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Studies of Ring Closure *via* Aryne Intermediates[1]

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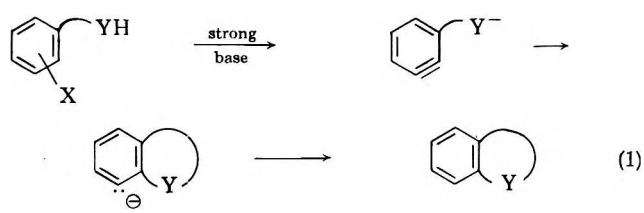
Several attempts, some successful, others not, to achieve ring closure *via* intramolecular nucleophilic addition to aryne intermediates are described. Cyclizations forming oxindole derivatives and the novel 2,1-benzisothiazoline 2,2-dioxide system are recorded. Instances in which ring closure was not realized owing to predominance of external addition of NH_2^- ion have been encountered, as has another case in which an initially formed substrate anion resisted aryne formation. Limitations of ring closure *via* aryne intermediates as a synthetic method are discussed.

It has recently been shown that an aryne[4,5] carrying a strong nucleophile in a side chain will often experience intramolecular addition of the nucleophile to the aryne "triple bond," forming a new ring fused to the original aromatic ring.[4-9] The process is illustrated in generalized notation by equation 1. As a principle

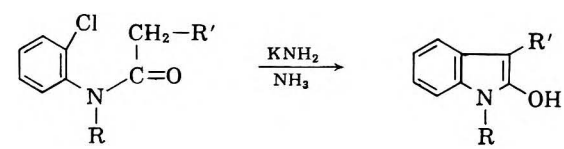


(1)

of synthesis, this reaction has wide applicability and considerable practical value. Studies of it also bring to light novel problems of reaction mechanism.

The present research continues our exploration of this type of reaction.

Experiments with N-acyl-*o*-Chloroanilines.—It was previously discovered[7,8] that acetoacet(*o*-chloro)anilide (Ia) afforded 3-acetyloxindole (IIa) in 78% yield on treatment with potassium amide in liquid ammonia. In the present work, phenylacet(N-methyl-*o*-chloro)-anilide (Ic) underwent ring closure to IIc in even better yield (91%). However phenylacet(*o*-chloro)anilide (Ib), which lacks the N-methyl group of Ic, was re-

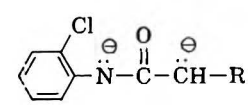


I II

a. R = H; R′ = $COCH_3$
b. R = H; R′ = C_6H_5
c. R = CH_3; R′ = C_6H_5
d. R = H; R′ = H
e. R = CH_3; R′ = H

covered unchanged almost quantitatively from exposure to the same reaction conditions.

We believe that Ib resists aryne formation because it is rapidly and completely converted by potassium amide into dianion IIIb,[10] in which there is a large degree of localization of negative charge on the nitrogen atom. By mesomerism, the nitrogen atom



IIIa. R′ = $COCH_3$
b. R′ = C_6H_5

shares its negative charge with ring carbon atoms, thereby decreasing the acidity of ring hydrogens so much that they become unreactive with potassium amide. It has been noted in other instances that a high concentration of negative charge on an atom next to a benzene ring tends to protect halogens on that ring from being involved in aryne formation.[7,9,11]

In the case of dianion IIIa, an aryne is formed. Evidently the keto and amide carbonyl groups together sufficiently well accommodate the carbanion and

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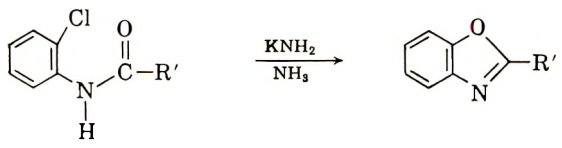
(4) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).
(5) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961).
(6) R. Huisgen and co-workers, *Angew. Chem.*, **69**, 268 (1957); *Ber.*, **92**, 203, 424, 429 (1959); **93**, 1496 (1960).
(7) J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, **80**, 2021 (1958); **83**, 1691 (1961).
(8) J. F. Bunnett, B. F. Hrutfiord, and S. M. Williamson, *Org. Syntheses*, **40**, 1 (1906).
(9) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
(10) R. B. Meyer and C. R. Hauser, *ibid.*, **26**, 3696 (1961).
(11) C. R. Hauser and G. F. Morris, *ibid.*, **26**, 4740 (1961).

nitranion charges so that relatively little negative charge is forced onto ring carbon atoms.

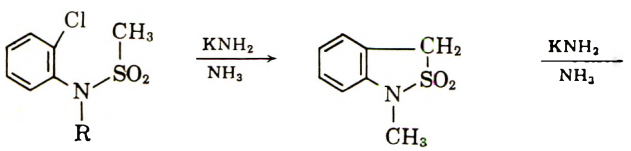
Acet(N-methyl-*o*-chloro)anilide (Ie) was converted into N-methyloxindole (IIe) in 16% yield by the action of potassium amide in ammonia. This shows that an amide carbonyl group is at least partially successful in activating carbanion formation at an otherwise unactivated α-carbon. Again the parent amide without the N-methyl group behaved differently. Id reacted with potassium amide in ammonia to form 2-methylbenzoxazole (IVd) in 37% yield. This resembles



Id. R′ = CH_3 IVd. R′ = CH_3
f. R′ = C_6H_5 f. R′ = C_6H_5

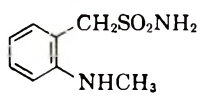
the transformation of benz(*o*-chloro)anilide (If) into 2-phenylbenzoxazole (IVf) in 69% yield under similar conditions.[7]

Experiments with N-Methanesulfonyl-*o*-chloro-anilines.—It seemed that the sulfonyl group of a sulfonamide should promote carbanion formation at an adjacent carbon atom. Methanesulfon(N-methyl-*o*-chloro)anilide (Vb) on treatment with potassium amide in ammonia (containing some ether) for one hour afforded,



Va. R = H
b. R = CH_3

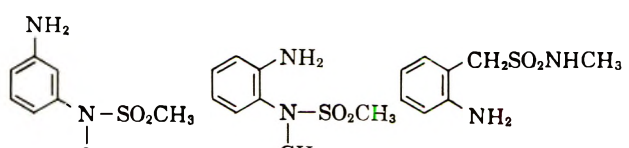
VI



VII

however, not the expected ring closure product VI, but rather a white compound, m.p. 137.5–138.5°, whose analysis was compatible with the formula $C_8H_{12}N_2O_2S$. Let us call this "compound A."

The solubility of compound A in dilute hydrochloric acid, its analysis, and analogy with cases described below suggested that simple aminodechlorination had occurred, *via* a benzyne mechanism, forming VIII or its *ortho* isomer IX. The latter was synthesized by



VIII IX X

an unequivocal route; though its melting point (137–138°) was nearly the same as that of compound A, the mixture melting point was depressed and the infrared spectra were different. Compound A also differed from authentic VIII.

Authentic VIII and IX were acquired by condensing the appropriate nitroanilines with methanesulfonyl chloride, methylating the resulting sulfonamides with methyl sulfate, and finally reducing the nitro groups with stannous chloride.

Reinvestigation of the reaction of Vb with potassium amide in ammonia revealed that the product formed in a short (15 min.) reaction time was not compound A, but rather a neutral substance, m.p. 91–92°, whose analysis and n.m.r. spectrum were consistent with structure VI. The yield was 66%. A repeated reaction of one hour's duration yielded a mixture of VI (37%) and compound A (43%). This suggested that potassium amide slowly acted upon VI to produce compound A. Indeed, it was found that 68% of VI was converted into compound A during an hour's exposure to ring closure conditions; 22% of VI was recovered unchanged.

Two modes of action of potassium amide upon VI were conceivable. Amide ion might initiate aryne formation by attacking the hydrogen *ortho* to nitrogen, with subsequent fission of the C_{Ar}—N bond and finally nucleophilic addition of amide ion, forming X or its *meta* isomer. Or it might effect nucleophilic displacement on sulfur, generating VII. Apart from the fact that the m.p. of compound A differs from that (110–111°) reported for X,[12] identification of compound A as VII was indicated by the observation that compound A did not give the diazotization–azo coupling test characteristic of aromatic primary amines and by its n.m.r. spectrum. The latter revealed, besides the aromatic protons, two protons (the methylene group) at the same field as the methylene group of VI and three protons at higher field than in VI.

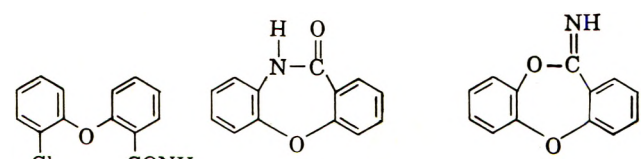
The proper name of VI is 1-methyl-2,1-benzisothiazoline 2,2-dioxide. Although benz-2,1-isothiazole is known,[13] we have not found any record of previous synthesis of a derivative of 2,1-benzisothiazoline 2,2-dioxide.

Methanesulfon(*o*-chloro)anilide (Va) reacted with four equivalents of potassium amide in ammonia (one-hour reaction time), but only basic, intractable oils were obtained.

Experiments with *o*-Chlorophenoxyacet- and Benzamides.—The action of strong base on a carboxamide carrying at least one hydrogen on nitrogen converts it to an anion in which the charge is shared between oxygen and nitrogen:

The reactions of Id and If, cited above, are testimony that such an anion can add via oxygen to an aryne "triple bond." Addition via nitrogen in an example of suitable geometry is also conceivable.

Accordingly 2-(*o*-chlorophenoxy)benzamide (XI) was exposed to potassium amide in ammonia in the hope

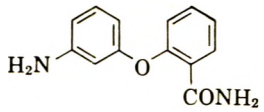


XI XII XIII

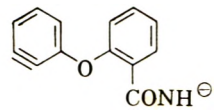
(12) U. M. Teotino and G. Cignarella, *J. Am. Chem. Soc.*, **81**, 4935 (1959).

(13) S. Gabriel and T. Posner, *Ber.*, **28**, 1025 (1895); J. Goerdeler and J. Kandler, *ibid.*, **92**, 1679 (1959).

of obtaining XII or XIII. The product isolated in 55% yield was, however, 2-(*m*-aminophenoxy)benzamide (XIV), identical with a sample procured by an unequivocal synthesis. Evidently aryne intermediate



XIV

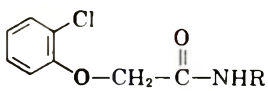


XV

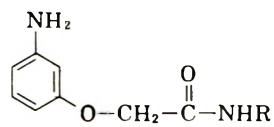
XV exists to such a large extent in conformations with $-CONH^-$ so remote from the aryne bond that external addition of amide ion prevails over intramolecular addition. That a cine-substitution product of *meta* orientation was formed is reasonable by analogy with the directing effect of the methoxy group in similar reactions.[14,15]

2-(*o*-Chlorophenoxy)benzoic acid was synthesized by the copper-catalyzed condensation of sodium *o*-chlorophenoxide with sodium *o*-iodobenzoate or *o*-chlorobenzoate. Both variations of this method were satisfactory. 2-(*o*-Chlorophenoxy)benzoic acid was then converted to its amide (XI) via the acid chloride. We got authentic XIV by copper-catalyzed reaction of sodium *m*-nitrophenoxide with sodium *o*-chlorobenzoate in 1-pentanol,[16] transformation of the resulting 2-(*m*-nitrophenoxy)benzoic acid to its amide, and finally stannous chloride reduction of the nitro group.

o-Chlorophenoxyacetamide (XVIa) and *o*-chlorophenoxyacetanilide (XVIb) were also submitted to the action of potassium amide in ammonia. None of the antici-



XVIa. R = H
b. R = C_6H_5

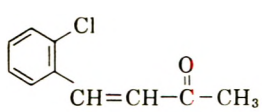


XVIIa. R = H
b. R = C_6H_5

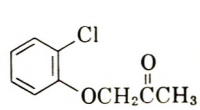
pated six-ring cyclization products was obtained. In both cases the presumed aryne intermediates added external amide ion preferentially, forming *m*-amino compounds XVIIa and XVIIb, respectively. Both were identical with authentic samples.

Authentic XVIIa and XVIIb were synthesized by condensation of sodium *m*-nitrophenoxide with sodium chloroacetate to *m*-nitrophenoxyacetic acid, reaction of the acid chloride with ammonia as well as aniline, and finally stannous chloride reduction of the nitroamides.

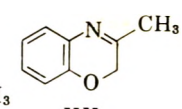
Experiments with Ketones.—It was hoped that potassium amide in ammonia would act upon *o*-chlorobenzalacetone (XVIII) to generate β-naphthol. How-



XVIII

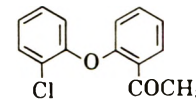


XIX

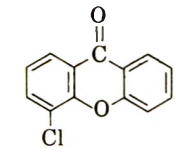


XX

ever, only tars were produced. The products from exposure of *o*-chlorophenoxyacetone (XIX) to ring closure conditions were also tarry, but a small amount of an unstable, pale yellow liquid whose properties resemble those reported for 2-methyl-2H-1,4-benzoxazine (XX)[17] was isolated. Formation of XX from XIX would parallel transformation of *o*-chlorophenylacetone to 2-methylindole as reported by Bunnett and Hrutfiord.[7]



XXI



XXII

2-(*o*-Chlorophenoxy)acetophenone (XXI) was made in 55% yield by treatment of 2-(*o*-chlorophenoxy)-benzoyl chloride with dimethylcadmium.[18] A lesser amount of 4-chloroxanthone (XXII) was obtained as a by-product. The latter was at first mistaken to be XXI, and was submitted to ring closure conditions. The product isolated in 26% yield was 3-aminoxanthone, representing aminodechlorination with rearrangement as might have been expected.[14,15] No well defined products were gained from exposure of XXI to potassium amide in ammonia.

Discussion.—Although the present research records further successes in formation of oxindole derivatives and a facile synthesis of the 2,1-benzisothiazoline 2,2-dioxide ring system, its principal contribution is toward defining the limitations of ring closure via aryne intermediates.

When cyclization does not occur according to the pattern of equation 1, the reason may be one of the following:

1. The substance subjected to the action of strong base may be converted into an anion with such a high concentration of negative charge on an atom next the ring that aryne formation is prevented.[7,9] In the present work, the unreactivity of Ib compared to the satisfactory cyclizations realized with Ia and Ic is an excellent illustration.

2. The side chain nucleophile may not be an effective competitor with the external strong base (in this work, potassium amide) in adding to the aryne bond. It may have inherently low nucleophilicity, or it may have an unfavorable steric relationship to the aryne function. In our experience, the occurrence of aminodechlorination in the reactions of XI, XVIa, and XVIb is illustrative. We tentatively conclude that carboxamide anions are relatively poor nucleophiles towards arynes, although we recognize that this disadvantage can be overcome by a superb steric relationship as in the arynes from Id and If. Clearly, reduction of the potassium amide concentration should favor intramolecular nucleophilic addition. We have not probed this variable systematically.

3. The expected ring closure product may itself react with the strong base reagent. This subsequent reaction may be fast, as in the example of diethyl 1,2,3,4 - tetrahydronaphthalene - 1,1 - dicarboxylate,[9] or recognizably slow as in the case of VI. In instances of the latter sort, complications can be avoided by employing a short reaction time.

(14) H. Gilman and S. Avakian, *J. Am. Chem. Soc.*, **67**, 349 (1945).
(15) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *ibid.*, **78**, 611 (1956).
(16) C. F. Koelsch and F. J. Lucht, *ibid.*, **71**, 3556 (1949).
(17) R. Stoermer and H. Brockerhof, *Ber.*, **30**, 1631 (1897).
(18) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

4. Reaction of the strong base with a side chain function may generate a different side chain nucleophile than anticipated. The reactions of *o*-chlorophenylacetone[7] and *o*-chlorophenoxyacetone (XIX) with potassium amide in ammonia are possible examples.

5. The substance submitted to the action of strong base may undergo some entirely different reaction in preference to ring closure. The cleavage of 2-chloro-2′,5′-dimethylbenzophenone by potassium amide in ammonia is an illustration.[19]

6. Intermolecular addition of side chain nucleophile to aryne "triple bond" may occur, giving rise to dimers, oligomers, or polymers. No certain example can be cited from experiments in liquid ammonia solvent.

7. Tars may be formed. This catch-all category, which is not foreign to our experience, can in principle include complications 2, 3, 5, and 6 as well as others, in various combinations.

With an understanding of the kinds of complications which can intrude, one is able to plan ring closure experiments with greater assurance. But he is handicapped by the imperfection of our knowledge of how strong bases such as potassium amide in ammonia react with various functional groups. Fortunately, this situation is gradually improving, in part by virtue of experimentation on ring closure reactions.

Experimental[20]

Preparation of Starting Materials. Phenylacet(*o*-chloro)anilide (Ib) was prepared by reaction of *o*-chloroaniline (7.0 g.) with phenylacetyl chloride (8.5 g.) in 75 cc. of carbon tetrachloride containing 4.3 g. of pyridine for 1.5 hr. The product (12 g.; 88%), crystallized from benzene as colorless needles, had m.p. 129–130° and was insoluble in water, difficultly soluble in ether, and carbon tetrachloride, and rather soluble in benzene and ethanol.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.88; N, 5.70; Cl, 14.46. Found: C, 69.12; H, 4.72; N, 5.97; Cl, 14.63.

Phenylacet(N-methyl-*o*-chloro)anilide (Ic).—A mixture of 7.0 g. of N-methyl-*o*-chloroaniline, 8.3 g. of phenylacetyl chloride, 4.0 g. of dry sodium bicarbonate, and 50 cc. of benzene was heated 5 hr. at reflux. The cooled mixture was extracted with concentrated aqueous sodium hydroxide, and the benzene layer was dried over solid potassium hydroxide, concentrated, and distilled at reduced pressure. The distillate, b.p. 178–185°/5 mm., weighed 7.0 g. (51%); it crystallized from petroleum ether, furnishing pale yellow prisms, m.p. 78–82°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.39; N, 5.39. Found: C, 69.50; H, 5.15; N, 5.13.

Acet(*o*-chloro)anilide (Id), m.p. 86–87° (lit.[21] 86.7°), acet(N-methyl-*o*-chloro)anilide (Ie), b.p. 126–132°/6 mm. (lit.[22] 142°/14 mm.), and methanesulfon(*o*-chloro)anilide (Va), m.p. 89–90° (lit.[23] 90.5°) were made substantially as described in the references.

Methanesulfon(N-methyl-*o*-chloro)anilide (Vb), m.p. 75–76°, was made by methylation of Va by methyl sulfate and aqueous alkali, and was crystallized from dilute ethanol.

Anal. Calcd. for $C_8H_{10}ClNO_2S$: C, 43.73; H, 4.55. Found: C, 43.76; H, 4.63.

2-(*o*-Chlorophenoxy)benzoic Acid. A. From *o*-Iodobenzoic Acid.—*o*-Iodobenzoic acid (25 g.) and potassium carbonate (7 g.) were combined in water, and the mixture was evaporated to dryness. Sodium metal (2.3 g.) was dissolved in 25 cc. of methanol, 38 g. of *o*-chloropenol was added, and the mixture was evaporated to dryness. The two residues were combined with 1 g. of copper powder and heated for 5 hr. at 170–180°. The cooled mixture was taken up in aqueous sodium carbonate solution, and the resulting mixture was treated with charcoal, filtered and acidified. The precipitated solid was extracted with hot water to remove *o*-iodobenzoic acid, and the residue was crystallized from dilute acetone, furnishing white needles, m.p. 128° (lit.[24] 123–124°).

Anal. Calcd. for $C_{13}H_9ClO$: C, 62.77; H 3.62. Found: C, 62.60; H, 3.66.

B. From *o*-Chlorobenzoic Acid.—To a solution of 9 g. of sodium metal in 300 cc. of methanol 25 g. of *o*-chlorophenol and 31 g. of *o*-chlorobenzoic acid were added, the solvent was evaporated, 1 g. of copper powder was added, and the mixture was heated at 180° (it melted) and finally to 220° (it solidified). The yield of 2-(*o*-chlorophenoxy)benzoic acid of m.p. 125–128° (128° after crystallization from methanol) was 35 g. (72%).

2-(*o*-Chlorophenoxy)benzamide (XI).—The above acid was converted to the acid chloride with thionyl chloride, and the latter was treated with aqueous ammonia. The product was crystallized from dilute methanol; m.p. 145°.

Anal. Calcd. for $C_{13}H_{10}ClNO_2$: C, 63.03; H, 4.04. Found: C, 62.90; H, 4.20.

o-Chlorophenoxyacetamide (XVIa), m.p. 149–150° (lit.[25] 149.5°), and *o*-chlorophenoxyacetanilide (XVIb), m.p. 125–127° (lit.[25] 121°), were prepared after Minton and Stephen.[25] Our XVIb was analyzed.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.24; H, 4.58. Found: C, 64.37; H, 4.76.

o-Chlorobenzalacetone (XVIII), b.p. 133–134°/6 mm. (lit.[26] 154–155°/17 mm.), was made after Vorländer.[26]

o-Chlorophenoxyacetone (XIX), b.p. 180–181°/65 mm. (lit.[27] 110–115°/4 mm.), was made after Bokarev and Mel'nikov,[27] except that chloroacetone was used instead of bromoacetone.

2-(*o*-Chlorophenoxy)acetophenone (XXI).—A Grignard reagent was prepared from magnesium metal (2.4 g.) and methyl iodide (14.2 g.) in ether, and to it 9.8 g. of anhydrous cadmium chloride was added and the mixture was heated at reflux for 70 min. The ether was removed, 50 cc. of benzene was added, and the mixture was vigorously stirred at reflux. The flask was cooled. The acid chloride obtained from 20 g. of 2-(*o*-chlorophenoxy)benzoic acid and 50 cc. of thionyl chloride in 50 cc. of benzene, with subsequent vacuum evaporation, was dissolved in 50 cc. of benzene and added dropwise with stirring. This caused active refluxing. The mixture was heated at reflux 1 hr. after completion of addition. By standard separation procedures, 3.0 g. (16%) of XXII, m.p. 135–136° (not depressed on admixture with an authentic sample[28]) and 11 g. (55%) of colorless XXI, b.p. 155–156°/3 mm., were isolated.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.15; H, 4.46. Found: C, 68.28; H, 4.43.

Preparation of Authentic Products (Actual or Conceivable). 2-Methylbenzoxazole (IVd), b.p. 95–96°/25 mm. or 197–199°/1 atm. (lit.[29] 200–201°/1 atm.), was made after Ladenburg.[29]

Methanesulfon(*m*-nitro)anilide was synthesized by condensation of *m*-nitroaniline (10.0 g.) with methanesulfonyl chloride (8.3 g.) in 56 cc. of pyridine on the steam bath for 2.5 hr. The product was isolated conventionally, and was crystallized from 95% ethanol. Cream-colored crystals, m.p. 161.5–163.5° (lit.[30] 164°), weighing 14.9 g. (95%), were obtained.

Anal. Calcd. for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73. Found: C, 39.01; H, 3.84.

Methanesulfon(N-methyl-*m*-nitro)anilide was made by heating a solution of 6.48 g. of the above product in 46 cc. of 16% aqueous sodium hydroxide with 16.0 g. of methyl sulfate 3 hr. at reflux, was isolated conventionally, and finally crystallized from 95% ethanol. It was obtained as colorless crystals (3.7 g.; 53%), m.p. 94–95°.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38. Found: C, 41.65; H, 4.35.

(19) J. F. Bunnett and B. F. Hrutfiord, Abstracts, 135th National Meeting of the American Chemical Society, Boston, April, 1959, p. 94-O; *J. Org. Chem.*, in press.

(20) Analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected.

(21) A. F. H. Lobry de Bruyn, *Rec. trav. chim.*, **36**, 135 (1916).

(22) P. Grammaticakis, *Bull. soc. chim.*, 761 (1949).

(23) C. S. Marvell, M. D. Helfrick, and J. P. Belsley, *J. Am. Chem. Soc.*, **51**, 1272 (1929).

(24) C. N. Deshpande, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.*, **2**, 33 (1957); *Chem. Abstr.*, **53**, 14100 (1959).

(25) T. H. Minton and H. Stephen, *J. Chem. Soc.*, 121, 1598 (1922).

(26) D. Vorländer, *Ann.*, **294**, 291 (1897).

(27) K. S. Bokarev and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **24**, 2014 (1954); *Chem. Abstr.*, **49**, 14678 (1955).

(28) S. N. Dhar, *J. Chem. Soc.*, 117, 1068 (1920).

(29) A. Ladenburg, *Ber.*, **9**, 1524 (1876).

(30) A. G. Kostsova, *Zh. Obshch. Khim.*, **24**, 618 (1954); *Chem. Abstr.*, **48**, 10537 (1954).

Methanesulfon(N-methyl-*m*-amino)anilide (VIII).—The above product (2.30 g.) was heated with stirring 60 min. on the steam bath with 8.4 g. of hydrated stannous chloride and 10 cc. of concentrated hydrochloric acid. The cooled mixture was basified, the precipitated tin hydroxides were removed by filtration, the filtrate was extracted with ether, and VIII was gained from the extract with ultimate crystallization from 95% ethanol. Pale yellow crystals (0.5 g.; 29%), m.p. 87.5–88.5°, were obtained.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04. Found: C, 47.93; H, 6.03.

Methanesulfon(*o*-nitro)anilide.—The method used for the *meta* isomer was unsuccessful. *o*-Nitroaniline (5.25 g.), 21 cc. of triethylamine, 15 g. of methanesulfonyl chloride, and 200 cc. of toluene were combined and heated 4 hr. at reflux. By conventional methods, 2.95 g. (36%) of pale yellow crystals (from 95% ethanol), m.p. 101–103°, were isolated.

Anal. Calcd. for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73. Found: C, 38.95; H, 3.89.

Methanesulfon(N-methyl-*o*-nitro)anilide, pale yellow crystals of m.p. 142–143°, was prepared in 88% yield by the procedure used for the *meta* isomer.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38. Found: C, 41.58; H, 4.40.

Methanesulfon(N-methyl-*o*-amino)anilide (IX), pale yellow crystals of m.p. 137–138°, was prepared in 65% yield by the procedure used for VIII, with the exception that the precipitated tin hydroxide as well as the filtrate was extracted with ether.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 48.19; H, 6.01; N, 13.82.

2-(*m*-Nitrophenoxy)benzamide was prepared by treating 2-(*m*-nitrophenoxy)benzoic acid[16] with thionyl chloride, and the resulting acid chloride with aqueous ammonia. The amide formed pale yellow prisms, m.p. 116–117°, on crystallization from ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87. Found: C, 60.54; H, 3.98.

2-(*m*-Aminophenoxy)benzamide (XIV) was obtained by stannous chloride reduction of the nitro amide. XIV formed colorless prisms (from benzene), m.p. 140–142°.

m-Nitrophenoxyacetamide, m.p. 179.5–182.5° (lit.[31] 178.5°), was prepared after Minton and Stephen.[31] It was reduced to *m*-aminophenoxyacetamide (XVIIa) by brief exposure to stannous chloride in hydrochloric acid on the steam bath; XVIIa was obtained as colorless crystals (from benzene), m.p. 118.5–119.5° (lit.[32] 123.5–124°).

***m*-Nitrophenoxyacetanilide**, m.p. 124–125° (lit.[31] 125°), was prepared after Minton and Stephen.[31]

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.79; H, 4.45. Found: C, 61.59; H, 4.53.

***m*-Aminophenoxyacetanilide (XVIIb)** was secured by reduction of the above nitro anilide with stannous chloride and hydrochloric acid on the steam bath for 1 hr. XVIIb was obtained as colorless crystals (from 95% ethanol), m.p. 123–124°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.34; H, 5.82; N, 11.55. Found: C, 69.31; H, 6.01; N, 11.70.

Reactions with Potassium Amide in Ammonia.—Except as otherwise stated, reactions were performed as described by Bunnett and Hrutfiord.[7]

Of Phenylacet(N-methyl-*o*-chloro)anilide (Ic).—Ic (1.5 g.) in 50 cc. of dry ether was treated with a solution of potassium amide (from 1.0 g. of potassium metal) in 500 cc. of liquid ammonia. Reaction time was 30 min. By standard procedures, 1.1 g. (91%) of IIc, m.p. 118–119° (lit.[33] 118–119°), was isolated as colorless leaflets (from diethyl ether and petroleum ether).

Of Acet(N-methyl-*o*-chloro)anilide (Ie).—Ie (5.4 g.) in 100 cc. of ammonia was treated for 60 min. with a solution of potassium amide (from 3.5 g. of potassium metal) in 400 cc. of ammonia. By standard procedures, 0.7 g. (16%) of IIe, m.p. 87–89° (lit.[34] 89°), was isolated as white needles (from petroleum ether).

Of Acet(*o*-chloro)anilide (Id).—To 5 g. of Id in 100 cc. of ammonia, a solution of potassium amide (from 4.7 g. of potassium metal) in 400 cc. of ammonia was added. Reaction time was 40 min. By standard procedures, 1.5 g. (37%) of IVd was isolated as a colorless liquid of b.p. 67–69°/6 mm. or 98°/26 mm. The infrared spectrum was identical to that of the authentic sample of 2-methylbenzoxazole (above).

Of Methanesulfon(N-methyl-*o*-chloro)anilide (Vb). First Run.—To 5.3 g. of Vb in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 4.4 g. of potassium metal) in ammonia was added. Reaction time was 60 min. The crude reaction product was fractionated by customary extraction procedures. From the fraction soluble in dilute hydrochloric acid, 1.8 g. (38%) of white needles, (from ethanol), m.p. 136–137°, was isolated. A negative test for chlorine and positive tests for nitrogen and sulfur were obtained.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 48.00; H, 6.00. Found: C, 47.82; H, 6.06.

Second Run. By the "one pot" technique of Bunnett and Skorcz,[9] 4.5 g. of Vb was allowed to react 15 min. with potassium amide (0.082 mole) in 300 cc. of ammonia. From the neutral fraction, 2.53 g. (66%) of VI was isolated as colorless crystals (from chloroform-petroleum ether), m.p. 91–92°.

Anal. Calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95. Found: C, 52.38; H, 4.96.

Third Run. Quantities and technique were as in the second run, but reaction time was 60 min. From the neutral fraction, 1.63 g. (43%) of VI, m.p. 90–92°, was isolated. The acid-soluble fraction yielded 1.5 g. (37%) of a compound, m.p. 137–138.5°, whose mixture m.p. with the substance of m.p. 136–137° from the first run was not depressed. For reasons stated in the text, this was taken to be VII.

The n.m.r. spectra of VI and VII were run at 60 Mc. in deuteriochloroform.[35] For VI, an unsplit three proton peak (the N-methyl group) showed a chemical shift of −3.1 p.p.m. relative to tetramethylsilane, and an unsplit two proton peak (the CH_2 group) showed a shift of −4.3 p.p.m. For VII, the peaks were again unsplit and the shifts were −2.8 p.p.m. and −4.35 p.p.m., respectively.

Of 1-Methyl-2,1-benzisothiazoline 2,2-Dioxide (VI).—A 2.5 g. sample of VI was treated with potassium amide (0.062 mole) in 300 cc. of ammonia for 60 min. by the technique of Bunnett and Skorcz.[9] Recovered VI, m.p. 89–91°, weighed 0.55 g. (22%), and 1.45 g. (68%) of sulfonamide VII, m.p. 136–138°, was isolated.

Of 2-(*o*-Chlorophenoxy)benzamide (XI).—To 3.5 g. of XI in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 2.2 g. of potassium metal) in ammonia was added. Reaction time was 60 min. Besides a small amount of recovered XI, 2.7 g. (77%) of XIV was isolated (from the acid-soluble fraction) as white prisms (from benzene), m.p. 144°. A positive diazotization–azo coupling test was obtained. The mixture m.p. with authentic XIV (above) was not depressed.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26. Found: C, 68.28; H, 5.19.

