 25% methylamine (12.2 g., 0.1 mole) followed by 60 ml. of dioxane was added dropwise to an ice-cooled, stirred solution of formaldehyde (15 ml., 37%, 0.2 mole) in 40 ml. of dioxane. After addition of 2,4-dichlorophenol (32.8 g., 0.2 mole) in 100 ml. of dioxane, the solution was stirred vigorously on an ice bath for 5 min. The stoppered flask was kept at room temperature for 16 days. The solvents were removed

(7) All melting points are uncorrected.

under reduced pressure at room temperature over a period of 18 hr. Upon addition of 200 ml. of ether to the resulting viscous oil, 4.1 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 180–182°, precipitated. The melting point after one recrystallization from methanol was 191–192°.

The filtrate was concentrated to half the original volume but no further solid separated. After addition of 10 g. of sodium hydroxide, the ether layer was separated. The aqueous layer was further extracted with 50 ml. of ether. Upon removal of the ether less than 0.1 g. of oil remained. Any benzoxazine would be expected in this fraction.

The aqueous extracts were neutralized to pH 1 with hydrochloric acid and extracted with one 100-ml. and two 50-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate. Removal of the ether gave 15.5 g. of 2,4-dichlorophenol (47% recovery).

The aqueous extracts containing an insoluble layer were neutralized with potassium bicarbonate. An additional 0.8 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 185–187°, was removed by filtration. The filtrate was extracted with one 150-ml. and one 100-ml. portions of ether. After drying the solution over sodium sulfate for 1 hr., the ether was removed by evaporation under the hood. The resulting oil was dissolved in acetone and 8 ml. of 37% hydrochloric acid was added. No precipitation resulted. The acetone was removed by evaporation under the hood. Upon addition of 150 ml. of water, 6.8 g. of N,N-bis-(3,5-dichloro-2-hydroxybenzyl)methylamine hydrochloride (18% based on the amine), m.p. 150–162°, was removed by filtration; the melting point was 164–166° after recrystallization from methanol solution to which water was added. Neutralization of the filtrate gave 7.65 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 180–190°; after recrystallization from methanol, the melting point was 190–191°. The total yield of the Mannich base was 12.55 g. (61%).

When the condensation was repeated except that the reaction time was 5 days, only Mannich base (70% yield) was isolated from the reaction mixture.

3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (IIb).—Cyclohexylamine (9.9 g., 0.1 mole) in 30 ml. of 1,4-dioxane was added dropwise to a solution of 7.0 g. of paraformaldehyde (0.23 mole) in 10 ml. of ethanol containing 1 sodium hydroxide pellet and 10 ml. of 1,4-dioxane. 2,4-Dichlorophenol (16.4 g., 0.1 mole) in 30 ml. of 1,4 dioxane was added then and the solution was warmed at 65° for 1 hr. The temperature was increased to 85° and kept there for 4 hr. The solution was cooled and the solvents were evaporated at room temperature under reduced pressure. The liquid residue was added to 30 ml. of ethanol. Crystals (10.2 g., 36% yield) were removed by filtration; the melting point was 56–57° after recrystallization from petroleum ether (b.p. 60–110°).

Attempted Synthesis of N,N-Bis(3,5-dichloro-2-hydroxybenzyl)-cyclohexylamine (IIIb) from 2-Cyclohexylaminomethyl-4,6-dichlorophenol (Ib).—A solution of 1 ml. of 37% aqueous formaldehyde (0.012 mole) in 5 ml. of dioxane was added to 3.0 g. of Ib (0.011 mole) dissolved in 25 ml. of dioxane. A solution of 2.0 g. of 2,4-dichlorophenol (0.012 mole) in 5 ml. of dioxane was added, and the reaction solution was kept at room temperature for 13 days. The solvents were removed at room temperature under reduced pressure. The yellow oily residue was dissolved in 15 ml. of methanol and cooled. The solid (1.88 g., 60% yield) was removed by filtration; the melting point was 54–55° after recrystallization from petroleum ether. A mixture melting point with the product (IIb) from the above procedure was not depressed.

Conversion of 3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (IIb) to 2-Cyclohexylaminomethyl-4,6-dichlorophenol (Ib) in Hot Ethanol.—3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (1.3 g., 0.045 mole) was dissolved in 30 ml. of hot ethanol and the solution was refluxed for 10 min. and then cooled. The solid (1.1 g., 89% yield), m.p. 155–156°, which separated was removed by filtration. A mixture melting point with an authentic sample of 2-cyclohexylaminomethyl-4,6-dichlorophenol (Ib) was not depressed.

Reaction of 2,4-Dibromophenol with Formaldehyde and Methylamine.—To 6.2 g. of 25% methylamine (0.05 mole) in 20 ml. of dioxane was added dropwise with cooling 7.5 ml. of 37% formaldehyde (0.10 mole) in 10 ml. of dioxane. To the resulting solution was added 25.19 g. of 2,4-dibromophenol (0.1 mole) in 20 ml. of dioxane. The mixture was agitated throughout the addition of the reagents and was cooled in an ice bath. After the reagents had been added, the solution was stirred for 5 min. and then kept in the dark for 3 days at room temperature. Upon removal of the solvents under reduced pressure at room temperature a solid began to form. After addition of 75 ml. of ether, the mixture was cooled and 90 ml. of water containing 65 ml. of 37% hydrochloric acid was added. The mixture was shaken well and the aqueous layer was separated. The aqueous layer was further extracted with three 50-ml. portions of ether. The combined ether extracts were placed in a beaker and the ether was allowed to evaporate; 16 g. of 2,4-dibromophenol, m.p. 59–63°, was recovered.

2-Aminoethanol was added to the aqueous extracts until no further precipitate formed. The resulting white solid (7.5 g.), m.p. 187–189°, was removed by filtration and washed with 25 ml. of cold methanol; after three recrystallizations from toluene, the melting point was 195–196°. The analysis of the product was consistent with that for 2,4-dibromo-6-methylaminomethylphenol. An additional 0.3 g. of this product was obtained from the methanol washings. The total yield of Mannich base was 73%. Concentration of the methanol filtrate yielded 1.3 g. of solid, m.p. 115–126°, which melted at 125–128° after recrystallization from toluene. This corresponded to a 13% yield of N,N-bis(3,5-dibromo-2-hydroxybenzyl)methylamine.

When the reaction time in the above experiment was extended from 3 days to 2 weeks an 88% yield of the latter product was obtained.

Mixed Carboxylic Anhydrides in the Grignard Reaction. I. Synthesis of Aldehydes from Formic Acetic Anhydride[1]

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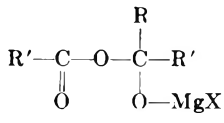
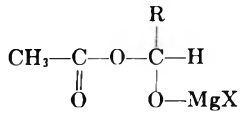
Reactions of formic acetic anhydride with Grignard reagents at −70° revealed a new method of aldehyde synthesis. Aldehydes predominated strongly over ketones in the products obtained with five aromatic Grignard reagents, less strongly with aliphatic ones. Initial study of the influences exerted by the structures of the reagents, and by reaction conditions, on the proportions of the products, indicated that both electronic and steric effects were significant.

Newman and his co-workers[2] found that, when simple carboxylic anhydrides reacted with Grignard reagents at about −70°, good yields of ketones were obtained, with little or no appearance of the tertiary alcohols which, theoretically, might have been formed by further reaction with additional Grignard reagent. They attributed the suppression of such secondary reactions to the stabilities and the diminished solubilities, at low temperatures, of the complexes (see following)



formed by addition of one molecule of RMgX to one of the carbonyl groups of $(R'\text{–}CO)_2O$. Grignard reactions with a number of unsymmetrical cyclic anhydrides also have been reported.[3] The use of mixed carboxylic anhydrides in such reactions, however, does not appear to have received earlier attention. The present paper describes a study of the behavior of formic acetic anhydride with ten Grignard reagents at low temperatures; a later paper will deal with a similar study of higher mixed acetic anhydrides.

Formic acetic anhydride was of unique interest because in every instance one of the two possible carbonyl products of its primary reaction was an aldehyde. If this could actually be obtained, and if it could be made to predominate over the accompanying methyl ketone, the process might be regarded as a new method of aldehyde synthesis.[4] Recent attempts to prepare aldehydes with formic acetic anhydride by means of the Friedel–Crafts reaction were completely unsuccessful,[5] the only carbonyl compounds produced by that method being methyl ketones; but the probable mechanisms of the two reactions differ so fundamentally that this did not necessarily foreshadow a similar failure with the Grignard reaction. Success appeared to depend principally on two things: a preferential addition of the Grignard reagent to the formyl group rather than to the acetyl group, and a degree of stability of the complex



at least comparable to the stabilities of other such complexes.

Table I shows the results obtained with aromatic Grignard reagents. The mole % of aldehydes and ketones in the total carbonyl products, determined by gas chromatography, are considered to be accurate. The estimated quantities are approximations, calculated from the weight ratios and from the weights of crude mixtures of both products.

Aldehydes predominated decidedly over ketones in all runs in which the solvent was ethyl ether. A small increase in both mole % and quantity of the aldehyde resulted when an excess of anhydride was used with phenylmagnesium bromide, the highest estimated quantities in any runs being obtained under such circumstances, but the *p*-tolyl Grignard reagent did not duplicate these increases.

Predominance of aldehydes over ketones may be attributed to the electronic and steric differences between hydrogen and methyl, which favored both the nucleophilic attack by R^- on the formyl carbon, and the stability of the resultant complex. The aldehyde–ketone ratio dropped sharply when tetrahydrofuran replaced ethyl ether as solvent, but without significant change in total quantity of carbonyl products, possibly indicating a substantial role for the steric factor.

An increased bias in favor of aldehydes was observed when phenyl was replaced, in the Grignard reagents, by the more nucleophilic tolyl groups. Presumably the drop in total quantity of carbonyl products, when the *o*-tolyl reagent was used, was caused by the steric obstacle placed by this group in the path of the formation of either of the two possible complexes with the anhydride. The diminished quantities of both products when *m*-chlorophenylmagnesium bromide was used, on the other hand, may be attributed at least partly to the weaker nucleophilic character of *m*-chlorophenyl, though this does not explain the failure to obtain more than a trace of ketone. The very low yields of both carbonyl products when the reaction was performed at 0° showed that a temperature much lower than this was as necessary for a successful aldehyde synthesis as it was for the ketone syntheses reported by Newman. The ratio of aldehyde to ketone was almost the same at 0° as in the runs made at −70°, but the quantities of both products were so small that this might be partly coincidence, particularly since the 0° runs were less consistent than the others.

(1) This paper was abstracted from part of the Ph.D. thesis of K. P. K., Jr., Louisiana State University, May, 1962.

(2) (a) M. S. Newman and W. T. Booth, Jr., *J. Am. Chem. Soc.*, **67**, 154 (1945); (b) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(3) (a) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); (b) M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950); (c) M. S. Newman and P. G. Scheurer, *ibid.*, **78**, 5004 (1956).

(4) See L. J. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941), for a survey of other ways of preparing aldehydes by use of Grignard reagents; see also A. Sisti, J. Burgmaster, and M. Fudim, *ibid.*, **27**, 279 (1962).

(5) (a) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **82**, 2380 (1960); (b) W. R. Edwards, Jr., and E. C. Sibille, *J. Org. Chem.*, **28**, 674 (1963).

TABLE I

RELATIVE AMOUNTS OF ALDEHYDES AND KETONES FROM FORMIC ACETIC ANHYDRIDE AND AROMATIC GRIGNARD REAGENTS, RMgBr[a]

R	Solvent	Molar ratio, anhydride–RMgBr	Temp., °C.	Mole % of each component in total carbonyl product: Aldehyde	Mole % of each component in total carbonyl product: Ketone	Estimated quantities, % of theory: Aldehyde	Estimated quantities, % of theory: Ketone
Phenyl	Ether	1:1	−70	82.9	17.1	35.8	7.4
o-Tolyl	Ether	1:1	−70	97.1	2.9	24.1	0.7
m-Tolyl	Ether	1:1	−70	97.1	2.9	33.3	1.0
p-Tolyl	Ether	1:1	−70	97.7	2.3	34.5	0.8
m-Chlorophenyl	Ether	1:1	−70	100(−)	0(+)	13.8	Trace
Phenyl	THF	1:1	−70	53.5	46.5	23.8	20.6
Phenyl	Ether	2:1	−70	85.2	14.8	39.1	6.8
p-Tolyl[b]	Ether	2:1	−70	97.8	2.2	33.6	0.8
Phenyl	Ether	1:1	0	84.0	16.0	7.0	1.3

[a] Figures are averages of three or more reasonably agreeing runs, except where otherwise noted. Usual quantity of anhydride in each run was approximately 0.13 mole. [b] Averages of two runs.

TABLE II

RELATIVE AMOUNTS OF ALDEHYDES, KETONES, AND ALCOHOLS FROM FORMIC ACETIC ANHYDRIDE AND ALIPHATIC GRIGNARD REAGENTS, RMgX[a]

R	Mole % of each component in total carbonyl and hydroxyl products: Aldehyde	Ketone	*sec*-Alcohol	*t*-Alcohol	Mole %, total formyl product[b]	Mole %, total acetyl product[c]	Estimated quantities, % of theory: Aldehyde	Estimated quantities, % of theory: Ketone
Ethyl	0(+)	0(+)	53.1	46.9	53.1	46.9	Trace	Trace
Propyl	28.6	15.9	26.1	29.4	54.7	45.3	9.0	5.0
n-Butyl	48.0	27.6	7.8	16.6	55.8	44.2	26.8	15.4
n-Butyl[d]	36.5	21.6	17.9	24.0	54.4	45.6	21.9	13.0
Isobutyl	59.7	33.4	4.6	2.3	64.3	35.7	34.1	19.2

[a] Temp., −70°; solvent, ethyl ether; equimolar proportions of anhydride and Grignard reagent; quantity of each reagent, about 0.13 mole. Except where otherwise noted, X was bromine, and figures are averages of three or more runs. [b] Sum of mole % of aldehyde and secondary alcohol. [c] Sum of mole % of ketone and tertiary alcohol. [d] Grignard reagent was chloride instead of bromide; figures are averages of two runs.

There appeared to be little if any formation of alcohols by secondary reactions, when using aromatic Grignard reagents at −70°. No indication of methyldiphenylcarbinol was observed on the chromatogram of any run with phenylmagnesium bromide, though tests made with samples to which small amounts of this alcohol had been added showed that it would have been revealed if present. The authors were not able to detect diphenylcarbinol chromatographically, as it failed to show a recognizable peak; a small amount of it was isolated by distillation and recrystallization from the products of the 0° runs, but none could be isolated by similar procedure from any run made at −70°. The chromatograms of the products obtained from the tolylmagnesium bromides, and from *m*-chlorophenylmagnesium bromide, did not show any unidentified peaks which might have suggested the presence of alcoholic products of secondary reactions; but, since the chromatographic characteristics of these alcohols were not determined, the possibility that they may have been present, but undetected, cannot be excluded. However, the residues which should have contained any such alcohols, after distillation of the aromatic aldehydes and ketones, were very small in all runs made at −70°.

Table II shows the results of reactions of formic acetic anhydride with aliphatic Grignard reagents. In most of these there was substantial alcohol formation. Relative molar proportions of all four possible products (aldehydes, ketones, and secondary and tertiary alcohols) were determined chromatographically; the estimated quantities, as before, are approximations. In this table, the sum of the mole % of each aldehyde and of its corresponding secondary alcohol has been regarded as the true measure of the total initial attack of the Grignard reagent on the formyl carbon atom, and had been tabulated under "Mole %, total formyl product." Similarly "Mole %, total acetyl product," combining ketone and tertiary alcohol, is a measure of the entire initial attack on the acetyl carbon. The data in these two columns give further evidence of steric influences. The bias in favor of the combined products of formyl attack was small and nearly constant, increasing very slightly with increase in the size of R, as long as R was an unbranched alkyl group. It increased substantially with isobutyl, with its moderately greater steric potential, but still fell short of the pronounced bias in favor of the aldehyde which was observed whenever R was an aryl group and the solvent was ethyl ether.

Estimated quantities of both carbonyl products of the alkylmagnesium bromides increased in the order ethyl < propyl < *n*-butyl < isobutyl, while alcohols decreased, rather irregularly, in the same order. The extreme minuteness of the amounts of carbonyl products which were obtained from the ethyl and propyl reagents is not readily explained. It is possible that the complexes formed by the two smallest alkyl groups used in this work were much more soluble at −70° than the others, and were, therefore, more exposed to further attack by additional Grignard reagent; this is in harmony with Newman's theory[2] that low solubilities of the complexes were largely responsible for the good ketone yields which he and his co-workers obtained with simple anhydrides.

Butylmagnesium bromide and the analogous chloride gave almost identical ratios of total formyl prod-

uct to total acetyl product, revealing an apparent indifference to the identity of the halogen in the initial attack. Alcohol production by secondary attack, however, was appreciably greater with the chloride. It may be significant that here again the secondary reaction increased with decrease in size of the Grignard reagent.

Although use of the reaction as a practical means of aldehyde synthesis seems at present to be somewhat remote, it is possible that further work with this or other mixed formic anhydrides may discover special situations in which, because of higher yields than those described here, or unsuitability of other methods, it might find such application. Tentatively, a relatively good yield appears most likely when the Grignard reagent is aromatic, when it possesses appreciable but not extreme hindering potential, and when its aryl group is distinctly nucleophilic.

A possible hazard accompanying the use of formic acetic anhydride was revealed when small samples of two different batches of it, stored under laboratory conditions in sealed glass tubes (one for 4 months, the other for about 1 week) were sent away for elemental analysis. The analyst[6] reported that both exploded violently as the tubes were opened. No similar behavior has been shown by unconfined formic acetic anhydride, or, with perhaps one exception,[7] by other mixed acetic anhydrides, either in the present work or in any earlier work with which the authors are familiar.

Experimental

Formic Acetic Anhydride.—This reagent was made by passing slightly more than the theoretical amount of ketene into reagent grade formic acid in an absorption vessel immersed in an ice–water bath.[8] The crude anhydride was subjected to suction (45 mm. at 0° for 10 min.) to remove excess ketene. It was then distilled at the same pressure, and the fraction collected at 44.5–46.5° was used immediately in a Grignard reaction. Results of a typical preparation were yield of anhydride, 39.4%; n^{20}D 1.3882, lit.[9] n^{20}D 1.3880; neut. equiv. 44.7 (calcd., 44.03). Fractional distillations of the anhydride were made with a vacuum-jacketed Vigreux-type column, 9 cm. high and 11 mm. in diameter. Similar columns of appropriate size were used for distillation of the products of the subsequent Grignard reactions.

Grignard Reaction.—Grignard reagents were made by methods similar to those outlined by Vogel,[10] and their strengths were determined by acid titration.[11] They were used, usually, within 1–2 hr.

In a typical run, a solution of about 0.13 mole of formic acetic anhydride, in 120 ml. of anhydrous ethyl ether or tetrahydrofuran, was placed in a 500-ml. round-bottomed flask equipped with stirrer, dropping funnel, and drying tubes. A temperature between −78° and −70° was maintained throughout the reaction by immersion in Dry Ice and acetone in a dewar flask. An equimolar quantity of Grignard reagent, in the same solvent as the anhydride, was added dropwise over a period of about 1 hr. The reaction was allowed to proceed, with continued cooling and stirring, for about 2 hr. after addition was complete. The reaction mixture was then allowed to warm to −10°, and hydrolyzed with saturated aqueous ammonium chloride. Separation of the organic phase, washing, extraction of aqueous phase and washings, and drying with anhydrous sodium sulfate were performed as described by Newman.[2] The combined ethereal solution was then concentrated, by distillation of ether, to a volume of 75–100 ml. Samples of this were analyzed by gas chromatography, to determine the relative proportions of aldehyde, methyl ketone, and (if present and measurable) secondary and tertiary alcohols. Reaction mixtures obtained from ethyl and propyl Grignard reagents were chromatographed both before and after distillation of ether, to ensure the detection of any volatile products.

Approximate estimates of the absolute quantities of aldehyde and ketone were then made, in most cases, by fractionally distilling the ethereal solutions at appropriate pressures, collecting the material which distilled over a range extending from slightly below the boiling point of the aldehyde to slightly above that of the ketone. This fraction was regarded as a crude mixture composed principally of the two carbonyl products, and the quantity of each one was calculated from the weight of the fraction, and from the ratio of the two which had been determined chromatographically. Corrections were made for any other component (such as unchanged halide) which could not be separated from the aldehyde–ketone mixture by distillation, and whose presence and quantity relative to aldehyde and ketone had been determined chromatographically. Estimated quantities of alcohols in Table II were calculated in a similar manner. In runs made with propylmagnesium bromide and isobutylmagnesium bromide, the total amount of aldehyde and ketone present in the reaction product was determined by the carbonyl titration method.[12] Because of the small quantities employed, complete recovery of the products was not attempted in the runs described here.

Most chromatographic measurements were made on a Beckman GC-2 gas chromatograph with a 6-ft. 20% silicon SF 96 on 30/60 Silocel column. This instrument did not give satisfactory resolution of unchanged *m*-chlorobromobenzene and the corresponding aldehyde; therefore, in runs involving the former, it was replaced by a Barber Colman IDS chromatograph Model 20 with a 200-ft. Apiezon L capillary column, and the high boiling material which would have clogged this column was removed by preliminary distillation. To validate identifications, and determinations of weight ratios, comparable runs were made with solutions (in ether or THF[13]) containing known amounts of authentic samples of the reaction products, including runs in which appropriate amounts of recognized impurities were also present. Materials used in these calibrations included all aldehydes, ketones, and aliphatic alcohols mentioned in the tables, and also methyldiphenylcarbinol.

Identifications of reaction products were based primarily on comparisons of their retention times with those of the authentic samples. In addition, relatively pure samples of those aldehydes, ketones, and alcohols which were formed in sufficient quantities were obtained by repeated fractional distillations of the crude mixtures from which their quantities had been calculated, and their identities were verified by determinations of boiling points, refractive indices, and melting points of derivatives. These were found to be in good agreement with values reported in the literature. Products which were further identified in this way included all aldehydes mentioned in the Tables except propanal; acetophenone, and all the aliphatic ketones except butanone; and diethyl- and dipropylcarbinols.

(6) Galbraith Laboratories, Inc., Knoxville, Tenn.

(7) W. R. Edwards, Jr., and W. M. Henley [*J. Am. Chem. Soc.*, **75**, 3587 (1953)] reported an explosion during an attempt to prepare acetic oxalic anhydride from silver oxalate and acetyl chloride, undiluted, at room temperature.

(8) C. D. Hurd and A. S. Roe, *ibid.*, **61**, 3355 (1939).

(9) R. E. Dunbar and F. C. Garven, *ibid.*, **77**, 4161 (1955).

(10) A. Vogel, "Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1956, pp. 257, 756.

(11) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).

(12) W. M. Bryant and D. M. Smith, *ibid.*, **57**, 57 (1935).

(13) Tetrahydrofuran.

Substituent Effects in the Lossen Rearrangement of Benzoyl Acylhydroxamates[1a]

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The rates and kinetic parameters of Lossen rearrangements of sodium salts of a series of benzoyl acylhydroxamates have been determined. The results are discussed in terms of polar and steric effects of substituent groups.

The rates of rearrangement reactions are influenced by proximal and nonproximal substituents of a migrating group. The effects of such proximal substituents are of special interest. *ortho*-Substituted phenyl groups migrate slower than the corresponding *para* derivatives in acid-catalyzed rearrangement of symmetrical aromatic pinacols.[2a] Examples of rate acceleration are known: *ortho*-substituted benzoic acids react with hydrazoic acid (the Schmidt reaction) faster than do the *meta* and *para* derivatives,[2b] the Curtius reaction proceeds more rapidly with *ortho*-substituted benzazides than with the *meta* and *para* isomers,[3] and *ortho* derivatives of the potassium salts of acylated benzohydroxamic acids in alkaline media undergo the Lossen rearrangement faster than do the corresponding *meta* and *para* compounds.[4]

A rate study of the effect of substituents of the migratory group in the Lossen rearrangement (eq. 1) in the aliphatic series (R = alkyl) was undertaken to learn if the substituent effects are the same or different from those observed in the aromatic series (R = aryl).

$$\mathrm{RCONHOCOPh} \xrightarrow[-\mathrm{H_2O}]{\mathrm{NaOH}} \mathrm{RC\bar{N}OCOPh} \xrightarrow{\mathrm{Na^+}} \mathrm{RN{=}C{=}O + PhCO_2Na} \quad (1)$$

The rates of rearrangement of a series of sodium benzoyl acylhydroxamates (R = alkyl) have now been measured in 0.093 *N* aqueous ammonia solution[5]; a colorimetric method for following the concentration of the benzoyl acylhydroxamates also has been developed.[6] First-order kinetics with respect to sodium benzoyl acylhydroxamate were observed in all instances. The results are summarized in Table I.

TABLE I

KINETIC RESULTS[a] FOR LOSSEN REARRANGEMENT OF $\mathrm{Na^+[RCONOCOC_6H_5]^-}$ IN 0.093 *N* AMMONIA

R	CH_3–	CH_3CH_2–	$(CH_3)_2CH$–	$(CH_3)_3C$–
$10^6 k_1$, 20°[b]			35.3	31.1
30°		11.3	178	149
40°	<1.6[f]	54.0		
Relative Rates,[c] 40°	<0.03[f]	1.00	14.9	12.0
ΔH^{*}[d]		29.2	28.0	27.1
ΔS^{*}[e]		+15.1	+16.6	+13.3

[a] First-order constants, sec.$^{-1}$, average of three determinations. Average deviation from the mean is less than 2% except for R = $(CH_3)_3C$, 30°, 2.5%; R = CH_3CH_2, 40°, 5.6%; and R = CH_3, 8.9%. [b] Accurate to ±0.05° except for determinations for R = CH_3, ±0.1°. [c] Values for R = $(CH_3)_2CH$ and $(CH_3)_3C$ were calculated from the rate constants calculated from activation parameters by means of the usual equation (see ref. 21). [d] Enthalpy of activation, kcal./mole. [e] Entropy of activation, cal./deg. mole, calculated from rate constants at 30° and ΔH^{*}. [f] These are maximum values (see ref. 9).

Equation 2 represents the accepted mechanism[4,5,7,8] of the Lossen rearrangement; migration of R from carbon to nitrogen probably occurs simultaneously with

$$\mathrm{RC\bar{N}OCOR'} \longrightarrow \left[\mathrm{R{-}\overset{\overset{\mathrm{O}}{\|}}{C}{=}N{-}O{-}CO{-}R'}\right]^{-} \longrightarrow \mathrm{RN{=}C{=}O + R'CO_2^-} \quad (2)$$

I

the heterolytic cleavage of the hydroxamate anion. Reaction of the intermediate isocyanate with water, ammonia, or the amine from hydrolysis of the isocyanate yields the observed products. Electron-donating substituents in R and electron-withdrawing substituents in R′ increase the rate of the Lossen rearrangement when R and R′ are *meta*- or *para*-substituted aryl groups.[4]

Inspection of Table I reveals that, as R is progressively changed from methyl[9] to *t*-butyl, the rate of the reaction increases except for the change from R = isopropyl to *t*-butyl. The electron-donating polar effect of the added methyl groups is expected to facilitate the rearrangement in agreement with the results obtained with aromatic systems.[4] A rate increase of at

(1) (a) A major portion of this research was completed while D. C. B. was a National Science Foundation Postdoctoral Fellow at The Ohio State University, January–August, 1962; (b) to whom inquiries should be directed, Western Michigan University.

(2) (a) W. E. Bachmann and F. H. Moser [*J. Am. Chem. Soc.*, **54**, 1124 (1932)] have listed the migratory aptitudes for this rearrangement; (b) M. E. D. Hillman, Ph.D. dissertation, The Ohio State University, Columbus, Ohio, 1958.

(3) Y. Yukawa and Y. Tsuno, *J. Am. Chem. Soc.*, **80**, 6346 (1958).

(4) R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(5) W. B. Renfrow, Jr., and C. R. Hauser [*ibid.*, **59**, 2308 (1937)] and Bright and Hauser[4] found that hydrolysis of the aroyl acylhydroxamates to the corresponding acylhydroxamic and arylcarboxylic acids is minimal when the Lossen rearrangement is carried out in 0.1 *N* aqueous ammonia. The compounds in the present study, except sodium benzoyl acetohydroxamate, undergo the Lossen rearrangement as fast as or faster than the compounds previously studied in 0.1 *N* ammonia solution.[4] Therefore, since variation in R (eq. 1) should have little effect upon the hydrolytic cleavage of the benzoyl group whether R is alkyl or aryl, except for variation in steric hindrance to hydrolysis in certain less favored conformations, hydrolysis of the compounds in the present study is minimal except with sodium benzoyl acetohydroxamate which may hydrolyze at a rate comparable to its rate of rearrangement (see ref. 9).

(6) Previous workers[5] obtained a rate constant of 0.00138 min.$^{-1}$ for rearrangement of potassium benzoyl benzohydroxamate at 30° in 0.10 *N* ammonia using a gravimetric procedure. By the method of the present study a value of 0.00109 min.$^{-1}$ at 30° in 0.093 *N* ammonia was obtained. Similarly, the rate constants obtained in the previous study[4] for $\mathrm{K[RCONOCOC_6H_5]}$ where R = cyclohexyl and 2-phenylethyl are of the same magnitude as the rate constants obtained in the present study for $\mathrm{Na[RCONOCOC_6H_5]}$ where R = isopropyl and ethyl, respectively.

(7) J. Hine, "Physical Organic Chemistry," 2d Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 335.

(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 498–502.

(9) The rate constant in Table I for R = CH_3 is a maximum possible value for the Lossen reaction and is a combination of rates of the Lossen reaction and hydrolysis of sodium benzoyl acetohydroxamate to acetohydroxamic acid and sodium benzoate and/or to sodium acetate and benzoates and hydroxylamine. Acetohydroxamic acid in 0.093 *N* aqueous ammonia at 40° is destroyed (measured colorimetrically) about half as fast as sodium benzoyl acetohydroxamate reacts under the same conditions.

least 33-fold occurs for the change from R = methyl to ethyl and an increase of 15-fold for the change R = ethyl to isopropyl. Little steric effect seems likely for the change from methyl to ethyl; the difference in rates is ascribed to the polar effect of the added methyl group. The smaller rate increase for the change from ethyl to isopropyl than from methyl to ethyl and the actual decrease in rate for the change from isopropyl to *t*-butyl is probably due to steric effects operating to reduce the rate of reaction. At least two modes of operation of such steric effects can be visualized if the transition state of the rearrangement can be represented as in I. Considerable bond breaking between the nitrogen and oxygen in the transition state will account for the observed polar effects. The two steric effects are greater hindrance to solvation in the transition state than in the initial state, and kinetic-energy steric effects, *i.e.*, greater hindrance to internal motions in the transition state than in the initial state.[10] Both of these steric effects operate in the same direction. Taft,[11] in his work on the separation of polar, steric, and resonance effects, found that the polar effects of successive α-methyl substitution are approximately additive while the steric effects are not, but instead accumulate at an increasing rate with successive α-methyl substitution. The results of the present study seem consistent with that view.

A rate-accelerating steric effect as observed in the Schmidt,[2b] Curtius,[3] and Lossen[4] reactions of *ortho*-substituted phenyl systems is possible if transition state I lies close to products; this effect is minor, however, compared to the other steric effects in the present system.

The steric effects of *ortho* substituents in the Schmidt,[2b] Curtius,[3] and Lossen[4] reactions of aromatic systems in general increase the rates of reaction. In the Lossen reaction of the aliphatic derived compounds reported herein, however, the steric effects of the α-substituents appear to have the opposite effect.

Experimental

Neutralization equivalents were determined in aqueous ethanol solution with phenolphthalein as indicator. All monohydroxamic acids gave a maroon color with aqueous ferric chloride.

The monohydroxamic acids or their salts were prepared by adaptation of previous methods[5,12]: acetohydroxamic acid, m.p. 89.5–91.0°, lit.[12a] 88–89°; propionohydroxamic acid, obtained as its potassium salt which was converted directly to benzoyl propionohydroxamate; isobutyrohydroxamic acid, m.p. 116.5–117.3°, lit.[12b] 116°; pivalohydroxamic acid, m.p. 163.6–164.1° dec. (*Anal.* Calcd. for $C_5H_{11}NO_2$: N, 11.95. Found: N, 12.0).

The benzoyl acylhydroxamates were prepared by adaptation of a previous method[13]: benzoyl acetohydroxamate, m.p. 97–99° (lit.[12a] 98–99°), neut. equiv. 173 (calcd. 179); benzoyl propionohydroxamate, m.p. 114.1–114.9° (lit.[13] 115–116°), neut. equiv. 197 (calcd. 193); benzoyl isobutyrohydroxamate, m.p. 145.2–146.4° (lit.[12b] 148°), neut. equiv. 212 (calcd. 207); benzoyl pivalohydroxamate, m.p. 105.8–107.0° (*Anal.*[14] Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; neut. equiv., 221. Found: C, 64.98; H, 6.80; N, 6.25; neut. equiv., 233).

Sodium Salts of Benzoyl Acylhydroxamates.—These kinetic reagents were prepared by a method similar to that used previously.[12a,b,13] Separate solutions of equivalent amounts of the benzoyl acylhydroxamate and sodium hydroxide were prepared in minimum amounts of methanol, cooled to *ca.* −10°, and mixed. Addition of ether to the solution precipitated the salt, which was removed by filtration and stored in a freezer (−20°) after a brief atmospheric drying period.

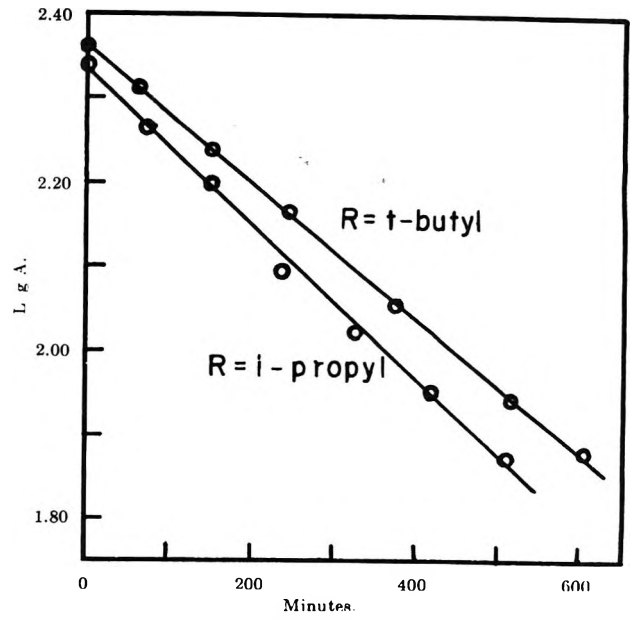

Fig. 1.—Typical rate data at 20° for Na[RCONOCOC$_6$H$_5$].

N-Alkylureas.—Approximately 0.025 *M* solutions (except the propiono derivative, 0.012 *M*) in 0.1 *N* ammonia of the sodium salts of benzoyl propiono-, isobutyro-, and pivalohydroxamates were allowed to stand for sufficient time to ensure complete reaction (in some cases the reaction mixtures from the kinetic runs on a compound were combined and worked up). The solutions were evaporated to dryness *via* an air current or under reduced pressure at 40° or less. The residue was extracted with hot benzene or ethyl acetate and the urea then crystallized from the extraction solvent. The infrared spectra were consistent for the ureas.

N-Ethylurea 19% yield (crude), was recrystallized to m.p. 90–92°, lit.[15] 92.1–92.4°. N-Isopropylurea, 33% yield (crude), was recrystallized to m.p. 151.1–152.1°, lit.[16] 154°. When the reaction was run in 1 *N* ammonia, a 61% yield was obtained.

N-*t*-Butylurea, 32% yield, had m.p. 177.2–178.2° dec., lit.[17a] 172° dec., lit.[17b] 183° dec. A sample from another reaction had m.p. 180.5–181.5° dec. and no depression when mixed with the first sample. When the reaction was run in 1 *N* ammonia, a 40% yield was obtained.

Kinetic Methods and Calculations.—It has been shown[18] that benzoyl benzohydroxamate is converted almost entirely into benzhydroxamic and benzoic acids by heating with 3–6 *N* sodium hydroxide. A variant of this method was adopted for the conversion of the benzoyl acylhydroxamates into the monohydroxamic acids, which react with ferric chloride to produce colored complexes suitable for colorimetric analysis.[19] Beer's law is obeyed within the estimated accuracy of the colorimeter and the aliquot measure.

The initial concentration of the alkali salts of the benzoyl acylhydroxamates in all kinetic runs was 0.0250 *M* except for one run with sodium benzoyl acetohydroxamate in which it was 0.0500 *M*. All solutions were prepared by adding a weighed sample of the sodium benzoyl acylhydroxamate to an aliquot of 0.093 *N* ammonia.

(10) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 652 ff.

(11) Ref. 10, pp. 600–602.

(12) (a) L. W. Jones, *Am. Chem. J.*, **20**, 1 (1898); (b) L. W. Jones and A. W. Scott, *J. Am. Chem. Soc.*, **44**, 407 (1922).

(13) L. W. Jones and L. Neuffer, *ibid.*, **39**, 659 (1917).

(14) Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1797 (1929).

(16) A. Conduche, *Ann. chim. phys.*, [8]**13**, 66 (1908).

(17) (a) A. Schneegans, *Arch. Pharm.*, **231**, 677 (1893); (b) M. Brander, *Rec. trav. chim.*, **37**, 83 (1918).

(18) E. Mohr, *J. prakt. Chem.*, [2]**71**, 133 (1905).

(19) It is not necessary that the conversion be 100% complete in order to be sure that the absorbance is proportional to the concentration of benzoyl acylhydroxamate, but rather that the conversion proceeds to the *same per cent* completion each time the procedure is carried out. The latter is the case in the present study since the conditions used for the conversion make the process a strictly pseudo-first-order process.

Procedure.—A 1-ml. aliquot of the reaction mixture was pipeted into a 50-ml. volumetric flask containing a 5-ml. aliquot of aqueous sodium hydroxide (20 g. per 100 ml. of water) and the flask was heated for 10 min. on a steam bath. The flask was cooled and 2.3 ml. of concentrated hydrochloric acid was added in portions with intermittent cooling. A 25-ml. aliquot of aqueous ferric chloride solution (≥0.5 g. per 300 ml. of water plus several drops of concentrated hydrochloric acid) was added and the flask diluted to the mark with distilled water. The absorption of the solution was then immediately measured with a Klett-Summerson photoelectric colorimeter; the blank solution consisted of a 25-ml. aliquot of the ferric chloride solution diluted to 50 ml. The same ferric chloride solution was used throughout a kinetic run. The recorded time of the aliquot is that of complete drainage of the 1-ml. pipet.

The absorbancy (A) reading of the colorimeter is directly proportional to the concentration of the original sodium benzoyl aliphatic hydroxamate. The first-order rate equation then is[20]

$$\log (A - A_\infty) = \frac{-kt}{2.303} + \log (A_0 - A_\infty) \qquad (3)$$

The rate constants were determined from the slope of the graph of log A *vs.* t, $A_\infty = 0$. Good straight lines were obtained; see Fig. 1 for typical examples. All rates were followed to *ca.* 75% complete reaction except for those at 20° (to *ca.* 67% complete reaction) and the determinations of sodium benzoyl acetohydroxamate (to 40–50% complete reaction). The enthalpies and entropies of activation were calculated from rate constants determined at two different temperatures by use of the usual equation.[21]

(20) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 28.

(21) Ref. 20, p. 96.

Organic Disulfides and Related Substances. X. Synthesis of 2-Acetamidoethyl Arene- and Alkanethiolsulfonates[1a,b]

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Synthesis of 2-acetamidoethyl thiolsulfonates was studied as typifying alkyl arenethiolsulfonates and alkyl alkanethiolsulfonates, and also because of the possibility that the products would protect against ionizing radiation. Of numerous approaches examined, the most general was by reaction of a sulfonyl iodide and a silver thiolate; preparations were developed for requisite alkanesulfonyl iodides, a class hitherto unknown, and for a representative sodium alkanesulfinate needed as precursor to an iodide. A smooth but less general synthesis involved thioalkylation of sulfinate salts by a thiolsulfonate.

The previous paper of this series reported good protective activity against lethal effects of ionizing radiation for certain thiolsulfonates of structure RSO_2SR' (**1**) in which R and R′ were identical and were aminoethyl or derivatives thereof.[1b] This paper reports syntheses in which R′ is 2-acetamidoethyl. As group R, *p*-tolyl, methyl, and 2-ethylhexyl were chosen to typify the general classes of unsymmetrical alkyl arenethiolsulfonates and alkanethiolsulfonates.

Early syntheses of unsymmetrical thiolsulfonates have been reviewed.[2] Subsequent ones include reaction of a thiol with a sulfonic anhydride[3a] or with a sulfinic acid and ethyl nitrite,[3b] oxidation of an unsymmetrical disulfide[3c,d] or chlorinolysis of two symmetrical disulfides,[3e] and interaction of a disulfide with a sulfinic acid.[3f] All of these methods presently are handicapped, either intrinsically or for want of demonstration of their generality.

The syntheses found best by us thus far are illustrated in Chart I. The reaction of sulfonyl iodides and silver thiolates was our first choice for exploration because it had no obvious limitations except the unavailability of alkanesulfonyl iodides; methanesulfonyl chloride and silver 2-acetamidoethanethiolate (**2**) failed to give an isolable thiolsulfonate.

The reaction of iodides and silver thiolates has been used only with aromatic compounds.[4,5] For synthesis of an alkyl thiolsulfonate, *p*-toluenesulfonyl iodide first was used because it was readily obtainable by reaction of arenesulfinate salts in water with iodine in methanol.[4] With the silver thiolate (**2**) it gave the alkyl arenethiolsulfonate (**3**) in 47% yield. Ether, acetonitrile, benzene, and diglyme gave similar results as solvents; dimethyl sulfoxide reacted. The identity of **3**, and also of **4** and **5** described below, was established by analysis, infrared spectrum, and an acidic reaction on pH test paper upon treatment with *p*-thiocresol.[6]

The alkanesulfonyl iodides needed for synthesis of alkyl alkanethiolsulfonates **4** and **5** apparently represented an unknown class. They could not be obtained by the method used for *p*-toluenesulfonyl iodide; methanesulfonyl iodide was soluble in methanol–water and 2-ethylhexanesulfonyl iodide was hydrolyzed. Attempted conversion of methanesulfonyl chloride by means of sodium iodide failed, perhaps because of reduction.[7] Methanesulfonyl iodide was obtained in good

(1) (a) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1–3, 1962. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. Results are abstracted from portions of the Ph.D. dissertation of R. R. C., Vanderbilt University, 1963, and the forthcoming dissertation of T. F. P. (b) Paper IX: L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964). (c) Du Pont Postgraduate Teaching Assistant, 1962–1963. (d) Texaco Fellow in Chemistry, 1961–1962.

(2) R. Connor, "Organic Chemistry, An Advanced Treatise," Vol. I, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 906–908.

(3) (a) L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952). This method was used only for symmetrical thiolsulfonates, but should be adaptable to unsymmetrical ones. (b) G. Kresze and W. Kort, *Ber.*, **94**, 2624 (1961). (c) G. Leandri and A. Tundo, *Ann. chim.* (Rome), **44**, 74 (1954); *Chem. Abstr.*, **49**, 4563 (1955). (d) L. Field, H. Härle, T. C. Owen, and A. Ferretti, *J. Org. Chem.*, **29**, in press; (e) I. B. Douglas and B. S. Farah, *ibid.*, **24**, 973 (1959). (f) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 2384 (1962).

(4) D. T. Gibson, C. J. Miller, and S. Smiles, *J. Chem. Soc.*, **127**, 1821 (1925).

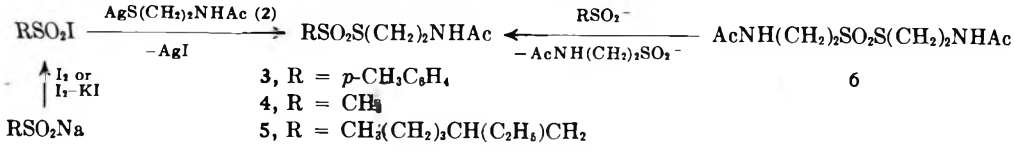
(5) R. Child and S. Smiles, *ibid.*, 2696 (1926).

(6) A consequence of the reaction $RSO_2SR' + R''S^- \rightarrow RSO_2^- + R'SSR''$ (*cf.* D. Barnard and E. R. Cole, *Anal. Chim. Acta*, **20**, 540 (1959), and ref. 1b and 3d).

(7) *Cf.* A. Perret and R. Perrot, *Bull. soc. chim. France*, [5]**1**, 1531 (1934).

Chart I

PREPARATION OF THIOLSULFONATES



yield, however, by reaction of aqueous solutions of iodine–potassium iodide and sodium methanesulfinate. Since the green-black product evolved iodine under vacuum it could not be dried for analysis, but its characterization seems assured by its conversion using the silver thiolate (**2**) to 2-acetamidoethyl methanethiolsulfonate (**4**) in 58% yield, as well as by the similarity of its infrared spectrum to that of methanesulfonyl chloride.

2-Ethylhexanesulfonyl iodide decomposed extensively when prepared in the manner used for methanesulfonyl iodide, probably because of hydrolysis. It was prepared by adding sodium 2-ethylhexanesulfinate to iodine in benzene–ether. The iodide, treated *in situ* with the silver thiolate (**2**) gave 2-acetamidoethyl 2-ethylhexanethiolsulfonate (**5**) in 79% yield.

Comment should be added on the preparation of sodium 2-ethylhexanesulfinate. It was obtained quantitatively by chlorinolysis of 2-ethylhexyl disulfide and alkaline hydrolysis, probably according to the following sequence.[3e,8]

$$(RS)_2 \xrightarrow{Cl_2} 2RSCl_3 \xrightarrow{AcOH} 2RS(O)Cl \xrightarrow{NaHCO_3} 2RSO_2Na$$

This procedure was based on the useful methods developed by Douglass and co-workers.[3e,8,9] Douglass, Brower, and Martin obtained sodium ethanesulfinate by hydrolysis of ethylsulfur trichloride, itself derived by chlorine oxidation of ethanethiol.[8] Douglass pointed out the ready availability of sulfinic acids from disulfide oxidation, but used them without isolation.[9] The present direct synthesis of an alkanesulfinate salt was quantitative and, if general, should be superior to methods now available.

The second approach to synthesis (Chart I) involved thioalkylation of a sulfinate salt by a thiolsulfonate. It proved to be the best method of those tried. The interchange equilibrium on which it is based has been studied in some detail,[10,11] but without report of yields of products, perhaps because of the difficulty of separating the desired thiolsulfonate. The method should be valuable for synthesis, however, in situations where the desired thiolsulfonate separates well from a solvent, while the other thiolsulfonate and sulfinate salts remain dissolved. This situation prevailed in the reaction of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**6**, water-soluble) with the appropriate sodium sulfinates (water-soluble), and thiolsulfonates **3**, **4**, and **5** (extractable into organic solvents) were obtained at room temperature in yields of 65–100%.

Other approaches to unsymmetrical thiolsulfonates proved unattractive. Ultraviolet irradiation of a sulfonyl iodide–disulfide mixture gave very low yields of impure thiolsulfonates (*cf.* Experimental). Reaction of thiols and sulfonic anhydrides under acidic conditions (presence of aluminum chloride or of a sulfonic acid), instead of with pyridine,[3a] resulted in no isolable amounts of thiolsulfonates; indeed, 2-acetamidoethanethiol and *p*-toluenesulfonic anhydride gave no significant amount of thiolsulfonate **3** even in the presence of pyridine.

Under a variety of conditions, di-*p*-tolyl- and dicyclohexylcarbodiimide failed to effect conversion of *p*-toluenesulfonic acid to *p*-tolyl *p*-toluenethiolsulfonate with *p*-thiocresol or to **3** with 2-acetamidoethanethiol. The adduct (**7**) of *p*-thiocresol and di-*p*-tolylcarbodiimide would not yield a thiolsulfonate with a sulfonic acid. The adduct (**7**), nevertheless, is not

$$C_7H_7SH + C_7H\text{-}N{=}C{=}NC_7H_7 \longrightarrow \underset{\mathbf{7}}{C_7H_7NHC(SC_7H_7){=}NC_7H_7}$$

without interest, since it exhibits some protection against ionizing radiation.[12] It may be added that thiolsulfonate **3** was poor in protective activity and toxic and that silver thiolate **2** was not protective; evaluations of **4** and **5** are pending.[12]

Efforts were unavailing to apply the chlorinolysis procedure of Douglass and Farah[3e] to synthesis of **3** from *p*-tolyl disulfide and 2-acetamidoethyl disulfide, *p*-tolyl *p*-toluenethiolsulfonate being the only isolable product. Since 2-acetamidoethyl disulfide alone in this procedure gave none of thiolsulfonate **6**, the amide function evidently interferes.

Also ineffective were efforts to develop a synthesis for thiolsulfonates which would be a counterpart of the preparation of alkylthiosulfates ($RSSO_3^-$) from an alkyl disulfide and a sulfite in the presence of cupric ammonium complex.[13] Thus attempted reaction of sodium *p*-toluenesulfinate and 2-acetamidoethyl disulfide in the presence of cupric ammonium sulfate gave no isolable amount of **3**.

We conclude that the sulfinate–thiolsulfonate interchange is the least burdensome route of those explored and the method of choice when availability and relative solubility of materials is satisfactory. The reaction of sulfonyl iodides with silver thiolates should be general; owing to the development of routes to alkanesulfonyl iodides, it should be practical as well.

Experimental[14]

Preparation of Thiolsulfonates from Sulfonyl Iodides and Silver 2-Acetamidoethanethiolate (2). A. 2-Acetamidoethyl *p*-Tol-

(8) I. B. Douglass, K. R. Brower, and F. T. Martin, *J. Am. Chem. Soc.*, **74**, 5770 (1952).

(9) I. B. Douglass, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p. 350.

(10) J. D. Loudon and A. Livingston, *J. Chem. Soc.*, 896 (1935).

(11) D. T. Gibson and J. D. Loudon, *ibid.*, 487 (1937).

(12) Protective activities against ionizing radiation were determined through the courtesy of Dr. T. R. Sweeney and Dr. D. P. Jacobus of the Walter Reed Army Institute of Research, Washington, D. C.

(13) J. M. Swan, *Nature*, **180**, 643 (1957).

(14) Melting points are corrected. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B Infracord spectrophotometer with films of liquids or Nujol mulls of solids. Moist extracts usually were dried using anhydrous magnesium sulfate or calcium sulfate and, after removal of drying agent by filtration, were evaporated in a rotating evaporator under reduced pressure for recovery of products.

uenethiolsulfonate (3).—2-Acetamidoethanethiol[16] was converted to silver 2-acetamidoethanethiolate (2), essentially according to the undetailed general procedure,[4] by adding silver nitrate (20 g.) in water (80 ml.) to the thiol (14 g.) in water (60 ml.); anhydrous sodium acetate (9.67 g.) in water (60 ml.) then was added, the mixture was cooled, and the white thiolate (2) was separated and dried under vacuum to a constant weight of 24.1 g. (90%).

The thiolate 2 (25.3 g.) was added during 0.5 hr. to 31.6 g. of *p*-toluenesulfonyl iodide[16] in 300 ml. of dry benzene. The solution was stirred for an additional 0.5 hr. Silver iodide and unchanged 2 were removed by filtration, and the benzene solution was washed with 10% aqueous solutions of sodium bicarbonate and sodium bisulfite (10 ml. of each). Drying and evaporation (40°) of the benzene solution gave 17 g. of dark tar. Chromatography on a 2.25 × 50 cm. column of acid-washed alumina, with ether–chloroform elution, gave 14.3 g. (47%) of thiolsulfonate **3** as white crystals, m.p. 58–61.5°. Recrystallization from ether gave 9.3 g. (30%) of pure **3**, m.p. 62.5–64°. The infrared spectrum of the **3** was consistent with expectation, bands being found at 3300, 1650, 1560, 1340, 1140, and 825 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{15}NO_3S_2$: C, 48.40; H, 5.54; N, 5.14; S, 23.45. Found: C, 48.38; H, 5.47; N, 5.06; S, 23.42.

B. **2-Acetamidoethyl Methanethiolsulfonate (4).**—Methanesulfonyl iodide was prepared: Iodine (6.85 g.) was dissolved in a solution of potassium iodide (13 g.) in water (20 ml.). The mixture then was poured with stirring into a solution of 5.0 g. of sodium methanesulfinate[18] in 20 ml. of water. Green-black needles which formed were removed by filtration, pressed dry under a rubber diaphragm, and amounted to 4.2 g. (82%) of presumed methanesulfonyl iodide, m.p. 85–90° dec. (Kofler). The infrared spectrum of the iodide was much like that of methanesulfonyl chloride, but with absorptions at slightly lower wave number; strong bands occurred at 1300, 1150, 960, and 730 cm.$^{-1}$. The iodide has fair stability, except under reduced pressure where iodine is evolved readily; after *ca.* 2 months of storage at atmospheric pressure, methanesulfonic acid and an unidentified white solid were left. Drying for analysis seemed impracticable and the presumed methanesulfonyl iodide was used directly.

For conversion to thiolsulfonate **4**, freshly prepared moist methanesulfonyl iodide was dried in a desiccator over calcium chloride at atmospheric pressure for 0.5 hr.; then 15.00 g. was dissolved in 400 ml. of dry benzene. The silver thiolate (**2**, 16.4 g.) was added during 20 min., and the mixture was stirred for 1 hr. more. The benzene solution was decanted and evaporated to yield 2.2 g. (16% of **4**) of yellow oil which solidified when chilled. Recrystallization from 1-butanol–pentane and ether–pentane gave 0.94 g. (7%) of **4**, m.p. 48–50°; the infrared spectrum of this material was identical with that of pure **4** described below.

The yellow precipitate left after decantation was washed with methanol. Evaporation of the methanol left 11.7 g. of oil. The oil upon standing for 2 days deposited 3.0 g. of 2-acetamidoethyl disulfide, which was removed by filtration. The residual oil was chromatographed on a 2.25 × 50 cm. column of acid-washed alumina. Elution with ether–chloroform yielded 7.3 g. (51%) of white **4**, m.p. 45–50° (a trace of disulfide remained up to 70°). Recrystallization of the second and third fractions (5.6 g.) from chloroform–carbon tetrachloride gave 2.75 g. (19%) of **4**, m.p. 45–49°. Several recrystallizations of the first fraction (1.7 g., 12%) gave **4** that had constant m.p. 52–53°; the infrared spectrum was consistent with expectation for **4**, bands being found at 3400, 1660, 1570, 1325 and 1140 cm.$^{-1}$.

Anal. Calcd. for $C_5H_{11}NO_3S_2$: C, 30.40; H, 5.62; N, 7.11; S, 32.55. Found: C, 30.18; H, 5.58; N, 7.09; S, 32.50.

In another experiment, purification was attempted of crude product by sublimation, zone melting, and paper chromatography, but none of these methods showed promise.

C. **2-Acetamidoethyl 2-Ethylhexanethiolsulfonate (5).**—Sodium 2-ethylhexanesulfinate was prepared: A stirred solution of 31.5 g. of 2-ethylhexyl disulfide and 13 g. of glacial acetic acid in 15 ml. of methylene chloride was cooled to −5°, and *ca.* 32 g. of chlorine was slowly introduced during *ca.* 1 hr. (by allowing a chilled container to warm). Water (10 ml.) then was added and the mixture was allowed to warm to room temperature. The solution was extracted with 10% aqueous sodium bicarbonate until the organic layer was neutral, and the aqueous extract then was evaporated. The solid left was extracted with several portions of hot absolute ethanol (total volume, 1 l.) which removed the sodium sulfinate. Evaporation of the ethanol left 44.0 g. (102%) of waxy sodium 2-ethylhexanesulfinate, which reduced aqueous permanganate and had infrared bands at 1015 and 1060 cm.$^{-1}$.

For preparation of 2-ethylhexanesulfonyl iodide, *in situ*, sodium 2-ethylhexanesulfinate (23.5 g.) was added to a stirred solution of 13.7 g. of iodine in 200 ml. of 3:1 benzene–ether.

After 10 min., 15.8 g. of silver thiolate 2 was added slowly during 40 min. with stirring. The mixture was stirred 1 hr. more, and the benzene–ether solution was decanted from the slimy precipitate. The precipitate was washed with benzene, ether, and chloroform. The organic solutions were washed with 10% aqueous sodium sulfite until colorless. Drying and evaporation of the organic solution gave 12.6 g. (79%) of oily **5**, $n^{26}D$ 1.4951, the infrared spectrum of which was essentially identical with that of the analytical sample described below. The oil could not be induced to crystallize, and 10.7 g. was chromatographed on a 2.25 × 50 cm. column of Merck acid-washed alumina with ether–chloroform elution. The yield was 8.0 g. (59%) of **5**, $n^{25}D$ 1.5048, the infrared spectrum of which was identical with that of analytically pure **5**. Short-path distillation at 90° (0.03 mm.) gave only a small amount of distillate ($n^{26}D$ 1.5008) after 10 hr. and much decomposition occurred.

Preparation of Thiolsulfonates by Thioalkylation of Sulfinate Salts with 2-Acetamidoethyl 2-Acetamidoethanethiolsulfonate (6). A. **2-Acetamidoethyl *p*-Toluenethiolsulfonate (3).**—A solution of **6** (1.34 g.)[19] in water (15 ml.) was added to a stirred solution of sodium *p*-toluenesulfinate (4.46 g.) in water (35 ml.). Benzene (*ca.* 50 ml.) was added, and the mixture was shaken mechanically for 3 hr. After an overnight period, the benzene layer was separated, dried, and evaporated to an oil, which solidified on standing. The yield of **3** was 0.90 g. (66%), m.p. 58–61°, undepressed by authentic **3**; the infrared spectrum was identical with that of pure **3** described above.

B. **2-Acetamidoethyl Methanethiolsulfonate (4).**—As in A, thiolsulfonate **6** (1.34 g.)[19] in water (15 ml.) was added to sodium methanesulfinate (2.55 g.)[18] in water (35 ml.). After the mixture had been shaken with benzene (100 ml., 5 hr.) and let stand, evaporation of the benzene layer gave only a small amount of thiolsulfonate **4**. The water layer, therefore, was extracted with ten 25-ml. portions of chloroform. The chloroform extract was separated, dried, and evaporated. The yield of **4** was 0.64 g. (65%), m.p. 50–51.5°, infrared spectrum identical with that of authentic **4**.

C. **2-Acetamidoethyl 2-Ethylhexanethiolsulfonate (5).**—As in A, thiolsulfonate **6** (1.34 g.)[19] in water (15 ml.) was added to sodium 2-ethylhexanesulfinate (5.00 g.) in water (35 ml.). The mixture was shaken with 100 ml. of benzene (5 hr.) and then let stand overnight. Evaporation of the benzene gave 1.53 g. (103%) of **5** as clear oil, $n^{25}D$ 1.5050. The infrared spectrum had strong $-SO_2-$ bands at 1140 and 1340 cm.$^{-1}$ and strong amide bands at 1550, 1670, and 3375 cm.$^{-1}$. In the light of earlier experience, the oily **5** was analyzed without further attempts to purify it.

Anal. Calcd. for $C_{12}H_{25}NO_3S_2$: C, 48.80; H, 8.54; N, 4.75; S, 21.75. Found: C, 48.88; H, 8.69; N, 4.95; S, 21.99.

Preparation of Thiolsulfonates by Irradiation of Sulfonyl Iodides in the Presence of Disulfides.—2-Ethylhexanesulfonyl iodide was prepared *in situ* by treating 6.7 g. of sodium 2-ethylhexanesulfinate with 4.06 g. of iodine in 150 ml. of benzene in a quartz flask. 2-Acetamidoethyl disulfide (1.70 g.) and 50 ml. more of benzene were added, and the mixture was strongly irradi-

(15) R. Kuhn and G. Quadbeck, *Ber.*, **84**, 844 (1951).

(16) Prepared by the general method of Gibson, Miller, and Smiles[4]; m.p. 82–84°, lit.[17] m.p. 84–85°.

(17) R. Otto and J. Tröger, *Ber.*, **24**, 479 (1891).

(18) From reduction of methanesulfonyl chloride with sodium sulfite according to L. Field and J. W. McFarland, *J. Am. Chem. Soc.*, **75**, 5582 (1953).

(19) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *ibid.*, **83**, 4414 (1961).

ated with ultraviolet light for 16 hr. The mixture then was washed with a solution of sodium sulfite and dried. Evaporation left 0.56 g. (13%) of dark oil, the infrared spectrum of which showed it to be largely 2-acetamido 2-ethylhexanethiolsulfonate (**5**), $n^{25}D$ 1.5103.

Reaction of *p*-toluenesulfonyl iodide (16 mmoles) and 2-acetamidoethyl disulfide (7.2 mmoles) in similar fashion gave a dark oil, which had an infrared spectrum indicating it to be largely **3**, but the yield was only 2%.

Irradiation of *p*-toluenesulfonyl iodide and *p*-tolyl disulfide, much as before, resulted in *p*-tolyl *p*-toluenethiolsulfonate in 7% yield; characterization was effected by melting point and the infrared spectrum. However, a control experiment in which the disulfide was omitted also resulted in about the same yield of the thiolsulfonate.

N,N,S-Tri-*p*-tolylisothiourea (7).—A solution of 8.37 g. of *p*-thiocresol in 50 ml. of benzene was added rapidly to a stirred refluxing solution of 15.00 g. of di-*p*-tolylcarbodiimide in 100 ml. of benzene; heating was continued for 4 hr. After 5 days at *ca.* 25°, the solution was evaporated and the solid was rubbed with boiling ethanol (175 ml.). Chilling of the entire mixture at 4° and filtration resulted in 19.85 g. (85%) of white solid, m.p. 85–90°. Recrystallization from hexane gave the adduct (**7**) as needles with constant m.p. 89.5–90.5°.

Anal. Calcd. for $C_{22}H_{22}N_2S$: C, 76.26; H, 6.40; S, 9.25. Found: C, 76.00; H, 6.45; S, 9.31.

Further Studies on the Anomalous Hunsdiecker Reaction of Triaryl-Substituted Aliphatic Acids

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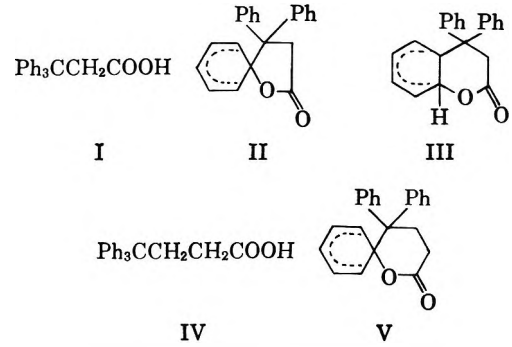
The phenyl shift previously observed in the Hunsdiecker reaction with β,β,β-triarylpropionic acids (such as I) failed to occur significantly with γ,γ,γ-triphenylbutyric acid (IV). Two sets of conditions were employed with IV. The normal Hunsdiecker reaction on the silver salt yielded primarily brominated parent acid, together with a small yield of the normal Hunsdiecker product, γ,γ,γ-triphenylpropyl bromide (VI). The recently described Cristol–Firth modification of the Hunsdiecker reaction using the free acid gave essentially the same results, though the yield of VI was increased. In addition, γ,γ,γ-triphenylbutyryl peroxide (X) was prepared and decomposed in refluxing carbon tetrachloride. No significant rearrangement of the γ,γ,γ-triphenylbutyryloxy radical (XII) was found. As a conclusion from these data, arguments are presented that the anomalous Hunsdiecker reaction of such triarylaliphatic acids proceeds in a radical fashion from the acyloxy radical and that it involves phenyl migration in this radical. The migration is, however, sensitive to the ring size created during the migration, proceeding *via* a five-, but not a six-membered ring.

Previous work[2,3] has shown that β,β,β-triarylpropionic acids such as the parent acid I undergo rearrangement to aryl β,β-diarylacrylates upon attempted degradation by the Hunsdiecker reaction,[4] with little bromodecarboxylation being observed. An Ar_1-5 type intermediate (II),[5] rather than an Ar_2-6 type intermediate (III), appeared to explain the course of the rearrangement, but the radical or ionic nature of the process has remained a difficult point to settle.[6]

As a natural extension of this work, the question arose as to whether rearrangement *via* an Ar_1-6 intermediate (V) might occur. A study of γ,γ,γ-triphenylbutyric acid (IV) in the Hunsdiecker reaction was made, therefore, and the results of this study are reported here. In addition, the recent report of Cristol and Firth[7] on the bromodecarboxylation of acids using the free acid, bromine, and excess mercuric oxide in the dark led us to examine both the above triphenylbutyric acid (IV) and the previously studied acid I in their process as well.



II, III, and V apply either as ionic or radical species

The preparation of acid I was as before,[2] while the synthesis of acid IV was straightforward and followed the sequence shown (eq. 1). The displacement reaction

$$\text{I} \xrightarrow[\text{(2) LiAlH}_4]{\text{(1) SOCl}_2} \underset{(92\%)}{\text{Ph}_3\text{CCH}_2\text{CH}_2\text{OH}} \xrightarrow{\text{P} + \text{I}_2} \underset{(77\%)}{\text{Ph}_3\text{CCH}_2\text{CH}_2\text{I}} \xrightarrow[\text{DMSO}]{\text{NaCN}} \underset{(71\%)}{\text{Ph}_3\text{CCH}_2\text{CH}_2\text{CN}} \xrightarrow[\Delta]{\text{H}_2\text{SO}_4} \underset{(\text{IV}, 94\%)}{\text{Ph}_3\text{CCH}_2\text{CH}_2\text{COOH}} \quad (1)$$

using sodium cyanide failed under the other conditions tried, *viz.*, refluxing the reactants in aqueous alcohols or ethylene glycol. The beneficial use of dimethyl sulfoxide solvent in such reactions previously has been

(1) Taken in part from the M. S. thesis of J. A. L., Loyola University, May, 1963.

(2) J. W. Wilt and D. D. Oathoudt, *J. Org. Chem.*, **21**, 1550 (1956); **23**, 218 (1958).

(3) J. W. Wilt and J. L. Finnerty, *ibid.*, **26**, 2173 (1961).

(4) R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956).

(5) Throughout this paper, our designation of these as Ar_m-n type rearrangements carries no implication that anchimeric assistance is involved. Our use of the term is meant simply to convey the site of the eventual substitution on the aromatic ring and the size of the ring in the intermediate.

(6) The absence of rearrangement with β,β,β-tris(*p*-nitrophenyl)propionic acid led us to suggest an *ionic* pathway earlier,[2] but the small substituent effects observed later[3] confused the issue and no compelling evidence either way had been found prior to the present study. It is interesting to note that the Ar_2-6 pathway is equally effective as the Ar_1-5 in certain solvolyses [R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3114 (1957)] and, therefore, it might be expected to be an equally likely route for the present rearrangement. Though the Ar_2-6 route (see III) does not occur in the anomalous Hunsdiecker reactions of β,β,β-triarylpropionic acids,[3] it seemingly has been observed with β-phenylisovaleric acid (dissertation, C. E. Berr, University of California at Los Angeles, 1952) and quite recently with β,β-diphenylpropionic acid [U. K. Pandit and I. P. Dirk, *Tetrahedron Letters*, **14**, 891 (1963)]. In both cases dihydrocoumarin derivatives were the products. Steric effects probably occasion the switch from Ar_2-6 to Ar_1-5 as the acid studied changes from the two mentioned above to I and its derivatives.

(7) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

TABLE I

SUMMARY OF RESULTS

Acid	Method	Reaction, %[a]	Decarboxylation, %[b]	Rearrangement, %[c]	RBr, %[d]
I[e]	Hunsdiecker	24	1	23	None
IV[e]	Hunsdiecker	10	10	None	3
I	Cristol–Firth	47	21	26	4
IV	Cristol–Firth	36	34	2	28

[a] The sum of the per cents of decarboxylation and rearrangement. [b] Measured as carbon dioxide evolved, through precipitation as barium carbonate. [c] Measured as phenol, collected as tribromophenol, produced by the saponification of the reaction product. [d] The yield of isolated and characterized halide. [e] As silver salt.

noted for bromides and chlorides[8] and the present instance would indicate its utility for iodides also.