Of *o*-Chlorophenoxyacetamide (XVIa).—To 4.5 g. of XVIa in 200 cc. of ammonia, a solution of potassium amide (from 3.9 g. of potassium metal) in ammonia was added. Reaction time was 30 min. By standard procedures, 0.6 g. (15%) of XVIIa, m.p. 122–123°, was isolated as white needles. The identity of this with authentic XVIIa (above) was established by mixture m.p. and the identity of the infrared spectra of the two samples.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.12; H, 6.10; N, 16.82.

Of *o*-Chlorophenoxyacetanilide (XVIb).—To 5.2 g. of XVIb in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 3.2 g. of potassium metal) in ammonia was added. Reaction time was 70 min. By standard procedures, 3.5 g. (79%) of XVIIb, m.p. 125°, was isolated as prisms (from benzene) or needles (from dilute ethanol). The identity of this with authentic XVIIb (above) was established by mixture m.p. and identity of infrared spectra.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.64; H, 5.88.

Of *o*-Chlorophenoxyacetone (XIX).—To 6.5 g. of XIX in 100 cc. of ammonia a solution of potassium amide (from 4.5 g. of potassium metal) in ammonia was added. Reaction time was 60 min. The product was largely brown tarry substances soluble in dilute hydrochloric acid. By chromatography on alumina and distillation at reduced pressure (b.p. 145°/6 mm.),

(31) T. H. Minton and H. Stephen, *J. Chem. Soc.*, 121, 1591 (1922).

(32) W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **39**, 2423 (1917).

(33) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952).

(34) O. Hinsberg and J. Rosenzweig, *Ber.*, **27**, 3253 (1894); R. Stolle, D. R. P. 335,763 (June 14, 1914); P. Friedlaender, "Fortschritte der Teerfarbenfabrikation," Vol. 13, 1923 p. 446.

(35) The n.m.r. spectra were obtained through the courtesy of Dr. H. Agahigian of Olin Mathieson Chemical Co., New Haven, Conn.

a small amount of pale yellow liquid with an amine-like odor was obtained. This turned brown on exposure to the air, gave a positive ferric chloride test, a negative test for chlorine and a positive test for nitrogen, and with chloroplatinic acid formed a salt melting above 250°. These properties match those reported by Stoermer and Brockerhof[17] for 2-methyl-2H-1,4-benzoxazine (XX).

Anal. Calcd. for $(C_9H_9NO)_2 \cdot 2HCl \cdot PtCl_4$: C, 30.68; H, 2.84; N, 3.98. Found: C, 30.63; H, 3.41; N, 4.03.

Results from a run with a 10-min. reaction time were similar.

Of 4-Chloroxanthone (XXII).—To 1.7 g. of XXII in 100 cc. of ether and 100 cc. of ammonia a solution of potassium amide (from 1.1 g. of potassium metal) was added. Reaction time was 30 min. By standard procedures, 3-aminoxanthone, m.p. 233–234° (lit. 232° for 3-aminoxanthone,[36] 199–200° for 4-aminoxanthone[37]), was isolated in 26% yield.

(36) F. Ullmann and C. Wagner, *Ann.*, **355**, 395 (1907).

(37) S. Akagi and T. Iwashige, *J. Pharm. Soc. Japan*, **74**, 610 (1954); *Chem. Abstr.*, **48**, 10742 (1954).

Experiments Directed toward the Total Synthesis of Terpenes. IV. The Synthesis of (±)-Sandaracopimaradiene and (±)-Pimaradiene[1,2]

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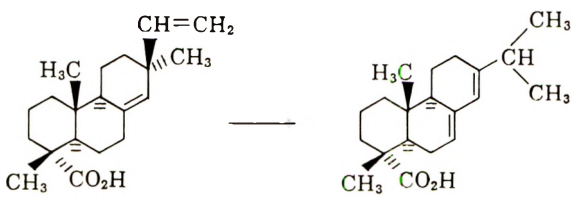
Two synthetic sequences for the conversion of (±)-14-podocarpanone (**11**) to (±)-sandaracopimaradiene (**2**) and (±)-pimaradiene (**3**) are described. The first route involves the methylation of (±)-13-ethylidene-14-podocarpanone (**23**), while a second, milder pathway proceeds through (±)-13-podocarpen-13-carboxaldehyde (**31**).

The synthetic challenge presented by the diterpenoid resin acids, such as abietic acid and the pimaric acids, while similar to that of the steroids, has been overlooked until recently because of the lack of any significant therapeutic effect associated with the diterpenes. The solution to the synthetic problems associated with the steroids has not only brought about renewed interest[3] in the resin acids, but also laid an experimental foundation of incalculable value to one rising to the challenge of these acids. As a part of this resurgence of interest in the diterpenes, we began an integrated program directed toward elaborating methods suitable to the total synthesis of the pimaric acids. The pimaric acids, rather than the more common abietic acid, were chosen as a goal since it appeared reasonable to expect that acid catalyzed rearrangement of these acids would ultimately lead to abietic acid. That such was indeed the case was later shown by Wenkert and co-workers[6a] when they effected the isomerization of (+)-pimaric acid to (−)-abietic acid by treatment with sulfuric acid.

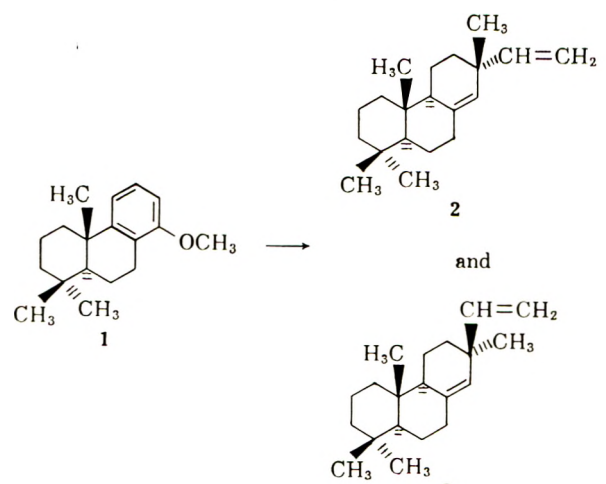


(+)-Pimaric acid (−)-Abietic acid

As a result, a total synthesis of the synthetically more complex pimaric acid would represent a formal total synthesis of abietic acid.

Much as has been done by previous workers,[3] our program was divided into two main phases: one directed toward the construction of a tricyclic acid possessing the appropriate substituents on the *trans*-fused A and B rings and an aromatic C-ring[4]; coupled with this, a program was initiated to investigate methods suitable for the conversion of a model aromatic system to a compound having the ring C substitution pattern of the pimaric acids. In this manner, the procedures developed in the latter phase would be available for application to the intermediate that resulted from the former phase, and hence lead to a scheme for the total synthesis of the pimaric acids.

The work described herein is concerned with the methods that we were able to develop for the construction of the ring C substitution pattern of the pimaric acids. The first choice to be made was that of an appropriate model for this work, and while in principle a simple monocyclic system could serve as such a model, we chose instead the tricyclic ether **1**.[5] The rationale behind this choice was that a tricyclic model, lacking only the asymmetry at C-4, would more closely approximate the tricyclic acid resulting from the other phase of the program. An equally important factor was that a stereorational route for the conversion of the ether **1** to the dienes **2** and **3** offered the opportunity to test the earlier stereochemical assignments[6] of the pimaric acids



(1) For a preliminary report of this work, see R. E. Ireland and R. W. Schiess, *Tetrahedron Letters*, No. **25**, 37 (1960).

(2) This investigation was supported by the National Science Foundation through a research grant (G-5912).

(3) For a recent review, see N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.*, **16**, 117 (1962).

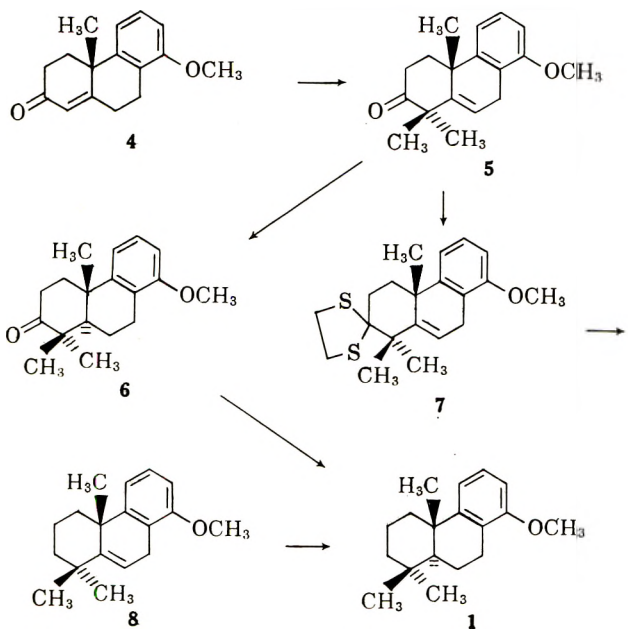
(4) R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962).

(5) Steroid numbering is used throughout, and although formulas of only one enantiomer are drawn, they are taken to represent a racemate except where indicated.

(6) (a) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959); (b) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959); (c) B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958).

by comparison with the derived pimaradienes. Of added interest at the outset of this work was that the diterpenoid hydrocarbon rimuene was proposed to have the sandaracopimaradiene structure **2**.[7] Hence, by employing the tricyclic ether **1** for our model experiments, we were in a position to test this proposal.

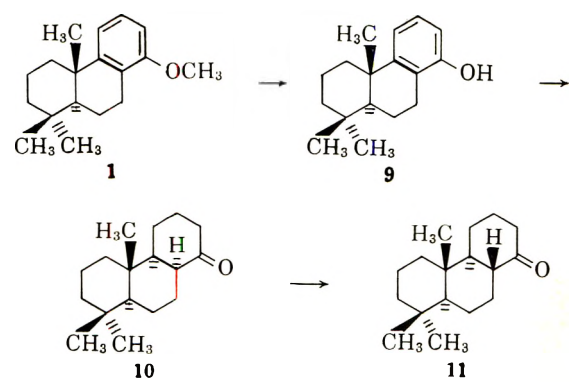
For the ether **1** to serve an efficient model, it must be readily available in large quantities, a condition that was readily satisfied by the application of methods found earlier by those concerned with the construction of polycyclic intermediates for steroid total synthesis. In particular, large quantities of the tricyclic ketone **4** were prepared from 5-methoxy-2-tetralone, following the excellent procedure described by Robinson and co-workers.[8] Introduction of the *gem*-dimethyl system at C-4 was cleanly accomplished in 75% yield according



to the conditions of Woodward and co-workers[9] by treatment of the ketone **4** with excess potassium *t*-butoxide and methyl iodide.

In our hands the obvious and more direct path from the ketone **5** to the ether **1**—namely, catalytic hydrogenation of the 5,6-double bond and reductive removal of the 3-ketone—proved unsatisfactory.[10] Thus, while the saturated ketone **6** was obtained in 50% yield by reduction over 10% palladium on carbon, its isolation in pure form required chromatography and was not readily amenable to large scales. This result, coupled with only a 60% yield of the ether **1** on Wolff–Kishner reduction[11] of the saturated ketone **5**, made us look for another route. A better sequence for effecting the conversion of the ketone **5** to the desired ether **1** was found in the desulfurization of the dithioketal **7**. This ketal was prepared in 97% yield by the elegant procedure of Fieser,[12] and on desulfurization with W-2 Raney nickel[13] in alcohol solution, the olefin **8** resulted in an 81% yield. Finally, catalytic hydrogenation over 10% palladium on carbon afforded a 95% yield of the desired ether **1**. The high yields obtained in these easy steps made this sequence quite attractive. In this manner, the ketone **5** could be converted to the ether **1** in an over-all 81% yield by a method that required the minimum of time and was readily adapted to the large scales necessary.

Our supply of the ether **1** assured, we turned our attention to the modification of the aromatic ring. We had specifically chosen to work with a model with a C-14 oxygen function, for when the aromatic ring was saturated, we could expect to obtain the more stable B/C-ring fusion through enolization of a C-14-keto function. The more stable B/C ring fusion, however, is determined by the orientation of the C-9 hydrogen. Thus, if C-9 hydrogen is α-oriented, the desired B/C-*trans* fusion is more stable than the B/C-*cis* juncture (*trans-anti-trans* > *trans-anti-cis*), but if the C-9 hydrogen were β-oriented, the more stable fusion is that where the rings are *cis*-locked (*trans-syn-cis* > *trans-syn-trans*). It was possible to assure the introduction of a C-9α-oriented hydrogen through the agency of chemical reduction where the more stable *anti* backbone would be expected, but this would require the use of forcing metal–ammonia reduction conditions[14] where the yields are not high. Therefore, it seemed more profitable to investigate the catalytic reduction of the aromatic ring.



To this end the free phenol **9** was prepared in 90% yield from the ether **1** by treatment with hydrobromic–hydriodic acid in glacial acetic acid. Reduction of this phenol over ruthenium in alcohol solution[15] occurred rapidly and afforded a saturated alcohol, which without purification was oxidized with Jones reagent[16] in cold acetone. The crystalline ketone that resulted in a 95% crude yield from this treatment melted at 65–67° when analytically pure (40% yield). When this ketone was chromatographed on alumina, a new ketone, melting at 73–73.5° was obtained in 90% yield. Similarly, if the saturated alcohol were oxidized with Jones reagent[16] and the crude product purified by filtration through

(7) L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmhurst, *Tetrahedron Letters*, No. **8**, 13 (1959). The authors are indebted to Professor Briggs for providing us with a sample of rimuene.

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

(9) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(10) This route proved a satisfactory sequence for R. B. Turner and P. E. Shaw [*Tetrahedron Letters*, No. **18**, 24 (1960)] who also prepared the ether **1** as well as the ketone **11**. However, in view of the different experimental conditions employed by these workers, our synthesis is included here.

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

(12) L. F. Fieser, *ibid.*, **76**, 1945 (1954).

(13) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

(14) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956).

(15) W. S. Johnson, E. G. Rogier, and J. Ackerman, *ibid.*, **78**, 6322 (1956).

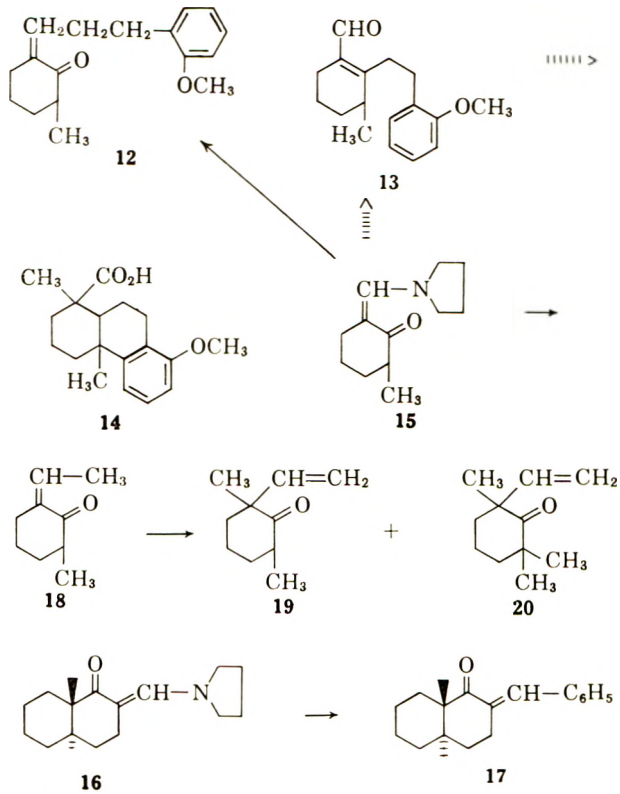
(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also, C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

alumina, the 73° ketone was obtained in 86% over-all yield from the phenol **9**.

The behavior of the two ketones obtained in this sequence suggests that the C-9 hydrogen has been introduced in the α-orientation and that the 67° ketone is the less stable *trans-anti-cis* ketone **10** which is isomerized by the basic alumina to the more stable *trans-anti-trans* ketone **11**.

Firstly, the observation that the 5,6-double bond in such tricyclic systems is saturated solely by attack of the α-face of the molecule[17] provides good precedence for saturation of the aromatic system taking a similar steric course. A more compelling argument was found on comparison of the solution infrared spectra of the two ketones **10** and **11**. While these spectra were similar, there were significant differences in the 900–1400-cm.$^{-1}$ region which precluded these two ketones being polymorphic forms of the same substance. On theoretical groups, one can also argue that had saturation of the aromatic ring occurred by β-addition of hydrogen, the resulting *trans-syn-cis* ketone[18] would be the more stable of the pair and would not have undergone isomerization on alumina.[19] Therefore, the assignment of the desired *trans-anti-trans* structure **11**[10] to the 73° ketone appeared to be on firm ground, and we proceeded further with the synthetic scheme.

At this point we called on some experience gained from our work on the first phase of the general resin acid synthesis. The plan envisioned for the construction of the necessary tricyclic acid involved the addition of 2-(*o*-methoxyphenyl)ethylmagnesium bromide to a derivative of 2-hydroxymethylene-6-methylcyclohexanone to generate the aldehyde **13**, which could be methylated, oxidized and cyclized to afford the desired acid **14**. The derivative we chose was the pyrrolidine eneamine **15**,[20] which proved more stable and more readily prepared on a large scale than the more familiar isopropyl ether.[21] However, unlike the isopropyl ether, we found that the addition of the organometallic reagent (either the magnesium or the lithium reagent) did not take place in the desired 1,2-sense to generate the aldehyde **13** after acid hydrolysis, but rather in the 1,4-sense[22] and thereby afforded the unsaturated ketone **12**. This conclusion is based on the observations that the infrared spectrum of this material lacked a band attributable to an aldehydic hydrogen at 2750 cm.$^{-1}$ and



the substance also failed to deposit metallic silver from Tollens reagent. Also indicative of the presence of a cisoid α,β-unsaturated ketone system was a maximum in the ultraviolet spectrum at 245 mμ (ϵ 7600). Further confirmation of the 1,4-mode of addition of organometallic derivatives to the pyrrolidinomethylene ketones was found when 2-benzylidene-1-decalone (**17**)[23] was obtained in 95% yield by treatment of the eneamine ketone **16** with phenylmagnesium bromide.

Even though these results left much to be desired from the standpoint of preparing the acid **14**, they opened up an excellent avenue for the production of alkylidene ketones—compounds that are not readily available by direct condensation of aliphatic aldehydes and ketones. Thus, when the pyrrolidinomethylene ketone **15** was treated with methylmagnesium bromide, a 54% yield of the ethylidene ketone **18** resulted.

Taking advantage of the ready availability of the ethylidene ketone **18**, we investigated the alkylation reaction with methyl iodide and potassium *t*-butoxide. When the ketone **18** was methylated using the standard reaction conditions,[9] only a very low yield of monomeric product was formed. The obvious conclusion to be drawn from such a result is that the base establishes an equilibrium between the ketone and its enolate and that polymerization *via* Michael-type addition of the enolate to un-ionized ketone takes place before (or more rapidly than) methylation. To overcome this difficulty, we employed a large excess (36-fold) of potassium *t*-butoxide on the premise that if all the ketone could be enolized, the enolate itself would not undergo polymerization. It was gratifying to find that this was indeed the case since, when the ketone **18** was methylated under these conditions, there resulted a 75% yield of a mixture of the ketones **19** and **20**. There was very little of the monomethylated product formed because of the large excess of reagents; it was possible, however, to isolate

(17) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962).

(18) R. F. Church and R. E. Ireland, *J. Org. Chem.*, **27**, 17 (1962).

(19) This argument relies on the assumption that hydrogenation of the ring occurs completely during one adsorption on the catalyst and thereby introduces all of the hydrogens from the same side and generates a B/C-*cis* ring fusion. If a multiadsorption process were involved then, barring the steric requirements of the molecule, a B/C-*trans* fusion could theoretically be produced. The 9α,8β-B/C *trans* system would lead to the stable *trans-anti-trans* ketone—a condition we did not observe. However, the 9β,8α-B/C *trans* system would lead to the base labile *trans-syn-trans* ketone on oxidation. If such were the case, then the isomerization of the initially formed ketone on alumina would be from a *trans-syn-trans* ketone to a *trans-syn-cis* one. This latter situation is very unlikely, for even if the hydrogenation were to be a step-wise process, the fewer double bonds remaining in ring C, the more attack of the α-face should be favored by the puckering of the ring. Secondly, the product of the reduction appears to be stereochemically quite homogeneous—a result that would not be expected of a stepwise reduction, for there would certainly be some of the C-9 hydrogen introduced in the α-orientation even by a step-wise process. Finally, the authentic *trans-syn-cis* ketone has recently been prepared[18] in these laboratories and was shown to differ from the stable 73° ketone described here by comparison of their infrared spectra and depression of the mixture melting point.

(20) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).

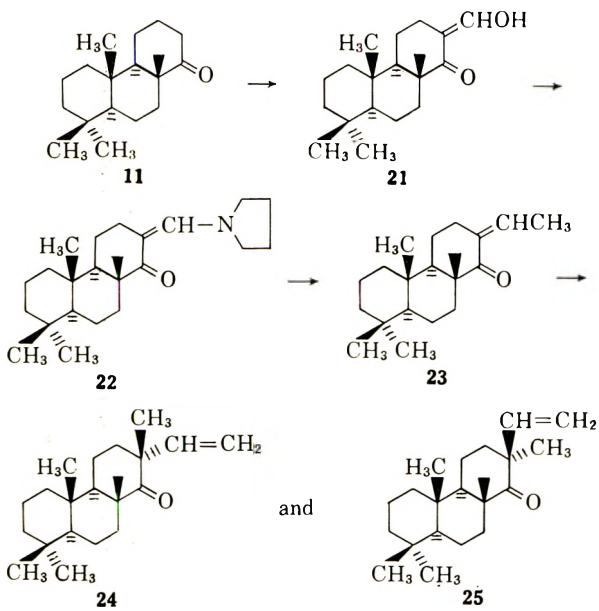
(21) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).

(22) C. Jutz, *Ber.*, **91**, 1867 (1958).

(23) W. S. Johnson, *J. Am. Chem. Soc.*, **65**, 1317 (1943).

the pure trimethyl ketone **20** by distillation. That the methylation had occurred on the α-carbon with shift of the double bond out of conjugation was shown both by the characteristic bands of the vinyl group at 3.24, 5.48, 6.18, 10.08, and 10.94 μ in the infrared spectrum of the product and by the absence of the conjugated ketone chromophoric system in the ultraviolet spectrum [λ_{max}^{alc} 301 mμ (ϵ 75)].

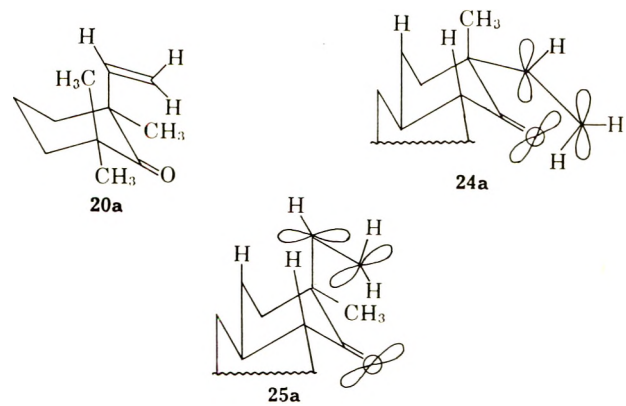
Although these methylation conditions were sufficiently vigorous to methylate both the α and the α' positions of the ethylidene ketone **18**, we felt that were they applied to (±)-13-ethylidene-14-podocarpanone (**23**), there would be a good chance of observing only methylation at the 13-position in view of the difficulty previous workers have had in effecting angular methylation.[23,24] To this end, (±)-14-podocarpanone (**11**) was converted to its hydroxymethylene[21] derivative **21** and thence to the pyrrolidinomethylene ketone **22**



11 **21** **22** **23** **24** **25**

in an over-all 83% yield by azeotropic removal of water from a benzene solution of the hydroxymethylene ketone **21** and pyrrolidine. Treatment of the eneamine **22** with methylmagnesium bromide in benzene–ether solution, followed by hydrolysis of the reaction mixture with 10% aqueous hydrochloric acid led to a 94% yield of the ethylidene ketone **23**. On methylation of the ketone **23** in the presence of a 130-fold excess of potassium *t*-butoxide, there was obtained a 71% yield of crude, monomeric product, the ultraviolet spectrum of which indicated that *ca.* 8% of the conjugated ketone still remained. By a process of crystallization and chromatography, we were able to isolate from this crude distillate a 9% yield of the pure equatorially methylated ketone **25**, m.p. 78–80°, and a 32% yield of the pure axially methylated ketone **24**, m.p. 69–70°. These crucial stereochemical assignments are based on the following reason processes. In the absence of major steric requirements, one would expect that methylation of the enolate of the ketone **23** to be governed by stereoelectronic control whereby the predominate product should be that resulting from axial attack.[25] Thus on theoretical grounds, one would expect that the ketone formed in preponderant yield from our methylation would be that having structure **24** [β-(axial)methyl]. If we assume that no selective loss of one ketone occurred during our fractionation of the crude product, then the 70° ketone, obtained in 32% yield, must have the structure **24**. Further, we observed that the 70° ketone was more strongly adsorbed on Florisil than its epimer. This would tend to indicate that the polar substituents on the 70° ketone are more exposed than those on the epimeric 80° ketone, and therefore suggests that the 70° ketone possesses the α-(equatorial)-vinyl grouping as required by structure **24**.

More rigorous evidence for this stereochemical assignment was found in an analysis of the ultraviolet spectra of the two ketones. In alcohol solution the 70° ketone exhibited a maximum at 292 mμ (ϵ 51), while the 80° ketone had its maximum at 294 mμ (ϵ 104). These values indicate, first of all, that the ketones are not methylated at C-8, for the maxima of both occur at significantly lower wave length than either tetramethylcyclohexanone [λ_{max}^{alc} 300 (ϵ 24)] or 2,2,6-trimethyl-6-vinylcyclohexanone (**20**) [λ_{max}^{alc} 301 (ϵ 75)], both of which are known to be $\alpha,\alpha,\alpha',\alpha'$-tetrasubstituted cyclohexanones. Secondly, the bathochromic shift observed between the two ketones indicates that the vinyl grouping in the 80° ketone is in a position to interact with the carbonyl group, while that in the 70° ketone is not. Molecular models of the two possible structures **24** and **25** show that while there is free rotation about the C-4 vinyl grouping bond, the more stable conformations are those indicated in structures **24a** and **25a**. It can be seen that only in structure **25a** can there be any interaction between the π_c orbital of the vinyl group and the nonbonding p_n-orbital of the carbonyl oxygen. Such an interaction should lead to a p_n-π_c^* transition of the type discussed by Labhart and Wagniere[26] and hence a bathochromic displacement of the carbonyl absorption should be observed in the spectrum of the ketone with structure **25a**. Because of the free rotation about the C-13 vinyl grouping bond, this interaction would not be expected to be as great in magnitude as some of the cases mentioned by these[26] and other authors.[27] That this change in the ultraviolet absorption of the two ketones was not due solely to solvent interaction was shown by their spectra in cyclohexane where the 80° ketone absorbed at 295 mμ (ϵ 98) and the 70° ketone at 294 mμ (ϵ 45). It is also interesting to



20a

24a

25a

(24) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937); A. J. Birch and R. Robinson, *ibid.*, 501 (1944).

(25) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961); W. S. Johnson, D. S. Allen, Jr., R. R. Hindersin, G. N. Sausen, and R. Pappo, *ibid.*, **84**, 2181 (1962).

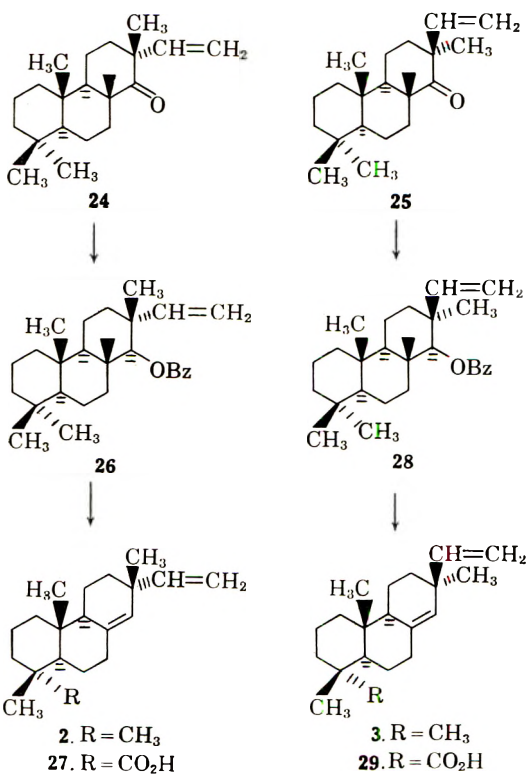
(26) H. Labhart and N. S. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

(27) S. Winstein, L. deVries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1961), and references cited therein.

note that the ultraviolet absorption of the vinyl cyclohexanone **20** is more intense than the analogous saturated 2,2,6,6-tetramethylcyclohexanone—a result that suggests the presence of the conformation **20a**. A similar effect has been observed by Cookson[28] for α,α-diphenylcyclohexanone, where one phenyl group must occupy an axial conformation. On the basis of this analysis and the circumstantial evidence cited above, we have assigned structure **25** to the 80° ketone and structure **24** to the 70° ketone.

The infrared spectra of the two epimeric vinyl ketones **24** and **25** also show a small, but noticeable shift in the position of the principle vinyl absorption band. This strong band occurs at 10.96 μ in the spectrum of the α-(equatorial) vinyl ketone **24**, whereas, this band was found to occur at 10.88 μ in the spectrum of the β-(axial) vinyl ketone **25**. We have found[29] throughout our work that this relationship between the conformation of the vinyl group and position of this band is quite diagnostic. For instance, methyl sandaracopimarate, methyl isopimarate and the corresponding sandaracopimaraidene and isopimaradiene all have an equatorial vinyl substituent and all show a strong band at 10.96–10.98 μ, whereas methyl pimarate and pimaradiene with axial vinyl groups absorb at 10.86–10.88 μ.

The final problem to be overcome in our quest for a route to the pimaradienes was the conversion of the C-14 ketone to a $\Delta^{8(14)}$ double bond. The first step in this process was the reduction of the ketones **24** and **25** to their corresponding alcohols by treatment with sodium in alcohol solution. In view of the homoallylic character of these alcohols, it was felt that in effecting their elimination, a nonionic process was necessary to prevent skeletal rearrangements. Therefore, the individual alcohols were not purified themselves but converted directly to their benzoates with benzoyl chloride in pyridine solution. In this fashion the ketone **24** led to the benzoate **26** in 81% yield and its epimer **25** afforded a 75% yield of the benzoate **28**. In each case the mode of reduction dictates that the C-14 oxygen bond be equatorial and hence *cis* to the C-8 hydrogen. Advantage was then taken of the concerted character of the pyrolytic ester elimination reaction to remove the elements of benzoic acid and generate the desired dienes. Thus, when the benzoate **26** was sublimed through a glass wool packed chamber heated at 430°, there was obtained a 79% yield of the diene **2**, while the same treatment of the benzoate **28** afforded an 82% yield of the diene **3**. Each diene was purified by filtration through an alumina column in pentane solution and shown to consist of only one component to the extent of at least 90% by gas-liquid chromatography. An important condition of the latter criterion of purity was that a mixture of the two dienes was readily resolved into its components under the same gas-liquid chromatographic conditions; the diene with the axial vinyl grouping **3** was retained on the column 0.89 as long as the equatorial vinyl diene **2**.