The acids I and IV[9] proved to be decidedly different under the usual Hunsdiecker conditions. No rearrangement of IV[9] was detected and the normal halide product, γ,γ,γ-triphenylpropyl bromide (VI), was isolated, albeit in low yield, together with a slight amount of carbon dioxide. The major product was an

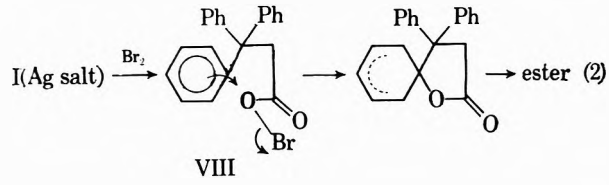
$$\text{IV} \longrightarrow \text{Ag salt} \xrightarrow[\text{CCl}_4]{\text{Br}_2} \underset{\text{VI}}{\text{Ph}_3\text{CCH}_2\text{CH}_2\text{Br}} + \text{CO}_2 + \text{acid mixture}$$

inseparable mixture of a brominated acid derived from starting material together with IV. In order to confirm its unrearranged structure, the bromide VI was converted into γ,γ,γ-triphenylbutyronitrile through reaction with sodium cyanide in dimethyl sulfoxide. This nitrile was identical with that produced from the iodide (eq. 1). In addition, the n.m.r. spectrum was in accord with the structure proposed for VI. The acid I[9] afforded no halide, very little carbon dioxide, and a significant amount of rearrangement under these same conditions, as reported.[2,3]

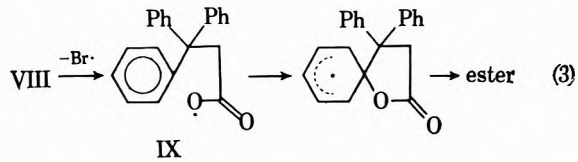
When both I and IV were subjected to the Cristol–Firth modification[7] of the Hunsdiecker reaction, significant differences were again noticed. The acid I again gave rearranged phenyl ester (determined as phenol) in essentially the same yield as under normal conditions. There was, however, a considerable increase in the carbon dioxide evolved and it proved possible for the first time in any of the studies on I to identify a halide product, triphenylbromoethylene (VII), isolated in low yield.[10] The acid IV, on the other hand, again failed to rearrange significantly. The major product was the halide VI, isolated in fair yield. These results are tabulated in Table I.

In all the reactions here studied, as before,[2,3] considerable amounts of the parent acids were recovered from the residues so that yields of products are higher than conversions in Table I would indicate. Certain other apparent reaction products were partially characterized, though their exact structures remain uncertain.

It is felt that the pronounced difference in the behavior of I and IV under the two sets of conditions employed in this study has a bearing on the mechanism of the 1,4-phenyl shift observed with I. *A priori*, the shift could occur in the hypobromite VIII[11] as shown (eq. 2). Such a path could proceed *via* either radical or ionic transition states. The possible *radical* displacement of bromine by phenyl in the hypobromite VIII can be dismissed, however, since neighboring group assistance in radical reactions is rare[12] and, specifically, such assistance by phenyl is absent in a number of radical rearrangements involving a phenyl shift.[13]



Alternatively, the hypobromite could first dissociate to the acyloxy radical IX followed by rearrangement of this radical as shown (eq. 3). Other possible paths *via*



Ar_2-6 intermediates are believed from earlier studies[2,3] not to be followed by I. We feel the bulk of the evidence favors a radical pathway for rearrangement from the acyloxy radical IX (eq. 3), at least for the reactions above room temperature.

Thus, generation of the (presumably nearly "free") acyloxy radical IX in three other studies, the Kolbe electrolysis of I (at 60°),[14] the decomposition of β,β,β-triphenylpropionyl peroxide (refluxing chlorobenzene),[15a] and the decomposition of *t*-butyl β,β,β-triphenylperpropionate (chlorobenzene, 100°),[15b] has produced in each case the very same skeletal transformation observed in the Hunsdiecker reaction of I.[2] Since none of the other studies mentioned had done so, we thought the corresponding γ,γ,γ-triphenylbutyryl peroxide (X) should be similarly decomposed to test the rearrangement ability of the acyloxy radical XII. Decomposition of this peroxide in refluxing carbon tetrachloride was rather slow, but the carbon dioxide yield was essentially quantitative (for the incomplete conversion of about 39%) and, significantly, only a trace of phenyl ester was found—in good agreement with the result of the Cristol–Firth treatment of IV (see Table I).

(8) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

(9) As the silver salts.

(10) Earlier,[2] a halide was detected (<4%), but we were unable to isolate it. The low yield in the present instance may well reflect the difficulty of isolation.

(11) The formation of an acyl hypobromite is generally accepted as the first stage in Hunsdiecker reactions; *cf.* ref. 4.

(12) D. L. Tuleen, W. G. Bentrude, and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 1938 (1963), and earlier papers; J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962).

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959, pp. 755 ff.

(14) H. Breederveld and E. C. Kooyman, *Rec. trav. chim.*, **76**, 297 (1957).

(15) (a) W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963); (b) W. H. Starnes, Jr., *J. Am. Chem. Soc.*, **85**, 3708 (1963).

$$IV \xrightarrow{SOCl_2} Ph_3CCH_2CH_2COCl \xrightarrow[ether]{Na_2O_2} (Ph_3CCH_2CH_2COO)_2$$
X

$$X \xrightarrow[\Delta]{CCl_4} CO_2 + \text{unchanged X} + \text{other products (trace phenyl ester)}$$

Therefore, it appears that the acyloxy radicals IX and XII *can* account for the experimental results, *viz.*, rearrangement in one case but not the other.

The situation in the usual (*i.e.*, silver salt) Hunsdiecker reaction of I and IV is, however, not quite so apparent. Thus, the rearrangement of I[9] occurs readily at 25° (and lower[16]), while the major process with IV[9] under these conditions is (ring) bromination, as shown.

$$IV(\text{Ag salt}) \xrightarrow{Br_2} Ph_3CCH_2CH_2COOBr \quad (XI)$$

$$XI \rightarrow \text{brominated IV}$$

$$XI \rightarrow Ph_3CCH_2CH_2COO\cdot \quad (XII)$$

$$XII \xrightarrow{\text{ester}} \text{(not observed)}$$

$$XII \rightarrow VI + CO_2$$

Because the dissociation of the hypobromites to the acyloxy radicals would be slower under these conditions, it could be that some rearrangement is occurring directly from the hypobromite VIII under these conditions; but it is simpler to explain the lower temperature results in the same way as the higher temperature ones. Thus, though the equilibrium (see below) might be less favorable, both hypobromites VII and XI are somewhat dissociated to their acyloxy radicals, IX then undergoing facile Ar_1-5 rearrangement and little competitive decarboxylation (which is more strongly temperature dependent)[17] while XII suffers decarboxylation instead, since rearrangement *via* an Ar_1-6 state is difficult. If one assumes a reversible hypobromite formation as shown, R–COOBr $\rightleftharpoons$ R–COO· + Br·, the (ring) bromination of IV is likewise understandable. The equilibrium above for VIII would be continuously shifted to the right since the acyloxy radical IX is removed *via* rearrangement. For XI the concentration of the hypobromite would be higher, since the acyloxy radical XII is removed primarily through decarboxylation, and this is slight (see Table I) at this temperature. The higher concentration of XI then affords more bromination of IV.[18]

The contrast in decarboxylation per cents obtained from I under the normal and modified (Cristol–Firth) Hunsdiecker conditions may be explained by the different temperatures involved. Earlier work[3] had indeed shown that the hypobromite intermediate involved underwent more decarboxylation with increasing temperature at the expense of rearrangement, presumably because the dissociation rate to acyloxy radical IX increased. It is of interest, however, that under Cristol–Firth conditions (77°) the rearrangement of I remained an effectively competitive process. This probably is a result of the excess mercuric oxide present. The hydrogen bromide produced in *the* rearrangement step is removed through reaction with the oxide and, therefore, does not convert the hypobromite reactant (which is believed to be formed under these conditions as well[7]) to the inert free acid. The primary change with the acid IV under the Cristol–Firth conditions was the expected one of more decarboxylation and bromide (VI) formation, in keeping with the proposed increase in the dissociation rate of the hypobromite XI.

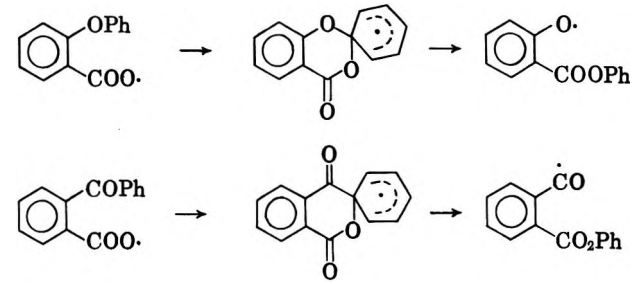
The isolation of triphenylbromoethylene (VII) represents the first decarboxylated product ever characterized in the Hunsdiecker reaction with I.[10] While its rearranged structure is in keeping with the rearrangement of the β,β,β-triphenylethyl radical[19] formed by decarboxylation of the acyloxy radical IX, as shown,

$$IX \xrightarrow{-CO_2} Ph_3CCH_2\cdot \longrightarrow Ph_2\dot{C}CH_2Ph \longrightarrow \longrightarrow$$

$$Ph_2C{=}CPh \xleftarrow{?} Ph_3CCH_2Br$$
VII XIII

such seeming support for the now accepted radical nature of the normal Hunsdiecker reaction may be misplaced. Even if the unrearranged β,β,β-triphenylethyl bromide (XIII) had been formed, it would most surely have been rearranged to VII by the mercuric bromide present.[20]

One can only speculate as to *why* an Ar_1-5 migration of phenyl is so facile compared to an Ar_1-6 migration in the acyloxy radicals IX and XII. It is curious, as a matter of fact, since Ar_1-6 phenyl to oxygen migrations have indeed been reported. Thus, the acyloxy radicals shown readily undergo phenyl to oxygen shifts.[21] However, and this may be crucial, these radicals have less tendency to decarboxylate, being aroyloxy, than would the acyloxy radical XII and, therefore, more



time to rearrange.[22] Since scale models (Fisher–Taylor–Hirschfelder or Dreiding) indicate that both the Ar_1-5 and Ar_1-6 intermediates, *once formed*, are reasonably comparable in strain (in fact, the model of V is easier to construct), it is clear that either the transition states

(16) The tri-*p*-*t*-butyl derivative of I rearranged at −12°.[3]

(17) The rearrangement step must have a rather low activation energy since it can occur at low temperatures,[16] while decarboxylation is known to increase with temperature (C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 476) and, from the data of Table I, must possess a higher activation energy than the rearrangement step.

(18) Ring halogenation *via* the acyl hypobromite has been observed frequently; *cf.* ref. 4, pp. 253 and 254.

(19) As observed in the decarbonylation of β,β,β-triphenylpropionaldehyde by D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952).

(20) The rearrangement of the corresponding chloride is "powerfully catalyzed" by metallic halides [J. C. Charlton, I. Dostrovsky, and E. D. Hughes, *Nature*, **167**, 986 (1951)].

(21) For the rearrangement of *o*-phenoxybenzoyloxy radical, *cf.* D. F. DeTar and A. Hlynsky, *J. Am. Chem. Soc.*, **77**, 4411 (1955). For the rearrangement of *o*-benzoylbenzoyloxy radical, *cf.* P. J. Bunyan and D. H. Hey, *J. Chem. Soc.*, **324**, 2771 (1962).

(22) The rearrangements cited[21] occurred in preference to decarboxylation by large ratios. Aroyloxy radical decarboxylation has been quoted to be endothermic by 4 kcal./mole, while acyloxy radical decarboxylation is exothermic by 12–14 kcal./mole [C. Walling, ref. 17, p. 493].

leading to the intermediates differ in some important regard, or that the cleavage rates of the intermediates are quite different. It is our feeling that the formation of the highly conjugated phenyl β,β-diphenylacrylate from II is of importance. The intermediate V cannot cleave to such a conjugated product. Further work is required to investigate this point and we are so engaged at present.

Experimental

All melting points were obtained on a calibrated Fisher-Johns block. Infrared spectra were obtained on a Perkin-Elmer Model 21 infrared spectrophotometer using a sodium chloride prism. Ultraviolet spectra were obtained with a Cary Model 11 recording spectrophotometer equipped with an IP-28 phototube using 1-cm. silica cells. The samples were prepared by incremental dilution as 95% alcoholic solutions. All carbon–hydrogen microanalyses were performed by Mr. R. L. Kilboy of Sinclair Research, Inc., Harvey, Ill. The n.m.r. spectrum was determined by Nuclear Magnetic Resonance Specialties, New Kensington, Pa.

β,β,β-Triphenylpropionic Acid (I).—Preparation from malonic acid and triphenylcarbinol by the literature route[23] gave white needles, m.p. 184° after one recrystallization from acetone, in 44% yield. The infrared spectrum has been reported.[2]

γ,γ,γ-Triphenylpropyl Alcohol.—The above acid was converted into its acid chloride (m.p. 142–143°, lit.[24] m.p. (crude) 132°) by means of thionyl chloride and reduced in the usual fashion with lithium aluminum hydride in ether. The alcohol was obtained as white crystals, 92%, m.p. 107.5–108°, lit.[25] m.p. 107–108°, after one recrystallization from petroleum naphtha (b.p. 118–144°).

γ,γ,γ-Triphenylpropyl Iodide.—This compound was prepared from the above alcohol *via* its interaction with a mixture of red phosphorus and iodine as given in the literature.[25] After one recrystallization from a benzene–ethanol mixture, the iodide was obtained as white crystals (77.5%, m.p. 178.5–179°, lit.[26] m.p. 174.5–175°). The infrared spectrum was in accord with the proposed structure, though some slight contamination by the starting alcohol was apparent (an absorption at 2.9 μ).

γ,γ,γ-Triphenylbutyronitrile.—By a literature method,[8] the above iodide was converted into the nitrile by the action of sodium cyanide in dimethyl sulfoxide. The nitrile was recrystallized from 95% ethanol and formed white crystals (71%, m.p. 139–140°, lit.[27] m.p. 137.5–138°, infrared 4.44 μ).

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.86; H, 6.47; N, 4.51.

All attempts to prepare the nitrile from the iodide by displacement using aqueous methanol, aqueous ethanol, or pure ethylene glycol were unsuccessful.

γ,γ,γ-Triphenylbutyric Acid (IV).—The above nitrile was hydrolyzed by a lengthy (*ca.* 12 hr.) reflux with a solution of sulfuric and acetic acids in water (1:1:1 by volume). The acid was recrystallized from aqueous alcohol and isolated as a white solid (94.4%, m.p. 159–160°, lit.[25] m.p. 154–156°, infrared 5.84 μ).

Hunsdiecker Reactions.—The preparation of the silver salts and the Hunsdiecker reactions were carried out as described elsewhere [2,3] In addition to the precautions mentioned there, all glassware for the present study was oven-dried for at least 45 min. at 110–115° just prior to use.

Reaction of I (Silver Salt).—A repetition of the reported reaction[2] gave 1% carbon dioxide, 23% rearrangement, and 57% recovered I, in excellent accord with earlier results.[3]

Reaction of IV (Silver Salt).—Silver γ,γ,γ-triphenylbutyrate (14 g., 0.033 mole) was treated as before[2] at 25 ± 2° with bromine (5.3 g., 0.033 mole) in carbon tetrachloride as solvent The carbon dioxide evolved was collected as barium carbonate (0.685 g., 0.0033 mole, 10.1%). Processing the reaction mixture yielded an acidic reddish material (8.79 g., m.p. 52–60°) which possessed an infrared spectrum virtually identical with that of IV. There were, however, some differences and an absorption at 12.25 μ indicated some aromatic *para* substitution had occurred.

Anal. Calcd. for a mixture of $C_{22}H_{20}O_2$ (42%) and $C_{22}H_{19}BrO_2$ (58%): C, 73.86; H, 5.58; Br, 11.71. Found: C, 73.75; H, 5.69; Br, 12.20.

The spectrum and analysis indicated that this crude product was a mixture of parent acid IV and its mono-*p*-bromo derivative, although we have only the spectral evidence for the position of the bromine. A chromatographic separation of the mixture was tried on alumina (Alcoa F-20) on a 150-cm. column, using successive elution with pentane, ether, ethanol, and acetic acid. A less-colored product (97.6% recovery) was obtained, but little separation was achieved. The chromatographed product (m.p. 69–70°) failed to give any evidence of reaction with warm alcoholic silver nitrate or with sodium iodide in acetone, again pointing toward an aromatic bromo compound, although not certainly, because even bromide VI (nonaromatic halide) failed to react with these reagents under these conditions.

Anal. Calcd. for $C_{22}H_{20}O_2$ (45%) and $C_{22}H_{19}BrO_2$ (55%): C, 74.36; H, 5.53; neut. equiv., 360. Found: C, 74.33; H, 5.54, neut. equiv., 383.

From the carbon tetrachloride phase, after removal of the solvent and extraction of the residue with warm hexane, there was obtained γ,γ,γ-triphenylpropyl bromide (VI, 0.33 g., 3%, m.p. 137.5–138.5°) which had an infrared spectrum identical with the bromide isolated later. Their mixture melting point was not depressed. There also was isolated from the carbon tetrachloride phase, a small amount of an unidentified compound that showed carbonyl absorption in the infrared. "Saponification" and acidification, followed by steam distillation, yielded no phenol, however, and this side product was not considered to be a phenyl ester.

Reaction of the Acids I and IV with Mercuric Oxide and Bromine (Cristol–Firth Treatment).—These reactions were performed in a light-sealed hood in a darkened room using flasks wrapped in lightproof cloth.

Reaction of I.—Reaction of I (10 g., 0.033 mole) in dry refluxing carbon tetrachloride (150 ml.) with bromine (5.3 g., 0.033 mole) and red mercuric oxide (ACS reagent, 5.4 g., 0.025 mole) under the literature conditions[7] led to the isolation of carbon dioxide as barium carbonate (1.33 g., 20.8%). Work-up of the reaction material by alkaline extraction and subsequent acidification gave recovered I (1.65 g., 17%, m.p. 183°). Removal of the carbon tetrachloride solvent and hexane treatment as before led to the isolation of triphenylbromoethylene [VII, 0.43 g., 4%, m.p. 113.5–115.5°, lit.[28] m.p. 115.5°, infrared 6.25 and 6.35 μ, λ_{max}^{alc} 285 mμ (ε 11,300)], which was identical in all respects with authentic material (*vide infra*). Saponification of the reaction mixture from another run (same scale) with aqueous–alcoholic sodium hydroxide under reflux, followed by acidification and steam distillation into bromine water, yielded tribromophenol (2.17 g., 26%, m.p. 92°, mixture melting point with authentic material undepressed). This established the presence of at least 26% phenyl ester (undoubtedly phenyl β,β-diphenylacrylate and its α-bromo derivative[2]) in the reaction product.

Reaction of IV.—Similar reaction of IV (10.43 g., 0.033 mole), red mercuric oxide (5.4 g., 0.025 mole), and bromine (5.3 g , 0.033 mole) in refluxing carbon tetrachloride (150 ml.) yielded carbon dioxide (33.5%, weighed as barium carbonate, 2.18 g.). The carbon tetrachloride phase was washed with two 100-ml. portions of 2% sodium hydroxide solution and then with water to neutrality. Removal of the solvent and extraction with hexane gave γ,γ,γ-triphenylpropyl bromide (VI, 3.26 g., 28%), m.p. (after two recrystallizations from a hexane–ethanol mixture) 144–145°; infrared in accord with structure proposed; n.m.r., singlet at 431 c.p.s. (downfield from TMS standard, A-60 instrument), 15 protons, and a triplet at 186 c.p s., 4 protons. This triplet was in the ratio 1:5:1 with a very small separation of peaks and indicated nearly magnetic equivalence (A_4) for the methylene protons instead of the possible A_2B_2 system.

Anal. Calcd. for $C_{21}H_{19}Br$: C, 71.80; H, 5.45. Found: C, 71.90; H, 5.19.

From acidification of the alkaline wash of the solvent phase and from the hexane-insoluble portion of the residue left upon removal of the solvent there was obtained a crude mixture (6.32 g.) which was probably a mixture of acids, as isolated from the Hunsdiecker reaction on IV. There was, however, a slight amo nt of a phenyl ester present because the ferric hydroxamate test for esters was

(23) L. Hellerman, *J. Am. Chem. Soc.*, **49**, 1738 (1927).

(24) A. Simonini, *Monatsh.*, **14**, 81 (1893).

(25) W. D. McPhee and E. G. Lindstrom, *J. Am. Chem. Soc.*, **65**, 2177 (1943).

(26) C. B. Wooster and R. A. Morse, *ibid.*, **56**, 1735 (1934).

(27) G. Wittig and D. Wittenberg, *Ann.*, **606**, 1 (1957).

(28) S. Apelgot, *et al.*, *Bull. soc. chim. France*, 533 (1952).

faintly positive and saponification, acidification, and steam distillation into bromine water did yield tribromophenol (0.16 g., 2%, m.p. 92°, mixture melting point undepressed). The reaction material after this treatment no longer gave a positive ester test. This reaction mixture was considered to be essentially entirely an acid mixture, however, by its behavior and infrared. The fact that not all of it was removed from the solvent by the alkaline wash is explained by the reluctance of acids like IV to be so extracted. They form soaps and emulsions, complicating such extraction techniques.

Triphenylbromoethylene (VII).—For comparison purposes (see above) this halide was prepared by the reaction of bromine in acetic acid with triphenylethylene (K & K Laboratories), as reported.[28] From the hydrocarbon (6.0 g., 0.0234 moles) the bromide was obtained as white needles (7.5 g., 97%), m.p. 117–118°, lit.[28] m.p. 115.5°, λ_{max}^{alc} 285 mμ (ε 9720). The infrared spectrum was in accord with the proposed structure and was identical with that of the halide isolated from the Cristol–Firth treatment of I (see above).

γ,γ,γ-Triphenylbutyryl Peroxide (X).—The acid IV was converted to its acid chloride in the usual fashion with thionyl chloride. The acid chloride (4.18 g., crude material *ca.* 12.5 mmoles) was added to dry ether (50 ml.) in which was suspended sodium peroxide (0.55 g., 7 mmoles). Three drops of water were added and the mixture was stirred at 0°. Another drop of water was added after each hour. After 2.5 hr., further sodium peroxide (*ca.* 0.1 g.) was added. After 3 hr., the initial yellow color (due to the sodium peroxide) had faded, whereupon the material was placed in the refrigerator overnight. Water (10 ml.) was added and the mixture was filtered at the pump. Acetone washes of the glassware were added to the collected precipitate, and the solution was allowed to evaporate in the air (4.05 g., quantitative yield). The peroxide was difficult to purify, but the following method afforded pure material, though with great loss. The crude peroxide above was treated with hot acetone (300 ml.), filtered from insoluble matter, and, while warm, diluted with water to cloudiness. The peroxide settled out on cooling as a white, microcrystalline solid (1.1 g., 28%), m.p. 116° dec. (on a block preheated to 100°), infrared 5.48 and 5.58 μ (peroxide C=O), iodometric titration gave a purity of >90%).

Anal.[29] Calcd. for $C_{44}H_{38}O_4$: C, 83.78; H, 6.07; O, 10.15. Found: C, 84.01; H, 6.06; O, 10.04.

Decomposition of the Peroxide X.—Several decompositions were carried out in the following way. A weighed amount of peroxide X (*ca.* 130 mg.) was refluxed in pure dry carbon tetrachloride (10 ml.) in a slow stream of nitrogen for 15 min., followed by 2-min. standing, with a previously tared Ascarite tube attached to the condenser. After the reaction, the Ascarite tube was reweighed to determine the carbon dioxide evolution. Evaporation (air) of the solvent left crystalline material which was then titrated for peroxide iodometrically. The results (averaged) indicated 39% carbon dioxide evolution (on the basis of 2 moles of carbon dioxide/mole of peroxide) and 67% peroxide recovered, implying (within error) essentially complete carbon dioxide evolution for the amount of peroxide reacted. From a decomposition carried out in the higher boiling solvent chlorobenzene, the entire reaction product was saponified and acidified. Steam distillation into bromine water indicated a trace (at most) of tribromophenol.

Conversion of γ,γ,γ-Triphenylpropyl Bromide (VI) to γ,γ,γ-Triphenylbutyronitrile.—The reaction product VI (1.8 g.), sodium cyanide (0.3 g.), and dimethyl sulfoxide (25 ml.) were heated with stirring at 130–140° for 50 min., at which time another 0.3 g. of sodium cyanide was added and the mixture heated 10 min. further. Addition of water and treatment of the ether phase in the usual way[8] gave the nitrile, which was recrystallized from ethanol (0.6 g., 40%), m.p. 135.5–137°, undepressed when admixed with the nitrile prepared from the iodide, infrared identical with that of the known.

(29) Galbraith Laboratories, Inc., Knoxville, Tenn.

Substituted γ-Lactones. XIII.[1] Nitration of Substituted α-Benzylidene-γ-butyrolactones

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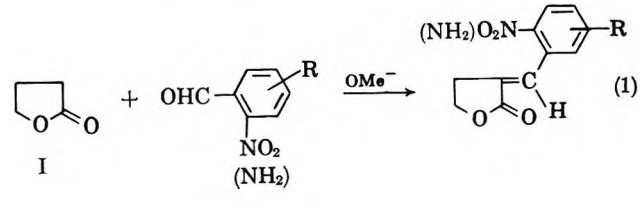
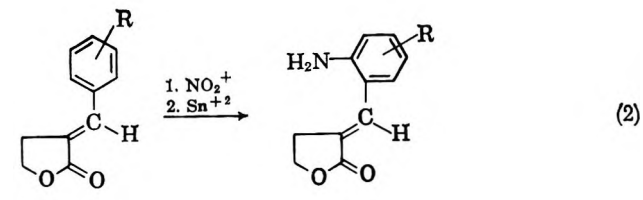
The nitration of various substituted α-benzylidene-γ-butyrolactones and -γ-valerolactones is reported. The substitution occurred generally at the same position where the corresponding benzoic acids and benzaldehydes were reported to undergo nitration. The factors influencing these electrophilic substitutions are discussed. The structures of the obtained nitro compounds were proved by oxidative degradation to the corresponding benzoic acids. Derivatives of the nitro compounds were prepared and some of their properties are reported.

Further exploration of a new rearrangement which α-(2-aminobenzylidene)-γ-butyrolactone (III) undergoes was attempted. This rearrangement was principally investigated as a convenient route toward a synthesis of dictamnine alkaloids.[1,4] Consequently, type III compounds with substituents like methoxy, ethoxy, and methylenedioxy were prepared. Two general methods for the synthesis of this type of compound are available: (1) condensation of the appropriate substituted benzaldehyde with γ-butyrolactone (I), or (2) nitration and reduction of an appropriate substituted α-benzylidene-γ-butyrolactone (II).

It was shown in a previous paper of this series[5] that the condensation of I with electron-withdrawing groups, *e.g.*, nitro or cyano groups, proceeded poorly or not at all. Attempts to use aminobenzaldehydes in this type of reaction led to excessive tar formation. Conse-





(1) Part XII: H. Zimmer and R. Walter, *Z. Naturforsch.*, **18b**, 669 (1963).

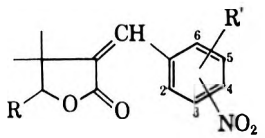
(2) National Institute of Health Fellow, 1961–1963.

(3) Postdoctoral Research Fellow, 1961–1963.

(4) (a) H. Zimmer, *Angew. Chem.* **73**, 144 (1961); 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961; (b) H. Zimmer, F. Haupter, J. Rothe, W. E. Schrof, and R. Walter, *Z. Naturforsch.*, **18b**, 165 (1963).

(5) H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959).

TABLE I



No.	R	Position of substituents 2	3	4	5	Position of NO_2 and derivatives	Formula	M.p., °C.	Solvent[a] of recrystn.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	H			OH		3	$C_{11}H_9NO_5$	161	M	56.17	55.85	3.86	4.26	5.96	6.28
2	H		OCH_2O			6	$C_{12}H_9NO_6$	183	M	54.80	54.83	3.51	3.45	5.30	5.39
3	H		OCH_2O			NH_2	$C_{12}H_{11}NO_4$	233–234	E	61.80	61.90	4.75	4.61	6.10	6.26
4	H		OCH_2O			$CNCH_2NH$	$C_{14}H_{12}N_2O_4$	203–205	M	61.79	62.14	4.44	4.71	10.29	10.01
5	H		OCH_2O			CH_3CONH	$C_{14}H_{13}NO_6$	257	E	61.09	61.14	4.76	4.59	5.09	5.06
6	H		OCH_2O			$4\text{-}NO_2PhSO_2NH$	$C_{18}H_{14}N_2O_9S$	268–269	DMF–M	51.68	49.85	3.35	3.37	6.70	6.59
7	H		OCH_2O			$4\text{-}NH_2PhSO_2NH$	$C_{18}H_{16}N_2O_6S$	244	E	55.67	55.61	4.15	4.21	7.21	7.37
8	H		OCH_2O			$3,5\text{-}NO_2PhCONH$	$C_{19}H_{13}N_3O_9$	289	E	53.40	53.52	3.07	3.19	9.83	9.82
9	H		OCH_2O			$PhCH{=}N$	$C_{19}H_{15}NO_4$	199	M	71.02	71.14	4.71	4.91	4.36	4.46
10	H			OCH_3		3	$C_{12}H_{11}NO_5$	161	M	57.83	56.91	4.45	4.52	5.62	5.74
11	H			OCH_3		NH_2	$C_{12}H_{13}NO_3$	180	M	65.74	66.60	6.97	6.22	6.39	6.30
12	H			OCH_3		CH_3CONH	$C_{14}H_{15}NO_4$	210	E	64.36	64.80	5.79	5.42	6.36	5.39
13	H			OCH_3		$4\text{-}NO_2PhSO_2NH$	$C_{18}H_{16}N_2O_7S$	199	E	53.47	53.69	3.99	3.98	6.93	7.14
14	H			OCH_3		$PhSO_2NH$	$C_{18}H_{17}NO_5S$	189	E	60.16	60.42	4.77	4.79	3.90	4.30
15	H			OCH_3		$4\text{-}NH_2PhSO_2NH$	$C_{18}H_{18}N_2O_5S$	198	D–P	57.75	57.07	4.85	5.07	7.48	7.46
16	H			OCH_3		$4\text{-}AcNHPhSO_2NH$	$C_{20}H_{20}N_2O_6S$	265	DMF–Et	57.69	57.43	4.84	4.97	6.73	6.77
17	H	OCH_3	OCH_3				$C_{13}H_{14}O_4$	92	M	66.66	67.14	6.02	6.02		
18	H	OCH_3	OCH_3			5	$C_{13}H_{13}NO_6$	219	M	55.91	56.19	4.70	4.46	5.02	5.01
19	H	OCH_3	OCH_3			NH_2	$C_{13}H_{15}NO_4$	159	M	62.64	62.22	6.07	6.13	5.62	5.71
20	H	OCH_3	OCH_3			CH_3CONH	$C_{15}H_{17}NO_5$	188–189	M	61.85	61.05	5.88	6.10	4.81	4.74
21	H	OCH_3	OCH_3			$PhCH{=}N$	$C_{20}H_{19}NO_4$	127–128	M	71.20	71.20	5.68	5.75	4.15	4.22
22	H			CH_3			$C_{12}H_{12}O_2$	104–105[b]	M	76.57	76.32	6.43	6.31		
23	H			CH_3		3	$C_{12}H_{11}NO_4$	125–126	M	61.80	62.32	4.75	4.94	6.01	6.13
24	H	OCH_3			OCH_3		$C_{13}H_{14}O_4$	97	M	66.66	66.45	6.02	5.84		
25	H	OCH_3			OCH_3	4	$C_{13}H_{13}NO_6$	182	M	55.91	55.66	4.70	4.73	5.02	5.36
26	H	OCH_3			OCH_3	NH_2	$C_{13}H_{15}NO_4$	214–215	M	62.64	62.62	6.07	6.11	5.62	5.64
27	H	OCH_3			OCH_3	CH_3CONH	$C_{15}H_{17}NO_5$	244–245	M	61.85	62.15	5.88	6.04	4.81	4.86
28	H		OCH_3	OCH_3		6	$C_{13}H_{13}NO_6$	165	M	55.91	55.57	4.70	4.70	5.02	5.10
29	H		OCH_3	OCH_3		NH_2	$C_{15}H_{15}NO_4$	162	M	62.64	62.41	6.07	6.19	5.62	6.10
30	H		OCH_3	OCH_3		CH_3CONH	$C_{16}H_{17}NO_5$	169–170	M	61.85	60.54	5.88	5.77	4.81	4.92
31	H		OCH_3	OCH_3		$4\text{-}NO_2PhSO_2NH$	$C_{19}H_{18}N_2O_9S$	234	D–P	52.54	52.60	4.18	4.97	6.45	5.80

32	H			$PhSO_2NH$	$C_{19}H_{19}NO_6S$	231	M	58.61	59.12	4.92	4.97	3.60	3.00
33	H	OCH_3	OCH_3	$4\text{-}NH_2PhSO_2NH$	$C_{19}H_{20}N_2O_6S$	235	D–P	56.43	56.14	4.99	4.88	6.93	6.71
34	H	OCH_3	OCH_3	$4\text{-}AcNHPhSO_2NH$	$C_{21}H_{22}N_2O_7S$	250	D–P	56.50	55.60	4.97	5.02	6.28	5.90
35	H	OC_2H_5	OC_2H_5	6	$C_{13}H_{17}NO_6$	171	E	58.63	58.33	5.58	5.42	4.56	4.61
36	H	OC_2H_5	OC_2H_5	NH_2	$C_{13}H_{19}NO_4$	149–150	E	64.96	64.71	6.91	6.83	5.05	5.08
37	H	OC_2H_5	OC_2H_5	CH_3CONH	$C_{17}H_{21}NO_5$	205–206	M	63.93	62.62	6.63	6.40	4.39	3.92
38	H	OC_2H_5	OC_2H_5	PhCH=N	$C_{22}H_{23}NO_4$	102–104	M	72.31	71.51	6.34	6.04	3.83	4.00
39	CH_3	Cl	Cl		$C_{12}H_{10}Cl_2O_2$	105	M	56.06	56.00	3.92	4.00		[c]
40	CH_3	Cl	Cl	6	$C_{12}H_9Cl_2NO_4$	169–170	M	47.7	47.61	3.00	3.09	4.64	4.80[d]
41	CH_3	OCH_2O		6	$C_{13}H_{11}NO_6$	168	M	56.32	56.27	4.00	3.88	5.05	5.37
42	CH_3	OCH_2O		NH_2	$C_{13}H_{13}NO_4$	174	M	63.15	63.34	5.30	5.28	5.67	5.89
43	CH_3	OCH_2O		$CNCH_2NH$	$C_{15}H_{14}N_2O_4$	195–196	M	62.93	63.48	4.93	4.98	9.76	10.18
44	CH_3	OCH_2O		CH_3CONH	$C_{15}H_{15}NO_5$	197	M	62.28	61.93	5.23	5.34	4.84	5.23
45	CH_3	OCH_2O		$3,5\text{-}(NO_2)_2PhCONH$	$C_{20}H_{15}N_3O_9$	219–220	E	54.43	54.55	3.43	3.46	9.52	9.69
46	CH_3	OCH_2O		PhCH=N	$C_{20}H_{17}NO_4$	164–165	M	71.63	71.54	5.11	5.18	4.18	4.08
47	CH_3	OCH_2O		PhCONH	$C_{20}H_{17}NO_5$	235	E	68.37	68.27	4.88	4.98	3.99	3.58
48	CH_3	OC_2H_5	OC_2H_5		$C_{16}H_{20}O_4$	108–109	M	69.54	69.37	7.30	7.08		
49	CH_3	OC_2H_5	OC_2H_5	6	$C_{16}H_{19}NO_6$	144–145	M	59.80	59.63	5.96	5.91	4.36	4.56
50	CH_3	OC_2H_5	OC_2H_5	NH_2	$C_{16}H_{21}NO_4$	196	M	65.95	66.03	7.27	7.46	4.81	4.84
51	CH_3	OC_2H_5	OC_2H_5	PhCH=N	$C_{23}H_{25}NO_4$	137	M	72.80	72.82	6.64	6.75	3.69	3.73

[a] D = dioxane, DMF = dimethylformamide, E = ethanol, Et = diethyl ether, M = methanol, P = petroleum ether. [b] Compound 22 has been published by H. Zimmer and J. Rothe [*J. Org. Chem.*, **24**, 28 (1959)], but the melting point was reported as 63–64°. [c] *Anal.* Calcd.: Cl, 27.58. Found: Cl, 27.81. [d] *Anal.* Calcd.: Cl, 23.47. Found: Cl, 23.59.

quently, route 1 was not used. Route 2, on the other hand, appeared much more promising for obtaining the desired class of compounds, since it previously was shown[6] that nitration of II led to a mixture of α-(2- and 4-nitrobenzylidene)-γ-butyrolactone which easily could be separated and then reduced to III (and the 4 isomer). This showed that the α-methylidene group in I possessed activating properties and, therefore, caused *ortho* and *para* orientation in electrophilic aromatic substitution. Therefore, it was hoped to obtain some *o*-nitro isomers as reaction products of the nitration of substituted II. This paper describes in some detail the results of the nitration of several type II compounds substituted by hydroxy, methoxy, ethoxy, methylenedioxy, chloro, and methyl groups.

Results and Discussion

The usual nitration procedures employing HNO_3–H_2SO_4 or H_2SO_4–KNO_3 which were applied in the nitration of II[6] did not work with the substituted type II compounds used in this study. Instead, only tars were obtained. Nitration, however, was accomplished with concentrated nitric acid (*d* 1.42) as nitrating agent. Care was taken that the temperature did not rise over 0–5°. Best results were achieved at about −10°, when yields of 95–100% of nitration product were obtained. On the other hand, type II compounds substituted by deactivating groups needed fuming nitric acid for nitration. Through the introduction of one nitro group the phenyl ring became so deactivated that under the elected conditions no further nitration took place. In Table I the compounds obtained by these nitrations are reported along with some of their derivatives.

The nitration occurred nearly always at the same position at which the corresponding benzoic acids or benzaldehydes were reported to undergo nitration. This can be readily explained by assuming that the strong electron-donating groups on the phenyl ring as used in this study were the only ones which exerted an orientation upon the incoming nitro group and, therefore, take preference over the weak *ortho–para* orientation power of the methylidene group. In Table II the results of nitration are reported and the findings are compared with the behavior of the corresponding benzoic acids and benzaldehydes under these conditions.

The only exception was compound 25. In this case, however, the deviation from the normal behavior can be accounted for by steric hindrance with the α-methylidene-γ-butyrolactone group possessing larger spatial requirements than either the carboxylic acid or the carboxaldehyde groups. In agreement with this assumption is the fact that α-(3,4,5-trimethoxybenzylidene)-γ-butyrolactone could not be nitrated, whereas the nitration of 3,4,5-trimethoxybenzoic acid was reported to take place at the 2-position.[7,8]

Compound 24 was expected to undergo nitration at 6-position. This is analagous to 2,5-dimethoxybenzoic acid, which was reported to have been nitrated, yielding the 6- and 3-nitro derivatives[9]; however, 24 underwent nitration at the 4-position. This is also in agreement

(6) H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 100 (1959).
(7) J. Pollak and H. Feldscharek, *Monatsh.*, **29**, 139 (1908).
(8) J. Harding, *J. Chem. Soc.*, **99**, 1585 (1911).
(9) See under *k*, Table II.

TABLE II

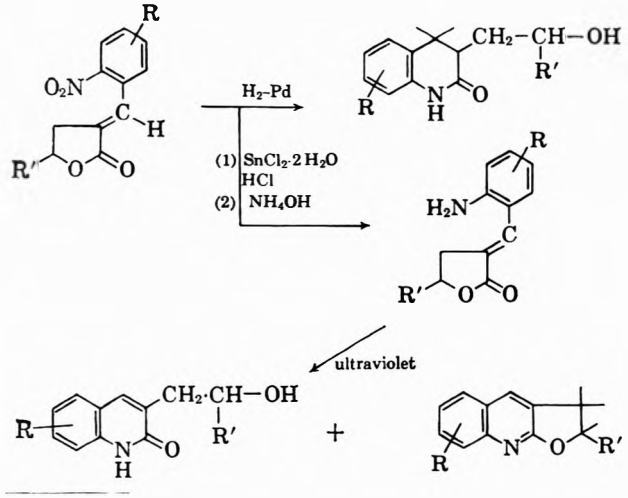
No. of compound in Table I	Position of nitration in corresponding benzoic acid	Ref.	Position of nitration in corresponding benzaldehyde	Ref.	Agreement of nitration position with substituted II
1	3	*a*	3	*b*	Yes
2,41	6	*c*	6	*d*	Yes
10	3	*e*		*f*	Yes
18	5	*g*	5,6	*h*	Yes
22	3	*i*	3	*j*	Yes
25	3,6	*k*	6,(3)	*k*	No
28	6	*l*	6	*m*	Yes
35,49	6	*n*	6	*o*	Yes
40	6	*p*	6	*q*	Yes

[a] See ref. 12. [b] M. Schöpff, *Ber.*, **24**, 3776 (1891); C. Paal, *ibid.*, **28**, 2413 (1895), and further references: K. Auwers and H. Röhrig, *ibid.*, **30**, 996 (1897). [c] See ref. 13. [d] R. Fittig and J. Remsen, *Ann.*, **159**, 134 (1871); F. Haber, *Ber.*, **24**, 624 (1891); G. Ciamician and P. Silber, *Gazz. chim. ital.*, **33I**, 371 (1903); A. H. Salway, *J. Chem. Soc.*, **95**, 1163 (1909); M. T. Bogert and F. R. Elder, *J. Am. Chem. Soc.*, **51**, 534 (1929). [e] See ref. 14. [f] A. Einhorn and J. P. Grabfield, *Ann.*, **243**, 370 (1880); E. Worner, *Ber.*, **29**, 157 (1896); M. P. De Lang, *Rec. trav. chim.*, **45**, 45 (1926). [g] See ref. 15. [h] W. H. Perkin, R. Robinson, and F. W. Stoyle, *J. Chem. Soc.*, **125**, 2357 (1924). [i] R. Fittig, and W. Ramsay, *Ann.*, **168**, 251 (1873); E. Kloppel, *Ber.*, **26**, 1733 (1893); M. L. van Scherpenzeel, *Rec. trav. chim.*, **20**, 158 (1901). [j] L. Gattermann, *Ann.*, **347**, 354 (1906); V. Hanzlik, and A. Bianchi, *Ber.*, **32**, 1288 (1899). [k] See ref. 10. [l] W. Merch, *Ann.*, **108**, 54 (1858); F. Tiemann and K. U. Matsmoto, *Ber.*, **9**, 938 (1876); Th. Zincke and B. Francke, *Ann.*, **293**, 177 (1897). [m] R. Pschorr and C. Sumuleanu, *Ber.*, **32**, 3412 (1899). [n] This study. [o] J. Szabo and E. Vinkler, *Acta Chim. Sci. Hung.*, **17**, 201 (1958). [p] See ref. 19. [q] Höchster Farbwerke, German Patent 254,467; A. Claus and A. W. Bücher, *Ber.*, **20**, 1624 (1887)

with the nitration of ω-bromo-2,5-dimethoxyacetophenone, which upon nitration yielded the 4-nitro derivative along with the 6-nitro isomer.[10]

The position at which the nitration took place on type II compounds was generally determined by potassium permanganate oxidation, which yielded the corresponding benzoic acid. All these acids were known compounds; in a few instances in which there were only scanty literature references available, the structures of the resulting benzoic acids were further confirmed by their n.m.r. spectra. Additional proof for the position of nitration was provided in the following ways. First, the type II compound was hydrogenated to yield the α-aminobenzyl-γ-lactone derivative, or, in cases in which nitration took place *ortho* to the methylidenelactone group, the corresponding 2-oxo-1,2,3,4-tetrahydroquinoline.[11] Secondly, only the nitro group was reduced to the amino group. Again, if the nitro group occupied the *ortho* position, type III compound could be rearranged by ultraviolet radiation[4] in alcoholic solution to yield the corresponding 2-oxoquinoline, the corresponding furoquinoline, or both products (Scheme I; details will be published in a forthcoming communication).

SCHEME I



(10) R. W. Bost and C. A. Howe, *J. Am. Chem. Soc.*, **73**, 5864 (1951).
(11) H. Zimmer and R. Walter, *Naturwiss.*, **50**, 331 (1963).

Experimental

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium in Max-Planck Institute, Mühlheim/Ruhr, Germany, and Aug. Peisker-Ritter, Mikroanalytisches Laboratorium, Brugg, Switzerland.

Condensations.—The condensations were run as described in literature.[5]

Nitrations. A. Nitration of α-Benzylidene-γ-butyrolactones with Activating Substituents in the Phenyl Group.—A solution of 250 ml. of nitric acid (*d* 1.42) was cooled by means of an ice–salt bath. While being stirred 50–80 g. of carefully powdered and dried α-benzylidene-γ-butyrolactone species was added. The internal temperature was held for the next 4 hr. at −10° and then permitted to rise to +5°. Nitration took place even though in some cases solution was not complete. The mixture was poured into 1000 ml. of water. A yellow precipitate occurred, which was filtered by suction and thoroughly washed with cold water and ice-cold ether. Recrystallization either from methanol or ethanol was performed.

B. Nitration of α-Benzylidene-γ-butyrolactones without Activating Substituents in the Phenyl Group.—A solution of 50 ml. of fuming nitric acid was cooled with ice and 5 g. of the carefully powdered compound was added keeping the temperature below +5°. After 30 min. the mixture was diluted with 150 ml. of water. It was treated further as described in A.

Verification of the Nitration Products. General Procedure. A. Verification of the Structures of the Compounds 1, 10, 18, 22, 25, 28, 35, and 49 (Table I).—To a suspension of 2 g. of α-nitrobenzylidene-γ-butyrolactone derivative in 300 ml. of water was added 7 g. of potassium permanganate. The temperature was held at 80–90° for 2–3 hr. The manganese dioxide was filtered off and the hot yellow solution was concentrated by evaporation to 50 ml. Acidification with 10% sulfuric acid gave free acid.

B. Verification of the Structures of the Compounds 2, 40, and 41.—The procedure was the same as A, except that the oxidation was performed at room temperature over a period of 4 hr. After acidification the solution was extracted with benzene, which was evaporated. The resulting oil was recrystallized from methanol. The melting points of these acids did agree with the ones reported in the literature, the only exception being 2,5-dimethoxy-4-nitrobenzoic acid. 3-Nitro-4-hydroxybenzoic acid was obtained from compound 1, m.p. 184–185°[12]; 6-nitro-3,4-methylenedioxybenzoic acid from compounds 2 and 41, m.p. 172°[13]; and 3-nitro-

(12) (a) F. Biehsinger and W. Bossum, *Ber.*, **48**, 1310 (1915); (b) A. Deninger, *J. prakt. Chem.*, [2]**42**, 552 (1890).
(13) (a) J. Jobst and O. Hesse, *Ann.*, **199**, 70 (1879); (b) E. Marneli, *Gazz. chim. ital.*, **39II**, 179 (1909); (c) J. B. Ekeley and M. S. Klemene, *J. Am. Chem. Soc.*, **50**, 2711 (1928).

4-methoxybenzoic acid[14] from compound 10, m.p. 186–187°. 5-Nitro-2,3-dimethoxybenzoic acid[15] had m.p. 178°. The n.m.r. spectrum showed a 2.85-c.p.s. splitting of the aromatic protons which is further evidence for the assumed structure.

Anal. Calcd. for $C_9H_9NO_6$: N, 6.17. Found: N, 6.28.

3-Nitro-4-methylbenzoic acid[16] had m.p. 190°. 4-Nitro-2,5-dimethoxybenzoic acid had m.p. 198°, lit.[10] m.p. 192–193°.

Anal. Calcd. for $C_9H_9NO_6$: N, 6.17. Found: N, 6.18.

Hydrogenation gave α-(4-amino-2,5-dimethoxybenzyl)-γ-butyrolactone, m.p. 108°. The infrared spectrum showed absorption peaks corresponding to a primary amino group (2.98 and 3.08 μ) and a carbonyl group (5.67 μ). The n.m.r. spectrum is in agreement with aromatic protons occupying the positions *para* to each other.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 63.65; H, 6.98; N, 5.59.

6-Nitro-3,4-dimethoxybenzoic acid[17] had m.p. 187° and 6-nitro-3,4-diethoxybenzoic acid[18] had m.p. 143–144°. 3,4-Diethoxybenzoic acid was nitrated at 0° with nitric acid (*d* 1.42); after purification it showed m.p. 144–145°. Mixture melting point with acid obtained by degradation showed no depression. 6-Nitro-3,4-dichlorobenzoic acid[19] had m.p. 164°.

Reduction of α-(Nitrobenzylidene)-γ-butyrolactones to α-(Aminobenzylidene)-γ-butyrolactones.—The general procedure has been published elsewhere.[5] It was altered so that only 180 ml. of hydrochloric acid was used and instead of chloroform in the Soxhlet extraction dry acetone was used. The advantage was that no tars occurred. All amines possessed a yellow color.

Schiff's Bases.—One-half gram of the appropriate amine was dissolved in 1 ml. of benzaldehyde and heated on the water bath for 30 min. Addition of 5 ml. of methanol and cooling in an ice bath caused precipitation of yellow needles. Recrystallization was performed from methanol.

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(14) (a) H. Salkowski, *Ann.*, **163**, 8 (1872); (b) V. Froelicher and F. B. Cohen, *J. Chem. Soc.*, **121**, 1656 (1922).

(15) (a) F. C. Cannell and J. L. Simonsen, *ibid.*, **105**, 159 (1913); (b) L. Rubenstein, *ibid.*, 649 (1926).

(16) See under 1, Table II.

(17) (a) Th. Zincke and B. Francke, *Ann.*, **293**, 192 (1897); (b) J. L. Simonsen and M. G. Rau, *J. Chem. Soc.*, **113**, 24 (1921).

(18) (a) A. G. Perkin and E. R. Watson, *ibid.*, **107**, 206 (1915); (b) O. L. Galmarini, *Anales asoc. quim. arg.*, **39**, 92 (1951); (c) T. Szabo and E. Vinkler, *Acta Chim. Sci. Hung.*, **17**, 201 (1958).

(19) (a) A. Claus and A. W. Bucher, *Ber.*, **20**, 1624 (1887); (b) P. Ruggli and H. Zaeslin, *Helv. Chim. Acta*, **19**, 439 (1936).

A Novel Synthesis of Nitroalkyl Ethers and Their Cleavage to Nitro Alcohols

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The reaction of 2-nitroalkyl acetates with alkali alkoxides and alkyl thiolates has been found to constitute a convenient route for the synthesis of 1-alkoxy-2-nitro alkanes and alkyl 2-nitroalkyl sulfides, respectively. Michael-type additions of 1-alkoxy-2-alkane nitronates to 2-nitro alkenes (prepared *in situ* from 2-nitroalkyl acetates) afford 1-alkoxy-2-alkyl-2,4-dinitro alkanes in satisfactory yields. Reaction of these nitro ethers with boron trichloride results in cleavage with the formation of 2-alkyl-2,4-dinitro 1-alkanols in good yield.

It has been well-established that the Michael-type addition of primary nitro alkanes to α-nitro alkenes gives the desired adducts only in poor yield.[2-6] On the other hand, the reaction affords high yields with secondary nitro alkanes. It seems, therefore, that in order to obtain good yields in the Michael-type addition with primary nitro alkanes, the latter should first be converted to secondary ones. Such a conversion is available readily in the methylolation reaction which converts primary nitro alkanes into secondary nitro alcohols.[7] However, at the basic conditions of the Michael-type addition, these nitro alcohols undergo demethylolation and cannot be employed satisfactorily. It was, therefore, the purpose of this investigation to convert the hydroxyl group in nitro alcohols into a group which would be stable under the conditions of the Michael-type addition, then to regenerate the hydroxyl group, and finally to convert by demethylolation the resulting polynitro alkanol into the polynitro alkane. While the first two goals of this research could be realized, the demethylolation step which required basic catalysis did not lead to the desired polynitro alkanes; instead, a rearrangement took place leading to isoxazoles.[8]

At the outset of this investigation it was hoped that acetals would be good protecting groups and would subsequently be removed readily. These expectations were, however, not fulfilled when tested on model compounds. For instance, 2-(2-nitro-2-methyl-1-propoxy)-tetrahydropyran which was prepared from dihydropyran and 2-nitro-2-methyl-1-propanol according to the procedure of Parham[9] could not be cleaved to the alcohol with dilute hydrochloric acid. Stronger acids such as concentrated hydrochloric acid or boron trichloride caused extensive tar formation. The acetal, bis(2-nitrobutoxy)methane[10] (I), was quantitatively converted to 2-nitro-1-butanol (II) by cleavage with boron trichloride but was found to be unstable at the conditions of the Michael-type reaction. I was readily hydrolyzed in basic medium to the alcohol (II) and formaldehyde.

$$\underset{\text{I}}{(H_3CCH_2CH(NO_2)CH_2O)_2CH_2} \xrightarrow{OH^-} \underset{\text{II}}{2H_3CCH_2CH(NO_2)CH_2OH} + CH_2O$$

Preparation of 1-Alkoxy-2-nitro Alkanes.—Because of the instability of nitroalkyl acetals at the conditions at which Michael-type additions are usually carried out, our investigation turned to 2-nitroalkyl ethers in which

(1) From the Ph.D. thesis of S. Markofsky, Purdue University, 1962.

(2) A. Lambert and H. A. Piggott, *J. Chem. Soc.*, 1489 (1947).

(3) C. T. Bahner and H. T. Kite, *J. Am. Chem. Soc.*, **71**, 3597 (1949).

(4) H. R. Snyder and W. E. Hamlin, *ibid.*, **72**, 5082 (1950).

(5) G. L. Shoemaker and R. W. Keown, *ibid.*, **76**, 6374 (1954).

(6) H. Feuer and R. Miller, *J. Org. Chem.*, **26**, 1348 (1961).

(7) H. B. Hass and E. F. Riley, *Chem. Rev.*, **39**, 373 (1943).

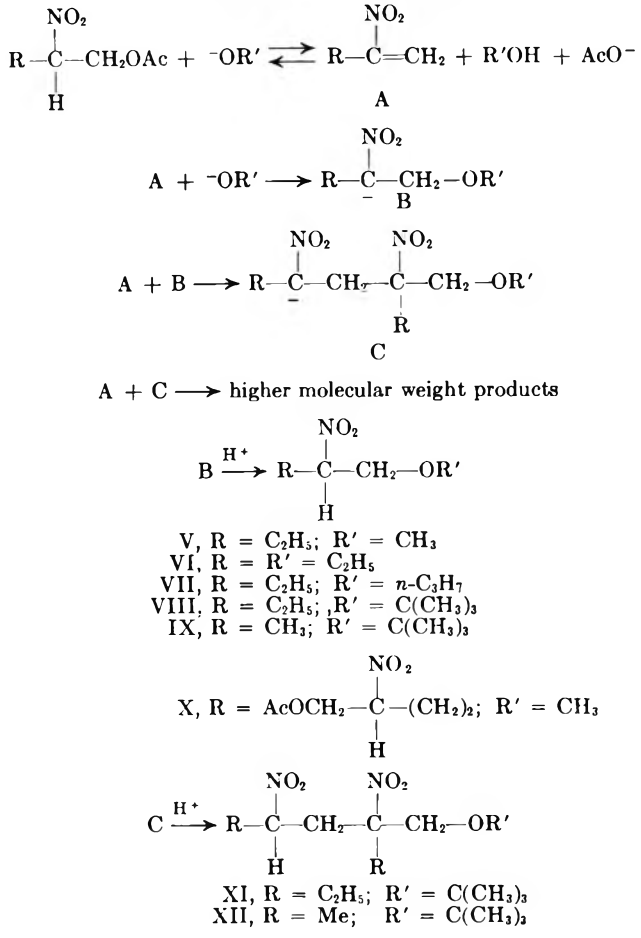
(8) This transformation is discussed in a subsequent paper. H. Feuer and S. Markofsky, *J. Org. Chem.*, **29**, 935 (1964).

(9) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).

(10) M. Senkus, *ibid.*, **69**, 1380 (1947).

SCHEME I

FORMATION OF 1-ALKOXY-2-NITRO ALKANES AND 1-ALKOXY-2-ALKYL-2,4-DINITRO ALKANES



the hydroxyl group is substituted by an alkoxy group. It was established that such groups are not affected by dilute base and that such ethers conveniently could be employed in Michael-type additions (see Scheme I).

2-Nitroalkyl ethers usually have been prepared by treating α-nitro alkenes with sodium alkoxides.[11-13] The disadvantage of this method is that α-nitro alkenes are difficult to work with because they (a) tend to decompose during purification which usually requires distillation, (b) are strong lachrymators, and (c) have a tendency to polymerize on standing.[14] Lambert, *et al.*,[12] recognized these difficulties and prepared 1-alkoxy-2-nitro alkanes from α-nitro alkenes which were generated *in situ* from 1,2-dinitro alkanes (III) or 2-nitroalkyl nitrates (IV) However, compounds of structure III or IV are not obtained in good yields, are difficult to purify and to store, and are explosive in nature.[15,16]

Recently, a more convenient way of synthesizing 2-nitroalkyl ethers presented itself due to the work of Feuer and Miller,[6] who showed that 2-nitro alkenes could be generated readily *in situ* from 2-nitroalkyl acetates in the presence of a base. We have now found that 1-alkoxy-2-nitro alkanes can be prepared much more conveniently by adding 2-nitroalkyl acetates slowly to a large excess of an alkali alkoxide (see Table I). An excess was employed in order to minimize the formation of high molecular weight products, formed by the addition of anions such as B and C to the nitro olefin. The nature of the higher molecular weight compounds was established for two cases. 1-*t*-Butoxy-2-ethyl-2,4-dinitrohexane (XI) and 1-*t*-butoxy-2-methyl-2,4-dinitropentane (XII) were obtained directly on treatment of 2-nitrobutyl acetate and 2-nitropropyl acetate, respectively, with potassium *t*-butoxide (see Table II).

A diether, 1,6-dimethoxy-2,5-dinitrohexane (X), was prepared also from the reaction between 1,6-diacetoxy-2,5-dinitrohexane[6] and sodium methoxide. Compound X was separated into its diastereomers by fractionated crystallization. It is of interest to note that the lower melting isomer did not isomerize to the higher melting one on treatment with acid. This is in contrast to the behavior of the 2,5-dinitro-1,6-hexanediols in which the lower melting isomer was found to undergo acid-catalyzed isomerization into the higher melting one.[17]

The convenient synthesis of 2-nitroalkyl ethers was extended to 2-nitroalkyl thioethers (see Table I). These thioethers were obtained in higher yield than the corresponding nitroalkyl ethers and the formation of higher molecular weight by-products was not observed. These findings are in agreement with those of Heath and Lambert, who had prepared a number of alkyl 2-nitroalkyl thioethers from nitro alkenes and sodium alkane thiolates.[18]

Preparation of 1-Alkoxy-2-alkyl-2,4-dinitro Alkanes.—The stability of 1-alkoxy-2-nitro alkanes in basic medium made it possible to employ them in Michael-type additions with α-nitro olefins which were generated *in situ* from 2-nitroalkyl acetates.

In order to obtain optimum yields of these Michael adducts, different solvent systems had to be used. For example, 1-*t*-butoxy-2-ethyl-2,4-dinitrohexane (XI) and 1-methoxy-2-ethyl-2,4-dinitrohexane (XIII) were prepared in high yield when the solvent was aqueous methanol. This same solvent system afforded 1-*t*-butoxy-2-ethyl-2,4-dinitropentane (XIV) only in small amounts. The major products consisted of black high molecular weight material which probably formed by the anionic polymerization of 2-nitro-1-propene. When the reaction was carried out heterogeneously in water as the solvent, the polymerization was minimized and XIV was obtained in 49% yield.

The reaction between sodium 1-*t*-butoxy-2-propanenitronate and 2-nitropropyl acetate gave the highest yield (44%) of 1-*t*-butoxy-2-methyl-2,4-dinitropentane (XII) when a mixture of tetrahydrofuran and water was employed as the solvent. Compound XII also was obtained directly from the reaction between 3 equivalents of 2-nitropropyl acetate and 4 equivalents of potassium *t*-butoxide. Under these conditions, the anion, 1-butoxy-2-propanenitronate, which formed *in situ*, added to 2-nitropropene which also was generated *in situ* to give XII in 36% yield. A summary of examples studied is presented in Table II.

(11) M. Senkus, U. S. 2,391,815 (Jan. 29, 1946); *Chem. Abstr.*, **40**, 4391 (1946).

(12) A. Lambert, C. W. Scaife, and A. E. Wilder-Smith, *J. Chem. Soc.*, 1474 (1947).

(13) W. Seagers and P. Elving, *J. Am. Chem. Soc.*, **71**, 2947 (1949).

(14) N. Levy and J. D. Rose, *Quart. Rev.* (London), **1**, 358 (1947).

(15) N. Levy, C. W. Scaife, and A. E. Wilder-Smith, *J. Chem. Soc.*, 1096 (1946).

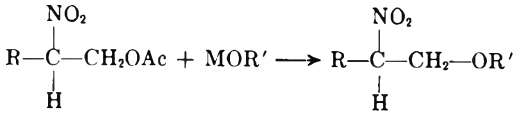
(16) N. Levy and C. W. Scaife, *ibid.*, 1100 (1946).

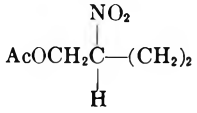
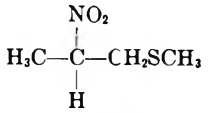
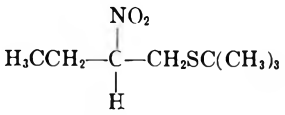
(17) H. Feuer and A. T. Nielsen, *Tetrahedron*, **19**, 65 (1963).

(18) R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947).

TABLE I

PREPARATION OF 2-NITROALKYL ETHERS AND THIOETHERS

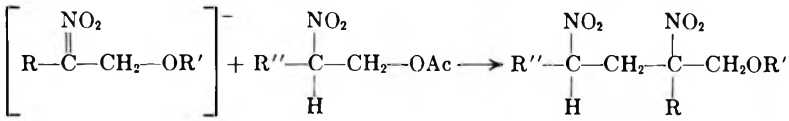


Nitro compound R	MOR' M; R'	Solvent	Product	Yield, %	B.p., °C. (mm.)
C_2H_5	Na; CH_3	CH_3OH	V	66[a]	69 (7)
C_2H_5	Na; C_2H_5	C_2H_5OH	VI	59[a]	80 (10)
C_2H_5	Na; n-C_3H_7	n-C_3H_7OH	VII	55[a]	89 (9)
C_2H_5	K; $C(CH_3)_3$	$(CH_3)_3COH$, THF[c]	VIII	40,[b] 52[a]	80 (5)
CH_3	K; $C(CH_3)_3$	$(CH_3)_3COH$, THF[c]	IX	38,[b] 57[a]	103 (35)
	Na; CH_3	CH_3OH	X	78[a,d]	
CH_3	$NaSCH_3$	CH_3OH		76[a]	100 (16)
C_2H_5	$NaSC(CH_3)_3$	CH_3OH		93[a]	87 (3)

[a] The reaction was carried out at 0–5°. [b] The reaction was carried out at room temperature. [c] Tetrahydrofuran (THF) was added to increase the solubility of potassium t-butoxide. [d] A mixture of diastereomers was obtained, m.p. 56–70°.

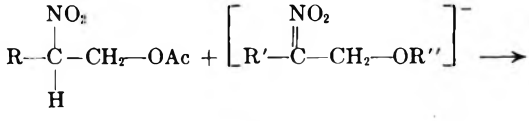
TABLE II

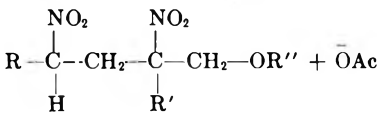
MICHAEL REACTIONS OF 2-NITROALKYL ETHERS



Nitro ethers R; R'	Nitro acetate R''	Product	Yield, %	B.p., °C. (μ)	M.p., °C.	$n^{20}D$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
C_2H_5; $C(CH_3)_3$	C_2H_5	XI	74[a]	70 (4)		1.4521	$C_{12}H_{24}N_2O_5$	52.16	8.75	10.14	52.25	9.00	10.17
CH_3; $C(CH_3)_3$	CH_3	XII	24[b]; 44[c]	85 (35)	52.4–59[d]		$C_{10}H_{20}N_2O_5$	48.37	8.12	11.28	48.61	8.31	11.08
C_2H_5; CH_3	C_2H_5	XIII	74[a]	69 (8)		1.4580	$C_9H_{18}N_2O_5$	46.14	7.75	11.96	46.19	7.60	11.98
C_2H_5; $C(CH_3)_3$	CH_3	XIV	49[b]	75 (10)		1.4516	$C_{11}H_{22}N_2O_5$	50.37	8.45	10.68	50.77	8.49	10.96
CH_3; $C(CH_3)_3$	C_2H_5	XV	66[b]	85 (1)	57–65[d]		$C_{11}H_{22}N_2O_5$	50.37	8.45	10.68	50.86	8.49	10.71

[a] The solvent was H_2O–CH_3OH. [b] The solvent was H_2O. [c] The solvent was H_2O–THF. [d] Constituted a mixture of diastereomers.





XIII, R = R' = C_2H_5; R'' = CH_3
XIV, R = CH_3; R' = CH_3CH_2; R'' = $C(CH_3)_3$
XV, R = C_2H_5; R' = CH_3; R'' = $C(CH_3)_3$

Cleavage of 2-Nitroalkyl Ethers.—The successful synthesis of 1-alkoxy-2-alkyl-2,4-dinitro alkanes (*vide supra*) indicated a route to the preparation of polynitro monoalcohols, provided that suitable conditions for ether cleavage could be achieved. In a preliminary investigation, a number of cleavage experiments were carried out with 1-alkoxy-2-nitro alkanes. It was found that 1-*t*-butoxy-2-nitrobutane (VIII) was cleaved in 59% yield with concentrated hydrochloric acid and in 65% yield with gaseous hydrogen chloride. Both cleavage reactions were accompanied by the formation of black tarry decomposition products. This decomposition was not unexpected since strong acids are known to affect primary and secondary nitro alkanes.[7,19] When 4 *N* hydrochloric acid was used only unchanged VIII was recovered.

In order to eliminate the decomposition of 1-alkoxy-2-nitro alkanes in the cleavage reaction with a strong acid such as hydrogen chloride, it was decided to investigate the applicability of an aprotic acid such as boron trichloride. Gerrard and Lappert[20] have reported that this reagent readily cleaved ethers in high yields and at low temperatures.

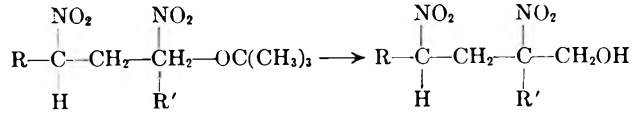
It was established that the simple nitro ethers (V, VI, and VIII) were readily cleaved by boron trichloride to the 2-nitrobutyl dichloroboronite which, on subsequent warming with methanol, was converted to 2-nitro-1-butanol (XVI) in high yield. In accordance with the proposed mechanism of ether cleavage with boron trichloride,[20] it would be expected that the ether in which the leaving group would form the most stable carbonium ion would cleave most readily.

(19) Henry Feuer and Arnold T. Nielsen, *J. Am. Chem. Soc.*, **84**, 688 (1962).

(20) W. Gerrard and M. F. Lappert, *Chem. Rev.*, **58**, 1081 (1958).

TABLE III

CLEAVAGE OF NITRO ETHERS WITH BORON TRICHLORIDE TO NITRO ALCOHOLS



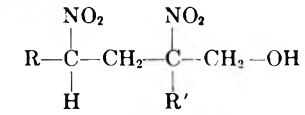
Nitro ethers R; R′	Product	Yield, %	B.p. °C. (μ)	M.p., °C.	$n^{20}D$	Formula	Calcd., % C	H	N	Found, % C	H	N
C_2H_5; C_2H_5	XVII	64	90 (1)		1.4740	$C_8H_{16}N_2O_5$	43.63	7.32	12.72	43.86	7.31	12.76
CH_3; CH_3	XVIII[a]	53		54.5–55.5		$C_6H_{12}N_2O_5$	37.50	6.29	14.58	37.50	6.37	14.31
CH_3; C_2H_5	XIX	56		30–32		$C_7H_{14}N_2O_5$	40.77	6.84	13.59	41.38	7.09	13.09
C_2H_5; CH_3	XX	67	90 (10)		1.4735	$C_7H_{14}N_2O_5$	40.77	6.84	13.59	40.74	6.83	13.89

[a] The nitro ether was dissolved in dichloromethane prior to treatment with boron trichloride.

Our experiments bear this out, since ether VIII containing a *t*-butoxy group was readily cleaved at ice-bath temperatures to XVI in 80% yield. On the other hand, temperatures of 25 and 38° were required with ethers V and VI carrying an ethoxy and methoxy group, respectively.

The importance of the formation of a stable carbonium ion in the ether cleavage with boron trichloride was further evidenced with 1-alkoxy-2-alkyl-2,4-dinitro alkanes. A number of attempts to cleave 1-methoxy-2-ethyl-2,4-dinitrohexane (XIII) resulted in only partial cleavage, and pure 2-ethyl-2,4-dinitrohexanol (XVII) could not be obtained. In contrast, when the reaction was carried out with 1-*t*-butoxy-2-alkyl-2,4-dinitro alkanes, cleavage occurred readily and 2-alkyl-2,4-dinitro 1-alkanols were obtained in reasonably good yield (see Table III).

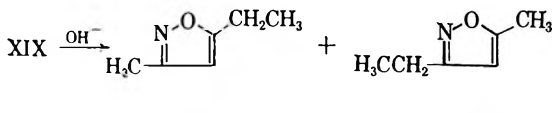
XI, XII, XIV, and XV $\xrightarrow[(2)\ CH_3OH]{(1)\ BCl_3}$



XVII, R = R′ = C_2H_5
XVIII, R = R′ = CH_3
XIX, R = CH_3; R′ = C_2H_5
XV, R = C_2H_5; R′ = CH_3

The cleavage of the *t*-butoxy ethers usually occurred at the reflux temperature of boron trichloride and a homogeneous solution was obtained. In the case of ether XII, however, the reaction was incomplete because of heterogeneity of the reaction mixture. Complete cleavage resulted by the addition of dichloromethane which rendered the reaction mixture homogeneous.