At this point it became important to compare the properties of our synthetic dienes **2** and **3** of known structure and stereochemistry with their optically active counterparts derivable from sandaracopimaric and pimaric acids, respectively. The conversion of these acids[30] to their dienes followed the classical reaction sequence: $RCO_2H \rightarrow RCH_2OH \rightarrow RCHO \rightarrow RCH{=}NNHCONH_2 \rightarrow RCH_3$. In each case, although the aldehydes, sandaracopimaral and pimaral, were isolated and characterized once, it was found more expedient to isolate them from the oxidation with Jones reagent[16] as their semicarbazones, for the free aldehydes were relatively unstable. Application of the Huang–Minlon modification[11] of the Wolff–Kishner reduction to these semicarbazones directly proved a very satisfactory method for preparing the desired optically active dienes (−**2**) and (+**3**).[31] Thus sandaracopimaric acid (**27**) afforded a 56% over-all yield of sandaracopimarodiene (−**2**), m.p. 41–42°, $[\alpha]_D$ −12°, and pimaric acid (**29**) gave a 66% over-all yield of pimaradiene (+**3**), m.p. 24–26°, $[\alpha]_D$ +99°. That no skeletal rearrangement had taken place during this degradation and that these dienes were indeed stereochemically and structurally the same as their parent acids was shown by the persistence at every stage of two characteristic skeletal vibrations at 854 cm.$^{-1}$ and 865 cm.$^{-1}$ in the infrared spectra of the intermediates, as well as the acids and the dienes themselves. The 800–900-cm.$^{-1}$ region of the infrared spectrum seems to be quite sensitive to the basic skeleton of the hydrophenananthrene system, for the pattern of bands in this region is insensitive to the type and stereochemistry of the substitution—*i.e.*, α or β-CO_2R, CHO, CH_2OH, CH_3 do not change the pattern—but is quite sensitive to both the position of the substituents on the periphery of the ring system, the stereochemistry of the backbone—*i.e.*, the *trans-syn*-$\Delta^{8(14)}$ system[18] absorbs at 860 cm.$^{-1}$ only—and the position of the nuclear double bond—*i.e.*, the *trans-anti*-Δ^7 system (iso-

(28) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956).
(29) See also, H. H. Bruun, *Acta Chem. Scand.*, **10**, 577 (1956).
(30) The authors are greatly indebted to Dr. O. E. Edwards for supplying us with generous quantities of these acids.
(31) The salient features of this degradation sequence are recorded in the experimental section, where they differ from earlier methods and may be of general use. The experimental procedures for the earlier stages have already been recorded by other workers.[32,40]
(32) R. E. Ireland and J. Newbould, *J. Org. Chem.*, **27**, 1931 (1962).

pimaric) exhibits three bands at 820 cm.$^{-1}$, 835 cm.$^{-1}$ and 860 cm.$^{-1}$.[32]

Comparison of the infrared spectra of the synthetic dienes **2** and **3** with sandaracopimaradiene (−**2**) and pimaradiene (+**3**) revealed their respective identities. Identical retention times were also obtained on gas-liquid chromatography between the synthetic dienes and their respective optically active counterparts. This identity between synthetic material of well founded structure and stereochemistry and the natural compounds provides good confirmation of the stereochemical assignments made by earlier workers.[6]

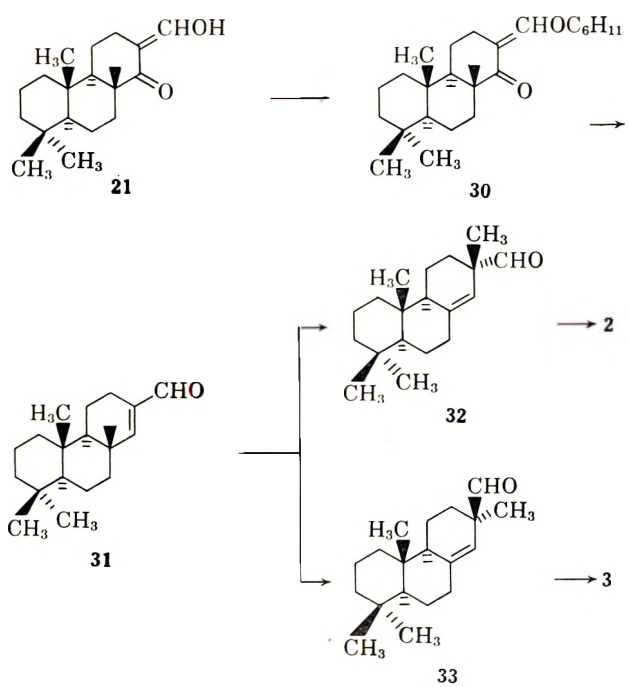
It was of interest to note that the infrared spectrum and gas-liquid chromatographic mobility of the diterpene rimuene,[2] proposed to have the sandaracopimaradiene structure, were quite different. Needless to say, the melting point of a mixture of rimuene (m.p. 54–55°) and sandaracopimaradiene (m.p. 41–42°) was depressed to room temperature. This represented the first clear-cut evidence that the structural proposal for rimuene was in error and is responsible for a reinvestigation of the chemistry of this diterpene.

Despite the success of the above synthesis of the ring C-substitution pattern of the pimaric acids, the final pyrolytic decomposition was considered a weak point in the synthetic scheme. Were it necessary to apply this sequence to the tricyclic acid **14** that was the goal of the first phase of our program, we felt that this last step would be fraught with experimental difficulties. Thus, in order to circumvent this step, we investigated another route to the dienes **2** and **3** from the ketone **11**.

As mentioned above, the earlier work of others had shown that the products from the alkoxymethylene ketones and organometallic reagents as well as hydrides led principally to 1,2-addition.[33] Acid-catalyzed allylic rearrangement[34] of the primary reaction product then formed an α,β-unsaturated aldehyde. With this precedence before us, we converted the ketone **11** to the cyclohexoxymethylene ketone **30** in 72% over-all yield by azeotropic removal of water from a benzene: *p*-toluenesulfonic acid solution of the hydroxymethylene derivative **21** and cyclohexanol. On reduction with methanolic sodium borohydride and then treatment with aqueous mineral acid, there resulted a 66% yield of the α,β-unsaturated aldehyde **31**.

Again in order to effect methylation of this conjugated carbonyl system, we had to resort to large excesses of base. However, in the case of the aldehyde, polymerization was not the main problem, for when insufficient base was used, unchanged aldehyde was recovered. The aldehyde appeared to be less readily enolized than the ethylidene ketone. When a 60-fold excess of potassium *t*-butoxide was employed, there was obtained a 77% yield of colorless, volatile, semicrystalline distillate that showed only a band for a saturated aldehyde in the infrared spectrum. By a process of careful chromatography, we were able to isolate first a 16% yield of the aldehyde **33**, m.p. 56–59°, and then a 28% yield of the epimer **32**, m.p. 76–78°. The chromatography was followed with the aid of gas-liquid chromatography under conditions such that the two aldehydes were easily resolved. The resultant crystalline aldehydes were shown to be substantially free from any impurities by this same technique.

It was a simple matter to complete our second route to the pimaradienes by treatment of the respective aldehydes **32** and **33** with methyl triphenylphosphonium bromide[35] in the presence of potassium *t*-butoxide. In this manner the aldehyde **32** afforded an 87% yield of the diene **2**, identical with that prepared by the former route and that from natural sandaracopimaric acid **27**. Similarly, the aldehyde **33** afforded a 96% yield of the epimeric diene **3**, identical with pimaradiene. The dienes prepared by this route were sufficiently free of contaminants to crystallize (no more than a trace of impurity is necessary to prevent the crystallization of the (±)-dienes). Thus we were able to add the final, aesthetically satisfying physical constant to those already recorded for the synthetic dienes **2** and **3** when it was found that (±)-sandaracopimaradiene melted at 22–25° while (±)-pimaradiene melted at 28–31°, and a mixture of the two remained an oil even at 0°.



Experimental[36]

7-Keto-1-methoxy-8,8,13-trimethyl-5,6,7,8,10,13-hexahydrophenanthrene (5).—The procedure used is essentially that of Woodward.[9] To a solution of 20 g. (0.513 g.-atom) of potassium in 640 ml. of dry *t*-butyl alcohol in a nitrogen atmosphere at room temperature was added all at once a solution of 41.5 g. (0.172 mole) of the unsaturated ketone **4** in 75 ml. of dry benzene. After stirring for 5 min. at room temperature, the red-orange solution was thoroughly chilled with an ice–water bath, and 64

(33) R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949); P. Seifert and H. Schinz, *Helv. Chim. Acta*, **34**, 728 (1951).

(34) M. Stiles and A. Longroy, *Tetrahedron Letters*, 337 (1961).

(35) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954).

(36) Unless specified otherwise, the term "petroleum ether" refers to reagent grade material boiling in the range 30–60°. All gas-liquid chromatograms were obtained on a Barber–Coleman Model 10 gas-liquid chromatography unit using a 6-ft. column packed with 15% diethylene glycol succinate on Chromosorb W. Melting points were determined on a Kofler Hot Stage and are corrected for stem exposure. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra that are recorded in microns were measured on a Perkin–Elmer Infracord Model 137 and those recorded in reciprocal centimeters were measured on a Perkin–Elmer Model 237 Spectrometer. Strong bands are marked (s); all others reported are of moderate intensity unless otherwise specified. Ultraviolet spectra were determined on a Cary Recording Spectrophotometer (Model 11 MS). Florisil refers to the product of the Floridin Company, Tallahassee, Florida, 60/100 mesh. A portion of the starting ketone **4** was supplied by HI Laboratories, 7878 Whitmore Lake Road, Whitmore Lake, Mich.

ml. of methyl iodide added all at once. A white precipitate began forming almost immediately, and the reaction mixture became warm. The mixture was stirred overnight while the ice melted, and then 400 ml. of water was added and most of the *t*-butyl alcohol removed by distillation at reduced pressure. The solid product, isolated from the aqueous liquor by ether extraction, was crystallized from ethyl alcohol and afforded 34.5 g. (75%) of the ketone **5**, m.p. 112–114.5°, which gave a bright yellow precipitate with 2,4-dinitrophenylhydrazine reagent. The analytical sample, obtained after several further crystallizations from the same solvent, melted at 115–116° with softening at 108° (reported,[10] m.p. 109.5–110.5°). A mixture of this material and the starting unsaturated ketone **4** melted over the range 93–100°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.86; H, 8.11.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1710 cm.$^{-1}$ (s) (> C=O, satd.); 1678 cm.$^{-1}$ (w) (> C = C <); 1260 cm.$^{-1}$ (s) (C—O—C).

7-Keto-1-methoxy-8,8,13-trimethyl-5,6,7,8,9,10,13,14-*trans*-octahydrophenanthrene (**6**).—A solution of 2.0 g. (7.4 mmoles) of the ketone **5** in 25 ml. of glacial acetic acid containing 200 mg. of suspended 10% palladium-on-carbon was stirred in a hydrogen atmosphere for 12 hr. during which time 209 ml. of hydrogen was absorbed (196 ml. of hydrogen calculated for 1 mol. equiv.). After removal of the catalyst by filtration and the acetic acid by distillation at reduced pressure, the residue was crystallized from ethyl alcohol and afforded 1.3 g. of an oily solid. This material was purified by elution from 80 g. of alumina (Fisher) with 1000 ml. of 20% ether:petroleum ether and crystallization from methanol. In this manner there was obtained 1.0 g. (50%) of saturated ketone **6** m.p. 93–96°. The analytical sample, m.p. 95.5–96.5° (reported,[10] m.p. 90–93°), was obtained after two further crystallizations from the same solvent.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.26; H, 8.86.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1710 cm.$^{-1}$ (s) (>C=O, satd.); 1260 cm.$^{-1}$ (s) (C—O—C).

7,7-Ethylenedithio-1-methoxy-8,8,13-trimethyl-5,6,7,8,10,13-hexahydrophenanthrene (**7**).—According to the procedure of Fieser,[12] a solution of 5.4 g. (0.02 mole) of the ketone **5** and 2.7 ml. of ethanedithiol in 25 ml. of glacial acetic acid was treated with 2.7 ml. of freshly distilled boron trifluoride etherate. After standing several minutes at room temperature, the solution was scratched to induce crystallization of the thioketal and then cooled for 2 hr. in a cold water bath (*ca.* 20°). Filtration of the mixture and washing the filter cake with methanol afforded 6.7 g. (97%) of the thioketal **7**, m.p. 175–177° with softening at 171°. The analytical sample, obtained after crystallization from acetone, was fine needles and melted at 177–178° with softening at 173°.

Anal. Calcd. for $C_{20}H_{26}OS_2$: C, 69.31; H, 7.56; S, 18.51. Found: C, 69.37; H, 7.58; S, 18.71.

The corresponding **propylenethioketal**, prepared in the same fashion in 87% yield from 39 g. (0.144 mole) of the ketone **5** and 20 ml. of 1,3-propanedithiol in 180 ml. of glacial acetic acid containing 20 ml. of boron trifluoride etherate, melted at 168–171°. The analytical sample, obtained after three crystallizations from acetone, was fine needles and melted at 171–172°.

Anal. Calcd. for $C_{21}H_{28}OS_2$: C, 69.95; H, 7.83; S, 17.79. Found: C, 69.99; H, 7.96; S, 17.70.

1-Methoxy-8,8,13-trimethyl-5,6,7,8,10,13-hexahydrophenanthrene (**8**).—To a well stirred suspension of 20 teaspoonfuls of W-2 Raney nickel[13] in 1 l. of absolute ethanol was added 17.0 g. (0.049 mole) of the ethylenethioketal **7**. and the mixture was stirred and refluxed overnight. After removal of the nickel by filtration, the solvent was evaporated at reduced pressure and the residue crystallized from ethyl alcohol. In this manner there was obtained 10.2 g. (81%) of the olefin **8**, m.p. 91–93°, as lustrous plates. The analytical sample, m.p. 93–94°, was obtained after two further crystallizations from the same solvent.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.27; H, 9.53.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1678 cm.$^{-1}$ (w) (> C=C <); 1250 cm.$^{-1}$ (s) (C—O—C).

1-Methoxy-8,8,13-trimethyl-*trans*-5,6,7,8,9,10,13,14-octahydrophenanthrene (**1**). (a) **By Hydrogenation of the Olefin 8.**—A mixture of 10.0 g. (0.04 mole) of the olefin **8** and 1.0 g. of 10% palladium-on-carbon in 100 ml. of cyclohexane and 150 ml. of glacial acetic acid was shaken overnight in a Parr hydrogenation apparatus at an initial pressure of 40 p.s.i. of hydrogen. After this time a drop of 4 p.s.i. was observed and the up-take of hydrogen ceased. After removal of the catalyst, the solution was diluted with water and the product isolated by ether extraction. Evaporation of the ether at reduced pressure and crystallization of the residue from ethyl alcohol afforded 9.8 g. (95%) of the saturated derivative **1**, m.p. 119.5–120.5° with softening at 117° (reported,[10] m.p. 114–115°). The melting point was not raised by further crystallization from alcohol.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.64; H, 10.15.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1255 cm.$^{-1}$ (s) (C—O—C).

The same saturated derivative **1**, m.p. 118.5–119.5° with softening at 114°, was obtained in 60% yield on reduction of 1.08 g. (4 mmoles) of the saturated ketone **6** with 1.0 ml. of hydrazine hydrate and 5.0 g. of potassium hydroxide in 20 ml. of diethylene glycol according to the Huang-Minlon modification[11] of the Wolff–Kishner reduction.

(b) **Directly from the Ketone 5.**—When 20 g. (0.074 mole) of the ketone **5** was converted to the propylenethioketal with 11.2 ml. of 1,3-propanedithiol in 100 ml. of glacial acetic acid containing 11.2 ml. of boron trifluoride etherate, there was obtained 25 g. of crude thioketal. This crude product was desulfurized with 30 teaspoonfuls of W-2 Raney nickel[13] in 1500 ml. of ethanol. The residue, obtained after removal of the catalyst by filtration and the solvent by distillation at reduced pressure, was hydrogenated as above over 20 g. of 10% palladium on carbon in 100 ml. of cyclohexane and 150 ml. of glacial acetic acid. After the same work-up as described in part **a**, there was obtained 15.4 g. (81%) of the octahydrophenanthrene **1**, m.p. 118.5–119.5°, after one crystallization from ethyl alcohol.

1-Hydroxy-8,8,13-trimethyl-*trans*-5,6,7,8,9,10,13,14-octahydrophenanthrene (**9**).—A solution of 15.5 g. (0.06 mole) of the ether **1** in 200 ml. of glacial acetic acid and 200 ml. of 48% aqueous hydrobromic acid containing 20 ml. of aqueous hydriodic acid (sp. gr. 1.5 g./cc.) was stirred and refluxed in a nitrogen atmosphere for 12 hr. After cooling, the reaction mixture was diluted with 250 ml. of water, and the precipitated phenol isolated by ether extraction. The residue, obtained after evaporation of the ether at reduced pressure, was crystallized from petroleum ether (90–100°) and afforded 13.1 g. (90%) of the phenol **9**, m.p. 152.5–154° (reported,[10] m.p. 146–148°). The melting point was not raised by further crystallization from methylcyclohexane or benzene:petroleum ether.

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.60; H, 9.86.

Infrared: $\tilde{\nu}_{max}^{Nujol}$ 3300 cm.$^{-1}$ (s) (O—H).

(±)-14-Podocarpanone (**11**).—According to the method developed by Johnson,[14] 6.24 g. (0.0256 mole) of the phenol **9** and 0.62 g. of ruthenium oxide in 70 ml. of ethanol were shaken under 1500 p.s.i. of hydrogen pressure at 50° for 8 hr. After cooling, the catalyst was removed by filtration and five such charges—a total of 31.2 g. (0.128 mole) of phenol—were combined, and the solvent removed at reduced pressure. The resulting crude alcohol was dissolved in 500 ml. of acetone, cooled to 0°, and oxidized with 35 ml. of Jones reagent.[15] The acetone solution was decanted from the precipitated salts and evaporated at reduced pressure. Cold water was added to the salts and this mixture combined with residue from the acetone portion. The crude ketone **10**, isolated from these aqueous liquors by ether extraction, amounted to 30 g. On chromatography of this material on 750 g. of alumina (Fisher), there was eluted 27.4 g. (86%) of the pure ketone **11**, m.p. 71–73°, with 4 l. of 2% benzene:petroleum ether. The analytical sample, m.p. 73–73.5°, was obtained after two crystallizations from methanol (reported,[10] m.p. 67–68°).

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.37; H, 11.48.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1701 cm.$^{-1}$ (s) (>C=O), 1148 cm.$^{-1}$ (w) and 1124 cm.$^{-1}$ (w).

In another experiment, 1.00 g. (0.004 mole) of crude oily alcohol from reduction was oxidized with 1.0 ml. of Jones reagent in 50 ml. of acetone at 0°. The reaction mixture was diluted with 250 ml. of water, and the ketone **10** isolated by ether extraction. When the crude crystalline product, amounting to 0.96 g. (95%), m.p. 60–65°, was crystallized two times from methanol, there resulted 0.40 g. (40%) of the pure *trans-anti-cis* ketone **10**, m.p. 65–67°. Exposure of 0.30 g. of this material in petroleum ether solution to 10 g. of alumina (Fisher), and then elution with 250 ml. of benzene afforded 0.27 g. (90% recovery) of the *trans-anti-trans* ketone **11**, m.p. 72–73°.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.33; H, 11.37.

Infrared: $\nu_{max}^{HCCl_3}$ 1703 cm.$^{-1}$ (s) (>C=O); 1175 cm.$^{-1}$ (w), 1151 cm.$^{-1}$ (w) and 1115 cm.$^{-1}$ (w).

2-Methyl-6-pyrrolidinomethylenecyclohexanone (15).—A solution of 73 g. (0.52 mole) of 2-methyl-6-hydroxymethylenecyclohexanone and 39 g. (0.52 mole) of pyrrolidine in 500 ml. of benzene was refluxed for 4 hr. under a Dean–Stark water separator. At the end of this period, there had collected 9.9 ml. of water. After the benzene was removed at reduced pressure, distillation of the residue afforded 95 g. (94%) of the pyrrolidinomethylene ketone **15**, b.p. 125–128° (0.12 mm.). Redistillation of this material gave the analytical sample, which boiled at 124–125° (0.05 mm.) ($n^{24.5}$D 1.5812 on supercooled liquid, m.p. 47–50°).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.60; H, 9.82; N, 7.21.

Infrared: λ_{max}^{film} 6.10 μ (>C=O); 6.48, 6.55 μ (s) (conj. C=C).

2β-(*o*-Methoxyphenyl)propylidene-6-methylcyclohexanone (12).—To the Grignard reagent prepared in 200 ml. of dry ether from 87 g. (0.405 mole) of 2-(*o*-methoxyphenyl)ethyl bromide and 11.1 g. (0.453 g.-atom) of magnesium was added 78.5 g. (0.406 mole) of the eneamine **15** in 150 ml. of dry ether, and the mixture was decomposed by the addition of 300 ml. of 2 *N* aqueous hydrochloric acid, and the product isolated from the ethereal layer after it was washed with water, saturated brine, dried (Na_2SO_4), and evaporated. Distillation of the resulting brown oil afforded 80.3 g. (77%) of the ketone **12**, b.p. 152–155° (0.3 mm.), n^{25}D 1.5457. The analytical sample, obtained after redistillation, boiled at 130–131° (0.05 mm.), n^{25}D 1.5452. This material failed to give any evidence of oxidation when treated with Tollens reagent.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.10; H, 8.58.

Ultraviolet: λ_{max}^{alc} 245 mμ (ϵ 7600). Infrared: λ_{max}^{film} 5.92 μ (s) (>C=O).

The 2,4-dinitrophenylhydrazone melted at 170–171.5° after three recrystallizations from ethyl acetate:methanol.

Anal. Calcd. for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found: C, 62.78; H, 5.86; N, 12.62.

2-Ethylidene-6-methylcyclohexanone (18).—To 200 ml. of a 0.78 *M* ethereal methylmagnesium bromide solution was added 27 g. (0.14 mole) of the eneamine **15** in 50 ml. of ether, and the reaction mixture stirred for 2 hr. After the addition of 150 ml. of 2 *N* aqueous hydrochloric acid, the ketone **18** was isolated from the ethereal extracts. Distillation of the light orange residue (14.2 g.; 74%) afforded 10.4 g. (54%), b.p. 129–131° (76 mm.), λ n^{23}D 1.4832. The analytical sample, obtained by redistillation, boiled at 63.5° (2.5 mm.), n^{23}D 1.4841.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.90; H, 10.16.

Ultraviolet: λ_{max}^{alc} 241 (ϵ 6950). Infrared: λ_{max}^{film} 5.92 μ (s) (>C=O); 6.18 μ (C=C).

The 2,4-dinitrophenylhydrazone melted at 156–157° after three recrystallizations from methanol.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.66; H, 5.65; N, 17.67.

2-Pyrrolidinomethylene-1-decalone (16).—A solution of 57.0 g. (0.315 mole) of 2-hydroxymethylene-1-decalone[21] and 41.0 ml. (35.5 g. 0.5 mole) of pyrrolidine in 300 ml. of benzene was refluxed under a Dean–Stark water separator for 4 hr.; at the end of this period *ca.* 6 ml. of water had collected. The benzene was removed at reduced pressure, and the light tan, crystalline residue crystallized from petroleum ether (b.p. 60–75°). In this manner there was obtained 60 g. (82%) of the eneamine **16**, m.p. 96–98°. The analytical sample, obtained as colorless leaflets after two further crystallizations from the same solvent, melted at 97–98°.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 6.00. Found: C, 77.10; H, 9.96; N, 5.85.

Infrared: $\lambda_{max}^{HCCl_3}$ 6.10 μ (s) (>C=O); 6.50 μ (s) and 6.58 μ (s) (conj. >C=C<).

2-Benzylidene-1-decalone (17).—To a solution of phenylmagnesium bromide [prepared from 1.50 g. (0.062 g.-atom) of magnesium and 6.3 ml. (9.42 g.; 0.06 mole) of bromobenzene] in 150 ml. of ether was added a solution of 10.0 g. (0.041 mole) of the eneamine **16** in 50 ml. of dry tetrahydrofuran. After the reaction had been stirred for 3 hr. at room temperature, 50 ml. of 5% aqueous hydrochloric acid was added and the product isolated by ether extraction. The crystalline residue obtained after removal of the ether was crystallized once from methanol and once from petroleum ether (b.p. 30–60°). In this manner there was obtained 8.2 g. (84%) of the benzylidene derivative **17**, m.p. 91–93 (reported,[22] m.p. 91–92°).

Methylation of 2-Ethylidene-6-methylcyclohexanone (18).—To a cooled solution of 30.7 g. (0.785 g.-atom) of potassium in 1000 ml. of dry *t*-butyl alcohol was added over a 20-min. period at room temperature in a nitrogen atmosphere a solution of 3.02 g. (0.022 mole) of the ethylidene ketone **18** in 50 ml. (114 g.; 0.8 mole) of methyl iodide. The cooling bath was removed after 10 min., and the reaction mixture stirred for an additional 14 hr. The neutral reaction mixture was filtered and the *t*-butyl alcohol removed by distillation at atmospheric pressure. Distillation of the residue, obtained after the usual work-up, afforded 2.53 g. (69%) of colorless, liquid boiling at 58–62° (4.5 mm.). Redistillation of this material afforded an analytically pure specimen of the ketone **20**, b.p. 52–53° (3.0 mm.).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.45; H, 11.03.

Ultraviolet: λ_{max}^{alc} 301 mμ (ϵ, 75). Infrared: λ_{max}^{film} 3.24 μ (vinyl hydrogen); 5.92 μ (s) (> C=O); 6.18 μ (> C=C <); 5.48 μ (w), 10.08 μ, 10.94 μ (s) (—CH=CH$_2$ grouping).

In other experiments under substantially the same conditions but where only a three to fourfold excess of base was employed, the yields of volatile material were from 25–35% and analysis by ultraviolet spectrum and gas-liquid chromatography indicated the presence of three major components: starting α,β-unsaturated ketone **18**, the trimethyl ketone **20**, and another material, presumed to be ketone **19**. The latter, however, was never obtained in a pure condition.

(±)-13-Pyrrolidinomethylene-14-podocarpanone (22).—To an ice-cooled suspension of 8.9 g. (0.165 mole) of commercial sodium methoxide in 150 ml. of dry benzene under a nitrogen atmosphere was slowly added a solution of 10.5 g. (0.043 mole) of the ketone **11** and 18.5 g. (0.25 mole) of ethyl formate in 50 ml. of dry benzene. After the reaction mixture had stirred overnight at room temperature, 75 ml. of water was added and the basic aqueous layer separated. The benzene layer was diluted with ether and extracted twice with 25-ml. portions of 5% aqueous sodium hydroxide. The combined basic solutions were washed with ether, cooled by addition of crushed ice, layered with *ca.* 75 ml. of ether, and acidified to Congo Red with ice cooled concentrated hydrochloric acid. The ethereal solution was separated, washed with water and saturated brine, and then dried (Na_2SO_4). Evaporation of most of the ether afforded 12.5 g. of the hydroxymethylene derivative **21** as alight yellow solid [λ_{max}^{film} 6.12 μ (s) and 6.34 μ (s) (β-ketoaldehyde)] that still retained some solvent.

This material, a sample of which imparted a dark green coloration to a 1% alcoholic ferric chloride solution, was not further purified but dissolved in 150 ml. of benzene and treated with 4.25 ml. (3.6 g.; 0.05 mole) of pyrrolidine. This mixture was refluxed under a Dean–Stark water separator for 2 hr. in a nitrogen atmosphere. When the benzene was removed at reduced pressure and the residue (13.50 g.) crystallized from *n*-hexane, there was obtained 9.84 g. (73%) of light tan solid, m.p. 152–154°. Concentration of the mother liquors afforded another 1.43 g. (10%) of only slightly less pure material, m.p. 150–153° with softening at 148°. The analytical sample, obtained as colorless needles after five crystallizations from *n*-hexane, melted at 154–156°.

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.70; N, 4.25. Found: C, 80.17; H, 10.65; N, 4.20.

Infrared: $\lambda_{max}^{HCCl_3}$ 6.10 μ (s) (conj. >C=O); 6.50 μ (s) and 6.58 μ (s) (conj. >C=C<).

(±)-13-Ethylidene-14-podocarpanone (23).—To a solution of methylmagnesium bromide [from 0.72 g. (0.03 g.-atom) of magnesium and excess gaseous methyl bromide] in 50 ml. of dry ether was added 2.407 g. (0.0073 mole) of the pyrrolidinomethylene ketone **22** in 25 ml. of dry benzene and the reaction mixture stirred for 1 hr. under a nitrogen atmosphere at room temperature. The Grignard complex was decomposed by adding 25 ml. of 10% aqueous hydrochloric acid. The ethereal layer separated, washed several times with water, saturated brine, and dried (Na_2SO_4). Evaporation of the ether at reduced pressure afforded 1.991 g. of crude unsaturated ketone as a yellow oil that rapidly crystallized on standing at room temperature. Evaporative distillation of this material at 130°/0.05 mm. afforded 1.882 g. (94%) of colorless, crystalline distillate, m.p. 70–72°. The analytical sample, obtained after crystallization three times from *n*-pentane, one time from ether and finally once

from *n*-pentane (all crystallizations effected by cooling to −70°), melted at 76–76.5°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.99; H, 10.96.

Ultraviolet: λ_{max}^{alc} 243 mμ (ε 7070). **Infrared:** λ_{max}^{film} 5.98 μ (s) (>C=O); 6.20 μ (s) (>C=C<).

The **2,4-dinitrophenylhydrazone** melted at 208–210° after crystallization from ethyl acetate.

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.05; H, 7.54; N, 12.33. Found: C, 66.11; H, 7.57; N, 12.27.

(±)-13α-Methyl-13β-vinyl-14-podocarpanone (25) and (±)-13β-Methyl-13α-vinyl-14-podocarpanone (24).—To a cooled (20°), stirred solution of 75 g. (1.93 g.-atoms) of potassium in 2500 ml. of dry *t*-butyl alcohol in a nitrogen atmosphere was added a solution of 4.104 g. (0.015 mole) of the ethylidene ketone **23** in 40 ml. of dry ether. After the orange-red reaction mixture had been stirred for 4 min., 125 ml. of methyl iodide was added over a period of 6 min. during which time a heavy white precipitate formed. The mixture was stirred for 1 hr. in the ice bath, and then 25 ml. more of methyl iodide was added and the suspension stirred overnight at room temperature. The snow white, neutral reaction mixture was filtered through Celite and concentrated to *ca.* 50 ml. Water was added, and the organic material isolated by ether extraction. The residue, obtained on evaporation of the ether, was evaporatively distilled at 190°/0.02 mm. In this manner there was obtained 3.067 g. (71%) of a thick, yellow, oily distillate, the ultraviolet spectrum of which indicated the presence of *ca.* 8% starting ethylidene ketone **23** [λ_{max}^{alc} 244 (ε 575)].

Crystallization of the distillate from 12 ml. of *n*-pentane at −70° afforded 1.561 g. of solid, m.p. 35–48°, and left 1.505 g. (**I**) as oily mother liquor. Recrystallization of the solid material from the same solvent gave 1.198 g. (**II**) of solid, m.p. 48–54°, and left 0.350 g. (**III**) as oily mother liquor. The fractions I, II, and III were chromatographed on Florisil as follows:

Fraction I.—Chromatography on 163 g. of Florisil afforded 235 mg. of the ketone **25**, eluted with 750 ml. of 25% benzene:petroleum ether, and 266 mg. of the ketone **24**, eluted with 1250 ml. of 50% benzene:petroleum ether. An intermediate fraction, eluted with 750 ml. of 50% benzene:petroleum ether and amounting to 34 mg. (8%), was the starting ethylidene ketone **23**.

Fraction II.—Chromatography on 110 g. of Florisil afforded 86 mg. of the ketone **25**, eluted with 400 ml. of 25% benzene:petroleum ether, and 946 mg. of the ketone **24**, eluted with 1900 ml. of 50% benzene:petroleum ether.

Fraction III.—Chromatography on 45 g. of Florisil afforded 84 mg. of the ketone **25**, eluted with 300 ml. of 25% benzene:petroleum ether and 171 mg. of the ketone **24**, eluted with 300 ml. of 50% benzene:petroleum ether.

Therefore, the total amount of the ketone **25** obtained was 405 mg. (9%), m.p. 74–77°, and that of the ketone **24** was 1.383 g. (32%), m.p. 66–69°.

The analytical sample of the ketone **25**, m.p. 78–80°, was obtained after four crystallizations from *n*-pentane at −70° and two from methanol at −10°.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.26; H, 11.18. Found: C, 83.33; H, 11.18.