The cleavage of ether XIV gave the expected alcohol (XIX), but its purification proved to be quite difficult. It was characterized by conversion into an isomeric mixture of 3-methyl-5-ethylisoxazole (XXI) and 3-ethyl-5-methylisoxazole (XXII) on treatment with aqueous base.[8]



XXI XXII

Experimental

2-(2-Nitro-2-methyl-1-propoxy)tetrahydropyran.—To a well-stirred mixture of 9.75 g. (0.08 mole) of 2-nitro-2-methyl-1-propanol and an excess amount of dihydropyran (45 ml.) was added 2 drops of concentrated hydrochloric acid and the temperature was maintained at 35–40° for 21 hr. At the end of this time, 20 ml. of ether was added, the resulting solution was washed with a saturated aqueous solution of sodium bicarbonate, the aqueous solution was extracted with ether, and the ethereal solution evaporated on a rotating evaporator to remove the ether and unchanged dihydropyran. Distillation at 68° and 2 mm. afforded an 88% yield of the pyran ether which had $n^{20}D$ 1.4521.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.26; H, 8.44; N, 6.91.

Cleavage of Bis(2-nitrobutoxy)methane (I). A. With Boron Trichloride.—At a temperature of −80°, 14.6 g. of bis(2-nitrobutoxy)methane[10] was added to an excess (40 ml.) of boron trichloride. After stirring the reaction mixture for 2 hr., it was brought to room temperature and the volatile boron trichloride was removed under vacuum. The crude 2-nitro-1-butyl dichloroboronite was then cooled to 0°, and excess methyl alcohol slowly was added. Evaporating the reaction mixture at room temperature and 20 mm. to remove methyl borate and excess methyl alcohol gave a quantitative yield of 2-nitro-1-butanol, $n^{20}D$ 1.4394, lit.[21] $n^{20}D$ 1.4390.

B. With Aqueous Sodium Hydroxide.—A 100-ml. three-necked flask equipped with an electric stirrer and thermometer, was charged with 14.5 g. (57 mmoles) of bis(2-nitrobutoxy)-methane and 6.0 g. (150 mmoles) of sodium hydroxide in 30 ml. of water. The contents were stirred for 8 hr. at 38° and then neutralized with glacial acetic acid. After the mixture was extracted with six 75-ml. portions of ether, the extract was evaporated on a rotating evaporator. Distillation of the residue at 93° and 5 mm. afforded a 65% yield of 2-nitro-1-butanol. The infrared spectrum of this material was superimposable on that of an authentic sample of 2-nitro-1-butanol.

1-Methoxy-2-nitrobutane (V).—A solution of sodium methoxide, prepared by dissolving 55.1 g. (2.4 g.-atoms) of sodium in 1740 ml. of methanol, was placed in a three-necked flask equipped with an electric stirrer. Then, 100 g. (0.62 mole) of 2-nitrobutyl acetate, dissolved in 500 ml. of methanol, was added dropwise at 0–5°, over a period of 6 hr. After stirring for 9 hr. more at room temperature, the solution was evaporated in an air stream to remove the solvent. When all of the methanol had been removed, 400 ml. of water was added to dissolve the salts and the solution was neutralized at 0° with 160 ml. of glacial acetic acid. The aqueous solution was extracted with four 750-ml. portions of ether; the extract was dried over anhydrous magnesium sulfate and evaporated on a rotating evaporator. Distillation at 69° and 7 mm. afforded a 66% yield of 1-methoxy-2-nitrobutane, $n^{20}D$ 1.4200, lit.[6] $n^{20}D$ 1.4217.

1-Ethoxy-2-nitrobutane (VI).—The experimental procedure was the same as for the corresponding methoxy derivative except that 48.8 g. (2.12 g.-atoms) of sodium was dissolved in 1100 ml. of ethanol prior to the addition of 44.1 g. (0.27 mole) of 2-nitrobutyl acetate. Distillation at 80° and 10 mm. afforded a 59% yield of 1-ethoxy-2-nitrobutane, $n^{20}D$ 1.4212, lit.[13] $n^{20}D$ 1.4212.

1-Propoxy-2-nitrobutane (VII).—The experimental procedure was the same as for the corresponding methoxy derivative except that 41.3 g. (1.8 g.-atoms) of sodium was dissolved in 1100 ml. of 1-propanol prior to the addition of 43.5 g. (0.27 mole) of 2-nitrobutyl acetate. Distillation at 89° and 9 mm. afforded a 55% yield of 1-propoxy-2-nitrobutane, $n^{20}D$ 1.4240, lit.[13] $n^{20}D$ 1.4238.

1-*t*-Butoxy-2-nitrobutane (VIII).—The experimental procedure was exactly the same as for the preparation of the other 2-nitro-

(21) B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 34 (1940).

alkyl ethers except that 90 g. (2.3 g.-atoms) of potassium was dissolved in a mixture of 1500 ml. of *t*-butyl alcohol and 350 ml. of tetrahydrofuran prior to the addition of 60 g. (0.37 mole) of 2-nitrobutyl acetate. Distillation at 80° and 5 mm. afforded a 52% yield of 1-*t*-butoxy-2-nitrobutane, $n^{20}D$ 1.4249.

Anal. Calcd. for $C_8H_{17}NO_3$: C, 54.83; H, 9.78; N, 7.99. Found: C, 55.01; H, 9.82; N, 8.04.

1-*t*-Butoxy-2-nitropropane (IX).—The experimental procedure was exactly the same as for the preparation of the other 2-nitroalkyl ethers except that 62 g. (1.59 g.-atoms) of potassium was dissolved in a mixture of 800 ml. of *t*-butyl alcohol and 200 ml. of tetrahydrofuran prior to the addition of 43.5 g. (0.31 mole) of 2-nitropropyl acetate, dissolved in 150 ml. of *t*-butyl alcohol. Distillation at 103° and 35 mm. afforded a 57% yield of 1-*t*-butoxy-2-nitropropane, $n^{20}D$ 1.4219. The nitro ether was injected into a G.E.-S.F. 96 on Chromosorb W gas chromatographic column and analytically pure 1-*t*-butoxy-2-nitropropane was collected and had $n^{20}D$ 1.4209.

Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.42; H, 9.59; N, 8.78.

Further distillation at 125° and 1 mm. afforded a 9% yield of 1-*t*-butoxy-2-methyl-2,4-dinitropentane (XII). The infrared spectrum and retention time (on the gas chromatogram) of this dinitro ether were the same as those of an authentic sample of XII (*vide infra*).

1,6-Dimethoxy-2,5-dinitrohexane (X).—The experimental procedure was essentially the same as for the preparation of 1-methoxy-2-nitrobutane except that 6.2 g. (270 mg.-atoms) of sodium was dissolved in 200 ml. of methanol prior to the addition of 13.1 g. (45 mmoles) of 1,6-diacetoxy-2,5-dinitrohexane.[6] The crude reaction product was sublimed at 50° and 1 μ to afford a 78% crude yield of the diastereomers of 1,6-dimethoxy-2,5-dinitrohexane, m.p. 56–70°. A portion of the mixture of isomers was repeatedly recrystallized from a minimum amount of hot (85°) dibutyl ether until a solid was obtained which had constant m.p. 90°. Sublimation of this material at 65° and 1 μ afforded a pure sample of the high-melting isomer of **1,6-dimethoxy-2,5-dinitrohexane**, m.p. 90°.

Anal. Calcd. for $C_8H_{16}N_2O_8$: C, 40.67; H, 6.83; N, 11.86. Found: C, 40.71; H, 6.73; N, 11.62.

In order to obtain the low-melting isomer, the mixture of diastereomers was dissolved in a minimum amount of ether at room temperature and pentane slowly was added to precipitate the high-melting isomer. The solution was boiled to coagulate the solids, filtered at room temperature, and the filtrate was cooled in Dry Ice to precipitate the 1,6-dimethoxy-2,5-dinitrohexane, enriched in the low-melting isomer. The entire process was repeated to concentrate further the low-melting material. The low-melting isomer was distilled several times at 25° and 1 μ until a constant melting point range of 22.5–23.5° was obtained. (The distillation was carried out in a sublimator, and the distillate was collected as a solid on the cold finger.)

Anal. Calcd. for $C_8H_{16}N_2O_6$: C, 40.67; H, 6.83; N, 11.86. Found: C, 40.65; H, 6.74; N, 11.99.

2-Nitropropyl Acetate.—Into a three-necked flask equipped with a stirrer were placed 195.2 g. (1.85 moles) of 2-nitro-1-propanol and an excess of acetic anhydride (600 ml.). Then, 1 ml. of concentrated sulfuric acid was added dropwise, and the reaction mixture was kept at 60° for 3.5 hr. Distillation at 80° and 5 mm. afforded an 83% yield of 2-nitropropyl acetate, $n^{20}D$ 1.4267.

Anal. Calcd. for $C_5H_9NO_4$: C, 40.81; H, 6.16; N, 9.52. Found: C, 40.90; H, 6.25; N, 9.45.

Methyl 2-Nitropropyl Sulfide.—A sodium methoxide solution was prepared by dissolving 17.3 g. (0.75 g.-atom) of sodium in 400 ml. of methanol. Then, 31 g. (0.65 mole) of methyl mercaptan was added to the methoxide solution at 0°. To the alkaline reaction mixture, containing sodium methylthiolate, was added dropwise with stirring at 0° 39.89 g. (0.27 mole) of 2-nitropropyl acetate. The mixture was kept at ice-bath temperatures for 3 hr. and acidified with a slight excess (50 ml.) of glacial acetic acid. The solution then was evaporated on a rotating evaporator to remove the solvent, 200 ml. of water was added to dissolve the inorganic salts, the aqueous solution was extracted with four 300-ml. portions of ether, and the extract was evaporated on a rotating evaporator. Distillation at 100° and 16 mm. afforded a 76% yield of methyl 2-nitropropyl sulfide, $n^{20}D$ 1.4790, lit.[18] b.p. 105° (20 mm.). The sulfide was characterized by its conversion to methyl 2-nitropropyl sulfone, m.p. 71.5°, lit.[18] m.p. 69–70°.

2-Nitrobutyl *t*-Butyl Sulfide.—The experimental procedure was the same as for the preparation of methyl 2-nitropropyl sulfide except that 13.4 g. (0.54 g.-atom) of sodium, dissolved in 250 ml. of methanol, was treated with 42.6 g. (0.47 mole) of *t*-butanethiol prior to the addition of 35 g. (0.215 mole) of 2-nitrobutyl acetate. Distillation at 87° and 3 mm. afforded a 93% crude yield of 2-nitrobutyl *t*-butyl sulfide. Three distillations were necessary to obtain a pure product with $n^{20}D$ 1.4710, lit.[22] $n^{25}D$ 1.469.

Cleavage of 1-*t*-Butoxy-2-nitrobutane (VIII). A. With Concentrated Hydrochloric Acid.—Into a three-necked flask equipped with an electric stirrer, were placed 9.44 g. (55 mmoles) of VIII and an excess (30 ml.) of concentrated hydrochloric acid. The reaction mixture was stirred at 0° for 30 min. and then at room temperature for 12 hr. The organic material was removed from the acid solution by continuous extraction with ether, and the ethereal solution was dried over anhydrous magnesium sulfate and then evaporated on a rotating evaporator. Distillation at 83° and 4 mm. afforded a 59% yield of 2-nitro-1-butanol, $n^{20}D$ 1.4396, lit.[21] $n^{20}D$ 1.4390.

B. With Gaseous Hydrogen Chloride.—An excess of dry hydrogen chloride was bubbled into 8.27 g. (46 mmoles) of VIII for 2 hr. at 0°. Distillation of the product at 83° and 4 mm. afforded at 65% yield of 2-nitro-1-butanol, $n^{20}D$ 1.4398.

C. With Boron Trichloride.—At a temperature of −80°, 14.9 g. (84.5 mmoles) of VIII was added to an excess (19.5 ml.) of boron trichloride. After 15 min., the flask was placed in an ice bath, and the reaction mixture was kept at 0° for 1 hr. Then, excess boron trichloride was removed under vacuum, the remaining 2-nitro-1-butyl dichloroboronite was cooled to 0°, and excess methanol was added very slowly. The reaction mixture was evaporated at room temperature and 20 mm. to remove methyl borate and excess methanol. Distillation of the residue at 66° and 1 mm. afforded an 80% yield of 2-nitro-1-butanol, $n^{20}D$ 1.4390. The infrared spectrum of this compound was superimposable on that of an authentic sample of 2-nitro-1-butanol.

Cleavage of 1-Methoxy-2-nitrobutane (V) with Boron Trichloride.—The experimental procedure was essentially the same as for the cleavage of VIII by procedure C except that 11.1 g. (83 mmoles) of V and 40 ml. of boron trichloride were employed. After the boron trichloride was removed *in vacuo*, the residue was kept at 38° for 6 hr. in order to decompose the boron trichloride–etherate complex. Work-up as described in procedure C afforded a 72% yield of 2-nitro-1-butanol, $n^{20}D$ 1.4400.

Cleavage of 1-Ethoxy-2-nitrobutane (VI) with Boron Trichloride.—The experimental procedure was essentially the same as above, except that 10 g. (68 mmoles) of VI and 25 ml. of boron trichloride were employed. The reaction mixture was maintained at room temperature for 2 hr. and boron trichloride and ethyl chloride were collected as condensates at −80°. Work-up of the residue afforded a 73% yield of 2-nitro-1-butanol, $n^{20}D$ 1.4380.

On addition of water to the condensate of ethyl chloride and boron trichloride at −80°, boric acid was formed. The ethyl chloride was then removed under vacuum as a gas. The infrared spectrum of this gas was essentially superimposable on that of a known sample of ethyl chloride.

1-Methoxy-2-ethyl-2,4-dinitrohexane (XIII).—A 500-ml. three-necked flask equipped with a mechanical stirrer was charged with 11.24 g. (0.284 mole) of sodium hydroxide dissolved in a mixture of 80 ml. of water and 120 ml. of methanol. The solution was cooled to 0–5°, and 37.8 g. (0.284 mole) of 1-methoxy-2-nitrobutane was added. The reaction mixture then was allowed to come to room temperature, and, after salt formation was complete, 23 g. (0.142 mole) of 2-nitrobutyl acetate was added dropwise at 0° over a 75-min. period. After the addition was complete, the reaction mixture was kept at 0° for 1 hr. and then at room temperature for 3 hr. At the end of this time, the methanol was removed under vacuum, water was added to dissolve the salts, and the aqueous solution was acidified with a slight excess (13 ml.) of glacial acetic acid. The solution was extracted with four 200-ml. portions of ether; the extract was dried over anhydrous magnesium sulfate and evaporated on a rotating evaporator. Distillation of the product at 85° and 10 μ gave a 74% yield of **1-methoxy-2-ethyl-2,4-dinitrohexane**. Repeated distillations of this material at 69° and 8 μ gave fractions with a $n^{20}D$ range of 1.4571–1.4582, due to the presence of two *dl* pairs. The fraction, $n^{20}D$ 1.4580, was analyzed.

(22) Carl T. Bahner, U. S. Patent 2,511,961; *Chem. Abstr.*, **44**, 8942 (1950).

1-*t*-Butoxy-2-ethyl-2,4-dinitrohexane (XI).—The experimental procedure was essentially the same as for the preparation of XIII except that 16.7 g. (95 mmoles) of 1-*t*-butoxy-2-nitrobutane was added to a solution of 3.74 g. (95 mmoles) of sodium hydroxide in a mixture of 47 ml. of water and 40 ml. of methanol prior to the addition of 7.75 g. (48 mmoles) of 2-nitrobutyl acetate. Distillation of the products at 65° and 2 mm. gave 8.21 g. of recovered 1-*t*-butoxy-2-nitrobutane. Further distillation at 84° and 10 μ afforded a 74% yield of **1-*t*-butoxy-2-ethyl-2,4-dinitrohexane (XI)**. The compound was redistilled at 70° and 4 μ into several portions (n^{20}D 1.4512–1.4522). The fraction, n^{20}D 1.4521, was analyzed.

1-*t*-Butoxy-2-ethyl-2,4-dinitropentane (XIV).—Sodium 1-*t*-butoxy-2-butanenitronate was prepared by the addition of 17.6 g. (0.1 mole) of 1-*t*-butoxy-2-nitrobutane to a stirred solution of 4 g. (0.1 mole) of sodium hydroxide in 100 ml. of methanol. After the mixture had been stirred for 4 hr., the solvent was removed in an air stream and the solid salt residue was dissolved in a minimum amount (30 ml.) of water. After 7.35 g. (0.05 mole) of 2-nitropropyl acetate was added, the procedure followed was essentially the same as for the preparation of XIII. Distillation at 75° and 10 μ afforded a 49% yield of XIV. Chromatographing with a G.E.–S.F. 96 on Chromosorb W column gave analytically pure 1-*t*-butoxy-2-ethyl-2,4-dinitropentane.

1-*t*-Butoxy-2-methyl-2,4-dinitrohexane (XV).—The experimental procedure was essentially the same as for the preparation of XIV except that sodium 1-*t*-butoxy-2-propanenitronate was dissolved in 30 ml. of water prior to the addition of 8.05 g. (0.05 mole) of 2-nitrobutyl acetate. Distillation at 85° and 1 μ afforded a 66% yield of XV. The nitro ether was recrystallized by dissolving it in hexane at room temperature and cooling the solution to Dry Ice temperatures. Nine recrystallizations followed by three sublimations at room temperature and 1 μ produced a pure sample of **1-*t*-butoxy-2-methyl-2,4-dinitrohexane**.

1-*t*-Butoxy-2-methyl-2,4-dinitropentane (XII) A. From Sodium 1-*t*-Butoxy-2-propanenitronate and 2-Nitropropyl Acetate.—The experimental procedure was essentially the same as for the preparation of XIV except that sodium 1-*t*-butoxy-2-propanenitronate was dissolved in a mixture of 30 ml. of water and 100 ml. of tetrahydrofuran (THF) prior to the addition of 9.1 g. (0.062 mole) of 2-nitropropyl acetate. The work-up procedure was the same as in the preparation of the other dinitro ethers, except that the THF was evaporated on a steam bath before the reaction mixture was neutralized with acetic acid. Distillation at 85° and 35 μ afforded a 44% yield of 1-*t*-butoxy-2-methyl-2,4-dinitropentane. The nitro ether was injected into a G.E.–S.F. 96 on Chromosorb W gas chromatographic column, and the sample collected was sublimed five times at 40° and 1 μ and had m.p. 52.5–59°.

B. **From Potassium *t*-Butoxide and 2-Nitropropyl Acetate.**—A solution of potassium *t*-butoxide, prepared by the dissolution of 25 g. (0.644 g.-atom) of potassium in a mixture of 370 ml. of *t*-butyl alcohol and 165 ml. of tetrahydrofuran, was placed in a three-necked flask equipped with a thermometer, addition funnel, and electric stirrer. The solution was cooled to 0–5°, and 71 g. (0.482 mole) of 2-nitropropyl acetate, dissolved in 150 ml. of *t*-butyl alcohol, was added dropwise over a period of 2.5 hr. After stirring for 8 hr. more, excess (36 g., 0.644 mole) potassium hydroxide, dissolved in 100 ml. of water, was added at 0° in order to convert any free nitro compounds to their potassium salts. After the solution was stirred at 0–5° for 2 hr. more, the reaction flask was placed in a water bath maintained at 56°, and the organic solvents were removed in an air stream. The aqueous solution was cooled to 0–5° and neutralized with 60 g. of glacial acetic acid dissolved in 100 ml. of water. The mixture was extracted with six 500-ml. portions of chloroform; the extract was dried over anhydrous magnesium sulfate and evaporated on a steam bath. Distillation of the residue at 84° and 10 mm. afforded 16.5 g. of 1-*t*-butoxy-2-nitropropane. When this compound was analyzed by gas chromatography, a peak was obtained which had the same retention time as a known sample of 1-*t*-butoxy-2-nitropropane.

Further distillation at 109° and 1 mm. afforded 14.5 g. (36% yield) of XII. XII gave a peak on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column which had the same retention time as an authentic sample of XII.

2-Ethyl-2,4-dinitro-1-hexanol (XVII).—An excess (12 ml.) of boron trichloride was added at −70° to a 100-ml. flask equipped with a magnetic stirrer, Dry Ice condenser, and drying tube. Then 5 g. (0.018 mole) of 1-*t*-butoxy-2-ethyl-2,4-dinitrohexane was added to the reaction flask. The cold bath was replaced with a water bath, and the mixture stirred rapidly for 6 min. at the reflux temperature of boron trichloride (13°). Immediately, after excess boron trichloride and other volatile substances were removed under vacuum, the residue was cooled to −70°. Excess methanol was added slowly down the sides of the flask (owing to exothermic nature of the reaction), and the reaction mixture very slowly was allowed to come to room temperature. Removing all volatile components at room temperature and 20 mm. left a dark liquid which gave off hydrogen chloride fumes. Therefore, the liquid was dissolved in 500 ml. of chloroform, and the resulting solution was extracted with water until the aqueous phase no longer gave a test for chloride ion with silver nitrate. After the chloroform was evaporated on a steam bath, the residue was distilled at 88° and 1 μ to afford a 64% yield of **2-ethyl-2,4-dinitro-1-hexanol**. Two redistillations at 90° and 1 μ gave an analytically pure sample of the nitro alcohol.

2-Ethyl-2,4-dinitro-1-pentanol (XIX).—The experimental procedure was the same as for the preparation of XVII except that 5 g. (19 mmoles) of 1-*t*-butoxy-2-ethyl-2,4-dinitropentane and 20 ml. of boron trichloride were employed. Distillation at 115° and 4 μ afforded a 56% yield of **2-ethyl-2,4-dinitro-1-pentanol**. Repeated distillations at 85° and 1 μ followed by several recrystallizations from hexane produced a fairly pure sample of the nitro alcohol, m.p. 30–32°.

2-Methyl-2,4-dinitro-1-hexanol (XX).—The experimental procedure was the same as for the preparation of XVII except that 5.3 g. (20.2 mmoles) of 1-*t*-butoxy-2-methyl-2,4-dinitrohexane and 20 ml. of boron trichloride were employed. Distillation at 105° and 4 μ afforded a 67% yield of XX. Several distillations at 90° and 10 μ gave an analytically pure sample of 2-methyl-2,4-dinitro-1-hexanol.

2-Methyl-2,4-dinitro-1-pentanol (XVIII).—The experimental procedure was the same as for the preparation of XVII except that 5 g. of 1-*t*-butoxy-2-methyl-2,4-dinitropentane was first dissolved in 30 ml. of dichloromethane prior to its addition to 10 ml. of boron trichloride. Distillation at 85° and 1 μ afforded a 53% yield of 2-methyl-2,4-dinitro-1-pentanol. The compound was purified for analysis by three recrystallizations from hexane, followed by four distillations at 70° and 1 μ. The nitro alcohol was distilled in a sublimator; the solid was collected on the cold finger and had m.p. 54.5–55.5°.

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Rearrangement of Secondary β-Dinitro Alkanes to 3,5-Dialkyl Isoxazoles

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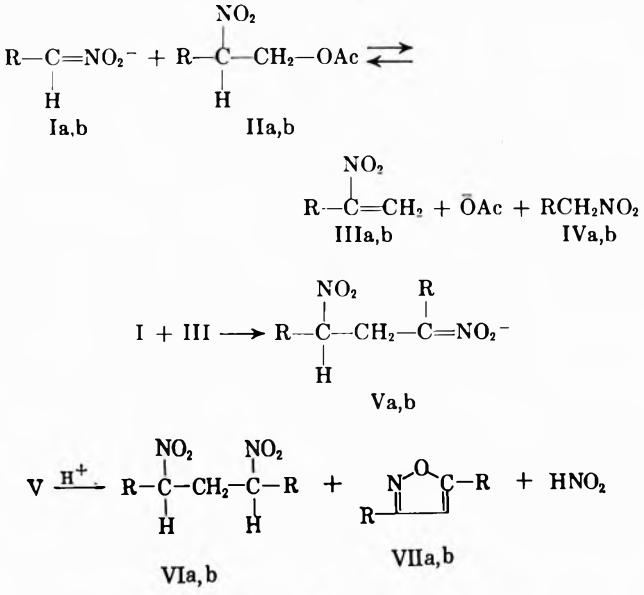
The Michael-type addition between sodium 1-alkane nitronates and α-nitro olefins, which are generated *in situ* from 2-nitroalkyl acetates leads largely to the formation of 3,5-dialkyl isoxazoles. The latter also are obtained by the demethylolation of 2-alkyl-2,4-dinitro 1-alkanols and by the rearrangement of secondary β-dinitro alkanes in weakly basic media.

The Michael-type addition between 2-alkane nitronates and α-nitro olefins generally proceeds in reasonably good yields.[2-6] In contrast, 1-alkane nitronates give the desired Michael adducts, secondary β-dinitro alkanes, only in poor yields. No explanations have been given to account for the poor yields in this reaction. There are, however, reports in the literature in which attempts to prepare phenyl-substituted β-dinitro alkanes gave rise largely to isoxazoles and isoxazoline N-oxides.[7-9] For example, Heim[7] obtained in the base-catalyzed reaction between phenylnitromethane and benzaldehyde, in addition to 1,2,3-triphenyl-1,3-dinitropropane and nitrostilbene, 3,4,5-triphenylisoxazole. Heim and other workers[8,10-12] were able to show that phenyl-substituted β-dinitro compounds were unstable in the presence of base and eliminated nitrous acid to form isoxazoline N-oxides and isoxazoles.

In a preliminary investigation of the reaction between sodium 1-propanenitronate (Ia) and 2-nitrobutyl acetate (IIa), from which 2-nitro-1-butene (IIIa) was generated *in situ*, Feuer and Miller[6] reported the formation of a mixture of low-boiling materials, in addition to the expected 3,5-dinitroheptane (VIa). The infrared spectrum of the mixture indicated the presence of a cyclic C=N linkage (6.25 μ).[13] We now have determined that the main component of this mixture was 3,5-diethylisoxazole (VIIa).



In this investigation, several attempts were made to improve the yield of VIa by carrying out the reaction between Ia and IIa in various solvents at room temperature; but in all cases the yield of VIa was low and VIIa was formed. For example, the reaction between excess (5 equivalents) Ia (sodium salt) and IIa in tetrahydrofuran (THF) afforded only a 16% yield of VIa. Similar results were obtained with Ia (lithium salt) in THF (22%) and Ia (sodium salt) in dimethyl sulfoxide (11%) and in methanol (4%). In all of these experiments, distillation of the acidified reaction mixtures gave foreruns which by vapor phase chromatography were found to contain the solvent, IVa, unchanged IIa, and the isoxazole (VIIa). 1-Methoxy-2-nitrobutane[6] was found also to be present when the solvent was methanol. All of these reactions also produced undistillable high molecular weight by-products which were probably formed by the addition of anions such as Va to the nitro olefin (IIIa).

No 3,5-dinitroheptane (VIa) was formed at all when Ia and IIa interacted in aqueous medium. In fact, these were the conditions at which VIIa was obtained in highest yield (66%). A small amount of another substance was isolated, but there was only enough material for an infrared spectrum, which indicated the presence of hydroxyl and nitro groups.

The identity of VIIa was established by an independent synthesis which followed the procedure of Harries and Haga.[14] Mono-oximation of 3,5-heptanedione gave a 63% yield of 3,5-diethylisoxazole, which had the same refractive index, infrared spectrum, and retention time (on the gas chromatogram) as VIIa.

The isolation of VIIa in varying amounts from the reaction of Ia (sodium salt) and IIa suggested that an anion of 3,5-dinitroheptane (VIa) was one of the possible intermediates in the formation of VIIa. This possibility was actually indicated by the fact that treatment of authentic VIa[6] with a weak base such as an aqueous solution of Ia (sodium salt) gave after two days a 37% yield of VIIa as established by gas chromatography. The yield of VIIa increased to 52% when the reaction mixture was allowed to stand for 2 weeks. The conversion of VIa to VIIa took place also in aqueous sodium hydroxide.

Compound VIIa was obtained also when 2-ethyl-2,4-dinitro-1-hexanol[15] (VIIIa) in a mixture of THF

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(10) A. Dornow and G. Wiehler, *Ann.*, **578**, 113 (1952).
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(15) H. Feuer and S. Markofsky, *J. Org. Chem.*, **29**, 929 (1964).

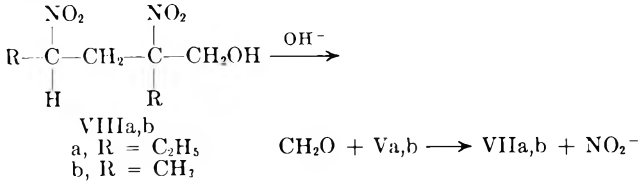
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME 3,5-DIALKYL ISOXAZOLES[a]

Isoxazole	Vinyl H	CH_2[b] of ethyl group[c]	5-CH_3	3-CH_3	CH_3[d] of ethyl group
3,5-Dimethylisoxazole	4.2		7.7	7.8	
3-Methyl-5-ethylisoxazole	4.2	7.4		7.8	8.8
3-Ethyl-5-methylisoxazole	4.2	7.4[e]	7.7		8.8
3,5-Diethylisoxazole	4.3	7.4[e]			8.8

[a] In τ values (see ref. 17; all values accurate to ± 0.05). [b] Measured relative to center of quartet. [c] The difference between the τ values of 3- and 5-substituted ethyl groups is less than τ 0.05. [d] Measured relative to center of triplet. [e] Methyl singlet overlaps high field component of quartet.

and methanol was made basic by slowly extracting sodium hydroxide from the thimble of a Soxhlet apparatus.



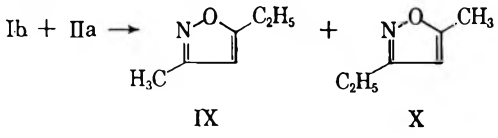
VIIIa,b
a, R = C_2H_5
b, R = CH_3

$$CH_2O + Va,b \longrightarrow VIIa,b + NO_2^-$$

In order to establish the utility of this novel preparation of isoxazoles, a number of reactions were carried out, in aqueous media, between various 1-alkane nitronates and 2-nitroalkyl acetates. Treatment of sodium ethanenitronate (Ib) with 2-nitropropyl acetate (IIb) gave 3,5-dimethylisoxazole[16] (VIIb) in 48% yield. In addition, a small amount of 3,4,5-trimethylisoxazole was isolated. This compound has been known to form directly by the rearrangement of Ib in aqueous medium.[17] A large residue of high molecular weight polymeric material was obtained also. It might have arisen from the anionic polymerization of 2-nitropropene (IIIb).

Compound VIIb was prepared also in 58% yield from the demethylolation of 2-methyl-2,4-dinitro-1-pentanol (VIIIb) in aqueous sodium hydroxide.

The reaction between Ib and IIa gave rise to the expected mixture consisting of 3-methyl-5-ethylisoxazole (IX) and 3-ethyl-5-methylisoxazole (X). This same isomeric mixture (IX and X) was obtained from (a) the reaction between Ia and IIb and (b) the respective



IX X

demethylolations[15] of 2-methyl-2,4-dinitro-1-hexanol and 2-ethyl-2,4-dinitro-1-pentanol.

It is of interest to note that vapor phase chromatographic analysis, on four different columns, of the reaction mixtures containing IX and X gave only one symmetrical peak. N.m.r. spectra, however, clearly indicated that an isomeric mixture of isoxazoles was present on comparison with an authentic sample of VIIb. The spectrum of VIIb showed two distinct methyl groups at τ[18] 7.7 and 7.8. Similarly, the mixture containing IX and X showed two distinct absorption peaks at τ 7.7 and 7.8 of approximately equal area, indicating that both 3-methyl- and 5-methyl-substituted isoxazoles were present and that IX and X had formed in about equal amounts. (The τ values of a number of 3,5-dialkyl isoxazoles are enumerated in Table I.)

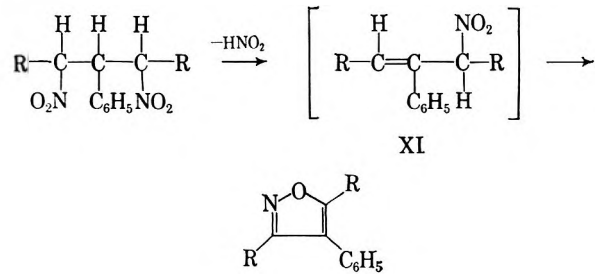
In order to assign τ values, IX and X were synthesized independently. Compound IX was prepared from acetohydroxamic chloride[19] and 1-butynylmagnesium bromide[20] by a method which followed essentially the procedure of Palazzo.[21] Similarly, X was prepared from propionohydroxamic chloride and 1-propynylmagnesium bromide.

The n.m.r. spectrum of authentic IX showed only one peak for the methyl group at τ 7.8, while X exhibited the methyl peak at τ 7.7. The n.m.r. spectrum of a synthetic mixture prepared from equal volumes of IX and X showed two absorptions at τ 7.7 and 7.8 and was superimposable on the spectrum of the mixture of isoxazoles obtained in the various experiments (*vide supra*). The synthetic mixture (IX and X) also gave only one symmetrical peak on four different gas chromatographic columns (see Experimental).

The infrared spectra of IX and X were almost identical. The main difference was that X had two bands, at 7.93 and 8.03 μ, which were absent in IX.

Discussion

The mechanism of the rearrangement of β-dinitro compounds to isoxazoles has never been established. Both Heim[7] and Dornow[10] suggested the formation of an olefinic intermediate (XI) which rearranged directly to the isoxazole. While an elimination reaction is certainly involved in this transformation, the direct



XI

loss of nitrous acid from an α,γ-dinitro compound on treatment with base is certainly not general. For instance, Keppler and Meyer[22] converted crude 1,3-dinitropropane to the monosodium salt with sodium ethoxide in absolute ethanol; also 2-methyl-2,4-dinitrohexane (XII) is apparently stable under basic conditions, since it can be prepared in high yield (87%) from the reaction of sodium 2-propanenitronate and 2-

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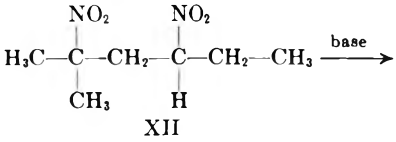
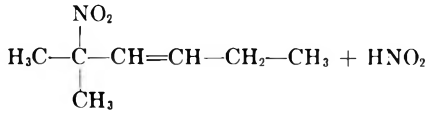
nitrobutyl acetate.[6] According to the suggestion of Heim and Dornow, XII should be unstable to base and lose nitrous acid.



XII



In order to gain more insight into the conversion of an α,γ-dinitro alkane to an isoxazole, a basic solution of 3,5-dinitroheptane (VIa) was tested by gas chromatography for the presence of 3,5-diethylisoxazole (VIIa). The characteristic peak of VIIa was completely absent even after 2 weeks, but acidification with glacial acetic acid or carbon dioxide resulted in the formation of VIIa and the evolution of nitrous acid. The latter was detected by the fact that it turned starch iodide paper blue and that a red azo dye formed on addition of sulfanilic acid and α-naphthylamine[23] to the reaction mixture.

This experiment did not rule out the possibility that some precursor of the isoxazole had formed already in the strongly basic solution[24] and on subsequent acidification was converted to the isoxazole. Therefore, the disodium salt of VIa was prepared first by adding a solution of VIa in methanol to a solution of sodium hydroxide. The salt was found to be highly hygroscopic and difficult to purify. Therefore the elemental analysis is only in fair agreement with the calculated values (see Experimental).

Subjecting the disodium salt of VIa to the same treatment as VIa (*vide supra*) gave the same results; VIIa was formed only after acidification of the aqueous solution of the salt.[25] It seems, therefore, that at least a mono-*aci* form of the dinitro compound must be involved in the rearrangement to the isoxazole[26] and not a direct elimination of nitrous acid as was suggested by Heim and Dornow.

Experimental

3,5-Diethylisoxazole (VIIa). A. From 2-Nitrobutyl Acetate and Sodium 1-Propanenitronate.—To a stirred solution of 55 g. (0.495 mole) of anhydrous sodium 1-propanenitronate in 75 ml. of water was added 16.15 g. (0.10 mole) of 2-nitrobutyl acetate. The mixture was stirred for 18 hr. at room temperature and acidified with 30 ml. of glacial acetic acid. After more water was added to dissolve the sodium acetate which was formed in the neutralization reaction, the mixture was extracted with ether until the extract was colorless, and the ethereal solution was dried over anhydrous magnesium sulfate and evaporated in an air stream. Distillation at 58° and 5 mm. afforded a 66% yield of **3,5-diethylisoxazole**. The infrared spectrum and gas chromatogram of the material were superimposable with those of an authentic sample of the isoxazole prepared by procedure B.

B. From 3,5-Heptanedione and Hydroxylamine Hydrochloride.—A solution of 1.63 g. (23.5 mmoles) of hydroxylamine hydrochloride dissolved in 7 ml. of water was carefully mixed with 2.5 g. (29.8 mmoles) of sodium bicarbonate dissolved in 6 ml. of water. This mixture was added to a stirred solution of 3 g. (23.5 mmoles) of 3,5-heptanedione dissolved in a mixture of 14 ml. of methanol and 3 ml. of water; then 5% hydrochloric acid was added to reach a pH of 6. The methanol was boiled off on a steam bath, the aqueous solution was extracted with six 50-ml. portions of ether, and the extract was dried over anhydrous magnesium sulfate. Distillation at 65° and 11 mm. afforded a 63% yield of VIIa, $n^{20}D$ 1.4490.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.80; H, 9.05; N, 11.25.

C. From 3,5-Dinitroheptane (VIa) in the Presence of Base.—A solution of 1.45 g. (13 mmoles) of sodium 1-propanenitronate dissolved in 2 ml. of water was added to 0.62 g. (3.26 mmoles) of 3,5-dinitroheptane (VIa). After the mixture was stirred vigorously for 48 hr. at room temperature, it was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIa. The yield, which was estimated by a comparison of the peak area with that of known samples of isoxazole, was 37%. After the reaction mixture had been allowed to stand for 2 weeks, the yield increased to 52%. The vapor phase analyses were carried out on a G.E.–S.F. 96 on Chromsorb W column.

The reaction mixture was then acidified with 1 ml. of glacial acetic acid, water was added to dissolve the salts, and the aqueous solution was extracted with three 7-ml. portions of ether. The extract was dried over anhydrous magnesium sulfate and evaporated on a steam bath. The residue was injected into a G.E.–S.F. 96 on Chromosorb W gas chromatographic column, and pure VIIa was collected with $n^{20}D$ 1.4492. The infrared spectrum of this compound was superimposable on the spectrum of VIIa, which was prepared by procedure B.

B. From a Basic Solution of Disodium 3,5-Heptanedinitronate after Acidification.—A solution of 0.4 g. (10 mmoles) of sodium hydroxide in 2 ml. of water was added to 0.47 g. (2.47 mmoles) of VIa, and the reaction mixture was stirred at room temperature for 2 weeks. Analysis of the mixture on a G.E.–S.F. 96 on Chromosorb W column indicated that no 3,5-diethylisoxazole was present.

One drop of the reaction mixture was then acidified with glacial acetic acid and the resulting solution was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIa but no 3,5-dinitroheptane was found to be present. Similar results were obtained on acidification of the reaction mixture with carbon dioxide.

E. From Disodium 3,5-Heptanedinitronate after Acidification.[25]—In a 10-ml. round-bottomed flask equipped with a magnetic stirrer were placed 0.0317 g. of disodium 3,5-heptanedinitronate and 2 ml. of degassed water. The resulting solution (pH 9) was stirred for 3 hr. at room temperature. Analysis as indicated in procedure D indicated that no 3,5-diethylisoxazole (VIIa) was present.

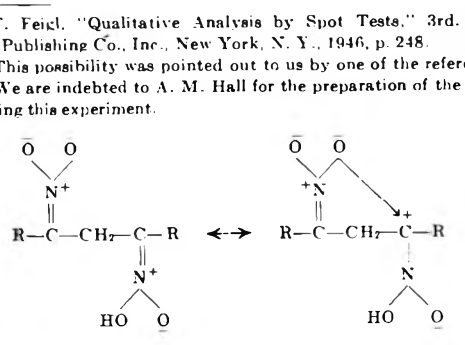
Four drops of the solution was acidified then with 4 drops of glacial acetic acid, and aliquots of the acidified solution were analyzed at intervals of 15 and 25 min. by gas chromatography. In the case of both samples, a peak was obtained which had the same retention time as an authentic sample of VIIa. The area of the peak was approximately the same with both samples.

F. From Demethylolation of 2-Ethyl-2,4-dinitro-1-hexanol (VIIIa).—The thimble of a Soxhlet extractor was charged with 0.5 g. (12.25 mmoles) of sodium hydroxide. Into a flask, connected to the Soxhlet apparatus, was placed 2.51 g. (11.14 mmoles) of VIIIa dissolved in a mixture of 7 ml. of methanol and 63 ml. of tetrahydrofuran. After the solution had been refluxed for 46 hr., the solvents were evaporated in an air stream, the residue was suspended in 50 ml. of ether and acidified with 1 ml. of glacial acetic acid. Then, water was added to dissolve the nitronate salt and to insure its complete acidification. The aqueous phase was extracted with three 100-ml. portions of ether; the extract was dried over anhydrous magnesium sulfate and evaporated on a rotating evaporator. Distillation of the residue at 60° and 10

(23) F. Feigl, "Qualitative Analysis by Spot Tests," 3rd. Engl. Ed., Elsevier Publishing Co., Inc., New York, N. Y., 1946, p. 248.

(24) This possibility was pointed out to us by one of the referees.

(25) We are indebted to A. M. Hall for the preparation of the salt and for performing this experiment.

(26) 

mm. afforded a 21% yield of VIIa. The infrared spectrum of this material, as well as its gas chromatogram, were essentially superimposable on those of an authentic sample of VIIa.

A fraction (0.2 g.), which distilled at 80° and 30 μ, was also obtained. The infrared spectrum of this substance was similar to that of the starting material (VIIIa).

Disodium 3,5-Heptanedinitronate.[25]—To a stirred solution of 0.902 g. (22.55 mmoles) of sodium hydroxide in methanol was added dropwise (1 hr.) at 3° a solution of 2.32 g. (12.54 mmoles) of VIIa in 50 ml. of methanol. After stirring for 1 hr. at 3° and for an additional 12 hr. at room temperature, the solution was concentrated *in vacuo* to a slurry; then 500 ml. of ether was added and the mixture was allowed to stir overnight. Filtering under dry nitrogen pressure and drying *in vacuo* gave 2.26 g. (77.0% yield) of tan-colored salt which charred at 180° but did not explode; λ_{max}^{Nujol} 6.2 μ (C=N stretch of alkyl nitronates).[27]

Anal. Calcd. for $C_7H_{12}N_2Na_2O_4$: C, 35.90; H, 5.13; N, 11.96; Na, 19.66; neut. equiv., 117. Found: C, 32.15; H, 5.41; N, 10.96; Na, 20.90; neut. equiv., 113.[28]

3,5-Dimethylisoxazole (VIIb). A. From Sodium Ethanenitronate and 2-Nitropropyl Acetate.—The experimental procedure used was essentially the same as for the preparation of VIIa (procedure A) except that anhydrous sodium ethanenitronate and 2-nitropropyl acetate were employed. Distillation at 130° and 760 mm. afforded a 48% crude yield of VIIb, $n^{20}D$ 1.4400. Injection into a Carbowax 20 M gas chromatographic column gave a pure sample of 3,5-dimethylisoxazole, b.p. 141° at 760 mm., $n^{20}D$ 1.4406; lit.[16] b.p. 142° at 748 mm., $n^{20}D$ 1.4416. In addition, a small amount 3,4,5-trimethylisoxazole was collected, m.p. 3°, lit.[17] m.p. 3.5°; $n^{20}D$ 1.4510, lit.[16] $n^{20}D$ 1.4529; b.p. 171° at 762 mm.

B. From Demethylolation of 2-Methyl-2,4-dinitro-1-pentanol (VIIIb).—A heterogeneous mixture of 173 mg. (0.9 mmole) of pure VIIIb in 1 ml. of 10% aqueous sodium hydroxide was boiled over a flame for 1 min., the solution was cooled to Dry Ice temperatures and acidified with 1 ml. of 10% hydrochloric acid. The solution was allowed to warm slowly to room temperature, and 1 ml. of chloroform was added *via* a pipet. The mixture was stirred vigorously and then the chloroform layer was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIIb prepared by procedure A. The yield, which was estimated by a comparison of the peak area with that of a known standard of approximately the same concentration of isoxazole, was 58%. A small amount of VIIIb was isolated on a Carbowax 20 M preparative column and had $n^{20}D$ 1.4413.

3-Methyl-5-ethylisoxazole (IX) and 3-Ethyl-5-methylisoxazole (X). A. From 2-Nitrobutyl Acetate and Sodium Ethanenitronate.—The experimental procedure used was essentially the same as for the preparation of 3,5-diethylisoxazole (procedure A), except that 78 g. (0.8 mole) of sodium ethanenitronate in 150 ml. of water and 64.4 g. (0.4 mole) of 2-nitrobutyl acetate were employed. The work-up procedure was the same except that the acidified reaction mixture was made basic again by the addition of 40 g. (1 mole) of sodium hydroxide in 150 ml. of water and extracted with six 800-ml. portions of chloroform. Distillation at 80° and 40 mm. afforded a 37% yield of a mixture consisting of IX and X. The mixture of isoxazoles gave only one symmetrical peak on a G.E.–S.F. 96 on Chromosorb W column, a Ucon polar column, a Craig polyester (succinate) column, and a Carbowax 20 M column. A pure sample of the isoxazole mixture was isolated on the Carbowax Column and had $n^{20}D$ 1.4453.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.21; N, 12.67.

B. From 2-Nitropropyl Acetate and Sodium 1-Propanenitronate.—The experimental procedure used was exactly the same as procedure A except that sodium 1-propanenitronate and 2-nitropropyl acetate were employed. Distillation at 65° and 37 mm. afforded a mixture of IX and X in 31% yield. The gas chromatogram and the infrared and n.m.r. spectra of this material were superimposable on the mixture of isoxazoles obtained from procedure A.

(27) H. Feuer, C. Savides, and C. N. R. Rao, *Spectrochim. Acta*, **19**, 431 (1963).

(28) H. Feuer and B. F. Vincent, Jr., *Anal. Chem.*, **35**, 598 (1963).

C. From the Demethylolation of 2-Methyl-2,4-dinitro-1-hexanol.—A heterogeneous mixture of 1 g. (4.85 mmoles) of 2-methyl-2,4-dinitro-1-hexanol[15] in 10 ml. of 10% aqueous sodium hydroxide was boiled over a flame for 1 min. until the solution became homogeneous. After boiling the solution for 1 min. more, it was cooled to 0–5° and acidified with 12 ml. of 10% hydrochloric acid. The solution was allowed to stand overnight at room temperature, cooled to 0–5°, and made basic by the slow addition of 10% aqueous sodium hydroxide. The aqueous solution then was extracted with five 50-ml. portions of chloroform; the extract was dried over anhydrous sodium sulfate and evaporated on a steam bath. Distillation at 65° and 75 mm. afforded 0.22 g. (41% yield) of a mixture of IX and X. The n.m.r. and infrared spectra as well as the gas chromatogram of the isoxazole mixture were superimposable on those of the mixture of isoxazoles prepared by procedure A. The isomeric mixture of isoxazoles was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}D$ 1.4459.

D. From Demethylolation of 2-Ethyl-2,4-dinitro-1-pentanol.—The experimental procedure used was essentially the same as for the demethylolation of 2-methyl-2,4-dinitro-1-pentanol.[15] When the products were analyzed on a Carbowax 20 M gas chromatographic column, a peak was obtained which had the same retention time as the mixture of isoxazoles prepared in procedure A.

3-Methyl-5-ethylisoxazole (IX).—A 500-ml. three-necked flask, equipped with a Dry Ice condenser, addition funnel, thermometer, and magnetic stirrer, was charged with an ethereal solution (220 ml.) of 1-butynylmagnesium bromide which had been prepared from 208 mmoles of ethylmagnesium bromide and excess 1-butyne by the method of Lai.[20] (The titer of the ethylmagnesium bromide was determined by adding a 1-ml. aliquot of it to 50 ml. of 0.25 *N* hydrochloric acid and back titrating with aqueous sodium hydroxide.) The mixture was cooled to 0°, and a dry ethereal solution (20 ml.) of acetohydroxamic chloride, which had been prepared by the method of Wieland[19] from 10 g. (169 mmoles) of acetaldoxime and 12 g. of chlorine, was added dropwise over a period of 1 hr. After stirring for 5 min. more at 0°, the mixture slowly was acidified with 180 ml. of 10% sulfuric acid and stirred for another hour. The reaction mixture was extracted with four 300-ml. portions of ether, and the extract was washed three times with a dilute solution of sodium hyposulfite. Then the ether extract was stirred with 400 ml. of a 20% solution of sodium hydroxide for 30 min., separated from the aqueous phase, filtered to remove a solid brown precipitate, dried over anhydrous magnesium sulfate, and finally evaporated on a steam bath. Distillation of the residue at 83° and 45 mm. afforded an 18% yield of **3-methyl-5-ethylisoxazole (IX)**. The isoxazole was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}D$ 1.4458.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.42; H, 8.47; N, 12.48.

3-Ethyl-5-methylisoxazole (X).—The experimental procedure was exactly the same as for the preparation of IX except that 1-propynylmagnesium bromide and propionohydroxamic chloride were employed. 1-Propynylmagnesium bromide was prepared from 208 mmoles of ethylmagnesium bromide and excess 1-propyne by the procedure developed by Lai.[20] Propionohydroxamic chloride was prepared by the procedure of Wieland[19] by adding 12 g. of chlorine to 12.4 g. (170 mmoles) of propionaldoxime in dilute hydrochloric acid.

Distillation of the reaction product at 90° and 73 mm. afforded an 18% crude yield of 3-ethyl-5-methylisoxazole. The isoxazole was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}D$ 1.4450.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.39; H, 8.48; N, 12.66.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of the work. We also wish to express gratitude to Professor N. Muller and Mr. W. Baitinger for their helpful interpretations of the n.m.r. data.

Notes

The Alkyl Nitrate Nitration of Active Methylene Compounds. III. The Nitration of Aliphatic Amides[1,2]

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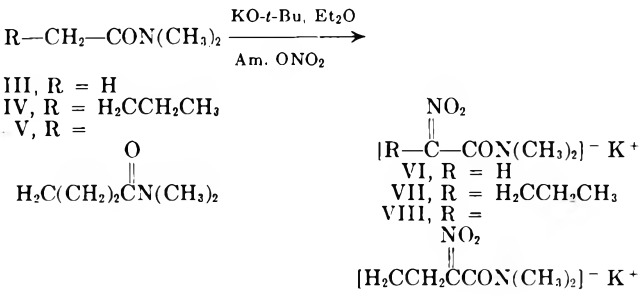
Received September 3, 1963

In continuation of our studies[2] of the alkyl nitrate nitration of active methylene compounds, we are now reporting our results with aliphatic amides.

When butyramide (I) and N-methylbutyramide (II) were subjected to the alkyl nitrate nitration with potassium *t*-butoxide and amyl nitrate, the desired salts of the α-nitro amides were not obtained; instead only the potassium salts of I and II were formed.[3] This was established by the fact that acidification of the salt of I gave essentially a quantitative recovery of I, and treatment of the salt of II with methyl iodide afforded N,N-dimethylbutyramide in a 98% yield.

Since these results indicated that the amido hydrogens interfered with the anion formation at the α-carbon atom which is essential for successful nitration to occur,[2] it was anticipated that the alkaline nitration would proceed readily with N,N-dialkyl-substituted amides.

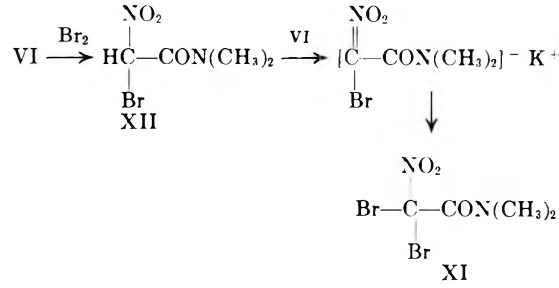
When N,N-dimethylacetamide (III), N,N-dimethylbutyramide (IV), and N,N,N′,N′-tetramethyladipamide (V) were subjected to the usual nitration conditions,[2] the expected salts of α-nitro-N,N-dimethylacetamide (VI), α-nitro-N,N-dimethylbutyramide (VII), and α,α'-dinitro-N,N,N′,N′-tetramethyladipamide (VIII) were obtained in good yield. The best solvent for these nitration reactions was found to be



diethyl ether because salts VI, VII, and VIII precipitated during the reaction and could be removed from the reaction mixture by simple filtration. When tetrahydrofuran was employed as the solvent, the isolation of the nitro salts was difficult because of their high solubility in this solvent.

The salts of these α-nitro amides were found to be highly hygroscopic and upon exposure to the atmosphere tended to decompose with charring because of their high heat of hydration. Attempts to convert these salts to the free α-nitro amides by acidification with hydrogen chloride in dry ether or with glacial acetic acid gave unstable products which evolved oxides of nitrogen.

The identity of these salts was established by conversion to their bromo derivatives[2] with correct analysis. Anhydrous bromination of salts VII and VIII proceeded normally to afford α-bromo-α-nitro-N,N-dimethylbutyramide (IX) and α,α'-dibromo-α,α'-dinitro-N,N,N′,N′-tetramethyladipamide (X). However, bromination of VI gave α,α-dibromo-α-nitro-N,N-dimethylacetamide (XI) instead of the expected monobromo compound (XII). Formation of XI can be explained by the interaction of unbrominated salt VI with XII to give the salt of XII which subsequently underwent reaction with bromine to give the final product (XI).



Experimental

α-Bromo-α-nitro-N,N-dimethylbutyramide (IX).—N,N′-Dimethylbutyramide[4] (11.5 g., 0.1 mole), dissolved in 60 ml. of dry ether, was added in 30 min. with stirring to a mixture of 18.5 g. (0.165 mole) of sublimed potassium *t*-butoxide and 70 ml. of dry ether at −70°. This was followed by the dropwise addition (20 min.) of 14.6 g. (0.11 mole) of amyl nitrate dissolved in 30 ml. of dry ether. The Dry Ice bath was removed, and the stirred reaction mixture was allowed to reach room temperature. Collecting the solid through a pressure filtration apparatus under nitrogen, washing with three 50-ml. portions of ether, and drying for 2 days *in vacuo* (1 μ) gave 16.0 g. (81%) of crude potassium α-nitro-N,N-dimethylbutyramide (VII).[5]

A stirred suspension of 1.98 g. (0.01 mole) of VII in 30 ml. of dry ether was cooled to 3° and a solution of 0.8 g. (0.01 mole) of bromine in 30 ml. of dry carbon tetrachloride was added dropwise while maintaining the temperature at 3–5°. After the reaction mixture was allowed to attain room temperature, potassium bromide was filtered off, and the solvent was removed *in vacuo*. Distilling the remaining oil at 35° (2 μ) in a sublimator and repeating the operation twice gave 1.91 g. (80%) of **α-bromo-α-nitro-N,N-dimethylbutyramide (IX)**, m.p. 73.5–74° (over-all yield based on N,N-dimethylbutyramide, 64.8%).

(1) From the Ph.D. thesis of B. F. Vincent, Jr., Purdue University, August, 1962.

(2) For previous publications, see H. Feuer, J. W. Shepherd, and C. Savides, *J. Am. Chem. Soc.*, **78**, 4364 (1956); H. Feuer and C. Savides, *ibid.*, **81**, 5826 (1959).

(3) J. N. Rakshit, *J. Chem. Soc.*, **103**, 1557 (1913).

(4) H. C. Brown and W. H. Bonner, *J. Am. Chem. Soc.*, **75**, 14 (1953).

(5) *Care* should be taken in handling the nitro amide salts because of their tendency to char on exposure to the atmosphere.

Anal. Calcd. for $C_6H_{11}BrN_2O_3$: C, 30.12; H, 4.60; Br, 33.47; N, 11.71. Found: C, 30.05; H, 4.55; Br, 33.39; N, 11.73.

α,α-Dibromo-α-nitro-N,N-dimethylacetamide (XI).—Potassium α-nitro-N,N-dimethylacetamide (VI, 13.5 g., 79% yield) was prepared from N,N-dimethylacetamide by the same procedure as described for VII.

Bromination of VI, as described for VII, gave 9.19 g. (41%) of **α,α-dibromo-α-nitro-N,N-dimethylacetamide (XI)**, m.p. 78–79° (over-all yield based on N,N-dimethylacetamide, 32.3%).

Anal. Calcd. for $C_4H_6Br_2N_2O_3$: C, 16.55; H, 2.06; Br, 55.17; N, 9.65. Found: C, 16.62; H, 2.04; Br, 55.01; N, 9.62.

N,N,N′,N′-Tetramethyladipamide (V).—Into a 1-l. three-necked flask, equipped with a stirrer, thermometer, and Dry Ice-cooled addition funnel topped by a drying tube, were placed 100 g. (0.546 mole) of adipyl chloride and 454 g. of dry ether. The flask was cooled to 3° and 100 g. (2.22 moles) of dimethylamine was added at such a rate that the reaction temperature did not exceed 10°. The reaction mixture then was stirred overnight at 3°, 500 ml. of water was added, and the solution was extracted continuously with ether for 4 days. Evaporating the solvent in a stream of air, recrystallizing the residue from hexane, and then subliming at 50° and 1 μ gave 30.3 g. (28%) of **N,N,N′,N′-tetramethyladipamide (V)**, m.p. 84–85°.

α,α′-Dibromo-α,α′-dinitro-N,N,N′,N′-tetramethyladipamide (X).—Into a dried flask were placed 18.5 g. (0.165 mole) of potassium *t*-butoxide and 90 ml. of purified tetrahydrofuran[2] (THF). The temperature of the reaction mixture was lowered to −20° and 10.2 g. (0.05 mole) of V was added in about 15 min. by means of a solid addition device. Then, an additional 60 ml. of THF was added, the temperature was lowered to −70°, and a solution of 14.6 g. (0.11 mole) of amyl nitrate in 30 ml. of THF was added dropwise in 20 min. Working up the reaction mixture, as described in the preparation of VII, gave 16.2 g. (89%) of crude dipotassium α,α′-dinitro-N,N,N′,N′-tetramethyladipamide (VIII).

Compound VIII (4.6 g.) was brominated as described in the preparation of IX. Sublimation (110° and 5 μ) of the solid which remained after evaporation of the solvent gave 2.7 g. (48%) of **α,α′-dibromo-α,α′-dinitro-N,N,N′,N′-tetramethyladipamide (X)**, m.p. 172–173° dec. (over-all yield based on V, 42.7%).

Anal. Calcd. for $C_{10}H_{16}Br_2N_4O_6$: C, 26.78; H, 3.57; Br, 35.71; N, 12.50. Found: C, 27.06; H, 3.89; Br, 35.90; N, 12.31.

Acknowledgment.—Support of this work by the Office of Naval Research is gratefully acknowledged.

Enamine Chemistry. VII. Cycloaddition Reactions of Ketene Acetals, O,N-Acetals, and N,N-Acetals

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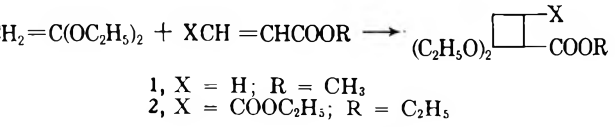
Received August 26, 1963

In an earlier paper of this series,[1] some cycloaddition reactions of enamines with electrophilic olefins were described. In this Note, a limited investigation of similar reactions of ketene acetals, O,N-acetals, and N,N-acetals is described.

Ketene diethyl acetal was found to react slowly with methyl acrylate in refluxing acetonitrile to give the cycloaddition product **1** in good yield. Although **1**

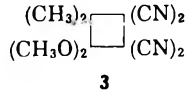


1, X = H; R = CH_3
2, X = $COOC_2H_5$; R = C_2H_5

gave the 2,4-dinitrophenylhydrazone of the corresponding β-keto ester, we were not able to obtain the free β-keto ester itself. Moderately vigorous, acid-catalyzed hydrolysis of **1** gave glutaric acid.

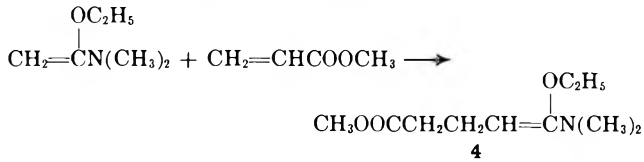
Ketene diethyl acetal reacted more slowly with diethyl fumarate in refluxing acetonitrile to give a poor yield of adduct **2**.

Under conditions comparable to those used with ketene diethyl acetal, no cycloaddition products were obtained from dimethylketene dimethyl acetal and either methyl acrylate or diethyl fumarate. Dimethylketene dimethyl acetal reacted readily with ethenetetracarbonitrile[2] to give adduct **3**.



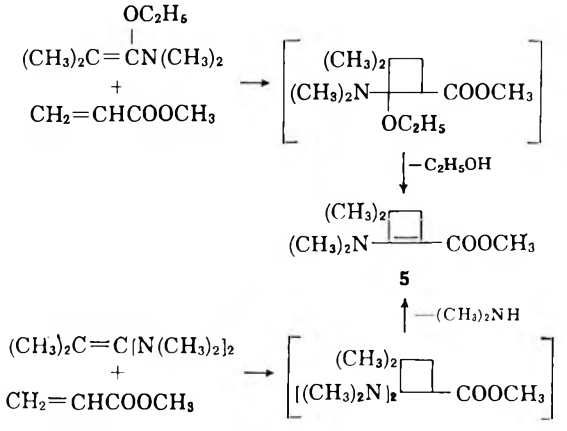
3

No cycloaddition products were obtained from the reactions of 1-ethoxy-N,N-dimethylvinylamine with electrophilic olefins. Instead, as shown for methyl acrylate, the Stork[3] adduct **4** was obtained.



4

Both 1-ethoxy-N,N,2-trimethylpropenylamine and N,N,N′,N′,2-pentamethyl-1-propene-1,1-diamine reacted with methyl acrylate to give the cyclobutene derivative **5** in poor yield, presumably by loss of alcohol and dimethylamine, respectively, from the initially formed cyclobutanes.



5

Experimental

1-Ethoxy-N,N-dimethylvinylamine.—This compound was prepared from N,N-dimethylacetamide by the method of Meerwein,[4] except that 1 mole of alcohol-free sodium ethoxide suspended in ether was used in place of excess ethanolic sodium

(1) Part IV of this series: K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

(2) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).

(3) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(4) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961).

ethoxide. Yields of 73 and 70% of 1-ethoxy-N,N-dimethylvinylamine, b.p. 124–125°, were obtained in runs of 1 and 3 moles, respectively.

1-Ethoxy-N,N,2-trimethylpropenylamine.—The procedure of Meerwein,[4] modified as described above, was applied to the preparation of this compound from N,N-dimethylisobutyramide. The product, b.p. 148–150° (63–65° at 40 mm.), $n^{20}D$ 1.4367, was obtained in 49% yield. Satisfactory elemental analyses were not obtained, possibly because the product reacted with atmospheric moisture. However, its physical properties, including infrared and n.m.r. spectra, were in agreement with the proposed structure. The infrared spectrum contained a strong absorption for >N—C=C< at 5.98 μ. The n.m.r.[5] spectrum consisted of the following absorptions (chemical shift, multiplicity, and assignment are shown): 3.63, quartet, O–CH_2–; 2.64, singlet, N–CH_3; 1.58, singlet, C=C–CH_3; 1.18 p.p.m., triplet, C–CH_3.

N,N,N′,N′,2-Pentamethyl-1-propene-1,1-diamine.—To a solution of N,N-dimethylisobutyramide (57.5 g., 0.5 mole) in tetrahydrofuran (250 ml.) was added phosgene (60 g., 0.6 mole). The resulting mixture was heated at 50–65° with stirring under a Dry Ice-cooled condenser for 1.5 hr., while carbon dioxide was evolved and the mixture separated into two liquid phases. The entire mixture was transferred to a heated dropping funnel and added rapidly to a mixture of dimethylamine (70 g., 1.55 moles), dioxane (150 ml.), and 48 g. of a 50% dispersion of sodium hydride in mineral oil, while the temperature was maintained at 0–10°. The resulting viscous slurry was allowed to stand for 18 days at room temperature, while protected from atmospheric moisture by drying tubes. The mixture was filtered, and the filtrate was distilled *in vacuo* to yield 22.5 g. (32%) of product, b.p. 60–62° (35 mm.), and 15 g. (26%) of recovered amide. Again, satisfactory elemental analyses could not be obtained. However, the infrared spectrum showed a strong absorption at 6.02 μ and the n.m.r. spectrum consisted of singlet absorptions at 2.6 and 1.5 p.p.m. assigned to N–CH_3 and C=C–CH_3 protons, respectively.

Methyl 2,2-Diethoxycyclobutanecarboxylate.—Ketene diethyl acetal (20 g., 0.172 mole), methyl acrylate (15 g., 0.174 mole), and acetonitrile (50 ml.) were combined and refluxed for 190 hr. Distillation of the mixture through a 6-in. Vigreux column gave 22 g. (63%) of methyl 2,2-diethoxycyclobutanecarboxylate, b.p. 52–55° (0.9 mm.), $n^{20}D$ 1.4324. The infrared spectrum showed no absorption between 5.9 and 6.7 μ, and the n.m.r. spectrum showed no olefinic proton absorption.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0. Found: C, 59.4; H, 9.2.

The 2,4-dinitrophenylhydrazone (prepared in methanol) melted at 143–145°.

Anal. Calcd. for $C_{12}H_{12}N_4O_8$: C, 46.7; H, 3.9. Found: C, 46.6; H, 4.2.

Hydrolysis of Methyl 2,2-Diethoxycyclobutanecarboxylate.—A mixture of methyl 2,2-diethoxycyclobutanecarboxylate (10 g., 0.049 mole), water (15 ml.), concentrated hydrochloric acid (5 drops), and enough methanol to produce a homogeneous solution was heated on the steam bath for 3.5 hr. in an open beaker. The mixture was cooled and filtered. The solid was recrystallized from benzene to give 4.8 g. (72%) of glutaric acid, which was identical with an authentic sample.

Diethyl 3,3-Diethoxy-1,2-cyclobutanedicarboxylate.—A mixture of ketene diethyl acetal (30 g., 0.259 mole), diethyl fumarate (41 g., 0.24 mole), and acetonitrile (75 ml.) was refluxed for 190 hr. Distillation of the mixture through a 3-in. Vigreux column gave 12 g. (17%) of diethyl 3,3-diethoxy-1,2-cyclobutanedicarboxylate, b.p. 103–109° (0.2 mm.), $n^{20}D$ 1.4421.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.3; H, 8.4. Found: C, 58.5; H, 8.3.

3,3-Diethoxy-4,4-dimethyl-1,1,2,2-cyclobutanetetracarbonitrile.—Dimethylketene dimethyl acetal (4.4 g., 0.038 mole) was added over a 5-min. period to ethenetetracarbonitrile (3.2 g., 0.025 mole) in acetonitrile (25 ml.). The temperature rose to 38° and then dropped to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from acetone–hexane to give 5.2 g. (85%) of 3,3-dimethoxy-4,4-dimethyl-1,1,2,2-cyclobutanetetracarbonitrile, m.p. 136–137°.

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 58.9; H, 5.0. Found: C, 59.0; H, 5.3.

Methyl 5-Dimethylamino-5-ethoxy-4-pentenoate.—Methyl acrylate (25.8 g., 0.3 mole) was combined with N,N-dimethyl-1-ethoxyvinylamine (34.5 g., 0.3 mole). The temperature of the mixture rose to 60° over a 0.5-hr. period and then dropped slowly to room temperature. Distillation gave 38 g. (61%) of methyl 5-dimethylamino-5-ethoxy-4-pentenoate, b.p. 63–67° (1 mm.), $n^{20}D$ 1.4574. The infrared spectrum showed, besides the ester band, a strong absorption at 6.04 μ, and the n.m.r. spectrum contained an olefinic proton triplet at 3.2 p.p.m.

Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0. Found: C, 60.0; H, 9.5; N, 6.9.

The same product was formed when the reaction was carried out at 10° and, on the basis of infrared spectral data, was present prior to distillation. When the analogous compound from ethyl acrylate, b.p. 67–70° (0.5 mm.), $n^{20}D$ 1.4536, was dissolved in ethanol and the resulting solution was added to dilute hydrochloric acid, there was obtained on distillation a 58% yield of diethyl glutarate, identical with an authentic sample.

Methyl 2-Dimethylamino-3,3-dimethyl-1-cyclobutene-1-carboxylate.—A mixture of 1-ethoxy-N,N,2-trimethylpropenylamine (24.8 g., 0.17 mole), methyl acrylate (15 g., 0.17 mole), and acetonitrile (75 ml.) was refluxed for 16 hr. Distillation of the reaction mixture gave 10 g. (40% recovery) of the ethoxyamine starting material and 8.5 g. (44% based on unrecovered starting material) of the product, b.p. 65–68° (0.8 mm.), $n^{20}D$ 1.5121.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.3; N, 7.6. Found: C, 65.7; H, 9.3; N, 7.4.

The infrared spectrum showed strong bands at 6.0 and 6.2 μ, and the n.m.r. spectrum was compatible with the proposed structure.

The compound gave the 2,4-dinitrophenylhydrazone of methyl 3,3-dimethyl-2-oxocyclobutanecarboxylate, m.p. 128.5–130°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8; N, 16.6. Found: C, 50.3; H, 5.1; N, 16.3.

Methyl 2-dimethylamino-3,3-dimethyl-1-cyclobutene-1-carboxylate also was obtained in 23% yield from methyl acrylate and N,N,N′,N′,2-pentamethyl-1-propene-1,1-diamine. Some of the diamine was recovered, apparently admixed with methyl 3-dimethylaminopropionate, which was formed by addition of dimethylamine to methyl acrylate.

(5) N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane.

Evidence Supporting the Occurrence of a 4,5-Dehydropyrimidine in Aminations of Halopyrimidines[1]

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The elimination–addition (benzyne) mechanism for nucleophilic aromatic substitution has been invoked in many heterocyclic systems; included among these are pyridines,[2] quinolines,[3] and pyridazines.[4] This mode of substitution apparently has not been postulated yet for such transformations in pyrimidines.

Because reactions involving a benzyne-type intermediate generally occur in cases of nonactivated aryl halides, 2-methyl-5-chloropyrimidine (I) was selected as a precursor for the 4,5-dehydropyrimidine. The C-5 of the pyrimidine ring is relatively electron-rich

(1) This investigation was supported by Grant CA-02857 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) For pertinent references, see (a) T. Kauffmann and F.-P. Boettcher, *Chem. Ber.*, **95**, 1528 (1962); (b) R. J. Martens and H. J. den Hertog, *Tetrahedron Letters*, **No. 15**, 643 (1962).

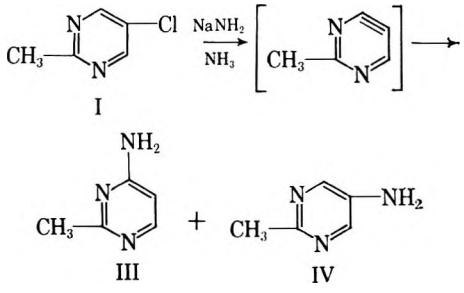
(3) T. Kauffmann, F.-P. Boettcher, and J. Hansen, *Ann.*, **659**, 102 (1962).

(4) T. Kauffmann and A. Risberg, *Tetrahedron Letters*, **No. 22**, 1459 (1963).

and hence less susceptible to reaction through the addition–elimination mechanism of substitution.

The chloro compound (I) was prepared by the decarboxylation of 2-methyl-4-carboxy-5-chloropyrimidine (II)[5] which was obtained from the condensation of acetamidine with mucochloric acid.

Treatment of I with sodium amide in liquid ammonia would be expected to yield 2-methyl-4-aminopyrimidine (III) and 2-methyl-5-aminopyrimidine (IV), providing the elimination–addition mechanism is operative.



Authentic samples of III and IV were prepared by the following procedures. Condensation of ethyl sodium formylacetate with acetamidine gave 2-methyl-4-hydroxypyrimidine (V).[6] Treatment of V with phosphorus oxychloride gave 2-methyl-4-chloropyrimidine (VI),[6] which was converted to III with aqueous ammonia. Urban and Schnider reported the preparation of IV by the reductive dehalogenation of 2-methyl-5-amino-4,6-dichloropyrimidine (VII).[7] We have synthesized IV by the decarboxylation of 2-methyl-4-carboxy-5-aminopyrimidine (VIII), which was obtained by the amination of 2-methyl-4-carboxy-5-bromopyrimidine (IX)[5] with aqueous ammonia. The bromo acid (IX) was prepared by condensing acetamidine with mucobromic acid.[5] The sample of IV obtained by the decarboxylation of VIII was identical with one prepared by the reduction of VII.[8]

2-Methyl-5-chloropyrimidine was treated with sodium amide in liquid ammonia for 2 hr., and the reaction mixture was analyzed by vapor phase chromatography. 2-Methyl-4-aminopyrimidine (III) was identified as a component of the mixture. This component was shown to have the same retention time as an authentic sample of III and when isolated exhibited an infrared spectrum identical with that of III. The presence of 2-methyl-5-aminopyrimidine (IV) can only be inferred. A component of the reaction mixture with a retention time identical with that of an authentic sample of IV was observed. The quantity obtained, however, was not sufficient for spectral comparison. Control experiments with III and IV indicated that interconversion of the two aminopyrimidines did not occur under the reaction conditions.

The formation of 2-methyl-4-aminopyrimidine (III) from I is consistent with a benzyne-type mechanism.[9] The determination of relative quantities of III and IV is precluded at this time by poor yields.

(5) Z. Budesinsky, *Collection Czech. Chem. Commun.*, **14**, 223 (1949).
(6) S. Gabriel, *Ber.*, **37**, 3638 (1904).
(7) R. Urban and O. Schnider, *Helv. Chim. Acta*, **41**, 1806 (1958).
(8) The authors are indebted to O. Schnider, R. Hoffmann-LaRoche and Co., Basel, Switzerland, for a sample of this compound.
(9) H. Heaney, *Chem. Rev.*, **62**, 81 (1962).

Experimental

Melting points were taken on a Mel-Temp apparatus. Infrared spectra were determined using a Beckman IR-5A spectrophotometer. All vapor phase chromatographic analyses were carried out on an F & M Model 500 gas chromatograph with a 0.25-in. o.d., 5-ft. stainless steel column packed with 8% Triton X-305 on Chromosorb W. The analyses were run isothermally at 153° using helium as a carrier gas (100 ml./min.).

Materials.—2-Methyl-5-chloropyrimidine (I),[5] 2-methyl-4-carboxy-5-chloropyrimidine (II),[5] 2-methyl-4-aminopyrimidine (III),[6] 2-methyl-4-hydroxypyrimidine (V),[6] 2-methyl-4-chloropyrimidine (VI),[6] 2-methyl-4-carboxy-5-aminopyrimidine (VIII),[5] and 2-methyl-4-carboxy-5-bromopyrimidine (IX)[5] were prepared according to procedures described in the literature.

2-Methyl-5-aminopyrimidine (IV) was prepared by heating 1.9 g. of VIII at 200° for 3 hr. in an oil bath. The reaction mixture was extracted for 12 hr. with benzene. Upon removal of the benzene *in vacuo* there was obtained a solid weighing 0.1 g. (8%), which was vacuum sublimed at 135° and 28 mm. The melting point of the sublimate was 155–157°. An authentic sample of IV[8] melted at 156–159° and exhibited an infrared spectrum identical with that of the product obtained from the decarboxylation of VIII.

Reaction of 2-Methyl-5-chloropyrimidine (I) with Sodium Amide in Liquid Ammonia.—The reaction conditions were similar to those by Pieterse and den Hertog employed in the amination of 3-chloropyridine.[10] Sodium amide was prepared from 0.37 g. of sodium, 12 ml. of anhydrous liquid ammonia, and 0.1 g. of ferric nitrate.[11] 2-Methyl-5-chloropyrimidine (I, 0.97 g.) was added cautiously to the stirred mixture. After the mixture was stirred and refluxed for 2 hr., the reaction was quenched with 1.0 g. of ammonium chloride. The ammonia was allowed to evaporate, and the resulting residue was extracted with benzene for 36 hr. The benzene was removed *in vacuo*, and the resulting residue was dissolved in methanol and diluted to 1 ml. Authentic samples of 2-methyl-4-aminopyrimidine (III) and 2-methyl-5-aminopyrimidine (IV) were found to have retention times of 13.0 and 14.8 min., respectively, under the column conditions stated above. The methanolic solution contained a component with a retention time of 13.0 min. When this component was collected, it exhibited an infrared spectrum identical with that of III. A component with a retention time identical with that of IV was detected, but it was not present in sufficient amounts for collection and spectral comparisons. By means of a quantitative correlation between weight of pyrimidine and chromatogram peak area, in which authentic samples of the aminopyrimidines were employed, the reaction mixture was found to contain these pyrimidines in only small amounts (<5%).

Control Experiments on 2-Methyl-4-aminopyrimidine (III) and 2-Methyl-5-aminopyrimidine (IV).—The aminopyrimidines were recovered in amounts up to approximately 50% when refluxed with sodium amide in liquid ammonia at −33° for 2 hr. The column conditions for the analysis were the same as those described above. In each instance, the aminopyrimidine under investigation was found to be the only component present in the reaction mixture.

(10) M. J. Pieterse and H. J. den Hertog, *Rec. trav. chim.*, **80**, 1376 (1961).
(11) T. H. Vaughn, R. R. Vogt, and J. Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

Synthesis of 3,5-Diaminopyrazole Hydrochlorides

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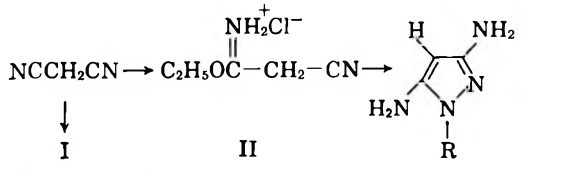
In 1894, von Rothenburg[1] reported that the condensation of malononitrile and hydrazine yielded a compound believed to be 3,5-diaminopyrazole (IIIa).

(1) R. von Rothenburg, *Chem. Ber.*, **27**, 685 (1894).

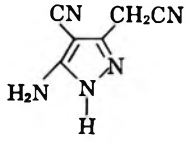
Subsequent reinvestigation by Taylor and Hartke[2] demonstrated that the actual product was 5-amino-4-cyano-3-cyanomethylpyrazole (IV), which was formed by the addition of hydrazine to the dimer of malononitrile, 1,1,3-tricyano-2-aminopropene-1. No authentic simple 3,5-diaminopyrazoles appear to have been described in the literature. An interest in new heterocyclic systems led us to investigate a synthetic route to this class of compounds.

When ethyl cyanoacetimidate hydrochloride (II)[3,4] was allowed to react with phenylhydrazine in ethanol, 3,5-diamino-1-phenylpyrazole hydrochloride (IIIb) was obtained. Similarly, the action of phenethylhydrazine on II gave 3,5-diamino-1-phenethylpyrazole hydrochloride (IIIc). Regrettably, the action of hydrazine itself on II failed; only intractable tars were formed.

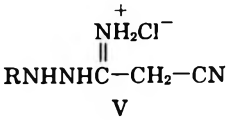


I II

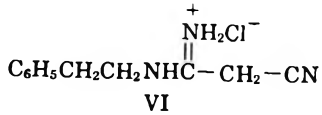
IIIa, R = H
b, R = C_6H_5, ·HCl
c, R = $C_6H_5CH_2CH_2$, ·HCl



IV

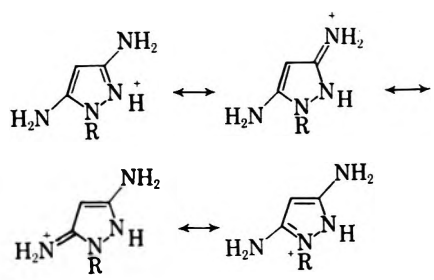


V



VI

Alternative structures for the products, the isomeric amidrazones V, were excluded on the basis of the n.m.r. spectra. In D_6-dimethyl sulfoxide solution, IIIb exhibits sharp singlets at 4.73 (1 proton) and 2.38 τ (5); IIIc exhibits singlets at 4.97 (1) and 2.55 τ (5), and triplets at 5.83 (2) and 7.05 τ (2). These chemical shifts differ markedly from those displayed by a reasonable model for V, cyano-N-phenethylacetamidine hydrochloride (VI).[4] The n.m.r. spectrum of VI exhibits resonance at 2.55 (5), 5.70 (2, singlet), 6.30 (2, triplet), and 7.05 τ (2, triplet). The absence of a two-proton singlet at 5.7 τ and the appearance of a one-proton singlet at 4.73 or 4.97 τ clearly excludes structure V and supports the cyclic structures IIIa and IIIb. The absence of nitrile bands in the infrared spectra of IIIa and IIIb is consistent with this interpretation.



VII

(2) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2452 (1959).
(3) A. H. Cook, G. Harris, and A. L. Levy, *J. Chem. Soc.*, 3227 (1949).
(4) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, **29**, 308 (1964).

Although the structures of the bases corresponding to III have been represented as 3,5-diaminopyrazoles, alternative tautomeric forms cannot be excluded. However, protonation of any tautomer can lead to VII, the most probable structure for the pyrazole salts III, in which a high degree of charge distribution is possible.

Experimental[5]

3,5-Diamino-1-phenylpyrazole Hydrochloride (IIIb).—To a solution of 7.4 g. (0.05 mole) of ethyl cyanoacetimidate hydrochloride[3,4] and 100 ml. of ethanol was added with stirring under nitrogen 5.4 g. (0.05 mole) of phenylhydrazine. After 30 min. the mixture was filtered, and the filtrate was evaporated under reduced pressure to a brown tar which crystallized from ethanol–ether. One recrystallization gave 2.3 g. (22%) of colorless needles, m.p. 230–231.5° dec. Two additional recrystallizations from ethanol–ether followed by a third recrystallization from ethanol afforded the analytical sample, m.p. 231–233° dec., λ_{max}^{MeOH} 249 mμ (ϵ 18,300).

Anal. Calcd. for $C_9H_{11}ClN_4$: C, 51.31; H, 5.23; Cl, 16.86; N, 26.60. Found: C, 51.37; H, 5.35; Cl, 17.19; N, 26.63.

3,5-Diamino-1-phenethylpyrazole Hydrochloride (IIIc).—To a solution of 1.48 g. (0.01 mole) of ethyl cyanoacetimidate hydrochloride[3,4] and 20 ml. of ethanol was added with stirring under nitrogen 1.4 g. (0.01 mole) of phenethylhydrazine.[6] After 30 min. the mixture was filtered, and the filtrate was evaporated under reduced pressure to a tan pasty solid. Two recrystallizations from acetonitrile gave 0.21 g. (9%) of colorless prisms, m.p. 160–162°. An additional recrystallization afforded the analytical sample, m.p. 160–161°, λ_{max}^{MeOH} 237 mμ (ϵ 13,300).

Anal. Calcd. for $C_{11}H_{15}ClN_4$: C, 55.35; H, 6.29; Cl, 14.88; N, 23.48. Found: C, 55.14; H, 6.42; Cl, 14.45; N, 23.97.

(5) Melting points were determined with a Hershberg apparatus and are uncorrected. Ultraviolet spectra were determined with a Cary 11 spectrophotometer. N.m.r. spectra were determined with a Varian Associates A-60 spectrometer by Mr. W. Fulmor and associates. Microanalyses were performed by Mr. L. M. Brancone and associates.
(6) Phenethylhydrazine, b.p. 108–113° (1–1.5 mm.), was liberated from the commercially available sulfate salt with ethanolic sodium methoxide.

The Synthesis of 2-Bromopyrimidines and 2,2′-Bipyrimidines

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Received August 21, 1963

The syntheses of 2-bromopyrimidine and 2,2′-bipyrimidine have been reported recently,[3] as well as a study of 2,2′-bipyrimidine as a color forming agent in analytical chemistry.[4] The purpose of the present study was to determine whether the reverse addition diazotization method for converting 2-aminopyrimidine to 2-bromopyrimidine[3] could be generalized for preparing new substituted 2-bromopyrimidines, and to determine whether the resulting substituted 2-bromopyrimidines could, in general, be coupled, with the elimination of bromine, to form new substituted 2,2′-bipyrimidines.

This study was successful as far as it was carried out. Additional work on the project had to be suspended,

(1) The author gratefully acknowledges a postdoctoral fellowship granted to him by Eli Lilly and Co., which financially supported this work.
(2) To whom correspondence should be addressed at Carothers Research Laboratory, E. I. du Pont de Nemours and Co., Experimental Station, Wilmington, Del.
(3) D. D. Bly and M. G. Mellon, *J. Org. Chem.*, **27**, 2945 (1962).
(4) D. D. Bly and M. G. Mellon, *Anal. Chem.*, **35**, 1386 (1963).

because, despite the use of rubber gloves and aprons, the author developed a high sensitivity to 2-bromo-4-chloro-6-methylpyrimidine, resulting in severe contact dermatitis on the hands; but, as a result of the study, it is felt that the diazotization and coupling reactions are general for nontautomeric pyrimidines, it being necessary only to vary the conditions somewhat for the individual compounds.

The large excess of inorganic reagents and long reaction times required in the reverse addition diazotization reactions are evidently due to the fact that the respective amines are only very slightly soluble in water and the contact between the reactants is poor. However, no other solvent system could be found which would adequately dissolve all of the reagents and reactants. In order to maintain a high concentration of nitrous acid for a long reaction time, the hydrobromic acid was introduced at a constant, very slow, drop rate by a pressure-controlled dropping capillary, and the temperature of the reaction vessel was maintained constant with a Wilkens Anderson Low Temp bath.

The infrared spectra of all the pyrimidines, determined on a Perkin-Elmer Model 221 instrument with sodium chloride optics, were consistent with proposed structures. In the visible region, the 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine gave a deep red color upon warming with a dilute solution of Cu(I), but formed no colored complex with Fe(II) or Fe(III). The ultraviolet spectra were determined on a Cary Model 10-11 spectrophotometer in distilled water using a distilled water reference.

Experimental[5]

Preparation of 2-Bromo-4,6-dimethylpyrimidine by Reverse Addition Diazotization.—A 24-g. quantity (0.214 mole) of 2-amino-4,6-dimethylpyrimidine was diazotized by the very slow addition of 114 ml. (1 mole) of concentrated hydrobromic acid to a solution containing the pyrimidine, 300 ml. of water, 300 g. of sodium bromide, and 70 g. (1 mole) of sodium nitrite at −3.2°. The addition of the acid took 24 hr. to completion.

The solution was then cleared of nitrogen oxides by an air stream, made strongly alkaline with cold 30% sodium hydroxide, and filtered. The precipitate and filtrate were each extracted with two 200-ml. portions of carbon tetrachloride and the extracts combined and evaporated to dryness. The residue was taken up in hot petroleum ether (b.p. 90–100°), cooled to 0°, and filtered. The filtrate was evaporated to give 9.4 g. (0.05 mole, 24%) of crystalline 2-bromo-4,6-dimethylpyrimidine. The product was further purified by sublimation *in vacuo* to give white crystals, m.p. 69.5–71.5°, a molecular weight of 183 (theory 187) as determined in chloroform by a Mechrolab osmometer, Model 301 A, and λ_{max} 256 and 217 mμ with log a_m = 3.62 and 3.83, respectively.

Anal. Calcd. for $C_6H_7BrN_2$: C, 38.5; H, 3.75; Br, 42.7; N, 15.0. Found: C, 38.5; H, 3.8; Br, 42.4; N, 15.2.

Scale-up of this reaction failed owing to very marked increase in foaming in the reaction mixture. The 4,6-dimethyl-2-pyrimidinol, also a product of the diazotization reaction, was isolated by adjusting the chloroform-extracted aqueous solution to pH 4.5, evaporating to dryness *in vacuo*, as with 2-pyrimidinol,[3] and extracting with hot ethyl acetate.

Preparation of 2-Bromo-4-chloro-6-methylpyrimidine by Reverse Addition Diazotization.—In like manner 2-amino-4-chloro-6-methylpyrimidine was diazotized by adding 228 ml. (2 moles) of concentrated hydrobromic acid to 40 g. (0.279 mole) of the pyrimidine mixed with 325 ml. of water, 300 g. of sodium bromide, and 140 g. (2 moles) of sodium nitrite at −3.2°. The addition of the acid took 44 hr. to completion.

After adjusting the solution to pH 7, the product was steam distilled, then crystallized from minimum petroleum ether (b.p. 60–70°) and vacuum dried to give 9.5 g. (0.049 mole, 16%) of crystalline 2-bromo-4-chloro-6-methylpyrimidine, m.p. 33–34°, molecular weight in chloroform of 210 (theory 208), and λ_{max} 260 and 217 mμ with log a_m = 3.68 and 3.85, respectively.

Anal. Calcd. for $C_5H_4BrClN_2$: C, 28.9; H, 1.9; Br, 38.1; Cl, 17.2; N, 13.5. Found: C, 28.9; H, 1.7; Br, 38.1; Cl, 17.2; N, 13.6.

The 4-chloro-6-methyl-2-pyrimidinol, also a product of the diazotization, floats to the top of the warm crude reaction mixture before steam distillation and can be skimmed off.

Preparation of 4,4′,6,6′-Tetramethyl-2,2′-bipyrimidine.—The experimental details were similar to those for 2,2′-bipyrimidine,[3] except that no nitrogen was used. A 20-g. (0.3 g.-atom) portion of activated[6] Natural Copper Fine 44-F was added all at once to 10 g. (0.053 mole) of 2-bromo-4,6-dimethylpyrimidine at reflux in 60 ml. of (calcium hydride-distilled) dimethylformamide. After 8 hr. of stirring at reflux, 5 g. of additional activated copper was added. After 24 hr. the mixture was cooled to room temperature, suction filtered, and the residue washed with a little water. The copper-product residue was then twice extracted for 2 min., respectively, with 200 ml. of concentrated ammonium hydroxide saturated with potassium cyanide. Each extraction was separated by suction filtration, and the combined filtrates then extracted with two 500-ml. portions of chloroform. The remaining copper residue was extracted once with chloroform.

The combined chloroform solutions were evaporated to dryness. The tarry residue was dissolved in 200 ml. of hot ethyl acetate, decolorized with Darco, filtered, and evaporated to yield 2.3 g. (0.01 mole, 26%) of tan, amorphous 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine. Sublimation did not give a pure product, but constant m.p. 131–132° was obtained by crystallizing the sublimed material from an ethyl acetate–petroleum ether solution. [The pyrimidine was dissolved in minimum hot ethyl acetate, hot petroleum ether (b.p. 90–100°) added until the solution was cloudy, and the mixture cooled to 0° and filtered.] The molecular weight, determined in chloroform as above, was 213 (theory 214) with λ_{max} at 248 mμ and log a_m = 4.17.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.4; H, 6.6; N, 26.2. Found: C, 65.1; H, 6.9; N, 26.1.

Attempted Synthesis of 4,4′-Dichloro-6,6′-dimethyl-2,2′-bipyrimidine.—It was attempted to prepare this compound by a procedure exactly analogous to the synthesis of 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine, and a reaction definitely took place on two different attempts. However, no one product was isolated, and the author had to give up the project due to his high sensitivity to the starting material. It is felt, however, that 4,4′-dichloro-6,6′-dimethyl-2,2′-bipyrimidine could be obtained, since the chlorine atoms should not interfere.[3]

(5) All melting points are uncorrected.

(6) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

Deuterium Exchange in the Pyridoxal-Leucine System[1]

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Deuterium exchange from a D_2O solvent is frequently used to confirm reaction mechanisms. The positions at which exchanges occur must be determined, and the total amount of deuterium incorporated at each position should be measured. These values then can be used to support or disprove a particular mechanism. A convenient procedure for accurate and direct determinations of both the location and extent of deuterium incorporated in a molecule uses mass spectral fragmentation data. A detailed discussion of the use

(1) Contribution no. 1297. Work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission.

of these data is given in a recent text by Biemann.[2] This approach was applied to the assay of leucine which had been isolated from the equilibrated reaction mixture of leucine and pyridoxal in D_2O.

$$\text{Leucine} + \text{pyridoxal} \underset{D_2O}{\overset{\text{alum catalyst}}{\rightleftharpoons}} \alpha\text{-keto acid} + \text{pyridoxamine} \quad (1)$$

Extent and specificity of labeling of the leucine was calculated from the mass spectra of pure leucine and that of the isolated product leucine. Pertinent portions of the spectra which were used for these calculations are tabulated in Table I. Discussions of the mass shifts and the information gained from a consideration of these shifts in several mass ranges are given below.

Table I

Mass Spectra of Leucine and Leucine-d_n

m/e	leu	leu-d_3	m/e	leu	leu-d_3
39[a]	5.6	3.3	84[b]		
40	0.8	2.1	85		
41	12.3	7.5	86	99.1	0.5
42	6.2	3.4	87		1.4
43	19.0	16.8	88	0.7	5.8
44	51.9	4.9	89	0.2	92.3
45	1.6	6.8	90		
46	3.0	7.9			
47		47.5			
			131[d]	100	
			132		
73[c]	1.0		133		5
74	86.0	3.0	134		95
75	13.0	85.0			
76		12.0			
77					

[a] $\Sigma_{39-47} = 31.2\%$; [b] $\Sigma_{84-90} = 25.0\%$; [c] $\Sigma_{73-77} = 9.6\%$; [d] $\Sigma_{131-134} = 0.3\%$ of the total ion yield.

Masses 131–134.—The parent ion peak from pure leucine appears at $m/e = 131$. This peak shifts almost entirely to $m/e = 134$ in the spectrum of deuterated leucine. One concludes that the sample is apparently 95% leucine-d_3. However, there is a high degree of uncertainty in this conclusion because of the low intensity of the parent ion peak (see footnote *d* of Table I).

Masses 84–90.—The amine fragment $[(CH_3)_2CH\text{-}CH_2CH{=}\overset{+}{N}H_2]$ at $m/e = 86$ is formed by a process whose activation energy is low[3] and no intramolecular mixing of protium and deuterium is expected prior to the bond rupture of the molecule-ion.[4] In addition, large peaks due to the loss of one or more protium atoms from the fragment are not present to complicate the calculations or the interpretation of the observed mass shifts. From the data recorded in this mass range (see Table I), the extent of trideuteration is calculated to be 92%, dideuteration 6%, and monodeuteration 1%. Less than 1% of the original leucine is undeuterated. No information about the position of the deuterium atoms is obtained from the consideration of these fragments. However, Junk and Svec[3] have confirmed that the amino hydrogens are readily exchanged in water at room temperature. Since the sample was recrystallized from water, the only possible distribution of the deuterium atoms is on carbon atoms.

Masses 73–77.—The decompositions which result in the peaks at $m/e = 74$ $[CH(NH_2)COOH]^+$ and $m/e = 75$ $[CH_2(NH_2)COOH]^+$ from leucine have been established.[3] These peaks shift to $m/e = 75$ and 76 in the mass spectrum of leucine-d_n. Thus, most of the α-protium has been replaced with deuterium. The remaining $m/e = 74$ peak in the mass spectrum of leucine-d_n is a measure of the amount of protium left on the α-carbon atom. This peak and the $m/e = 75$ are used to calculate the extent of labeling on the α-carbon position. The calculated result is 97% α-deuterated. It has already been shown that the sample is 92% trideuterated. A reasonable assumption is that the trideuterated leucine is mono-α and di-β since one would expect the sample to be leucine-d_2 if the γ-position were activated and leucine-d_7 if the δ-positions were activated.[5] The validity of this assumed distribution (mono-α and di-β) was established by the observation of the mass shifts in the 39–47 mass range.

Masses 39–47.—The fragment causing the peak at $m/e = 44$ is formed by the process shown in eq. 2.

$$H_3C\text{-}CH(CH_2\text{-}CH(COOH)\text{-}CH_2\text{-}H\cdots\overset{+}{N}H_2) \rightarrow H_3C\text{-}\underset{\underset{CH_2}{\|}}{CH} + H_2C{=}\underset{\underset{{}^+NH_3}{|}}{CH} + \cdot COOH \quad (2)$$

This peak from leucine contributes 51.9% of the total peak intensities observed in the 39–47 mass range. The peak at $m/e = 47$ from leucine-d_n contributes 47.5% of the total peak intensities observed in the same mass range. If the isotope effect[6] is assumed to be negligible, the ratio of these two peaks can be used to calculate the extent of trideuteration. The calculated value is 91.5% trideuteration which agrees with the value calculated from data in 84–90 mass range.

The observed $m/e = 47$, 46, 45, and 44 peaks cannot be used directly for the calculation of the extent of tri-, di-, mono-, and undeuterated leucine. Suitable corrections must be applied to the observed data because of the presence of interference peaks. These corrections were applied to the observed data using the method of successive approximations. The corrected peaks were then used to calculate the per cents listed in column 2 of Table II. These are compared with the

Table II

Composition of Leucine-d_3

No. of D	39–47	84–90	44 (leu) / 47 (leu-d_3)	Stat. 97% D
d_0	0.4	0.5		
d_1	4.4	1.4		0.3
d_2	5.6	5.8		8.5
d_3	89.6	92.3	91.5	91.3

(2) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 204–250 and references cited there.

(3) G. A. Junk and H. J. Svec, *J. Am. Chem. Soc.*, **85**, 839 (1963).

(4) W. H. McFadden and M. Lounsbury, *Can. J. Chem.*, **40**, 1965 (1962).

(5) It should be noted that the absence of a peak at $m/e = 77$ in the mass spectrum of leucine-d_n is experimental evidence that the γ-position is not deuterated. The energetically favorable process for formation of the rearranged fragment is migration of the protium (or deuterium if present) from the γ-position to the carboxyl oxygen. The mass of the rearranged fragment would be 77 if deuterium is on the γ-position and 76 if protium is on this position (see Table I).

(6) D. P. Stevenson and C. D. Wagner, *J. Chem. Phys.*, **19**, 11 (1951).

results obtained from a consideration of the mass ranges 84:90 (column 3) and the 44:47 ratio (column 4). Discrepancies between columns 2 and 3 are attributed to errors inherent in the approximations used to calculate the values in column 2 and to the isotope effect.[6] Possibly some mixing of protium and deuterium occurs prior to decomposition of the molecule–ion. Such mixing also would affect the results.

The expected distribution of d_0, d_1, d_2, and d_3 in the $(-\overset{|}{C}=\overset{|}{C}-\overset{|}{N}-)^+$ fragment was calculated assuming that the two β-positions had the same deuterium content as that calculated for the α-position (that is, 97%). These calculated values are listed in column 5 of Table II. Rather close agreement exists between these values and those derived from experimental data in the mass ranges 39–47 and 84–90.

Additional critical work would be necessary to unequivocally arrive at a complete interpretation of the observed isotopic exchange. However, the results obtained in this present work confirm that the pyridoxal–metal–amino acid reaction mechanism[7,8] proceeds through formation of the generally accepted Schiff base intermediate. The α-position protiums are replaced with deuteriums through tautomerization of the Schiff base. The β activation occurs by tautomerization of the Schiff base and/or the α-keto acid.

In conclusion, the reaction of amino acids with pyridoxal appears to be generally useful for the selective labeling of amino acids in both the α- and β-positions. Samples so labeled can be assayed rapidly, accurately, and directly using a mass spectral approach similar to that described in this report for leucine-d_3. Less than 0.1 mg. of sample is consumed per assay.

Experimental

Leucine.—Calbiochem grade A leucine which was vacuum sublimed at 170° was used.

Leucine-d_3.—A 6.6-g. sample of leucine and 500 mg. of pyridoxal hydrochloride (Sigma Chemical) were dissolved in 200 ml. of 99.5% D_2O. Ammonium or potassium alum (250 mg.) was added to catalyze the reaction. The mixture was then refluxed for ~24 hr. The deuterated leucine was isolated from the cooled reaction mixture and recrystallized ten times from hot water. The product was further purified by vacuum sublimation at 170°. The yield of purified product was 3.7 g.

Mass Spectra.—A General Electric analytical mass spectrometer, which had been converted for use of the crucible source technique, was used to establish the mass spectra. Instrumental conditions were ion chamber temp., ~105°; electron energy, 70 v.; trap current, 10 μa.; ion accelerating voltage, 2000 v.; and magnetic scanning.

If it is not possible to use the crucible source technique, the deuterium assay of the isolated amino acid can conveniently be accomplished by conversion of the amino acid to a volatile derivative and by subsequent assay using a conventional external heated inlet system.[9,10]

Acknowledgment.—The authors are indebted to L. Levine who prepared the deuterated leucine and to Dr. D. Metzler for helpful discussions.

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(8) A. E. Braunstein, "The Enzymes," Vol. 2, Academic Press, New York, N. Y., 1970, pp. 137–148.

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(10) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 260–296 and references cited there.

The Nuclear Magnetic Resonance Spectra of Some Thiopyran Derivatives

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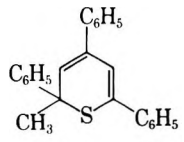
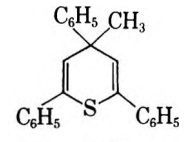
We[2] have reported earlier on the preparation of isomeric 2- and 4-methyl-2,4,6-triphenylthiopyrans by the coupling of 2,4,6-triphenylthiopyrylium ion with methylmagnesium bromide. The assignment of structure was based on a chemical degradation by desulfurization.



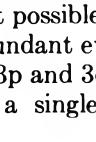
I, m.p. 119°



II, m.p. 97°

The structures have now been confirmed by their n.m.r. spectra in carbon tetrachloride with shifts calibrated by audiofrequency sidebands. Compound II shows single sharp peaks at 8.40 and 4.31, and a broad structured band centered at 2.88 τ in the proper ratio of 3:2:15. Compound I shows single sharp peaks at 8.14, 4.17, and 3.23, and broad structured bands centered at 2.66 and 2.38 τ in the ratio of 3:1:1:10:5.

The n.m.r. shifts in I, compared to II, as well as the ultraviolet absorption at much longer wave lengths for I (λ_{max} 257, 347 mμ)[2] compared to II (λ_{max} 235 mμ)[2] support the view that considerable cyclic conjugation occurs in I which is not possible for II. This would be consistent with the abundant evidence that the dimensions and geometry of 3p and 3d orbitals on sulfur permit conjugation past a single intervening saturated carbon atom.[3]



III

Such cyclic conjugation, not possible for II where cyclic conjugation is blocked cleanly at the 4-position, would explain the ultraviolet spectra and the downfield shifts of *all* hydrogens in I as compared to II. The larger downfield shift for one of the ring hydrogens in I could be explained readily since the 3-carbon is essentially "directly" joined to sulfur leading to a downfield chemical shift. We suggest that the hydrogens of the phenyl group on the saturated 2-carbon in I are those shifted further downfield than those on the 4- and 6-phenyls.

The n.m.r. spectrum of I sulfoxide,[2] m.p. 146–147°, shows sharp bands at 8.01, 4.03, and 3.32, and a relatively sharp band at 2.86 τ in the ratio of 3:1:1:15. The normal position for the aromatic hydrogens suggests there is little of the added cyclic conjugation effect indicated by structure III when the sulfide sulfur is

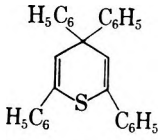
(1) Supported in part by National Science Foundation Grant No. 19470.

(2) G. Suld and C. C. Price, *J. Am. Chem. Soc.*, **84**, 2090 (1962).

(3) See C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962, pp. 51–55.

converted to sulfoxide. The shifted position for the ring hydrogens could then be due to a direct chemical shift by the electron-attacting sulfoxide group. The downfield shift for the methyl group may be analogous to that observed by Morin[4] in penicillin sulfoxide and indicates that the 2-methyl group is *cis* to the sulfoxide oxygen.[5]

The crystalline tetraphenylthiopyran, m.p. 157°, reported earlier[6] has been confirmed as the 2,4,4,6 isomer (IV) by n.m.r. bands at 2.87 and 4.00 τ in the ratio of 10:1.[6] Efforts to isolate a pure sample of the 2,2,4,6 isomer from the yellow oily residues after crystallization of IV were unsuccessful.[7]



IV

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(6) G. Suld and C. C. Price, *ibid.*, **84**, 2094 (1962).

(7) By Dr. Mikio Hori; the n.m.r. spectra were run on a Varian HR-60 instrument.

The Polynitration of Indolines. 5,7-Dinitration

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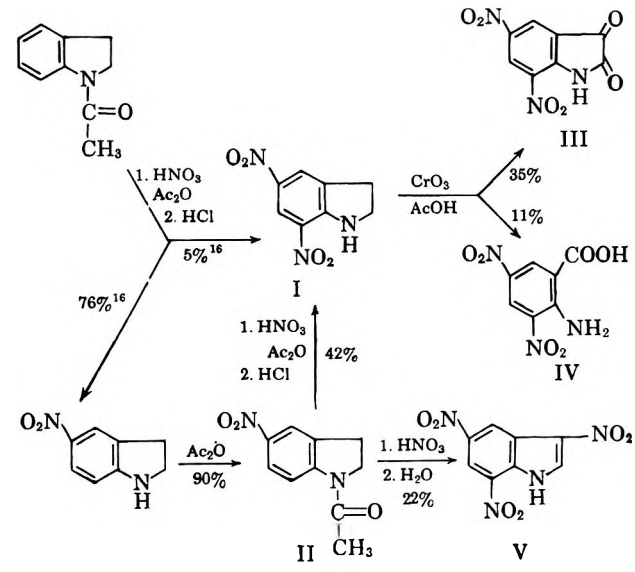
As indoles do not nitrate in the 7-position,[2] synthetic approaches to 7-nitroindoles have depended largely on ring closure to a benzene ring in which a nitro group has been prelocated in the potential 7-position.[3-14] The recently described[15,16] general method for preparation of indoles containing a nitro group in the benzene ring, by nitration of the corresponding indolines following by dehydrogenation, has only been applied to the synthesis of 5- and 6-nitroindoles. An adaptation of the indoline method, involving nitration of the indole–sodium bisulfite adduct and subsequent alkaline hydrolysis, recently has been used, *however*, for the synthesis of both 5- and 7-nitroindole.[17] Evidence for 5,7-dinitration of an acylindoline is available from an earlier example: Strychnine[18] is degraded by 20% nitric acid[19] (in a reaction which involves nitration, oxidation, and hydrolysis) to 5,7-dinitroindole-2,3-dicarboxylic acid (dinitrostrycholcarboxylic acid),[20] which undergoes decarboxylation to what was proved to be 5,7-dinitroindole-2-carboxylic acid (dinitrostrychol),[4,20,21] or further nitration in fuming nitric acid to 3,5,7-trinitroindole-2-carboxylic acid (trinitrostrychol).[4,20]

Nitration of 1-acetylindoline is reported to give 5-nitroindoline (64[22]–74[16]%), and a dinitroindoline (5%) of melting point 243–244°, which was assumed to be 5,7-dinitroindoline (I).[16] In this paper we report proof that dinitration of 1-acetylindoline and mononitration of the presumed intermediate, 1-acetyl-5-nitroindoline (II), gives 5,7-dinitroindoline (I). Chromic acid oxidation of the dinitroindoline gave as degradation products the known compounds, 5,7-dinitroisatin (III) and 3,5-dinitroanthranilic acid (IV). Attempts to dehydrogenate I to the still unknown 5,7-dinitroindole were unsuccessful, either with palladium on carbon (also tried on the acetyl derivative of I) or with tetrachloro-1,2-benzoquinone, compound I being recovered unchanged in moderate yields.

Addition of 1-acetyl-5-nitroindoline to fuming nitric acid gave a trinitro derivative, which, as indicated by its low hydrogen content, is an indole. The compound is colorless in the solid state, but appears to dissociate as an acid in ethanol solution, with the longest wavelength absorption as a broad band at 413 mμ. The compound is tentatively assigned the structure 3,5,7-trinitroindole (V), and is believed to be formed by dehydrogenation of a probable intermediate, 1-acetyl-



(1) National Science Foundation Graduate Fellow, June, 1961–August, 1963.

(2) (a) L. R. Smith, Ph.D. thesis, University of Minnesota, May, 1960; *Dissertation Abstr.*, **21**, 1766 (1960); (b) W. E. Noland, Lowell R. Smith, and K. R. Rush, to be published.

(3) H. Bauer and E. Strauss, *Ber.*, **65**, 308 (1932).

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(14) A. Fraga, *Anales asoc. quim. arg.*, **50**, 162 (1962).

(15) T. Kinoshita, H. Inone, and E. Imoto, *Nippon Kagaku Zasshi*, **78**, 1372 (1957); *Chem. Abstr.*, **54**, 491 (1960).

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(17) J. Thesing, G. Semler, and G. Mohr, *Ber.*, **95**, 2205 (1962).

(18) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).

(19) J. Tafel, *Ann.*, **301**, 336 (1898).

(20) K. N. Menon and R. Robinson, *J. Chem. Soc.*, 773 (1931).

(21) K. N. Menon and R. Robinson, *ibid.*, 780 (1932).

(22) W. G. Gall, B. D. Astill, and V. Boekelheide, *J. Org. Chem.*, **20**, 1538 (1955).

5,7-dinitroindoline, followed by nitration of the resulting indole at the now available 3-position,[2] and subsequent deacetylation. The compound was resistant to chromic acid oxidation.

Experimental

Melting points were determined on a calibrated Fisher-Johns hot stage.

1-Acetyl-5-nitroindoline (II).—A solution of 5-nitroindoline[16] (8.63 g., 0.0525 mole) in acetic anhydride (100 cc.) was refluxed for 1 hr., then cooled, and the resulting mixture poured into an excess of water. The mixture was stirred until all of the acetic anhydride dissolved. The precipitate was recrystallized from acetone–methanol, yielding pale yellow needles (9.74 g., 90%), m.p. 177–179°; lit.[22] m.p. 173.5–175.5°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 231 (4.01), 340 (4.12); ν_{NH}^{Nujol} none, $\nu_{C=O}^{Nujol}$ 1667 (s), $\nu_{NO_2}^{Nujol}$ 1513 (s), 1319 (s) cm.$^{-1}$.

1-Acetyl-5,7-dinitroindoline.—Fuming nitric acid (*d* 1.5, 6 cc.) was added dropwise, with stirring, at a temperature maintained below 16°, to a mixture of 1-acetyl-5-nitroindoline (3.00 g., 0.0145 mole) and acetic anhydride (70 cc.) cooled initially to 10° in an ice bath. The resulting solution was then removed from the ice bath and stirred until the temperature reached 40°, at which point it was poured into ice–water and the mixture stirred until all of the acetic anhydride dissolved. The resulting precipitate was recrystallized from acetone–methanol, giving yellow needles (1.87 g., 51%), m.p. 207–212°. Sublimation at 200° (1 mm.) and recrystallization of the sublimate from acetone–methanol yielded the analytical sample, m.p. 210–212°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 226 (4.23), 265 infl. (3.75), 345 (4.02); $\nu_{C=O}^{Nujol}$ 1695 (s), ν_{NO}^{Nujol} 1546 (s), 1520 (s), 1344 (s), 1299 (vs) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_9N_3O_5$ (251.20): C, 47.81; H, 3.61; N, 16.73. Found: C, 48.05; H, 3.73; N, 16.45.

5,7-Dinitroindoline (I). A. From 1-Acetylindoline.—The compound was prepared,[16] along with 5-nitroindoline, by nitration of 1-acetylindoline, except that the procedure for purification of the dinitro product was changed. The crude dinitro product was not recrystallized from xylene but was dissolved in benzene–ethyl acetate (4:1 by volume) and placed on a column of neutral alumina (25 g.) which had been packed wet with petroleum ether (b.p. 60–68°). Elution with 4:1 benzene–ethyl acetate gave in 2% yield orange needles, m.p. 244–245°; lit.[16] 5%, yellow crystals, m.p. 243–244°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 238 (4.03), 263 (4.00), 364 (4.15), 404 infl. (3.90); ν_{NH}^{Nujol} 3290 (m), $\nu_{NO_2}^{Nujol}$ 1534 (ms), 1497 (ms), 1335 (ms), 1312 (s) cm.$^{-1}$.

Anal. Calcd. for $C_8H_7N_3O_4$ (209.16): C, 45.94; H, 3.37; N, 20.09. Found: C, 46.06; H, 3.42; N, 19.86.

B. From 1-Acetyl-5-nitroindoline.—Fuming nitric acid (*d* 1.5, 4 cc.) was added dropwise, with stirring, to a solution of 1-acetyl-5-nitroindoline (2.00 g., 0.00970 mole) in acetic anhydride (50 cc.) kept at 15°. The yellow solution was then stirred at room temperature for 0.75 hr., during which time it warmed up to a maximum temperature of 35°. The solution was poured into water and stirred until all of the acetic anhydride had dissolved. The resulting yellow precipitate was refluxed in concentrated hydrochloric acid (50 cc.) for 1 hr. and the mixture cooled. The precipitate was recrystallized from acetone–ethanol, with charcoal, yielding light orange needles (0.85 g., 42%), m.p. 244–245°. There was no depression in m.m.p. 244–245° with the sample prepared from 1-acetylindoline, and the infrared spectra in Nujol were identical.

Oxidative Degradation of 5,7-Dinitroindoline.—A solution of chromium(VI) oxide (1.50 g., 0.0150 mole) in water (5 cc.) was added to a suspension of 5,7-dinitroindoline (0.66 g., 0.00316 mole) in acetic acid (100 cc.). The resulting black solution was stirred at room temperature for 40 hr., and then poured into an excess of water. The green aqueous solution was extracted with ethyl acetate. The ethyl acetate solution was extracted with aqueous saturated sodium bicarbonate until carbon dioxide was no longer evolved. The ethyl acetate solution was then concentrated to a small volume, and petroleum ether (b.p. 60–68°) was added. The resulting orange precipitate was recrystallized from ethyl acetate–benzene, with charcoal, yielding 5,7-dinitroisatin (III) as orange-yellow crystals (0.26 g., 35%), m.p. 209–210°; lit.[23,24] m.p. 209–210°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 239 (4.07), 257 infl. (4.02), 323 (4.06), 393 (3.42); ν_{NH}^{Nujol} 3290 (m), $\nu_{C=O}^{Nujol}$ 1773 (s), 1754 (ms), 1631 (s), $\nu_{NO_2}^{Nujol}$ 1558 (s), 1541 (ms), 1337 (vs), 1289 (s) cm.$^{-1}$. There was no depression in m.m.p. 209–210° with a sample of m.p. 209–210° prepared[23] by nitration of isatin, and the infrared spectra in Nujol were identical.

The sodium bicarbonate extracts were acidified to pH 2 with aqueous hydrochloric acid, and the resulting solution was extracted with ethyl acetate. The ethyl acetate extracts were dried over magnesium sulfate and concentrated until only acetic acid remained as a solvent, and then water was added. The brown precipitate was recrystallized from methanol–water, yielding **3,5-dinitroanthranilic acid (IV)** as golden yellow needles (0.08 g., 11%), m.p. 256°; lit.[25,26] m.p. 256°, lit.[27] 265°, lit.[28] 268°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 237 (4.09), 336 (4.11), 392 (3.87); ν_{NH}^{Nujol} 3370 (m), 3250 (m), $\nu_{C=O}^{Nujol}$ 1672 (s), $\nu_{NO_2}^{Nujol}$ 1515 (ms), 1328 (vs) cm.$^{-1}$.

3,5,7-Trinitroindole (V).—1-Acetyl-5-nitroindoline (6.09 g., 0.0295 mole) was added slowly to fuming nitric acid (*d* 1.5, 24 cc.) at 5° and then the solution was poured into an excess of water. The resulting precipitate was recrystallized twice from acetone–methanol, once with charcoal, yielding white needles (1.67 g., 22%), m.p. 232–233°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 216 (4.30), 286 (4.11); does not obey Beer's law in the long wave-length region, λ_{max} 413 very broad: $c = 1.444 \times 10^{-4}$ mole/l. (3.03), $c = 6.19 \times 10^{-5}$ mole/l. (3.26), $c = 4.12 \times 10^{-5}$ mole/l. (3.37); ν_{NH}^{Nujol} 3360 (m), $\nu_{NO_2}^{Nujol}$ 1531 (s), 1379 (s), 1344 (s) or 1307 (s), cm.$^{-1}$. The compound is soluble in aqueous 1% sodium hydroxide but not in saturated sodium bicarbonate solution.

Anal. Calcd. for $C_8H_4N_4O_6$ (252.14): C, 38.11; H, 1.60; N, 22.22. Found: C, 38.25; H, 1.70; N, 21.76.

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The Free-Radical-Induced Reaction of Ethylene with 1,1,2,2-Tetrabromoethane

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Attempts to telomerize ethylene with 1,1,2,2-tetrabromoethane (TBE) to obtain compounds of the type $CHBr_2CHBr(C_2H_4)_nBr$ did not give rise to these materials but produced α,ω-dibromo *n*-alkanes. These appear to be products of the indirect telomerization of ethylene with bromine. Thus, when ethylene and TBE reacted under pressure in the presence of benzoyl peroxide at 100° the reaction product contained 1,2-dibromoethylene, 1,2-dibromoethane, 1,4-dibromobutane, 1,6-dibromohexane (putative), and bromobenzene. The latter undoubtedly originated from the initiator. Because of its low concentration, that component of the product assumed to be 1,6-dibromohexane could not be positively identified.

The relatively high concentration of 1,2-dibromoethylene and the fact that no other high-boiling materials were shown by gas chromatography clearly indictates that the expected telomerization between TBE and ethylene did not occur. Similar results were obtained in reactions between TBE and ethylene with thermal initiation at 200°.

The presence of both 1,2-dibromoethylene and 1,2-dibromoethane can be explained by the decomposition

Table I

Product Composition

Experiment no.	Reaction product composition in moles/100 g. Bromobenzene	1,2-Dibromoethylene	$Br(C_2H_4)_nBr$ $n = 1$	$n = 2$	$n = 3$
1	0.0038	0.043	0.037	0.0037	
2	0.025	0.14	0.070	0.062	0.005
3	0.040	0.16	0.074	0.041	0.0004

Table II

Initial Reaction Mixture Composition[a]

Experiment no.	Ethylene pressure, p.s.i.	Moles of C_2H_4 Dissolved in TBE[b]	In gas phase[c]	Total	Moles of benzoyl peroxide per mole of TBE
1	600	0.29	0.94	1.23	0.01
2	1400	0.46	4.72	5.18	0.1
3	1300	0.50	4.52	5.02	0.1

[a] At ambient temperature, 26°. [b] Approximate values obtained from an experimentally established solubility curve of ethylene in TBE as a function of pressure. [c] Calculated from literature data (J. B. Maxwell, "Data Book on Hydrocarbons," D. Van Nostrand Co., Inc., New York, N. Y., 1955).

of TBE into 1,2-dibromoethylene and bromine with the subsequent reaction between the latter and ethylene to give 1,2-dibromoethane. However, these are not the usual TBE decomposition products.[1] Neither does it explain the presence of 1,4-dibromobutane nor the possible presence of 1,6-dibromohexane.

A mechanism involving the following steps is proposed for the formation of these compounds.

$$CHBr_2—CHBr_2 + R\cdot \longrightarrow CHBr_2—CHBr\cdot + RBr \quad (1)$$

$$CHBr_2—CHBr\cdot \longrightarrow CHBr{=}CHBr + Br\cdot \quad (2)$$

$$Br\cdot + C_2H_4 \longrightarrow BrC_2H_4\cdot \quad (3)$$

$$BrC_2H_4\cdot + nC_2H_4 \longrightarrow Br(C_2H_4)_{n+1}\cdot \quad (4)$$

$$Br(C_2H_4)_{n+1}\cdot + CHBr_2—CHBr_2 \longrightarrow Br(C_2H_4)_{n+1}Br + CHBr_2—CHBr\cdot \quad (5)$$

1,2-Dibromoethane and 1,4-dibromobutane could also be formed by the following.

$$BrC_2H_4\cdot + Br\cdot \longrightarrow BrC_2H_4Br \quad (6)$$

$$2BrC_2H_4\cdot \longrightarrow Br(C_2H_4)_2Br \quad (7)$$

1,6-Dibromohexane cannot be produced by a chain termination step, but only by a mechanism similar to eq. 4 and 5. The positive identification of this material would thus be proof of a telomerization mechanism.

However, a material balance clearly indicates that the chain terminating steps of eq. 6 and 7 cannot be major contributors to the formation of the respective products, and agrees well with eq. 1–5. If reaction 7 is the major contributor to the formation of 1,4-dibromobutane, then, for 2 moles of bromobenzene produced in the initiation step, 1 mole of 1,4-dibromobutane should form. This is not borne out by the results as can be seen from Table I. Therefore, reaction 7 can be only a minor side reaction. Furthermore, if 1,2-dibromoethane is formed principally by reaction 6, then again 2 moles of bromobenzene would have been formed for each mole of 1,2-dibromoethane produced. Neither is this supported by the experimental results. Alternatively, if both reactions, as indicated in eq. 6 and 7, are occurring simultaneously then the sum of the moles of 1,2-dibromoethane and 1,4-dibromobutane should equal half the moles of bromobenzene, which was not found to be the case.

It, therefore, appears that the reaction between 1,1,2,2-tetrabromoethane and ethylene under free-radical conditions is a telomerization of ethylene by bromine, the tetrabromoethane acting as a bromine carrier. The low yields probably result from the low solubility of ethylene in TBE, which reached a value of only 40 mole % at 3000 p.s.i. at ambient temperature.

It is of interest to note that a similar reaction did not occur with 1,1,2,2-tetrachloroethane and ethylene. The product of this reaction consisted of a complex mixture of high-boiling materials containing only traces of 1,2-dichloroethane and 1,2-dichloroethylene.

Experimental

Reactions were performed in a 500-ml. rocking autoclave. Conditions common to all experiments were the amount of TBE, 100 ml. (0.855 mole); initiator, benzoyl peroxide; reaction temperature, 100°; reaction period, 3 hr. Reaction conditions which varied are given in Table II.

As part of the initiator was converted to benzoic acid the products were filtered prior to gas chromatographic analysis on silicone grease. The product of experiment 2, for example, was found to have the following composition: bromobenzene, 4%; 1,2-dibromoethylene, 26%; 1,2-dibromoethane, 13%; 1,4-dibromobutane, 13%; 1,6-dibromohexane (putative), 1%; 1,1,2,2-tetrabromoethane, 36%. The residual 7% consisted mainly of tribromoethylene and pentabromoethane, both of which are free-radical-induced decomposition products of TBE.[1] Identifications, except for 1,4-dibromobutane and 1,6-dibromohexane, were by retention time comparison. Bromobenzene and 1,4-dibromobutane were separated by fractional distillation and characterized by their specific gravity, refractive index, and infrared spectra. The material believed to be 1,6-dibromohexane had a gas chromatographically estimated boiling point of 251°, which is in fair agreement with the literature value of 243°.[2]

Acknowledgment.—We are grateful to the Israel Mining Industries for permission to publish this Note, and to U. Hashman for technical assistance.

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The Synthesis of Tetravinylmethane

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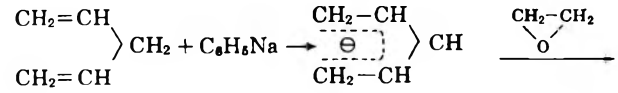
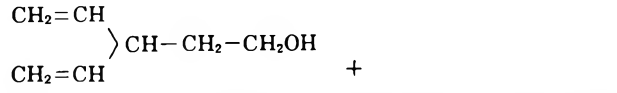
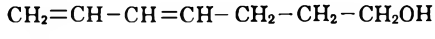
Although the tetravinyl derivatives of the Group IV elements silicon,[1a] germanium,[1b] tin,[1c] and lead[1d] have been reported, the corresponding tetravinylmethane has until now remained unknown. We now wish to report the synthesis of this compound by a novel reaction sequence.

1,4-Pentadiene was treated with a heptane suspension of phenylsodium, and the resulting mixture was treated with ethylene oxide, affording on work-up 3-vinyl-4-penten-1-ol (I) and 4,6-heptadien-1-ol (II).





I



II

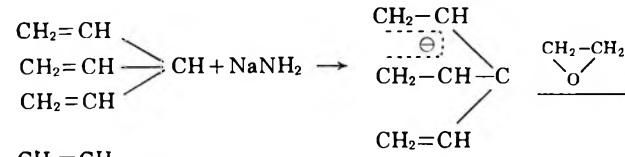
The mixture of I and II, obtained in 50–60% yield, was found to consist of 60–70% I. The isomeric alcohols were readily separated by fractional distillation: I, b.p. 53–55° (6 mm); II, b.p. 65–67° (6 mm). The structure of compound I was established by its infrared spectrum which showed bands at 1640 cm.$^{-1}$ (nonconjugated C=C stretch) and characteristic vinyl C–H bands at 3090, 3010, 1850, 1420, 992, and 913 cm.$^{-1}$.[2] Compound II exhibits a double band at 1640 and 1595 cm.$^{-1}$ (conjugated C=C), and bands at 1000, 945, and 898 cm.$^{-1}$ (C–H out-of-plane deformation assigned to *trans* internal conjugated olefin).

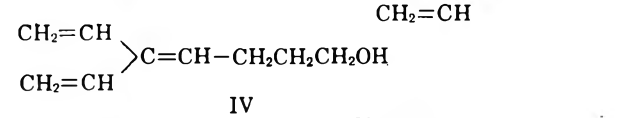
The n.m.r. spectrum of I showed absorption for two methylene hydrogens at 8.38, one tertiary allylic hydrogen at 7.14, two methylol hydrogens at 6.43, one hydroxyl hydrogen at 5.98, four terminal methylene hydrogens (multiplet) at 4.97, and two internal vinyl hydrogens at 4.24 τ. In addition, the spin–spin splittings and coupling constants are all consistent with structure I.

Compound II showed absorption for two hydrogens ($-CH_2-CH_2OH$) at 8.34, two allylic hydrogens at 7.86, two methylol hydrogens at 6.46, one hydroxyl hydrogen at 5.84, and five hydrogens comprising the conjugated system as a complex multiplet between 5.28 and 3.52 τ.

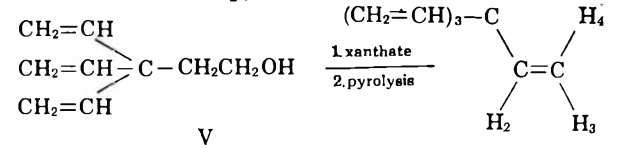
Compound I was converted to the xanthate, which was pyrolyzed at 250–300° to give 3-vinyl-1,4-pentadiene (trivinylmethane)[3] in 20–40% yield.

Trivinylmethane was treated with sodamide in liquid ammonia to give an intensely colored red solution. Reaction with ethylene oxide gave 5-vinyl-4,6-heptadien-1-ol (IV, 23%) and 3,3-divinyl-4-penten-1-ol (V, 77%) in 80% yield.





IV



V

Compounds IV and V were again easily separable by fractional distillation.

The infrared spectrum of V showed virtually the same absorptions already mentioned in connection with I, characteristic of terminal nonconjugated unsaturation, while IV exhibited a spectrum strongly indicative of conjugation (see Experimental).

Conversion of V to the xanthate and subsequent pyrolysis gave 3,3-divinyl-1,4-pentadiene (tetravinylmethane). The hydrocarbon showed bands in the infrared typical of terminal unsaturation (see Experimental), and a similarly typical[4] ABC grouping in its n.m.r. spectrum: $\tau_2 = 4.18$, $\tau_3 = 4.91$, $\tau_4 = 4.99$; $J_{23} = 8.75$, $J_{24} = 18.5$, $J_{34} = 2.0$ c.p.s. The area ratio of $H_3 + H_4$ to H_2 was 2.08 to 1.00 and no other absorptions were present.

Although the sodium derivatives of both 1,4-pentadiene and trivinylmethane have been reported[3,5] to give products arising almost exclusively from attack of the carbanion at the primary position, results obtained in these laboratories have indicated a more complex nature to the reactions of these species. The results of this investigation will be the subject of a future publication.

Experimental[6]

Reaction of Sodium Pentadiene with Ethylene Oxide.—1,4-Pentadiene (70 g., 1.03 moles) was added to a well-stirred suspension of phenylsodium (1.0 mole) in *n*-heptane. A slight rise in temperature was noted and the originally black suspension turned green. After stirring for 4.5 hr., ethylene oxide (45 g., 1.02 moles) in an equal volume of heptane was added maintaining the temperature below 35°. The resulting mixture was carefully decomposed with water; the organic layer was separated, washed, dried, and the solvent was distilled. The residue was distilled through a 24-in. tantalum spiral column to separate the olefinic alcohols from a considerable amount of β-phenylethanol, and the distillate was refractionated through an 18-in. spinning band column to give 3-vinyl-4-penten-1-ol (30.9 g.), b.p. 53–55° (6 mm), $n^{22}D$ 1.4530.

Anal. Calcd. for $C_7H_{12}O$: C, 75.00; H, 10.71. Found: C, 75.32; H, 10.81.

(1) (a) S. D. Rosenburg, J. J. Walburn, T. D. Stankovich, A. E. Balint, and H. E. Ramsden, *J. Org. Chem.*, **22**, 1200 (1957); (b) D. Seyferth, *J. Am. Chem. Soc.*, **79**, 2738 (1957); (c) S. D. Rosenburg, A. J. Gibbons, and H. E. Ramsden, *ibid.*, **79**, 2137 (1957); D. Seyferth and F. G. A. Stone, *ibid.*, **79**, 515 (1957); (d) E. C. Juenge and S. E. Cook, *ibid.*, **81**, 3578 (1959); B. Bartocha and M. Y. Gray, *Z. Naturforsch.*, **14b**, 350 (1959); L. Maier, *Angew. Chem.*, **71**, 161 (1959).

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter III.

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(5) R. Paul and S. Tchelitcheff, *Compt. rend.*, **224**, 1118 (1947); *idem.*, *Bull. soc. chim. France*, 108 (1948).

(6) All boiling points are uncorrected. Infrared spectra were determined with a Beckman Model IR-8 spectrophotometer. N.m.r. spectra were determined on a Varian A-60, 60-Mc./sec. high resolution spectrometer

In addition, 4,6-heptadien-1-ol (20.6 g.), b.p. 65–67° (6 mm), $n^{22}D$ 1.4882, was obtained. This material polymerized to a colorless viscous oil upon standing for several days.

Anal. Found: C, 74.93; H, 11.30.

Trivinylmethane.—3-Vinyl-4-penten-1-ol (100 g., 0.89 mole) was added slowly to an ether suspension of sodium hydride (23.5 g., 0.98 mole), and the mixture then was heated at reflux for 4 hr. Upon cooling, carbon disulfide (67.3 g., 0.89 mole) was added cautiously, and the resulting mixture again was heated at reflux for 1.5 hr. At the end of this time, methyl iodide (124 g., 0.88 mole) was added, and the mixture was heated for a final 1.5 hr. Solids were then dissolved by adding water, and the ether solution was separated, dried, and the ether was removed to give the crude xanthate (195 g.) which was pyrolyzed at 250–300° without further purification. The volatile pyrolysate was washed twice with 40% sodium hydroxide, then with water, and finally with saturated mercuric chloride solution. Distillation through an 18-in. spinning band column gave trivinylmethane (15 g.), b.p. 76.9°, $n^{24}D$ 1.4238 (lit.[3] b.p. 77°, $n^{20}D$ 1.4384).

Infrared spectrum (neat, liquid) showed bands at 3090(s), 3010(m), 2975(m), 1830(w), 1630(m), 1410(m), 992(s), 916(s), 691(m) cm.$^{-1}$.

The n.m.r. spectrum of this product showed absorptions at τ = 6.33 (quartet) assigned to the tertiary proton, and typical ABC type olefinic absorption: τ_2 = 4.20, τ_3 = 4.97, τ_4 = 5.01; $J_{23(cis)}$ = 9.0, $J_{24(trans)}$ = 17.5, J_{34} = 2.5 c.p.s. The H_2 quartet was split by the tertiary hydrogen into an octet with J = 6.0 c.p.s.

Reaction of Sodium Trivinylmethane with Ethylene Oxide.—Trivinylmethane (19.2 g., 0.20 mole) was added slowly to a suspension of sodamide in 75 ml. of liquid ammonia, prepared from 5.1 g. (0.22 g.-atom) of sodium. Ethylene oxide (10 g., 0.23 mole) was then added cautiously to the resulting deeply colored solution, and the ammonia was then replaced as solvent by ether. After the ammonia had been displaced, another 1 g. of ethylene oxide was added, and the reaction mixture was decomposed slowly with water. The ether layer was separated, washed, and dried. Removal of solvent gave 23.5 g. of light yellow crude alcohols. Gas chromatography showed the mixture to consist of 77% V and 23% IV. Distillation gave V, b.p. 48–50° (0.5 mm), $n^{24}D$ 1.4769, and IV, b.p. 57–60° (0.5 mm), $n^{24}D$ 1.5090.

Compound V showed significant bands in the infrared at 3330 (s, broad), 3090(s), 3005(m), 2970(m), 2940(s), 2895(sh), 1840 (w), 1630(m), 1405(m), 1045(s), 1023(s), 1000(s), 918(s) cm.$^{-1}$ (neat, liquid).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.16; H, 9.74.

Compound IV showed bands in the infrared at 3330(s), 2090 (m), 3010(m), 2955(s), 2870(m), 1800(w), 1620(m), 1595(m), 1420(m), 1052(s, broad), 978(s), 908(s), 850(m) cm.$^{-1}$ (neat, liquid). Upon standing for several days, IV was transformed into a clear, colorless polymer.

Tetravinylmethane.—The xanthate of 3,3-divinyl-4-penten-1-ol was prepared, in the same manner as previously described for 3-vinyl-4-penten-1-ol, from 14.1 g. of the alcohol, 2.4 g. of sodium hydride, 8.4 g. of carbon disulfide, and 15.5 g. of methyl iodide. The yield of crude xanthate was 21.5 g.

Pyrolysis yielded a light yellow liquid which was washed twice with concentrated potassium hydroxide solution, once with water, and finally with saturated mercuric chloride solution. The organic material was then dried and distilled through an 18-in. spinning band column to give 4.8 g. of tetravinylmethane, b.p. 119.5–121.0°, $n^{24}D$ 1.4531.

Anal. Calcd. for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.82; H, 10.61.

The compound showed bands in the infrared at 3090(s), 3070 (m), 3010(s), 2980(s), 1840(w), 1615(s), 1405(s), 1048(w), 1000(s), 918(s), 697(s), and 652(w) cm.$^{-1}$ (neat, liquid).

Acknowledgment.—The authors are indebted to Dr. H. T. White and Dr. M. H. Gianni for interpretation of the infrared and n.m.r. spectra, respectively, and to Mr. G. P. Beardsley for his assistance in the laboratory. This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by Army Ordnance under Contract No. DA-30-069-ORD-2487.

On the Instability of Methanesulfinyl Chloride

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A convenient preparative method[1] has made methanesulfinyl chloride, $CH_3S(O)Cl$ (I), and its homologs readily available. As work with I in our laboratory has continued, the instability of the compound has become increasingly evident. We have, for example, found it impossible to prepare samples of the compound entirely free of color. When a carefully purified sample is distilled under reduced pressure it appears to be colorless on leaving the condenser but a yellow color develops as the distillate accumulates in the receiver. On long standing the color deepens, hydrogen chloride is evolved, and ultimately a yellow solid precipitates. We also have observed that sulfinate esters prepared from I are always contaminated with traces of methanesulfonyl chloride.

The instability of I was emphasized when a 200-g. sample, sealed in a glass ampoule, exploded from internal gas pressure after standing on the laboratory shelf for several months. Our present practice is never to store samples of sulfinyl chlorides except under refrigeration.

The evidence indicates that the primary decomposition is a disproportionation into methanesulfonyl chloride (II) and methanesulfenyl chloride (III), the latter accounting for the yellow color.

$$\underset{\text{I}}{2\,CH_3S(O)Cl} \longrightarrow \underset{\text{II}}{CH_3SO_2Cl} + \underset{\text{III}}{CH_3SCl}$$

The liberation of hydrogen chloride would result from a secondary reaction of III with itself to form a variety of products.[2]

Several attempts were made to demonstrate the disproportionation. Refluxing of I at atmospheric pressure leads to the formation of II but methanesulfenyl chloride is highly unstable at such elevated temperatures (140–160°) and decomposes with the formation of hydrogen chloride and other products. It was thought best, therefore, to duplicate the temperature conditions under which I had decomposed on standing and have an agent present which would trap the methanesulfenyl chloride (III) as soon as it might be formed. Cyclohexene was chosen as the trapping agent since it reacts with III to form 2-chlorocyclohexyl methyl sulfide.[3]

Experimental

Freshly distilled methanesulfinyl chloride (49.3 g., 0.5 mole) and dry cyclohexene (22.1 g., 0.27 mole) were sealed in a clear glass ampoule and allowed to stand on a window sill for 167 days. The mixture slowly turned dark brown in color, but there was no evidence of pressure development when the seal was broken periodically. When the mixture was finally removed and distilled under reduced pressure it yielded 12.9 g. (0.12 mole) of methanesulfonyl chloride (II) and 21.8 g. (0.13 mole) of 2-chlorocyclohexyl methyl sulfide (IV) and an unidentified dark residue.

(1) I. B. Douglass, B. S. Farah, and E. G. Thomas, *J. Org. Chem.*, **26**, 1996 (1961); I. B. Douglass and B. S. Farah, *Org. Syn.*, **40**, 62 (1960).

(2) F. Schneicer, *Chem. Ber.*, **84**, 911 (1951).

(3) H. Böhme and H. J. Gran, *Ann.*, **577**, 68 (1952).

The infrared spectra of both II and IV were identical with those of authentic samples.