Ultraviolet: λ_{max}^{alc} 294 mμ (ε 104); $\lambda_{max}^{cyclohexane}$ 295 mμ (ε 98). **Infrared:** λ_{max}^{Nujol} 5.85 μ (s) (>C=O); 3.19 μ (w) (vinyl H); 6.12 μ (>C=C<); 5.44 μ (w), 10.08 μ (s) (—CH=CH_2).

The analytical sample of the ketone **24**, m.p. 69–70°, was obtained after two crystallizations from *n*-pentane at −70°.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.26; H, 11.18. Found: C, 83.14; H, 11.08.

Ultraviolet: λ_{max}^{alc} 292 mμ (ε 51); $\lambda_{max}^{cyclohexane}$ 294 mμ (ε 45). **Infrared:** λ_{max}^{Nujol} 5.85 μ (s) (>C=O); 3.20 μ (w) (vinyl H); 6.11 μ (>C=C<); 5.48 μ (w), 10.08 μ, 10.96 μ (—CH=CH_2).

(±)-14β-Benzoyloxy-13β-methyl-13α-vinylpodocarpane (26).—To a solution of 477 mg. (1.65 mmoles) of the ketone **24** in 50 ml. of ethanol was added 4 g. (0.174 g.-atom) of sodium, and the mixture refluxed under a nitrogen atmosphere until all the sodium had been consumed (*ca.* 2 hr.). Water was added, and the product isolated by extraction with 1:1 ether:petroleum ether; after the usual washing sequence, the ethereal solution was dried (Na_2SO_4), filtered, and evaporated. The residue so obtained amounted to 495 mg. of crude alcohol, which crystallized on standing.

The crude alcohol was dissolved in 3 ml. of dry pyridine, cooled to 0° and treated with 0.5 ml. of benzoyl chloride. After standing for 24 hr. at room temperature, the reaction mixture was poured into ice-water, and the precipitated benzoate isolated by ether extraction. A rough purification of the ester was effected by adsorption on 60 g. of Florisil in petroleum ether. Elution with 400 ml. of 30% benzene:petroleum ether afforded 640 mg. of solid material, which on crystallization from methanol gave 530 mg. (81%) of the pure benzoate **26**, m.p. 124–125°. The analytical sample, obtained after four crystallizations from methanol, melted at 125–126°.

Anal. Calcd. for $C_{27}H_{36}O_2$: C, 82.19; H, 9.71. Found: C, 82.01; H, 9.76.

Infrared: $\lambda_{max}^{HCCl_3}$ 5.88 μ (s) (>C=O); 6.12 μ (w) (>C=C<); 6.25 μ (w), 6.34 μ (w), 14.11 μ (s) (monosubst. phenyl).

(±)-14β-Benzoyloxy-13α-methyl-13β-vinylpodocarpane (28).—In a fashion similar to that described above for the benzoate **26** 3140 mg. (0.485 mmole) of the ketone **25** was reduced with 3.5 g. (0.152 g.-atom) of sodium in 35 ml. of ethanol.) The crude, solid alcohol obtained (144 mg.) was benzoylated in 1 ml. of pyridine with 0.1 ml. of benzoyl chloride. The resulting crude benzoate, after elution from 25 g. of Florisil with 300 ml. of 30% benzene:petroleum ether, amounted to 169 mg. Crystallization of this material from ether:ethanol at −20° afforded 137 mg. (75%) of the benzoate **28**, m.p. 82–84°. The melting point of this material was not raised by two further crystallizations from the same solvent pair.

Anal. Calcd. for $C_{27}H_{36}O_2$: C, 82.18; H, 9.71. Found: C, 82.15; H, 9.81.

Infrared: $\lambda_{max}^{HCCl_3}$ 5.87 μ (s) (>C=O); 6.11 μ (w) (>C=C<); 6.25 μ (w), 6.34 μ (w), 14.11 μ (s) (monosubst. phenyl).

(±)-13-Cyclohexoxymethylene-14-podocarpanone (30).—To a well stirred suspension of 8.1 g. (0.15 mole) of commercial sodium methoxide in 150 ml. of dry benzene under a nitrogen atmosphere was added dropwise with cooling a solution of 7.7 g. (0.031 mole) of the ketone **11** and 20 ml. of ethyl formate in 50 ml. of dry benzene. After stirring overnight at room temperature, the reaction mixture was worked up as described above, and the crude, solid hydroxymethylene derivative **21** (8.55 g.) used directly in the etherification experiment.

A solution of the hydroxymethylene derivative, 3.8 ml. (3.5 g.; 0.035 mole) of cyclohexanol and 10 mg. of *p*-toluenesulfonic acid monohydrate in 200 ml. of benzene was refluxed in a nitrogen atmosphere under a Dean–Stark water separator filled with Drierite. After 10 hr. the reaction mixture was cooled, washed successively with 5% aqueous sodium hydroxide and water, and then dried (Na_2SO_4). After filtration of the drying agent, the benzene was removed from the filtrate at reduced pressure, and the solid residue crystallized from methanol. In this manner there was obtained 6.43 g. (72%) of the enol ether **30**, m.p. 120–121°, as colorless plates. The analytical sample, obtained after two further crystallizations from the same solvent, showed the same melting point.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.21; H, 10.80.

Infrared: $\lambda_{max}^{HCCl_3}$ 3.18 μ (vinyl H); 6.00 μ (conj. >C=O); 6.35 μ (s) (conj. >C=C<); 9.45 μ (s) (C—O—C).

(±)-13-Podocarpene-13-carboxaldehyde (31).—To a solution of 4.03 g. (0.011 mole) of the enol ether **30** in 130 ml. of methanol was added a solution of 0.76 g. (0.02 mole) of sodium borohydride in 6 ml. of 0.1 *N* aqueous sodium hydroxide, and the reaction mixture stirred and refluxed for 2 hr. The solution was concentrated to approximately 50% of the original volume, water was added, and the product isolated by ether extraction. The dry ether extracts were concentrated to 75 ml. and stirred for 2 hr. at room temperature in a nitrogen atmosphere with 75 ml. of 3 *N* aqueous hydrochloric acid. After the usual work-up, there was obtained 3.8 g. of an oily, yellow crystalline mass which was evaporatively distilled at 120° (0.05 mm.) (bath temp.). The distillate on crystallization from methanol at −20° afforded 1.64 g. (56%) of the aldehyde **31**, m.p. 81–83°. Chromatography of the mother liquor (1.23 g.) on 100 g. of Florisil afforded 334 mg. of the aldehyde **31** by elution with 750 ml. of benzene; crystallization of this material from methanol at −20° gave 295 mg. (10%) of the pure aldehyde **31**, m.p. 81–83°. Thus, the total yield of aldehyde **31** was 1.935 g. (66%). The analytical sample, obtained on one further crystallization from the same solvent, still melted at 81–83°.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.18; H, 10.83.

Infrared: $\lambda_{max}^{HCCl_3}$ 3.66 μ (—C*H*O); 5.99 μ (s) (conj. >C=O); 6.11 μ (conj. >C=C<).

The **2,4-dinitrophenylhydrazone** melted at 254–255° after three recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{24}H_{32}N_4O_4$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.58; H, 7.47; N, 12.55.

(±)-13α-Methyl-Δ$^{8(14)}$-podocarpene-13β-carboxaldehyde (33) and (±)-13β-Methyl-Δ$^{8(14)}$-podocarpene-13α-carboxaldehyde (32). —A slurry of potassium *t*-butoxide in *t*-butyl alcohol was prepared by dissolving 20 g. (0.51 mole) of potassium in 400 ml. of dry *t*-butyl alcohol and then removing 100 ml. of alcohol by distillation under a nitrogen atmosphere with vigorous stirring. To this slurry was added 2.171 g. (8.35 mmoles) of the α,β-unsaturated aldehyde **31** in 20 ml. of dry benzene, and the deep orange reaction mixture was stirred and refluxed in a nitrogen atmosphere for exactly 5 min. The mixture was then cooled in an ice bath for 4 min., and then 40 ml. of methyl iodide was added all at once. The mixture refluxed vigorously for *ca.* 30. sec. and turned from a deep orange to a pale yellow color while a white precipitate formed. Stirring was continued for 1 hr. in the ice bath and then for 12 hr. at room temperature. The snow white reaction mixture was filtered through Celite, concentrated to *ca.* 50 ml. at reduced pressure on the steam bath, water added, and the products isolated by ether extraction. Evaporative distillation at 150° (0.05 mm.) of the residue (2.3 g.) obtained after removal of the solvent afforded 1.749 g. (77%) of colorless, semicrystalline distillate which was chromatographed on 200 g. of Florisil. After a small initial forerun eluted with petroleum ether, elution was continued with 13% benzene: petroleum ether with the following results:

Fraction	Weight, mg.	Vol. of solvent, ml.	G.l.c. analysis at 196°
A	272	1000	86% (33) 4% (32) 10% (impurity)
B	773	2500	40% (33) 57% (32) 3% (impurity)
C	500	1000 13% benzene: petroleum ether	2% (33)
		2000 40% benzene: petroleum ether	98% (32)

Rechromatography of fraction B on 170 g. of Florisil employing the same solvent pattern as above gave the following results:

Fraction	Weight, mg.	Vol. of solvent, ml.	G.l.c. analysis at 196°
A^1	121	600	93% (33) 2% (32) 5% (impurity)
B^1	471	2800	40% (33) 60% (32)
C^1	184	1500 40% benzene: petroleum ether	2% (33) 98% (32)

When fractions A and A^1 [393 mg. (17%)] were combined and evaporatively distilled at 140° (0.05 mm.) (bath temp.), there resulted 354 mg. (16%) of the aldehyde **33** as a colorless, crystalline distillate, m.p. 56–59°. Crystallization of this material from 2 ml. of pentane at −70° and then 2 ml. of methanol at −15° afforded 221 mg. (10%) of the analytically pure aldehyde **33** as fine plates, m.p. 58–60°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.30; H, 11.15.

Infrared: $\lambda_{max}^{HCCl_3}$ 3.67 μ (—C*H*O); 5.86 μ (s) (satd. >C=O); 6.05 μ (>C=C<).

The **semicarbazone**, prepared by the method of Fieser,[37] melted at 195–200° dec. after two crystallizations from methanol.

Anal. Calcd. for $C_{20}H_{33}N_3O$: C, 72.46; H, 10.03; N, 12.68. Found: C, 72.35; H, 10.06; N, 12.59.

The **2,4-dinitrophenylhydrazine**, prepared by the method of Shriner, Fuson, and Curtin, melted at 185–187° after three crystallizations from ethyl acetate:methanol.

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33 Found: C, 66.01; H, 7.61; N, 12.28.

When fractions C and C^1 [684 mg. (30%)] were combined and evaporatively distilled at 140° (0.05 mm.) (bath temp.), there resulted 635 mg. (28%) of the aldehyde **32** as a colorless, crystalline distillate, m.p. 76–78°. Crystallization of this material from 5 ml. of methanol at −15° afforded 500 mg. (22%) of this analytically pure aldehyde **32** as fine needles, m.p. 77–80°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.22; H, 11.02.

Infrared: $\lambda_{max}^{HCCl_3}$ 3.69 μ (—C*H*O); 5.85 μ (s) (satd. >C=O); 6.05 μ (>C=C<).

The **semicarbazone**, prepared by the method of Fieser,[37] melted at 226–228° after two crystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{33}N_3O$: C, 72.46; H, 10.03; N, 12.68. Found: C, 72.66; H, 9.96; N, 12.55.

The **2,4-dinitrophenylhydrazone**, prepared by the method of Shriner, Fuson, and Curtin, melted at 210–212° after four crystallizations from ethyl acetate:methanol.

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 66.16; H, 7.57; N, 12.22.

(±)-Sandaracopimaradiene (2). (a) **By Pyrolysis of the Benzoate (26).**—The benzoate **26** (64 mg., 0.16 mmole) was evaporatively distilled at 200° (0.05 mm.) (bath temp.) through a 2-ft. column packed with Pyrex glass wool and heated to 420–440°. The pyrolyzate that condensed (a mixture of solid and liquid amounting to 63 mg.) was dissolved in petroleum ether and adsorbed on 2 g. of Woelm alumina (Activity I). Elution with 20 ml. of petroleum ether afforded 35 mg. (79%) of the (±)-diene **2** as a colorless oil which was evaporatively distilled at 70–80° (0.05 mm) (bath temp.) to afford the analytical sample. Gas–liquid chromatography of this material at 150° indicated the presence of a single component to the extent of 95%. The infrared spectrum of this (±)-diene was indistinguishable from that of the (−)-diene (**−2**).

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 88.21; H, 11.81.

Infrared[38]: ν_{max}^{film} 3078 cm.$^{-1}$ (vinyl H); 1822 cm.$^{-1}$ (w), 1636 cm.$^{-1}$, 995 cm.$^{-1}$ and 907 cm.$^{-1}$ (—CH=CH$_2$ grouping); 1658 cm.$^{-1}$ (w) and 817 cm.$^{-1}$ (w) (trisubst. >C=C<); 854 cm.$^{-1}$ and 865 cm.$^{-1}$ (skeletal vibrations).

(b) **From the Aldehyde 32.**—To a solution of 1.017 g. (2.84 mmoles) of triphenylmethylphosphonium bromide in 15 ml. of anhydrous ether was added 2.8 ml. of a 0.95 *N* solution of potassium *t*-butoxide in *t*-butyl alcohol, and the mixture stirred for 1 hr. under a nitrogen atmosphere. Then a solution of 187 mg. (0.68 mmole) of the aldehyde **32** in 5 ml. of petroleum ether was added, and the reaction mixture stirred for 5 hr. The yellow mixture was treated with water and the organic material isolated by petroleum ether extraction. The semisolid residue (triphenylphosphonium oxide plus diene) obtained on evaporation of solvents was chromatographed on 6 g. of Woelm alumina (Activity I). Elution with 100 ml. of petroleum ether afforded 181 mg. of diene, which on evaporative distillation at 120–130° (0.05 mm.) (bath temp.) amounted to 162 mg. (87%) of pure (±)-sandaracopimaradiene (**2**). This material was homogeneous on gas-liquid chromatography under the same conditions described above in part (a), and could be crystallized from acetone at −20° whereupon the crystalline (±)-sandaracopimaradiene (**2**) showed a melting point of 22–25°. The infrared spectrum of the (±)-diene **2** prepared here was identical to that prepared in part a and to the (−)-diene **−2** prepared from sandaracopimaric acid (**27**).

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 88.21; H, 11.78.

(−)-Sandaracopimaradiene (−2).—A mixture of 220 mg. (0.64 mmole) of the sandaracopimaral semicarbazone in 8 ml. of diethylene glycol was heated with stirring under a nitrogen atmosphere to 100° whereupon the mixture became homogeneous. Solid potasiusm hydroxide (2.6 g.) was cautiously added, and the temperature gradually raised to 205°. At 170–180° evolution of gas was observed. After heating at 205° for 3 hr., the reaction mixture was cooled, diluted with water, and the product isolated by petroleum ether extraction in the usual manner. When the residue obtained on evaporation of the solvent was chromato-

(37) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Company, Boston, Mass., p. 85.

(38) Recorded on a Beckman IR-7 instrument through the courtesy of the Parke–Davis and Company spectrographic laboratory.

graphed on 5 g. of Woelm alumina (Activity I), there was obtained 135 mg. (78%) of the (−)-diene (−2), m.p. 39–41°, by elution with 50 ml. of petroleum ether. Crystallization of this material from ethyl alcohol afforded 126 mg. (73%) of the pure (−)-sandaracopimaradiene (−2), m.p. 41–42°, $[\alpha]^{25}D$ −12° (*c*, 224 mg./100 ml., $HCCl_3$). Gas-liquid chromatography of this material at 150° showed only one component with the same retention time as that of the (±)-diene 2; the infrared spectrum of this (−)-diene −2 was identical to that of the (±)-diene 2.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 87.97; H, 11.68.

(±)-Pimaradiene (3). (a) By Pyrolysis of the Benzoate 28.—Pyrolysis of 83 mg. (0.21 mmole) of the benzoate **28** under the same conditions as described above for the benzoate **26** afforded 54 mg. (93%) of semisolid, crude pyrolyzate. Chromatography of this material on 3 g. of Woelm alumina (Activity I) gave 47 mg. (82%) of the (±)-diene **3** as a colorless oil on elution with 30 ml. of petroleum ether. The analytical sample was obtained by evaporative distillation at 100° (0.05 mm.) (bath temp.). Gas-liquid chromatography of this material at 148° indicated the presence of a single component to the extent of 90% plus 10% of a less mobile material (possibly conjugated diene). The infrared spectrum of this (±)-diene **3** was identical to that of the (+)-diene +**3** obtained from pimaric acid (29).

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 88.26; H, 11.84.

Infrared: $\bar{\nu}_{max}^{film}$ 3080 cm.$^{-1}$ (vinyl H); 1832 cm.$^{-1}$ (w), 1638 cm.$^{-1}$, 995 cm.$^{-1}$ and 913 cm.$^{-1}$ (—CH=CH_2 grouping); 1660 cm.$^{-1}$ (w) and 818 cm.$^{-1}$. (w) (trisubst. > C=C<); 854 cm.$^{-1}$ and 856 cm.$^{-1}$ (skeletal vibrations).

(b) From the Aldehyde 33.—In exactly the same manner as described above, a solution of 207 mg. (0.76 mmole) of the aldehyde **33** in 5 ml. of petroleum ether was added to an etheral solution of methylenetriphenylphosphorane [prepared from 1.115 g. (3.10 mmoles) of triphenylmethylphosphonium bromide in 15 ml. of ether and 3.2 ml. of a 1.05 *N* solution of potassium *t*-butoxide in *t*-butyl alcohol] and the mixture stirred for 6 hr. at room temperature under a nitrogen atmosphere. Isolation of the product was accomplished by petroleum ether extraction and chromatography of the organic material on 7 g. of Woelm alumina (Activity I) afforded 218 mg. of colorless oil, eluted with 100 ml. of petroleum ether. Evaporative distillation of this material at 120° (0.05 mm.) (bath temp.) gave 203 mg. (99%) of pure (±)-pimaradiene (**3**), m.p. 28–31°. Gas-liquid chromatography of this material at 148° indicated the presence of a single component to the extent of 96% plus 4% of a less mobile impurity with the same retention time as (±)-sandaracopimaradiene (arising from a slight contamination of the starting aldehyde **33** by its epimer). The infrared spectrum of this material was identical to that of (+)-pimaradiene (+**3**) and the (±)-pimaradiene (**3**) prepared by pyrolysis.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 88.10; H, 11.75.

The melting point of a mixture of this material and (±)-sandaracopimaradiene (**2**), m.p. 22–25°, was depressed below 0°.

(+)-Pimaradiene (+3).—In the same fashion as that described above for the preparation of (−)-sandaracopimaradiene (−2), 400 mg. (1.16 mmoles) of the pimaral semicarbazone was decomposed by heating under nitrogen with 5.0 g. of potassium hydroxide in 15 ml. of diethylene glycol. Chromatography of the resulting hydrocarbon on 10 g. of Woelm alumina (Activity I) afforded 278 mg. (88%) of (+)-pimaradiene (+**3**) m.p. 24–26°, $[\alpha]^{25}D$ +99° (*c*, 510 mg./100 ml. $HCCl_3$) eluted with 70 ml. of petroleum ether as a clear, colorless oil at room temperature. Gas-liquid chromatography of this material at 148° showed the presence of only one component with the same retention time as (±)-pimaradiene (**3**). The infrared spectra of the (+)-pimaradiene (+**3**) and the (±)-pimaradiene (**3**) were identical.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.17; H, 11.83. Found: C, 87.97; H, 11.83.

Sandaracopimarol.—A solution of 900 mg. (2.85 mmoles) of methyl sandaracopimarate,[39] m.p. 64–65.5°, and 50 ml. of dry ether was reduced with 2.5 ml. of saturated, ethereal lithium aluminum hydride (1.2 *M*) and worked up using 0.23 ml. of water and 0.18 ml. of 10% aqueous sodium hydroxide. After removal of the ether at reduced pressure on the steam bath, evaporative distillation of the residue at 135° (0.02 mm.) afforded 776 mg. (93%) of a glass.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.27; H, 11.18. Found: C, 83.04; H, 11.16.

Infrared: λ_{max}^{film} 2.94 μ (s) (—OH); 3.29 μ (w) (vinyl H); 5.48 μ (w), 6.12 μ, 10.02 μ and 11.98 μ (—CH=CH_2 grouping); 6.04 μ (w) and 12.2 μ (w) (trisubst. >C=C<); 11.55 μ and 11.70 μ (skeletal vibrations).

Sandaracopimaral Semicarbazone.—A solution of 620 mg. (2.15 mmoles) of sandaracopimarol in 40 ml. of acetone was oxidized with 0.6 ml. of Jones reagent[16] and worked-up by addition of water and extraction with ether. The crude aldehyde crystallized on trituration with petroleum ether at −70°, and after two crystallizations of the solid from methanol, there resulted 377 mg. (62%) of sandaracopimaral, m.p. 49–50°.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.75; H, 10.68.

Infrared: λ_{max}^{film} 3.69 μ (s) (—C*H*O); 5.80 μ (s) (>C=O); 5.48 μ (w), 6.12 μ, 10.02 μ and 11.99 μ (—CH=CH_2) grouping); 6.02 μ (w) and 12.18 μ (w) (trisubst. >C=C<); 11.55 μ and 11.72 μ (skeletal vibrations).

Sandaracopimaral Semicarbazone, m.p. 218–220° with softening at 215° from methanol, was prepared from 286 mg. (1.0 mmole) of sandaracopimaral, m.p. 48–50°, in 94% yield by using the method of Fieser.[37]

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.42; H, 9.68. Found: C, 73.40; H, 9.70.

Pimaral Semicarbazone.—A solution of 1.0 g. (3.16 mmoles) of methyl pimarate, m.p. 66–67.5° (reported,[6b] m.p. 69°) in 50 ml. of dry ether was reduced with 2.75 ml. of a saturated, ethereal solution of lithium aluminum hydride (1.2 *M*). After the addition of 0.25 ml. of water and then 0.20 ml. of 10% aqueous sodium hydroxide, the precipitated salts were removed by filtration, and the ether evaporated at reduced pressure on the steam bath. The crude pimarol was not further purified but dissolved in 30 ml. of acetone and oxidized at 0–5° with 0.8 ml. of Jones reagent.[16] After addition of water to the reaction mixture, the pimaral was isolated by ether extraction and characterized by its infrared spectrum (λ_{max}^{film} 3.20 μ (w) (vinyl H); 3.70 μ (w) (—C*H*O); 5.82 μ (s) (>C=O); 6.13 μ (w) (>C=C<); 10.05 μ and 10.92 μ (s) (—CH=CH_2); 11.58 μ and 11.72 μ (skeletal vibrations). When the crude aldehyde was converted directly to the semicarbazone by the method of Fieser,[37] there resulted 750 mg. (75%) of pimaral semicarbazone, m.p. 213–216° dec. (reported, m.p. 205–210°[41] and 223–225°[40]) after two crystallizations from methanol. This material was submitted for combustion analysis because of the apparent discrepancy in the observed melting point and those previously reported.

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.42; H, 9.68. Found: C, 73.49; H, 9.76.

(39) O. E. Edwards, A. Nicolson, and M. N. Rodger, *Can. J. Chem.*, **38**, 663 (1960).

(40) N. A. Sörensen and T. Bruun, *Acta Chem. Scand.*, **1**, 112 (1947); G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 3870 (1948).

(41) D. H. R. Barton, T. Bruun, and N. A. Sörensen, *Acta Chem. Scand.*, **5**, 1356 (1951).

Experiments Directed toward the Total Synthesis of Terpenes. V. The Synthesis of the (±)-9-Isopimaradienes[1,2]

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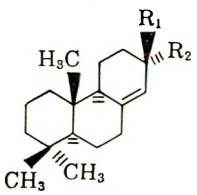
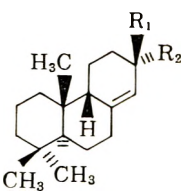
The *trans-syn-cis* ketone **14** has been synthesized *via* the pyrolytic rearrangement of the vinyl ether **9**. Conversion of this ketone **14** to the (±)-9-isopimaradienes **3** and **4** has been accomplished by methylation of the aldehyde **16**. The diene **3** is shown to be different from isopimaradiene and the diene **4** from rimuene. A new structure is proposed for isopimaric acid and, hence, isopimaradiene.

The synthesis[4] of (±)-sandaracopimaradiene (**1**) and (±)-pimaradiene (**2**) served to establish methods suitable for the elaboration of the ring C substitution pattern of the pimaric acids. With these methods available to us, it was natural to consider the synthesis of the remaining representative of the pimaric acids—namely, isopimaric acid. Again it seemed wise to restrict our initial efforts to the hydrocarbon isopimaradiene (**3**), lacking as it does the asymmetry and functionality at C-4.



1. $R_1 = -CH_3$; $R_2 = -CH=CH_2$.
2. $R_1 = -CH=CH_2$; $R_2 = -CH_3$.



3. $R_1 = -CH_3$; $R_2 = -CH=CH_2$.
4. $R_1 = -CH=CH_2$; $R_2 = -CH_3$.

The structure and stereochemistry of isopimaric acid—and hence isopimaradiene (**3**)—has been the subject of extensive investigations beginning with its isolation in 1948 by Harris and Sanderson.[5] While in retrospect it is an easy matter to find flaws in the reasoning used to arrive at the structure **3**, at the outset the universal agreement of these investigators appeared to leave little doubt that the isopimaric acid system did indeed contain the interesting *trans-syn*-$\Delta^{8(14)}$-dodecahydrophenanthrene system shown. It was not until our synthetic work was nearly finished that it became apparent that this was not the correct structure. Thus a project that began as a test of modern synthetic methods became in the end a means for determining the structure of the natural product—a more classical result that one might not think necessary with the tools available today for structure determination.

As if to heighten the intrigue already inherent in this project, midway through our work Wenkert and Beak[6] reported that their spectral findings established that the diterpenoid hydrocarbon rimuene[7] had the stereochemistry shown in structure **4**. While such a structure was an obvious candidate for rimuene when the dienes[4,6] related to the three naturally occurring resin acids were ruled out, there are obvious flaws in this reasoning that Wenkert and Beak chose to ignore. Thus rimuene is quite stable toward mineral acid catalyzed isomerization,[7] while isopimaric acid [as well as isopimaradiene (*vide infra*)] is the most labile[5b,e] of the resin acids toward this treatment. Such a result can hardly be attributed solely to a change in stereochemistry at C–13. Similarly, inspection of even the small portion of the n.m.r. spectrum of rimuene reported by Wenkert and Beak[6] reveals a broad signal centered at 4.64 τ due to the nuclear vinyl hydrogen. The breadth of this signal is clearly inconsistent with the $\Delta^{8(14)}$-structure proposed by these workers, as the C-14-vinyl hydrogen cannot be strongly spin-coupled, lacking, as it does, any adjacent protons. Thus, it seemed unlikely that the stereochemical assignment made by these workers was correct even before our synthesis of the isomeric dienes **3** and **4** was complete.

Another point that was overlooked by Wenkert and Beak[6] and foreshadowed our results relative to the isopimaric acid structure was the clearly resolved doublet due to the nuclear vinyl hydrogen in the n.m.r. spectrum of methyl isopimarate. For the reasons stated above, such a signal could not be due to a C-14-vinyl hydrogen and was the first indication we had that the structure of isopimaric acid (and hence, isopimaradiene), too, was incorrect.

The key to the synthesis of the 9-isopimaradienes **3** and **4** was the construction of the *trans-syn-cis* ketone **14**.[8] Since the ketone **14** could not be obtained by any obvious modification of the synthesis used earlier for the isomeric *trans-anti-trans* ketone,[4] we were in need of a new route to the phenanthrene system. The opportunity to explore such a route presented itself as a result of our experiments[9] in connection with the Claisen rearrangement of the allyl vinyl ether **5**. It was previously shown[9] that the aldehyde obtained by the pyrolysis of the ether **5** possessed the α-(axial)-oriented acetaldehyde residue. This information opened the

(1) For a preliminary account of this work, see R. F. Church and R. E. Ireland, *Tetrahedron Letters*, 493 (1961); taken in part from the Ph.D. thesis of R. F. Church, University of Michigan, 1961.

(2) This work was supported in part by a Research Grant H-4179 from the National Heart Institute, National Institutes of Health.

(3) Dow Chemical Company Fellow, 1958–1959; Sun Oil Company Fellow, 1959–1960.

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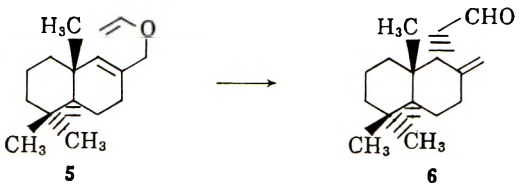
(5) (a) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 2081 (1948); (b) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959); (c) O. E. Edwards and R. Howe, *Chem. Ind.* (London), 537 (1959); (d) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959); (e) B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958); (f) A. K. Bose, *Chem. Ind.* (London), 1105 (1960); (g) H. H. Bruun, *Acta Acad. Aboensis, Math. et Phys.*, **19** (3), 7 (1954); (h) H. H. Bruun, *Finska Kemistsamfundets Medd.*, **63**, 22 (1954); (i) H. H. Bruun, *Acta Chem. Scand.*, **6**, 798 (1952); (j) H. H. Bruun, I. Fishmeister, and E. Stenhagen, *ibid.*, **13**, 379 (1959); (k) H. H. Bruun, R. Ryage, and E. Stenhagen, *ibid.*, **12**, 789 (1958); (l) Le-van-Thoi and J. Ourgand, *Bull. soc. chim. France*, 202 (1956); (m) G. W. A. Milne and H. Smith, *Chem. Ind.* (London), 1307 (1961).

(6) E. Wenkert and P. Beak, *J. Am. Chem. Soc.*, **83**, 998 (1961).

(7) L. H. Briggs, B. F. Cain, and R. C. Cambie, *Tetrahedron Letters*, No. **8** 17 (1959).

(8) Since completion of our work, two other reports of the synthesis of related *trans-syn-cis*-perhydrophenanthrene systems have appeared: S. K. Balasubramanian, *Tetrahedron*, **12**, 196 (1961), and E. Wenkert, V. I. Stenberg, and P. Beak, *J. Am. Chem. Soc.*, **83**, 2320 (1961).

(9) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **27**, 1118 (1962).



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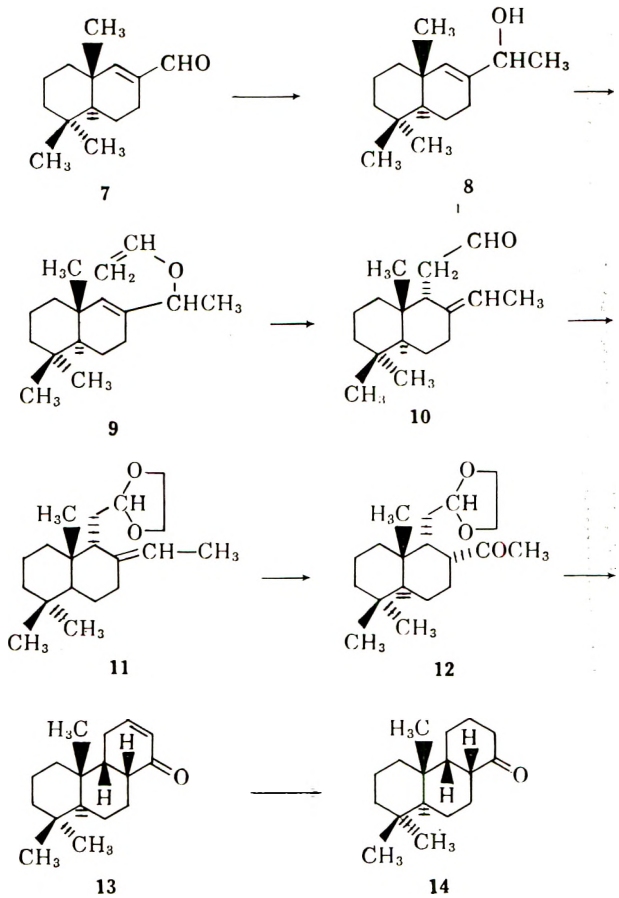
way to the construction of an analogous system with the desired *syn* relationship between the C_{10}—CH_3 and the C_9—H.