Acknowledgment.—We wish to thank the donors of the Petroleum Research Fund administered by the American Chemical Society for support of the research in the course of which the above observation was made.

s-Triazines. I. Reaction of Vinylmagnesium Chloride with Cyanuric Chloride

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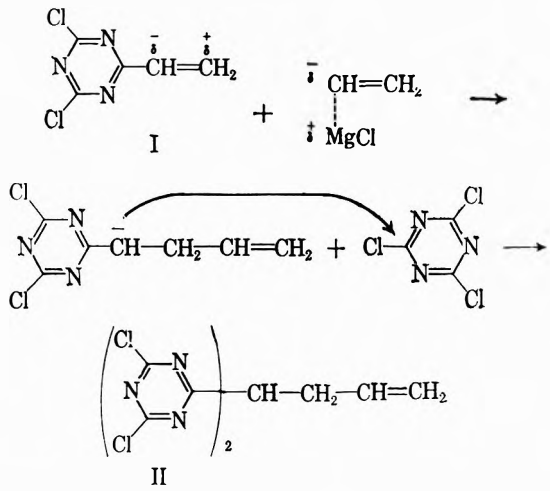
Condensation of alkylmagnesium halides with cyanuric chloride was reported to give 2-alkyl-4,6-dichloro-*s*-triazines.[2] When applied to vinylmagnesium chloride, this reaction could be expected to yield 2,4-dichloro-6-vinyl-*s*-triazine (I).

The reaction gave a product boiling at 198° (10 mm.), somewhat higher than expected for structure I. The elemental analysis of the crystallized product was in good agreement with I, but its molecular weight was double that of I.

The product showed an inflection in the ultraviolet at 255 mμ (cyclohexane) but no maximum. It exhibited infrared bands at 925 ($C{=}CH_2$ out of plane in phase deformation), 1852 (overtone of the deformation band), 1648 (C=C stretching), and 980 cm.$^{-1}$ (C=CH out of plane deformation), consistent with monosubstituted ethylene[3]; one at 1520 (triazine ring stretching) and a band at 848 cm.$^{-1}$, characteristic of a dichlorotriazine (*cf.* 2,4-dichloro-6-ethyl-*s* triazine,[4] showing corresponding bands at 1500 and 848 cm.$^{-1}$).

The n.m.r. spectrum was characteristic of a typical allyl group. The olefinic hydrogens formed an ABX pattern with AB ($=CH_2$) near 4.97 τ and X (—CH—) at 4.15 τ, with $J_{trans} \cong 17$ c.p.s., $J_{cis} \cong 9$ c.p.s. The four X lines were split further into triplets (J = 6.6 c.p.s.) due to coupling to the adjacent $-CH_2-$ group. The $-CH_2-$ resonance appeared at 6.91 τ as a triplet. Finally, at 5.48 τ, a one-proton 1-2-1 triplet (J = 7.5 c.p.s.) was observed. It was concluded that this absorption could be assigned to another CH hydrogen to which the CH_2 was also coupled. The entire spectrum is, therefore, consistent with the structure $CH_2{=}CH{-}CH_2CH$. A vinyl triazine, on the other hand, would be expected to show a typical vinyl spectrum of 12 to 15 lines in the 3.0- to 4.3-τ region, as has been observed in 2,4-dimethyl-6-vinyl-*s*-triazine[5] in these laboratories.

All the data are consistent with structure II, the formation of which can be rationalized as follows.



I

II

The original nucleophilic attack of vinyl anion on cyanuric chloride forms 2,4-dichloro-6-vinyl-*s*-triazine (I). The vinyl carbon in the 2-position would be much more electrophilic than the ring carbons in cyanuric chloride, and would undergo a very fast attack by a second molecule of the Grignard reagent. The resulting carbanion at the 1-position of the sidechain will now attack cyanuric chloride and produce II. An attack of the carbanion on I would give rise to high molecular weight by-products, which always accompanied product II.

It is not surprising that the great susceptibility of I to nucleophilic attack would preclude any accumulation of it in the reaction mixture. Indeed, even in reactions performed at −40°, in nonpolar media, in high dilution, and with other organometallic reagents (vinyllithium and tetravinyltin), no trace of the monomer (I) could be detected.

Experimental

1,1-Di(2',4'-dichloro-1',3',5'-triazin-6'-yl)but-3-ene (II).—A solution of vinylmagnesium chloride (0.2 mole) in tetrahydrofuran (total volume 62.5 ml., 3.34 *N*) was added over an 8-min. period to a stirred solution of 18.44 g. (0.1 mole) of cyanuric chloride in 400 ml. of methylene dichloride at −30 to −15°. Stirring was continued at −15° for 1.5 hr., by which time a negative test with Gilman's reagent[6] was obtained. The very dark solution was decomposed at −30° by dropwise addition of 18 ml. of water, followed by addition of anhydrous magnesium sulfate (20 g.) and of diatomaceous earth (10 g.). The solution was filtered, the cake was washed with methylene dichloride, and the solvent was evaporated under reduced pressure at 20°. The black residue was extracted with 200 ml. of pentane at 20°. The pentane solution was decolorized with charcoal, and the solvent was evaporated. The residue (16.7 g.) was estimated by its infrared and ultraviolet absorption to contain *ca.* 80% of II. Distillation gave (a) cyanuric chloride (4.3 g., 23.3% γ) which sublimed at 90° (11 mm.) and (b) product II (3.85 g., 21.9% γ), b.p. 198° (10 mm.), as a pale yellow oil which solidified at room temperature. The low recovery of distilled material was due to its polymerization during the distillation. Crystallization from pentane gave colorless rosettes of needles, m.p. 74.2–75.0° (cor.).

Anal. Calcd. for $C_{10}H_6Cl_4N_6$: C, 34.12; H, 1.72; Cl, 40.29; N, 23.87; mol. wt., 352.03. Found: C, 34.29; H, 1.89; Cl, 40.50; N, 23.89; mol. wt., 354.

Acknowledgment.—The authors wish to thank Dr. J. E. Lancaster and Dr. F. C. Schaefer for the interpretation of n.m.r. spectra.

(1) To whom correspondence should be addressed at Aldrich Chemical Co., Milwaukee, Wis.

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Grignard Reactions of Polyhalocarbons. II. *In Situ* Grignard Reactions of Carbon Tetrahalides with Organochlorosilanes

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September 3, 1963

Tseng has reported[2] that carbon tetrabromide in ether reacts vigorously with magnesium; no statement is made concerning the products of this reaction. He also observed that under the same conditions there is no reaction between magnesium and carbon tetrachloride. Reychler[3] had earlier established that carbon tetrachloride is not only unreactive but inhibits, perhaps mechanically by the formation of a coating on the magnesium, the Grignard reaction in ether of such active halides as methyl iodide, ethyl iodide, ethyl bromide, and bromobenzene. In addition to these few papers the literature also contains accounts of reactions of carbon tetrahalides with preformed Grignard reagents, but no other reports of attempted reaction between a carbon tetrahalide and magnesium were found.

Discussion

Carbon tetrabromide in tetrahydrofuran solution was found to react vigorously with magnesium shavings. No products could be isolated from the resulting carbonaceous residue. When an organochlorosilane was added to the tetrahydrofuran in which the magnesium was suspended and the carbon tetrahalide was added dropwise at a rate just sufficient to maintain reflux, the reaction was just as vigorous, and, after hydrolysis and distillation, fair to good yields of tetrakis-, tris-, and bissilylmethanes were obtained. This suggests that the conditions imposed by the *in situ* procedure, *i.e.*, a high concentration of organochlorosilane in the immediate vicinity of the magnesium surface where the carbon tetrahalide at relatively low concentrations reacts, tend to favor ensuing reaction of the Grignard intermediate with organochlorosilane rather than with additional carbon tetrahalide.

The general reaction is summarized in eq. 1 following.

$$CX_4 + Mg + R_3SiCl \xrightarrow{\text{tetrahydrofuran}} \text{products} \xrightarrow{H_2O} \begin{cases} (R_3Si)_4C \\ (R_3Si)_3CH \\ (R_3Si)_2CH_2 \end{cases} + MgXCl \quad (1)$$

Although carbon tetrachloride did react under the conditions employed, the reaction was too slow to be of synthetic value. Carbon tetrabromide, bromotrichloromethane, and dibromodichloromethane reacted readily to give fair to good yields of the products shown in Table I.

In addition to the tetrasubstituted methanes, it can be seen in both eq. 1 and Table I that considerable quantities of tri- and disubstituted methanes were obtained. This was also true for *in situ* Grignard reactions of 1,1-dihalides which yielded monosilyl as well as disilyl products and the reactions of 1,1,1-trihalides which yielded monosilyl and disilyl as well as trisilyl substituted products.[4] It is of interest that no tetra- or trisubstituted methanes were isolated in the reaction employing dimethylphenylchlorosilane, the most sterically hindered organochlorosilane. The least sterically hindered organochlorosilane, dimethylchlorosilane, gave the highest yield of tetrasubstituted methane. The significance of this remains obscure until the origin of the hydrogen atoms in the reduced products and the nature of the reaction intermediates are established.

Table I

In Situ Grignard Reactions of Carbon Tetrahalides and Organochlorosilanes

Tetrahalide	Silane	Products — Structure	Yield, %[a]
CBr_4	$(CH_3)_3SiCl$	$[(CH_3)_3Si]_4C$[b]	27.6
		$[(CH_3)_3Si]_3CH$	39.8
		$[(CH_3)_3Si]_2CH_2$	4.9
$BrCCl_3$	$(CH_3)_3SiCl$	$[(CH_3)_3Si]_4C$	20.2
		$[(CH_3)_3Si]_3CH$	21.3
Br_2CCl_2	$(CH_3)_3SiCl$	$[(CH_3)_3Si]_4C$	29.6
		$[(CH_3)_3Si]_3CH$	26.0
		$[(CH_3)_3Si]_2CH_2$	4.5
CBr_4	$(CH_3)_2HSiCl$	$[(CH_3)_2HSi]_4C$[b]	59.5
CBr_4	$(CH_3)_2C_6H_5SiCl$	$[C_6H_5(CH_3)_2Si]_2CH_2$	67.5

[a] Based on carbon tetrahalide. [b] Compounds here reported for the first time.

The tetrasilylmethanes are structurally interesting compounds because of their molecular geometry. The large and spherically symmetrical tetrakis(trimethylsilyl)methane molecule (the carbon analog of which has never been reported) has a surface comprised of twelve geometrically equivalent methyl groups. Somewhat surprisingly, it is a high melting crystalline material which appears from visual observations to undergo a phase transition to another solid form at about 195–210°. Such behavior is similar to that of tetramethylmethane and some other spherically symmetrical molecules in which free rotation of the molecule within the crystal lattice occurs.

Experimental

Materials.—J. T. Baker purified magnesium turnings were used in this work. Commercial tetrahydrofuran was dried by distillation from lithium aluminum hydride. Commercial carbon tetrahalides were used without further purification. The organochlorosilanes were supplied by Dow Corning Corp.

Analytical.—The carbon and hydrogen analyses and the silicon analyses of tetrakis(trimethylsilyl)methane and tetrakis(dimethylsilyl)methane were done by Galbraith Laboratories, Knoxville, Tenn. The melting points are uncorrected. The structures of the two new compounds were confirmed by H^1 n.m.r. analysis. A Varian A-60 spectrometer was used. Yields are based on weight of tetrahalide used.

(1) Multiple Fellowship on Silicones sustained by Dow Corning Corp. and Corning Glass Works.

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Grignard Reactions with *in Situ* Trimethylchlorosilane.—In a three-necked flask equipped with dropping funnel, stirring rod, and condenser, was placed 58.8 g. (2.42 g.-atoms) of magnesium. The apparatus was dried by heating under a stream of dry nitrogen. To the flask was added 262 g. (2.42 moles) of trimethylchlorosilane and 600 ml. of tetrahydrofuran. This was heated to reflux, external heat was removed, and, at a rate to maintain reflux, 200 g. (0.603 mole) of carbon tetrabromide in 200 ml. tetrahydrofuran were added. After the addition which required 2.5 hr. and 2 hr. reflux, the mixture was poured over cracked ice and filtered. The unchanged magnesium weighed 3.2 g. Solvent and hexamethyldisiloxane were removed from the organic layer at atmospheric pressure. From the crude products 36 g. of precipitate was filtered. The filtrate was fractionated at reduced pressures yielding the products that follow: (1) 20.2 g. of 4-trimethylsilybutanol (see ref. 4 for origin of this product), b.p. 125° at 100 mm.; $n^{25}D$ 1.4332, lit.[5] $n^{25}D$ 1.4315; d^{25}_4 0.833, lit.[5] d^{25}_4 0.830. r_D Calcd.: 0.3121. Found: 0.3122. (2) 4.7 g. (4.9%) of bis(trimethylsilyl)methane, b.p. 71° at 100 mm.; $n^{25}D$ 1.4134, lit.[6] $n^{20}D$ 1.4170; d^{25}_4 0.750, lit.[6] d^{20}_4 0.752. r_D Calcd.: 0.3347. Found: 0.3328. (3) 55.7 g. (39.8%) of tris(trimethylsilyl)methane, b.p. 101° at 20 mm.; $n^{25}D$ 1.4605, lit.[7] $n^{20}D$ 1.4630; d^{25}_4 0.8275, lit.[7] d^{20}_4 0.836. r_D Calcd.: 0.3320. Found: 0.3313.

From the residue, 16.5 g. of solid was extracted with benzene. After removal of the benzene, this was combined with the precipitate filtered from the crude products above and recrystallized from absolute ethanol, yielding 50.5 g. (27.6%) of tetrakis(trimethylsilyl)methane, melting point, sublimes.

Anal. Calcd. for $C_{13}H_{36}Si_4$: C, 51.20; H, 11.90; Si, 36.86; mol. wt., 304.8. Found: C, 51.40; H, 11.81; Si, 36.60; mol. wt. (ebullioscopic), 323.

The H^1 n.m.r. spectrum consists of a single peak at τ = 9.8 p.p.m. using cyclohexane as the internal reference. Grignard reactions of bromotrichloromethane and dibromodichloromethane were run in the way described above for carbon tetrabromide. A trace of iodine was used to initiate reaction with the bromotrichloromethane. Products were characterized as above; yields are given in Table I.

Reaction with *in Situ* Dimethylchlorosilane.—To 56.8 g. (2.34 g.-atoms) of magnesium, 276 g. (2.92 moles) of dimethylchlorosilane, and 600 ml. of tetrahydrofuran was added at a rate to maintain reflux 200 g. (0.603 mole) of carbon tetrabromide in 200 ml. of tetrahydrofuran. The addition period of 2.75 hr. was followed by 5-hr. reflux. The mixture was poured over crushed ice, neutralized with sodium bicarbonate, and the organic layer was washed with water. The crude products, after the addition of 500 ml. of methanol, were cooled to the temperature of Dry Ice–acetone and 63.1 g. of precipitate was filtered off. The filtrate was distilled and in fractions boiling at about 160° at 50 mm. an additional 28.6 g. of solid crystallized. The two crystalline products were mixed and recrystallized from 95% methanol–5% ethanol, yielding 88.7 g. (59.5%) of tetrakis(dimethylsilyl)-methane, m.p. 115°.

Anal. Calcd. for $C_9H_{28}Si_4$: C, 43.46; H, 11.34; Si, 45.19. Found: C, 43.60; H, 11.43; Si, 45.27.

The H^1 n.m.r. spectrum consists of two peaks, a doublet at τ = 9.8 p.p.m. and a septet at τ = 5.9 p.p.m. with a coupling constant of 4 c.p.s. The intensity ratio of the doublet to the septet is approximately 6:1 and tetramethylsilane is the internal reference.

Reaction with *in Situ* Phenyldimethylchlorosilane.—To 14.6 g. (0.60 g.-atoms) of magnesium, 102.2 g. (0.60 mole) of phenyldimethylchlorosilane, and 150 ml. of tetrahydrofuran was added dropwise 50 g. (0.15 mole) of carbon tetrabromide in 50 ml. of tetrahydrofuran. The reaction mixture was treated as described above. Distillation yielded 28.8 g. (67.5%) of bis-(phenyldimethylsilyl)methane, b.p. 131° at 1 mm.; $n^{25}n$ 1.5404, lit.[8] $n^{25}D$ 1.5426; d^{25}_4 0.960, lit.[8] d^{25}_4 0.961. r_D Calcd.: 0.3285. Found: 0.3270.

Acknowledgment.—The authors are grateful to P. C. Lauterbur and J. J. Burke for the H^1 n.m.r. spectra and their interpretation.

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Hydrogenolysis of the Grignard Reagent

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In the course of some studies on the Grignard reagent, we had occasion to investigate the hydrogenolysis reaction. While hydrogenolysis of organometallic compounds is not new, there has been no report of hydrogenolysis of the Grignard reagent.

We found that ether solutions of the Grignard reagent react readily and cleanly with hydrogen without a catalyst according to the following equation.

$$2RMgX + 2H_2 \longrightarrow 2RH + MgX_2 + MgH_2$$

This reaction is general for a large number of Grignard reagents. The reaction conditions and results obtained with a variety of Grignard reagents are summarized in Table I. Runs of shorter duration with ethylmagnesium chloride at 100° showed that the reaction was 28% complete in 1 hr. and 43% complete in 3 hr.

It is obvious from Table I that some Grignard reagents react with hydrogen more readily than others. There appears to be no simple correlation of relative reactivity with the structure of the alkyl group. Such factors as the molecular aggregation of the Grignard reagent and the equilibria among the various species, monomer, dimer, dialkylmagnesium, and magnesium halide could affect the rate of the hydrogenolysis reaction. Furthermore, the system is heterogeneous and even the relative solubilities of the Grignard reagents at elevated temperatures are unknown.

We have found further that Grignard reagents are stable with respect to olefin elimination. Deuterium reacted with isopropylmagnesium chloride at 75° and at 125°. In both cases mass spectrometer analysis of the gaseous products showed that the propane produced contained only one deuterium atom. Hydrolysis of the ether-insoluble product with H_2O produced HD. The deuterium reaction can thus be written as shown.

$$2\ i\text{-PrMgCl} + 2D_2 \longrightarrow 2\ i\text{-PrD} + MgD_2 + MgCl_2$$

These experiments also show that hydrogenolysis does not proceed by an olefin elimination mechanism.

Experimental

Fisher certified reagent grade ethyl bromide, ethyl iodide, allyl bromide, *n*-butyl chloride, phenyl chloride, phenyl bromide, and benzyl chloride were used as received. Isopropyl chloride and *sec*-butyl chloride (Eastman) and neopentyl chloride (Matheson, Coleman and Bell) also were used as received. Eastman *t*-butyl chloride was distilled prior to use, and both methyl chloride and ethyl chloride (Ethyl Corporation) were vaporized through a calcium chloride drying tube. Mallinckrodt anhydrous ether and Domal high purity sublimed magnesium granules (Dominion Magnesium Co., Ltd., Haley, Ont.) were used without purification.

Grignard Preparation.—In general the Grignard reagents were prepared in 1-mole quantities from 27 g. of magnesium, 300 ml. of ether, and 1 mole of halide. A three-necked, 1-l. creased flask equipped with an air-driven stirrer, Dry Ice condenser, and addition funnel served as the reaction vessel. A blanket of argon was maintained on the reaction mixture at all times. The

Table I

Hydrogenolysis of Grignard Reagents[a]

Grignard	Hydrogenolysis (based on insoluble Mg), % 50°	75°	100°	125°	150°
CH_3MgCl	0	0	0	76	
C_2H_5MgCl	0	7, 14	100, 100	100	
C_2H_5MgBr		15	53	100	
C_2H_5MgI	10, 17	50, 60			
$(CH_3)_2CHMgCl$	80, 100	100	100	100	
$CH_2{=}CHCHMgBr$	10	89			
$CH_3CH_2CH_2CH_2MgCl$		0	85		
$CH_3CH_2CH(CH_3)MgCl$	0, 24[b]	79, 81	93	100	
$(CH_3)_3CMgCl$	0, 0	6, 13	47, 47	100	
$(CH_3)_3CCH_2MgCl$		0[c]	0[c]	60[c]	95[c]
C_6H_5MgCl			0[d]	44[d]	100[d]
C_6H_5MgBr		0	0, 15	53, 67	100
$C_6H_5CH_2MgCl$		0	0		

[a] 150 ml. of 2 *M* solutions in ether were used except where noted. Reactions were run 12 hr. at 5000-p.s.i.g. hydrogen. [b] Temperature rose to 70° momentarily. [c] Concentration was 1 *M*. [d] Concentration was 1.3 *M*.

superiority of argon or helium over nitrogen was demonstrated by Owens, *et al.*[1]

Usually the reaction was initiated by simply warming a concentrated ether solution of halide in the presence of magnesium. Once the reaction started, more ether was added, after which a 50% halide solution in ether was added dropwise over a period of several hours. The neopentyl Grignard could not be initiated in this manner but addition of 1 ml. of ethyl bromide led to quick initiation.

Phenylmagnesium chloride was prepared by refluxing a mixture of 40 g. of magnesium, 400 ml. of chlorobenzene, and 1 g. of aluminum chloride overnight. A high speed stirrer was used to agitate the refluxing mixture. Excess chlorobenzene was removed by vacuum pumping at 130°. The residue was washed thoroughly with hexane and filtered in a nitrogen box. Ether was added to the dried residue, and this mixture was then filtered. The filtrate was 2 *M* in phenylmagnesium chloride.

Both methyl chloride and ethyl chloride were used as ether solutions. In order to prevent loss of halide from these solutions by evaporation, a Dry Ice condenser was simply placed on top of the addition funnel. The Grignard preparation proceeded in the normal manner.

Standardization.—All Grignard reagents were filtered in a nitrogen box and then standardized. Initially, the method of Gilman[2] was used; later on, most of the magnesium analyses were done by Versene titration. Halogen was determined by the Volhard method. In most cases the magnesium and halogen analyses agreed to within 1%. Where appreciable Wurtz coupling occurred, notably with the allyl and *t*-butyl Grignard reagents, excess magnesium halide was present.

Hydrogenolysis Procedure.—In general the standardized Grignard solution was diluted with ether to a concentration of 2.00 *M*. A 150-ml. aliquot was charged into a 250-ml. Magne-Dash autoclave. This mixture was heated at 50, 75, 100, 125, or 150° for 12 hr. under 5000-p.s.i.g. hydrogen.

After the reaction mixture had been cooled and vented, it was filtered in a nitrogen box. Both precipitate and filtrate were analyzed for magnesium by Versene titration, for halide by the Volhard method, and by gas evolution, where applicable, by measuring the gas evolved upon hydrolysis of a weighed sample. The vent gas, where applicable, was analyzed by a mass spectrometer. The per cent hydrogenolysis was calculated on the basis of the magnesium present in the precipitate. In the case of the bromides and iodides the precipitate was predominantly magnesium hydride but did contain a small amount of halide. In the case of the reaction product from ethylmagnesium bromide, for example, the amount of halogen present was 11.6 wt. %. This was reduced to 4.1% by extraction with tetrahydrofuran overnight. The purity of the magnesium hydride is thus 95 wt. %, or 99.8 mole %.

For chlorides a mixture of magnesium chloride and magnesium hydride was obtained. The product from the hydrogenolysis of ethylmagnesium chloride at 100° was extracted with tetrahydrofuran. The magnesium chloride was extracted out, leaving the insoluble magnesium hydride in the precipitate.

Acknowledgment.—The support of the Advance Research Projects Agency, Department of Defense, under whose sponsorship this work was conducted, is gratefully acknowledged.

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A Convenient Laboratory Preparation of Pure $\Delta^{9,10}$-Octalin

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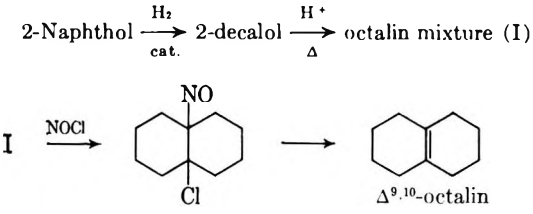
Numerous preparations for $\Delta^{9,10}$-octalin have been described.[1] It generally seems conceded[2,3] that the best method for making the pure compound involves the following four-step sequence.



While purity of product by this method is excellent, some of the steps are tedious.[4] An optimistic estimate of over-all yield would be 50% based on 2-naphthol.

We demonstrated earlier[5] that lithium dissolved in methylamine effectively reduces naphthalene to a

(1) See Elsevier ["Encyclopedia of Organic Chemistry," Vol. 12, Elsevier Publishing Co., Houston, Tex., 1948, p. 76] for a compilation of these methods.

(2) W. G. Dauben, E. C. Martin, and G. J. Fonken, *J. Org. Chem.*, **23**, 1205 (1958).

(3) A. S. Hussey, J. F. Sauvage, and R. H. Baker, *ibid.*, **26**, 256 (1961).

(4) For example, high pressure hydrogenation equipment has been used in the first step [see W. P. Campbell and G. C. Harris, *J. Am. Chem. Soc.*, **63**, 2721 (1941)]. A hydrogen pressure of 2000 p.s.i. and temperatures of 150–170° are recommended.

(5) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955).

mixture of octalins. More recently we have found[6] that the addition of certain secondary amines to such reduction mixtures greatly increases the selectivity of the reducing system.

In extending this work we have found that, by carrying out the reduction of naphthalene with lithium in a solvent consisting of ethylamine and dimethylamine, a mixture composed of 80% $\Delta^{9,10}$-octalin and 20% $\Delta^{1,9}$-octalin can be obtained in one convenient step. The purification of this mixture also has been modified to avoid the troublesome nitrosyl chloride treatment.[7]

It has been shown[8] that bis-3-methyl-2-butylborane, because of its high steric requirements, adds quite selectively to hindered carbon–carbon double bonds. We have found this reagent very effective in removing the 20% impurity of $\Delta^{1,9}$-octalin from the original mixture. Presumably it adds preferentially to the less hindered (relative to the $\Delta^{9,10}$) $\Delta^{1,9}$ isomer. Upon oxidation with hydrogen peroxide the adduct is presumably converted to an alcohol,[9] which permits a facile separation from the $\Delta^{9,10}$-octalin.

Our two-step preparation of $\Delta^{9,10}$-octalin proceeds in an over-all 50–54% yield, based on the starting naphthalene.

Experimental

Reduction of Naphthalene.—A mixture containing 25.6 g. (0.2 mole) of naphthalene and 250 ml. *each* of anhydrous ethylamine and dimethylamine was placed in a 1-l. three-necked round bottom flask fitted with a mechanical stirrer and a Dry Ice condenser. After this was stirred briefly, 11.55 g. (1.65 g.-atoms) of lithium wire cut into 0.5-cm. pieces was added all at once. After the mixture was stirred for 14 hr., the Dry Ice condenser was replaced by a water condenser and the solvent was allowed to evaporate. Anhydrous conditions were maintained during this process by having a drying tube attached to the condenser. The flask was then placed in an ice bath and the grayish white residue was decomposed by the dropwise addition of about 100 ml. of water (*Caution!*) accompanied by occasional slow stirring. The mixture was filtered under aspirator vacuum, and the precipitate was washed four times with 25–30-ml. portions of diethyl ether. The ether layer was separated and the aqueous layer was extracted several more times with 25-ml. portions of diethyl ether. The combined ether extracts were dried over anhydrous calcium sulfate. The solvent was removed and the residual liquid was distilled. A 19–20-g. fraction (75–80%), boiling at 72–77° at 14 mm., was collected. Analysis by vapor phase chromatography (Apiezon L column, 148°, 25-p.s.i. helium pressure) showed that the product contained 80% $\Delta^{9,10}$-octalin and 20% $\Delta^{1,9}$-octalin.

Purification of $\Delta^{9,10}$- and $\Delta^{1,9}$-Octalin Mixture.—In a 1-l. three-necked round-bottom flask equipped with a magnetic stirrer, dropping funnel, and a reflux condenser attached to a mercury trap was placed 4.7 g. (0.125 mole) of sodium borohydride, 23.1 g. (0.33 mole) of 2-methyl-2-butene, and 100 ml. of anhydrous tetrahydrofuran. This mixture was stirred for 15 min., and then 23.5 g. (0.165 mole) of boron trifluoride etherate dissolved in 22 ml. of anhydrous tetrahydrofuran was added dropwise over a 45-min. period. The rate of the addition was initially slow, but could be increased gradually. The octalin mixture prepared above was then added dropwise over a 10-min. period. After the mixture was stirred for 3.5 hr., 50 ml. of water was added dropwise with slow stirring. Thirty-five milliliters of 3 *N* sodium hydroxide was next added dropwise over a 10-min. period, followed by 35 ml. of 30% hydrogen peroxide over a 45-min. period. After stirring for 5 hr. at 44–45°, the mixture was cooled and the layers were separated. The ether layer was washed several times with 30-ml. portions of water and was then dried over calcium sulfate. After ether removal, the residual liquid was distilled under a nitrogen atmosphere. The fraction (12–13 g.) boiling at 75–77° at 14 mm. was collected, representing a yield of 50–54% based on naphthalene. Analysis of this material by v.p.c. indicated it was 99% pure $\Delta^{9,10}$-octalin[10], $n^{20}D$ 1.4990.

Acknowledgment.—The authors are grateful to the National Science Foundation for financial assistance which made this work possible.

(6) R. A. Benkeser, R. K. Agnihotri, and M. L. Burrous, *Tetrahedron Letters*, **No. 16**, 1 (1960).

(7) Since the same 80:20 ratio was obtained (ref. 3) using the four-step reaction sequence, undoubtedly the nitrosyl chloride purification method described in ref. 3 would also be successful with our mixture.

(8) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961).

(9) H. C. Brown, "Hydroboration," W. A. Benjamin Inc., New York, N. Y., 1962, p. 69.

(10) The identity of the $\Delta^{9,10}$-octalin was readily established by its n.m.r. spectrum which showed a complete lack of vinyl hydrogens., characteristic of the other octalin isomers. Likewise the v.p.c. retention time relative to *trans*-decalin agreed well with that reported [J. W. Powell and M. C. Whiting, *Tetrahedron*, **12**, 163 (1961)].

The Solvent Sensitivity of the Charge-Transfer Band of Tropylium Iodide

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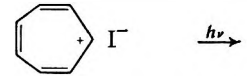
Solutions of tropylium iodide in nonpolar solvents are quite sensitive to air and light. A simple apparatus (Fig. 1) permits the preparation of such solutions with the exclusion of light and air. The solvent sensitivity of the charge-transfer band can then be measured. Conventional technique in the preparation of solutions in nucleophilic, polar solvents is used since an acidic medium is required. The transition energies for the charge-transfer band in different solvents (eq. 1) show a good linear correlation with the solvent polarity values, Z[2], with a slope somewhat greater than unity.



(1)

The colors of tropylium halides have been attributed to the occurrence of charge-transfer transitions,[3] and the position of the charge-transfer band in methylene chloride has been measured.[4]

Tropylium iodide was prepared by adding excess concentrated hydriodic acid to hot ethanolic tropylium fluoborate, cooling, rapidly filtering, and drying the crystals on a high-vacuum line. The crystals were bright red, m.p. *ca.* 125° dec. Solvents (methylene chloride, acetonitrile, isopropyl alcohol, acetone) were spectrophotometric grade and were degassed before distillation into the reservoir of the apparatus (Fig. 1). Mixing was effected immediately before measurement of the spectra with a Cary Model 14 spectrophotometer. The low rate of solution[4] observed for tropylium iodide in all but the most polar solvents along with a decrease in the intensity of the charge-transfer band dependent on the solvent, light, oxygen, and impurities forced us to focus our attention exclusively on the position of the maximum rather than the intensity

(1) Alfred P. Sloan Fellow, 1960–1964.

(2) E. M. Kosower: (a) paper presented at a Symposium on Molecular Interactions in Liquid Solution, Société de Chimie Physique, June 4–8, 1963, Paris; (b) *J. Am. Chem. Soc.*, **80**, 3253 (1958).

(3) (a) E. M. Kosower and P. E. Klinedinst, Jr., *ibid.*, **78**, 3493 (1956); (b) W. v. E. Doering and H. Krauch, *Angew. Chem.*, **68**, 661 (1956).

(4) K. M. Harmon, F. E. Cummings, D. A. Davis, and D. J. Diestler, *J. Am. Chem. Soc.*, **84**, 3349 (1962).

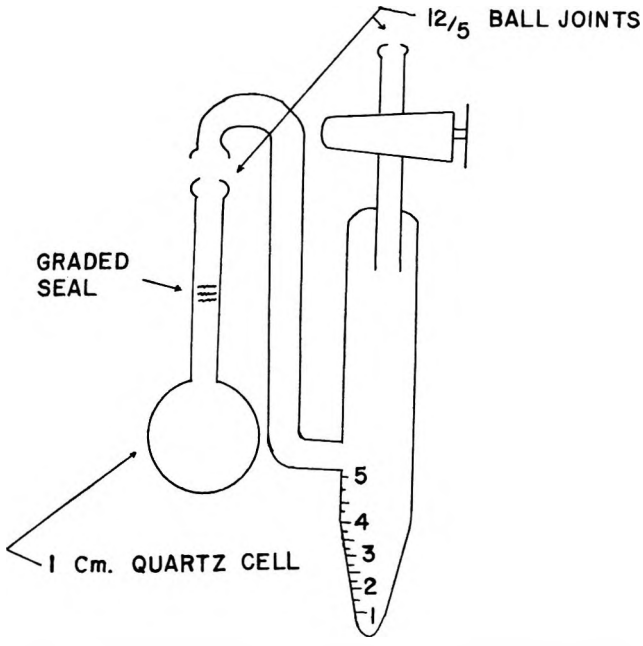


Fig. 1.—Apparatus for the preparation of solutions in degassed solvents. The sample is weighed directly into the quartz cell. After evacuation and flushing with solvent vapor, solvent is distilled into the graduated reservoir (3.5–4.0 ml.). Mixing may be effected immediately before the spectrum is measured. A black-painted wooden piece is used to enlarge the working space in the Cary 14 sample compartment.

of the absorption. No effect of concentration on the position of the maximum was *noted*. The charge-transfer band disappeared in carefully degassed acetone with unusual celerity, but the reaction responsible for the disappearance was not investigated.

The tropylium iodide was weighed directly into the quartz cell, either that of Fig. 1 or a 1-cm. stoppered cell. The polar solvents, water, methanol, and ethanol, were nitrogen-saturated and contained *ca.* 0.05 *N* hydriodic acid. Some five to ten minutes were required before a stable maximum was obtained in these solvents, and the steady decrease in the intensity of the charge-transfer band obviated accurate measurement of the maxima. The maximum in water was duplicated when sulfuric acid (0.1 *N*) was used; the latter solution was not particularly sensitive to light. Fourteen hours exposure to a 100-watt light led to the disappearance of both the charge-transfer band and absorption due to iodide ion (at 2260 Å.).

The data for tropylium iodide are summarized in Table I, and the correlation with *Z* is shown in Fig. 2. The fact of the correlation and the magnitude of its slope suggests that the previously proposed theoretical analysis is reasonable, *i.e.*, that the stabilization of the ion-pair ground state by solvent is equal to the destabilization of the excited state in comparison to the same states in a nonpolar medium.[2b,5] Attempts to calculate the ground state interaction energy in a solvent like acetonitrile by considering reasonable models for the structure of the *cybotactic region*[2b] lead to quantities which are somewhat too large. This is not surprising since the desired interaction energy represents the difference between a large attraction and large repulsion. Although the detailed energetics of the excited state are ignored in this approach, it would seem like a reasonable way to evaluate the ground state interactions derived from the spectroscopic data.

(5) An analysis of this type was originally proposed for halide ions. L. Pauling, *Phys. Rev.*, **34**, 954 (1929).

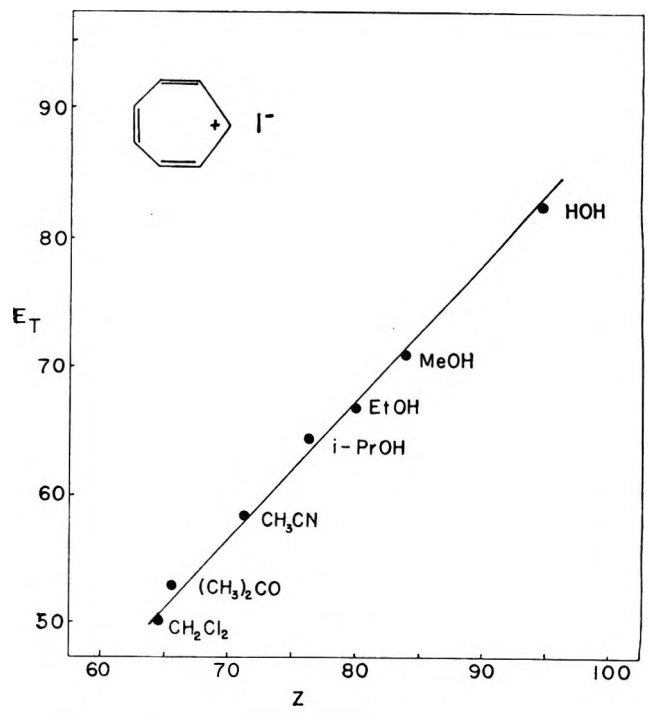


Fig. 2.—A plot of the transition energies for the charge-transfer band of tropylium iodide against the *Z* values for the solvents used (ref. 2b).

Table I

Charge-Transfer Band Maxima of Tropylium Iodide

Solvent (Z^a)	λ_{max}, Å.	$E_T{}^b$	Comment
Water (94.6)[c]	3457	82.7	I^- (0.1 *N* H_2SO_4) had no absorption between 3000 and 4000 Å., I_3^- had λ_{max} 3514 Å.
Methanol (83.9)[c,d]	4035	70.9	Charge-transfer band disappeared at moderate rate
Ethanol (80.0)[c,d]	4295	66.6	Charge-transfer band disappeared at moderate rate
Isopropyl alcohol (76.3)[c]	4432	64.5	Solubility low
Acetonitrile (71.3)	4905	58.3	Second maximum at 3300 Å.[e,f]
Acetone (65.7)	5390	53.0	Fast scan necessary since charge-transfer band disappears rapidly ($t_{0.5}$ *ca.* 14 min.)
Methylene chloride (64.5)	5715[g]	50.0	
	4090	69.9	Second maximum[g,h]

[a] Ref. 2b. [b] In kcal./mole. [c] Contained *ca.* 0.05 *N* HI. [d] *Z*-values corrected for water content. [e] The second band was only visible in the most dilute solutions. Its shape is *not* that of a charge-transfer band. [f] Exposure to light produced triiodide ion, λ_{max} 3610 Å. [g] Previously reported at 575 and 422 mμ (ref. 3). [h] ΔTE 19.9 kcal./mole [theoretical for $^2P_{1.5}$–$^2P_{0.5}$ 21.7 kcal./mole, *cf.* E. M. Kosower, *et al.*, *J. Am. Chem. Soc.*, **82**, 2188 (1960)].

Acknowledgment.—Support of the National Institutes of Health made the foregoing studies possible. A gift of tropylium fluoborate from Professor William D. Closson, Department of Chemistry, Columbia University, was helpful.

Kishner Eliminative Reduction of α-Halo Ketones[1]

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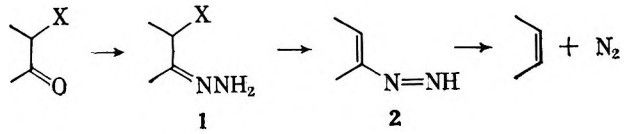
A reasonable reaction path for Kishner eliminative reduction of α-substituted ketones to olefins[2] involves hydrazone formation (→ **1**), internal elimination of the α-substituent (**1** → **2**), and collapse of alkenyldiimide **2** to olefin and nitrogen.[3] The temperature at which Kishner eliminative reduction occurs depends on the



1 **2**

ease of elimination of the α-substituent. For example, it can be inferred that normal α-alkoxy ketones need high temperatures (>150°) to effect their reduction.[2] α-Phenoxypinacolone[2], however, is reduced to 3,3-dimethylbutene at 90° and α,β-epoxy ketones[4] undergo Kishner eliminative reduction to allylic alcohols at room temperature under nonbasic conditions. By extrapolation, Kishner eliminative reduction of α-sulfonyloxy ketones also should proceed under mild conditions, and we contemplated this unknown reaction as potentially satisfying a need which had arisen in other work for converting an acyloin to an olefin under mild conditions. First, however, we considered Kishner eliminative reduction of the more readily available α-halo ketones.

A survey of the literature on the reaction of α-halo ketones with hydrazine surprisingly[5a] drew an almost complete blank, and the little that could be found was not encouraging. In an entirely different endeavor, Macbeth found no nitrogen evolution from the reaction of 1-chloropropanone with excess hydrazine hydrate in alcohol.[6] There is, of course, no lack of possible reactions which might suppress the occurrence of eliminative reduction,[5b] one of the most likely being illustrated by the reported conversion of phenacyl chloride to phenacylhydrazine.[7] However, detection of Kishner eliminative reduction by observation of nitrogen evolution suggested a simple exploratory plan and we used this method to examine the reaction of hydrazine with 2-chlorocyclohexanone, a lucky choice as later events showed.

2-Chlorocyclohexanone, as distinct from 1-chloropropanone, with a large excess of hydrazine hydrate in alcohol, gave a small *but definitely not zero* amount of nitrogen (6%). Modification of reaction conditions, using potassium acetate to buffer the system in all cases, raised the yield of nitrogen to 35% by using only two to three equivalents of hydrazine hydrate. Eventually, a 75% yield was obtained by adding two to three equivalents of 95% hydrazine to a boiling solution of α-halo ketone in dimethoxyethane.[8] The isolation of cyclohexene from the product established that Kishner eliminative reduction was actually occurring, but a definitive correlation of nitrogen and olefin yields was not possible because cyclohexene could not be extracted quantitatively from dimethoxyethane solution. The necessary data were, however, provided by the 2α-halocholestanone series (halogen = F, Cl, Br, and I), where reduction was most effectively accomplished by adding the α-halo ketone to a two-phase system of boiling cyclohexene[9] or cyclohexane and excess hydrazine hydrate containing potassium acetate.[10] The results of these experiments are given in Table I.[11] It is

TABLE I

2α-Halocholestanone	% nitrogen	% 2-cholestene
F	75	71
Cl	67	68
Br	64	62
I	54	54

quite clear that the amounts of nitrogen evolved and 2-cholestene formed were the same, even for the α-iodo ketone which is the most susceptible to reductive displacement on halogen.[12] 2-Cholestene was isolated from the washed product by percolation of a hexane solution through a column of alumina. This simple separation from the residue of more polar products yielded by evaporation of the filtrate white crystals of 2-cholestene, $[\alpha]D$ +64°, with melting points ranging from 70–73° to 72–74° (lit.[13] m.p. 74.5–75°, $[\alpha]D$ +69°;

(1) Grateful acknowledgment is made of financial support from the Petroleum Research Fund (grant 1116-A4) and Research Corporation (Frederick Gardner Cottrell grant).

(2) The scope of the reaction has been reviewed by N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3269, 3272 (1955).

(3) See D. J. Cram and J. S. Bradshaw, *ibid.*, **85**, 1108 (1963), for references and a study of the decomposition of alkyldiimides.

(4) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); *cf.* Huang-Minlon and Chung-Tungshun, *Tetrahedron Letters*, **No. 19**, 666 (1961).

(5) (a) Surprisingly, because of the voluminous literature related to the reaction of α-halo ketones with amines; (b) for references, see C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).

(6) E. L. Hirst and A. K. Macbeth, *J. Chem. Soc.*, 904 (1922).

(7) M. Busch and W. Foerst, *J. prakt. Chem.*, **119**, 287 (1928).

(8) This variation in yield can perhaps be ascribed to nucleophile-promoted diversions *after* alkenyldiimide formation. Tautomerization of alkenyldiimide to α,β-unsaturated hydrazone is one possibility. Another possibility is the formation of α-substituted hydrazones, from which the α-substituent can no longer be eliminated, by conjugate addition of hydrazine, alcohol, or water to alkenyldiimide. See V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **72**, 2290 (1950), and C. Djerassi, *ibid.*, **71**, 1003 (1949).

(9) Cyclohexene was used as solvent to prevent reduction of olefinic product by diimide to saturated hydrocarbon. Diimide can arise from oxidation of hydrazine and, although air oxidation was avoided by flushing the apparatus with an inert gas, and displacement by hydrazine on the halogen of the α-halo ketone was shown not to occur, no disadvantage can be seen to using (at least in part) an olefinic solvent which can competitively absorb any diimide formed. See E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *ibid.*, **83**, 3725 (1961), for references to diimide reductions. Note that reduction of 2-cholestene by diimide is implied in the Kishner eliminative reduction of 2-acetoxy-3-cholestanone; cholestane was found to be the main product [see L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944)].

(10) The success of this system may be related to protection of alkenyldiimide from nucleophiles (see ref. 8). Rapid hydrazone formation results from projection through the interface of the highly polar carbonyl group and α-halogen atom. Elimination of halide may occur also at the interface, but surely is followed by withdrawal of the nonpolar cholestenyldiimide into the hydrocarbon phase.

(11) Also reduced by this method and reported here for completeness was 2α-fluorodihydrotestosterone (generously supplied by Dr. R. E. Counsell, Searle) in 70% yield.

(12) See G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950); included is the example of reductive dehalogenation by collidine of 2α-iodo-3-cholestanone to 3-cholestanone.

(13) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

m.p. 75°, $[\alpha]D$ +65.5°, +67.4°). The olefin was characterized by quantitative hydrogenation (1.00 equivalent of hydrogen absorbed) and conversion to 2β,3α-dibromocholestane.

After the work described so far was completed, other potential olefin syntheses, starting from 1,2-diols,[14] seemed more promising and our investigation of the Kishner eliminative reduction was terminated with a cursory survey of the scope of the reaction, based on the determination of nitrogen evolution. Table II gives the results of treating a variety of α-halo and α-sulfonyloxy ketones in dimethoxyethane solution with two to three equivalents of 95% hydrazine. Yields were good only for the α-halo cyclohexanones, decreasing sharply in the vertical columns with decreasing electrophilicity of the ketones.[15] The horizontal order[16] parallels both the electrophilicities of α-halo ketones (F > Cl > Br) and the resistance to elimination of the α-substituent in competitive reactions.[17]

To sum up, Kishner eliminative reduction of α-halo and α-sulfonyloxy ketones has been observed for the first time. Yields were sufficiently high in the conversion of α-halocyclohexanones to cyclohexenes that, for this special case, Kishner eliminative reduction should be considered as a practical alternative to the established two-step sequence *via* α-halohydrins.[18,19] Poor yields were, however, obtained from α-sulfonyloxy ketones and most other α-halo ketones.

TABLE II

α-Substituted ketone	Temp., °C.	% nitrogen F	Cl	Br	OSO_2R
2-Methylcyclohexanone	85		69		
Cyclohexanone	RT	0	61	52	36[a]
	85	79	74	54	15[a]
Cyclopentanone	RT		[b]		
Butanone	85			30[c,d]	
Propanone	RT	0		26[c]	17[c,e]
	85	10[c]	40[c]	32[c]	10[c,e]
	160[f]	32[c]			
Acetophenone	85		10		
Cyclodecanone	RT				0[a]
	85				0[a]

[a] OTs. [b] 40% of an unanalyzed mixture of nitrogen and cyclopentene. [c] Based on the assumption that the gas evolved contained equal amounts of nitrogen and olefin. [d] V.p.c. of the evolved gas showed that it contained equal amounts of *cis*- and *trans*-2-butene. The mixture of 2-butenes was contaminated with methyl bromide, presumably arising from demethylation of solvent by hydrogen bromide and indicating that potassium acetate does not act very rapidly as a buffer. [e] OMes. [f] Boiling diglyme.

Experimental[20]

Materials.—Dimethoxyethane, diglyme, and cyclohexene were distilled from lithium aluminum hydride. Chloropropanone, 3-bromo-2-butanone (Eastman Kodak), 2-chlorocyclohexanone, and 2-chlorocyclopentanone (Aldrich) were distilled. Generously supplied were 2-fluorocyclohexanone (Dr. A. S. Kende, American Cyanamid) and the dimethyl ketal of 2α-fluorocholestanone (Professor E. V. Jensen). 2α-Fluorocholestanone, m.p. 173–174°, lit.[21] m.p. 173–174°, was obtained by hydrolysis of the ketal with a few drops of concentrated hydrochloric acid in aqueous tetrahydrofuran solution. Prepared according to the literature were fluoropropanone[22]; bromopropanone[23]; mesyloxypropanone[24]; 2-bromocyclohexanone[25]; 2-chloro-2-methylcyclohexanone[26]; 2α-chlorocholestanone,[27] m.p. 179–181°, $[\alpha]D$ +52° (lit.[28] m.p. 182°, +54°); 2α-bromocholestanone,[29] m.p. 167–169°, $[\alpha]D$ +43.5° (lit.[28] m.p. 169°, +42°); 2α-iodocholestanone,[12] m.p. 131.5–133° dec. (lit.[28] m.p. 127°).

2-Tosyloxycyclohexanone.[30]—A solution of 1.0 g. (4.4 mmoles) of 2-hydroxycyclohexanone dimer (Aldrich) and 3.0 g. (15.7 mmoles) of tosyl chloride in 10 ml. of pyridine was allowed to stand for 12 hr. at 5°. The solution was poured into iced hydrochloric acid, extracted with ether, and washed. Crystallization of the crude product from ether yielded 1.3 g. (55%) of product, m.p. 73–76°. Further crystallization from ether gave an analytical sample with m.p. 75–76°.

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.20; H, 6.01; S, 11.93. Found: C, 58.13; H, 6.02; S, 11.72.

2-Tosyloxycyclodecanone.[30]—A solution of 1.0 g. (5.9 mmoles) of 2-hydroxycyclodecanone (Aldrich) and 1.5 g. (7.9 mmoles) of tosyl chloride in 3 ml. of pyridine similarly yielded 0.9 g. (47%) of product, m.p. 82–85°. Further crystallization from ether yielded an analytical sample with m.p. 86–87°.

Anal. Calcd. for $C_{17}H_{24}O_4S$: C, 62.95; H, 7.46; S, 9.87. Found: C, 62 98; H, 7.40; S, 9.75.

Small Scale Reductions.—To a 25-ml. flask connected through a condenser to a gas-collection buret and containing a magnetic stirring bar, 3.0 ml. of solvent, 1.5 g. (15 mmoles) of potassium acetate, and 1 mmole of α-substituted ketone was added the appropriate amount of 95% hydrazine or hydrazine hydrate. Vigorous stirring was maintained until no more gas was evolved (*ca.* 5 to 10 min.). The amount of gas collected was measured at room temperature, corrected for vapor pressure, and reduced by the appropriate blank reading.

Exemplary Large Scale Reduction of 2-Chloro-2-methylcyclohexanone.—To a 3-l. three-necked flask fitted with a stirrer and attached to a gas-measuring device (wet test meter, Precision Scientific Co.) were added 810 ml. of dimethoxyethane, 40 g. (0.41 mole) of potassium acetate, and 60 g. (0.41 mole) of 2-chloro-2-methylcyclohexanone. To the mixture, which was stirred and heated to reflux, was added dropwise 23 g. (0.68 mole) of 95% hydrazine. After a short induction period (*ca.* 3 min.) gas was evolved rapidly. A sample of gas was collected after bubbling through the wet test meter. Mass spectrometry showed, by comparison with pure nitrogen, that the collected gas was nitrogen, purity 95%. When no more gas was evolved (total collected corresponded to a yield of 65% nitrogen) the yellow-orange solution was cooled. Water (2 l.) and 4 l. of methylbutane were added to extract the methylcyclohexene. The lower phase was extracted with two 250-ml. portions of methylbutane which were added to the upper phase and washed with 2 l. of water, 2 l. of dilute sodium hydroxide solution, and two 2-l. portions of water. After drying with magnesium sulfate, the solution was percolated through a column of *ca.* 500 g. of silica gel (Davison).[31] The column was washed with more methylbutane, and the combined filtrates were distilled to yield

(14) See, for example, E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

(15) See M. S. Newman in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 237.

(16) At 85°. Note that fluoride is a sufficiently poor leaving group that Kishner eliminative reduction of α-fluoro ketones is not observed at room temperature.

(17) See A. Streitwieser, Jr., *Chem. Rev.*, **56**, 653 (1956).

(18) See J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

(19) Note that the ease of reduction of α-halohydrins by zinc follows the trend I > Br > Cl and that no α-fluorohydrins have been reduced to olefins.

(20) Melting points are corrected. A 4-dm. tube was used to measure optical rotations which were determined photoelectrically with a Rudolph Model 80 polarimeter.

(21) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(22) H. Kitano and K. Fukui, *Kogyo Kagaku Zasshi*, **59**, 395 (1956); *Chem. Abstr.*, **51**, 11282 (1957).

(23) P. A. Levene, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 88.

(24) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

(25) J. Allinger and N. E. Allinger, *Tetrahedron*, **2**, 64 (1958).

(26) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Syn.*, **37**, 8 (1957).

(27) B. Ellis and V. Petrow, *J. Chem. Soc.*, 3869 (1953).

(28) General reference: L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

(29) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953). See E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962), for comment on the possibility of 5–15% contamination of this bromo ketone with cholestanone.

(30) Prepared by Dr. R. V. Coombs.

(31) This purification is not only simple and effective, but also desirable on the grounds of safety. Attempted distillation (oil bath at 120°) of the crude product from reduction of 2-chlorocyclohexanone resulted in a violent explosion after most of the cyclohexene had distilled.

15.85 g. (41%) of 1-methylcyclohexene, b.p. 109–109.5°, $n^{25}D$ 1.4509 (lit.[32] 109.5°, $n^{20}D$ 1.4505). Extraction of the olefin was not quantitative as shown in a blank experiment; authentic 1-methylcyclohexene (Aldrich, distilled), subjected to the same isolation procedure, was recovered in 70% yield.

Reduction of 2α-Bromocholestanone.—To a 100-ml. three-necked flask containing a magnetic stirrer and attached through a condenser to a gas buret were added 13 ml. (0.4 mole) of hydrazine hydrate, 2 g. (20 mmoles) of potassium acetate, and 10 ml. of cyclohexene. The flask was heated until the cyclohexene boiled, and a solution of 2.004 g. (4.3 mmoles) of 2α-bromocholestanone in 30 ml. of cyclohexene was added dropwise over 10 min. while maintaining stirring and boiling. Heating was continued for 30 min. The light yellow mixture was cooled, extracted with ether–water, dried, evaporated, dissolved in hexane, and percolated through a column of acid-washed alumina (Merck). Evaporation of the filtrate yielded 995 mg. (64%) of 2-cholestene, m.p. 72–74°, $[\alpha]D$ +64°. Recrystallization from ether–ethanol (2:1) gave white needles of 2-cholestene in 95% yield, m.p. 73–75°, $[\alpha]D$ +65°.

Poorer results were obtained if the reagents were all mixed before heating. Thus a mixture of 2.009 g. of 2α-bromocholestanone, 13 ml. of hydrazine hydrate, 2 g. of potassium acetate, and 13 ml. of cyclohexene heated to reflux yielded a darker reaction mixture and only 269 mg. (19%) of 2-cholestene, m.p. 72–74°.

2α,3β-Dibromocholestane.—To a solution of 109 mg. (0.29 mmole) of 2-cholestene, m.p. 73–75°, in 2 ml. of ether was added dropwise a solution of bromine in acetic acid until a slight excess of bromine was present. Evaporation of solvent and crystallization of the residue from ether–ethanol gave 76 mg. (49%) of white plates of 2α,3β-dibromocholestane, m.p. 123–124°, lit.[28] m.p. 125°.

Hydrogenation of 2-Cholestene.—Microhydrogenation of 40.6 mg. (0.11 mmole) of 2-cholestene, m.p. 72–74°, in acetic acid using 10% palladium on carbon as catalyst, led to the slow (*ca.* 6 hr.) uptake of 1.00 equivalent of hydrogen. Work-up of the solution gave a light yellow residue which was dissolved in hexane and percolated through a short alumina column. Evaporation of the filtrate yielded 34 mg. (85%) of crude cholestane, m.p. 75–80°. The melting point was raised to 79–80°, lit.[28] m.p. 80°, by crystallization from ether–ethanol.

(32) G. Egloff, "Physical Constants of Hydrocarbons," Vol. 2, Reinhold Publishing Corp., New York, N. Y., 1940, p. 326.

Tropone. Selenium Dioxide Oxidation of 1,3,5-Cycloheptatriene

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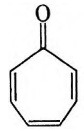
Received November 7, 1963

There are several methods known for the preparation of tropone (2,4,6-cycloheptatrien-1-one, I).[1–5] They range in scope from the degradation of tropinone[4] to produce I, to the formation of bis-2,4,6-cycloheptatrien-1-yl ether (III) from the hydrolysis of tropilium salts and subsequent disproportionation of the ether to give I and 1,3,5-cycloheptatriene (II).[2,3]



I

II

We have observed a direct oxidation of II by selenium dioxide in buffered aqueous dioxane to give I in about 25% yield. This reaction, though not high in yield, affords a simple one-step preparation of I from commercially available starting materials. The reaction can readily be adapted to large scale, and the inorganic product, selenium, can be recovered and reoxidized to selenium dioxide if desirable.[6]

Experimental

Preparation of Tropone.—To a solution of potassium dihydrogenphosphate (13.5 g., 0.1 mole) in water (33 ml.) was added 1,4-dioxane (330 ml.), 1,3,5-cycloheptatriene (43.0 g., 0.46 mole, Shell Chemical Corp., contained 6% toluene), and selenium dioxide (53.0 g., 0.48 mole, Matheson, Coleman and Bell). The mixture was warmed on the steam bath (90°) for 15 hr., allowed to cool to room temperature, and then filtered. The filtrate was poured into water (750 ml.) and extracted three times with 250-ml. portions of methylene chloride. The organic extract was washed with 10% sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to a dark brown liquid. Distillation of this liquid gave 12.8 g. (25%) of pale yellow tropone, b.p. 91–92° at 4 mm., $n^{23}D$ 1.6152. The infrared spectrum of this material was identical with that reported by Doering.[5]

Acknowledgment.—The author wishes to thank Shell Chemical Corporation for its generous supply of 1,3,5-cycloheptatriene.

(1) J. Birch, M. Graves, and F. Stansfield, *Proc. Chem. Soc.*, 282 (1962).
(2) T. Nozoe, T. Ikemi, and H. Sugiyama, *Chem. Ind.* (London), 932 (1960).
(3) A. P. ter Borg, *Helv. Chim. Acta*, **43**, 457 (1960).
(4) J. Meinwald, S. Emerman, N. Yang, and G. Büchii, *J. Am. Chem. Soc.*, **77**, 4401 (1955).
(5) M. von E. Doering and F. Detert, *ibid.*, **73**, 877 (1951).
(6) N. Rabjon, "Organic Reactions," Coll. Vol. V, R. Adams, Ed., John Wiley and Sons, New York, N. Y., 1949, p. 345.

The Reaction of Chlorocarbene with Styrene

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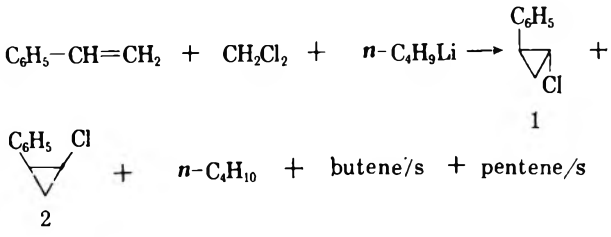
A number of carbenes or "carbene-like" species have been added to styrene to give substituted phenylcyclopropanes.[1] Closs and co-workers[2] have generated chlorocarbene from methylene chloride and methyl- or *n*-butyllithium and added it to various olefins to give substituted chlorocyclopropanes. The work which is now reported was undertaken to study the addition of chlorocarbene to styrene.

When ethereal *n*-butyllithium, prepared from *n*-butyl bromide and lithium, was allowed to react with methylene chloride in the presence of excess styrene, two stereoisomeric 1-chloro-2-phenylcyclopropanes were isolated in low yields in addition to several gaseous products. The yields of 1 (4.1%) and 2 (4.9%) are based on distilled material, assuming equal thermal conductivities on gas chromatographic (g.c.) analysis. The structural

(1) (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956); (b) W. J. Dale and P. E. Swartzentruber, *J. Org. Chem.*, **24**, 955 (1959); (c) A. Nagasaka and R. Oda, *Kogyo Kagaku Zasshi*, **59**, 1024 (1956); (d) H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4990 (1961); (e) A. Burger and W. L. Yost, *ibid.*, **70**, 2198 (1948); (f) R. J. Mohrbacher and N. H. Cromwell, *ibid.*, **79**, 401 (1957); (g) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959); (h) G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961).
(2) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960), and subsequent papers.



assignments are based primarily on the nuclear magnetic resonance (n.m.r.) spectra and to a lesser extent on their physical properties. The n.m.r. spectrum (CCl_4) of **1** showed a broad multiplet centered at δ −7.07[3] (5.00)[4] for the aromatic protons, an octet at −3.07 (1.00) for the proton on the chlorine-bearing carbon, an octet at −2.28 (1.00) for the benzylic proton, and at least eight peaks at −1.35 (2.50) for the two remaining cyclopropyl protons. Isomer **2** also showed four sets of peaks at δ −7.20 (5.00, singlet), −3.28 (1.00), −2.27 (1.08), and −1.28 (2.10), respectively. The high resolution n.m.r. spectra of the proton, H_A, on the chlorine-bearing carbon and the benzylic proton, H_B, for the two isomers are shown in Fig. 1 and 2. Analysis of these spectra show the coupling constants between H_A and H_B to be 3.3 c.p.s. for the isomer assigned the *trans* structure and 7.7 c.p.s. for the other isomer. It has been fairly well-established that *cis* protons on a cyclopropane ring have a larger coupling constant than do *trans* protons.[5] The relative chemical shifts for H_A of the two isomers also are consistent with the assigned structures, since the proton on the chlorine-bearing carbon of the *cis* isomer is usually found at a lower field.[5b,c,6] The relative boiling points and refractive indices of **1** and **2** are also in agreement with the assigned structures. A number of cases have been reported in which the *cis* cyclopropyl compounds had the higher values for both of these physical properties.[2,5b,c,6,7]

The slight predominance of the *cis* isomer isolated is in accord with the findings of Closs and co-workers[2,5b] who also found a preference for the *cis* isomers. However, this result may be fortuitous, since the yields are quite low and may only reflect the product distribution after a portion of the primary product has reacted further. An indication that the latter may have occurred was found in the isolation of a high-boiling liquid which contained cyclopropyl protons as shown by n.m.r. spectroscopy. The origins of the *n*-butane, butene/s, and pentene/s in this type of reaction have been discussed elsewhere.[2,8]

In contrast to the above results utilizing *n*-butyllithium, the reaction of methyllithium, prepared from methyl iodide and lithium, with methylene chloride and styrene in ether at either 5–10° or −70° led to the formation of phenylcyclopropane (**3**, 10%) and 1-methyl-2-phenylcyclopropane (**4**, 20%) in addition to a complex mixture of gases. No **1** or **2** could be detected.

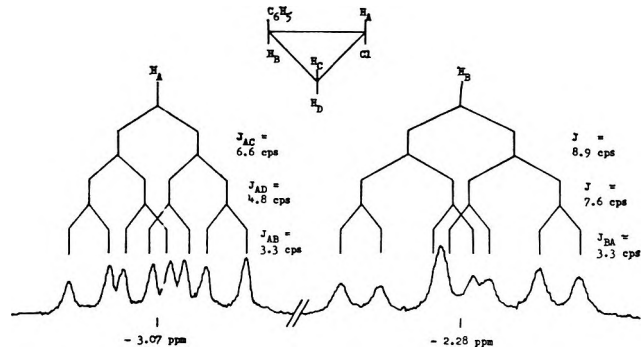


Fig. 1.—Partial n.m.r. spectrum of *trans*-1-chloro-2-phenylcyclopropane (**1**).

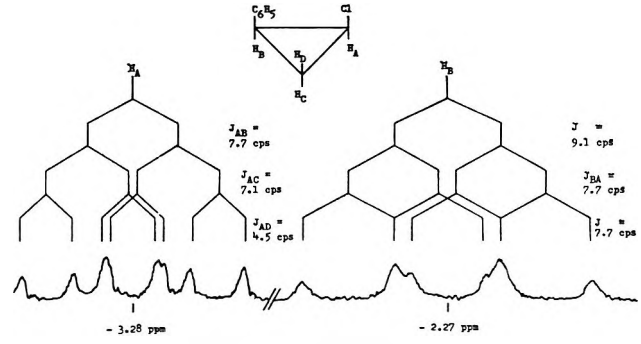
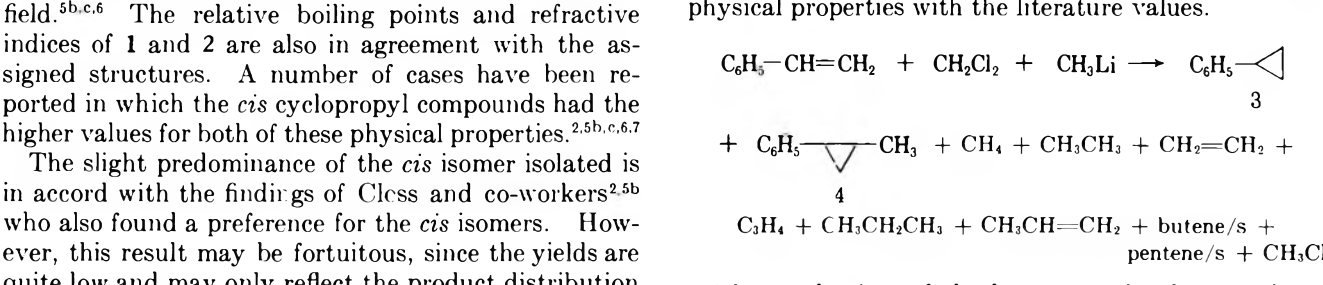


Fig. 2.—Partial n.m.r. spectrum of *cis*-1-chloro-2-phenylcyclopropane (**2**).

The identity of the cyclopropanes was based on elemental analyses, spectral data, and comparison of the physical properties with the literature values.



The mechanism of the latter reaction has not been determined, but several possible reaction paths could be visualized. Initial formation of a complexed carbene ($:CH_2$)[9] could give use to **3**. The presence of lithium iodide could account for the formation of this complexed carbene in a manner analogous as that described by Schöllkopf and Paust[10] for the formation of alkoxy carbenes. Formation of methylcarbene[11] could lead to **4**. Alternatively, various combinations of halogen–metal exchange, alkylation, and hydrolysis of **1** or **2** could give **3** and **4**.[12] The gaseous products probably arose from interaction of methyllithium, methylene chloride, and chlorocarbene. Reactions between methylene halides and organometallic compounds to give products analogous to some of those reported here have been described.[13]

(3) δ in p.p.m. from tetramethylsilane used as an internal reference.

(4) Integrated area.

(5) (a) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); (b) G. L. Closs, R. A. Moss, and J. J. Coyle, *ibid.*, **84**, 4985 (1962); (c) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).

(6) D. E. Applequist and A. H. Peterson, *J. Am. Chem. Soc.*, **82**, 2372 (1960).

(7) R. G. Kelso, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.* **77**, 1751 (1955).

(8) (a) J. F. Eastham and G. W. Gibson, *J. Org. Chem.*, **28**, 280 (1963); (b) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **81**, 4996 (1959); (c) G. L. Closs, *ibid.*, **84**, 809 (1962).

(9) For possible related reactions, see (a) W. T. Miller, Jr. and C. S. Y. Kim, *ibid.*, **81**, 5008 (1959); (b) L. Friedman and J. G. Berger, *ibid.*, **82**, 5758 (1960); (c) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., New York, N. Y., 1962, p. 500.

(10) U. Schöllkopf and J. Paust, *Angew. Chem.*, **75**, 670 (1963).

(11) G. L. Closs and L. E. Closs, *Tetrahedron Letters*, **No. 10**, 38 (1960).

(12) For pertinent references, see (a) H. M. Walborsky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 75 (1962); (b) H. M. Walborsky and F. J. Impastato, *J. Am. Chem. Soc.*, **81**, 5835 (1959), ref. 6.

(13) (a) A. A. Morton and F. Fallwell, Jr., *ibid.*, **60**, 1429 (1938); (b) G. Wittig and H. Witt, *Chem. Ber.*, **74B**, 1474 (1941).

Reaction of methylene bromide with methyllithium and styrene gave **3** as the only identifiable cyclopropyl derivative (1.3%). The formation of **3** is analogous to the results obtained by Miller and Kim with cyclohexene.[9a,14]

$$C_6H_5{-}CH{=}CH_2 + CH_2Br + CH_3Li \longrightarrow$$

$$C_6H_5{-}\langle\,\rangle + CH_3Br + C_2H_5Br + CH_3I$$

3

Experimental[15]

Reaction of Styrene with Methylene Chloride and *n*-Butyllithium. Preparation of *trans*-(1) and *cis*-1-Chloro-2-phenylcyclopropane (2).—A solution of *n*-butyllithium was prepared according to the method of Gilman and co-workers[16] from *n*-butyl bromide (68.5 g., 0.50 mole) and lithium (7.7 g., 1.11 g.-atoms) in 325 ml. of dry ether. The butyllithium solution was added under an atmosphere of dry helium over a period of 1.5 hr. to a stirred solution of inhibitor-free styrene (208.2 g., 2.00 moles) and methylene chloride (84.9 g., 1.00 mole) held at 5–10°. After the addition was complete, the mixture was stirred at 10–22° for 2 hr. After washing with water and drying ($CaCl_2$), the solution was distilled to give a fraction, b.p. 5–7°, consisting of *n*-butane (4.6 g.), butene/s (0.04 g.), and pentene/s (0.13 g.) by mass spectral analysis. Continued distillation gave a mixture, b.p. 34–49° (1 atm.–22 mm.), shown by g.c. to be ether, methylene chloride (72% recovery), styrene (94% recovery), and a component which was probably benzoic acid, *ca.* 0.1 g. (see following experiment). A third fraction, b.p. 47–51° (0.7 mm.), 1.84 g., was separated by preparative g.c. ($^3/_{16}$ in. × 20 ft. silicone gum rubber column, 190°, helium flow rate 60 ml./min.). The first component eluted was **1**, b.p. *ca.* 47° (0.7 mm.), $n^{25}D$ 1.5390; λ_{max}^{neat} 3.31 (m), 3.43 (w), 6.27 (m), 6.70 (s), 6.90 (m), 7.30 (w), 7.98 (s), 8.26 (w), 9.10 (w), 9.36 (m), 9.62 (m), 9.71 (m), 9.99 (w), 10.09 (m), 10.62 (m), 10.92 (w), 11.28 (m), 11.58 (w), 13.12 (s), 14.31 (s), and 14.73 (s) μ.