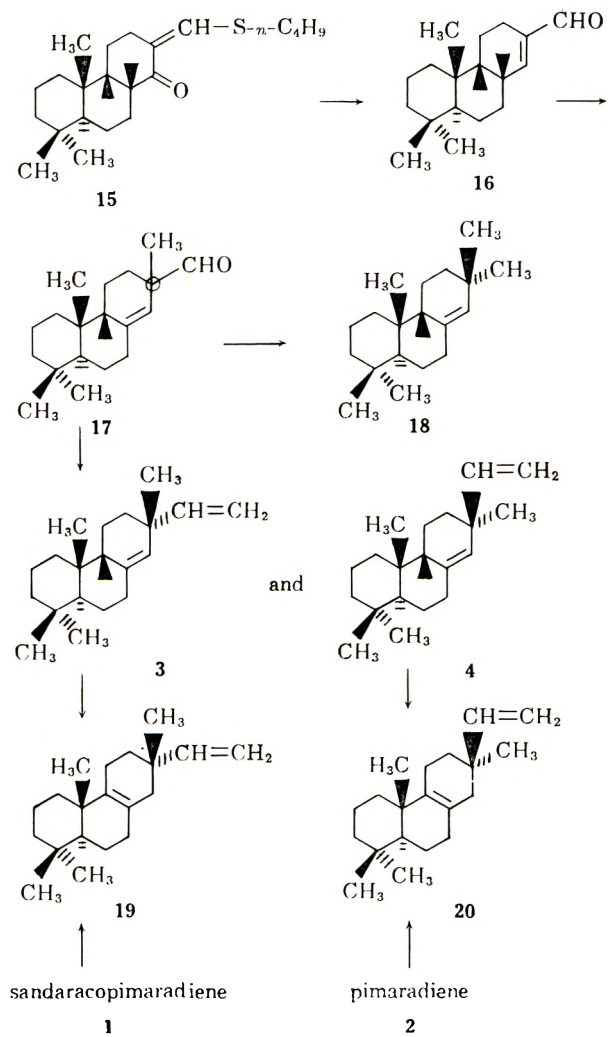
The aldehyde **7**, available from earlier work,[9] was converted to the allylic alcohol **8** in 77% yield through the agency of methyllithium. Equilibration[10] of this alcohol with excess ethyl vinyl ether afforded the vinyl ether **9** in 66% yield. We attribute the markedly lower



7 8 9 10 11 12 13 14

yield observed in the formation of the vinyl ether **9** as compared with the 91% yield observed in the formation of the ether **5** to the secondary *vs.* primary nature of the hydroxyl function. The vinyl ether **9** was also less stable than its homolog **5** and more susceptible to hydrolysis. However, pyrolysis[11] of the chromatographically pure material generated as high as a 97% yield of the corresponding aldehyde **10**. While the stereochemistry of the newly introduced acetaldehyde residue was surely known, the configuration of the ethylidene group was not determined, as this wou be of no consequence to the sequel. The aldehyde **10** was quite susceptible to air oxidation and was characterized as the corresponding acid (silver oxide oxidation[12]), its methyl ester, and the acetal **11**, prepared in 91% yield by acid catalyzed, azeotropic removal of water from a solution of the aldehyde and ethylene glycol in benzene. On hydroboration[13] the acetal **11** afforded an alcohol which was not purified but oxidized directly with Jones reagent[14] to the corresponding ketone. Chromatography of this oxidation mixture served not only to remove any impurities but also to equilibrate the C-8 acetyl residue through its enol and thus establish the α-(equatorial) orientation. In this manner we were able to realize a 60% over-all yield of the crystalline keto acetal **12**. Achievement of our first goal was readily accomplished by acid-catalyzed acetal hydrolysis and then acid-catalyzed aldol-type cyclization of the crude keto aldehyde. The tricyclic unsaturated ketone **13** formed in this way in 65% yield was reduced in 95% yield to its saturated analog **14** over 10% palladium on carbon. The alarm created by the observation that the melting point of this *trans-syn-cis* ketone **14** (78–79.5°) was the same as that of the isomeric *trans-anti-trans* ketone (78–80°) prepared earlier[4] was quieted when on admixture the melting point was dramatically depressed to 45–67°; the infrared spectra of the two ketones also showed significant differences in the 7–16-μ region.

The remaining steps of the synthesis closely paralleled the aldehyde method used earlier[4] for the construction



15 16 17 18 3 and 4 19 20

sandaracopimaradiene pimaradiene

1 2

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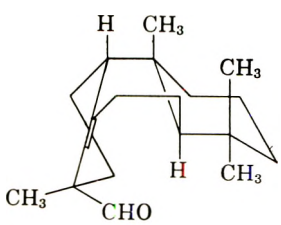
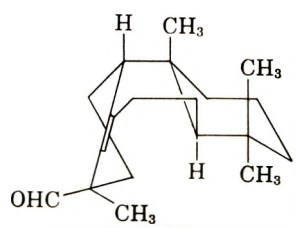
(13) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also, C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

of (±)-sandaracopimaradiene (**1**) and (±)-pimaradiene (**2**). Thus the ketone **14** was converted to the 13-*n*-butylthiomethylene derivative **15** by the standard procedure[15] in an average yield of 79%. Sodium borohydride reduction of this derivative **15**, and then steam distillation of the crude product from aqueous sulfuric acid[16] afforded a 70% over-all yield of the aldehyde **16**. It proved to be more difficult to effect enolization of the aldehyde **16** than its *trans-anti-trans* epimer,[4] for it was not until a solution of this aldehyde in benzene–*t*-butyl alcohol containing a 210-fold excess of potassium *t*-butoxide was refluxed for one-half hour that any appreciable coloration due to the enolate could be detected. Addition of methyl iodide to this mixture then effected the desired end and afforded an 81% yield of 13-methylated material **17**, together with 8% starting aldehyde and 11% of unidentified material, as measured by gas-liquid chromatography. The presence of two methylated aldehydes in approximately equal proportions was also determined by this technique. Unfortunately, these aldehydes were not as stable as those obtained in the *trans-anti-trans* series,[4] and on column chromatography over Florisil extensive decomposition occurred. We were able to isolate a small amount of the more strongly adsorbed aldehyde in a crystalline, analytically pure state, but its epimer could not be obtained in a pure condition. By virtue of this chromatographic behavior, we tentatively assigned the crystalline isomer the 13-α-methyl-13β-aldehydo structure **17b**. This assignment proved to be correct (*vide infra*) and pointed up the interesting effect of the conformation of the *trans-syn*-$\Delta^{8(14)}$-structure on the adsorption of these molecules. It can be seen from structures **17a** and **17b** that although the β-aldehydo grouping in isomer **17b** is quasi-axial, it is more exposed and thus more available for adsorption than the α-aldehyde in the quasi-equatorial position in the epimer **17a**. Such a reversal of the more common trend can be attributed to the *syn*-backbone which forces the β-ring to adopt the boat conformation.



17a



17b

Lacking a satisfactory method of preparatively separating the unstable aldehydes **17**, the synthesis was completed by treating the aldehyde mixture with methylenetriphenylphosphorane,[17] and thereby generating a mixture of the dienes **3** and **4** together with small quantities of impurities. It was found that this much more stable diene mixture was readily resolved by gas-liquid chromatography on a polyester column, and by application of this technique on a preparative scale we were able to isolate pure samples of the individual dienes A and B.

The problem of discerning which of our pure diene samples A and B corresponded to which of the structures **3** and **4** was greatly facilitated by the availability of sandaracopimaradiene **1** and pimaradiene **2** of rigorously established structure from our earlier work.[4] Thus by application of the acid-catalyzed isomerization technique of Edwards,[5b] sandaracopimaradiene **1** was transformed into $\Delta^{8,9}$-sandaracopimaradiene (**19**)[18] and pimaradiene **2** to $\Delta^{8(9)}$-pimaradiene (**20**). In this manner the only difference between the two series—namely, the asymmetry at C-9—was removed. It was satisfying to find that a similar acid treatment of the diene A (eluted first on gas-liquid chromatography) led to $\Delta^{8(9)}$-sandaracopimaradiene (**19**) and thereby established the structure **3** for this diene. Similarly, the diene B (eluted second from the gas-liquid column) was rearranged to $\Delta^{8(9)}$-pimaradiene (**20**), and thus must possess the structure **4**. In confirmation of our tentative structural assignment to the crystalline methylated aldehyde **17b** mentioned above, we found that treatment of this aldehyde **17a** with methylenetriphenylphosphorane[17] led to a 96% yield of the diene **4**.

While these interrelationships conclusively establish the stereochemistry of the two dienes **3** and **4** at C-13, they represent strong but only circumstantial evidence for the $\Delta^{8(14)}$-position of the nuclear double bond. As will be evident below, this became an extremely important point, and in order to gain more evidence for this assignment, the mixture of aldehydes **17** was reduced to the olefin **18** in 91% yield by employing the Huang–Minlon modification[19] of the Wolff–Kishner reduction. The n.m.r. spectrum of this olefin showed a single, uncoupled signal at 5.30 τ for the vinyl hydrogen present and thereby verified the $\Delta^{8(14)}$-position for the double bond. As a check on the reliability of this method of analysis, the corresponding *trans-anti-trans* olefin was prepared in a similar fashion in 92% yield from the epimeric mixture of *trans-anti-trans* aldehydes obtained previously.[4] Again the n.m.r. spectrum showed the presence of only a single, uncoupled band due to the C-14 vinyl hydrogen at 5.13 τ. Thus these observations, taken together with the demonstrated *trans-syn-cis* stereochemistry of the ketone **14** and the interrelation of the dienes **3** and **4** with the previously synthesized[4] pimaradienes **1** and **2**, conclusively establish the structure and stereochemistry of the dienes **3** and **4** as shown.

There remained but to compare the properties of the synthetic dienes **3** and **4** with isopimaradiene[20] and rimuene.[7] In view of the analysis presented above, it was not surprising to find that both the infrared spectrum and relative mobility on gas-liquid chromatography (Table I) of rimuene were markedly different from

(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

(16) This procedure proved superior to the acid hydrolysis used in the previous work[4] as it prevented the formation of any appreciable quantities of dithioacetal from the aldehyde and liberated *n*-butyl mercaptan in the presence of mineral acid.

(17) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954).

(18) When $\Delta^{8(9)}$-sandaracopimaradiene (**19**) was obtained from (−)-sandaracopimaradiene (−**1**) by this same procedure, it crystallized and was found to melt at 52–53° after recrystallization from methanol. The close correspondence between the melting point of this material and that (m.p. 51–52°) described by V. Galik, J. Kuthan, and F. Petrů [*Chem. Ind.* (London), 722 (1960)] for the compound obtained by desulfurization of the ethylenethioacetal of sandaracopimaral prompts us to suggest their identity. The substance obtained by Petrů and originally reported to be rimuene was later shown by these workers to be different from the natural product by a direct comparison of the two materials. It is reasonable to conclude that isomerization of the $\Delta^{8(14)}$ double bond to the more highly substituted $\Delta^{8(9)}$ position could have taken place on the surface of the Raney nickel catalyst used for the desulfurization.

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

(20) Prepared from isopimaric acid in 48% over-all yield by the same sequence employed earlier[4] (see the Experimental).

TABLE I

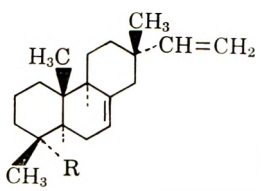
RELATIVE MOBILITY OF DIENES ON GAS-LIQUID CHROMATOGRAPHY

Rimuene	0.72	Pimaradiene	0.89
Diene **3**	0.74	Sandaracopimaradiene	1.00 (ref. std.)
Diene **4**	0.89	Isopimaradiene	1.23

those of the diene **4**. This result again struck down a proposed structure for rimuene and points up the need of more definitive chemical evidence before further structural assignments are made.

Quite surprising, however, was the lack of correspondence between the infrared spectrum and relative mobility on gas-liquid chromatography (Table I) between the synthetic diene **3** and isopimaradiene. Particularly striking were the differences in the 800–900-cm.$^{-1}$ region. The absorption in this region, which we have come to associate[4] with the gross hydrophenanthrene structure and stereochemistry, was quite simple in the spectrum of the synthetic diene **3** (ν_{max}^{film} 860 cm.$^{-1}$) and more complex in the spectrum of isopimaradiene and its derivatives (ν_{max}^{film} 820 cm.$^{-1}$, 835 cm.$^{-1}$ and 860 cm.$^{-1}$).

The non-identity of the synthetic diene **3** of known structure and stereochemistry with isopimaradiene occasioned a more thorough examination of the data available on the structure of the natural product. The evaluation of this evidence, together with some new results, are described in the following article[21] where it is shown that isopimaric acid—and thus isopimaradiene—possess the *trans-anti*-Δ^7-structures **21** and **22**, respectively.



21. R = —CO_2H
22. R = —CH_3

Experimental[22]

5,5,9β-Trimethyl-2-(1-hydroxyethyl) *trans*-Δ^1-octalin (8).—To a well stirred solution of 0.16 mole of methyllithium in 200 ml. ether (prepared by bubbling methyl bromide into a cooled, stirred svspension of 2.2 g. (0.315 mole) of lithium in 200 ml. of ether) was added 22.5 g. (0.11 mole) of chromatographically pure 2-carboxaldehyde-5,5,9β-trimethyl-*trans*-Δ^1-octalin (**7**) in 50 ml. of ether, and the solution was stirred at room temperature for 8 hr. Saturated aqueous ammonium chloride (100 ml.) was added, and the product isolated by ether extraction in the usual manner. Evaporation of the ether and distillation of the residue afforded 18.60 gm. (77%) of the allylic alcohol **8**, b.p. 105–106° (0.3 mm.). The analytical sample, obtained by redistillation, boiled at 92° (0.15 mm.).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.89; H, 11.75.

Infrared: λ_{max}^{film} 2.90 μ (s) (O—H); 9.39 μ (s) (C—O).

Vinyl Ether of 5,5,9β-trimethyl-2-(1-hydroxyethyl)-*trans*-Δ^1-octalin (9).—In a typical run, 3.75 g. (17.0 mmoles) of 5,5,9β-trimethyl-2-(hydroxyethyl)-*trans*-Δ^1-octalin (**8**) was dissolved in 40 ml. of freshly distilled ethyl vinyl ether containing 540 mg. of mercuric acetate. After the solution had been refluxed in a nitrogen atmosphere for 6 hr., 1 g. of anhydrous sodium carbonate was added, and the mixture was stirred 0.5 hr. The ethereal solution was decanted, the solid sodium carbonate was washed well with ether, and the combined ethereal fractions were evaporated on the steam bath under a stream of nitrogen. Chromatography of the residue on 130 g. of alumina afforded 2.790 g. (66%) of the vinyl ether (eluted with 3 l. of petroleum ether) which was of sufficient purity for use in the Claisen rearrangement. The vinyl ether **9** was characterized by its infrared spectrum [λ_{max}^{film} 3.12 μ (w) (vinyl H); 6.10 μ (s) and 6.20 μ (s) (vinyl ether)], but due to its sensitivity to atmospheric moisture, no satisfactory analytical values could be obtained.

5,5,9β-Trimethyl-2-ethylidene-*trans*-decal-1α-ylacetaldehyde (10).—A Carius tube containing 1.035 g. (4.2 mmoles) of the vinyl ether **9** under nitrogen was placed in an oil bath at 195°, and the temperature was maintained between 190–200° for 3 hr. The tube was cooled and the aldehyde was chromatographed on 100 g. of Florisil. After elution with 500 ml. of petroleum ether removed 30 mg. of oil, 1500 ml. of 3% ether:petroleum ether eluted 1.003 g. (97%) of the aldehyde **10**. In several runs it was found that the crude aldehyde before chromatography was of sufficient purity for acetalization without further purification. In four runs in which the aldehyde was purified by chromatography, the yields ranged from 89–97%.

Infrared: λ_{max}^{film} 3.67 μ (*CH*O); 5.80 μ (s) (>C=O); 6.00 μ and 12.15 μ) (>C=CH—CH_3).

5,5,9β-Trimethyl-2-ethylidene-*trans*-decal-1α-ylacetic Acid.—To a solution of 946 mg. of the aldehyde **10**, containing some allylic alcohol **8** in 50 ml. of ethanol containing 1.00 g. of silver nitrate and 10 ml. of water was added over a period of 1 hr. with rapid stirring a solution of 0.95 g. of sodium hydroxide in 35 ml. of water. The mixture was stirred for 4 hr. at room temperature, diluted with 50 ml. of water, and filtered. The clear filtrate was extracted three times with 40-ml. portions of ether (evaporation of the combined ether extracts afforded 400 mg. of recovered allylic alcohol **10**, identified by its infrared spectrum), acidified with excess concentrated hydrochloric acid, and the precipitated acid isolated by ether extraction. After the usual washing and drying procedure, removal of the ether and crystallization of the solid residue from ethyl acetate:petroleum ether afforded 545 mg. of the acid, m.p. 150–151°. The analytical sample, obtained after one further crystallization from the same solvent pair, also melted at 150–151°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.68. Found: C, 77.19; H, 10.53.

The methyl ester, prepared in 80% yield by the action of ethereal diazomethane on the acid, was a liquid which was evaporatively distilled at 90° (bath temp.) (0.1 mm.) for analysis.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.43; H, 10.73.

Infrared: λ_{max}^{film} 5.78 μ (s) (>C=O) and 8.71 μ (s) (C—O—C).

Acetal of 5,5,9β-Trimethyl-2-ethylidene-*trans*-decal-1α-ylacetaldehyde (11).—A solution of 1.003 g. (4.04 mmoles) of the aldehyde **10**, 1 ml. of ethylene glycol, and 30 mg. of *p*-toluenesulfonic acid in 40 ml. of benzene was heated under reflux for 40 min. using a Dean–Stark water separator filled with Drierite to remove water from the distillate. After the usual work-up and removal of the solvent, the residue was chromatographed on 45 g. of alumina. Elution with 2.5% ether:petroleum ether afforded 1.079 g. (91%) of the acetal **11** of sufficient purity to be used directly in the hydroboration experiment to follow. The analytical sample was obtained by evaporative distllation at 110° [bath temp. (0.2 mm.)].

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.97; H, 11.12.

Infrared: λ_{max}^{film} 8.82 μ (s) (acetal); 6.00 μ and 12.20 μ (>C=CHCH$_3$).

Acetal of 5,5,9β-Trimethyl-2α-acetyl-*trans*-decal-1α-ylacetaldehyde (12).—To 25.0 ml. of a 0.083 *M* solution of diborane in dry tetrahydrofuran (prepared by the addition of boron trifluoride–ethereate to a suspension of sodium borohydride in tetrahydrofuran, filtration, and gasometric standardization) in a

(21) See also, R. E. Ireland, and J. Newbould, *J. Org. Chem.*, **27**, 1931 (1962), and W. Antkowiak, J. W. ApSimon, and O. E. Edwards, *J. Org. Chem.*, **27**, 1930 (1962), for preliminary reports of these results.

(22) Unless specified otherwise, the term "petroleum ether" refers to reagent grade material boiling in the range 30–60°. All gas–liquid chromatograms were obtained on a Barber–Coleman Model 10 gas-liquid chromatography unit using a 6-ft. column packed with 15% diethylene glycol succinate on Chromosorb W. Melting points were determined on a Kofler Hot Stage and are corrected for stem exposure. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Unless otherwise specified infrared spectra were measured on a Perkin–Elmer Infracord Model 137, and strong bands are marked (s); all others reported are of moderate intensity unless otherwise specified. Ultraviolet spectra were determined on a Cary recording spectrophotometer (Model 11 MS). *Florisil* refers to the product of the Floridin Company, Tallahassee, Fla., 60/100 mesh.

nitrogen atmosphere was added with stirring a solution of 1.00 g. (3.4 mmoles) of the acetal olefin **11** in 8 ml. of tetrahydrofuran. Stirring was continued for 2 hr. at room temperature, and then 5 ml. of 10% aqueous sodium hydroxide was added followed by 5 ml. of 30% hydrogen peroxide. After the reaction mixture was heated under reflux for 1 hr., 100 ml. of water was added, and the product isolated in the usual manner by ether extraction. The residue obtained after removal of the ether was not further purified but dissolved in 20 ml. of acetone, cooled to 0°, and oxidized with 0.90 ml. (7.1 meq.) of Jones reagent.[14] After the addition of 100 ml. of cold water, the product was isolated by ether extraction in the usual manner. The oily residue, obtained after removal of the ether, was chromatographed on 40 g. of alumina. Elution with 1200 ml. of 1% ether:benzene afforded 870 mg. of crystalline keto acetal **12**. After one crystallization of this material from petroleum ether (b.p. 60–75°), there remained 633 mg. (60%) of material, m.p. 126–130°, of sufficient purity to be used in further experiments. The analytical sample, obtained by further crystallization from the same solvent, melted at 132–133.5°.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.83; H, 10.57.

Infrared: $\lambda_{max}^{HCCl_3}$ 5.87 μ (s) (>C=O); 8.82 μ (s) (acetal).

(±)-9-Isopodocarpen-12-one-14 (13).—To a solution of 6.70 g. (21.6 mmoles) of the keto acetal **12** in 80 ml. of acetone was added 20 ml. of 10% aqueous hydrochloric acid, and the reaction mixture was allowed to stand 2 hr. at room temperature. The solution was then diluted with 30 ml. of saturated aqueous sodium chloride, and the product isolated in the customary fashion by ether extraction. A solution of the crude keto aldehyde, obtained by removal of the ether and not further purified, in 100 ml. of benzene containing 100 mg. of *p*-toluenesulfonic acid was heated under reflux in a nitrogen atmosphere for 1.5 hr. After the usual work-up, removal of the solvent left a crystalline solid which was chromatographed on 200 g. of alumina. Elution with 4 l. of benzene afforded 4.6 g. of the ketone **13**. After crystallization of this material from petroleum ether (b.p. 60–75°), there remained 3.50 g. (65%) of material melting at 113–115°. The analytical sample, obtained by one more crystallization from the same solvent, melted at 116–117°.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.75; H, 10.44.

Ultraviolet: λ_{max}^{alc} 227 mμ (ϵ 8700). **Infrared:** $\lambda_{max}^{HCCl_3}$ 6.01 μ (s) (α,β-unsaturated >C=O).

(±)-9-Isopodocarpanone-14 (14).—A solution of 500 mg. (2.03 mmoles) of the ketone **13** in 10 ml. of glacial acetic acid in which was suspended 50 mg. of 10% palladium-on-carbon was stirred in a hydrogen atmosphere at room temperature for 3 hr., during which time 51.3 ml. (100%) of hydrogen was absorbed. After removal of the catalyst by filtration, most of the acetic acid was removed at reduced pressure, and the residue was treated with water and ether. The ethereal solution was separated, washed, and dried in the usual manner and evaporated at reduced pressure. On crystallization of the residue from petroleum ether (b.p. 60–75°) there was obtained 475 mg. (95%) of the ketone **14**, m.p. 78–79.5°, in an analytically pure condition.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.28; H, 11.38.

Infrared: $\lambda_{max}^{HCCl_3}$ 5.91 μ (saturated (s) >C=O).

The melting range of a mixture of this ketone and the isomeric *trans-anti-trans* ketone,[4] m.p. 78–80°, was depressed to 45–67°.

(±)-13-*n*-Butylthiomethylene-9-isopodocarpanone-14 (15).—Hydroxymethylation of 569 mg. (2.3 mmoles) of the ketone **14** was accomplished according to the standard procedure by employing 6.0 g. (0.12 mole) of sodium methoxide and 10 ml. (0.12 mole) of ethyl formate in 20 ml. of benzene. The crude derivative, obtained in essentially quantitative yield, in 15 ml. of benzene containing 0.025 ml. of *n*-butyl mercaptan and 10 mg. of *p*-toluenesulfonic acid was heated under reflux in a nitrogen atmosphere for 4 hr. After the customary work-up, there was obtained 629 mg. (79%) of the crystalline thiomethylene derivative (**15**), m.p. 70–73°. The analytical sample, obtained by crystallization of this derivative from petroleum ether (b.p. 60–75°), melted at 73–74°.

Anal. Calcd. for $C_{22}H_{36}OS$: C, 75.81; H, 10.41; S, 9.19. Found: C, 75.83; H, 10.30; S, 9.32.

Infrared: λ_{max}^{film} 6.01 μ (s) (conj. >C=O); 6.48 μ (s) (conj. >C=C<).

(±)-9-Isopodocarp-13-ene-13-carboxaldehyde (16).—A solution of 600 mg. (1.7 mmoles) of the thiomethylene derivative **15** in 30 ml. of methanol was reduced with a solution of 1.0 g. (26 mmoles) of sodium borohydride in 8 ml. of 0.1 *N* aqueous sodium hydroxide. After stirring for 2 hr. at room temperature, most of the methanol was removed at reduced pressure, and the product isolated by ether extraction. The crude reduction product was washed into a solution of 200 ml. of diethylene glycol and 100 ml. of 10% aqueous sulfuric acid by using a small quantity of ether, and the acidic mixture subjected to steam distillation. Ether extraction of 4 l. of steam distillate and chromatography of the solute on 30 g. of alumina afforded 408 mg. of crystalline material, eluted with 500 ml. of 50% benzene:petroleum ether. Crystallization of this solid from petroleum ether (b.p. 60–75°) gave 312 mg. (70%) of the aldehyde **16**, m.p. 107.5–109°, in an analytically pure condition.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.08; H, 10.91.

Infrared: $\lambda_{max}^{HCCl_3}$ 3.64 μ (w) (C*H*O); 5.96 μ (s) (conj. >C=O); 6.08 μ (conj. >C=C<).

(±)-13-Methyl-9-isopodocarp-8(14)-ene-13-carboxaldehyde (17).—A solution of 416 mg. (1.44 mmoles) of the aldehyde **16** in 15 ml. of benzene was added to a slush prepared from 12 g. (0.3 mole) of potassium in 240 ml. of *t*-butyl alcohol contained in a nitrogen atmosphere. After stirring and heating this reaction mixture under reflux for 0.5 hr., the suspension was cooled in an ice bath for 4 min., and then 40 ml. (86 g.; 0.6 mole) of methyl iodide was added all at once. The mixture was stirred for 8 hr. at room temperature; 100 ml. of water was added and most of the *t*-butyl alcohol removed at reduced pressure. The product was isolated by ether extraction in the usual manner and evaporatively distilled at 140–145° (bath temp.) (0.02 mm.). In this manner there was collected 422 mg. of colorless distillate which on gas-liquid chromatography was shown to be comprised of 36% methylated aldehyde isomer A **17a**, 40% of isomer B **17b** [together representing 81% of methylated aldehyde **17**], 8% of starting aldehyde **16**, and 16% of less mobile, unidentified impurity. Infrared spectral analysis showed the presence of both a saturated aldehyde (band at 5.78 μ) and conjuated unsaturated aldehyde (weaker band at 5.91 μ).

Chromatography of 255 mg. of a similar distilled mixture on 25 g. of Florisil led to extensive decomposition and recovery of only 80% of the material. Besides several oily early fractions, there was obtained 88 mg. of a crystalline sample of isomer B **17b** (identified by relative mobility on gas-liquid chromatography) eluted with 1200 ml. of 10% benzene:petroleum ether, and 21 mg. of the aldehyde **16** (identified by comparison of infrared spectra) eluted with 300 ml. of benzene. After two crystallizations of the aldehyde isomer B **17b** from petroleum ether at −78°, there was obtained a 26-mg. sample melting at 82–87° and shown to be 99% pure by gas-liquid chromatography.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.13; H, 11.19.

(±)-9-Isopimaradiene (4) and (±)-9-Iso-sandaracopimaradene (3).—The distilled mixture of aldehydes **17** described above (422 mg.) was dissolved in 10 ml. of dry ether and added under nitrogen to a stirred suspension of 3.18 g. (9.0 mmoles) of triphenylmethylphosphonium bromide and 930 mg. (8.3 mmoles) of powdered potassium *t*-butoxide in 80 ml. of petroleum ether. The mixture was stirred for 10 hr. at room temperature, 30 ml. of water added, and the organic layer separated and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent was chromatographed on 20 g. of alumina. Elution with 100 ml. of petroleum ether afforded a mixture of dienes A **3** (49%) and B **4** (46%) together with 5% of what was probably the conjugated diene from the aldehyde **16** (percentages obtained by gas-liquid chromatography).

This mixture of dienes was separated by gas-liquid chromatography on a column 9 ft. long and 0.5 in. in outside diameter, packed with a stationary phase of 15.3% ethylene glycol–succinic acid polyester on Chromosorb W support. This column was found to have *ca.* 600 theoretical plates. Using the Barber–Coleman Model 10 apparatus, a column temperature of 200° and argon pressure of 16 p.s.i., the dienes A **3** and B **4** were eluted at 13 and 16 min., respectively. Collection was accomplished by passing the effluent gases alternately through each of two short, 8-mm. i.d. tubes packed with a small plug (*ca.* 0.5–1 gm.) of alumina, from which the individual dienes could be readily eluted with petroleum ether. Employing 5-μl. samples, a total of 145 μl. of the diene mixture afforded 29 mg. of diene A **3** and 34 mg. of diene B **4**. Each diene was individually evaporatively distilled at 100–110° (bath temp.) (0.2 mm.) and analyzed

by gas-liquid chromatography. Diene A **3** was found to be 98% pure (2% of diene B) with a mobility relative to (−)-sandaracopimaradiene (−1) of 0.74 and diene B **4** was found to be 99% pure (1% of diene A) with a mobility relative to the same reference standard of 0.89.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found for diene A **3**: C, 88.08; H, 11.76. Found for diene B **4**: C, 87.93; H, 11.76.

Infrared[23]: **Diene A (3).**—ν_{max}^{film} 3080 cm.$^{-1}$ (w) (vinyl H); 1835 cm.$^{-1}$ (w), 1639 cm.$^{-1}$, 995 cm.$^{-1}$, and 918 cm.$^{-1}$ (—CH=CH_2); 1662 cm.$^{-1}$ (w) and 819 cm.$^{-1}$ (w) (trisubst. >C=C<); 860 cm.$^{-1}$ (skeletal vibration).

Diene B. (4).—ν_{max}^{film} 3080 cm.$^{-1}$ (w) (vinyl H); 1820 cm.$^{-1}$ (w), 1635 cm.$^{-1}$, 997 cm.$^{-1}$ and 910 cm.$^{-1}$ (—CH=CH_2); 1660 cm.$^{-1}$ (w) and 818 cm.$^{-1}$ (w) (trisubst. >C=C<); 861 cm.$^{-1}$ (skeletal vibration).

When 22 mg. (0.08 mmole) of the aldehyde isomer B (**17b**) was treated as above with 1.09 gm. (3.0 mmoles) of triphenylmethylphosphonium bromide and 310 mg. (2.8 mmoles) of powdered potassium *t*-butoxide in 20 ml. of petroleum ether, there resulted 21 mg. (96%) of the corresponding diene after chromatographic purification over alumina. The infrared spectrum and relative mobility on gas-liquid chromatography of the diene prepared in this manner were identical to those of the diene B **4** obtained from the mixture above.

8(9)-Sandaracopimaradiene (19): From (−)-Sandaracopimaradiene (−1).—A solution of 40 mg. of (−)-sandaracopimaradiene, (−1) m.p. 41–42°, in 10 ml. of dry chloroform was cooled in an ice–salt bath and treated with a stream of dry hydrogen chloride for 4 hr. The solution was diluted with 40 ml. of petroleum ether, washed with two 15-ml. portions of water, one 15-ml. portion of 10% aqueous sodium bicarbonate, and dried (Na_2SO_4). After filtration and removal of the solvent, the residue was eluted from 5 g. of alumina with 20 ml. of petroleum ether and then evaporatively distilled at 100–110° (bath temp.) (0.2 mm.). In this manner there was obtained 38 mg. (95%) of 8(9)-sandaracopimaradiene (**19**), m.p. 45–50°. The analytical sample, obtained after two crystallizations from methanol, melted at 52–53°.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.12; H, 11.92.

Infrared[23]: ν_{max}^{hlm} 3080 cm.$^{-1}$ (w) (vinyl H); 1822 cm.$^{-1}$ (w), 1640 cm.$^{-1}$, 995 cm.$^{-1}$, and 910 cm.$^{-1}$ (—CH=CH_2).

From Diene A (3).—Treatment of 23 mg. of the diene A **3** (98% pure by gas-liquid chromatography) in the same manner led to the production of 22 mg. (96%) of (±)-8(9)-sandaracopimaradiene (**19**), as an oil. Gas-liquid chromatography indicated the presence of a single substance, the relative mobility of which was identical to the material obtained above from the natural diene. The infrared spectra of the natural and synthetic dienes were identical.

8(9)-Pimaradiene (20). From (+)-Pimaradiene.—When 38 mg. of (+)-pimaradiene (**4**) was rearranged by treatment with dry hydrogen chloride in 10 ml. of dry chloroform in exactly the same manner as described above, there resulted 37 mg. (96%) of the 8(9)-pimaradiene (**20**), as an oil. The analytical sample was obtained by evaporative distillation at 100–110° (bath temp.) (0.2 mm.). Gas-liquid chromatography of this material showed the presence of a single component to the extent of 99%.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.05; H, 11.75.

Infrared[23]: ν_{max}^{film} 3080 cm.$^{-1}$ (w) (vinyl H); 1820 cm.$^{-1}$ (w), 1638 cm.$^{-1}$, 995 cm.$^{-1}$, and 908 cm.$^{-1}$—CH=CH_2).

From Diene B (4): When 42 mg. of the diene B **4** (99% pure by gas-liquid chromatography) in 10 ml. of dry chloroform was rearranged with dry hydrogen chloride as described above, there resulted 41 mg. (96%) of (±)-8(9)-pimaradiene (**20**), as an oil. Gas-liquid chromatography indicated the presence of a single substance, the relative mobility of which was identical to the material obtained above from the natural diene. The infrared spectra of the natural and synthetic dienes were identical.

(±)-13,13-Dimethyl-9-isopodocarp-8(14)-ene (18).—A solution of 180 mg. (0.66 mmole) of the distilled mixture of aldehydes **17** and 1 ml. of 98–100% hydrazine hydrate in 16 ml. of diethylene glycol was heated in a nitrogen atmosphere at 100° for 30 min. and then at 140° for 30 min. Then 1.26 g. of potassium hydroxide was added, and the temperature raised to 210° and held there for 3 hr. The reaction mixture was cooled, diluted with water, and the product isolated with petroleum ether in the usual fashion. Chromatography of the residue, obtained after removal of the solvent, on 5 g. of alumina affords 161 mg. of oil, eluted with 30 ml. of petroleum ether. After evaporative distillation of this material at 110° (bath temp.) (0.2 mm.), there remained 156 mg. (91%) of the olefin **18**. Gas-liquid chromatography of this material showed the presence of one component to the extent of 94%.

Anal. Calcd. for $C_{19}H_{32}$: C, 87.61; H, 12.39. Found: C, 87.51; H, 12.43.

Infrared: λ_{max}^{film} 11.61 μ (skeletal vibration).

N.m.r.[24]: 5.30 τ (3.0 c.p.s. ½ band width) (vinyl H); 9.00 τ, 9.14 τ (area double other signals), 9.16 τ, and 9.21 τ (five quaternary methyl groups).

(±)-13,13-Dimethylpodocarp-8(14)-ene.—In the same fashion as described above for its 9β-epimer (**17**) 418 mg. (1.53 mmoles) of an epimeric mixture of 13-methylpodocarp-8(14)-en-13-carboxaldehyde[4] was reduced in 16 ml. of diethylene glycol with 1 ml. of 98–100% hydrazine hydrate and 1.26 g. of potassium hydroxide. After the same work-up, chromatography and distillation procedure, there resulted 358 mg. (90%) of the olefin as an oil. This material was shown to consist of a single component to the extent of 96% by gas-liquid chromatography.

Anal. Calcd. for $C_{19}H_{32}$: C, 87.61; H, 12.39. Found: C, 87.48; H, 12.41.

Infrared: λ_{max}^{film} 11.55 μ and 11.71 μ (skeletal vibrations).

N.m.r.[24]: 5.13 τ (3.0 c.p.s. ½ band width) (vinyl H); 8.92 τ, 9.15 τ (area triple other signals) and 9.30 τ (five quaternary methyl groups).

(−)-Isopimaradiene.—Reduction of 470 mg. (1.5 mmoles) of methyl isopimarate,[5a] m.p. 61–63°, with lithium aluminum hydride in ethereal solution in the customary manner afforded 430 mg. (99%) of isopimarol, as an oil. The analytical sample was obtained by evaporative distillation at 135° (bath temp.) (0.02 mm.).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.10; H, 11.03.

Infrared: λ_{max}^{film} 2.91 μ (O—H); 3.20 μ (w) (vinyl H); 5.48 μ (w), 6.08 μ, 10.00 μ, and 10.98 μ (s) (—CH=CH_2); 11.62 μ, 11.98 μ, and 12.20 μ (skeletal vibrations).

When 425 mg. (1.5 mmoles) of isopimarol was oxidized with 0.36 ml. of Jones reagent[14] in 25 ml. of acetone, there resulted 425 mg. of crude isopimaral, as an oil, after the usual work-up.[4]

Infrared: λ_{max}^{film} 3.68 μ (s) (—C*H*O); 5.80 μ (s) (>C=O); together with all the vinyl and skeletal bands recorded above.

This crude isopimaral was not further purified but converted directly to the semicarbazone by treatment of a methanol solution with 0.80 ml. of a standard[25] aqueous solution of semicarbazine hydrochloride and 13 drops of pyridine. In this fashion there was obtained 270 mg. (53%) of isopimaral semicarbazone, m.p. 219–221°, after two crystallizations from methanol.

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.42; H, 9.68. Found: C, 73.58; H, 9.76.

When 220 mg. (0.64 mmole) of this semicarbazone was reduced, according to the procedure described earlier,[4] in 8 ml. of diethylene glycol with 2.6 g. of potassium hydroxide, there resulted 154 mg. (90%) of isopimaradiene $[\alpha]^{26}D$ −28° (c, 208 mg./100 ml., $CHCl_3$) in an analytically pure condition after chromatography on alumina and evaporative distillation at 90° (bath temp.) (0.05 mm.). This material was entirely homogeneous by gas-liquid chromatography and had a mobility relative to (−)-sandaracopimaradiene (−1) of 1.23. Neither this relative mobility nor the infrared spectrum of isopimaradiene were the same as the diene **3**.

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.25; H, 11.69.

Infrared[23]: ν_{max}^{film} 3080 cm.$^{-1}$ (w) (vinyl H); 1821 cm.$^{-1}$ (w), 1639 cm.$^{-1}$, 995 cm.$^{-1}$, and 910 cm.$^{-1}$ (—CH=CH_2); 1669 cm.$^{-1}$ (w) (trisubst. >C=C<); 860 cm.$^{-1}$, 835 cm.$^{-1}$ and 820 cm.$^{-1}$ (skeletal vibrations).

Acknowledgment.—The authors greatly appreciate the assistance given them by Dr. O. E. Edwards of the National Research Council (Canada) in providing

(23) Determined on a Beckman IR-7 instrument through the courtesy of the Parke-Davis and Company spectrographic Laboratory.

(24) Measured at 60 Mc. in deuteriochloroform related to tetramethylsilane as an internal standard on a Varian Associates HR-60 spectrometer.

(25) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 85.

generous supplies of the resin acids. Grateful appreciation is also due to Professor M. T. Rogers of Michigan State University as well as Dr. Edwards for the n.m.r. spectra. We are grateful to Professor L. H. Briggs of the University of Auckland (New Zealand) for providing a sample of rimuene.

Experiments Directed toward the Total Synthesis of Terpenes. VI. The Stereochemistry of Isopimaric Acid[1,2]

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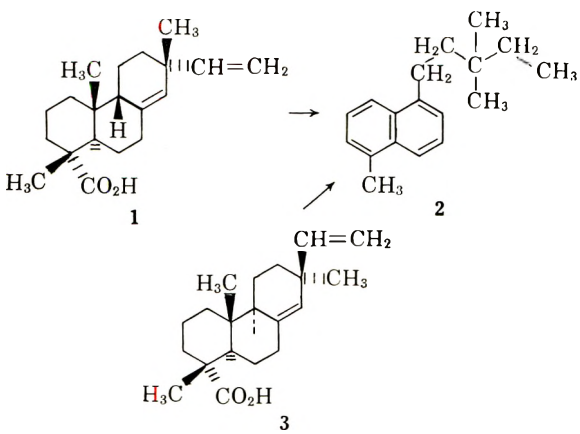
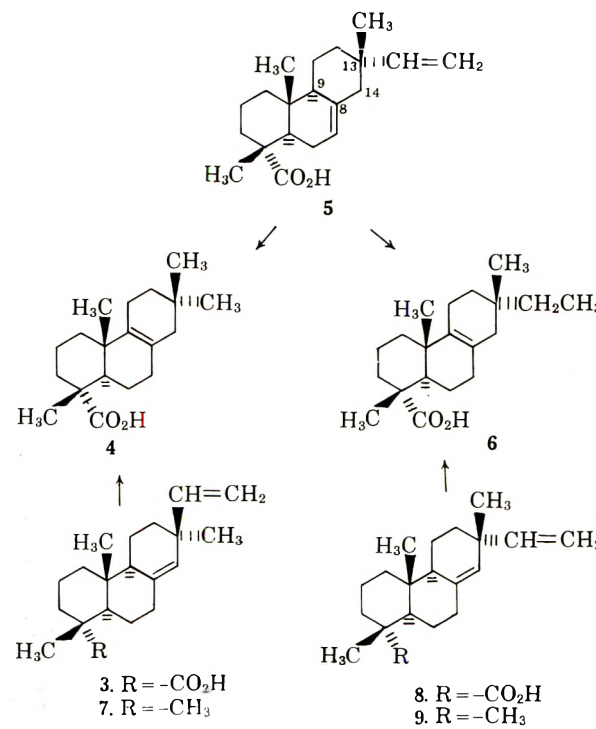
The stereochemistry of isopimaric acid (**5**) is elucidated by conversion to 13,13-dimethylpodocarpane (**16**), and comparison of this hydrocarbon with its racemate (**22**).

The synthesis of the epimeric (±)-9-isopimaradienes[3] conclusively showed that the long accepted structure **1** for isopimaric acid was incorrect, when neither diene was found identical with isopimaradiene. Needless to say, this result occasioned careful scrutiny of the properties of this acid and its corresponding diene to determine where the discrepancy lay.

In the initial investigation of the structure of isopimaric acid in 1948, Harris and Sanderson[4a] suggested that the resin acid had the pimaric acid carbon skeleton, and it was as a result of their degradation of both isopimaric (**1**) and pimaric (**3**) acid to the same naphthalenoid hydrocarbon (**2**) that they placed the nuclear double bond of both acids in the 8(14)-position. This proof of the position of this double bond has been accepted by all subsequent workers, in spite of some of the contortions to which they had to resort in order to rationalize their results. While such an interrelation would appear substantial enough, the reaction sequence used involved several reactions, such as ozonization and palladium-catalyzed dehydrogenation, during which skeletal rearrangements and redistributions might have occurred. Application of the more modern methods together with spectral interpretations seems advisable.



The well executed and extensive studies of Edwards and his collaborators[4b,c] have served to establish more rigorously that isopimaric (**5**) and pimaric (**3**) acids have the same carbon skeleton. Thus, both acids were converted to the same $\Delta^{8(9)}$-19-norpimaric acid (**4**).[4c] While this transformation establishes the identity of the carbon skeletons of the two acids, it implies nothing concerning their relative stereochemistry at C-9 and C-13 nor the location of the nuclear double bond.



Correlation[5] of isopimaric (**5**) and sandaracopimaric (**8**) acids through the identity of the $\Delta^{8(9)}$-dihydrosandaracopimaric acid (**6**) obtained from both acids meant that isopimaric acid (**5**) must differ from sandaracopimaric acid (**8**) only in the stereochemistry at C-9 and/or the location of the nuclear double bond. The latter possibility was not considered at the time.

Several investigations[4b-m,5] have been made of the stereochemistry at C-13 of the pimaric acids. While all

(1) For a preliminary report of this work, see R. E. Ireland and J. Newbould, *J. Org. Chem.*, **27**, 1930 (1962).

(2) This work was made possible through a grant from the National Science Foundation (G-19481).

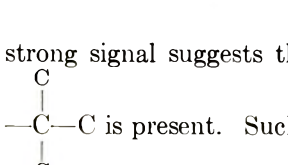
(3) R. F. Church and R. E. Ireland, *J. Org. Chem.*, **28**, 17 (1963).

(4) (a) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 2081 (1948); (b) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959); (c) O. E. Edwards and R. Howe, *Chem. Ind.* (London), 537 (1959); (d) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959); (e) B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958); (f) A. K. Bose, *Chem. Ind.* (London), 1105 (1960); (g) H. H. Bruun, *Acta Acad. Aboensis, Math. Phys.*, **19** (3), 7 (1954); (h) H. H. Bruun, *Finska Kemistsam-Fredets Medd.*, **63**, 22 (1945); (i) H. H. Bruun, *Acta. Chem. Scand.*, **6**, 798 (1952); (j) H.H. Bruun, I. Fishmeister, and E. Stenhagen, *ibid.* **13**, 379 (1959); (k) H. H. Bruun, R. Ryage, and E. Stenhagen, *ibid.*, **12**, 789 (1958); (l) Le-van-Thoi and J. Ourgand, *Bull. soc. chim. France*, 202 (1956); (m) G. W. A. Milne and H. Smith, *Chem. Ind.* (London), 1307 (1961).

(5) O. E. Edwards, A. Nicolson, and M. N. Rodger, *Can. J. Chem.*, **38**, 663 (1960).

of these are subject to the criticism that the differences in chemical and spectral properties used to draw stereochemical conclusions are very small and tenuous, all give the same result—*i.e.*, the vinyl group of pimaric acid (**3**) is beta(quasi-axial) oriented and that of isopimaric (**5**) and sandaracopimaric (**8**) acids is alpha(quasi-equatorial) oriented. Recently, the stereorational syntheses of both pimaradiene (**7**) and sandaracopimaradiene (**9**) in these laboratories[6] have verified not only these stereochemical assignments at C-13, but also the correctness of the positioning of the nuclear double bond in the two acids between carbons 8 and 14 in a fashion that is not subject to the above criticism.[7]

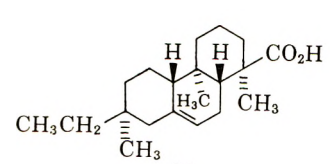
While these results are definitive with regard to the stereochemistry and structure of pimaric (**3**)[4b,d,e] and sandaracopimaric (**8**)[5] acids, they are only deductive proof that the structure of isopimaric acid is represented by the formulation **1**. This reasoning becomes strong if one accepts (as did previous workers) the original degradative work of Harris and Sanderson.[4a] However, that there must have been a rearrangement during this degradation sequence is indicated by even the small portion of the n.m.r. spectrum of methyl isopimarate reported by Wenkert and Beak.[8] It is clear in this spectrum that the signal due to the nuclear vinyl hydrogen of methyl isopimarate is a doublet, while that of methyl sandaracopimarate is only a singlet. The latter situation is what is to be expected for a hydrogen on a carbon with no adjacent hydrogens with which it is spin coupled, and is consistent with the structure **8** for sandaracopimaric acid.[5] The doublet in the spectrum of methyl isopimarate is therefore not consistent with the 8(14)-position for the double bond, since the nuclear vinyl hydrogen must be spin-coupled with at least one adjacent allylic hydrogen. This situation is more nearly satisfied if the nuclear double bond of isopimaric acid is in either the 7(8)- or the 9(11)-position, where the C-7 or C-11 vinyl hydrogen would be split by coupling with the C-6 or C-12 methylene. Both positions satisfy the requirement that double bond is readily isomerized by anhydrous mineral acid to the more highly substituted 8(9)-position.[5b] A tentative conclusion as to which of the two possible trisubstituted locations is more likely can be made by inspection of the full n.m.r. spectrum of methyl isopimarate, where a strong signal due to a pair of uncoupled hydrogens appears centered at 8.04 τ. This is the region of the spectrum where signals due to the allylic hydrogens are expected to appear, and this strong signal suggests that the system



is present. Such is clearly possible only if isopimaric acid has the double bond in the 7(8)-position. This location is also more consistent than the 9(11)-position with the biogenetic hypothesis for these resin acids. Definitive proof of this suggestion has recently been provided by the work of Edwards and coworkers.[9]

Acceptance of the 7(8)-position for the nuclear double bond necessitates a re-evaluation of the stereochemical assignment at C-9, for there is now no compelling reason to retain the *trans-syn* backbone. Thus the fact that sandaracopimaric acid (**8**) differs from isopimaric acid (**5**) can be attributed solely to the difference in the location of the nuclear double bond without requiring the C-9 hydrogen to be beta-oriented in the latter acid. Of course, there is no reason, *a priori*, that the C-9 hydrogen in isopimaric acid (**5**) could not be beta-oriented as well as the double bond be in the 7(8)-position. This point had to be proved.

At the outset there was some evidence suggesting that the C-9 hydrogen in isopimaric acid (**5**) was indeed alpha-oriented. Thus the rotatory dispersion curve[4f] of dihydroisopimaric acid **10** is a plain negative curve. On reinterpretation in light of the 7(8)-double bond assignment, the closest analogy to this system is Δ^5-cholestene (**11**) which also exhibits a plain negative rotatory dispersion curve.[10] If this analogy is valid, and it would indeed appear to be, then the C-9 hydrogen of the resin



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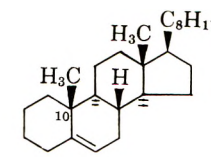

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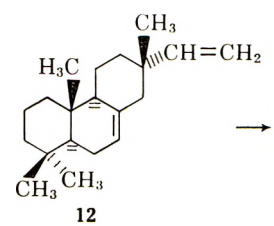
acid must be oriented in the same fashion as the C-10 methyl group of the steroid—*i.e.*, betaoriented.

In order to gain more definitive proof of this assignment for the C–9-hydrogen, we have degraded isopimaradiene (**12**),[3] itself a simple degradation product of isopimaric acid (**5**) in which the critical C-9 position has not been disturbed, to the pentamethyl hydrocarbon **16**. This was effected by first conversion of the diene **12** to the olefin **13** by the same sequence used by Edwards[4c]



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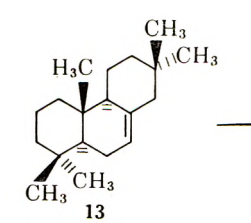

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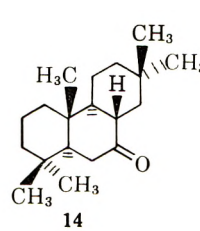

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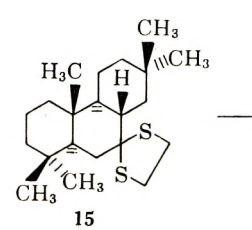

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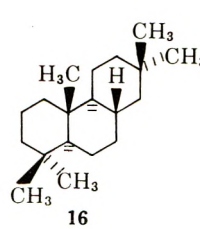

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(6) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(7) The anticlimatic report of Milne and H. Smith[4m] of the partial synthesis of dihydropimaradiene is claimed as a proof of the stereochemistry of pimaric and isopimaric acids. Not only is this work subjectively evaluated evidence (even after a long introduction by the authors criticizing the previous work of others), but again the authors overlook the possibility of the 7(8)-position for the nuclear double bond in isopimaric acid.

(8) E. Wenkert and P. Beak, *J. Am. Chem. Soc.*, **83**, 998 (1961).

(9) W. Antkowiak, J. W. ApSimon, and O. E. Edwards, *J. Org. Chem.*, **27**, 1930 (1962).

(10) C. Djerassi, W. Closson, and A. E. Lipman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

to prepare 19-norpimaric acid. Thus hydroxylation of isopimaradiene (**12**) with one equivalent of osmium tetroxide in dioxane afforded the corresponding diol.

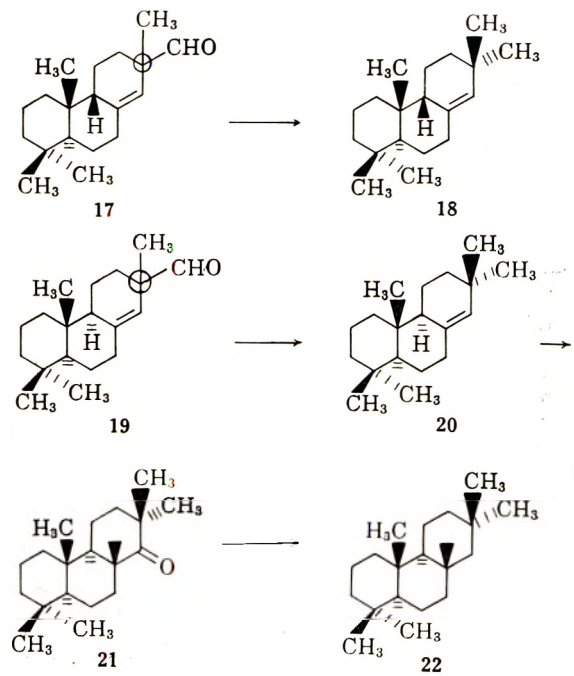
This diol was an oil but on cleavage with periodic acid in ether, there resulted an olefinic aldehyde from which a 51% overall yield of semicarbazone could be isolated. The formation of a mono-aldehyde showing no ketone carbonyl absorption in its infrared spectrum attests to the attack by the osmium tetroxide principally at the vinyl grouping. On modified[6] Wolff–Kishner reduction this semicarbazone produced an 82% yield of the desired olefin (**13**).

Further degradation was carried out by hydroboration[11] and oxidation[12] of the olefin (**13**) to introduce the ketone function at C-7. The crude ketonic product was chromatographed on basic alumina in order to insure isomerization of any of the less stable ketone—the *trans-anti-cis* product, if the C-9 hydrogen were alpha oriented or the *trans-syn-trans* material if it were beta oriented. By this procedure we were able to isolate a 60% yield of the ketone (**14**).

In order to ensure that the B/C ring fusion remained in its more stable configuration and was not isomerized during the reduction, we chose to use the desulfurization of the dithioketal to remove the C-7 ketone. This desulfurization sequence has been shown[13] to proceed independent of the stereochemistry at the α-carbon atoms, while it is conceivable that the ketone with the less stable B/C ring fusion (in equilibrium with the more stable ketone (**14**) in the presence of acid or base) might undergo reduction more rapidly than its epimer and lead to an inhomogeneous hydrocarbon of no stereochemical value. Thus conversion[14] of the ketone (**14**) to its ethylenedithioketal (**15**) and desulfurization of this crude material produced the desired hydrocarbon (**16**), m.p. 53.5–54°, in 78% yield. This hydrocarbon was either the 13,13-dimethylpodocarpane (**16**) shown or its C-9 epimer, 13,13-dimethyl-9-isopodocarpane, depending on the orientation of the C-9 hydrogen in the original isopimaric acid (**5**). The sequence used here to obtain this hydrocarbon can in no way have affected the stereochemistry at this center, and thus definition of the structure of this hydrocarbon will settle the point in question.

To gain information concerning the stereochemistry of the hydrocarbon (**16**) we turned to intermediates available from our syntheses of the pimaradienes.[3,6] We had previously[3] prepared both of the aldehydes (**17**) and (**19**) and converted them by Wolff–Kishner reduction to the corresponding olefins (**18**) and (**20**). Neither of these olefins was identical with the olefin (**16**) obtained above from isopimaradiene (**12**), further confirmation that isopimaric acid (**5**) did not possess an 8(14)-double bond.

Inasmuch as the olefin (**20**) was not only more readily available than its epimer (**18**), but also possessed the C-9 hydrogen in the expected alpha orientation, we chose to remove the double bond in this isomer first. In order to assure that the olefin (**20**) was converted to the (±)*trans-anti-trans* hydrocarbon (**22**), we again employed the same hydroboration[11] and oxidation[12] sequence as above, so as to introduce the C-14 ketone function. This ketone (**21**), after chromatography on basic alumina to effect equilibration at C-8, was available in 70% yield from the olefin (**20**). Conversion[14] of the ketone (**21**) to its ethylenedithiolketal and then desulfurization with W-2 Raney nickel led to a 74% overall yield of the racemic modification of the hydrocarbon (**22**), as an oil. Comparison of the infrared spectrum of this racemic hydrocarbon and that of the optically active analog (**16**) obtained from isopimaradiene (**12**) revealed their identity and thus conclusively established that the C-9 hydrogen was alpha-oriented in the isopimaric acid (**5**) series. This evidence, taken together with that of Edwards and coworkers[9] which conclusively defines the 7(8)-position for the nuclear double bond, firmly proves the structure of this resin acid to be as shown in formula **5**.



Experimental[15]

13β-Methylpodocarp-7-ene-13α-carboxaldehyde Semicarbazone.—A solution of 1.08 g. (4.0 mmoles) of isopimaradiene[3] in 20 ml. of dry dioxane was treated with 1.00 g. (4.0 mmoles) of osmium tetroxide and the black solution allowed to stand at room temperature for 17 hr. The solution was then saturated with hydrogen sulfide, filtered, the filter cake washed with methylene chloride and the combined filtrates evaporated to dryness at reduced pressure. The resulting crude, oily diol (930 mg.) was not purified, but dissolved in 50 ml. of dry ether and treated with a solution of 570 mg. (3.0 mmoles) of periodic acid in 30 ml. of dry ether. After stirring for 1 hr. at room temperature, the ethereal solution was decanted from the precipitated iodic acid, washed with water, 10% aqueous potassium bicarbonate, water,

(11) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *ibid.*, **82**, 4233 (1960).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also, C. Djerassi, R. R. Engle, and A. Powers, *J. Org. Chem.*, **21**, 1547 (1956).

(13) R. E. Ireland and J. A. Marshall, *ibid.*, **27**, 1620 (1962).

(14) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(15) Unless specified otherwise, the term "petroleum ether" refers to reagent grade material boiling in the range 30–60°. All gas–liquid chromatograms were obtained on a F & M Scientific Company Model 500 gas-liquid chromatography unit using a 6-foot column packed with 10% diethylene glycol succinate on Chromosorb P, and were temperature programmed. Melting points were determined on a Kofler Hot Stage and are corrected for stem exposure. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Infrared spectra were measured on a Perkin–Elmer Model 237 spectrometer and are recorded in cm.$^{-1}$ ($\tilde{\nu}$); strong bands are marked (s); all others reported are of moderate intensity unless otherwise specified. Florisil refers to the product of the Floridin Company, Tallahassee, Florida, 60/100 mesh.

saturated salt solution, dried (Na_2SO_4) and evaporated. The infrared spectrum (recorded on a Perkin–Elmer Infrarecord 137) of this crude aldehyde showed λ_{max}^{film} 3.2 μ (w) (vinyl H); 3.67μ (w) (C*H*O); and 5.82 μ (s) (>C=O).

Formation of the semicarbazone was accomplished by treatment of a methanol solution of this crude aldehyde with 3.0 ml. of a standard[16] aqueous solution of semicarbazide hydrochloride and 10 drops of pyridine. In this manner there was obtained 770 mg. (51%) of the derivative, m.p. 218–222°. After several crystallizations from methanol there remained 485 mg. of analytically pure material, m.p. 222–223°.

Anal. Calcd. for $C_{20}H_{33}N_3O$: C, 72.46; H, 12.68; N, 10.03. Found: C, 72.37; H, 12.75; N, 10.29.

13,13-Dimethylpodocarp-7-ene (13).—Employing the same procedure described earlier,[3] 450 mg. (1.36 mmoles) of the above semicarbazone in 36 ml. of diethylene glycol was reduced by heating at 210° under a nitrogen atmosphere with 12.0 g. of potassium hydroxide. After the usual work-up and passage through an alumina (30 g.) column in petroleum ether, there was obtained 290 mg. (82%) of the olefin **13**, evaporatively distilled at 110° (bath temperature; 0.1 mm.), m.p. 29–31°.

Anal. Calcd. for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.51; H, 12.23.

Infrared: $\tilde{\nu}_{max}^{film}$ 3040 cm.$^{-1}$ (w) (vinyl H); 1664 cm.$^{-1}$ (w) (>C=C<); 860 cm.$^{-1}$, 828 cm.$^{-1}$ and 810 cm.$^{-1}$ (skeletal vibrations).

13,13-Dimethylpodocarpanone-7 (14).—To a solution of 170 mg. (0.654 mmole) of the olefin **13** in 5 ml. of dry tetrahydrofuran was added 10 ml. (2.7 mmoles) of a 0.27 *M* solution of diborane in dry tetrahydrofuran, and the reaction mixture stirred in a nitrogen atmosphere at room temperature for 1 hr. The excess diborane was decomposed by the addition of 4 ml. of 10% aqueous sodium hydroxide and the alkylborane oxidized with 4 ml. of 30% aqueous hydrogen peroxide. After heating this mixture for 1.5 hr. under reflux, the product was isolated by ether extraction in the usual manner. The crude alcohol so formed was oxidized with 0.2 ml. of Jones reagent,[12] and the resulting, crude solid ketone chromatographed on 15 g. of alumina. Elution with 400 ml. of 25% benzene:petroleum ether afforded 121 mg. (67%) of the ketone **14**. Crystallization of this material from petroleum ether gave 108 mg. (60%) of this ketone, m.p. 151–151.5°, in an analytically pure condition.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.43; H, 11.77.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1698 cm.$^{-1}$ (s) (>C=O).

13,13-Dimethylpodocarpane (16).—To a solution of 105 mg. (0.38 mmole) of the ketone **14** in 0.4 ml. of ethanedithiol was added 0.4 ml. of boron trifluoride etherate, and after standing 1 hr. at room temperature, the precipitated dithioketal **15** (184 mg. crude weight) was collected by filtration. The infrared spectrum of this material show no carbonyl band.

A solution of this crude dithioketal in 40 ml. of ethanol was stirred and heated under reflux overnight with 10 g. of W-2 Raney nickel.[17] After removal of the catalyst by filtration, the filtrate was evaporated to dryness and the residue passed through 5 g. of alumina in petroleum ether. There resulted 92 mg. (93%) of solid hydrocarbon, m.p. 50–53°. Crystallization of this material from ethanol afforded 78 mg. (78%) of the hydrocarbon **16**, m.p. 53.5–54.0°, in an analytically pure condition. This material was eluted at 203° on gas-liquid chromatography[15] when the rate of heating was 7.9°/min.; this analysis showed the substance to be entirely homogeneous.

Anal. Calcd. for $C_{19}H_{34}$: C, 86.96; H, 13.04. Found: C, 86.77; H, 12.82.

Infrared: $\tilde{\nu}_{max}^{supercooled\ liquid\ film}$ 970 cm.$^{-1}$ (w) 940 cm.$^{-1}$ (w) and 850 cm.$^{-1}$ (w) together with the normal bands associated with the C—H and C—C vibrations.

(±)-13,13-Dimethylpodocarpanone-14 (21).—To a solution of 107 mg. (0.413 mmole) of the olefin **20**[5] in 10 ml. of dry tetrahydrofuran was added 1.5 ml. (1.10 mmoles) of a 0.73 *M* solution of diborane in dry tetrahydrofuran and the reaction mixture was stirred at room temperature in a nitrogen atmosphere for 1 hr. Then 3 ml. of 10% aqueous sodium hydroxide and 3 ml. of 30% hydrogen peroxide were added, and the mixture heated under reflux for 1 hr., after which the product was isolated by ether extraction in the usual manner. The crude alcohol was not purified but dissolved in 6 ml. of acetone and oxidized with 0.15 ml. of Jones reagent.[12] Chromatography of the crude, solid ketone on 10 g. of alumina afforded 80 mg. (70%) of the ketone **21**, m.p. 58–60°, eluted with 200 ml. of 25% benzene:petroleum ether. The analytical sample was obtained by evaporative distillation of this material at 80° (bath temperature; 0.025 mm.).