Anal. Calcd. for C_9H_9Cl: C, 70.83; H, 5.94; Cl, 23.23; mol. wt., 152.6. Found: C, 71.60, 71.80; H, 6.16; 6.39; Cl, 22.37, 22.48; mol. wt., 152 (mass spectrometry).[17]

The second compartment eluted was **2**, b.p. *ca.* 51° (0.7 mm.), $n^{25}D$ 1.5506; λ_{max}^{neat} 3.31 (m), 6.28 (m), 6.71 (s), 6.91 (m), 7.39 (w), 7.81 (s), 8.15 (w), 8.61 (w), 9.12 (w), 9.29 (m), 9.62 (m), 9.71 (m), 9.87 (m), 10.79 (m), 10.90 (m), 12.29 (m), 13.03 (s), 13.70 (s), and 14.30 (s) μ.

Anal. Calcd. for C_9H_9Cl: C, 70.83; H, 5.94; Cl, 23.23; mol. wt., 152.6. Found: C, 71.35, 71.43; H, 6.02, 6.09; Cl, 23.17; 23.29; mol. wt., 152 (mass spectrometry).[17]

The distillation residue, 3.8 g., was dissolved in 50 ml. of carbon tetrachloride, and slow addition of 300 ml. of methanol precipitated polystyrene. Filtration and evaporation of the filtrate gave 0.90 g. of dark brown oil which was distilled, b.p. 140–200° (0.2 mm.). Preparative g.c. gave crude separation of one major component from several minor ones. The component separated had an n.m.r. spectrum which showed a multiplet centered at δ −7.1 (1.00) and two partially resolved multiplets centered at −1.2 and −0.9 (1.35).

Reaction of Styrene with Methylene Chloride and Methyllithium. Reaction at 5–10°.—A solution of methyllithium was prepared according to the method of Gilman and co-workers[18] from methyl iodide (71.0 g., 0.50 mole) and lithium (7.7 g., 1.11 g.-atoms) in 325 ml. of dry ether. The methyllithium solution was added dropwise under dry nitrogen over a period of 1 hr. to a stirred solution of styrene (208.2 g., 2.00 moles) and methylene chloride (84.9 g., 1.00 mole) held at 5–10°. After stirring at room temperature for 2 hr., the reaction mixture was poured into 500 ml. of water and shaken, and the organic layer was separated. The aqueous layer was extracted with methylene chloride, and the combined organic solutions were washed with water and dried. After distillation of the ether, methylene chloride, and styrene (88% recovery), a mixture of products, b.p. 70–97° (50 mm.), and 44.6 g. of residue were obtained. The mixture was separated by preparative g.c. into three components. The first component eluted was identified as benzoic acid by mixture melting point and infrared spectroscopy.

The second component eluted was identified as phenylcyclopropane (**3**), $n^{25}D$ 1.5310, lit.[19] b.p. 90–91° (52 mm.), lit.[19c] $n^{25}D$ 1.5309; n.m.r. spectrum (CCl_4): a multiplet centered at δ −7.05 (5.00) for aromatic protons, a multiplet at −1.85 (1.07) for the benzylic proton, and a multiplet at −0.80 (3.95) for the remaining cyclopropyl protons. The n.m.r. spectrum is in fair agreement with that given by Bumgardner.[19] The infrared spectrum was identical with that given by Dale and Swartzentruber.[15b]

Anal. Calcd. for C_9H_{10}: C, 91.47; H, 8.53; mol. wt., 118. Found: C, 91.09, 91.48; H, 8.04, 8.31; mol. wt., 118 (mass spectrometry).

The third component eluted was identified as 1-methyl-2-phenylcyclopropane (**4**), $n^{25}D$ 1.5205, lit.[19g] b.p. 78–79° (20 mm.), lit.[19g] $n^{25}D$ 1.5204; λ_{max}^{neat} 3.29, 3.37, 6.21, 6.68, 6.89, 9.70, 13.11, 13.38, 13.69, and 14.26 μ; n.m.r. spectrum (CCl_4): a singlet at δ −7.12 (5.00) for the aromatic protons, a sextet at −2.05 (0.95) (J = 6.1, 8.5, and 8.5 c.p.s.) for the benzylic proton, and a multiplet at −0.83 (6.38) for the methyl and the remaining cyclopropyl protons.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15; mol. wt., 132. Found: C, 90.83, 90.90; H, 8.90, 9.04; mol. wt., 132 (mass spectrometry).

The isolated **4** was analyzed by g.c. (Apiezon L column) and shown to consist of two components. The larger component made up 98–99% of the material. These may be the *cis* and *trans* isomers.

Reaction at −70 to −65°.—The preceding reaction was repeated using the same amounts of methyllithium and styrene and a larger amount of methylene chloride (425 g., 5.00 moles). The methyllithium was added over a period of 2 hr. at such a rate that the reaction mixture was maintained at −70 to −65°. After the addition was completed, the mixture was allowed to come to room temperature with stirring over a period of 15 hr. Mass spectral analysis of the gaseous products showed the presence of major amounts of methane, ethylene, propylene, propane, and butene/s. Minor amounts of ethane, methyl chloride, pentene/s, and a C_4H_4 component were present also. Work-up of the reaction mixture as before gave styrene (84% recovery), **3** (0.04%), **4** (1.5%), a trace of benzoic acid, and 13.5 g. of distillation residue. Analysis of the residue by n.m.r. spectroscopy indicated it to be mainly polystyrene.

Reaction of Styrene with Methylene Bromide and Methyllithium.—A solution of methyllithium prepared in the usual manner from methyl iodide (71.0 g., 0.50 mole) and lithium (7.7 g., 1.11 g.-atoms) in 325 ml. of ether was added under dry helium over a period of 1.5 hr. to a stirred solution of styrene (208.2 g., 2.00 moles) and methylene bromide (173.9 g., 1.00 mole) held at 5–10°. After completion of the addition, the reaction mixture was stirred at 10–23° for 2 hr. Mass spectral analysis of the gaseous reaction products showed a trace of methane (*ca.* 0.008 g.) and ethylene (*ca.* 0.01 g.). The reaction mixture was washed with water and dried. Distillation gave a mixture, b.p. 32–21° (1 atm.–0.9 mm.). Mass spectral and g.c. analyses showed the following composition: methyl bromide (3.7 g.), ethyl bromide (7.4 g.), methyl iodide (9.8 g.), methylene bromide (62% recovery), styrene (80% recovery), benzoic acid (0.2 g.), and **3** (5.9 g.). No **4** or any higher boiling materials such as 1-bromo-2-phenylcyclopropane could be detected by

(14) See also W. Kirmse and B. G. v. Wedel, *Ann.*, **666**, 1 (1963).

(15) Boiling points were uncorrected. Elemental microanalyses were determined by Mr. L. E. Swim and co-workers. Infrared spectra were obtained by Dr. R. D. Moss and co-workers with a Perkin-Elmer Model 137 Infracord. The n.m.r. spectra were obtained by Dr. J. P. Heeschen and co-workers with a Varian A-60 spectrometer operating at 60 Mc./sec. The chemical shifts are reported as δ in p.p.m. from tetramethylsilane which was used as an internal reference. Relative areas are given in parentheses. Mass spectral gas analyses were determined by Mr. E. O. Camehl, and molecular weight determinations by mass spectroscopy were by Mrs. W. L. Dilling. G.c. analyses were determined with an F & M Model 500 programmed temperature gas chromatograph. Preparative g.c. separations were carried out by Mr. H. W. Moll and co-workers.

(16) R. G. Jones and H. Gilman, "Organic Reactions," Coll. Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 352.

(17) The mass spectra of **1** and **2** were nearly identical. The isotopic abundance ratio at the parent peaks verified the presence of one chlorine atom per molecule. Therefore, the formula of each compound was C_9H_9Cl.

(18) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **55**, 1252 (1933).

(19) C. L. Bumgardner, *ibid.*, **83**, 4420 (1961).

g.c. The distillation residue, 28.6 g., was dissolved in 200 ml. of carbon tetrachloride, and the polystyrene was precipitated by the slow addition of 600 ml. of methanol. Evaporation of the filtrate gave 1.90 g. of dark brown liquid. Distillation of the liquid, b.p. 160–200° (0.1 mm.), and g.c. analysis showed the presence of at least four components. The n.m.r. spectrum of this fraction showed two multiplets centered at δ −1.2 (1.75) and −0.9 (1.00).

Acknowledgment.—The author wishes to thank Dr. J. C. Little and Dr. Y. Chang for many helpful discussions during this work.

Reactions of 1-(Chloromethyl)naphthalenes

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In a previous study of the reactions of methyl substituted 1,4-epoxy-1,4-dihydronaphthalenes,[1] two alkyl substituted 1-(chloromethyl)naphthalenes were obtained readily by reaction of the epoxides with dry hydrogen chloride in methanol. In view of the potential synthetic value of the (chloromethyl)naphthalenes, and also because some of their reactions appeared to be somewhat unusual, it was desired to study their behavior more fully. For this purpose three alkyl-substituted 1-(chloromethyl)naphthalenes were prepared and used, namely, 4-methyl-,[2] 2,3,4-trimethyl-,[1] and 4-methyl-2,3-diethyl-.[1] Some reactions of the second compound were reported previously.[1]

The Wurtz reaction with sodium, in octane as reaction medium, gave the expected products, one of which, 1,2-bis(4-methyl-1-naphthyl)ethane (I), had been described before.[3] *n*-Octane was chosen as solvent since its boiling temperature is high enough to liquify the sodium metal for efficient reaction. Apparently the reaction is not rapid under these conditions, since in some cases unreacted chloro compound was recovered. No attempt was made to improve the yields, but it is likely that a higher-boiling inert liquid should be more effective.

Hydrolysis of the (chloromethyl)naphthalenes failed in all cases to give the corresponding alcohols, but invariably gave the ethers. Although it has been reported[4] that 1-(hydroxymethyl)-4-methylnaphthalene was obtained in this way in very low yield together with much of the ether, we were not able to confirm this. Similarly, 1-(chloromethyl)-2,3,4-trimethylnaphthalene gave only bis(2,3,4-trimethyl-1-naphthyl methyl) ether,[1] and 1-(chloromethyl)-4-methyl-2,3-diethylnaphthalene gave a 78% yield of bis(4-methyl-2,3-diethyl-1-naphthyl methyl) ether (VI).

Displacement of the chlorine by methoxyl was readily accomplished by boiling methanol or sodium methoxide in methanol. It is interesting to note that, whereas 1-(methoxymethyl)-2,3,4-trimethylnaphthalene[1] is a solid, its homolog, 1-(methoxymethyl)-4-methyl-2,3-diethylnaphthalene (III), is a liquid which failed to solidify after cooling several hours at −40°. It is also worth noting that, when the chloromethyl compound is boiled with methanol containing a little aqueous hydrochloric acid, the product is the ether. Thus, 1-(chloromethyl)-4-methyl-2,3-diethylnaphthalene gave a 45% yield of the ether VI.

1-Methoxymethyl)-4-methyl-2,3-diethylnaphthalene (III) was subjected to a Zeisel methoxyl analysis[5] and the residue was worked up to see if it contained some of the alcohol. However, the product proved to be the hydrocarbon, 1,4-dimethyl-2,3-diethylnaphthalene (IV), apparently the result of complete reduction by the hydriodic acid. The identity of this product was confirmed by reducing 1-(chloromethyl)-4-methyl-2,3-diethylnaphthalene with zinc and acid to obtain the same compound (IV).

Several attempts were made to make the Grignard reagent of the (chloromethyl)naphthalenes. Success was achieved only in the case of 1-(chloromethyl)naphthalene, whose Grignard was converted to 1-naphthylacetic acid (VII).[6] It had been reported[7] that this reaction goes to 88–92% completion. In several attempts it was found impossible to obtain any Grignard reaction with the 1-(chloromethyl)naphthalenes substituted by methyl groups in the 4-, or 2-, 3-, and 4-positions, or by methyl in the 4-, and ethyl groups in the 2- and 3-positions. In ether as solvent, catalysts such as iodine, ethylene bromide, and methyl iodide were tried, but no reaction took place even after 2 hr. at reflux temperature followed by 24 hr. at room temperature. In every case the starting material was recovered nearly quantitatively.

Experimental[8]

1,2-Bis(4-methyl-1-naphthyl)ethane (I).—1-(Chloromethyl)-4-methylnaphthalene (0.400 g., m.p. 61–62°) was dissolved in 20 ml. of *n*-octane, sodium (1 g.) was added, and the mixture refluxed for 3 hr. at 110–115°. The warm mixture was filtered then thoroughly cooled at 0–10°, and the crystalline product was filtered and washed with cold hexane. The yield was 0.160 g. (50%), m.p. 154–155°, lit.[3] m.p. 152–153°. The ultraviolet spectrum in cyclohexane, λ_{max} mμ (log ϵ), showed absorption at 213 sh (4.78), 230 (5.03), 269 sh (3.87), 283 (4.11), 292.5 (4.23), 303 (4.13), and 316 (3.34); lit.[3] 228 (5.05), 292 (4.2), and 302 (4.1).

1,2-Bis(2,3,4-trimethyl-1-naphthyl)ethane (II).—1-(Chloromethyl)-2,3,4-trimethylnaphthalene[1] (0.200 g.) was dissolved in 10 ml. of *n*-octane, sodium (0.5 g.) was added, and the mixture refluxed for 4 hr. On cooling the filtered solution, the product did not crystallize. The solvent was removed under vacuum; the residue was taken up in hexane and chromatographed on a column of neutral alumina. The first fraction consisted of some starting material, while the second yielded 0.12 g. (72%) of the product, m.p. 195–200°. Recrystallization from hexane gave m.p. 207.8–209°. The ultraviolet spectrum in cyclohexane, λ_{max} mμ (log ϵ), showed absorption at 219 sh (4.82), 233 sh (5.07), 235 (5.09), 275 sh (3.88), 2.87 (4.07), 298 (4.18), 311 (4.08), and 323 (3.32).

Anal. Calcd. for $C_{28}H_{30}$ (366.5): C, 91.80; H, 8.20. Found: C, 91.67; H, 8.36.

1-(Methoxymethyl)-4-methyl-2,3-diethylnaphthalene (III).—

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(2) G. Darzens and A. Levy, *Compt. rend.*, **202**, 73 (1936).

(3) M. F. Hebbelynck and R. Martin, *Bull. soc. chim. Belges*, **61**, 635 (1952).

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(5) K. G. Stone, "Determination of Organic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 203.

(6) G. Lock, *Österr. Chemiker. Ztg.* **51**, 77 (1950).

(7) O. Grummitt and A. Buck, *J. Am. Chem. Soc.*, **65**, 295 (1943).

(8) Melting points are corrected. The authors are grateful to Dr. G. Slomp and his staff at the Upjohn Co., Kalamazoo, Mich., for determining the ultraviolet spectra which were run on a Cary Model 15 spectrophotometer.

1-(Chloromethyl)-4-methyl-2,3-diethylnaphthalene[1] (0.200 g.) was added to a solution of sodium (0.1 g.) in 10 ml. of absolute methanol. After refluxing for 1 hr., the mixture was filtered, the solvent was removed under vacuum, and the residue was taken up in hexane and chromatographed on neutral alumina to give 0.120 g. (60%) of an oil which did not solidify at −40°. The infrared spectrum showed a strong absorption at 1050–1100 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O$ (242.3): C, 84.29; H, 9.09; OMe, 12.8. Found: C, 84.08; H, 9.13; OMe, 11.5.

In another experiment, 1-(chloromethyl)-4-methyl-2,3-diethylnaphthalene (0.200 g.) was boiled for 5 min. with 3 ml. of methanol, the mixture was poured into water, the oil was extracted with benzene, and the latter was removed to leave the crude oily product. This oil was converted to its picrate which was placed on a column of silica gel. Pouring hexane through the column gave an eluate containing 0.12 g. (60%) of the product, identical with that obtained before.

1,4-Dimethyl-2,3-diethylnaphthalene (IV). Method A.—A 0.100-g. sample of III was boiled for 1 hr. with 58% hydriodic acid in the manner used in the usual Zeisel alkoxyl analysis.[5] After the methyl iodide had been removed and determined quantitatively, the residual solution was poured into water, the oil which separated was extracted with hexane, and the solution was clarified with carbon and then passed through a column of neutral alumina to give 0.040 g., m.p. 53.1–54°, which was not further purified. The infrared spectrum showed no hydroxyl absorption.

Method B.—1-(Chloromethyl)-4-methyl-2,3-diethylnaphthalene (0.200 g.) was dissolved in 10 ml. of glacial acetic acid, 1 ml. of concentrated hydrochloric acid was added, and then 1 g. of zinc dust. After refluxing for 2 hr., the mixture was cooled, poured into water, and the product was extracted with hexane and dried over potassium carbonate. Chromatographic separation on neutral alumina gave a fraction, 0.080 g. (46%), m.p. 56.2–57.1°, identical with that obtained by method A. The ultraviolet spectrum in ethanol, λ_{max} mμ (log ε), showed absorption at 214 (4.44), 234 (4.91), 264 sh (3.26), 274 sh (3.52), 286 (3.70), 295 (3.74), 306 sh (3.59), and 324.5 (2.75).

Anal. Calcd. for $C_{16}H_{20}$ (212.3): C, 90.56; H, 9.44. Found: C, 90.30; H, 9.83.

1,2-Bis(4-methyl-2,3-diethyl-1-naphthyl)ethane (V).—A solution of 1(chloromethyl)-4-methyl-2,3-diethylnaphthalene (0.200 g.) in 10 ml. of *n*-octane was refluxed for 4 hr. with 0.5 g. of sodium. Filtering and cooling thoroughly gave no precipitate. The solvent was removed under vacuum, and the residue was stirred with cold methanol leaving 0.080 g. (50%) of a solid, m.p. 168–170°. Purification of its hexane solution on a column of neutral alumina gave 0.050 g. of product, m.p. 175.8–176.9°. The ultraviolet spectrum in cyclohexane, λ_{max} mμ (log ε), showed absorption at 219 sh (4.76), 233 (5.01), 239 (5.09) 266 sh (3.60), 276 sh (3.82), 289 (4.02), 300 (4.13), 310 (4.03), and 324 (3.37).

Anal. Calcd. for $C_{32}H_{38}$ (422.6): C, 90.99; H, 9.01. Found: C, 90.44; H, 9.69.

Bis(4-methyl-2,3-diethyl-1-naphthyl methyl) Ether (VI).—1-(Chloromethyl)-4-methyl-2,3-diethylnaphthalene (0.200 g.) was dissolved in 5 ml. of methanol, 2 drops of concentrated hydrochloric acid was added, and the solution refluxed 15 min. The solvent was removed under vacuum, the residue was dissolved in the minimum amount of boiling hexane, and the solution was cooled to give 0.070 g. (45%), m.p. 184–185°. Recrystallization from hexane gave m.p. 187–187.5°.

The same product was obtained by refluxing the chloromethyl compound with 30% sodium carbonate or potassium hydroxide solution overnight. In this way the yield was 78% of VI, m.p. 188–188.4°. The ultraviolet spectrum in ethanol, λ_{max} mμ (log ε), showed absorption at 218 sh (4.80), 230 (5.14), 236 (5.19), 263 sh (3.65), 274 sh (3.91), 284 (4.09), 294 (4.18), 305.5 (4.07), 323 (3.17), and 326 sh (3.07).

Anal. Calcd. for $C_{32}H_{38}O$ (438.6): C, 87.67; H, 8.67. Found: C, 87.22; H, 8.88.

1-Naphthylacetic Acid (VII).—Magnesium turnings (1.26 g.) and 10 ml. of dry ether were added to a nitrogen-filled flask, ethylene bromide (5 drops) and 10% of a solution of 1-(chloromethyl)naphthalene (3 g. in 25 ml. of dry ether) were added. After heating to 30° for 1 hr., no apparent reaction had occurred. Addition of a small crystal of iodine started the reaction and the initial yellow-brown color turned greenish yellow. Thereupon, the remaining 90% of the chloromethylnaphthalene solution was added during 90 min. at 25–30°. After standing overnight under nitrogen, dry carbon dioxide was passed through the solution for 15 min., forming a white precipitate. The ether was removed, the residue was dissolved in methanol, and the solution was clarified with carbon and then evaporated to dryness to leave 0.85 g. (27%) of product, m.p. 121–124°. Solution in dilute alkali, filtration of the alkaline solution, and acidification of the filtrate gave a pure product, m.p. 127–127.5°, lit.[6] m.p. 127°.

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The Structure of the Morpholine β-Iodophenylacetylene Complex

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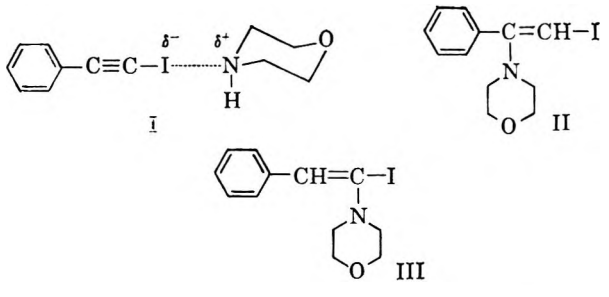
The crystalline compound, $C_{12}H_{14}ONI$, which is formed when morpholine and β-iodophenylacetylene react exothermically has been examined by X-ray crystal structure analysis. The results are in agreement with the charge transfer formula I, which was suggested by Southwick and Kirchner[1] to be the possibility most consistent with the chemical and physical properties of the compound. The alternative possibilities represented by formulas II and III have been shown to be incorrect.



The complex forms clear, colorless, prismatic crystals which deteriorate and become yellow when exposed to X-rays. The crystal data are as follows: monoclinic, space group $P2_1/c$, uniquely determined from the systematic extinctions ($h0l$) absent for $l = 2n + 1$, ($0k0$) absent for $k = 2n + 1$; cell dimensions $a = 8.97 \pm 0.01$ Å., $b = 4.93 \pm 0.01$ Å., $c = 29.48 \pm 0.04$ Å., $\beta = 96.2 \pm 1.0°$, $V = 1295$ Å.^{3}. With four molecules in the unit cell, the calculated density is 1.75 g./cm.^{3}. Due to the instability of the crystals in a wide range of solvents, a reliable measurements of density could not be made.

The structure was determined from the Fourier projection down the short b axis, using the iodine position for the heavy-atom phase determination of the ($h0l$) structure factors. The iodine coordinates were obtained from the b axis Patterson projection. With the observed structure amplitudes and the calculated structure phases from the iodine contribution alone, the Fourier projection shown in Fig. 1 was obtained. All atoms except the hydrogens were clearly resolved. With only the iodine contribution a structure factor agreement index of 0.24 was obtained. Using the

(1) P. L. Southwick and J. R. Kirchner, *J. Org. Chem.*, **27**, 3305 (1962).

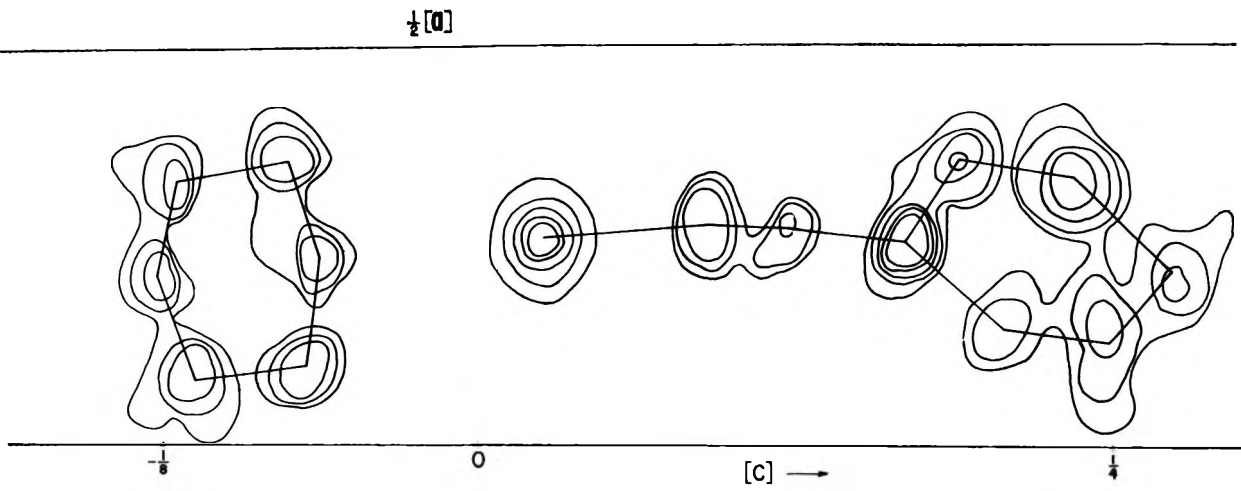


Fig. 1.—Electron density projection of the $C_{12}H_{14}ONI$ complex; contour levels 1/Å.^{2} starting at three, for C, N, O; contour levels 20e/Å.^{2} for I, starting at ten.

atomic coordinates calculated from the Fourier projection, there was one significant phase change and a better agreement factor of $R = 0.18$ was obtained. The slight apparent departure from linearity of the side-chain portion of iodophenylacetylene which is indicated in Fig. 1 may represent experimental error.

Southwick and Kirchner proposed structures I, II, or III for the compound $C_{12}H_{14}ONI$. After considering the results of hydrogenation or reduction with lithium aluminum hydride, and the infrared, ultraviolet, and nuclear magnetic resonance spectra, they concluded that I is most probably the correct structure. However, owing to the instability of the compound, they regarded their structure determination as inconclusive and suggested this X-ray structure determination.

The exclusion of formulas II and III is unambiguous on the basis of the Fourier projection shown in Fig. 1. The only alternatives to formula I which remain would be others of the same geometry as I but having the iodine atom adjacent not to the nitrogen of the morpholine structure, but to a different atom, such as the oxygen.

The existence of other charge transfer complexes in which a basic nitrogen is coordinated with the iodine of an organic iodide[2] suggests that formula I is indeed the correct representation of the substance. Bjornvatten and Hassel[2] found the length of the iodine–nitrogen bond in the quinoline–iodoform complex to be 2.99 Å. The iodine to nitrogen distance in the Fourier *projection*, shown in Fig. 1, is 2.51 Å., which is compatible with an *actual* distance of about 2.9 Å.

An isotropic temperature factor of 2.5 Å.$^{-2}$ was assumed for the iodine and one of 4.0 Å.$^{-2}$ for the light atoms.

Experimental

Owing to the instability of the compound and the frequency of twinning, much difficulty was experienced in obtaining a crystal suitable for X-ray diffraction intensity measurements. A small untwinned crystal, grown by slow evaporation of a normal hexane solution, was sealed in a 0.3-mm. glass capillary. Upon exposure to X-rays for about 80 hr., some decomposition was indicated by a color and shape change of the crystal and by a spread of the diffraction spectra.

The intensity measurements were made visually from CuKα multifilm Weissenberg photographs. For many high angle reflections the CuKα_1 and CuKα_2 spectra were completely resolved. For these reflections the intensity of the CuKα_1 reflection was measured and multipled by a factor of 1.5. For partially resolved reflections a linear interpolation method due to Sakurai[3] was used. After interfilm scaling and averaging of resulting intensity values, the 292 observed ($h0l$) intensities were reduced to structure factor amplitudes by the standard Lorentz and polarization corrections. About 36 reflections were observed to have intensities too small to be measured and these were arbitrarily assigned a value of one-third of the weakest intensity measureable. No absorption corrections were applied to the data. The computations were carried out on an IBM 1620 computer using the programs of Shiono, Hall, and Chu,[4] and of Beurskens.[5]

Acknowledgment.—The author would like to thank Professor P. L. Southwick for suggesting the problem and for providing the crystals; Dr. R. McMullan and Professor G. A. Jeffrey for their valuable help and criticism; and the U. S. Public Health Service for the financial support of this undergraduate summer work.

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(4) R. Shiono, D. Hall, and S. Chu, Technical Report No. 43, The Crystallography Laboratory, The University of Pittsburgh, Pittsburgh, Pa.

(5) P. Beurskens, The Crystallography Laboratory, The University of Pittsburgh, Pittsburgh, Pa., unpublished work.

The Cuprous Chloride-Catalyzed Reaction of Diazomethane with Norbornene Derivatives

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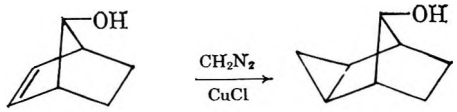
The cuprous ion-catalyzed reaction of diazomethane with olefins recently has been applied in syntheses of cyclopropyl compounds from a number of cyclic hydrocarbons.[1] The intermediate in this catalyzed reaction is also reactive enough to form cyclopropyl derivatives or homologs directly from aromatic compounds.[1,2] We should like to report the stereochemistry of this reaction with regard to formation of cyclopropyl compounds

(1) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963); G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961); J. P. Chesick, *J. Am. Chem. Soc.*, **84**, 3250 (1962).

(2) E. Muller and H. Fricke, *Ann.*, **661**, 38 (1963); E. Muller, H. Kessler, H. Fricke, and H. Suhr, *Tetrahedron Letters*, **No. 16**, 1047 (1963); E. Vogel, W. Wiedemann H. Kiefe, and W. F. Harrison, *ibid.*, **No. 11**, 673 (1963).

from derivatives of norbornene and report the utility of this reaction in a case where the widely used Simmons–Smith synthesis[3] (involving reaction of olefin with methylene iodide–zinc copper couple) has given poor results.

Passage of a stream of nitrogen gas containing diazomethane through a solution of *anti*-7-norbornenol (I) in ether at 0° in the presence of cuprous chloride resulted in formation of *anti*-8-tricyclo[3.2.1.$0^{2,4}$]octanol (II), m.p. 75–76°, in 40% yield after recrystallization. The presence of a cyclopropyl ring in II is indicated by an



I II

infrared absorption band at 1040 cm.$^{-1}$.[4] More specifically, this group was indicated by two complex n.m.r. multiplets centered at τ 9.4 and 10.04 and corresponding to three hydrogens and one hydrogen, respectively.[5]

The formation of *exo* product in the addition of a methylene unit to norbornene by the Simmons–Smith procedure has been inferred[3,6,7] on the basis of preferred direction of approach to norbornene.[8] The *exo* configuration of the cyclopropyl methylene group in II has been established by an X-ray crystallographic analysis[9] on the *p*-bromobenzenesulfonate of II. No *endo* isomer was isolated from the reaction although an unknown substance was present in the crude product to the extent of 9% (gas–liquid phase chromatographic analysis).

The Simmons–Smith reaction intermediate does not react with aromatic systems, and it is stereoselective in its reaction with norbornene.[1,3,6] The formation of predominate *exo* product (II) in the cuprous ion–diazomethane reaction indicates that, although the intermediate is active enough to react with aromatic systems, it still is selective in its approach to the norbornene double bond. Catalyzed reaction of diazomethane with 7-norbornadienyl acetate resulted in a methylene addition product which is a mixture of isomers as indicated by distinct sets of n.m.r. absorption for different olefinic and acetate hydrogens. Like copper-catalyzed reactions of other diazo compounds, the intermediate from cuprous ion and diazomethane appears to be discriminate in its direction of approach to olefins, but it has low discriminating ability between two olefinic bonds.[10]

All of our earlier attempts to prepare II by the Simmons–Smith procedure failed; however, it recently has been obtained by this method in quantities too small to be fully characterized.[7] Although the Simmons–Smith reaction is subject to directive[11] and accelerative[12] influences of hydroxyl groups close to the double bond of olefinic alcohols, the configuration of alcohol I is *anti* and the hydroxyl group is prevented sterically from lending aid to the formation of a cyclopropyl ring. Instead, the iodomethylzinc iodide apparently is destroyed by the alcohol in a side reaction.[11] In contrast, the cuprous chloride-catalyzed reaction of diazomethane I readily occurs.

The possibility of "forcing" this catalyzed reaction to completion by continued addition of diazomethane, while monitoring the result by gas–liquid phase chromatography of samples taken during the reaction, leads to easy isolation of relatively pure product. This feature of the reaction and its simplicity suggests that it may be generally useful, especially in cases where the Simmons–Smith reaction fails or occurs only in low yields.

The solvolytic reactivity of the *p*-bromobenzenesulfonate ester of alcohol II is being studied as a measure of participation of the cyclopropyl group in carbonium ion formation at the 7-position of the bicyclo[2.2.1]-heptane ring structure.

Experimental

General Procedure.[13]—The diazomethane generator[14] consisted of a 250-ml. three-necked flask, in an ice bath, containing 45 ml. of a magnetically stirred 50% potassium hydroxide solution. Diethyl ether (100 ml.) formed an upper layer in the flask. Addition of N-methyl-N-nitrosurea, in approximately 1-g. lots, generated diazomethane which dissolved in the ether layer. This addition was carried out over several hours during the reaction so that at no time was there a very high concentration of diazomethane in the ether; the yellow color of the solution acted as a guide to concentration. A continuous stream of nitrogen was bubbled through the ether layer. This carried the diazomethane through a drying tube (KOH pellets) and through an inlet tube to the bottom of a solution of olefin in ethyl ether. This solution, containing *ca.* 0.3 g. of suspended cuprous chloride (B.D.H.,[15] A.R. grade) was in a 50-ml. flask fitted with a magnetic stirrer and a water condenser. This reaction flask was cooled also in an ice bath. No attempt was made to retain high concentrations of diazomethane in the reaction flask by condensing the leaving vapors at Dry Ice temperature. Although this is wasteful of diazomethane, the danger of explosions is, in our experience, eliminated. Ether was replenished in the generator flask and in the reaction flask as it was swept out by the nitrogen stream. The progress of the reaction was monitored by gas–liquid chromatography of the ether solution and the generation of diazomethane continued until the olefin was consumed. Initial experiments with norbornene as substrate yielded the known[3] tricyclo[3.2.1.$0^{2,4}$]octane, however 2-norbornanol was formed in one run where water was present in the reaction flask.

Preparation of *anti*-8-Tricyclo[3.2.1.$0^{2,4}$]octanol (II).—Diazomethane generated from 8.87 g. of N-methyl-N-nitrosurea reacted with 3.3 g. of *anti*-7-norbornenol[15b] in 40 ml. of ether containing 0.3 g. of cuprous chloride. After 6 hr., the olefin was completely consumed and two major products (ratio of 10:1) were indicated by g.l.p.c. After filtration to remove cuprous chloride and evaporation of the ether, crystallization from petroleum ether (b.p. 65–110°) yielded 1.49 g. (40% based on olefin, 14% based on diazomethane generated) of alcohol II, m.p. 75–76°. More product II was contained in the mother liquor and could be obtained pure by g.l.p.c. on an Apiazon J column at 140°.

(3) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959); *Org. Syn.*, **41**, 72 (1961).

(4) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co., London, 1958, p. 29.

(5) R. S. Boikess and S. Winstein, *J. Am. Chem. Soc.*, **85**, 344 (1963); V. Georgian, J. F. Kerwin, M. E. Wolff, and F. F. Owings, *ibid.*, **84**, 3594 (1962).

(6) K. B. Wiberg and W. J. Bartley, *ibid.*, **82**, 6375 (1960).

(7) A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *ibid.*, **84**, 4865 (1962).

(8) For *exo* addition of dihalocarbenes to norbornene, see W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963); R. C. De Selms and C. H. Combs, *ibid.*, **28**, 2206 (1963); E. Bergman, *ibid.*, **28**, 2210 (1963).

(9) Private communication from J. Trotter and A. Macdonald, University of British Columbia.

(10) P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, 443 (1961); see also K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *J. Am. Chem. Soc.*, **84**, 1015 (1962).

(11) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).

(12) S. Winstein and J. Sonnenberg, *ibid.*, **83**, 3235 (1963).

(13) See ref. 1 for similar procedures.

(14) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. 1943, p. 165.

(15) (a) British drug houses; (b) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.25; H, 9.71.

The n.m.r. spectrum[16] of this compound in CCl_4 showed absorption at τ 6.47, 7.13, and 7.97 in ratios 1:1:2, corresponding to bridge hydrogen, hydroxyl hydrogen, and two bridgehead hydrogens. In addition, there were four complex bands centered at *ca.* τ 8.3 and 8.7 (total of four hydrogens), *ca.* 9.3 (three hydrogens), and 10.04 (one hydrogen). These correspond, respectively, to the four *exo/endo* hydrogens, three hydrogens of the cyclopropyl ring, and a fourth cyclopropyl hydrogen at highest field.[6]

The *p*-bromobenzenesulfonate ester of II, recrystallized from petroleum ether, melted at 83–83.5°.

Anal. Calcd. for $C_{14}H_{15}BrO_3S$: C, 48.98; H, 4.40. Found: C, 49.17; H, 4.50.

Reaction of CH_2N_2–CuCl with 7-Norbornadienyl Acetate.[15]—Reaction of diazomethane generated from 23.3 g. of N-methyl-N-nitrosurea with 9.0 g. of 7-norbornadienyl acetate over 8 hr. gave a product, separated by g.l.p.c. on a 5-ft. Ucon polar column at 110°, with analysis agreeing with addition of one methylene unit to the diolefin.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.40; H, 7.25.

The n.m.r. spectrum of this sample showed it to be *ca.* a 3:1 mixture of two compounds arising from addition to either of the double bonds of the diolefin. That is, there were triplets at τ 3.65 and 4.32 (area ratio 3:1) for olefinic hydrogens, singlets at 5.55 and 6.02 (ratio 1:3) for bridge hydrogens, multiplets centered at 7.10 and 7.65 (ratio *ca.* 3:1), peaks at 8.08 and 8.12 (ratio *ca.* 1:3) for acetate hydrogens, and a broad multiplex at *ca.* 9.0 for cyclopropyl hydrogens.

Acknowledgment.—We thank the National Research Council for support of this work and the Department of Scientific and Industrial Research, U. K., for a N.A.T.O. studentship for J. I. Wells.

(16) N.m.r. spectra were determined on a Varian A-60 spectrometer.

Trisarylmethanes. Synthesis of Diarylcarbinol Precursors by Controlled Catalytic Hydrogenation

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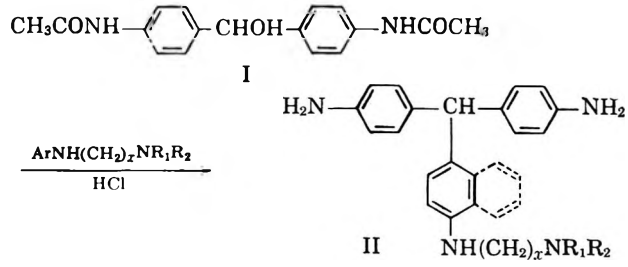
Previous studies in these laboratories[1] have demonstrated that pararosaniline pamoate and certain closely related compounds are effective in experimental schistosomiasis and paragonimiasis. Simple trisarylmethanes also have been reported to be effective against intestinal helminths, filariae, trichomonads, and trypanosomes.[2] It was, therefore, of interest to prepare various trisarylmethanes, including basically substituted compounds of structure II, for biological evaluation and for use as synthetic intermediates. The present communication describes a novel method for the preparation of selected diarylcarbinols, namely the controlled catalytic hydrogenation of the corresponding diaryl ketones, and their conversion to various trisarylmethanes.

The most attractive route to trisarylmethanes of structure II appeared to be condensation[3] of the corresponding aromatic amine[4,5] with 4,4′-diaminobenzhydrol. Wichelhaus[6] describes the conversion of 4,4′-diaminobenzophenone to the benzhydrol with sodium amalgam. This technique, however, is unattractive for large scale work. The erratic nature of this benzophenone–benzhydrol conversion with other reagents is evident from the literature. Treatment of 4,4′-diaminobenzophenone with tin and hydrochloric acid[7] or of 4-butyroylamino-4′-nitrobenzophenone with palladium and hydrogen[8] leaves the ketone function intact. Reduction of 4,4′-diaminobenzophenone with excess lithium aluminum hydride gives the hydrogenolysis product, 4,4′-methylenedianiline.[9] Numerous attempts in these laboratories to effect the reduction to the benzhydrol utilizing a variety of standard chemical and catalytic methods failed.

Efforts to convert 4′,4‴-carbonylbisacetanilide[10] to 4′,4‴-(hydroxymethylene)bisacetanilide (I) were more successful. Chemical reduction gave positive



but still unsatisfactory results, whereas catalytic hydrogenation under standard conditions gave primarily the hydrogenolysis product, 4′,4‴-methylenebisacetanilide. Fortunately, application of Kindler's procedure,[11] involving the use of a palladium catalyst, poisoned with nicotinamide or N,N-diethylnicotinamide, afforded I in 63% yield. Although the carbinol exhibited a variable melting point which was an unsatisfactory criterion of purity, the ultraviolet spectrum[12] (λ 254 mμ, E_1^1 1120, no absorption over 300 mμ) afforded an excellent method for detecting residual ketone (λ 231 mμ, E_1^1 614; λ 306 mμ, E_1^1 1060) during purification. The controlled catalytic hydrogenation technique also was used successfully for the preparation of 4′,4‴-(hydroxymethylene)bistrifluoroacetanilide (61%), 4-methylbenzhydrol[13] (80%), 4-chlorobenzhydrol[14] (35%), and 4-aminobenzhydrol[9] (59%), but failed with 4-bromobenzophenone, 4-hydroxybenzophenone, 4-(dimethylamino)benzophenone, 4-hydroxybenzophenone acetate ester, 2-benzoylbenzoic acid, and 4,4′-bis(dimethylamino)benzophenone. The moderate success achieved with 4-chlorobenzophenone is noteworthy in view of the known susceptibility of

(1) E. F. Elslager, F. W. Short, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *Nature*, **190**, 628 (1961).

(2) For a brief review, see R. J. Schnitzer and F. Hawking, "Experimental Chemotherapy," Vol. I, Academic Press, New York, N. Y., 1963, pp. 200, 296, 789, 809, 906.

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(12) Ultraviolet spectra were obtained in ethanol on a Cary 11 recording spectrophotometer.

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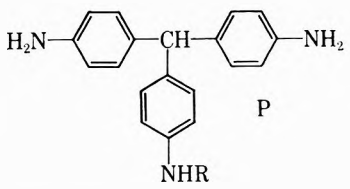
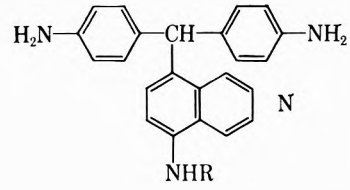
(14) A. E. Chichibabin and A. A. Shesler, *J. Russ. Phys. Chem. Soc.*, **56**, 149 (1925); *Chem. Abstr.*, **19**, 3269 (1925).

TABLE I
TRISARYLMETHANES





Compd. no.	Structural type	R	M.p., °C.	Yield purified, %	Purification solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	P	H	245 dec.	32	A	$C_{19}H_{19}N_3 \cdot 3HCl$[b,c]	57.22	57.22	5.56	5.64	10.54	10.64
2	P	C_2H_5	233 dec.	30	A	$C_{21}H_{23}N_3 \cdot 3HCl \cdot 3H_2O$[d]	52.45	52.32	6.71	6.64	8.74	9.12
3	N	H	273–277	40	B	$C_{23}H_{21}N_3$	81.38	81.20	6.24	6.34	12.38	12.52
4	P	$(CH_2)_2N(C_2H_5)_2$	200 dec.	49	C	$C_{28}H_{32}N_4 \cdot 4HCl \cdot 0.75H_2O$[e]	54.80	55.05	6.90	7.18	10.23	10.16
5	P	$(CH_2)_3N(CH_2)_5$	219–229 dec.	55	D	$C_{27}H_{34}N_4 \cdot 4HCl \cdot 2H_2O$[f]	54.36	54.55	7.10	7.17	9.39	9.45
6	N	$(CH_2)_2N(C_2H_5)_2$	177–179	45	E	$C_{29}H_{34}N_4$	79.41	79.14	7.81	7.90	12.78	12.75

[a] A, dilute hydrochloric acid; B, not recrystallized; C, ethanol–methanol (9:1); D, crude product extracted with warm methanol; E, methanol. [b] E. Fischer and O. Fischer, *Ann.*, **194**, 272 (1878). [c] Contains 7.15% water by Karl Fischer water determination (analytical values reported are corrected for water). Cl: calcd., 26.67; found, 26.63. [d] Water: calcd., 11.24; found, 10.40. Cl: calcd., 22.11; found, 22.32. [e] Water: calcd., 2.47; found, 2.62. [f] Water: calcd., 6.04; found, 5.50. Cl: calcd., 23.78; found, 23.51.

aromatic halogen to hydrogenolysis in the presence of palladium.

The trisarylmethanes II (Table I) were obtained readily by refluxing an ethanol solution of the diarylcarbinol and the aromatic amine in the presence of concentrated hydrochloric acid. Primary or secondary naphthylamines and anilines gave comparable yields.

Experimental[15]

4',4'''-(Hydroxymethylene)bisacetanilide (I).—A solution of 200 g. (0.675 mole) of 4',4'''-carbonylbisacetanilide[10] in 1.5 l. of methanol was hydrogenated over 4.0 g. of 20% palladium-on-charcoal catalyst[16] poisoned with 0.01 g. of nicotinamide at 26° and an initial hydrogen pressure of 50 p.s.i.g. After 1 equivalent of hydrogen had been absorbed, the catalyst was collected by filtration, and the filtrate was evaporated to dryness *in vacuo*. Ultraviolet assay of the crude product (207 g.) indicated the presence of approximately 10% of the starting ketone. The crude hydrol was divided into two equal portions and each was crystallized from 2 l. of acetonitrile yielding a total first crop of 107 g. An additional 20 g. of product separated after the filtrates were allowed to stand at room temperature for 24 hr. The ratio of solvent to crude product (20 ml./g.) is crucial in the purification since the use of a lower ratio leads to coprecipitation of the starting material. The hot crystallization mixture should be allowed to cool slowly to room temperature and filtered promptly; it should not be refrigerated. The total yield of purified material was 63%; it melted at 174.5–176.5°, resolidified at 195°, and remelted at 258–266°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.46; H, 6.07; N, 9.44.

4',4'''-Carbonylbistrifluoroacetanilide.—To a solution of 226 g. (1.06 moles) of 4,4'-diaminobenzophenone in 800 ml. of dimethylformamide was added gradually a solution of 550 g. (2.62 moles) of trifluoroacetic anhydride in an equal amount of dimethylformamide. The mixture cautiously was heated to its boiling point and then boiled under reflux for 3 hr., cooled, and poured into iced water. The suspension was neutralized with ammonium hydroxide and filtered. Recrystallization of the crude product from 95% ethanol gave 315 g. (73%) of product, m.p. 235–236°.

Anal. Calcd. for $C_{17}H_{10}F_6N_2O_3$: C, 50.50; H, 2.49; N, 6.93. Found: C, 50.79; H, 2.70; N, 7.67.

4',4'''-(Hydroxymethylene)bistrifluoroacetanilide.—A mixture of 19 g. (0.047 mole) of 4',4'''-carbonylbistrifluoroacetanilide, 300 ml. of ethanol, and 2 drops of N,N-diethylnicotinamide was hydrogenated as described previously over 1.0 g. of 20% palladium on charcoal. The crude product recrystallized from dilute ethanol gave 12 g. (61%) of purified material, m.p. 213–214°.

Anal. Calcd. for $C_{17}H_{12}F_6N_2O_3$: C, 50.25; H, 2.98; N, 6.89. Found: C, 49.95; H, 3.18; N, 7.17.

4,4',4''-Methylidynetrianiline (Compound 1, Table I).—A solution of 60 g. (0.2 mole) of 4',4'''-(hydroxymethylene)bisacetanilide, 18.6 g. (0.2 mole) of aniline, and 20 ml. of concentrated hydrochloric acid in 600 ml. of 95% ethanol was heated under reflux for 4 hr. Concentrated hydrochloric acid (250 ml.) was added, and the mixture was heated under reflux for an additional 6 hr. Upon cooling, a yellow solid was deposited (32.6 g.). It was purified by dissolving in water, adding concentrated hydrochloric acid until a solid formed, warming to effect solution, and cooling to give 24.4 g. (32%) of the hydrated trihydrochloride salt. Conversion to the free base was effected by addition of ammonium hydroxide to an aqueous solution of the salt. Recrystallization of the base (ethanol) gave 4,4',4''-methylidynetrianiline, m.p. 207–210°.

The other trisarylmethanes (Table I) were prepared similarly. Because they did not precipitate directly from the reaction mixture, the solvent was removed *in vacuo*; compounds 2 and 5 were triturated with 2-propanol and crystallized as indicated, while compounds 3, 4, and 6 were dissolved in water, converted to the bases, and processed.

4-Methylbenzhydrol.—A solution of 19.6 g. (0.1 mole) of 4-methylbenzophenone in 150 ml. of methanol was hydrogenated over 0.5 g. 20% palladium on charcoal poisoned with 0.1 g. of nicotinamide. The mixture was filtered from the catalyst, concentrated to dryness, and recrystallized from petroleum ether (b.p. 30–60°) to give 15.7 g. (80%) of product, m.p. 53–55°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.74; H, 7.38.

When only 0.01 g. of nicotinamide was used, the hydrogenation proceeded rapidly to the diphenylmethane.

Acknowledgment.—The authors wish to express their appreciation to Mr. Charles E. Childs and associates for the microanalytical data, and to Dr. John M. Vandenbelt and associates for the spectral data.

(15) Melting points (corrected) were taken on a Thomas Hoover capillary melting point apparatus.

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General Base Catalysis for Imidazole-Catalyzed Hydration of *sym*-Dichloroacetone[1]

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Evidence implicating the imidazole side chain of a histidine residue as a constituent of the active site of several enzymes including trypsin, chymotrypsin, and

ribonuclease,[2] has focused considerable attention on the mechanism of catalysis of nonenzymatic reactions by imidazole. Imidazole is known to function, in a variety of reactions, as both a nucleophilic and general base catalyst.[2,3] This molecule possesses several structural features which make it a particularly suitable catalyst.[3b] In particular, imidazole is unusual in that the attack of one nitrogen atom may be aided by proton removal from the other nitrogen atom by a second base molecule.[2c,3b] Bruice and co-workers have demonstrated catalysis of *p*-nitrophenyl acetate hydrolysis by the anion of imidazole substituted with electron-withdrawing groups,[4] but have suggested that the corresponding reaction path is probably not important for imidazole itself owing to the weakly acidic character of this molecule.[5] However, Kirsch and Jencks have demonstrated hydroxide ion catalysis for the imidazole-catalyzed hydrolysis of several esters.[6] In addition, Jencks and co-workers have established general base catalysis, by a second imidazole molecule, for the imidazole-catalyzed hydrolysis of phenyl benzoates and certain phenyl acetates.[6,7] In these reactions, imidazole functions as a nucleophilic catalyst involving the intermediate formation of acyl imidazoles. Evidence presented below strongly suggests that catalysis by imidazole, acting as a general base, rather than nucleophilic, catalyst, is also subject to catalysis by a second imidazole molecule.

In Fig. 1, first-order rate constants for the hydration of *sym*-dichloroacetone[8] at 25° are shown as a function of the concentration of imidazole and N-methylimidazole in 95% dioxane–5% water and 95% dioxane–5% deuterium oxide. In the case of the imidazole-catalyzed reactions, the rate constants increase more rapidly than the concentration of catalyst. Plots (not shown) of k_{obs}/[Im] against [Im] yield good straight lines for the data in both water and deuterium oxide, strongly suggesting the presence of a term in the rate law for this reaction proportional to the first power of imidazole concentration (intercept) and a term proportional to the second power of imidazole concentration (slope). From these plots came the following rate laws.

$$k_{obs}^{H_2O}\,(\text{min.}^{-1}) = 2.36[\text{Im}] + 3.55[\text{Im}]^2 \quad (1)$$

$$k_{obs}^{D_2O}\,(\text{min.}^{-1}) = 0.84[\text{Im}] + 1.40[\text{Im}]^2 \quad (2)$$

Curves for imidazole catalysis shown in Fig. 1 are calculated lines based on these rate expressions. In contrast, the rate law for catalysis of *sym*-dichloroacetone hydration by N-methylimidazole, a molecule of basicity similar to that of imidazole, but for which a general base-catalyzed reaction is excluded, shows only a first-order term in catalyst concentration.

$$k_{obs}^{H_2O}\,(\text{min.}^{-1}) = 1.54[\text{Im}] \text{ and } k_{obs}^{D_2O}\,(\text{min.}^{-1}) = 0.45[\text{Im}]$$

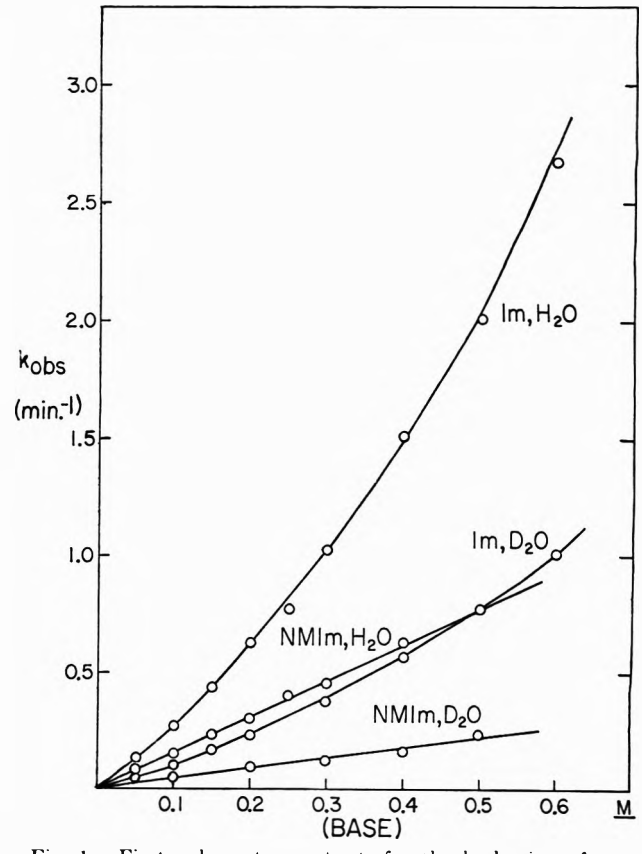
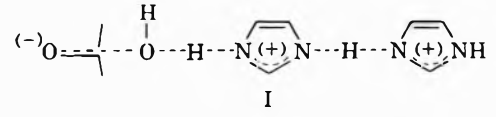


Fig. 1.—First-order rate constants for the hydration of *sym*-dichloroacetone in 95% dioxane–5% water and 95% dioxane–5% deuterium oxide as a function of the concentration of imidazole and N-methylimidazole at 25°. Points are experimental; lines are calculated (see text). Reactions followed spectrophotometrically at 290 mμ; 0.03 *M* *sym*-dichloroacetone.

The term in the rate law for the hydration of *sym*-dichloroacetone which is second order in imidazole concentration may be most simply accounted for in terms of either general base catalysis for general base catalysis of *sym*-dichloroacetone hydration (I) or general base catalysis of water attack on a pre-equilibrium tetrahedral intermediate formed from the imidazole anion



I

and substrate.[9] The second alternative seems unreasonable on chemical grounds since the intermediate should be less reactive than the starting material.[3b] Furthermore, there is no change in the absorption spectrum of *sym*-dichloroacetone on the addition of 1 *M* imidazole to this substrate indicating that, under these conditions, detectable amounts of this intermediate are not formed. In addition, the rate laws for catalysis of this reaction by several other secondary and tertiary amines exhibit only first-order terms in catalyst concentration.[8] The decreased rates of catalysis in deuterium oxide compared to water, $k_H/k_D = 2.8$ for the first-order term and 2.5 for the second-order term, are consistent with transition state I, although it might have been expected that the solvent deuterium isotope effect for the latter term would have been the larger of the two. The solvent deuterium isotope effect for the second-order

(1) Supported by a grant (GB-431) from the National Science Foundation. Contribution No. 1176 from Department of Chemistry, Indiana University.

(2) (a) F. H. Westheimer, *Adv. Enzymology*, **24**, 441 (1962); (b) D. E. Koshland, Jr., *ibid.*, **22**, 45 (1960); (c) E. A. Barnard and W. D. Stein, *ibid.*, **20**, 51 (1958); (d) M. Bender, *Chem. Rev.*, **60**, 53 (1960).

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term may be accounted for in terms of transition state I provided one assumes either that, in the transition state, the proton transferred between the imidazole molecules is quite asymmetrically placed[10] or that the position of the proton transferred from water to imidazole in the transition state is altered by the presence of the second imidazole molecule. The strongest evidence in favor of transition state I is the failure to observe a second-order term in the rate law for catalysis by N-methylimidazole. N-Methylimidazole is similar to imidazole in terms of structure and base strength but cannot lose a proton from one nitrogen atom concurrent with the attack of the other. Although other kinetically indistinguishable mechanisms for the reaction involving two imidazole molecules cannot be rigorously excluded, the present evidence strongly suggests that transition state I is correct for this reaction. The imidazole-catalyzed hydration of *sym*-dichloroacetone appears to be the only known case of general base catalysis for general base catalysis.

The fact that reported kinetic runs were carried out in unbuffered solutions raises the possibility of a contribution to the observed rates from a reaction involving hydroxide ion or the imidazole anion, particularly at high imidazole concentrations. The imidazole catalysis data cannot be explained on the basis of concurrent reactions of imidazole and hydroxide ion since no hydroxide ion reaction was observed in the presence of N-methylimidazole, an equally strong base. General base catalysis of imidazole catalysis by either hydroxide ion or the imidazole anion cannot be rigorously excluded although such reactions, in the absence of detectable direct attack of hydroxide ion on the substrate, seem quite unlikely. Furthermore, such reactions should not depend on the square of the imidazole concentration since the concentration of hydroxide ion or the imidazole anion depends, approximately, on the square root of imidazole concentration. Thus the rate law would have contained terms proportional to the first and to the three-halves powers of imidazole concentration. At any event, such reactions would be mechanistically similar to that proposed in I. A second-order term in imidazole concentration is observed in buffered reaction mixtures containing 90% of the imidazole as the free base and 10% as the hydrochloride. This second-order term may, of course, be due to a reaction involving an imidazole–imidazolium ion or its kinetic equivalent. Many such reactions have been observed for the hydration of *sym*-dichloroacetone catalyzed by a variety of acid–base pairs.

Imidazole, in contrast to N-substituted imidazoles, is known to be associated, presumably through hydrogen-bonded structures, in nonpolar media such as benzene, naphthalene, and carbon tetrachloride.[11] This observation raises a question as to the extent of imidazole self-association in 95% aqueous dioxane. Although experimental data concerning this point are not available, the observed rate laws suggest that imidazole is probably not largely associated in this solvent, since, if dimer formation were to approach completion, one would obtain only first-order rate dependence on imidazole concentration. Regardless of the extent of imidazole association, the observation that the first-order rate constants increase more rapidly than imidazole concentration indicates that the imidazole dimer is a more effective catalyst than the monomeric species for this reaction.

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Experimental

Materials.—Imidazole was recrystallized twice from benzene, and N-methylimidazole and *sym*-dichloroacetone were redistilled before use. Dioxane was purified according to the method given by Wiberg.[12] Distilled water was employed throughout. "95% aqueous dioxane solutions" were prepared by diluting 5 volumes of water to 100 volumes with dioxane.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell compartment as previously described.[13] All reactions were carried out at 25°. Rate laws for reactions exhibiting both first- and second-order terms in catalyst concentration were derived from plots of k_{obs}/[catalyst] against [catalyst]. The rate coefficient for the first-order term was evaluated from the intercept of such plots at zero catalyst concentration, and the second-order rate coefficients were evaluated from the slopes of these plots.

Acknowledgment.—We are indebted to Dr. William P. Jencks, Brandeis University, for communicating his findings concerning base catalysis for imidazole-catalyzed reactions prior to publication.

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The Mechanism of Acid-Catalyzed Methyl Orthobenzoate Hydrolysis[1,2]

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Results of determinations of entropies of activation, volumes of activation, Bunnett's w values, and correlation of hydrolysis rates with the Hammett H_0 acidity function, strongly suggest that the acid-catalyzed hydrolysis of formals,[3-6] acetals,[3-7] ketals,[4] and ethyl orthoformate[4,5] does not involve solvent as a nucleophilic reagent in the transition state (A-1). In contrast, Kwart and Price have suggested, principally on the basis of correlation of the rate of hydrolysis of methyl ortho-*p*-nitrobenzoate with a solvent composition–acidity function,[8] that the acid-catalyzed hydrolysis of methyl orthobenzoates, a reaction related to those indicated above, does involve solvent as a nucelophilic reagent in the transition state (A-2).[9] More re-

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(2) Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963. Abstracts, p. 18Q.

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(6) M. Kreevoy and R. Taft, Jr., *ibid.*, **77**, 3146 (1955).

(7) D. McIntyre and F. A. Long, *ibid.*, **76**, 3240 (1954).

(8) (a) H. Kwart and L. B. Weisfeld, *ibid.*, **80**, 4670 (1958); (b) H. Kwart and A. Goodman, *ibid.*, **82**, 1947 (1960).

(9) H. Kwart and M. Price, *ibid.*, **82**, 5123 (1960).

cently, DeWolfe and Jensen have pointed out that the observations of Kwart and Price may be interpreted in a fashion consistent with an A-1 mechanism for this reaction and, on the basis of the magnitude of the entropy of activation and deuterium solvent isotope effect, have suggested that the correct mechanism is, in fact, A-1.[10] We have further investigated the mechanism of the acid-catalyzed hydrolysis of methyl orthobenzoate employing a technique closely related to the rate–product criterion originally used by Ingold and coworkers for the identification of unimolecular solvolysis reactions.[11] Results of this investigation strongly support the conclusion of DeWolfe and Jensen that this reaction proceeds by an A-1 mechanism.

In Table I, first-order rate constants for the decomposition of methyl orthobenzoate at pH 5.45 in aqueous solutions of hydroxylamine are listed. The first-order rate constants are independent of the total hydroxylamine concentration over the concentration range 0 to 0.9 M. Over this concentration range, the fraction of methyl orthobenzoate yielding the hydrolysis product, methyl benzoate, decreases from 1.0 to 0.15 (Table I). Thus, at the highest concentration of hydroxylamine employed, approximately 85% of the orthobenzoate yields a hydroxylamine addition product, probably N-hydroxymethyl benzimidate.[12] Methyl benzoate does not react with hydroxylamine at a detectable rate under these experimental conditions. The fraction of methyl orthobenzoate yielding methyl benzoate as product may be accurately calculated assuming that the ortho ester, as the conjugate acid, undergoes a rate-determining unimolecular decomposition yielding an intermediate carboxonium ion which is then rapidly partitioned between water, yielding methyl benzoate, and hydroxylamine, yielding a hydroxylamine addition product. The calculated fractions of ortho ester yielding methyl benzoate (Table I) were obtained by assuming that the free base of hydroxylamine is 2000-fold more reactive than water toward the carboxonium ion. Quite similar results also were obtained at pH 4.25 employing semicarbazide as the nucleophilic reagent (Table I). The first-order rate constants for methyl orthobenzoate disappearance are independent of semicarbazide concentration up to at least 1.2 M, and the observed product composition may be quantitatively accounted for by assuming that the free base of semicarbazide is 275-fold more reactive than water toward the carboxonium ion. Employing the reasonable assumption that the amine addition products do not arise from an S$_N$2 attack of amine on a tetrahedral intermediate formed from the attack of water on the ortho ester, these results strongly suggest that solvent does not participate as a nucleophilic reagent in the rate-determining step of acid-catalyzed methyl orthobenzoate hydrolysis.

Table I

First-Order Rate Constants and Product Composition for the Acid-Catalyzed Decomposition of Methyl Orthobenzoate in Aqueous Solutions of Hydroxylamine and Semicarbazide at 25°

[Hydroxylamine]$_{total}$, M	[Semicarbazide]$_{total}$, M	pH	k_{obs}, sec.$^{-1}$	f_{obs}[a]	f_{calcd}[b]
0.00		5.45	0.00035	1.00	1.00
.10			.00030	0.57	0.58
.20			.00033	.41	.41
.30			.00033	.31	.31
.40			.00032	.26	.25
.50			.00038	.21	.20
.60			.00028	.18	.18
.70			.00028	.16	.16
.90			.00038	.15	.13
	0.00	4.25	.0058	1.00	1.00
	.16		.0071	0.55	0.61
	.40		.0053	.38	.38
	.80		.0053	.26	.24
	1.20		.0052	.18	.17

[a] Fraction of methyl orthobenzoate yielding methyl benzoate as product. [b] Calculated fraction of methyl orthobenzoate yielding methyl benzoate as product assuming that the free base of hydroxylamine is 2000-fold more reactive and that the free base of semicarbazide is 275-fold more reactive than water toward a unimolecular decomposition product of methyl orthobenzoate (see text).

The above conclusion is supported by the finding of a positive entropy of activation for this reaction. First-order rate constants for the hydrolysis of methyl orthobenzoate at several temperatures and pH 4.65 and 4.97 are listed in Table II together with the calculated activation energies. From this data the entropy of activation at 25° has been calculated as +8.2 e.u. at pH 4.97 and +8.6 e.u. at pH 4.65.[13] These values are somewhat more positive than those obtained by DeWolfe and Jensen[10] for the hydrolysis of ethyl orthobenzoate,

Table II

Rate Constants and Activation Parameters for the Hydrolysis of Methyl Orthobenzoate at pH 4.65 and 4.97 at Several Temperatures

pH	Temperature, °K.	k_{obs}, sec.$^{-1}$	E_a, cal./mole	ΔS^*, e.u.
4.97	297.7	0.00096	17,800	8.2
	300.6	.00138		
	303.5	.00149		
	306.4	.00248		
	309.7	.00308		
	312.2	.00400		
4.65	297.6	.00197	17,600	8.6
	300.8	.00277		
	303.8	.00354		
	306.8	.00510		
	310.6	.00630		

but both sets of data fall within the range for acid-catalyzed reactions thought to occur without the participation of solvent as nucleophilic reagent.[5]

The first-order rate constants for the hydrolysis of methyl orthobenzoate in water and deuterium oxide were found to increase linearly with the hydrogen ion concentration over the pH range 3.60 to 4.97 and over the pD range 4.47 to 5.54. From the slopes of plots of the first-order rate constants against hydrogen ion concentration, the second-order rate constant for this reaction was calculated as 113 mole^{-1} sec.$^{-1}$ in water and 250 mole^{-1} sec.$^{-1}$ in deuterium oxide. The solvent

(10) R. H. DeWolfe and J. L. Jensen, *J. Am. Chem. Soc.*, **85**, 3264 (1963).

(11) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1962, and references therein.

(12) For a discussion of the reaction of amines with ortho esters, see E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.*, **28**, 1108 (1963), and references therein.

(13) Owing to an error in calculation, the value of the entropy of activation given in ref. 2 is incorrect.

deuterium isotope effect, k_{H2O}/k_{D2O}, is, therefore, 0.45, a value similar to those found for related reactions[14] and nearly identical with the value found by DeWolfe and Jensen for the hydrolysis of ethyl orthobenzoate.[10] This solvent deuterium isotope effect is consistent with either pre-equilibrium substrate protonation or with general acid catalysis by the hydrated proton, provided that, in the transition state, the proton is largely transferred to the substrate.[15] This condition appears to be met in the present case since Kwart and Price have observed a Brønsted α value of 0.74 for general acid catalysis of methyl orthobenzoate hydrolysis.[9] The observation that methyl orthobenzoate hydrolysis is subject to general acid catalysis[9,10] suggests, but does not prove, that the specific acid-catalyzed reaction is, in fact, general acid catalysis by the hydrated proton.

Experimental

Materials.—Methyl orthobenzoate was prepared from benzotrichloride as previously described.[16] Other reagents were recrystallized or redistilled before use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder as previously described.[17,18] At the conclusion of several runs involving the hydrolysis of methyl orthobenzoate in the presence of hydroxylamine or semicarbazide, the amount of methyl benzoate produced was determined by the ferric chloride–hydroxylamine method of Lipmann and Tuttle.[19] Ionic strength was adjusted to 0.50 with potassium chloride in all kinetic runs.

Measurements of pH were made with the glass electrode and a Radiometer Model PHM 4c pH meter. Values of pD were obtained from measured pH values and the relationship pD = pH + 0.40.[20] This relationship was verified for our pH meter using carefully neutralized acetate buffers.