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.45; H, 11.70.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1700 cm.$^{-1}$ (s) (>C=O).

(±)-13,13-Dimethylpodocarpane (22).—A solution of 80 mg. (0.29 mmole) of the ketone **21** in 0.2 ml. of ethanedithiol was treated with 0.2 ml. of boron trifluoride etherate, and the reaction mixture allowed to stand at room temperature for 0.5 hr. Then dilution with 2 ml. of methanol, filtration and chromatography of the solid on 5 g. of alumina afforded 92 mg. (90%) of white, crystalline thioketal eluted with 100 ml. of petroleum ether. Sublimation of a small sample of this material at 160° (bath temperature; 0.025 mm.) gave the thioketal, m.p. 181–183°, in an analytically pure condition.

Anal. Calcd. for $C_{21}H_{36}S_2$: C, 71.52; H, 10.29; S, 18.19. Found: C, 71.43; H, 10.11; S, 18.15.

The remainder of the above thioketal was heated overnight with 6 g. of W-2 Raney nickel[17] in 15 ml. of ethanol. After the usual work-up and passage of the hydrocarbon in petroleum ether through 5 g. of alumina, there was obtained 56 mg. (74% overall yield) of the hydrocarbon **22** as an oil. The analytical sample was obtained by evaporative distillation at 80° (bath temperature; 0.025 mm.). The infrared spectrum of a liquid film and mobility on gas-liquid chromatography[15] of this material was identical to that of the hydrocarbon **16** obtained above.

Anal. Calcd. for $C_{19}H_{34}$: C, 86.96; H, 13.04. Found: C, 87.15; H, 12.74.

Acknowledgment.—The authors wish to thank Dr. O. E. Edwards of the National Research Council (Canada) for making his results available to us prior to publication and for many helpful discussions of this problem. The invaluable assistance of Professor Glenn T. Berchtold of Massachusetts Institute of Technology in obtaining numerous n.m.r. spectra is gratefully acknowledged.

(16) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 85.

(17) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

Perhydroindanone Derivatives. I. Applicability of the Diels–Alder Reaction[1a]

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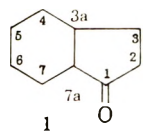
The reactions summarized in Charts I and II have been carried out to explore the use of the Diels–Alder reaction for the preparation of variously substituted perhydroindanones.

In anticipation of synthetic work directed toward the synthesis of the gibberellins,[2] we have investigated both the syntheses and chemical properties of a number of perhydroindanone systems **1**. Since we envision these systems, **1**, to be models of the A-B ring system in the gibberellins, we have been particularly concerned with those derivatives which bear methyl and/or carboxyl substituents at position 7.



1

In this and the subsequent paper of this series, we have explored the possible utility of various cyclopentenones as dienophiles in the Diels–Alder reaction as well as the possible use of a 3-vinyl-2-cyclopenten-1-one as a diene. This latter approach is summarized by the reactions outlined in Chart I which start with the reactive 4-cyclopentene-1,3-dione (**2**).[3]

Because of the instability of intermediates **9** and **10**, these materials were handled as partially purified intermediates. Since very mild reaction conditions were employed for the various Diels–Alder reactions summarized in Chart I, we have assumed that the adducts obtained are the result of kinetically controlled processes. Accordingly, the reactions are expected to proceed by *cis, endo* addition of the dienophile to the diene and reaction of the diene **10** with dienophiles may be expected to occur from the less hindered side.[4] These considerations lead to the indicated stereochemical assignments. The stereochemistry of the diketone **7** has been established by degradation.[3e] The question of the relative stabilities of *cis* and *trans* ring fusions in 3a,4,7,7a-tetrahydro-1-indanone systems is examined in a subsequent paper of this series. The structure tentatively assigned the adduct **11a** is based on the observation[5] that terminally substituted dienes and monosubstituted dienophiles afford predominantly the product with the substituents vicinal to one another. The

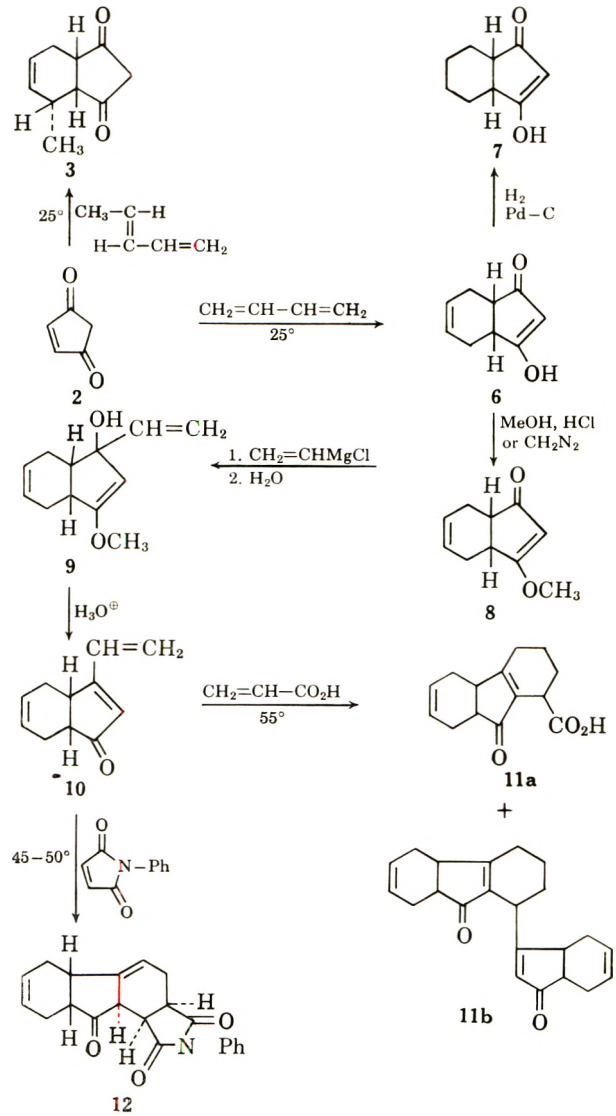


CHART I

general synthetic approach to perhydroindanones represented by the reaction sequence **8** → **9** → **10** → **11a** was considered unattractive because of the instability of intermediates **9** and **10** and, particularly, the low yield (4.9% of **11a**) obtained in the last step of the sequence.

(1) (a) Supported in part by National Science Foundation Grant No. G-9486. (b) National Science Foundation Predoctoral Fellow, 1958–1962.

(2) For a recent review see J. F. Grove, *Quart. Rev.*, **15**, 56 (1961).

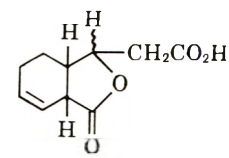
(3) (a) C. H. DePuy and E. F. Zaweski, *J. Am. Chem. Soc.*, **81**, 4920 (1959). (b) C. H. DePuy and C. E. Lyons, *ibid.*, **82**, 631 (1960). (c) C. H. DePuy and P. R. Wells, *ibid.*, **82**, 2909 (1960). (d) C. H. DePuy, R. D. Thurn, and M. Isaks, *J. Org. Chem.*, **27**, 744 (1962). (e) V. F. Kucherov and L. I. Ivanova, *Dokl. Akad. Nauk, SSSR*, **131**, 1077 (1960); *Chem. Abstr.*, **54**, 21021 (1960).

(4) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(5) (a) I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *J. Gen. Chem., USSR*, **25**, 75 (1955). (b) I. N. Nazarov, Y. A. Titov, and A. I. Fuznetsova, *Acad. Sci. USSR, Chem. Sci. Bull.*, 1224 (1959). (c) Although the diene system in structure **10** has substituents at both the 1 and 2 positions of the diene, the carbonyl function at position 1, being capable of resonance interaction with the diene system, may be expected to determine the product orientation. For example, reaction of 1-phenyl-2-methyl-1,3-butadiene with acrylic acid produced 2-methyl-3-phenyl-4-carboxycyclohexene [K. Alder, J. Hayden, K. Hemibach, and K. Neufang, *Ann.*, **586**, 110 (1954)].

(6) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

(7) K. Alder and W. Vogt, *Ann.*, **570**, 190 (1950). From dimerization of the acid **13a**, the lactone pictured below was isolated.



We next investigated the use of pentadienoic acid derivatives **13** and **14**[6] as dienes in Diels–Alder reactions. These investigations, outlined in Chart II, indicated that the dienes **13** could be employed with reactive dieneophiles (4-cyclopentene-1,3-dione, N-phenylmaleimide), but not with the less reactive dieneophile, cyclopentenone (**18**). We were unable to isolate an adduct from the diene **14** with any of the dieneophiles studied; this lack of reactivity is presumably attributable to steric interference with the existence of the diene **14** in the required cisoid conformation.[4] The stereochemistry assigned adducts **15** and **17** is based on the previously discussed considerations. The diene dimer **19** obtained either in the presence or absence of cyclopentenone is analogous to the previously reported dimerization of the acid **13a**.[7] Although the *trans* stereochemistry of the carbon–carbon double bond in the side chain was apparent from the infrared spectrum of **19** we did not establish the stereochemistry of the two substituents on the cyclohexene ring. An attempt to utilize the tetrahydroindenone **20** as a dienophile resulted in the isolation of the isomer **21**; no Diels–Alder adduct was isolated.

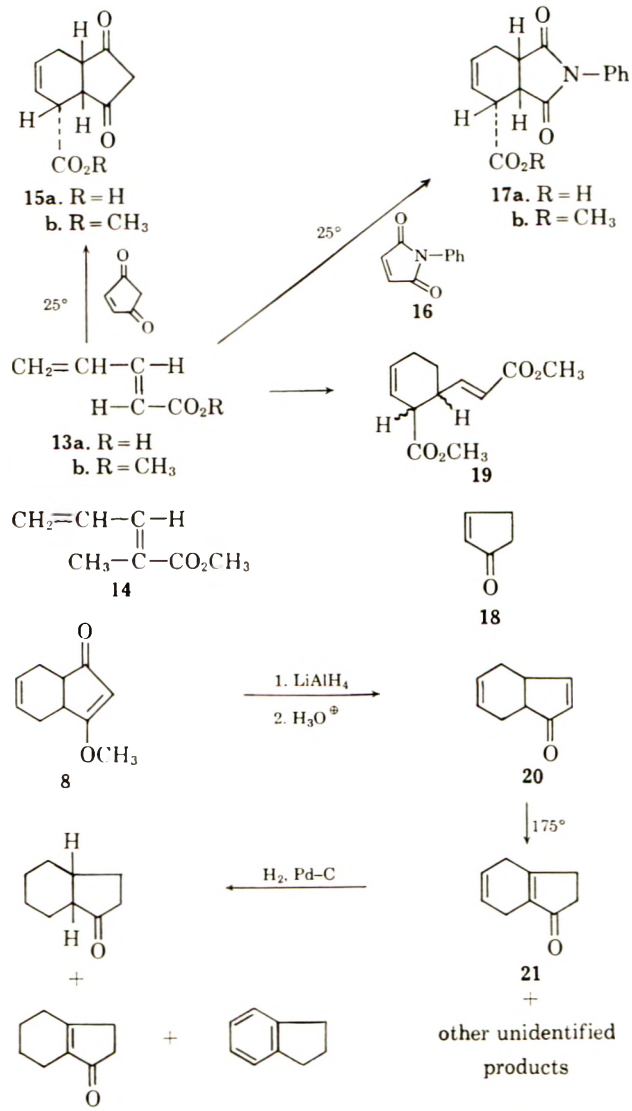


CHART II

Experimental[8]

***cis*-3a,4,7,7a-Tetrahydroindane-1,3-dione (6).**—A solution of 75.0 g. (0.78 mole) of 4-cyclopentene-1,3-dione, 90 ml. (58 g. or 1.1 moles) of butadiene and 0.3 g. of 2,5-di-*t*-butylhydroquinone in 220 ml. of benzene was allowed to stand in an autoclave at room temperature for 12 days. An additional 40 ml. (26 g. or 0.48 mole) of butadiene was added and the mixture was allowed to stand for an additional 5 days. After the reaction mixture had been filtered to separate 94.4 g. (80.6%) of the crude product, m.p. 157.5–161°, concentration of the mother liquor followed by crystallization from ether afforded 6.02 g. (8% recovery) of the unchanged starting material, m.p. 33–34.5°. Recrystallization from a methanol–ethyl acetate mixture afforded the pure adduct **6** as white prisms, m.p. 160–161.5° (lit.[3e] 157.5–158.5°), with infrared absorption[9] at 1635 and 1585 cm.$^{-1}$ (enolic β-diketone) and a ultraviolet maximum[10] at 244.5 mμ (ε 15,400)

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.72.

A suspension of 25.7 g. (0.17 mole) of the enolic diketone **6** in 70 ml. of methanol which had been saturated with hydrogen chloride was stirred at room temperature for 8 hr. The resulting solution was added, dropwise and with stirring, to an excess of cold (10°), aqueous potassium carbonate. After the resulting mixture had been extracted with ether, the ethereal solution was washed with water, dried, and concentrated. Distillation of the residue afforded 23.31 g. (83%) of the **enol ether 8**, b.p. 91–96° (0.07 mm.), which solidified on standing, m.p. 40.3–41.7°. Recrystallization from ether afforded the pure enol ether as white prisms, m.p. 42.5–42.6°, with infrared absorption[11] at 1685 cm.$^{-1}$ (C=O) and 1595 cm.$^{-1}$ (C=C) and an ultraviolet maximum at 239 mμ (ε 15,700). Acidification of the aqueous potassium carbonate layer from this preparation followed by appropriate manipulations separated 1.16 g. (4.5%) of the starting material.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.11; H, 7.41.

Reaction of 2.00 g. (13 mmoles) of the enolic diketone **6** with excess diazomethane in an ether–methanol mixture followed by concentration and distillation afforded 1.90 g. (87%) of the same enol ether **8**, b.p. 105° (0.9 mm.), m.p. 37.5–39.0°, identified by comparison of the infrared spectra of the two samples.

7-Methyl-*cis*-3a,4,7,7a-tetrahydroindane-1,3-dione (3).—A solution of 242 mg. (2.5 mmoles) of the enedione **2**, 430 mg. (6.3 mmoles) of *trans*-1-methylbutadiene (b.p. 39–41°, $n^{21.5}$D 1.4298, lit.,[12] 41.5–41.9°, n^{20}D 1.4292–1.4306) and a few crystals of 2,5-di-*t*-butylhydroquinone in 1 ml. of benzene was allowed to stand at room temperature for 2 days. Filtration separated 368 mg. (89%) of the crude adduct, m.p. 145–146.5°. The pure enolic diketone **3** crystallized from a methanol–ethyl acetate mixture as white microprisms, m.p. 149.5–150.5°, whose melting point was raised to 150.7–151° by sublimation under reduced pressure. The product has broad infrared absorption[9] at 1590 and 1630 (shoulder) cm.$^{-1}$ (enolic β-diketone) with an ultraviolet maximum at 245 mμ (ε 15,000).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.91; H, 7.15.

***cis*-Hexahydroindane-1,3-dione (7).**—A solution of 1.28 g. (8.6 mmoles) of the enolic diketone **6** in 25 ml. of methanol was hydrogenated at room temperature and atmospheric pressure over 130 mg. of a 30% palladium-on-carbon catalyst. After the absorption of 239 ml. (9.7 mmoles) of hydrogen, the reaction was stopped and the mixture was filtered and then concentrated. Crystallization of the residue from an ether–ethyl acetate mixture afforded 0.86 g. (67%) of the enolic diketone **7** as white plates, m.p. 86.6–88°. The pure diketone **7**, obtained after recrystal-

(8) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The n.m.r. spectra were determined with a Varian, Model A-60, n.m.r. spectrometer.

(9) Determined as a suspension in a potassium bromide pellet.

(10) Determined as a solution in 95% ethanol.

(11) Determined in chloroform solution.

(12) J. F. Bussert, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **78**, 6076 (1956). Our diene sample, prepared by the dehydration of *trans*-2-penten-4-ol in the presence of potassium acid sulfate at 130–170°, contained more than 95% of the *trans* isomer as judged from its gas chromatograph and infrared spectrum.

lization, melted at 87.9–89.3° (lit.,[3e] 86–86.5°) and exhibits infrared absorption[11] at 1725, 1635, and 1590 (broad) cm.$^{-1}$ (partially enolized β-diketone) with an ultraviolet maximum[10] at 243 mμ (ε 17,000).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.90; H, 8.10.

Preparation and Reactions of the Trienone 10.—A cold (0°) ethereal solution of 12.76 g. (0.078 mole) of the enol ether **8** was added, dropwise and with stirring in a nitrogen atmosphere, to 100 ml. (0.107 mole) of a 1.07 *N* solution of vinylmagnesium chloride in tetrahydrofuran. After the addition was complete, the mixture was stirred at 0° for 2 hr. and then treated with saturated, aqueous ammonium chloride (adjusted to pH 7 by the addition of aqueous ammonia). After the organic layer had been separated and the aqueous phase had been extracted with ether, the combined organic solutions were dried and concentrated to leave 15.2 g. of the crude alcohol **9** as a yellow oil with infrared absorption[13] at 1705 cm.$^{-1}$ (weak, C=O impurity), 1645 and 1620 cm.$^{-1}$ (C=C) and 925 cm.$^{-1}$ (CH=CH_2). To a cold (0°) solution of 14.4 g. of the crude alcohol **9** and 10 mg. of 2,5-di-*t*-butylhydroquinone in 120 ml. of tetrahydrofuran was added 45 ml. of a cold (0°), very dilute, aqueous solution of sulfuric acid (1 drop of sulfuric acid in 100 ml. of water). After the addition was complete, the mixture was stirred at 0° for 30 min. and then diluted with 500 ml. of ice–water and extracted with petroleum ether. This extract was dried and concentrated under reduced pressure at room temperature. Distillation of the residue in a short-path still afforded 3.10 g. of the crude trienone **10** as a yellow oil, b.p. 92–98° (0.2 mm.) with infrared absorption[13] at 1710 cm.$^{-1}$ (cyclopentenone C=O), 1640 and 1605 cm.$^{-1}$ (C=C) and 990 and 930 cm.$^{-1}$ (CH=CH_2), and an ultraviolet maximum[10] at 262 mμ (ε 14,400).

A solution of 415 mg. (2.6 mmoles) of the crude trienone **10**, 28.5 mg. of 2,5-di-*t*-butylhydroquinone and 477 mg. (2.7 mmoles) of N-phenylmaleimide in 1.5 ml. of benzene was heated to 45–50° under a nitrogen atmosphere for 40 hr. Chromatography of the crude product on Merck acid-washed alumina separated 185 mg. (39% recovery) of N-phenylmaleimide (eluted with benzene) and 414 mg. (48%) of the crude adduct **12**, m.p. 186–194° (eluted with methanol). Several recrystallizations from methanol and from ethyl acetate afforded the pure adduct **12** as white crystals, m.p. 203.5–205.5°, with infrared absorption[11] at 1780 (weak) and 1715 (broad, intense) cm.$^{-1}$ (C=O of 5-membered imide and cyclopentanone) and an ultraviolet maximum[10] at 221 mμ (ε 16,000).[14]

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.48; H, 5.95; N, 4.01.

A mixture of 1.134 g. (7.1 mmoles) of the crude trienone **10**, 0.512 g. (7.1 mmoles) of acrylic acid, and 2 mg. of 2,5-di-*t*-butylhydroquinone was heated to 55° in a sealed tube for 5 days. The partially polymeric reaction mixture was then extracted with methylene chloride and the organic layer was extracted with aqueous sodium bicarbonate solution. After this aqueous extract had been acidified and extracted with chloroform, the chloroform solution was dried and concentrated to leave a white solid. Recrystallization from ethyl acetate afforded 80.1 mg. (4.9%) of the adduct **11a** as white prisms, m.p. 187–188°, with broad infrared absorption[11] in the 3μ region (associated O—H) as well as peaks at 1750 and 1700 cm.$^{-1}$ (carboxyl and cyclopentenone C=O) and 1660, 1645, and 1630 cm.$^{-1}$ (C=C). The product has an ultraviolet maximum[10] at 236 mμ (ε 10,800). The n.m.r. spectrum[15] (60 Mc.) has a triplet (J = 4 c.p.s.) centered at 4.22 τ (2H, vinyl C—H), a series of broad, poorly resolved peaks in the region 6.8–8.0 τ (10H, allylic C—H and carboxyl OH) and a broad peak centered at 8.2 τ (4*H*, nonallylic CH_2).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.36; H, 6.86.

After the methylene chloride solution containing neutral material from the reaction had been dried and concentrated, trituration of the residue with ether separated a solid. Recrystallization of this solid from an ether–ethyl acetate mixture afforded 0.138 g. (12%) of the dimer **11b** as white prisms, m.p. 130–133°. This material was shown to be identical with a subsequently described sample by a mixed melting-point determination and comparison of infrared spectra.

After a mixture of 1.31 g. (8.2 mmoles) of the crude trienone **10** and 890 mg. (11.8 mmoles) of α-methylacrolein had been heated to 55° for 5 days, chromatography of the crude product on 40 g. of neutral alumina separated 0.5425 g. (41%) of the dimer **11b**, m.p. 129–133°. Recrystallization from an ether–ethyl acetate mixture afforded the pure dimer **11b** as white prisms, m.p. 135.8–136.7°, with infrared absorption[11] at 1690 cm.$^{-1}$ (cyclopentenone C=O), 1640, and 1615 cm.$^{-1}$ (C=C), an ultraviolet maximum[10] at 235 mμ (ε 20,000) and n.m.r.[16] peaks (60 Mc.) at 4.19 τ (5*H*, broad, vinyl C—H), a series of broad unresolved peaks in the region 6.4–8.0 τ (15*H*, allylic C—H) and a broad, partially resolved peak centered at 8.22 τ (4*H*, nonallylic CH_2).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.29; H, 7.60.

3a,4,7,7a-Tetrahydroindenone (20).—To a cold (0°) solution of 68.0 g. (0.414 mole) of the enol ether **8** in 200 ml. of ether was added gradually with stirring, a solution of 6.5 g. (0.17 mole) of lithium aluminum hydride in 250 ml. of ether. The resulting mixture was refluxed, with stirring, for 1 hr. and then cooled and 25 ml. of water was added. The mixture was poured into excess cold, 10% aqueous sulfuric acid, and the ether layer was separated. After the aqueous phase had been extracted with ether, the combined organic extracts were washed successively with aqueous sodium bicarbonate and water and then dried and concentrated. After short-path distillation of the residue to separate 48.0 g. of colorless liquid containing[17] 75–80% of the desired product **20**, fractional distillation through a 40-cm. spinning-band column afforded 17.51 g. (32.4%) of fractions, b.p. 118–119° (20 mm.), $n^{25}D$ 1.5250–1.5256, containing[17] more than 95% of the desired ketone **20** as well as 23.56 g. of intermediate fractions, b.p. 104–118° (20 mm.), $n^{25}D$ 1.5044–1.5243, containing mixtures of the desired ketone **20** and lower boiling impurities. The pure ketone **20** has infrared absorption[13] at 1710 cm.$^{-1}$ cyclopentenone C=O) and at 1595 cm.$^{-1}$ (C=C) with ultraviolet maxima at 221 mμ (ε 8500) and 315 mμ (ε 40). The n.m.r. spectrum[13] (60 Mc.) of the material has two quadruplets centered at 2.52 τ (1*H*, J = 6 and 3 c.p.s., vinyl proton *beta* to C=O) and 3.91 τ (1*H*, J = 6 and 2 c.p.s., vinyl proton *alpha* to C=O), a partially resolved multiplet centered at 4.23 τ (2*H*, vinyl protons of cyclohexene ring), a broad multiplet centered at 6.74 τ (1*H*, tertiary proton alpha to C=O), and a complex multiplet in the region 7.4 to 8.0 τ attributable to the remaining 5 allylic protons in the molecule.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.47; H, 7.76.

A solution of 4.8 g. (0.028 mole) of the unsaturated ketone **20**, 4.7 g. (0.028 mole) of dicyclopentadiene and 0.2 g. of 2,5-di-*t*-butylhydroquinone in 7 ml. of benzene was heated to 175° for 2 days in a sealed tube. Distillation of the reaction mixture in a short-path still separated 6.24 g. of volatile material, b.p. 90–140° (0.3 mm.). A solution of this material in an ether–petroleum ether mixture deposited 2.85 g. (60%) of the crude dienone **21**, m.p. 61–74°. This product was sublimed under reduced pressure and then recrystallized from an ether–petroleum ether mixture to separate the pure dienone **21** as white prisms, m.p. 76.5–77°, yield 1.68 g. (35%). The product has infrared absorption[13] at 1700 cm.$^{-1}$ (cyclopentenone C=O) and 1675 and 1635 cm.$^{-1}$ (C=C) with an ultraviolet maxima[10] at 220 mμ (ε 6,000) and 244 mμ (ε 6,400).[18] The n.m.r. spectrum[13] (60 Mc.) of the product has a partially resolved multiplet centered at 4.24 τ attributable to two vinyl protons and a complex series of peaks in the region 7 to 8 τ attributable to eight allylic protons.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.38; H, 7.40.

The product **21** formed a semicarbazone which crystallized from methanol as a white solid, m.p. 235° dec., yield 60%.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.61; H, 6.83; N, 21.88.

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(13) Determined in carbon tetrachloride solution.

(14) The absence of an ultraviolet maximum in the region 235–240 mμ indicates that the adduct has structure **12** rather than the alternative structure in which the ketone and double bond functions are conjugated.

(15) Determined as a solution in perdeuteriodimethylformamide.

(16) Determined as a solution in deuteriochloroform.

(17) A gas chromatography column packed with Dow Corning silicone fluid no. 710 on 60–80-mesh firebrick was employed for this analysis.

(18) The appearance of the maximum at abnormally long wave length is comparable to the spectra of 2,5-dihydroacetophenone [245 mμ (ε 5000)] and 6-methyl-2,5-dihydroacetophenone [245 mμ (ε 5000)]. See (a) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 52 (1946); (b) E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *ibid.*, 607 (1949); (c) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

The gas chromatograph[17] of the mother liquors remaining after removal of the ketone **21** indicated a complex mixture of products which was not further investigated.

A solution of the dienone **21** (50 mg. 0.37 mmole) in 15 ml. of ether was hydrogenated at atmospheric pressure and room temperature over 10 mg. of 5% palladium-on-charcoal catalyst. When hydrogen uptake had ceased (6.6 ml. of 0.80 equiv.), the solution was filtered and concentrated. The gas chromatogram[17] of the crude product indicated the presence of three major components identified by comparison of retention times and infrared spectra of collected samples with the data for authentic samples.[19] The three products (in order of elution) were indane (*ca.* 20% of the mixture), *cis*-hexahydro-1-indanone (*ca.* 20% of the mixture), and 4,5,6,7-tetrahydro-1-indanone (*ca.* 45% of the mixture.)

Cyclopentane-1,3-dione (4) and Its Methyl Enol Ether 5.—Reduction of 4-cyclopentene-1,3-dione (2.00 g., 0.028 mole) with zinc in acetic acid as previously described[3a] afforded the enolic cyclopentane-1,3-dione (**4**) (1.75 g., 49%) as white prisms from a methanol–ethyl acetate mixture, m.p. 151–152° (lit.[3a] 149–150°), with an ultraviolet maximum[10] at 243 mμ (ε 17,500) and infrared absorption (Nujol mull) comparable to that reported[20] (only broad, general absorption with no distinguishing peaks).

Reaction of the diketone **4** (0.924 g., 9.4 mmoles) with an excess of diazomethane in an ether–methanol mixture followed by concentration left an oil which on sublimation gave 0.8155 g. (77%) of 3-methoxy-2-cyclopenten-1-one (**5**) as white prisms, m.p. 49–50°. Recrystallization from an ether–cyclohexane mixture followed by sublimation gave the pure enol ether, m.p. 51.3–52.1°, with infrared absorption[13] at 1705 (C=O), 1680 (C=C—OC), and 1600 cm.$^{-1}$ (C=C) and an ultraviolet maximum[10] at 237 mμ (ε 20,000). The n.m.r. spectrum[13] (60 mc.) of this material has a triplet (J = 1 c.p.s.) at 4.75 τ (1*H*, vinyl C—H), a singlet at 6.16 τ (3H, OCH_3) and a series of peaks corresponding to an A_2B_2 pattern centered at 7.58 τ (4*H*, CH_2).

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19; m.w., 112. Found: C, 64.02; H, 7.29; mol. wt., 112 (mass spectrum).

Attempted Reaction of Methyl *trans*-2,4-Pentadienoate (13b) with Cyclopentenone (18).—A solution of 22.4 g. (0.27 mole) of cyclopentenone,[21] 18.75 g. (0.167 mole) of the diene **13b** and 4.7 g. of 2,5-di-*t*-butylhydroquinone in 50 ml. of benzene was heated to 115–125° in an autoclave for 13 days. The resulting mixture was chromatographed on 370 g. of neutral alumina. The nonpolymeric product, eluted with benzene, was distilled in a short-path still to separate 5.994 g. of yellow liquid, b.p. 110–112° (0.25 mm.), containing[17] one major component. Fractional distillation through a Holtzmann column separated 2.0195 g. of colorless liquid, b.p. 104° (0.04 mm.), n^{25}D 1.4942, containing[17] only the previously mentioned major component, namely the diester **19**. This material has infrared absorption[13] at 1740 (shoulder) and 1730 cm.$^{-1}$ (unconj. and conj. ester C=O) and 1655 cm.$^{-1}$ (C=C) with ultraviolet maxima[10] at 207 mμ (ε 11,800) and 302 mμ (ε 83). The n.m.r. spectrum[13] (60 Mc.) exhibits a quadruplet centered at 3.11 τ (1H, J = 16 and 8 c.p.s. vinyl proton beta to ester function) a multiplet at approximately 4.2 τ (3*H*, vinyl proton alpha to ester function and two vinyl protons of the cyclohexene moiety), a singlet at 6.33 τ (6H, $COOCH_3$) and broad unresolved absorption in the region 6.7–8.5 τ.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.55; H, 7.23.

Methyl 2,4-pentadienoate **13b** (81 mg., 0.72 mmole) was dissolved in five times its volume of benzene and the mixture was saturated with 2,5-di-*t*-butylhydroquinone. This mixture was sealed in an ampule and was heated to 120° for 12 days. The mixture was concentrated to a heavy oil which was distilled (b.p.~110° at 0.06 mm.) to give 37 mg. of a liquid which had infrared absorption[13] identical to that of the material characterized above.

Diels–Alder Reactions with Pentadienoic Acid (13a) and Its Ester (13b).—A mixture of 5.16 g. (0.046 mole) of the ester **13b**, 5.23 g. (0.054 mole) of the enedione **2**, and 380 mg. of 2,5-di-*t*-butylhydroquinone was allowed to stand at room temperature under nitrogen for 23 days. A solution of the resulting mixture in a methanol–ethyl acetate mixture deposited 4.55 g. of the adduct **15b**, m.p. 181–182.5°. Extraction of the mother liquor with aqueous potassium carbonate followed by acidification of the aqueous extract and appropriate manipulations afforded an additional 0.491 g. (total yield 5.04 g. of 53%) of the adduct. Recrystallization gave the pure enolic diketo ester **15b** as white prisms, m.p. 182.9–183.9°, with infrared absorption[9] at 1735 cm.$^{-1}$ (ester C=O) and 1630 (shoulder) and 1580 cm.$^{-1}$ (enolic β-diketone) with an ultraviolet maximum at 244 mμ (ε 13,800).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.84. Found: C, 63.17; H, 5.75.