Activation parameters were obtained from second-order rate constants measured at several temperatures and the Eyring equation, $\ln k = \ln ekT/h + \Delta S^*/R - E_a/RT$.[21]

(11) K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).
(15) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 3214 (1961).
(16) S. M. McElvain and J. T. Venerable, *ibid.*, **72**, 1661 (1950).
(17) W. P. Jencks, *ibid.*, **81**, 475 (1959).
(18) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).
(19) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).
(20) P. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).
(21) S. Glasstone, K. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941.

The Reaction of Guanazole and Diformylhydrazine[1]

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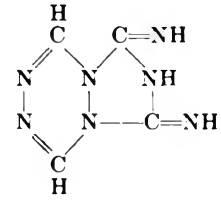
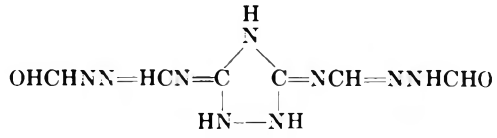
Received September 27, 1963

Papini and Checchi[2] treated equimolar quantities of guanazole (3,5-diamino-1,2,4-triazole) and diformylhydrazine and obtained a compound, $C_4H_5N_7$, to which they assigned the structure 7,8-dihydro-6,8-diimino-6*H*-*s*-triazolo[1,2-*a*]-*s*-tetrazine (I). Wiley and Hart[3] treated 1 mole of guanazole with 2 moles of diformylhydrazine and obtained a product to which they tentatively assigned the empirical formula $C_6H_9N_9O_2$[4] and the structure 3,5-bis{[(2-formylhydrazono)methyl]-imino}-1,2,4-triazolidine (II).

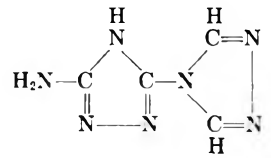


I



II

In the present work, we have found that the material obtained by Wiley and Hart is not $C_6H_9N_9O_2$ but a tetarto hydrate, $C_4H_5N_7 \cdot 1/4H_2O$,[5] of the material obtained by Papini and Checchi. Further, the product of the equimolar reaction, postulated as I, is in fact the isomeric 5-amino-3,4′-bi-1,2,4-triazole (III).



III

The reaction of 2 moles of diformylhydrazine and 1 mole of guanazole by the procedure of Wiley and Hart[3] gave two distinct products. The first of these (A-1) was obtained on rapid cooling of the water used to extract the reaction melt. The elementary analysis of A-1 fitted the empirical formula $C_4H_5N_7$. On standing, the aqueous extract deposited a second solid (A-2) whose carbon–hydrogen analysis was substantially the same as that given by Wiley and Hart. However, the nitrogen analysis of A-2 did not fit the empirical formula $C_6H_9N_9O_2$.

The formula $C_6H_9N_9O_2$ had been assigned on the basis of carbon–hydrogen analysis and the fact that the material did not appear to lose water on drying. When a sample of A-2 was dried for 24 hr. at 60° (1 mm.), there was no detectable weight loss and no change in microanalysis. When the same sample was dried for 24 hr. at 150° (1 mm.) water was given off and the resulting material was identical with A-1. In addition, A-2 could be converted to A-1 by solution in the minimum amount of boiling water, followed by quick cooling.

This unusual dehydration was repeatedly confirmed and, in fact, samples of A-1 prepared from A-2 in this manner could be air-dried without retaining or regaining water. Similarly, A-1 gave A-2 on solution in excess boiling water and very slow cooling.

(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by the Bureau of Naval Weapons, RMMP, under Contract NOrd 18728. Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.
(2) P. Papini and S. Checchi, *Gazz. chim. ital.*, **82**, 735 (1952).
(3) R. H. Wiley and A. J. Hart, *J. Org. Chem.*, **18**, 1368 (1953).
(4) Based on the remainder of their paper, it is assumed that the formula $C_6H_6N_4O_2$ in the Experimental section of the paper by Wiley and Hart is a typographical error.
(5) Based on X-ray powder patterns this material may be $2(C_4H_5N_7) \cdot 1/2H_2O$ or $4(C_4H_5N_7) \cdot H_2O$, but the evidence is not conclusive.

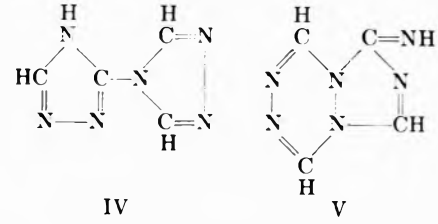
The ultraviolet spectra of A-1 and A-2 were identical in aqueous solution. In the infrared region, A-1 and A-2 had similar but slightly shifted spectra. Karl Fischer analysis of A-2 showed the presence of water and that this water remained after drying at 60° (1 mm.).[6] On the basis of these data plus elemental analysis, the formula $C_4H_5N_7 \cdot 1/4H_2O$, rather than $C_6H_9N_9O_2$, was assigned to compound A-2. That A-2 is a true quarter-hydrate was further demonstrated by the fact that microanalyses on five separate preparations of A-2 were identical for carbon, hydrogen, nitrogen, and oxygen within analytical limits. Additionally, weight loss of samples predried at 60° (1 mm.) and then heated at 150° (1 mm.) was constant.

Both the existence of a tetarto hydrate and the dehydration of a hydrate by recrystallization from water are known but rare phenomena in organic chemistry.[7] It would seem likely that this unusual and unexpected combination of circumstances led to the assignment of structure II.

The equimolar reaction of diformylhydrazine and guanazole by the procedure of Papini and Checchi[2] gave results similar to those above. Two products, B-1 and B-2, were obtained and these were identical with A-1 and A-2, respectively. It was, therefore, concluded that the reaction of guanazole with either 1 or 2 moles of diformylhydrazine gave a compound, $C_4H_5N_7$, or its *tetarto-hydrate*, $C_4H_5N_7 \cdot 1/4H_2O$, as the only product.

Structure I had been proposed on the basis that, working with a large excess of diformylhydrazine over guanazole, only a one to one reaction occurred. However, it subsequently has been noted in these laboratories[8] that reaction of only one amino group is a characteristic of many reactions of guanazole. Since the condensation of diformylhydrazine with aromatic and heteroaromatic amines to give triazoles is a known process,[3,9-11] we were led to believe that the structure represented by $C_4H_5N_7$ might be III, rather than I.

Reductive deamination of III gave a compound, $C_4H_4N_6$, identical with that prepared by Wiley and Hart[3] by the reaction of 3-amino-1,2,4-triazole and diformylhydrazine. They correctly had assigned the structure 3,4′-bi-1,2,4-triazole (IV) to this material, but the possibility remained that this compound might be the isomeric triazole (V) arising from reductive deamination of a tautomer of I and by condensation of diformylhydrazine with a tautomer of 3-aminotriazole. The nuclear magnetic resonance spectrum of this material showed only two peaks in a 2 (τ 0.79) to 1 (τ 1.17) ratio in the C–H region. These are assigned to the two equivalent C–H bonds in one triazole ring of IV and one C–H bond in the second triazole ring. V would be expected to show three peaks of equal intensity in this region. In addition, the infrared spectrum of this material showed no bands in the 1600–1700-cm.$^{-1}$ region (=NH) and a broad band at 2700–2900 cm.$^{-1}$ (triazole ring N–H). These data confirmed IV as the correct structure of the reaction product obtained from 3-amino-1,2,4-triazole and diformylhydrazine and this, in turn, confirmed III as the structure of the guanazole–diformylhydrazine reaction product.



IV V

Experimental[12]

Reaction of Guanazole and Diformylhydrazine at a 1 to 2 Mole Ratio (Method of Wiley and Hart[3]). Compound A-1.—A mixture of guanazole (3.96 g., 0.040 mole) and diformylhydrazine (7.04 g., 0.080 mole) was heated at 180° for 1 hr. The cooled, solidified melt was then dissolved in boiling water. Rapid cooling of the aqueous solution gave 4.2 g. of white, crystalline solid, m.p. >350°. An analytical sample was prepared by several rapid recrystallizations from the minimum amount of water.

Anal. Calcd. for $C_4H_5N_7$: C, 31.79; H, 3.31; N, 64.90. Found: C, 32.03; H, 3.19; N, 64.97.

Compound A-2.—Prolonged cooling of the reaction mixture gave an additional 1.1 g. of white, crystalline solid, m.p. >350°. An analytical sample was prepared by several slow recrystallizations from excess water.

Anal. Calcd. for $C_4H_5N_7 \cdot 1/4H_2O$: C, 30.87; H, 3.54; N, 63.02. Found: C, 30.58; H, 3.68; N, 62.63.

The reaction filtrate was evaporated to dryness at reduced pressure. The semisolid residue was triturated with 100 ml. of absolute methanol to give an additional 0.6 g. of compound A-5 as insoluble material. The reaction yield based on a one to one reaction and the anhydrous A-1 was 96%.

Interconversion of A-1 and A-2.—A sample of A-1, dissolved in excess boiling water and the solution then allowed to cool slowly, gave a precipitate whose infrared spectrum was identical with that of A-2. A sample of A-2, dissolved in the minimum amount of boiling water and the solution then rapidly cooled, gave a precipitate whose infrared spectrum was identical with that of A-1. A finely ground sample of A-2 was heated for 24 hr. at 150° (1 mm.). The resultant material was identical with A-1 (infrared, ultraviolet).

Anal. Calcd. for $C_4H_5N_7$: C, 31.79; H, 3.31; N, 64.90. Found: C, 31.94; H, 3.47; N, 65.14.

Equimolar Reaction of Guanazole and Diformylhydrazine (Method of Papini and Checchi).—This procedure gave products, B-1 and B-2, which were identical (analysis, infrared and ultraviolet) with A-1 and A-2. The interconversions described for compounds A-1 and A-2 also were performed with compounds B-1 and B-2.

3,4′-Bi-1,2,4-triazole (IV). A. Reaction of 3-Amino-1,2,4-triazole and Diformylhydrazine (Method of Wiley and Hart[3]).—Diformylhydrazine (0.40 g., 0.0046 mole) and 3-amino-1,2,4-triazole (0.39 g., 0.0046 mole) were mixed and heated at 160° for 0.5 hr. The cooled, solidified melt was dissolved in 25 ml. of boiling water. The precipitate which formed on chilling the aqueous solution was recrystallized from water to give 0.30 g. (48%) of small, colorless needles, m.p. 304–306° sl. dec. (lit. m.p.[3] 300–302° dec.).

B. Reductive Deamination of 5-Amino-3,4′-bi-1,2,4-triazole (III).—A slurry of 2.0 g. (0.013 mole) of the hydrated form of III in 25 ml. of 10% hydrochloric acid, cooled to 5°, was treated with a solution of 1.8 g. (0.026 mole) of sodium nitrite in 5 ml. of water at 5°. Solution of III was rapid and complete. After 0.25 hr., 12 g. (0.091 mole) of cold 50% aqueous hypophosphorous acid was added. The resulting solution evolved a considerable

(6) The insolubility of A-2 in solvents necessary for water determination precluded an accurate water analysis, but approximate values of 2–4% corresponded well with the theoretical 2.89%.

(7) *Cf.* Discussion of R. S. Tipson in "Technique of Organic Chemistry," Vol. III, part I, 2nd Ed., A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp. 551, 552.

(8) G. Papp, American Cyanamid Co., unpublished results.

(9) G. Pellizzari and C. Massa, *Atti. accad. Lincei*, [5]**10**, i, 363 (1901); *Chem. Zentr.*, **II**, 124 (1901).

(10) G. Pellizzari and M. Bruzzo, *Atti. accad. Lincei*, [5]**10**, i, 414 (1901); *Chem. Zentr.*, **II**, 125 (1901).

(11) G. Pellizzari and A. Alciatore, *Atti. accad. Lincei*, [5]**10**, i, 444 (1901); *Chem. Zentr.*, **II**, 353 (1901).

(12) All melting points are uncorrected and were taken on a capillary melting apparatus.

amount of gas. The reaction flask was then loosely stoppered and refrigerated for 24 hr. The solution was neutralized with 2 *N* potassium hydroxide and concentrated to 20 ml. by boiling. On cooling, a white precipitate formed. Recrystallization from water gave 0.82 g. (44%) of small, colorless needles, m.p. 306–308° sl. dec.

Anal. Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.94; N, 61.77. Found: C, 35.34; H, 3.07; N, 61.73.

The materials in A and B had identical infrared and ultraviolet spectra, and a mixture melting point showed no depression.

Acknowledgment.—The authors are indebted to the Research Service Department, Stamford Research Laboratories, American Cyanamid Company, for microanalyses and aid in the interpretation of infrared, ultraviolet, and nuclear magnetic resonance spectra.

Direction of Ring Opening in the Reaction of Episulfides with Amines[1]

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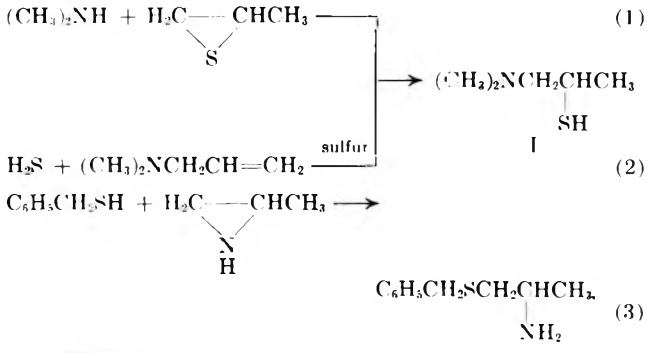
Received October 14, 1963

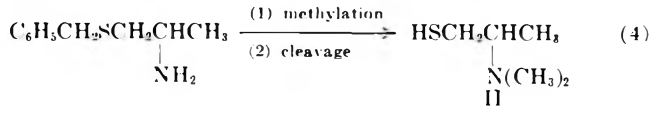
The reaction of isobutylene sulfide with amines has been investigated by Snyder and co-workers[2] who found that displacement occurred at the primary carbon to give tertiary mercaptans as products. Propylene sulfide was used in one instance in their work, but the structure of the product was not investigated. It has also been shown that cleavage of the styrene sulfide ring with secondary amines takes place at the primary carbon atom.[3] In a study of the reaction of propylene sulfide with dimethylamine, however, Hansen[4] concluded that the episulfide ring is opened at the secondary carbon to give 2-dimethylamino-1-propanethiol. Since ring opening reactions of episulfides are of interest in the synthesis of amino mercaptans for evaluation as radioprotectants, we have investigated this reported difference in reactivity of propylene sulfide. Our finding, contrary to that of Hansen's, is that the direction of ring opening in the propylene sulfide–dimethylamine reaction is the same as in the isobutylene sulfide–amine reaction, *i.e.*, the product is 1-dimethylamino-2-propanethiol.

Our approach to establishing the direction of ring opening consisted of comparing the products obtained by the reactions shown in eq. 1, 2, and 4.



(1) This work was done, in part, under Contract DA-49-193-MD-2069 with the U. S. Army Medical Research and Development Command.

(2) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2672 (1947).



Thiolation of dimethylallylamine, in the presence of sulfur to suppress free-radical type addition, gave authentic 1-dimethylamino-2-propanethiol (I). The isomeric addition product, 1-dimethylamino-3-propanethiol, was prepared previously[5] by ultraviolet light-promoted addition of hydrogen sulfide to the hydrochloride of dimethylallylamine. Authentic 2-dimethylamino-1-propanethiol (II) was obtained by opening propylenimine with benzyl mercaptan, methylating the resulting 2-aminopropyl benzyl sulfide, and removing the benzyl group with sodium in liquid ammonia. Meguerian and Clapp[6] have shown that thiophenol opens unsymmetrical ethylenimines in the manner shown in eq. 3. The hydrochloride melting points, the refractive indices, and the boiling points of the products from reactions 1 and 2 were the same. The corresponding properties of II differ significantly from I. These properties, for all three of the dimethylaminopropanethiol isomers, are listed in Table I.

TABLE I

Compound	B.p., °C. (mm.)	$n^{25}D$	Hydrochloride m.p., °C.
$(CH_3)_2NCH_2CHCH_3$ (I)	70 (88)	1.4557	166–167
SH			
$HSCH_2CHCH_3$ (II)	70 (70)	1.4704	120–121
$N(CH_3)_2$			
$HSCH_2CH_2CH_2N(CH_3)_2$[a]	73.5–74.5 (50)	1.4658	105–107

[a] See ref. 5.

The n.m.r. spectra[7] of I obtained by reactions 1 and 2 were identical. A doublet at 1.23 p.p.m. (equivalent to three protons) was characteristic of CH_3 protons in CH_3–CH–SH structures. In the n.m.r. spectrum of II the corresponding doublet was at 1.00 p.p.m., consistent with our observation that nitrogen raises the frequency of nearby protons a smaller degree than does sulfur. Both spectra were dominated by the single strong resonance from the CH_3–N protons at 2.20 p.p.m.

In the earlier work[2] on reaction of amines with isobutylene sulfide the products were shown to be tertiary mercaptans by a color test and by the ease of formation of sulfenyl iodides. In our investigation the isobutylene sulfide–piperidine reaction was repeated, and the n.m.r. spectrum of the product was consistent with that expected for 1-(1-piperidyl)-2-methyl-2-propanethiol. A single sharp peak, equivalent to six CH_3 protons, was observed at 1.27 p.p.m. The two methylene protons between the quaternary carbon and tertiary nitrogen gave a single sharp peak at 2.28 p.p.m. During the course of the work 1-*n*-octylamino-2-methyl-2-propanethiol and 1-*n*-decylamino-2-methyl-2-propanethiol were

(3) R. Daniels, B. D. Martin, and B. K. Lee, Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 33N; J. M. Stewart, *J. Org. Chem.*, **28**, 596 (1963).

(4) B. Hansen, *Acta Chem. Scand.*, **13**, 151 (1959).

(5) S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **27**, 2846 (1962).

(6) G. Meguerian and L. B. Clapp, *J. Am. Chem. Soc.*, **73**, 2121 (1951).

(7) The n.m.r. spectra were determined with a Varian A-60 console using a 12-in. magnet. Chemical shifts are given in parts per million from tetramethylsilane.

prepared by reaction of the appropriate amine with isobutylene sulfide. Since these compounds are new to the literature and provide further examples of the isobutylene sulfide–amine reaction, the syntheses are described in the Experimental section.

Experimental[8]

1-Dimethylamino-2-propanethiol (I). A. Addition of Hydrogen Sulfide to Dimethylallylamine.—A mixture of 325 g. (3.8 moles) of dimethylallylamine,[5] 450 g. (13.2 moles) of hydrogen sulfide, and 4 g. of sulfur was heated in an autoclave under autogenous pressure at 85° for 5 hr. Distillation of the reaction mixture under reduced pressure through a 2-ft. column packed with glass helices gave 80–85 g. (18%) of I, b.p. 55° at 47 mm., $n^{20}D$ 1.4558. Analysis of this product by gas–liquid chromatography (Carbowax 20 on Teflon, programmed between 100° and 250°) indicated 100% purity.

B. Reaction of Dimethylamine with Propylene Sulfide.—This reaction, according to the procedure of Hansen,[4] gave a 47% yield of 1-dimethylamino-2-propanethiol, b.p. 70° at 88 mm., $n^{20}D$ 1.4557; lit.[4] (as the other isomer) b.p. 71° at 88 mm., $n^{20}D$ 1.4538. Treatment of the free base with hydrochloric acid, followed by recrystallization of the product from a mixture of 2-propanol and heptane, gave the amine hydrochloride, m.p. 166–167°, lit.[4] (as the other isomer) m.p. 167°.

Anal. Calcd. for $C_5H_{14}ClNS$: C, 38.57; H, 9.06; N, 9.00; S, 20.59. Found: C, 38.61; H, 9.17; N, 8.95; S (as mercaptan), 19.3.

2-(Benzylthio)-1-methylethylamine.—Propylenimine (1 mole, 57 g.) was added slowly to a stirred solution of 124 g. (1 mole) of benzyl mercaptan in 200 ml. of tetrahydrofuran at room temperature. A very slight temperature rise occurred. The solution was allowed to stand at room temperature for 2 days and then was heated under reflux for 3 hr. The volatile materials were removed by distillation from a steam bath, leaving 150 g. of a pale yellow oil. The latter was distilled *in vacuo* through a 15-in. Vigreux column, giving, after a small forecut of unchanged benzyl mercaptan, 100 g. (55%) of the desired amino sulfide, b.p. 78–80° at 0.2 mm., $n^{20}D$ 1.5597.

Anal. Calcd. for $C_{10}H_{15}NS$: C, 66.24; H, 8.34; N, 7.73. Found: C, 66.2; H, 8.3; N, 7.3.

2-(Benzylthio)-*N*,*N*,1-trimethylethylamine.—A solution of 90 g. (0.5 mole) of 2-(benzylthio)-1-methylethylamine in 130 g. (2.5 moles) of 95% formic acid was prepared with cooling; to this was added 115 ml. (1.5 moles) of commercial 37% aqueous formaldehyde. The clear solution was heated on a steam bath until the evolution of carbon dioxide was vigorous (*ca.* 2–3 min.). The heat was removed until the reaction had subsided (*ca.* 10 min.), and then heating was resumed (steam bath) for 10 hr. After cooling, 80 ml. of 12 *N* hydrochloric acid was added, and the solution was stripped at 100° under aspirator pressure. The residue was dissolved in 100 ml. of water, and the solution was made basic by the addition of a solution of 50 g. of sodium hydroxide in 200 ml. of water. The organic layer (oil) was separated, and the aqueous layer was extracted twice with ether. The ether extracts were combined with the oil, and the solution was washed well with water. After drying over potassium carbonate, the ether was distilled. The dark-colored residual oil was distilled under a high vacuum to give the desired amine in an 88% yield (92 g.), b.p. 80° at 0.1 mm., $n^{20}D$ 1.5401.

Anal. Calcd. for $C_{12}H_{19}NS$: C, 68.84; H, 9.15; N, 6.69. Found: C, 68.72; H, 9.20; N, 6.4.

2-Dimethylamino-1-propanethiol (II).—A solution of 75 g. (0.36 mole) of 2-(benzylthio)-*N*,*N*,1-trimethylethylamine in *ca.* 1000 ml. of liquid ammonia was prepared. To this, small pieces of sodium were added with stirring until the resulting blue coloration persisted for an hour; about 15 g. of sodium was required. Ammonium chloride (*ca.* 50 g.) was added, and the ammonia was evaporated. The residue was mixed with 300 ml. of 2-propanol under nitrogen, and the mixture was heated to boiling. After cooling in an ice bath, the mixture was filtered under nitrogen; the solids were washed twice with ether. The ether and alcoholic filtrate were combined and the solvents were removed. The residue was distilled through a short Vigreux column under reduced pressure giving 19 g. (45%) of the desired aminothiol, b.p. 70° at 70 mm., $n^{20}D$ 1.4704; lit.[4] (as the other isomer) b.p. 78.5° at 70 mm., $n^{20}D$ 1.4684. Conversion of the product to the hydrochloride gave, from a mixture of 2-propanol and heptane, small white crystals, m.p. 120–121°, lit.[4] (as the other isomer) m.p. 114–115°.

Anal. Calcd. for $C_5H_{14}ClNS$: C, 38.57; H, 9.06; N, 9.00; S, 20.59. Found: C, 38.6; H, 9.3; N, 8.9; S (as mercaptan), 19.1.

1-(1-Piperidyl)-2-methyl-2-propanethiol.—A solution of 44 g. (0.5 mole) of isobutylene sulfide[2] and 42.5 g. (0.5 mole) of piperidine was heated on a steam bath for 20 hr. Fractional distillation of the product gave a 71% yield of 1-(1-piperidyl)-2-methyl-2-propanethiol b.p. 54.5° at 2.5 mm., $n^{20}D$ 1.4842; lit.[2] b.p. 47° at 2.5 mm., $n^{20}D$ 1.4840.

Anal. Calcd. for $C_9H_{19}NS$: C, 62.37; H, 11.05; N, 8.08; S, 18.5. Found: C, 62.31; H, 11.09; N, 7.8; S (as mercaptan), 17.6.

The hydrochloride (from 2-propanol) melted at 193–194°, lit.[2] m.p. 198–199°.

1-*n*-Octylamino-2-methyl-2-propanethiol.—A solution of 84.3 g. (0.57 mole) of *n*-octylamine in 180 ml. of benzene and 20 ml. of ethanol was heated under reflux, while a solution of 24.4 g. (0.28 mole) of isobutylene sulfide in 90 ml. of benzene and 10 ml. of ethanol was added dropwise over a period of 3 hr. After heating overnight, the reaction solution was fractionally distilled to give a 43% yield of the desired aminothiol, b.p. 105–108° at 0.25 mm., $n^{20}D$ 1.4620. Treating a methanolic solution of the free base with concentrated hydrochloric acid, stripping the solution to dryness, and recrystallizing the residue from tetrahydrofuran gave 1-*n*-octylamino-2-methyl-2-propanethiol hydrochloride, m.p. 163–164.5°.

Anal. Calcd. for $C_{12}H_{28}ClNS$: C, 56.77; H, 11.11; N, 5.52; S, 12.63. Found: C, 56.8; H, 11.3; N, 5.8; S (as mercaptan), 12.93.

1-*n*-Decylamino-2-methyl-2-propanethiol.—A solution of 89 g. (0.57 mole) of *n*-decylamine and 25 g. (0.28 mole) of isobutylene sulfide was heated 20 hr. on a steam bath. The reaction solution was fractionally distilled through a 60-cm. column packed with glass helices to give a 66% yield of the desired aminothiol, b.p. 121° at 1 mm., $n^{20}D$ 1.4642. This was converted to the hydrochloride in the same manner as described above for the *n*-octyl homolog, m.p. 151–153°.

Anal. Calcd. for $C_{14}H_{32}ClNS$: C, 59.65; H, 11.44; N, 4.97; S, 11.37. Found: C, 59.65; H, 11.3; N, 5.4; S (as mercaptan), 11.7.

Acknowledgment.—The authors are grateful to Mr. Vernon Thornton, Dr. R. S. Silas, and Miss Joy Yates of these laboratories for obtaining and interpreting the n.m.r. spectra.

(8) All melting points are uncorrected.

Novel Complexes of Metallocenes with π-Acceptors

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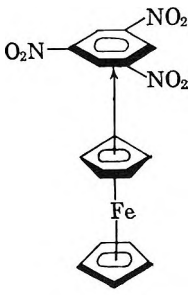
The objective of this study was to investigate the possibility of preparing charge transfer complexes of metallocenes, where either the π-cyclopentadienyl ring as in I or the coordinated metal as in II might act as an electron donor to a π-acceptor, such as *p*-chloroanil or *sym*-trinitrobenzene. Though much work has been done on the synthesis of metallocinium salts of aromatic acids, such as the ferrocinium and nickelocinium picrates,[2,3]

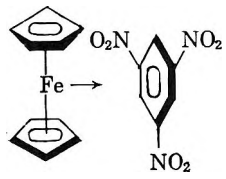
(1) To whom all inquiries should be addressed.

(2) G. Wilkinson, M. Rosenblum, M. C. Whiting, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).

(3) G. Wilkinson, P. L. Pauson, and F. A. Cotton, *ibid.*, **76**, 1970 (1954).



I



II

there have been no reports on their formation of intermediate π-complexes.

A common method for preparing metallocinium salts of organic acids consists of oxiding the metallocene with benzoquinone or air in the presence of the organic acid of interest.[2] It would seem logical to expect in these reactions the formation of an intermediate complex involving charge transfer between the metallocene and benzoquinone, with the latter ultimately yielding hydroquinone. In accord with this hypothesis, we have found that ferrocene, nickelocene, and cobaltocene react quite readily with benzoquinone and other π-acceptors to form a series of complexes.

The specific complexes isolated include 1:2 nickelocene–*p*-chloroanil, 1:1 and 1:2 cobaltocene–*p*-chloroanil, and 1:1 cobaltocene–*sym*-trinitrobenzene. In addition to these complexes, it was found that ferrocene forms complexes with *p*-benzoquinone, *p*-chloroanil, tetrachlorophthalic anhydride, and 1,2,4,5-tetracyanobenzene in the melt and in various solvents. It was not possible, however, to isolate stable complexes of ferrocene with these π-acceptors.

The properties of the isolable complexes range from those of high melting salts, in the case of 1:2 nickelocene–*p*-chloroanil and 1:2 cobaltocene–*p*-chloroanil, to relatively low melting charge transfer complexes, in the case of 1:1 cobaltocene–*p*-chloroanil and 1:1 cobaltocene–*sym*-trinitrobenzene. All of these substances are deeply colored solids, and they possess a new ultraviolet absorption band (in acetonitrile) which may be attributable to charge transfer interaction. In addition, they are all relatively stable in air, in contrast to the oxidative instability of nickelocene and cobaltocene, in particular.

The infrared spectra of these complexes (in Nujol) show bands similar to those of the free metallocenes (or metallocinium ions) but differ vastly from those of the free *p*-chloroanil and *sym*-trinitrobenzene. In particular, it appears that there is a marked interaction between the metal in the metallocene and carbonyl group (in chloroanil) or nitro group (in trinitrobenzene). The ultraviolet absorption spectra (in acetonitrile) show bands similar to those of both the metallocene and metallocinium ion for the chloroanil complexes, while only the metallocinium ion appears evident in the case of the trinitrobenzene complex. In each case a new absorption band is present in the region of 430–450 mμ which may be due to charge transfer interaction.

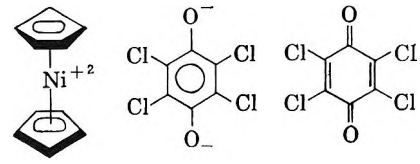
Electron spin resonance studies of the solids at 25° suggest in each case the presence of negative aromatic radicals, based on the *g* values, though the spin concentration varies markedly with the complex in question. In particular, 1:2 cobaltocene–*p*-chloroanil gave a very strong e.s.r. signal, 1:2 nickelocene–*p*-chloroanil a very weak signal, and the 1:1 complexes gave signals of intermediate intensity.

Based on the e.s.r. results it appears that 1:2 cobaltocene–*p*-chloroanil may be formulated as a charge transfer radical ion salt, *viz.*, π-$Cp_2Co^+CA^-CA$. The other properties also appear, in the main, consistent with this formulation.

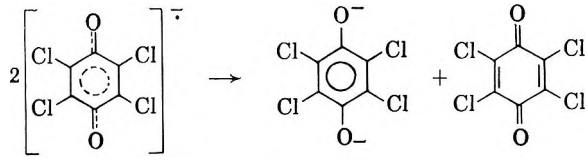
The 1:1 complexes, on a similar basis, would appear to be best represented as charge transfer complexes wherein there is only slight charge transfer in the solid state, *i.e.*, π-$Cp_2Co^{+\delta}CA\cdot^{-\delta}$. The presence of metallocinium ions in the acetonitrile solutions, on the other hand, as indicated by the ultraviolet spectra, may be attributable to the following dissociation.[4]

$$\pi\text{-}Cp_2Co^{+\delta}TNB^{-\delta} \longrightarrow \pi\text{-}Cp_2Co^+ + TNB^-$$

The e.s.r. results obtained for 1:2 nickelocene–*p*-chloroanil are surprising in view of those obtained for the cobaltocene analog. In particular, it appears from these results that the nickelocene complex may be best represented by a structure, such as follows.



Significant charge transfer interaction may occur between the hydroquinone anion and quinone to yield the 1:2 composition. The formation of a nickelocinium salt containing the π-Cp_2Ni^{+2} cation[3] may be due to the strong electron affinity of chloroanil or chloroanil radical ions, coupled with the driving force of nickel to achieve the inert gas configuration. The formation of the tetrachlorohydroquinone anion rather than two chloroanil radical ions would suggest that the following disproportionation is favored.



In conclusion, it appears that the ease of forming isolable complexes of metallocenes with π-acceptors correlates with the electron donor–acceptor properties of the components. Thus, whereas tetracyanoquinonedimethane gives isolable complexes with ferrocene,[5,6] nickelocene,[6] and cobaltocene,[5] the weaker π-acceptor *p*-chloroanil gives complexes with only nickelocene and cobaltocene, and the still weaker π-acceptor *sym*-trinitrobenzene gives an isolable complex only with the

(4) It would in fact appear that, whereas the trinitrobenzene complex is essentially completely ionized in acetonitrile, the chloranil complexes dissociate to yield significant quantities of the free metallocene.

$$\pi\text{-}Cp_2Co^+CA^-CA \rightleftharpoons \pi\text{-}Cp_2Co + 2\ CA$$

(5) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.*, **84**, 3374 (1962). The only complexes reported were the 1:2 metallocene–TCNQ complexes.

(6) Independently prepared at Melpar prior to the preceding publication. The 1:2 ferrocene–TCNQ complex decomposes at 134° and has an electrical resistivity of 6.95 ohm-cm. (pellet pressed at 17,000 p.s.i.). No melting point was reported by the previous workers for this substance.

strongest electron donor cobaltocene. The specific type of complex formed, on the other hand, is apparently dependent upon the donor–acceptor combination in question. In no case, however, does simple charge transfer between the π-cyclopentadienyl ring and π-acceptor appear evident.

Experimental[7]

General Procedure.—The complexes were prepared by mixing dry benzene solutions of the purified components, in varying quantities, and filtering the immediately precipitated products. The products then were slurried with additional dry benzene, filtered, and dried *in vacuo* at 25°. All operations were conducted in a drybox under an atmosphere of dry argon.

1:2 Nickelocene–*p*-Chloroanil.—This complex was obtained in 76% yield based on the nickelocene used. It is a dark brown solid which exhibits no change to 350° under argon, is soluble in water and benzene, slightly soluble in acetonitrile, and appears stable in air (melting point unchanged after 3 days in air); λ_{max}^{Nujol} 3.20 (w), 7.10 (m) new, 8.9, 9.0 doublet (m) new, 10.0 (m), 11.2 (s), and 12.6 μ (m) new. The infrared bands at 6.05, 13.35, and 14.10 μ, due to *p*-chloroanil, and that at 13.0 μ, due to nickelocene, were absent. The ultraviolet spectrum was $\lambda_{max}^{CH_3CN}$ 236 mμ (log ϵ 3.98), 249 (3.93), 256 (3.97), 269 (3.98), 289 (3.89), 310 (3.73), and 449 (3.11) new. Employing a conventional X-band electron spin resonance spectrometer with a 12-in. Varian magnet, the solid product at 25° gave a very weak signal corresponding roughly to about 10^{-7} spins per formula weight (see below), and a *g* value of 2.0084 with an approximate line width of 13 gauss.

Anal. Calcd. for $[C_{10}H_{10}Ni]$ $[C_6Cl_4O_2]_2$: C, 38.8; H, 1.47; Cl, 41.8; Ni, 8.63. Found: C, 39.3; H, 1.96; Cl, 41.5; Ni, 8.65.

Cobaltocene–*p*-Chloroanil (1:1 and 1:2 Complexes.).—Use of a 1:1 mole ratio of the reactants results in the immediate precipitation of an olive green solid in 92% yield, based on cobaltocene. It decomposes at 105–110° under argon to a yellow solid. The cobalt and chlorine results correspond to a 1:1 complex, while the carbon and hydrogen results are somewhat high.[8] The solid product gave an e.s.r. signal corresponding roughly to about 0.02–0.2 spins per formula weight and a *g* value of 2.0059 with approximate line width of 10 gauss.

Anal. Calcd. for $[C_{10}H_{10}Co]$ $[C_6Cl_4O_2]$: C, 44.2; H, 2.32; Cl, 32.7; Co, 13.6. Found: C, 45.7; H, 3.18; Cl, 32.7; Co, 13.6.

Use of a 1:2 ratio of the reactants, with standing for an hour in the drybox, results in a dark green solid in 78% yield, based on the cobaltocene. It decomposes at 228° to a black liquid under argon, is slightly soluble in water with some decomposition (recovered solid decomposes at 238°), insoluble in benzene, slightly soluble in acetonitrile, and appears stable in air; λ_{max}^{Nujol} 3.29 (m), 6.52 (s), 6.77 (s) new, 7.12 (s) new, 8.83 (s) new, 9.32 (w), 9.94 (m) new, 10.17 (s) new, 11.08 (s) new, 11.39 (w), 11.62 (m) new, 14.00 (m), and 14.75 μ (s) new. The infrared bands at 6.05, 8.01, 8.17, 8.35 (triplet), 9.0–9.2, 13.35, and 14.10 μ, due to chloroanil, and the band at 12.95 μ, due to cobaltocene, were absent. The ultraviolet spectrum was $\lambda_{max}^{CH_3CN}$ 260 mμ (log ϵ 4.54), 289 (3.84), 320 (3.69), 421 (3.43) new, and 448 (3.58) new. The solid gave a very strong e.s.r. signal corresponding roughly to about one spin per formula weight and a *g* value of 2.0060 with an approximate line width of 11 gauss.

Anal. Calcd. for $[C_{10}H_{10}Co]$ $[C_6Cl_4O_2]_2$: C, 38.8; H, 1.47; Cl, 41.8; Co, 8.6. Found: C, 39.0; H, 1.53; Cl, 41.3; Co, 9.0.

Cobaltocene–*sym*-trinitrobenzene was obtained in 95% yield. It is a brown solid, m.p. 125°, stable in air, slightly soluble in acetonitrile, and moderately soluble in water with apparent hydrolysis (recovered solid, m.p. 115°); λ_{max}^{Nujol} 3.28 (m), 6.29 (m) 6.60 (w), 8.20 (s) new, 9.65 (m) new, 10.0 (w), 11.60, 11.74 doublet (m) new, 12.93 (w), and 13.65 μ (w). The infrared absorption patterns in 6.5–7.5- and 13–16-μ regions were markedly different from those of *sym*-trinitrobenzene. The bands at 5.46 and 9.36 μ, due to *sym*-trinitrobenzene, were absent. The ultraviolet spectrum was $\lambda_{max}^{CH_3CN}$ 262 mμ (log ϵ 4.95) and 427 (3.61) new. The solid gave an e.s.r. signal corresponding roughly to about 0.05 spins per formula weight and a *g* value of 2.0051 with a line width of about 16 gauss.

Anal. Calcd. for $[C_{10}H_{10}Co]$ $[C_6H_3N_3O_6]$: C, 47.7; H, 3.26; N, 10.4; Co, 14.7. Found: C, 47.3; H, 3.37; N, 10.2; Co, 14.3.

Ferrocene–*p*-Benzoquinone.—The resistivity of 1:1, 1:2, and 2:1 molar ratios was measured at 25–160° between copper electrodes under nitrogen. In every case, the 1:2 complex of ferrocene to *p*-benzoquinone showed a substantially lower resistance than the 1:1 and 2:1 mixtures at comparable temperatures. The 1:1 mixture exhibited a greater resistance than the 2:1 mixture at 120–125°. At all other temperatures, its resistance was also less than that of the 2:1 mixture. In all cases, the resistance was found to decrease in an essentially reversible manner with an increase in temperature. The 1:1 complex appears to form at about 105° and melts at 116–125°. Its resistivity at 120° is approximately 6.3×10^8 ohm-cm. All attempts to isolate a stable complex at 25° failed.

Acknowledgment.—The authors wish to thank Dr. Hannibal DeSchmertzing for the elemental analysis, Mr. Lester Shubin for the spectroscopic measurements, and Mr. Van Townsend for the e.s.r. measurements.

(7) All melting points were determined in a sealed capillary tube under argon and are uncorrected.

(8) Possibly owing to some residual cobaltocene.

Ullmann Condensation

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Received August 22, 1963

Although the Ullmann condensation[1] has been used as a synthetic tool for over 50 years, its mechanism has received little attention. We recently undertook a mechanism study and herein report the results of the first phases of the work.[2]

A series of competitive reactions between a variety of unactivated aromatic halides were carried out with potassium phenoxide in diglyme solvent ($CH_3OCH_2CH_2OCH_2CH_2OCH_3$) catalyzed by copper salts. The product ratios were determined by gas chromatographic techniques. These ratios when corrected for statistical, analytical, and concentration errors were used to construct the relative rate sequence described in Table I. These results are essentially what one might expect from a nucleophilic aromatic substitution.[3,4]

The slight retardation due to a methyl substituent,[5] the activation due to substitution of an additional halo group,[5] and the slightly higher reactivity of the *meta* dihalo *vs.* the *para* dihalo compounds[6] appear to be typical of nucleophilic aromatic substitution. The same applies to the higher reactivity of the β- *vs.* α-naphthalenes.[7]

The halogen mobilities provide another interesting clue to the mechanism. They are in the order, I $\sim$ Br > Cl >> F, and the differences are somewhat larger than those usually observed for nucleophilic

(1) The Ullmann condensation, the copper-catalyzed reaction between aromatic halides and alkali metal phenoxides or anilines to yield aryl ethers or arylamines, should be distinguished from the Ullmann coupling reaction used to form biaryls from aromatic halides [see A. R. Surrey, "Name Reactions in Organic Chemistry," Academic Press, New York, N. Y., 1954].

(2) A more detailed kinetic study will be reported later.

(3) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 394 (1951).

(4) W. G. Dauben, *J. Am. Chem. Soc.*, **70**, 2420 (1948).

(5) E. Berliner and L. C. Monack, *ibid.*, **74**, 1574 (1952).

(6) A. F. Holleman and W. J. DeMooy, *Rec. trav. chim.*, **35**, 27 (1915).

(7) E. Berliner, M. J. Quinn, and P. J. Edgerton, *J. Am. Chem. Soc.*, **72**, 5305 (1950).

TABLE I

RELATIVE RATES

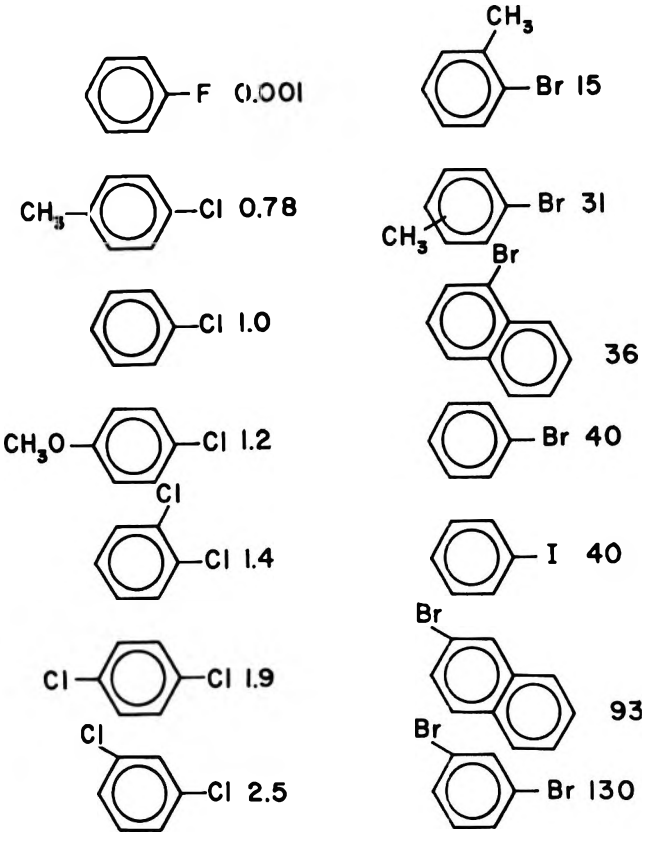

TABLE II

HALOGEN MOBILITIES[a]

Reaction type	I	Br	Cl	F
Ullmann condensation	40[b]	40	1	$\sim 10^{-3}$
E2	190	41	1	
SN2	80	30 to 40	1	
SN1	100	25 to 60	1	$\sim 10^{-5}$

[a] The data for E2, SN2, and SN1 reactions were obtained from C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 339. [b] More precise kinetic measurements show the I:Br ratio to be about 3.

aromatic substitution. We believe these results point to a rate-determining step involving carbon–halogen bond cleavage. Our data are summarized in Table II and are compared with similar data for reactions known to involve carbon–halogen bond cleavage in the rate step.

Experimental

Competitive Reactions.—In a flask equipped with a stirrer, condenser (fitted with azeotrope adapter), thermometer, and gas inlet were placed 0.025 mole of KOH, 0.05 mole of phenol, and 10 ml. of toluene. The mixture was heated under a small nitrogen flow at 100–115° until all of the water was removed. To this mixture was added 10 ml. of diglyme (practical grade[8]) and 0.1 mole each of the haloaromatics (usually two), followed by 0.1 g. of $CuCl_2$. The solution was then refluxed at 160° for 15 hr. The reaction mixture was poured into ice–water, extracted into CCl_4, dried, and the CCl_4 solution was used directly for gas chromatographic analysis.

The following runs were made and are reported with corrected product ratios: fluorobenzene *vs.* *p*-chlorotoluene 1:~1000, chlorobenzene *vs.* *p*-bromotoluene 1:31, iodobenzene *vs.* *p*-bromotoluene 1:0.77, chlorobenzene *vs.* *p*-chloroanisole 1:1.2, bromobenzene *vs.* *p*-bromotoluene 1:0.78, chlorobenzene *vs.* *p*-dichlorobenzene 1:1.9, bromobenzene *vs.* *m*-dibromobenzene 1:3.2, bromobenzene *vs.* α-bromonaphthalene 1:0.9, α-bromonaphthalene *vs.* β-bromonaphthalene 1:2.6, *o*-, *m*-, and *p*-bromotoluene 1:2:2, *o*-, *m*-, and *p*-dichlorobenzene 1:1.7:1.3.

Gas Chromatographic Analysis.—The gas chromatographic analyses were performed on an F and M Model 1720 instrument equipped with a 1 m. × 0.25 in. column packed with Anakrom ABS (50–60 mesh) impregnated with 2% *m*-bis[*m*-(*m*-phenoxyphenoxy)phenoxy]benzene. The column temperature was programmed between 100 and 300°, the detector block containing a hot filament was kept at 285°, and the injection block was kept at 287°. The eluent was helium, the flow rate was 30 ml./min., and the pressure was maintained at 50 p.s.i.g.

An Ott compensating planimeter was used to measure peak areas, and standard mixtures were run concurrently to provide correction factors.

(8) Matheson, Coleman and Bell.

The Facile Isomerization of 4-Methylene-2-oxazolidinones to 4-Methyl-4-oxazolin-2-ones

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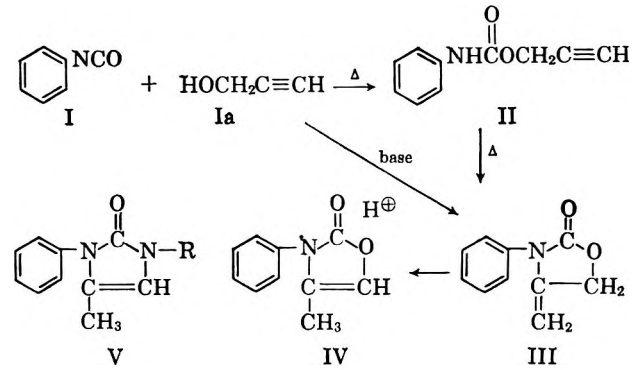
Received October 31, 1963

We have shown that heating propargyl alcohol with phenyl isocyanate to 65° gave the carbanilate (II). Furthermore, heating the same reactants or the preformed carbanilate (II) to 160° gave the cyclized 4-methylene-2-oxazolidinone[1] (III). Other investigators obtained III directly from I and Ia using catalytic amounts of pyridine,[2] sodium acetate,[3,4] potassium hydroxide,[5] and sodium methoxide.[6] This did not seem



reasonable since we have shown that the treatment of propynylureas with strong acid or strong base gave the 4-methyl-imidazolin-2-one[7,8] (V) containing an endocyclic double bond in contrast to the exocyclic double bond of III. It was equally puzzling to note that Sisido, *et al.*,[5] obtained the endocyclic analog (IV) in the reaction of I and Ia with base, but a footnote states

(1) P. J. Stoffel and A. J. Speziale, *J. Org. Chem.*, **28**, 2814 (1963); **28**, 2917 (1963).
(2) M. D. Cameron, U. S. Patent 2,844,590 (July 22, 1958).
(3) S. L. Shapiro, V. Bandurco, and L. Freedman, *J. Org. Chem.*, **26**, 3710 (1961).
(4) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **27**, 2927 (1962).
(5) R. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *ibid.*, **27**, 2663 (1962).
(6) N. Shachat and J. J. Bagnell, Jr., *ibid.*, **28**, 991 (1963).
(7) P. J. Stoffel and A. J. Speziale, *J. Am. Chem. Soc.*, **84**, 501 (1962).
(8) P. J. Stoffel and A. J. Speziale, *J. Org. Chem.*, **27**, 3079 (1962).

that they also obtained III in one experiment, which they could not repeat in subsequent attempts.

We now wish to report that heating I with strong acids as catalysts to 185° gives only the carbanilate (II) and no cyclized product (III or IV). The addition of excess base readily converts II to III with no appearance of IV. Now, however, on adding acid, III is quantitatively converted to IV. In all cases, III must be formed prior to the isomerization to IV.

We assigned the structure[1] of III by n.m.r. spectrum which showed a singlet at τ 2.75, a triplet at 5.05, and a quartet at 5.85 with an intensity ratio of 5:2:2 (m.p. 97.1–97.8°). After treatment with acid, the n.m.r. spectrum showed a singlet at τ 2.75, a quartet at 3.40, and a doublet at 8.15 with an intensity ratio of 5:1:3 (m.p. 56.5–57.2°). This product (IV) has the same melting point and the same n.m.r. spectrum of that reported by Shachat, *et al.*,[6] as a minor product in the preparation of III.

We note that Sisido, *et al.*,[5] neutralized with excess acid during the work-up of their product which accounts for the isolation of IV in all cases but one. Shachat, *et al.*,[6] used "just sufficient acid to neutralize the base," but even so this would probably account for a minor amount of IV found. A similar acid-catalyzed isomerization has been reported in the related triazole series.[9,10]

Experimental

4-Methylene-3-phenyl-2-oxazolidinone (III).—A solution of phenyl isocyanate (11.9 g., 0.1 mole), propargyl alcohol (5.6 g., 0.1 mole), and sodium acetate (0.1 g.) was stirred until a strongly exothermic reaction had subsided. Two recrystallizations from methanol gave small white granules, m.p. 97.2–97.5°; the yield was 82.5%.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.18; N, 8.00. Found: C, 68.4; H, 5.22; N, 8.11.

The same compound was obtained using pyridine, potassium hydroxide, or by heating to 160° without catalyst.

4-Methyl-3-phenyl-4-oxazolin-2-one (IV).—One-gram samples of III were dissolved in sulfuric, *p*-toluenesulfonic, and trifluoroacetic acids. Dilution with water or evaporation on a Rinco evaporator gave the isomerized product. Recrystallization from hexane gave soft white plates, m.p. 56.5–57.2°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.18; N, 8.00. Found: C, 68.5; H, 5.21; N, 8.06.

(9) Y. Yura, *Chem. Pharm. Bull.* (Tokyo), **10**, 1087 (1962).
(10) W. Batty and B. Weedon, *J. Chem. Soc.*, 786 (1949).

The Effect of Ionic Structure on the Hydrogenation of 1-Methyl-4-(2,2-diphenyl-2-hydroxyethyl)piperazine

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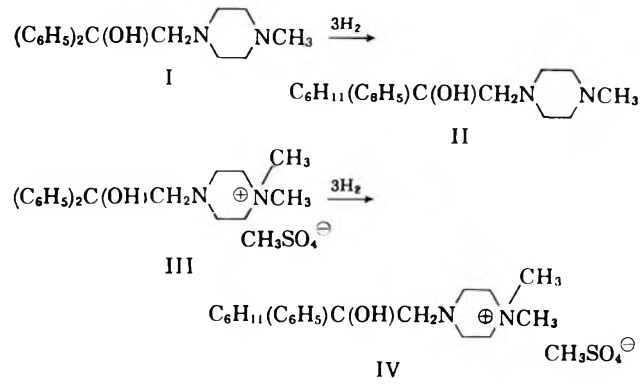
Maxted has discussed the poisoning effect of nitrogen bases on catalytic hydrogenation and the means of overcoming it by converting the offending atom to an ionic or shielded form.[1] It, therefore, appeared of interest to study the reduction of 1-methyl-4-(2,2-diphenyl-2-hydroxyethyl)piperazine (I) as acid salt or quaternary salt to determine whether there is any difference in the protective effect of the two ionic forms.



Results of the hydrogenation studies are summarized in Table I. It is evident that, despite the large group at N^4 which may prevent poisoning to some extent, more rapid and more complete reaction takes place when sufficient acid is present to neutralize that nitrogen atom. A comparison of reduction B, where the dihydrochloride salt is partially neutralized to the monohydrochloride salt, and reduction D seems to give an indication that quaternization gives better protection against poisoning. This is more clearly indicated in the attempts to reduce both rings with platinum oxide. No success was achieved with the dihydrochloride salt of I. In contrast when III is hydrogenated in the presence of acid to neutralize the N^4 atom, 1,1-dimethyl-4-(2,2-dicyclohexyl-2-hydroxyethyl)piperazinium methosulfate V is obtained in good yield. This shows that the difficulty in converting both rings is due to partial poisoning, not geometry. Hydrogenation results also indicate that rhodium catalysts are less sensitive to base effect than platinum.

TABLE I

HYDROGENATION CONDITIONS[a]

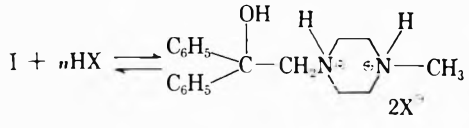
Experiment	Substrate	Catalyst	Ratio, %	Time, hr.	Product	Yield, %
A	I[b]	[f]	3		II	85
B	I[b,c]	[f]	3	[i]	II	84
C	I[b,d]	[g]	7	7	II	80
D	III	[f]	5	20	IV	78
E	III[e]	[f]	2.5	20	IV	80
F	III	[h]	35	14[j]	IV	84
G	III[e]	[h]	35	6	IV	85

[a] Except where noted, hydrogenations were carried out at 55–60° and 2-atm. pressure with 0.03 mole of substrate in 3.0 ml. of water. [b] Dihydrochloride salt used, pH of solution 1.5. [c] Solution adjusted to pH 3.0 by the addition of sodium hydroxide solution. [d] pH of solution changed to 4.0–5.0. [e] Three cubic centimeters of acetic acid added. [f] Platinum oxide. [g] 5% rhodium on alumina. [h] 5% rhodium on carbon. Reduction carried out at room temperature. [i] Uptake of hydrogen only 30% in 20 hr. When the pH of the solution was lowered to 1.5 by the addition of hydrochloric acid the rate of uptake increased markedly. Reduction was complete in 6 hr. more. [j] Uptake was 70% in 5–6 hr.

(1) E. B. Maxted, "Advances in Catalysis," Vol. III, Academic Press, Inc., New York, N. Y., 1951.

(2) Examination of molecular models of I and II shows that one of the benzene rings is generally out of plane, but they can be rotated so that both rings will make contact with the catalyst surface.

It appears from this study that ionic structure does exert a strong and helpful influence on the hydrogenation of the title compound. Furthermore, we would like to suggest that the difficulty in reducing both rings when starting with the dihydrochloride salt of I can be due to the fact that the conversion of I to Ia is reversible. Therefore, complete or sufficient conversion of the poisoning nitrogen atom, particularly at N^1, to a nonpoisoning form cannot be achieved.



Ia

n = 2 or more; X = Cl, CH_3COO

In the case of the quaternary salt III, a single species, incapable of reversibility, exists at N^1, and only a small amount of acid is necessary to counteract the effect of the other nitrogen atom.

Experimental

Compound II was prepared from I by the method described in the literature[3,4] (experiment I in the Table). Compound IV was prepared from III and identified by melting point and mixture melting point with a known standard.[3,4]

Attempts to Reduce Both Rings.—Experiment I was followed using a 5% weight ratio of platinum oxide. After 48 hr., uptake of hydrogen, which had stopped, amounted to about 4 molar equivalents (3 equivalents were absorbed in 7 hr.). About 70% of impure II dihydrochloride hemihydrate was recovered, plus 25% of a product, which from analysis could be a mixture of the hemihydrate and the anhydrous salt of II, melting up to 255°.[3]

Other attempts with more catalyst or with the base I in glacial acetic acid also failed to go to completion.

1,1-Dimethyl-4-(2,2-dicyclohexyl-2-hydroxyethyl)piperazinium Methosulfate (V).—A solution of 12.67 g. (0.03 mole) of III in 30 ml. of water and 3 ml. (0.05 mole) of glacial acetic acid was hydrogenated under 2-atm. pressure at 55–60° in the presence of 0.63 g. of platinum oxide. Uptake for 0.18 mole (6 H_2) was complete in 20 hr. The solution was filtered from the catalyst and concentrated to dryness under reduced pressure. The residue was treated with anhydrous alcohol and benzene and reconcentrated to ensure complete removal of water and acetic acid. The residue was recrystallized from hot isopropyl alcohol and dried to constant weight before analysis; yield 78%.

Anal. Calcd. for $C_{21}H_{42}N_2O_5S$: C, 58.03; H, 9.74; N, 6.45; O, 18.41; S, 7.38. Found: C, 58.30; H, 9.75; N, 6.58; O, 18.38; S, 7.45.

The melting point of the product varied because of the difficulty of removing water or solvent. After recrystallization, it melted at 175–178°. After thorough drying for 3 days at 100°, the melting point rose to 182–185°.

In a similar reduction 8 g. of 5% rhodium on carbon[5] was used. In another reduction in the absence of acid, 10 g. of the same catalyst brought about uptake of 0.18 moles of hydrogen in 36 hr. (3 equivalents were absorbed in 3 hr.). In each case, V was obtained in 75–80% yield.

Infrared examination of the products of the three experiments showed no evidence of benzenoid structure.

Acknowledgment.—The author is indebted to Mr. E. F. Shelberg (now retired) and Mr. O. Kolsto of this laboratory for the microanalyses and to Mr. W. Washburn also of this laboratory for infrared spectroscopy.

(3) H. E. Zaugg, R. J. Michaels, H. J. Glenn, L. R. Swett, M. Freifelder, G. R. Stone, and A. W. Weston, *J. Am. Chem. Soc.*, **80**, 2763 (1958).

(4) H. E. Zaugg, M. Freifelder, R. J. Michaels, and A. W. Weston, U. S. Patent 2,980,683 (April 18, 1961).

(5) The rhodium catalysts are available from Engelhard Industries, Newark, N. J.

Condensation of Formaldehyde with Reissert Compounds

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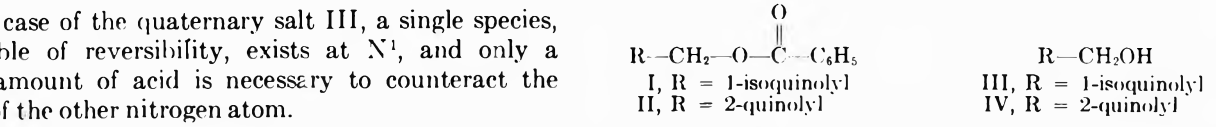
Received August 16, 1963

Formaldehyde has been condensed with Reissert compounds, 2-benzoyl-1,2-dihydroisoquinaldonitrile and 1-benzoyl-1,2-dihydroquinaldonitrile, in a reaction analogous to that previously described for other aldehydes[2–5] to yield 1-isoquinolylcarbinyl benzoate (I) and 2-quinolylcarbinyl benzoate (II), respectively.



Saponification of the hydrochlorides of esters I and II gave the expected 1-isoquinolylcarbinol (III) and 2-quinolylcarbinol (IV), respectively. The 1-isoquinolylcarbinol obtained had a melting point of 77–79° as compared with a reported value of 65°.[6] That this was actually 1-isoquinolylcarbinol (III) was confirmed by elementary analysis and by reduction by the method of Buck, *et al.*,[7] to the known 1-methylisoquinoline. This appears to be a more advantageous method for preparing III than that previously described.[6]

Experimental[8]

Hydrochloride of 1-Isoquinolylcarbinyl Benzoate (I).—To a solution of 10.4 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile[9] in 150 ml. of dry ether and 75 ml. of dry dioxane maintained at 0° in an atmosphere of pure nitrogen was added 0.04 mole of freshly prepared phenyllithium. Gaseous formaldehyde, formed by the depolymerization of paraformaldehyde, was introduced into the resultant red solution by means of a slow stream of nitrogen. The addition was continued until the red color was discharged and a white suspension formed. The mixture was stirred for 1 hr. at 0°, then for an additional hour at room temperature. Sufficient ether was added to increase the total volume to 500 ml., and the mixture was extracted with 12 ml. of water and then two 50-ml. portions of 10% hydrochloric acid. Cooling of the hydrochloric acid solution in an ice bath gave a white solid which was removed by filtration. This afforded 7.24 g. (61.4%) of the hydrochloride of I. After several recrystallizations from ethanol, the melting point was 177–180° dec.

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: C, 68.15; H, 4.79; N, 4.67; Cl, 11.83. Found: C, 68.13; H, 4.64; N, 4.82; Cl, 12.07.

1-Isoquinolylcarbinol (III).—This compound was obtained by refluxing a solution of 8.6 g. (0.028 mole) of the hydrochloride of I and 10.0 g. of potassium hydroxide in a mixture of 60 ml. of ethanol and 25 ml. of water for 8 hr. The majority of the ethanol

(1) Undergraduate Petroleum Research Fund Scholars for academic years, 1961–1962 and 1962–1963, respectively.

(2) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

(3) F. D. Popp and W. E. McEwen, *ibid.*, **79**, 3773 (1957).

(4) F. D. Popp and W. E. McEwen, *ibid.*, **80**, 1181 (1958).

(5) E. G. Podrebarac and W. E. McEwen, *J. Org. Chem.*, **26**, 1165 (1961).

(6) B. R. Brown, D. Ll. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145 (1951).

(7) J. S. Buck, W. H. Perkin, Jr., and T. S. Stevens, *ibid.*, 1471 (1925).

(8) All melting points are corrected. Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(9) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

was removed by distillation and 60 ml. of water added. Extraction of the basic solution with ether afforded an almost quantitative yield of III, which after several recrystallizations from a 1:3 mixture of benzene and low boiling (b.p. 30–60°) petroleum ether had m.p. 77–79° (lit.[6] m.p. 65°).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.50; H, 5.70; N, 8.80. Found: C, 75.76; H, 5.77; N, 8.63.

Benzoic acid was obtained upon acidification of the alkaline solution remaining.

The phenylurethane derivative of III was obtained as a white crystalline solid from carbon tetrachloride, m.p. 148–150°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.22; H, 5.29; N, 9.76.

Conversion of 1-Isoquinolylcarbinol (III) to 1-Methylisoquinoline.—A 2.0-g. portion of III was reduced[7] to 1-methylisoquinoline (0.51 g., 28.2%). This was characterized as its picrate, which after recrystallization from ethanol had m.p. 231–232° (lit.[10] m.p. 230–232°), and as its methiodide, which after recrystallization had m.p. 207–208° (lit.[10] m.p. 208°).

Hydrochloride of 2-Quinolylcarbinyl Benzoate (II).—This compound was prepared from 10.4 g. (0.04 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile[11] in exactly the same manner as described above for the hydrochloride of I; 8.5 g. (72.1%) was obtained. Recrystallization from ethanol gave m.p. 107–109°.

Anal. Calcd. for $C_{17}H_{14}NClO_2$: C, 68.15; H, 4.79; N, 4.67; Cl, 11.83. Found: C, 67.78; H, 5.01; N, 4.48; Cl, 10.72.

2-Quinolylcarbinol (IV).—This compound was obtained in almost quantitative yield from the saponification of 4.0 g. (0.013 mole) of the hydrochloride of II in a manner analogous to that described above for III. Recrystallization from a 1:3 mixture of benzene and low boiling petroleum ether gave m.p. 65–67° (lit.[12] m.p. 66–68°).

The phenylurethane derivative of IV had m.p. 127–129° (lit.[12] m.p. 128–130°).

Acknowledgment.—The authors wish to thank the American Chemical Society Petroleum Research Fund for its support.

(10) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).
(11) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).
(12) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

The Preparation of Formic Benzoic Anhydride

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Although formic acetic anhydride may be prepared readily,[2] examination of the literature revealed no references to formic benzoic anhydride (I).

Formic benzoic anhydride has been prepared by the action of benzoyl chloride on a twofold excess of sodium formate in diethylene glycol dimethyl ether (DMC) or tetrahydrofuran (THF). The infrared spectrum of I in carbon tetrachloride solution showed carbonyl bands at 1785 and 1755 cm.$^{-1}$, in addition to strong bands at 1045 and 1020 cm.$^{-1}$. The proposed structure was confirmed by the neutralization equivalent of a hydrolyzed sample and by elemental analysis, although a slightly high value for carbon was obtained (presumably due to decomposition of I before analysis of the sample could be made). Reaction of I with aniline afforded both formanilide and benzoic acid in good yields. The formation of formanilide rather than benzoic acid anilide is analogous to the behavior of formic acetic anhydride.[2]

Although a small amount of I was isolated by distillation, there was extensive thermal decomposition. To obtain larger amounts of material, the reaction (in THF) was allowed to go almost to completion and was filtered from sodium chloride and unchanged sodium formate while there was still a small amount of benzoyl chloride present. The reaction could be followed conveniently by infrared. In this manner, formic benzoic anhydride, contaminated with small amounts of both benzoic acid (decomposition product of I) and benzoyl chloride, was obtained after removal of solvent.

If the reaction of sodium formate with benzoyl chloride was allowed to go to completion, formic benzoic anhydride was found to decompose in the reaction mixture to benzoic acid with the evolution of a gas (probably carbon monoxide). The infrared spectra of samples removed periodically throughout the reaction showed that this decomposition did not begin until essentially all of the benzoyl chloride had reacted. This suggests the possibility that small amounts of sodium formate dissolved in the reaction medium are catalyzing the observed decomposition.

Experimental[3]

Preparation of Formic Benzoic Anhydride.—To a stirred suspension of 80 g. (1.178 moles) of pulverized sodium formate in 100 ml. of dry DMC was added 82.8 g. (0.589 mole) of benzoyl chloride over a period of 65 min. (internal temperature 8–9°). After addition was complete, the mixture was stirred for 2.7 hr. at 9–15° and filtered under nitrogen. The infrared spectrum of the colorless filtrate showed bands at 1785, 1755, 1045, and 1020 cm.$^{-1}$, which were assigned to formic benzoic anhydride. There was no benzoic acid carbonyl, and it appeared that most of the benzoyl chloride had reacted. After the solution had stood overnight at room temperature, infrared analysis indicated that no decomposition had taken place. An aliquot of the above filtrate was distilled through a micro Vigreux column to yield 10.15 g. of formic benzoic anhydride, b.p. 64.5° (0.45 mm.)–69° (0.60 mm.). There was a white crystalline residue of 6.51 g., the infrared spectrum of which showed a strong benzoic acid carbonyl at 1695 cm.$^{-1}$. Infrared analysis showed the distillate to contain formic benzoic anhydride contaminated with a small amount of benzoic acid. Formic benzoic anhydride was purified by placing a small amount of the distillate in a sublimation apparatus and distilling the liquid at room temperature and high vacuum onto a cold finger cooled with ice–water. A sample of this purified material was hydrolyzed with water and a neutralization equivalent was obtained on the liberated acids.

Anal. Calcd. for $C_8H_6O_3$: C, 64.0; H, 4.03; neut. equiv., 75.06. Found: C, 64.8; H, 4.29; neut. equiv., 75.2

When a similar reaction mixture was not filtered from excess sodium formate but was stirred for 19.3 hr. at 19–37° after the completion of the benzoyl chloride addition, the infrared spectrum of the mixture showed a benzoic acid carbonyl at 1695 cm.$^{-1}$ and no trace of formic benzoic anhydride.

In THF, 100 hr. was required for the reaction of sodium formate (0.589 mole) with 0.294 mole of benzoyl chloride to go almost to completion. The temperature was varied from 0 to 53°, and the reaction was followed carefully by observing the disappearance of the 876-cm.$^{-1}$ band of benzoyl chloride in the infrared. The formic benzoic anhydride obtained after dilution of the reaction mixture with pentane, filtration, and removal of solvent from the filtrate was contaminated with only small amounts of benzoic acid and benzoyl chloride.

The reaction of I with aniline in ether solution afforded a 65.5% yield of formanilide, m.p. 43–49° (m.p. 47–50° after recrystn.), and a 74.5% yield of benzoic acid, m.p. 120–122°. Formanilide and benzoic acid were identified by their infrared spectra and by mixture melting points with authentic samples.

(1) Northern Regional Laboratory, 1815 N. University St., Peoria, Ill.
(2) C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958), and references quoted therein.
(3) Melting points and boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer.

Acknowledgment.—The author thanks Dr. T. H. Coffield for helpful discussions throughout the course of this work.

A Chart of Ultraviolet Absorption Maxima of Semicarbazones

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Received September 11, 1963

A Colthup-type chart of the principal ultraviolet absorption maximum in the spectra in chloroform of several hundred 2,4-dinitrophenylhydrazones[1] suggested some possible utility in a similar analysis of the spectra of the other major carbonyl derivative, the semicarbazone. The source of data was again the three published volumes of "Organic Electronic Spectral Data"[2] supplemented by a rather unproductive search of *Chemical Abstracts* for 1960–1962. (Though many such spectra must have been published in those years, they appear to have been too widely scattered for indexing under general headings in Abstracts.)

A total of over 400 distinct semicarbazone spectra, nearly all of them in ethanol as solvent, were found. A frequency plot of the raw data for the entire group showed the largest numbers of entries in the 224–230- and 260–272-mμ regions, these corresponding to saturated and α,β-unsaturated carbonyl derivatives, respectively. In indexing the entries for the chart of Fig. 1 about 270 compounds were used, the remainder either lacking an identifiable structure or falling outside the classes of the index.

It is well-known that semicarbazone spectra are characterized by a moderately large bathochromic shift and an increase in molar absorptivity as compared to the parent carbonyl compounds.[3,4] A fairly regular increase in λ_{max} with the number of double bonds conjugated with the carbonyl and a corresponding rise in log ε also are noted generally.

As compared to either the carbonyl compounds or the 2,4-dinitrophenylhydrazones, however, the semicarbazones appear strikingly insensitive to most minor structural influences on their spectra. For example, aldehyde semicarbazones seldom differ enough from those of ketones to warrant separate chart entries, and the substitution of alkyl groups in α,β-unsaturated carbonyl compounds (*cf.* Woodward's rules) has an inappreciable effect on the semicarbazone spectra.

The only important structural effects are found in acetylcyclohexenes, methyl alkenyl ketones, and a few related compounds where the semicarbazones absorb at somewhat shorter wave lengths than other α,β-unsaturated systems (*cf.* Dorfman[5] for some explanatory

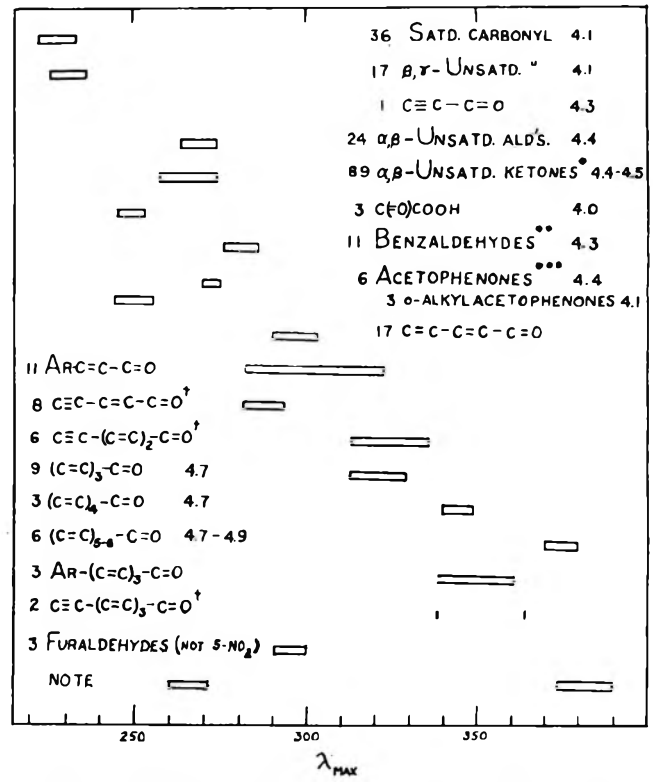

Fig. 1.—Principal maxima in the ultraviolet spectra of semicarbazones. Number of compounds in each class is given at left, and approximate log ε at right (when scatter of data is small); *, acetylcyclohexenes with λ_{max} near 260 mμ; **, salicylaldehyde falls below this indicated range for other benzaldehydes; ***, and higher homologs; †, includes some compounds with triple bond position interchanged with one of the double bonds. (Note that this last group consists of ten 5-nitro-2-furylcarbonyl compounds, each having two maxima.)

notes on these), and in *o*-alkylacetophenones and a few highly alkylated cyclohexene derivatives where steric hindrance appears to account for decreased λ_{max} and log ε. An outstanding anomaly is the higher cycloalkenones whose semicarbazones absorb at 215 and 230 mμ,[6] well below the usual region for α,β-unsaturated compounds.

For classification purposes in Fig. 1 compounds with isolated multiple bonds or other functions have all been grouped under the saturated carbonyl heading.

Acknowledgment.—This work was partially supported by a grant (CA-05607) from the National Cancer Institute of the Public Health Service. The author is also grateful to Pamela Ferguson for her help in processing the data.

(1) J. P. Phillips, *J. Org. Chem.*, **27**, 1443 (1962).

(2) "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960; Vol. II, H. E. Ungnade, Ed., 1960; Vol. IV, J. P. Phillips and F. C. Nachod, Ed., 1963.

(3) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworth and Co., London, 1961.

(4) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, London, 1957.

(5) L. Dorfman, *Chem. Rev.*, **53**, 85 (1953).

(6) N. J. Leonard and F. H. Owens, *J. Am. Chem. Soc.*, **80**, 6039 (1958).

Structure of Ylangene

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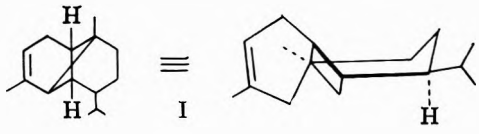
The structure of ylangene previously has not been proposed, although it had been isolated from many

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Mention of specific brand names does not constitute endorsement by the U. S. Department of Agriculture and is for identification only.

natural products.[2-5] Recently ylangene has been found by this laboratory to be a constituent of both grapefruit and orange essential oils. It also has been found to be one of the major sesquiterpenic constituents of cubeb oil.

Nuclear magnetic resonance spectra of ylangene and copaene were strikingly similar. Both spectra showed the presence of one vinyl proton, one vinyl methyl, one unsplit methyl, and two doublet methyls. The remaining protons were unresolved as the spectra were obtained using a microcell. This data and the molecular weight of 204 and 206 for ylangene and dihydroylangene (ylangane) by mass spectroscopy, respectively, indicated a tricyclic monoolefinic sesquiterpene hydrocarbon whose structure is similar to copaene, the latter obtained from cubeb oil according to Sörm.[6] Copaene recently has been shown by Büchi[7] to have structure I.



I

The infrared spectrum of ylangene was consistent with the copaene structure further demonstrating similarity absorbing at 790 and 780 cm.$^{-1}$, respectively, indicating a trisubstituted olefin. The mass spectrum cracking patterns of ylangene and copaene, shown in Fig. 1, differ only in minor details, strongly indicating identical structures. Reduction of ylangene and copaene with PtO_2/H_2 in the Paar apparatus resulted in the absorption of 1 mole of hydrogen by each, yielding ylangane and copane, respectively. The infrared spectra of these reduced sesquiterpenes were similar but not identical, and only minor differences were again noted between the mass spectra of these two compounds.

That ylangene and copaene are stereoisomers was shown by the reduction of both with Pd–carbon at 240° and 1550 p.s.i. of hydrogen, which is specific for the rupture of the cyclobutane ring according to Lukina,[8] to yield the single product cadinane. Attempts at reduction under less stringent conditions yielded only ylangane and copane, respectively. Furthermore, isomerization of both ylangene and copaene on silica gel at 100° for 30 min. yielded one major product and two minor products. The major product from both sources gave identical infrared spectra, and the three products from ylangene had the same retention times by gas chromatography and were in the same proportions as the analagous products from copaene. It is proposed that the mechanistic path followed by both ylangene and copaene during isomerization on silica gel is the same as that proposed for α-pinene[9] *i.e.*, attack on the allylic carbon with subsequent bond rupture between it and the tertiary carbon. This indicates that the cyclobutane ring has the same configuration in both

(2) M. Holub, V. Herout, and F. Sorm, *Chem. Listy*, **52**, 2348 (1958).
(3) O. Motl, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 1656 (1960).
(4) M. Holub, V. Herout, M. Horak, and F. Sörm, *ibid.*, **24**, 3730 (1959).
(5) V. Herout and D. I. Dimitrov, *Chem. Listy*, **46**, 432 (1952).
(6) J. Pliva, M. Horak, V. Herout, and F. Sorm, "Die Terpene. I. Sesquiterpene," Akademie Verlag, Berlin, 1960, pp. S220 and S197.
(7) G. H. Büchi, S. H. Feairheller, P. DeMayo, and R. E. Williams, *Proc. Chem. Soc.*, 214 (1963).
(8) M. Yu. Lukina, S. V. Zotova, and B. A. Kazanskii, *Dokl. Akad. Nauk. SSSR*, **116**, 793 (1957).
(9) V. P. Wystrach, L. H. Barnum, and M. Garber, *J. Am. Chem. Soc.*, **79**, 5786 (1957).

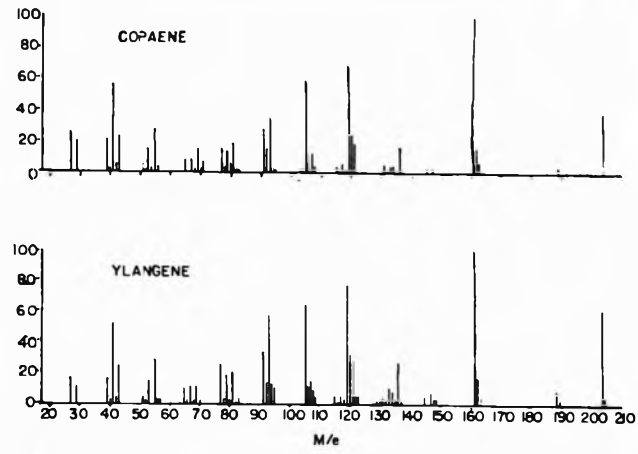
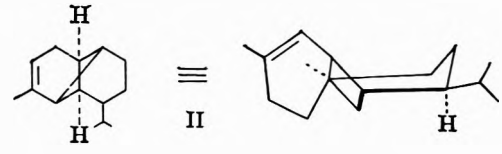


Fig. 1.—Mass spectral cracking pattern of copaene and ylangene.

sesquiterpenes. Assuming that the configuration at the isopropyl group remains the same and the difference lies at the ring junction centers, a structure (II) is proposed for ylangene. Manipulation of a Dreiding stereomodel of the probable cadinene precursor lends added support for the view.



II

Experimental

Reduction of Ylangene and Copaene.—Palladium-on-carbon catalyst was prepared according to the method of Brown and Brown.[10] Fifty microliters of ylangene and 10 mg. of catalyst were placed in an autoclave and heated to 240° under a hydrogen pressure of 1550 p.s.i. for 4.5 hr. A gas chromatograph having an 18 ft. × 1/4 in. 25% Carbowax 20M on 30/60 Chromosorb-P column with a helium flow of 60 ml./min. and a column temperature of 160° yielded only one peak. The material represented by this peak was collected and shown to be identical with cadinane[11] by comparative infrared spectroscopy.

Copaene was treated in a manner described above for ylangene to yield identical results.

Isomerization of Ylangene and Copaene on Silica Gel.—Twenty microliters of ylangene were placed in a vial containing sufficient silica gel (Fisher Cat. No. S157) to form a slurry and heated at 100° for 30 min.

Acknowledgment.—The authors are indebted to Dr. Werner Herz for the n.m.r. studies.

(10) C. A. Brown and H. A. Brown, *ibid.*, **84**, 2827 (1962).
(11) See ref. 6, p. S50.

Ozonolysis of β-Brazan

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β-Brazan (I), or benzo[*b*]naphtho[2,3-*d*]furan, is known to be present in coal tar to a limited extent. Recently, this material has become available in ton quantities from Ruetgerswerke A. G. in Germany.[2]

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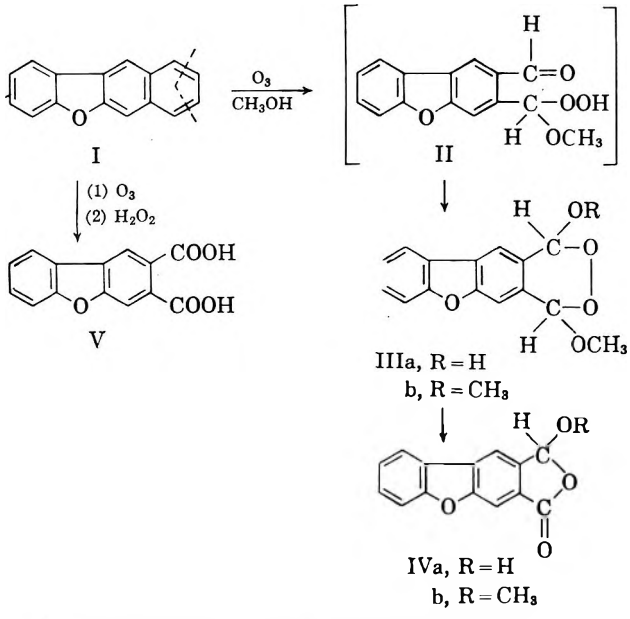
(2) Terra Chemicals, Inc., 500 Fifth Ave., New York 36, N. Y.

Previous work in this laboratory indicated that the parent compound, dibenzofuran, was resistant to attack by ozone.[3] It seemed of interest, therefore, to determine whether β-brazan would react with ozone. It was expected that the 7,8 and 9,10 bonds of β-brazan would be cleaved, ultimately yielding disubstituted derivatives of dibenzofuran. This was indeed found to be the case, and five compounds, not previously reported in the literature, have been isolated. Potentially, this offers a new route for the synthesis of certain difficultly accessible 2,3-disubstituted derivatives of dibenzofuran.

The ozonolysis was conducted in the protic solvent, methanol, to avoid the formation of ozonides or polymeric peroxides. Since I is virtually insoluble in methanol, a fine suspension was prepared by dissolving it in boiling carbon tetrachloride or methylene chloride followed by cooling and addition of methanol. Best results were obtained when the ozonolysis was conducted at about −25°. Approximately two molecular equivalents of ozone were absorbed before unchanged ozone escaped. The compounds which were isolated are those which would be predicted on the basis of the Criegee[4] mechanism for ozonolysis.

The probable course of the ozonolysis of I in methanol is shown below. Admittedly, such a scheme is an oversimplification. However, it does show in logical sequence the compounds that have been isolated. This reaction sequence is analogous to that which is known to occur during the ozonolysis of naphthalene in methanol,[5] although the yields of products are much lower and two different position isomers are possible with some of the compounds.



(Where applicable, only one position isomer is shown.)

The experimental results lead to the following conclusions. At the end of the ozonolysis, the cold methanolic reaction mixture contains high concentrations of a methoxy hydroperoxide (II). This is evidenced by a strong lead tetraacetate test for hydroperoxide. With time and/or with an increase of temperature, the equilibrium shifts toward the more-stable and less-soluble cyclic tautomer (IIIa) which is a hemiperacetal. The best yield (34%) of crude hemiperacetal was obtained by evaporating the solvent mixture at reduced pressure, adding methanol, and filtering to collect the solids. The crude product was difficult to purify but appeared to be quite stable after purification. This hemiperacetal was assigned the structure of 1-(or 4-)hydroxy-4-(or -1-)methoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane (IIIa) on the basis of its infrared spectrum and elemental analysis. However, it is not known whether this material is one isomer or a mixture of the two possible isomers.

An acid-catalyzed conversion of the hemiperacetal to a peracetal (IIIb) was effected by adding hydrogen chloride gas to the methanolic mixture and allowing it to stand at room temperature overnight. The best yield of peracetal obtained was 36%. This peracetal is very stable and could be purified by crystallization from tetrahydrofuran. The material was assigned the structure of 1,4-dimethoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane (IIIb) on the basis of its infrared spectrum and elemental analysis.

The peracetal was decomposed in boiling aqueous sodium hydroxide to give, after acidification, a good yield of a cyclic aldehyde acid (IVa), as the only product. Crystallization from aqueous acetone gave a 91% yield of purified aldehyde acid. This material was assigned the structure of 2-(or 3-)formyldibenzofuran-3-(or -2-)carboxylic acid (IVa) on the basis of its infrared spectrum, neutralization equivalent, and elemental analysis. This aldehyde acid fails to react with 2,4-dinitrophenylhydrazine at room temperature, and this, along with the infrared spectrum, indicates that it exists as the cyclic lactol form. Again it is not known whether this material is one isomer or a mixture of the two possible isomers.

A cyclic aldehyde ester (IVb) was only once isolated from a reaction mixture. A methanolic filtrate from the isolation of the peracetal was allowed to stand overnight. Crystallization occurred, yielding a small amount (4%) of aldehyde ester, which melted in a narrow range. This material was assigned the structure of methyl 2-(or 3-)formyldibenzofuran-3-(or -2-)-carboxylate (IVb) on the basis of its infrared spectrum and elemental analysis. The infrared spectrum indicated that this aldehyde ester also exists as the cyclic lactol form. Attempts to prepare this aldehyde ester by refluxing the peracetal (IIIb) for 18 hr. in methanol which had been saturated with dry hydrogen chloride gas were unsuccessful. The product obtained melted lower, and over a wide range, although the infrared spectrum was very similar to that of the authentic material. A similar result was obtained by esterification of the aldehyde acid (IVa) in methanol. It is postulated that these low-melting solids are a mixture of the two possible position isomers of the aldehyde ester. For unknown reasons, apparently a single isomer was isolated originally in the one experiment.

(3) In two exploratory tests, we found that dibenzofuran was resistant to attack by ozone. In chloroform at −20°, using 1 mole equivalent of ozone, 90% of the starting material was recovered. In methanol at room temperature, using 3.2 mole equivalents of ozone, a 71% recovery was obtained. The reaction products were not identified.

(4) R. Criegee, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **18**, 111 (1957).

(5) (a) P. S. Bailey and F. J. Garcia-Sharp, *J. Org. Chem.*, **22**, 1008 (1957); (b) R. H. Callighan and M. H. Wilt, *ibid.*, **26**, 5212 (1961).

Finally, a dicarboxylic acid (V) was obtained in 25% yield by an alkaline hydrogen peroxide oxidation of an ozonolysis reaction mixture. The purified product was assigned the structure of dibenzofuran-2,3-dicarboxylic acid (V) on the basis of its neutralization equivalent and elemental analysis.

Attempts to isolate and identify products other than those described above were unsuccessful. The remaining material was an intractable, viscous oil with an odor somewhat similar to that of methyl salicylate. The infrared spectrum of this oil indicated that it was probably a complex mixture of materials.

Experimental

The β-brazan used in this work was a commercial material estimated to be 97–98% pure. The methanol and carbon tetrachloride were ACS reagent grade. All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectrophotometer fitted with a sodium chloride prism. Elemental analyses were performed by the Mellon Institute Microanalytical Laboratory and the Galbraith Laboratories, Knoxville, Tenn. Other reagents mentioned were of the purest quality obtainable. The ozonator and accessory equipment have been described previously.[6]

1-(or 4-)Hydroxy-4-(or -1-)methoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane (IIIa).—A fine suspension of β-brazan (10.9 g., 0.05 mole) in a mixture of 200 ml. of carbon tetrachloride and 100 ml. of methanol was treated with an oxygen stream containing approximately 5 wt. % ozone at −25° (Dry Ice–ethanol bath) and at a flow rate of 17 l./hr. for 4.5 hr. Under these conditions, 5.05 g. (0.105 mole) of ozone was passed into the mixture. Some ozone escaped unabsorbed during the last 0.5 hr. After flushing with oxygen, the cold reaction mixture gave a positive test for hydroperoxide. The solvent was then removed in a flash evaporator under reduced pressure at 30° and the residue was treated with 50 ml. of methanol. After 15 min., the white solids were removed by filtration, washed with *n*-heptane, and dried in a vacuum desiccator. A 4.6-g. (34%) yield of crude 1-(or 4-)hydroxy-4-(or -1-)methoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane, melting at 138–153°, was obtained. The crude material was difficult to purify owing to decomposition; however, several triturations with acetone gave a small amount of purified material, m.p. 163–164°. The infrared spectrum showed a strong hydroxyl band at 2.9 μ but no carbonyl band.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.16; H, 4.44; OCH_3, 11.40. Found: C, 66.22; H, 4.56; OCH_3, 11.62.

1,4-Dimethoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane (IIIb).—β-Brazan was ozonized as described above. After flushing with oxygen, the solvent was removed in a flash evaporator under reduced pressure at 30°. The residue was treated with 50 ml. of methanol, saturated with dry hydrogen chloride, and allowed to stand at room temperature overnight. The white solids were removed by filtration, washed with methanol, then with *n*-heptane, and dried in a vacuum desiccator. A 5.2-g. (36%) yield of 1,4-dimethoxy-5,6-(2,3-dibenzofurano)-2,3-dioxane, m.p. 181–183°, was obtained. On recrystallization from tetrahydrofuran, the product melted at 182–183°. The material gave a slow but definite active oxygen test with potassium iodide. The infrared spectrum did not show a hydroxyl or carbonyl band, but it showed ether bands at 7.5 and 9.0 μ. Although concentrated hydrochloric acid also catalyzes the conversion of hemiperacetal to peracetal, the yield was lower than that obtained using the anhydrous gas.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.14; H, 4.93; OCH_3, 20.95. Found: C, 67.22; H, 4.84; OCH_3, 20.68.

2-(or 3-)Formyldibenzofuran-3-(or -2-)carboxylic Acid (IVa).—A mixture of IIIb (4.7 g.) and 200 ml. of 2.5% aqueous sodium hydroxide was refluxed for 30 min., during which time solution occurred. The resulting light yellow solution was acidified with concentrated hydrochloric acid while hot. Precipitation occurred, and the solids were removed by filtration, washed with water, and dried in vacuum desiccator. The product was crystallized from 300 ml. of aqueous acetone (1:1). A 3.6-g. (91%) yield of 2-(or 3-)formyldibenzofuran-3-(or -2-)carboxylic acid melting at 202–205° was obtained. The infrared spectrum showed a hydroxyl band at 2.9 and a single carbonyl band at 5.7 μ. The aldehyde acid fails to react with 2,4-dinitrophenylhydrazine solution at room temperature, indicating that it exists in the cyclic lactol form. Similar results were obtained by starting with a crude mixture of IIIa and IIIb melting at 170–175°.

Anal. Calcd. for $C_{14}H_8O_4$: C, 70.00; H, 3.35; neut. equiv., 240. Found: C, 70.05; H, 3.48; neut. equiv., 241.

Methyl 2-(or 3-)Formyldibenzofuran-3-(or -2-)carboxylate (IVb).—This aldehyde ester was isolated in only one experiment, and the results could not be duplicated. β-Brazan was ozonized as previously described. After flushing with oxygen, the turbid, yellow reaction mixture was poured into a 600-ml. beaker, 2 ml. of concentrated hydrochloric acid was added, and the mixture was allowed to stand at room temperature overnight. Filtration gave a 1.6-g. yield (11%) of IIIb, m.p. 180–182°. The solvent was removed in a flash evaporator under reduced pressure at 30° and the residue was treated with 50 ml. of methanol. Filtration gave an additional 1.7-g. yield (12%) of crude IIIb melting at 150–163°. Concentrated hydrochloric acid (2 ml.) was added to the methanolic filtrate and the mixture was allowed to stand overnight. Precipitation occurred, and the product was removed by filtration, washed with a little methanol, and dried in a vacuum desiccator. A 0.5-g. yield (4%) of methyl 2-(or 3-)formyldibenzofuran-3-(or -2-)carboxylate, m.p. 205–207°, was obtained. The infrared spectrum showed a single carbonyl band at 5.7 and a band at 7.5 μ which seems to be typical for methyl ethers. Attempts to prepare this aldehydic ester by refluxing IIIb for 18 hr. in methanol which had been saturated with dry hydrogen chloride were unsuccessful. Instead, the product obtained melted at 157–163°, although the infrared spectrum was very similar to that of the authentic material. A similar result was obtained by esterification of IVa in methanol. It is postulated that these low-melting solids are a mixture of the two possible position isomers of the aldehyde ester. For unknown reasons, apparently a single isomer was isolated in the original experiment.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96; OCH_3, 12.20. Found: C, 70.61; H, 4.03; OCH_3, 12.43.

Dibenzofuran-2,3-dicarboxylic Acid (V).—A fine suspension of β-brazan (10.9 g., 0.05 mole) in a mixture of 200 ml. of methylene chloride and 100 ml. of methanol was treated with an ozone–oxygen stream (70 mg. O_3/l.) at room temperature and at a flow rate of 44 l./hr. for 95 min. Under these conditions, 4.87 g. (0.102 mole) of ozone was passed into the reaction mixture. Most of the solids dissolved, and an orange solution remained after ozonolysis. The solvent mixture then was removed in a flash evaporator under reduced pressure at 30° and the solid residue was refluxed for 30 min. with 200 ml. of 2.5% aqueous sodium hydroxide. After cooling to room temperature, the mixture was filtered, yielding 2.7 g. (25% recovery) of crude β-brazan, which was identified by its infrared spectrum. The alkaline filtrate was heated to incipient boiling, 20 ml. of 30% hydrogen peroxide was added, and the mixture was stirred 30 min. An additional 20 ml. of 30% hydrogen peroxide was added then and the stirring was continued 30 min. longer. After cooling to room temperature, the mixture was filtered to remove a small amount of undissolved solids and was made acidic with concentrated hydrochloric acid. A fine precipitate resulted and was agglomerated by heating. The solids were removed by filtration, washed with water, and dried in a vacuum desiccator. A 4.0-g. yield (41% based on the β-brazan consumed) of crude dibenzofuran-2,3-dicarboxylic acid, m.p. 282–290°, was obtained. Crystallization of this crude material from an acetone–water mixture (2:1) gave a 2.4-g. (25%) yield of material, m.p. 291–293°.

Anal. Calcd. for $C_{14}H_8O_5$: C, 65.62; H, 3.15; neut. equiv., 128.0. Found: C, 65.64; H, 3.35; neut. equiv., 128.3.

Acknowledgment.—This work was performed by the Coal Chemicals Research Project, sustained by the United States Steel Corporation, to whom the authors are grateful for permission to publish these results. The assistance of Mr. J. R. Harris in the obtaining of infrared spectra is gratefully acknowledged.

(6) R. H. Callighan, M. F. Tarker, Jr., and M. H. Wilt, *J. Org. Chem.*, **25**, 820 (1960).

Preparation and Reactions of Di-*n*-butylantimonylithium and Di-*n*-butylantimonymagnesium Reagents[1]

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Received October 16, 1963

The preparation of diphenylantimonysodium[2] from diphenyliodostibine and sodium in liquid ammonia as well as diphenylantimonylithium[3] by lithium cleavage of triphenylstibine previously has been described. The preparation of the corresponding dialkylantimony organometallics have not been described.[4] This note describes the preparation and some of the reactions of di-*n*-butylantimonylithium and di-*n*-butylantimonymagnesium in tetrahydrofuran (THF).

These reagents can be prepared conveniently in good yield by the reaction of di-*n*-butylbromostibine with either freshly cut lithium strips or magnesium shavings in tetrahydrofuran at room temperature (eq. 1 and 2).

$$(n\text{-}C_4H_9)_2SbBr + 2\,Li \xrightarrow{THF,\ 28^\circ} (n\text{-}C_4H_9)_2SbLi + LiBr \quad (1)$$

$$2(n\text{-}C_4H_9)_2SbBr + 2Mg \xrightarrow{THF,\ 28^\circ} [(n\text{-}C_4H_9)_2Sb]_2Mg + MgBr_2 \quad (2)$$

Substitution of either ethyl ether or dioxane for tetrahydrofuran completely inhibits the formation of di-*n*-butylantimonymagnesium even in the presense of ethyl bromide. Di-*n*-butylantimonylithium (unlike diphenylantimonylithium) could not be prepared by cleavage of tri-*n*-butylstibine by lithium in refluxing tetrahydrofuran.

Di-*n*-butylallylstibine was obtained when allyl bromide reacted with either di-*n*-butylantimonylithium (73%) or di-*n*-butylantimonymagnesium (31%). Reaction of chlorotrimethylsilane with di-*n*-butylantimonymagnesium yielded trimethylsilyldi-*n*-butylstibine (22%), a colorless, highly pyrophoric liquid. Instead of the desired tetra-*n*-butyldistibine, reaction of di-*n*-butylbromostibine with the magnesium reagent yielded tri-*n*-butylstibine (37%) along with antimony metal and a black, air-reactive solid believed to be polymeric *n*-butylstibine.[5]

Considerable tri-*n*-butylstibine was isolated from both the methanolysis (43%) and carbonation (66%) of the di-*n*-butylantimonymagnesium reagent at −60°. An examination of the infrared spectra of both reaction mixtures just after reaction indicated the absence of either the desired hydride or carboxylate. This is consistent with the formation, initially, of the distibine in the methanolysis or carbonation of the di-*n*-butylantimonymagnesium reagent followed by its thermal and catalytic decomposition to tri-*n*-butylstibine, antimony, and polymeric *n*-butystibine upon work-up.

Experimental[6]

Di-*n*-butylbromostibine.—The procedure used is a modification of Morgan and Davies.[7] A flask containing 221 g. of tri-*n*-butylantimony dibromide (0.488 mole) was heated slowly with stirring to a bath temperature of 220° over a period of 4 hr. At a bath temperature of 210°, *n*-butyl bromide began to distil out of the reaction mixture and continued until 50 ml. (93%) was obtained. The reaction mixture was fractionally distilled two times to yield 113.0 g. (74%) of di-*n*-butylbromostibine, b.p. 68° (0.10 mm.). The product was a mobile yellow liquid which did not fume in the air but slowly deposited di-*n*-butylantimony oxybromide when left in an open beaker.

Anal. Calcd. for $C_8H_{18}BrSb$: Br, 25.3. Found: Br, 25.1.

Diisobutylbromostibine, b.p. 64–66° (0.10 mm.), was similarly prepared in 81% yield by the pyrolysis of triisobutylantimony dibromide.

Di-*n*-butylallylstibine.—To a stirring mixture of 1.32 g. of freshly cut lithium strips (0.19 g.-atom) in 50 ml. of THF at room temperature, 30.0 g. of di-*n*-butylbromostibine (0.095 mole) in 50 ml. of THF was added dropwise over a period of 1 hr. The temperature rose to 45° and remained there throughout the addition while the reaction mixture gradually turned a deep red color. After an additional 2 hr. of stirring at room temperature, the reaction mixture was filtered. No unchanged lithium was observed (100% conversion). A 50-ml. THF solution containing 11.5 g. of allyl bromide (0.095 mole) then was added to the reaction mixture (15 min.) and stirring was maintained overnight. The reaction mixture (now yellow) was hydrolyzed with 20 ml. of saturated ammonium chloride solution at 0° and the THF layer was dried over magnesium sulfate. Fractional distillation of the THF layer yielded 19.0 g. (73%) of di-*n*-butylallylstibine, b.p. 54–56° (0.05 mm.).

Anal. Calcd. for $C_{11}H_{23}Sb$: Sb, 43.9. Found: Sb, 44.1.

The infrared spectrum of the product showed bands characteristic of the allyl group ($\nu_{C=C}$ 1625 cm.$^{-1}$) and butyl groups (2880, 1455, 1140, and 865 cm.$^{-1}$).

Di-*n*-butylallylstibine was similarly prepared in 31% yield by the reaction of di-*n*-butylantimonymagnesium with allyl bromide and by the reaction of allylmagnesium bromide with di-*n*-butylbromostibine (54%). All infrared spectra were superimposable.

Trimethylsilyldi-*n*-butylstibine.—Di-*n*-butylantimonymagnesium was prepared by the dropwise addition (2 hr.) of 30.0 g. of di-*n*-butylbromostibine (0.095 mole) in 50 ml. of THF to a stirring mixture of 2.3 g. of magnesium shavings (0.10 g.-atom) in THF. Filtration of the dark brown reaction mixture yielded 0.15 g. of unchanged magnesium (94% conversion) as well as magnesium bromide. To the filtered reaction mixture was added a 25-ml. THF solution of 10.8 g. of chlorotrimethylsilane (0.10 mole) over a period of 15 min., after which stirring was maintained overnight at room temperature. After filtration, the mixture was fractionally distilled and the fraction distilling at b.p. 80–87° (0.40 mm.) was retained and redistilled to yield 6.5 g. (22%) of trimethylsilyldi-*n*-butylstibine, b.p. 48–50° 0.025 mm.). The product was a colorless water-reactive liquid which spontaneously ignited upon contact with the atmosphere.

Anal. Calcd. for $C_{11}H_{27}SbSi$: Si, 9.1. Found: Si, 8.7.

The infrared spectrum of the product showed bands characteristic of the trimethylsilyl group (1240, 830, and 810 cm.$^{-1}$) as well as bands characteristic of butyl groups.

Attempted Preparation of Tetra-*n*-butyldistibine.—Di-*n*-butylbromostibine (20.0 g., 0.063 mole) in 20 ml. of THF was added to to di-*n*-butylantimonymagnesium reagent prepared from 20 g. of di-*n*-butylbromostibine (0.063 mole) and 1.45 g. of magnesium (0.063 g.-atom), and the reaction mixture was allowed to stir overnight at room temperature. Filtration and fractional distillation of the THF solution yielded 7.0 g. (37%) of tri-*n*-butylstibine, b.p. 62–64° (0.05 mm.), lit. b.p. 131° (12 mm.).

(1) The structures of these reagents have not been elucidated. For the sake of conciseness the above nomenclature is used throughout the discussion.

(2) L. A. Woods and H. Gilman, *Proc. Iowa Acad. Sci.*, **48**, 251 (1941).

(3) D. Wittenberg and H. Gilman, *J. Org. Chem.*, **23**, 1063 (1958).

(4) The preparation of tetramethyldistibine from dimethylbromostibine and sodium or lithium in liquid ammonia has been described [see A. E. Burg and L. R. Grant, *J. Am. Chem. Soc.*, **81**, 1 (1959)].

(5) The thermal decomposition of tetramethylstibine yielded trimethylstibine and antimony while a silicone grease-catalyzed decomposition of the distibine yielded trimethylstibine and polymeric methylstibine (see ref. 4, p. 5).

(6) Tetrahydrofuran, ethyl ether, and dioxane were distilled over sodium ribbon and stored under nitrogen. A nitrogen atmosphere was used for all reactions and other manipulations. The toxicities of the alkyl stibines are unknown, and it is advisable to use caution in the handling of these materials.

(7) G. T. Morgan and G. R. Davies, *Proc. Roy. Soc.* (London), **110**, 523 (1926).

Anal. Calcd. for $C_{12}H_{27}Sb$: Sb, 41.6. Found: Sb, 41.4.

Attempted preparation of the distibine using di-*n*-butylantimonylithium also resulted in 22% tri-*n*-butylstibine. In both reactions an antimony mirror was noted in the distilling flask. The distillation residue was a black solid which contained butyl groups (infrared) and which also gave a qualitative test for antimony. Upon standing in the air, this black solid turned white. The similarities in physical properties between polymeric methylstibine (see ref. 4, p. 5) and this material strongly suggest that it is polymeric *n*-butylstibine.

An Abnormal Fluorination with Sulfur Tetrafluoride

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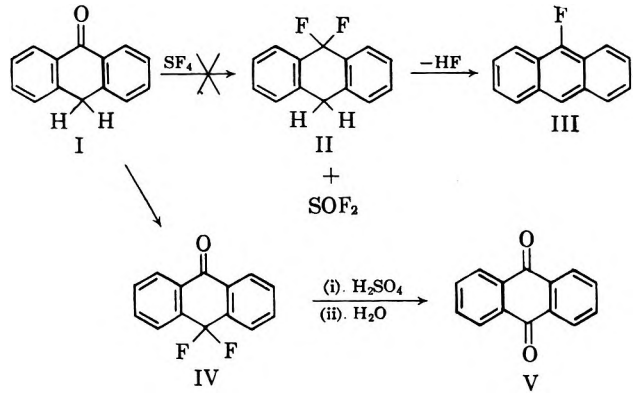
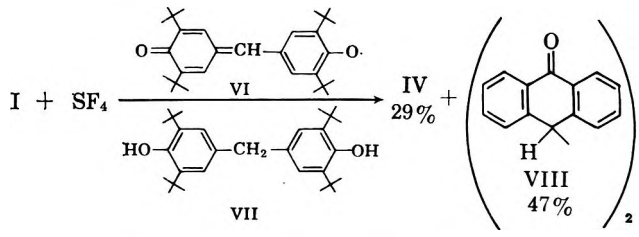
The recent discovery and exploitation of the general reaction of sulfur tetrafluoride with the carbonyl function to produce *gem*-difluorides[1] suggested a feasible synthesis of 9-fluoroanthracene, which was required for another investigation. Sulfur tetrafluoride would be expected to convert anthrone (I) to 9,9-difluoro-9,10-dihydroanthracene (II), which should easily lose the elements of hydrofluoric acid under conditions of either acid or base catalysis to give 9-fluoroanthracene (III). The product of the reaction was, however, neither II nor III, but 10,10-difluoroanthrone (IV). Compound IV was identified by its carbon–hydrogen analysis, by



the presence in the infrared spectrum of an absorption at 1677 cm.$^{-1}$ characteristic of aromatic ketones,[2] and by the absence of n.m.r. signals characteristic of diarylmethylene protons.[3] The position of the fluorine substituents was confirmed by the hydrolysis of IV to anthraquinone (V) under acid conditions, a reaction typical of *gem*-difluorides which can form conjugated ketones by hydrolysis.[4] The best yield (85%) of IV was obtained when methylene chloride was employed as a solvent. In the absence of solvent, the yield of IV was 48%.

Although sulfur tetrafluoride is an oxidizing agent under some circumstances,[5] it has not been observed before to attack the carbon–hydrogen bond under mild conditions. Such attack suggests a free-radical chain mechanism analogous to halogenations by molecular chlorine and bromine. To test this hypothesis, the fluorination was run in the presence of small amounts of the radical scavenger, 2,6-di-*t*-butyl-α-(3,5-di-*t*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy radical (VI)[6] and the antioxidant, 4,4′-dihydroxy-3,5,3′,5′-tetra-*t*-butyldiphenylmethane (VII). It was expected that methylenic fluorination would be inhibited and recovery of starting material would be possible. If this had been the case, the reaction with sulfur tetrafluoride would have been repeated in the presence of VI and VII at increased temperatures in the hope that the normal carbonyl fluorination would occur. The result, however, of the addition of VI and VII to the reaction mixture was to cause the formation of 10,10′-bianthrone (VIII) in 47% yield. The yield of IV was reduced to 29%. Compound I was recovered quantitatively from a control experiment in which an ethylene



chloride solution of I, containing small amounts of VI and VII, was heated at the temperatures used in the inhibited fluorination of I.

The fact that VI and VII inhibit to some extent the formation of IV supports the proposed radical chain mechanism. To account for the formation of VIII, an ionic Friedel–Crafts reaction of fluoroanthrone with the phenolic tautomer of anthrone may be suggested, but the matter has been investigated no further in this work.

Experimental[7]

10,10-Difluoroanthrone (IV).—Anthrone, 19.4 g. (0.100 mole), was purged with nitrogen under vacuum in a 183-ml. stainless steel reaction bomb, 24.5 g. (0.226 mole) of sulfur tetrafluoride (E. I. du Pont de Nemours and Co., Organic Chemicals Dept., technical) and 5.5 g. (0.28 mole) of anhydrous hydrofluoric acid were distilled into the bomb, and 75 ml. of cold methylene chloride was injected through the bomb port with a hypodermic syringe. After 16.3 hr. at 69°, 34.2 g. of dark solid was washed out of the bomb with water. Sublimation at 80° and 0.2 mm. pressure of 10.0 g. of the dark solid gave 5.72 g. (85% yield) of 10,10-difluoroanthrone (IV), m.p. 130–149° dec., identified by comparison of its infrared spectrum with that of an analytical sample. An analytical sample, m.p. 141–142°, was prepared by several recrystallizations from cyclohexane followed by sublimation.

Anal. Calcd. for $C_{14}H_8F_2O$: C, 73.04; H, 3.50. Found: C, 72.97; H, 3.57.

The carbonyl absorption of IV occurred at 1677 cm.$^{-1}$ in the infrared (KBr disk). The n.m.r. spectrum had a multiplet cen-

(1) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

(2) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 137.

(3) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(4) Y. Kitahara, M. C. Caserio, F. Scardiglia, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 3106 (1960).

(5) W. C. Smith, *ibid.*, **82**, 6176 (1960).

(6) (a) P. D. Bartlett and T. Funahashi, *ibid.*, **84**, 2596 (1962); (b) M. S Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).

(7) Melting points are uncorrected. We thank P. McMahon, D. Johnson, and associates for the infrared spectra; O. Norton, D. Johnson, and associates for the n.m.r. spectra; and J. Nemeth and associates for the microanalyses. Details may be found in the Ph.D. thesis of R. Searle, University of Illinois, 1963.

tered at τ 1.7 (area 1) and another multiplet centered at τ 2.2 (area 3.2). A small amount of IV was dissolved in concentrated sulfuric acid. Water was added and the resulting precipitate was identified as anthraquinone by comparison of its infrared spectrum with that of an authentic sample.

In another experiment, 19.4 g. (0.100 mole) of anthrone, 39.6 g. (0.366 mole) of sulfur tetrafluoride, and a small amount of anhydrous hydrofluoric acid were heated together in a 185-ml. stainless steel bomb at 75° for 11 hr. and at 98° for 50 min. The crude product was extracted with hexane to give 14.6 g. of dark solid. Sublimation of 3.00 g. of the solid with 76% recovery gave a 48% yield of 10,10-difluoroanthrone, m.p. 100–143°, identified by comparison of its infrared spectrum with that of an analytical sample.

2,6-Di-*t*-butyl-α-(3,5-di-*t*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy radical (VI) was prepared by the method of Kharasch,[6b] oxidation of 4,4′-dihydroxy-3,5,3′,5′-tetra-*t*-butyldiphenylmethane (VII, Ethyl Corporation, antioxidant 702) with potassium ferricyanide, and was used without purification.

Reaction of Anthrone with Sulfur Tetrafluoride in the Presence of Radical Scavengers.—To 9.00 g. (0.0464 mole) of anthrone, purged with nitrogen in a 183-ml. stainless steel reaction bomb, was added 25.2 g. (0.234 mole) of sulfur tetrafluoride, 0.42 g. (0.0010 mole) of VI, 0.31 g. (0.00073 mole) of VII, 70 ml. of methylene chloride, and 0.5 ml. (0.03 mole) of water. The bomb was heated at 70° for 40 min., allowed to remain at room temperature for 23 hr., and then heated at 70° for 19 hr. The bomb contents were extracted with methylene chloride, and the extract was washed with sodium carbonate solution and water, dried, and evaporated to leave 10.3 g. of brown solid. 10,10-Difluoroanthrone (IV), identified by comparison of its infrared spectrum with that of an authentic sample, was obtained with 25% recovery (29% yield) from 1.10 g. of the crude product by sublimation. Of the crude product, 2.00 g. was washed with 3:1 benzene–hexane to leave 0.825 g. of 10,10′-bianthrone (VIII, 47% recovery, 47% yield), identified by comparison of its infrared spectrum with that of an authentic sample. Recrystallization of 0.749 g. of crude VIII from benzene without change in infrared spectrum gave 0.459 g. (29% yield) of a sample, m.p. 263–271° dec., lit.[8] m.p. *ca.* 270–275° dec.

Control for the Reaction of Anthrone with Sulfur Tetrafluoride in the Presence of Radical Scavengers.—A solution of 1.00 g. (0.00515 mole) of anthrone, 0.050 g. (0.00012 mole) of VI, and 0.040 g. (0.000094 mole) of VII in 9 ml. of ethylene chloride was heated at 70–75° for 17.2 hr. The solvent was evaporated to leave 0.934 g. (93%) of anthrone, identified by comparison of its infrared spectrum with that of an authentic sample. Recrystallization from benzene–hexane produced a sample, 0.569 g. (57%), with m.p. 151–167° (no blackening up to 300°), whose infrared spectrum was unchanged.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We are also indebted to the National Science Foundation for partial support.

(8) J. S. Meek, W. B. Evans, V. Godefroi, W. R. Benson, M. F. Wilcox, W. G. Clark, and T. Tiedeman, *J. Org. Chem.*, **26**, 4281 (1961).

d-Betuligenol from *Rhododendron maximum* L.

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d-Betuligenol is *d*-4-(*p*-hydroxyphenyl)-2-butanol.[1] The levoratatory enantiomorph, *l*-betuligenol, was first isolated from the bark of the white birch (*Betula alba*) as the β-*d*-glucopyranoside called *betuloside*.[2] Rhododendrin, a glycoside from *Rhododendron fauriae* leaves,[3] and its aglycone, rhododendrol, were subsequently shown to be identical with betuloside and *l*-betuligenol, respectively.[4] It has been unequivocally established that the carbohydrate moiety is attached *via* the aliphatic hydroxyl group.[5] Sosa[1] apparently assumed that the betuligenol he found co-occurring with the glucoside in *Betula alba* was the *l*-form since he reported no specific rotation for it. The isolation of *d*-betuligenol from *R. maximum* in this laboratory was incidental to another investigation, but its occurrence in a species so closely related to one from which the levorotatory isomer had been previously isolated as the glucoside is considered of sufficient interest to warrant this report. The identity of the *d*-betuligenol is established by the data in Table I. Its isolation did not involve conditions which would have hydrolyzed a glucoside.

TABLE I

PHYSICAL PROPERTIES OF BETULIGENOLS

	From betuloside[a]	From *R. maximum*
M.p., °C.	81.5	81–83
$[\alpha]_D$ in ethanol	−18.5° (*c* 3.88)	+17.1° (*c* 2.0)
M.p. of monobenzoate, °C.	68–69	65–66
$[\alpha]_D$ of monobenzoate in ethanol	−12.8° (*c* 1.69)	+14.0° (*c* 1.0)

[a] By either acidic or enzymatic hydrolysis. The data are from ref. 1.

Experimental[6]

Isolation of *d*-Betuligenol.—Fresh *Rhododendron maximum* leaves and twigs (730 lb.) collected in North Carolina in February were ground and extracted by the procedure of Wood, *et al.*[7]

The final chloroform extract was concentrated to a viscous dark green syrup. This was dissolved in 2 l. of methanol–water (9:1) and washed with 2 l. of *n*-hexane. Addition of 4 l. of chloroform to the aqueous methanol layer caused separation of a small aqueous layer, which was discarded. After the solvent was stripped from the methanol–chloroform solution, the 180 g. of dark sirupy residue was dissolved in 500 ml. of ethyl acetate and chromatographed on a column made from 1 kg. of Davison No. 950 silica gel (60–200 mesh) and eluted with ethyl acetate. The first 2.5 l. of eluate collected was concentrated to give 19.1 g. of residue, which was rechromatographed on a similar column of 400 g. of the adsorbent. The first 800 ml. of ethyl acetate eluate gave 12.44 g. of oily crystalline residue. Recrystallization of this from chloroform gave 8.74 g. of *d*-betuligenol having the properties given in Table I.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.07; H, 8.36.

The infrared spectrum (chloroform, Beckman IR 4) contained a sharp hydroxyl band at 2.75 and a broader one near 3.00 μ. An aromatic doublet appeared at 6.20 and 6.25, and a sharp intense band was present at 6.58 μ. The ultraviolet spectrum (ethanol) contained peaks at 224 mμ (ε 7960) and 279 (1910) as well as a shoulder near 284. The compound gave a positive iodoform test.

***d*-Betuligenol Benzoate.**—*d*-Betuligenol (500 mg.) was dissolved in 10 ml. of 10% sodium hydroxide and 1 ml. of benzoyl chloride was added. The reaction mixture was shaken vigorously for 10 min. The white solid which precipitated was removed by filtration, washed thoroughly with water, dried, and recrystallized from cyclohexane. The yield of monobenzoate with the properties recorded in Table I was 410 mg.

(1) A. Sosa, *Ann. chim.* (Paris), **14**, 5 (1940).

(2) A. Sosa, *Compt. rend.*, **196**, 1827 (1933).

(3) R. Kawaguchi, K. G. Kim, and H. K. Kim, *J. Pharm. Soc. Japan*, **62**, 4 (1942); *Chem. Abstr.*, **44**, 9634 (1950).

(4) K. G. Kim, *J. Pharm. Soc. Japan*, **63**, 103 (1943); *Chem. Abstr.*, **45**, 4222 (1951).

(5) G. Zemplen, R. Bognar, and L. Boskovitz, *Ber.*, **77**, 784 (1944).

(6) All melting points were taken on a Kofler stage.

(7) H. B. Wood, Jr., V. L. Stromberg, J. C. Keresztesy, and E. C. Horning, *J. Am. Chem. Soc.*, **76**, 5689 (1954).

4-(*p*-Methoxyphenyl)-2-butanone Semicarbazone.—To 1.0 g. (6.0 mmoles) of *d*-butuligenol in 5 ml. of methanol was added 10 mmoles of diazomethane[8] in 100 ml. of ether, and the resulting solution was left at room temperature overnight, during which time the solution was allowed to concentrate spontaneously. The product was dissolved in chloroform and extracted twice with 0.1 *N* sodium hydroxide. The 555-mg. residue from the chloroform layer would not crystallize, but its infrared spectrum (chloroform) no longer contained the broad hydroxyl band at 3.00 μ. To this product in 12 ml. of pyridine was added slowly a solution of 1.8 g. (18 mmoles) of chromium trioxide in 18 ml. of pyridine. The reaction mixture was stirred 2 hr., 100 ml. of ice–water was added, the resulting solution was acidified with hydrochloric acid, and the product was extracted with chloroform. The 435 mg. of oil thereby obtained afforded a crystalline semicarbazone, m.p. 170–173° (lit[1] m.p. 176°), after recrystallization from a mixture of ethanol and water.

(8) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166, note 3.

Hydrogen Bonding in 1,4-Substituted Butane-1,4-diols[1]

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An extensive investigation of the hydrogen-bonding propensities of 2,3-substituted butane-1,4-diols demonstrated the utility of the infrared spectroscopic approach to the elucidation of conformational details.[4] This study was restricted intentionally to compounds with no substituents upon the hydroxyl-bearing carbon atoms in order to avoid expected complications: primary, secondary, and tertiary alcohols absorb at different positions in the O–H stretching region of the infrared,[5,6] and all three types of alcohols differ in their proton-donating and -accepting abilities.[6] The present report, dealing with such 1,4-substituted butane-1,4-diols, illustrates the limitations encountered.

Table I summarizes the observed spectroscopic data. The appearance of the free peak followed expectations from literature examples. Primary hydroxyl groups absorbed near 3636 cm.$^{-1}$, secondary hydroxyl groups from 3623 to 3628 cm.$^{-1}$, and tertiary hydroxyl groups from 3611 to 3619 cm.$^{-1}$, normal positions for these types of alcohols.[5,6] For compounds containing only one substitution type (*e.g.*, compounds **1**, **2**, **3**, **6**, **7**, **9**, and **10**) only one free peak was prominent. The other compounds (**4**, **5**, and **8**) showed two free peaks. It is well-known that primary alcohols are the weakest acceptors and the strongest donors, while tertiary alcohols are the strongest acceptors and the weakest donors.[6] In unsymmetrical cases such as the primary–tertiary example (**5**), the major hydrogen-bonding conformation utilizes the primary OH as proton donor and the tertiary OH as acceptor; hence, the 3636-cm.$^{-1}$ band (free primary OH) appears only as a shoulder. Analogous situations are true for compounds **4** and **8**. As suggested by Cole and Jefferies,[5a] spectral shifts (differences in frequencies between free and bonded peaks) in such situations should be measured from the lower intensity free peak.

In our previous study of 1,4-diols, spectral shifts varied from $\Delta\nu$ = 91–196 cm.$^{-1}$.[4] In Table I, despite the changes of substitution type, variations are much less ($\Delta\nu$ = 157–167 cm.$^{-1}$). This illustrates very well the compensating electronic effects of the terminal alkyl substituents on alcohol proton-donating and -accepting abilities.[6] Again, such electron-donating substituents increase the basicity of the adjacent oxygen, but decrease the acidity of the hydroxyl hydrogen. Furthermore, it appears that all of the compounds are quite similar with regard to conformational restrictions and there are no severe steric interactions. Even in the case of the two diastereoisomeric hexane-2,5-diols, very little difference was observed in either $\Delta\nu$ or in the ratio of the integrated free and bonded peak areas (A_f/A_b, Table I).

Besides $\Delta\nu$, the second feature of hydrogen-bonding spectra ordinarily amenable to analysis is the relative areas of the free and bonded peaks. For diols of the same type, these areas should be indicative of the extent of intramolecular association. In the present instance, although only 1,4-diols were examined, the substitution type varied. Therefore, direct comparisons are hazardous, since primary, secondary, and tertiary hydroxyl stretching peaks are known to have different integrated intensities,[5b] in general decreasing with increased substitution. This factor alone should result in a decreased A_f/A_b ratio, provided the bonded peak intensity does not vary similarly with substitution type. In addition, the "*gem*-dialkyl" effect, the increased tendency toward ring formation induced by alkyl substituents,[4] also would be expected to reduce the A_f/A_b ratio (compare compounds **1**, **2**, and **3**). The actual data (Table I) are not particularly revealing. All of the alkyl-substituted diols show A_f/A_b values less than that of the parent, butane-1,4-diol, but in the case of compounds **4** through **10** the cause of this behavior cannot be interpreted with certainty. Even the diastereoisomers (**6** and **7**) show no appreciable difference, despite the fact that the *dl*-compound must have one quasiaxial methyl group on the hydrogen-bonding ring, whatever the conformation of this ring may be.[4]

The hydroxyl stretching peaks for four commercially available 2-butyne-1,4-diols, which compounds served as synthetic precursors for some of the saturated diols, are also given in Table I (**11** to **14**). The spectrum of butyne-1,4-diol, examined previously,[4] showed only one major peak at the abnormal position for primary alcohols, 3610 cm.$^{-1}$. The shift from the usual region was attributed to hydrogen bonding with the π-electrons of the triple bond.[4,7] Compounds **11** to **14** also absorbed from 3610 to 3615 cm.$^{-1}$, but in these instances it is impossible to say with certainty whether these peaks are π-bonded or free. There is very little shift

(1) Paper XII of a series on hydrogen bonding; paper XI, ref. 4. Taken from the Ph.D. thesis of W. F. B., Princeton University, 1964.

(2) American Cyanamid Junior Research Fellow, 1960–1962; National Institutes of Health Fellow, 1962–1963.

(3) Alfred P. Sloan Research Fellow.

(4) L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger, and L. Eberson, *J. Am. Chem. Soc.*, **86**, 650 (1964).

(5) (a) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956); (b) T. D. Flynn, R. L. Werner, and B. M. Graham, *Australian J. Chem.*, **12**, 575 (1959); (c) C. S. Cook and I. H. Reese, *ibid.*, **14**, 211 (1961).

(6) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

(7) P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *ibid.*, **80**, 6691 (1958).

TABLE I

PHYSICAL AND SPECTROSCOPIC PROPERTIES OF SUBSTITUTED BUTANE-1,4-DIOLS

No.	Compound	Configuration	M.p. or b.p. (mm.), °C.	Lit. ref.	ν free	ν bonded	Δν	A_f/A_b[a]
1	Butane-1,4-diol			*b*	3636	3477	159	1.0
2	2-Methylbutane-1,4-diol	*dl*		*b*	3636	3477	159[c]	0.59
3	2,2-Dimethylbutane-1,4-diol			*b*	3636	3477	159[c]	0.35
4	Pentane-1,4-diol	*dl*	94 (0.45)	*d*	3636 sh[e] 3627[f]	3469	167	0.75
5	4-Methylpentane-1,4-diol		92 (1.0)	*g*	3635 sh[e] 3619[h]	3468	167	0.97
6	2,5-Hexanediol	*dl*	*i*	*j*	3627	3466	161	0.66
7	2,5-Hexanediol	*meso*	*i*	*j*	3628	3470	158	0.58
8	2-Methylhexane-2,5-diol	*dl*	88 (1.5)	*k*	3623 sh[f] 3617[h]	3466	157	0.71
9	2,5-Dimethylhexane-2,5-diol		89.6–90.5	*l*	3617	3459	158	0.85
10	1,1′-Ethylenedicyclohexanol		129.8–131.0	*m*	3611	3451	160	0.52
11	4-Methyl-2-pentyne-1,4-diol		*n*	*l*, *p*	3615[o,s]			
12	2,5-Dimethylhexyne-2,5-diol		95–97	*l*, *q*	3613[o]			
13	3,6-Dimethyl-4-octyne-3,6-diol		58–59.4	*l*, *r*	3615[o]			
14	1,1-Ethynylenedicyclohexanol		103.6–105	*l*, *q*	3610[o]			

[a] The planimeter area of the free peak over the area of the bonded peak. [b] Data from ref. 4. [c] These compounds gave unsymmetrical bonded peaks; see ref. 4. The compounds **4–10**, reported here, gave only symmetrical bonded peaks. [d] O. Philipow, *J. prakt. Chem.* [2] **93**, 162 (1916). [e] Primary free OH. [f] Secondary free OH. [g] A. Franke and A. Kohn, *Monatsh. Chem.*, **28**, 1006 (1904). [h] Tertiary free OH. [i] Samples collected from alumina chromatography could not be crystallized; lit. [j] m.p. 24.5–25.5° (*dl*-), 40–41° (*meso*-). The samples collected were, however, separated by ten fractions containing no material, and isomer separation obviously was realized. [j] K. Serck-Hanssen, S. Ställberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, **5**, 220 (1953). [k] M. S. Losanitsch, *Compt. rend.*, **154**, 392 (1911). [l] Commercially available from Air Reduction Chemical Co. [m] *Anal.* Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.33; H, 11.78. [n] Liquid, boiling point of this sample not determined. [o] May be bonded to triple bond, but it is impossible to distinguish this from the tertiary free OH in these instances (see text). [p] E. T. Roe, J. M. Stutzman, J. T. Scanlan, and D. Swern, *J. Am. Oil Chemists' Soc.*, **29**, 18 (1952). [q] G. H. Whitfield (to I. C. I., Ltd.), British Patent 735,118; *Chem. Abstr.*, **50**, 8721 (1956). [r] V. I. Nikitin and S. D. Savrauskaya, *Zh. Obshch. Khim.*, **25**, 1106 (1955). [s] Peak unsymmetrical on high frequency side (see text).

from the free peak positions of corresponding saturated compounds; compare **9** (3617 cm.$^{-1}$) with **12** (3613 cm.$^{-1}$), and **10** (3611 cm.$^{-1}$) with **14** (3610 cm.$^{-1}$). Compound **11** does show asymmetry as a shoulder on the high frequency side of the OH absorption, but this can reasonably be attributed to the presence of both secondary and tertiary alcohol groups in this molecule. The important and obvious feature of the spectra of these molecules is the complete absence of intramolecular OH. . .O interactions; the minimum O. . .O (5.1 Å.) and OH. . .O (4.6 Å.) distances are clearly much too great to permit such intramolecular associations.

We conclude that the spectroscopic data of all these compounds fit expectations reasonably well, but that very little additional conformational information can readily be obtained from an analysis of the hydrogen-bonding interactions of these molecules.

Experimental

Source and Preparation of Diols.—Compounds **1**, **2**, and **3** (Table I) had been included in the previous investigation.[4] Pentane-1,4-diol (**4**) was obtained by lithium aluminum hydride reduction of 3-acetylpropanol (Aldrich Chemical Co.). 4-Methylpentane-1,4-diol (**5**) and 1,1′-ethylene dicyclohexanol (**10**) were prepared by catalytic hydrogenation in methanol with platinum oxide catalyst of 4-methyl-2-pentyne-1,4-diol (**11**) and 1,1′-ethynylenedicyclohexanol (**14**), both available from Air Reduction Chemical Co. 2-Methylhexane-2,5-diol (**8**) was prepared by the addition of 3 moles of methylmagnesium iodide to ethyl 3-formylpropionate (Union Carbide Chemical Co.), followed by work-up in the usual fashion. Compounds **9**, **12**, and **13** were furnished by Air Reduction Chemical Co.

The isomeric 2,5-hexanediols (**6** and **7**) were obtained by chromatographic separation on an alumina column of an isomeric mixture (Aldrich Chemical Co.). Two distinct fractions were collected, the first on elution with ether containing 0.5% methanol, and the latter, after ten fractions containing no material, on elution with a mixture of 90% ether and 10% methanol. All attempts to induce crystallization of the two liquid fractions failed. In view of the clean separation, we feel these are the two diastereoisomers. Infrared spectra were determined on the materials as obtained from the column.

Physical constants and literature citations for the compounds studied appear in Table I. Melting points are corrected but boiling points are not. The infrared curves were determined in the same fashion as outlined previously.[4] All determinations were made in *ca.* 0.002 *M* concentration in carbon tetrachloride solution using 1-cm. silica cells and a Perkin-Elmer Model 421 grating spectrometer, equipped with scale expansion. For the purpose of this investigation, the integrated intensities of the free and bonded peaks were determined with the use of a planimeter and were used to interpret the results. The estimated accuracy of this area data is 10%.

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Reaction of Trinitromethyl Compounds with Hydroperoxide Ion

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Alkaline hydrogen peroxide rapidly and quantitatively reduces trinitromethyl compounds, except esters of trinitroethanol, to the corresponding 1,1-dinitro anions.[1] This general analytical prodedure was modi-

(1) D. J. Glover, *Tetrahedron*, **19**, Suppl. 1, 219 (1963).

Table I

Potassium Salts of Terminal Dinitromethyl Compounds[a]

Potassium salt of	Yield, %	Potassium Calcd.	Potassium Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1,1-Dinitropropane		22.70	22.92	20.92	21.12	2.93	3.18	16.28	16.23
			22.62		20.85		3.10		16.17
1,1-Dinitropentane	70	19.53	19.65	30.00	30.06	4.53	4.40	14.00	14.15
			19.83		30.25		4.66		14.18
4,4-Dinitrobutyric acid[b]	67	28.71	28.88	17.64	17.32	2.22	2.30	10.29	10.54
			28.71		17.84		2.30		10.67

[a] See ref. 5 for spectral data. [b] Dipotassium salt, monohydrate.

fied to produce pure samples of the potassium dinitromethyl compounds for elemental analysis and for spectral determinations. Glover and Kamlet[2] have reported previously a method for preparing potassium salts of dinitromethyl compounds using potassium iodide. Where side reactions are possible (such as saponification), the iodide procedure is preferred.[3] For example, methyl 4,4,4-trinitrobutyrate readily gave the potassium salt of methyl 4,4-dinitrobutyrate with iodide, but with hydroperoxide a mixture of dipotassium 4,4-dinitrobutyrate and dipotassium 4,4-dinitrobutenoate was formed (see Table I for potassium salts of terminal dinitromethyl compounds).

Like iodide ion, hydroperoxide ion did not give 2,2-dinitroethanol from 2,2,2-trinitroethanol, but produced potassium nitroform, probably by deformylation.

Experimental[4]

Reduction Procedure.—To 0.01 mole of trinitromethyl compound in 25 ml. of methanol was added 5 ml. of 30% hydrogen peroxide. The solution was mixed and cooled in an ice bath to about 5–10°. Methanol (20 ml.) containing 4 g. of potassium hydroxide (0.07 mole) was cooled and added slowly with swirling. The solution became yellow immediately and a yellow solid began to precipitate. After all the potassium hydroxide was added, the solid was filtered cold with suction and washed with three 10-ml. portions of methanol.

The solid was then taken up in no more than 5 ml. of water and the mixture warmed gently to effect solution. If all of the peroxide was not washed out, this solution frothed until all the colorless gas was expelled. Two to three pellets of potassium hydroxide were then added and dissolved. Then methanol was added, if necessary, to cause precipitation to start. After about 5 min. the solid was filtered, washed with methanol, and dried at room temperature in a vacuum desiccator.

Attempted Preparation of Methyl Potassium 4,4-Dinitrobutyrate.—Methyl 4,4,4-trinitrobutyrate, 2.65 g. (0.0112 mole), was dissolved in 25 ml. of methanol in a 250-ml. erlenmeyer flask, and 5 ml. of 30% hydrogen peroxide was added at 25°. Potassium hydroxide, 2.2 g. (0.039 mole), in 10 ml. of methanol was added slowly with stirring. The solution became deep red and the temperature rose to 40–50°. The solution was cooled in an ice bath and a sticky solid precipitated. The liquid was decanted and methanol was added to the solid, which then became crystalline. The yellow-orange solid (I) was filtered and 2 g. of solid potassium hydroxide was added to the filtrate and dissolved, causing further precipitation. The solid which precipitated was filtered off and combined with the first batch (I) in methanol. The solid did not all dissolve when this mixture was warmed. After cooling the solution in an ice bath, the yellow-orange solid was filtered and dried in a vacuum desiccator. One gram of product was obtained.

The filtrate from the second batch of I, when evaporated by heating to one-fourth its volume (now 10 ml.), became quite red. The solution was cooled in an ice bath and a red solid (II) precipitated. The precipitate was filtered, and slurried with boiling methanol, and this mixture was cooled and filtered. While methanol-wet, the solid was quite red, but appeared to become yellowish when dry. After drying, the solid (II) weighed 0.15 g. The ultraviolet spectra showed λ_{max} water 381 mμ for I and 409 mμ[5] for II.

Anal. Calcd. for $C_4H_4K_2N_2O_6$ (I, dipotassium 4,4-dinitrobutyrate): K, 30.72. Found: K, 30.97.

Anal. Calcd. for $C_4H_2K_2N_2O_6$ (II, dipotassium 4,4-dinitrobutenoate): K, 30.98. Found: K, 29.43.

(2) D. J. Glover and M. J. Kamlet, *J. Org. Chem.*, **26**, 4734 (1961).

(3) For the reaction of 1,1,1,3-tetranitropropane with hydroperoxide, see M. J. Kamlet, J. C. Dacons, and J. C. Hoffsommer, *ibid.*, **26**, 4881 (1961).

(4) *Caution:* As these compounds are explosive, they should be handled with appropriate precautions.

(5) M. J. Kamlet and D. J. Glover, *J. Org. Chem.*, **27**, 537 (1962), give 410 mμ (log ε 3.92) for this long wave-length peak.

The Twist-Boat Form of Cyclohexane

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In a number of recent discussions by organic chemists[2] of the twist-boat (C_2) form of cyclohexane, it has been stated or implied that the torsional or dihedral angles (ω_1 and ω_2 in I) of this molecule are 30 and 60°, a conclusion apparently arrived at by considering that these angles arise *halfway* through a pseudorotation cycle from one boat form to the next in which the relevant dihedral angles change from 0 to 60° and 60 to 60°, respectively. In fact, these angles are 33.2 and 70.6°; they may be computed from the equations given by Hazebroek and Osterhoff[3] in their earlier development of the flexible cyclohexanes (although these authors did not actually compute them) or more simply from the general equations for distances between points in space derived by the present author.[4]

These equations easily can be simplified for those cases with all bonds of equal length (d) and all bond angles tetrahedral (τ), the distances between atoms 1 and 4 (r_{14}) and between 1 and 5 (r_{15}), for example, being

$$r_{14}^2 = d^2(41-16\cos\omega)/9$$

$$r_{15}^2 = 16d^2[11-4(\cos\omega_1 + \cos\omega_2) - \cos\omega_1\cos\omega_2 + 3\sin\omega_1\sin\omega_2]/27$$

In the twist-boat form of cyclohexane (I), $l_1^2 = l_2^2 = 8/3$ (as a function of the intercepted tetrahedral angle) if the C–C bond length, d, is taken as unity. Since $l_1^2 = f_{15}(\omega_1,\omega_1)$, a solution of the second equation yields

(1) Alfred P. Sloan Foundation Fellow.

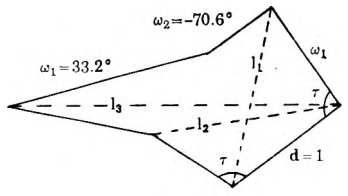
(2) *Cf.*, W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960); K. E. Howlett, *J. Chem. Soc.*, 4353 (1957); N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959); R. D. Stolow, *ibid.*, **81**, 5806 (1959).

(3) P. Hazebroek and L. J. Osterhoff, *Discussions Faraday Soc.*, **10**, 87 (1951).

(4) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

$l_1^2 = 8/3 = 32/3 - [8(\cos \omega_1 + 1)/3]^2/3$ and $\cos \omega_1 = 0.837$ ($\omega_1 = 33.2°$)

Similarly, $l_2^2 = f_{15}(\omega_1,\omega_2)$, from which $\cos \omega_2 = 0.332$ ($\omega_2 = 70.6°$).



I

It is of value to point out this correction for two reasons, the first being that certain conformation conclusions can be very different. Thus, the axial length $l_3 = f_{11}(\omega_2) = 3.07$ Å. compared to 2.95 Å. for the chair (1,4-distance, $\omega = 60°$) or incorrect twist-boat ($\omega_2 = 60°$), so that calculations for quantities such as dipole moments could be seriously affected. Furthermore, a dihedral angle, ω_2, of 70.6° implies that *trans* fusion of a cyclopentane ring will be less strained than a *cis* fusion,[4] whereas if $\omega_2 = 60°$, there is no difference.

Secondly, it may be useful to emphasize that the dihedral angle changes in a given ring during pseudorotation are not simply linear. Table I illustrates the dihedral angle changes during pseudorotation of the boat forms of cyclohexane, discussed above, and the chair forms of cycloheptane (with tetrahedral bond angles),[4] for comparison.

TABLE I[a]

Cyclohexane			Cycloheptane		
Boat ⇄	twist-boat ⇄	boat	Chair ⇆	twist-chair ⇆	chair
60	33.2	0	62.0	55.1	62.0
0	33.2	60	−99.6	−79.8	−62.0
−60	−70.6	−60	81.7	103.2	99.6
60	33.2	0	0.0	−42.8	−81.7
0	33.2	60	−81.7	−42.8	0.0
−60	−70.6	−60	99.6	103.2	81.7
			−62.0	−79.8	−99.6

[a] All values in degrees.

Finally, it should be noted that dihedral angles of 30° and 60° do not form a ring. This can be shown by their substitution into the equation[4] for $r_{17} = f_{17}(\omega_1,\omega_2)$, which yields $r_{17} \neq 0$.