After a solution of 0.75 g. (7.7 moles) of the acid **13a**, 0.75 g. (7.8 mmoles) of the enedione **2**, and 3 mg. of 2,5-di-*t*-butylhydroquinone in 3 ml. of benzene had been allowed to stand at room temperature for 10 days, the solid which separated was filtered and washed with ether to leave 175 mg. (11%) of the crude adduct, m.p. 184.7–185° dec. Recrystallization from a methanol-ethyl acetate mixture gave the pure adduct **15a** as white solid, m.p. 191.3° dec., with infrared absorption[9] at 1695 cm.$^{-1}$ (carboxyl C=O) and 1655 and 1595 cm.$^{-1}$ (enolic β-diketone) and an ultraviolet maximum at 245 mμ (ε 15,200).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.89; H, 5.38.

A solution of 100 mg. (5.8 mmoles) of N-phenylmaleimide **16** and 65 mg. (5.8 mmoles) of the ester **13b** in 0.5 ml. of benzene saturated with 2,5-di-*t*-butylhydroquinone, was allowed to stand at room temperature for 18 days and then concentrated under reduced pressure. Trituration of the residue with ether left 147 mg. (87%) of the crude adduct, m.p. 120–123°. Recrystallization from an ether–ethyl acetate mixture followed by sublimation under reduced pressure afforded the pure adduct **17b** as white prisms, m.p. 123–124°. The product has infrared absorption[11] at 1710 (broad) cm.$^{-1}$ with shoulders at 1740 and 1780 cm.$^{-1}$ (C=O of ester and five-membered imide) with end absorption in the ultraviolet[10] and a point of inflection at 215 mμ (ε 2,600).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30. Found: C, 67.23; H, 5.27.

After solution of 165 mg. (9.5 mmoles) of the imide **16** had 118 mg. (8.3 mmoles) of the acid **13a** in 1 ml. of benzene had been allowed to stand at room temperature for 40 hr., the solid which separated was recrystallized from methanol to give 165 mg. (50%) of the adduct **17a** as white prisms, m.p. 225–226.5° dec. Recrystallization raised the decomposition point to 230–231°. The material has infrared absorption[9] at 1775 and 1730 cm.$^{-1}$ (C=O of inside in a five-membered ring) and 1690 cm.$^{-1}$ (carboxyl C=O) with end absorption in the ultraviolet[10] (at 214 mμ, ε 11,000).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.33; H, 4.66; N, 5.22.

(19) See H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).

(20) J. H. Boothe, R. G. Wilkinson, S. Kushner, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 1732 (1953).

(21) Prepared by the procedure of C. H. DePuy and E. L. Eilers, *J. Org. Chem.*, **24**, 1380 (1958).

Perhydroindanone Derivatives. II. Stability Relationships[a,2]

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The *cis* and *trans* isomers of perhydro-1-indanone (**6** and **7**), 7-methylperhydro-1-indanone (**12** and **13**), 3a,4,7,7a-tetrahydro-1-indanone (**4** and **5**) and 7-methyl-3a,4,7,7a-tetrahydro-1-indanone (**9** and **10**) have been prepared and the positions of *cis–trans* equilibrium determined.

Having found previously[3] that cyclohexenone could serve as a preparatively useful dieneophile with reactive dienes provided high temperatures (175–200°) and excess diene were employed, we elected to study the reaction of cyclopentenone (**1**) with butadiene (**2**)[4] and *trans*-1-methylbutadiene (**3**, piperylene), as possible preparative routes to perhydroindanone derivatives. The results of these studies are summarized in Chart I. At the temperatures employed for reaction of butadiene (**2**) with cyclopentenone (**1**), partial equilibration of the expected, kinetically favored isomer **4**[5] with its epimer **5** was observed, the equilibration being more nearly complete at higher temperatures. The corresponding reaction with piperylene could be effected at lower temperature; the expected[5] *cis* isomer **9** was the major product at 80–100° and diminished in amount as the reaction temperature was raised to 160°. Although the 7-methyltetrahydroindanones **9** and **10** were the major products of this reaction, at least two additional components were present as minor by-products. The formulation of these by-products as isomers of structure **11** was indicated by the spectral properties of these materials and by their dehydrogenation to 4-methylindanone (**15**). Each of the tetrahydroindanones **4, 5, 9,** and **10** could be hydrogenated to form the corresponding hexahydroindanone **6, 7, 12,** and **13** as the predominant product.

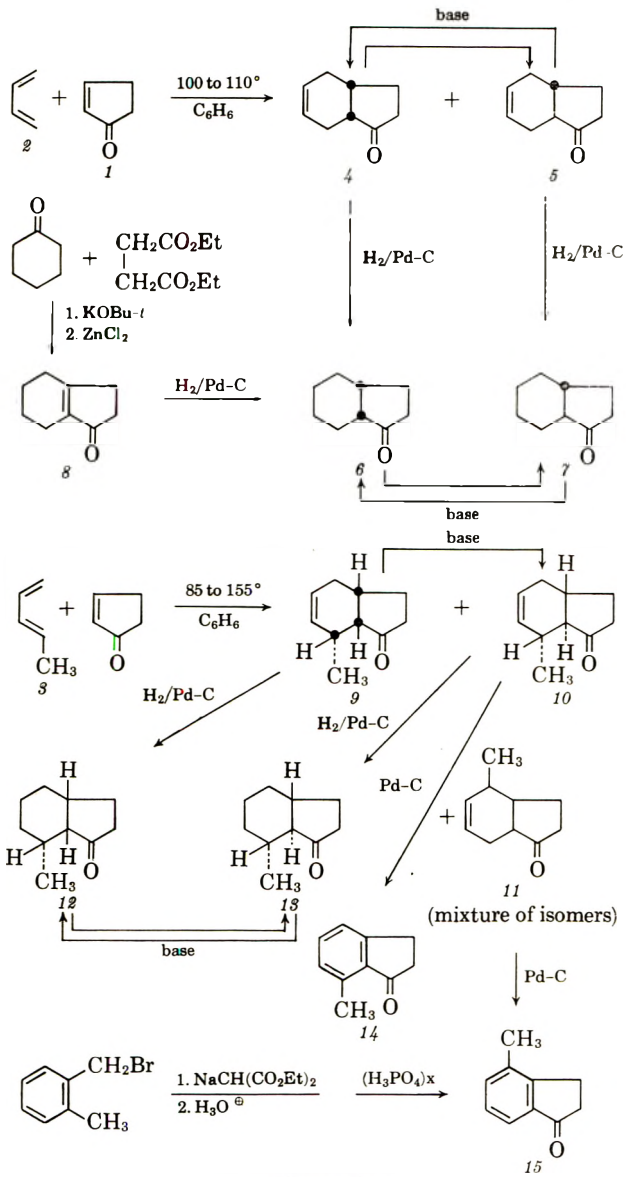


CHART I

Since we wished to obtain the tetrahydroindanone **16** as a possible precursor of 7-carboxy-7-methyl-1a,3a,4,-5,6,7-hexahydroindanone, the transformations outlined in Chart II were explored. Although dehydrohalogenation of the crude bromo ketone **17** afforded small amounts of this desired ketone **16**, identified by comparison with a subsequently described sample,[6] the major product was the endocyclic isomer **18**. Since this product **18** was the only tetrahydroindanone obtained by isomerization of **9** and **10** under a variety of conditions, we are led to the conclusion that the endocyclic isomer **18** is appreciably more stable than the exocyclic isomer **16** in spite of the fact that both substances contain a tetrasubstituted carbon–carbon double bond. Although these observations could be construed as additional data concerning the relative stabilities of double bonds exocyclic and endocyclic to a

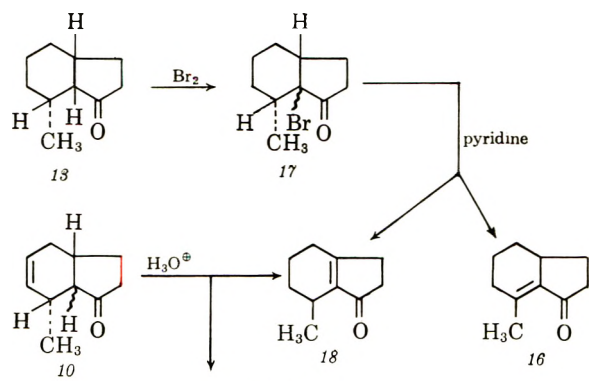


CHART II

(1) (a) Supported in part by National Science Foundation Grant No. G-9486; (b) National Science Foundation Predoctoral Fellow, 1958–1962.

(2) Part I, *J. Org. Chem.*, **28**, 27 (1963).

(3) H. O. House, W. F. Gannon, R. S. Ro, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1463 (1960) and references cited therein.

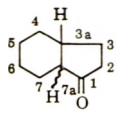
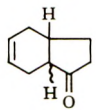
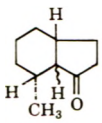
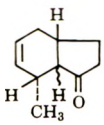
(4) Although the product characterization was rather fragmentary, this reaction has been reported by E. Dane and K. Eder, *Ann.*, **539**, 207 (1939).

(5) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(6) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

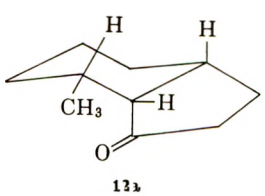
TABLE I

EQUILIBRATION OF THE TETRAHYDRO- AND HEXAHYDROINDANONES

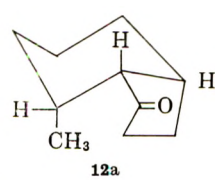
Structure	K_{equil} for *cis* ⇌ *trans*
 6 and **7**	0.33
 4 and **5**	0.90
 12 and **13**	3.08
 9 and 10	>50

five-membered ring,[7] we believe that the primary source of destabilization in structure **16** derives from a serious eclipsing interaction between the methyl group and carbonyl oxygen atom which will exist if *pi* orbital overlap between the carbon–carbon double bond and the carbonyl function is to be maintained.

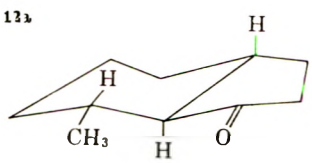
It was of interest to determine the positions of equilibrium for the various tetrahydro- and hexahydroindanone epimers which had been prepared. These data, listed in Table I, were conveniently obtained by equilibrating each of the various compounds in triethylamine solution at 100°. It is apparent that the presence of a methyl group at position 7 and *trans* to the hydrogen atom at position 3a reverses the usual stability order of perhydroindan-1-ones where the *cis* isomer is more stable.[8] The examples reported here represent an additional case[9] in which conformational effects can alter the usual order of stability. Apart from the obvious 1,3-diaxial interaction in conformation **12b** of the *cis*



13b



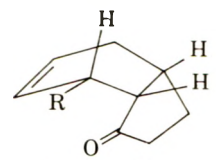
12a



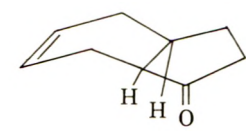
13a

isomer **12**, the general tendency of a *cis*-fused five-membered ring in a perhydroindane to flatten the six-membered ring[10] tends to increase the interaction between the equatorial methyl group and axial carbonyl function in conformation **12a**. This interaction is greatly diminished in the *trans* isomer **13a** where the five-membered ring tends to increase the puckering of the six-membered ring.[10]

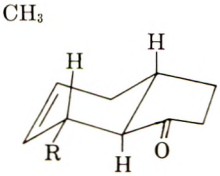
The effect of introducing a 5,6-double bond into these molecules was surprising since previous work[11] with octalin systems had suggested that introduction of a double bond in an analogous position tended to flatten the six-membered ring containing the double bond and, consequently, to favor a *cis* ring fusion (or at least to destabilize a *trans* ring fusion). As will be noted in Table I, exactly the reverse effect is found in the perhydroindanone system. We believe the most reasonable explanation for this effect to be that the *cis*-fused tetrahydroindanones **4** and **9** exist in suitably twisted modifications of the boat conformations **4a, 4b,** and **9a** to avoid serious bond angle deformations in spite of the resulting increase in steric interactions. In the *trans* isomers **5** and **10** the usual chair conformations **5a** and **10a** offer a satisfactory compromise between bond angle deformation and steric interactions. It is interesting to note that a combination of the effects of a 7-methyl substituent and a 5,6-double bond completely reverse to usual order of stability expected in the perhydroindan-1-one system.



4a. R = H
9a. R = CH_3



4b



5a. R = H
10a. RCH

Experimental[12]

3a,4,7,7a-Tetrahydro-1-indanones 4 and 5.—A solution of 85 g. (1.04 moles) of cyclopentenone,[13] 200 g. (3.7 moles) of butadiene and 10 g. of 2,5-di-*t*-butylhydroquinone in 250 ml. of benzene was heated to 110° for 12 days in an autoclave. The resulting mixture was concentrated under reduced pressure and then distilled to separate 128 g. of a liquid mixture, b.p. 36–100° (8 mm.), containing,[14] in addition to unchanged cyclopentenone and other low-boiling components, a mixture of 40% of the *trans* isomer **5** (the first eluted) and 60% of the *cis* isomer **4**. Fractional distillation with a 70-cm. spinning band column afforded 41.7 g. (29%) of fractions, b.p. 91–92° (5–7 mm.), containing[14] varying proportions of the two tetrahydroindenones **4** and **5**. Several of the higher-boiling fractions [b.p. 92° (5 mm.), $n^{25}D$ 1.5038] contained[14] the pure *cis* isomer **4** which exhibits infrared absorp-

(7) For discussion and leading references see (a) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958); (b) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Zacura, *ibid.*, **82**, 1750 (1960).

(8) (a) W. Hückel, M. Sachs, J. Yantschulewitsch, and F. Nerdel, *Ann.*, **518**, 155 (1935); (b) G. Quinkert, *Experientia*, **13**, 381 (1957); (c) N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960).

(9) J. F. Biellmann, D. Francetic, and G. Ourisson, *Tetrahedron Letters*, No. **18**, 4 (1960).

(10) (a) E. L. Eliel and C. Pillar, *J. Am. Chem. Soc.*, **77**, 3600 (1955); (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, pp. 275–278.

(11) For references and discussion see S. K. Balasubramanian, *Tetrahedron*, **12**, 196 (1961).

(12) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The n.m.r. spectra were measured at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer.

(13) Prepared by the procedure of C. H. DePuy and K. L. Eilers, *J. Org. Chem.*, **24**, 1380 (1958).

(14) A gas chromatography column packed with Dow Corning silicone fluid no. 710 on 60–80-mesh firebrick was employed for this analysis.

tion[15] at 1735 cm.$^{-1}$ (cyclopentanone C=O) and at 1655 cm.$^{-1}$ (C=C) with weak end absorption (ϵ 400 at 210 mμ) in the ultraviolet[16] as well as a maximum at 284 mμ (ϵ 26). The n.m.r. spectrum[15] exhibits a peak (insufficient resolution to determine splitting pattern) at 4.42 τ (2*H*, vinyl C—H) and a complex series of peaks in the region 7.4 to 8.6 τ (10H, saturated C—H).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88; mol. wt., 136. Found: C, 79.13; H, 8.86; mol. wt., 136 (mass spectrum.)

Refractionation of the lower boiling fractions separated the pure *trans* isomer, b.p. 99° (12 mm.), $n^{25}D$ 1.4942, with infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O) and at 1635 cm.$^{-1}$ (C=C) with an ultraviolet maximum[16] at 288 mμ (ϵ 34) and weak end absorption (ϵ 294 at 210 mμ). The n.m.r. spectrum[15] has two peaks (separated by 3 c.p.s.) centered at 4.37 τ (2H, vinyl C—H) as well as a series of peaks in the region 7.4 to 8.7 τ (10 H, saturated C—H).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88; mol. wt., 136. Found: C, 79.15; H, 8.89; mol. wt., 136 (mass spectrum).

When the reaction was repeated with 10 g. (0.185 mole) of butadiene, 5 g. (0.061 mole) of cyclopentenone, 0.4 g. of 2,5-di-*t*-butylhydroquinone, and 10 ml. of benzene at 100° for 4 days, the mixture of tetrahydroindanones obtained [0.984 g. of 12%, b.p. 81–88° (10 mm.)] contained[14] 24% of the *trans* isomer **5** and 76% of the *cis* isomer **4**.

Reaction of either the *cis* (**4**) or *trans* (**5**) isomer with ethanolic 2,4-dinitrophenylhydrazone containing a few drops of hydrochloric acid produced the same **2,4-dinitrophenylhydrazone** (shown by a mixed melting point and comparison of infrared and ultraviolet spectra) as orange microplates from an ethanol–ethyl acetate mixture, m.p. 201–201.5° dec., yield 46.5% from the *cis* isomer **4** and 42.5% from the **trans** isomer **5**. The material has an ultraviolet maximum[17] at 364 mμ (ϵ 22,800). We have tentatively assigned the *trans* configuration (*cf.* **5**) to this derivative.

Anal. Calcd. for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.07; H, 5.15; N, 17.52.

7-Methyl-3a,4,7,7a-tetrahydro-1-indanones 9 and 10.—A solution of 16.02 g. (0.195 mole) of cyclopentenone,[13] 30 g. (0.44 mole) of *trans*-1-methyl-1,3-butadiene,[18] and 2.04 g. of 2,5-di-*t*-butylhydroquinone in 30 ml. of benzene was heated to 155° for 55 hr. Two consecutive distillations of the reaction mixture separated 20.63 g. (71%) of a mixture of adducts, b.p. 95–104° (13 mm.), which contained[14] 70% of the *trans* isomer **10** as well as several minor components. Fractional distillation with a 70-cm. spinning band column separated fractions, b.p. 97–98° (13 mm.), $n^{25}D$ 1.4872 which contained[14] more than 95% of the *trans* isomer **10**. The **2,4-dinitrophenylhydrazone of the trans ketone 10** was obtained as a red microcrystalline solid from an ethanol–ethyl acetate mixture, m.p. 231–231.5°, yield 65%, with an ultraviolet maximum at 364 mμ (ϵ 23,500).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.29; H, 5.42; N, 16.81.

A pure sample of the *trans* ketone **10**, collected by gas chromatography,[14] has infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O) and at 1635 cm.$^{-1}$ (C=C) with an ultraviolet maximum[16] at 292 mμ (ϵ 31) and weak end absorption (ϵ 404 at 210 mμ). The n.m.r. spectrum[15] has broad, poorly resolved absorption centered at 4.51 τ (2 H, vinyl C—H) with a series of peaks in the region 7.4 to 8.6 τ (9 H, saturated C—H) and a doublet (J = 7 c.p.s.) centered at 8.83 τ (3 H, CH_3).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 80.15; H, 9.63; mol. wt., 150 (mass spectrum).

A mixture of 636 mg. (4.2 mmoles) of the ketone **10**, 6 ml. of *p*-cymene and 125 mg. of a 30% palladium-on-carbon catalyst was refluxed for 17 hr. and then filtered and chromatographed on neutral alumina. The crude product, **7-methyl-1-indanone (14)**, eluted with benzene amounted to 249 mg. (40.5%), m.p. 40–50°. Recrystallization from petroleum ether afforded 130 mg. (21%) of the indanone as pale yellow needles, m.p. 52–53.3°, and addition recrystallization followed by sublimation raised the melting point to 54.7–55.2°. The product has infrared absorption[15] at 1705 cm.$^{-1}$ (cyclopentenone C=O), ultraviolet maxima[16] at 248 mμ (ϵ 13,600), and 297 mμ (ϵ 2630) and a series of n.m.r. peaks[19] in the region 2.4 to 3.1 τ (3 H, aromatic C—H) as well as a singlet at 7.39 τ (3*H*, CH_3) and series of peaks having the pattern of an A_2B_2 system in the region 6.7 to 7.6 τ (4*H*, CH_2).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.20; H, 6.83.

The indanone **14** formed a **2,4-dinitrophenylhydrazone** as red prisms from a methanol–ethyl acetate mixture, m.p. 290–290.5° dec., yield 83%, with ultraviolet maxima[17] at 255 mμ (ϵ 16,300), 293 mμ (ϵ 10,800) and 386 mμ (ϵ 34,400).

Anal. Calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.58; H, 4.15; N, 16.97.

A 760-mg. sample (5.0 mmoles) of a fraction from this Diels–Alder reaction which was enriched in the minor components and contained less than 10% of the *trans* ketone **10** was mixed with 7.5 ml. of *p*-cymene and 225 mg. of a 30% palladium-on-carbon catalyst and refluxed for 24 hr. After filtration, the crude product was chromatographed on neutral alumina to separate 160 mg. (22%) of 7-methyl-1-indanone (**14**), m.p. 48–52° (eluted with benzene-petroleum ether mixtures) and 20 mg. (3%) of 4-methyl-1-indanone (**15**), m.p. 97–97.8° (eluted with benzene). Both products were identified by mixed melting-point determinations and comparison of infrared spectra.

An authentic sample of **4-methyl-1-indanone** (**15**), prepared from α-bromo-*o*-xylene as previously described,[20] was isolated as microprisms from petroleum ether, m.p. 97.5–98.2° (lit.,[20] 99–100°). The product has infrared absorption[15] at 1715 cm.$^{-1}$ (cyclopentenone C=O), ultraviolet maxima[16] at 250 mμ (ϵ 13,800) and 296 mμ (ϵ 3050), and a series of n.m.r. peaks[19] in the region 2.2 to 3.0 τ (3*H*, aromatic C—H) as well as a singlet at 7.68 τ (3*H*, CH_3) and a series of peaks having the pattern of an A_2B_2 system in the region 6.7 to 7.6 τ (4*H*, CH_2).

After a solution of 30.1 g. (0.366 mole) of cyclopentenone, 33 g. (0.486 mole) of *trans*-1-methyl-1,3-butadiene, and 1.5 g. of 2,5-di-*t*-butylhydroquinone in 50 ml. of benzene had been heated to 85° for 7 days, distillation of the mixture separated 22.52 g. (41%) of a mixture of adducts, b.p. 92–100° (10 mm.), containing[14] 68% of the *cis* ketone **9** and 15% of the *trans* ketone **10**. A sample of the pure *cis* ketone **9** collected from the gas chromatogram[14] has infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O), an ultraviolet maximum[16] at 297 mμ (ϵ 31) with weak end absorption (ϵ 650 at 210 mμ) and an n.m.r. peak[15] at 4.42 τ (2 H, vinyl C—H) with a doublet (J = 7 c.p.s.) centered at 8.75 τ (3*H*, CH_3) and a series of peaks in the region 7.2 to 8.6 τ (9 *H*, saturated C—H).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 80.01; H, 9.40; mol. wt., 150 (mass spectrum).

After a solution of 120 mg. (0.80 mmole) of the *cis* ketone **9** in five times its volume of triethylamine had been heated to 120° overnight, only the *trans* ketone **10** could be detected[14] in the solution. An ether solution of the reaction mixture was washed with dilute, aqueous hydrochloric acid, dried, concentrated, and distilled to separate 93 mg. (77%) of the pure *trans* ketone **10** identified with the previously described sample by comparison of retention times and infrared spectra.

A solution of 1.00 g. (6.7 mmoles) of the mixture of Diels–Alder adducts containing 68% of the *cis* ketone **9** in ethyl acetate was hydrogenated over 15 mg. of a 5% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake (153 ml. or 1.03 equiv.) ceased, the solution was filtered and concentrated to leave a liquid exhibiting three gas chromatographic peaks[14,21] corresponding to the *cis*-perhydroindanone **12** (57%), the *trans*-perhydroindanone **13** (12%), and one of the 4-methylperhydro-1-indanones (31%). A sample of the pure **7-methyl-*cis*-perhydro-1-indanone** (**12**) collected[14] from the gas chromatograph has infrared absorption[15] at 1735 cm.$^{-1}$ (cyclopentanone C=O) with broad, partially resolved n.m.r. absorption[15] in the region 7.5 to 9.0 τ including a doublet (J = 7 c.p.s.) centered at 8.77 τ (CH_3).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59; mol. wt., 152. Found: C, 78.72; H, 10.59; mol. wt., 152 (mass spectrum).

A solution of 920 mg. (6.1 mmoles) of the mixture of Diels–Alder adducts containing more than 95% of the *trans* ketone **10** in 20 ml. of ethyl acetate was hydrogenated over 70 mg. of a 5% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake (154 ml. of 1.11 equiv.) had ceased, the mixture was filtered, concentrated, and distilled to separate 687 mg. (74%) of colorless liquid, b.p.

(15) Determined in carbon tetrachloride solution.
(16) Determined in ethanol solution.
(17) Determined in chloroform solution.
(18) Prepared as described in ref. 2.
(19) Determined as a solution in perdeuteriochloroform.
(20) S. Dev, *J. Indian Chem. Soc.*, **32**, 403 (1955).
(21) A 100-ft. capillary column packed with Dow Corning silicone fluid no. 710 was employed for this analysis.

105° (20 mm.), which contained[14] more than 95% of the *trans* isomer **13**. A pure sample of the **7-methyl-*trans*-perhydro-1-indanone** (**13**), collected from the gas chromatograph[14] had infrared absorption[15] at 1740 cm.$^{-1}$ with broad, partially resolved n.m.r. absorption in the region 7.5 to 9.0 τ including a doublet (J = 4 c.p.s.) centered at 8.86 τ (CH_3).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59; mol. wt., 152. Found: C, 78.64; H, 10.61; mol. wt., 152 (mass spectrum).

4,5,6,7-Tetrahydro-1-indanone (**8**).—3-Carbethoxy-3-(1-cyclohexenyl)propionic acid[22] was converted to the tetrahydroindanone **8** as previously described.[23] The product, obtained as a colorless liquid, b.p. 121–125° (15 mm.), n^{27}D 1.5200 [lit.[23] b.p. 83.5–85° (2 mm.), n^{18}D 1.5260], has infrared absorption[15] at 1700 cm.$^{-1}$ (cyclopentenone C=O) and at 1645 cm.$^{-1}$ (C=C), an ultraviolet maximum[16] at 237 mμ (ϵ 13,500) and complex n.m.r. absorption in the region 7.2 to 8.6 τ with no peak at lower field attributable to a vinyl proton.

A solution of 1.882 g. (13.8 mmoles) of the tetrahydroindanone **8** in 35 ml. of methanol was hydrogenated over 401 mg. of a 5% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake (330 ml. or 1.06 equiv.) ceased, the mixture was filtered, concentrated, and distilled to separate 1.6305 g. (85%) of *cis*-perhydro-1-indanone (**6**), b.p. 98° (16 mm.), which was identified with a subsequently described sample by comparison of retention times and infrared spectra.

7-Methyl-4,5,6,7-tetrahydro-1-indanone (**18**).—To a solution of 600 mg. (3.95 mmoles) of the *trans* ketone **13** in 10 ml. of ether, cooled to 0°, was added dropwise and with stirring, 650 mg. (4 mmoles) of bromine. The mixture was stirred for 10 min. and then concentrated and a solution of the residue in petroleum ether was washed with water and concentrated. A solution of the residual yellow oil (which darkened on standing) in 10 ml. of pyridine was refluxed under nitrogen for 8 hr. and then diluted with ether and filtered to separate the pyridine hydrobromide. The organic filtrate was washed successively with aqueous hydrochloric acid, water, aqueous sodium bicarbonate, and water and then dried and concentrated. Distillation of the residue in a short-path still afforded 348 mg. (59%) of a pale yellow oil which contained[14] the tetrahydroindanones **18** (85%) and **16** (15%). A sample of the tetrahydroindanone **16** was collected and identified with an authentic sample[6] by comparison of retention times and ultraviolet spectra. The pure tetrahydroindanone **18**, collected from the gas chromatograph, has infrared absorption[15] at 1700 cm.$^{-1}$ (cyclopentenone C=O) and at 1640 cm.$^{-1}$ (C=C), an ultraviolet maximum[16] at 238 mμ (ϵ 11,300) and complex n.m.r. absorption[16] in the region 7.3 to 8.7 τ (11 H, saturated C—H) as well as a doublet (J = 7 c.p.s.) centered at 8.95 τ (3 H, CH_3).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.37.

Comparable mixtures of the tetrahydroindanones **16** and **18** were obtained by dehydrohalogenation of the crude bromo ketone thermally, with collidine or with lithium chloride and dimethylformamide. A solution of 424 mg. (2.82 mmoles) of the tetrahydroindanone **10** in 5 ml. of a 1 M solution of sulfuric acid in a benzene–acetic acid mixture (1:2 by volume) was heated to 125° in a sealed ampoule for 18 hr. After the mixture had been diluted with 50 ml. of petroleum ether and washed with aqueous sodium hydroxide, the organic layer was washed with water, dried, and concentrated. Distillation of the residue afforded 93 mg. (23%) of a liquid, b.p. 130–140° (20 mm.), which contained[14] 85% of the tetrahydroindanone **18**. A sample of the product was collected and identified with the previously described sample by comparison of retention times, infrared spectra, and ultraviolet spectra.

Perhydro-1-indanones 6 and 7.—A solution of 1.30 g. (9.56 mmoles) of the *trans* ketone **5** in 25 ml. of ether was hydrogenated over 150 mg. of a 30% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake ceased (260 ml. or 1.2 equiv.) the mixture was filtered, concentrated and distilled to separate 789.3 mg. (64%) of the *trans*-perhydroindanone **7**, b.p. 81.5–86.5° (10 mm.), n^{27}D 1.4764, containing[14] less than 9% of the *cis* isomer **6**. The product has infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[16] at 288 mμ (ϵ 29) and 237 mμ (ϵ 37, this latter peak is apparently attributable to contamination with a small amount of the unsaturated ketone **8**) and broad n.m.r. absorption[15] in the region 7.5 to 9.2 τ with no peaks attributable to vinyl hydrogen.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21; mol. wt., 138. Found: C, 78.30; H, 10.33; mol. wt., 138 (mass spectrum).

A solution of 400 mg. (2.95 mmoles) of the *cis* ketone **4** in 15 ml. of ether was hydrogenated over 40 mg. of a 30% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the absorption of hydrogen (59 ml. or 0.91 equiv.) ceased, the mixture was filtered and concentrated to leave 293 mg. (73%) of colorless liquid[24] containing 80% of the *cis* isomer **6** and 20% of the unsaturated ketone **8** (identified by comparison of the infrared spectra of a collected sample and the previously described material). The *cis* isomer **6**, collected from the gas chromatogram,[14] contained less than 11% of the *trans* isomer **7** and has infrared absorption[15] at 1740-cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[16] at 288 mμ (ϵ 22) and at 237 mμ (ϵ 71, apparently attributable to contamination with a small amount of the unsaturated ketone **8**), broad n.m.r. absorption[15] in the region 7.5 to 9.2 τ with no peaks attributable to vinyl hydrogen and a molecular weight (mass spectrum) of 138.

Equilibration Studies.—The positions of equilibrium listed in Table I were obtained by dissolving each of the *cis* and *trans* isomers in four times its volume of triethylamine. The solutions were sealed in ampoules and heated to 100°, samples being removed periodically for analysis.[14] For these analyses, the columns were calibrated by use of standard mixtures. The equilibrations were allowed to proceed until the values obtained with each *cis-trans* pair of isomers agreed to within 1%.

(22) This diester, b.p. 148–153° (0.47 mm.), n^{25}D 1.4921, was prepared as described by W. S. Johnson, C. E. Davis, R. H. Hunt, and G. Stork [*J. Am. Chem. Soc.*, **70**, 3021 (1948)], who report n^{25}D 1.4830, b.p. 150–155° (0.5 mm.).

(23) D. W. Mathieson, *J. Chem. Soc.*, 3248 (1953).

(24) The *cis* isomer **6** is reported to boil at 72–73° (6 mm.) with n^{25}D 1.4813. See ref. 23.

Perhydroindanone Derivatives. III. Acid-catalyzed Ring Closure[1,2]

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The preparation (Chart II) and cyclization (Chart I) of the lactone **2** to form the tetrahydroindanones **1**, **3**, and **4** are described.

The successful use of acid-catalyzed ring closures for the production of tetrahydroindanone[3] prompted us to consider this synthetic method for the preparation of appropriately substituted tetrahydroindanones. In particular our failure to obtain a satisfactory yield of the 7-methyltetrahydroindanone (**1**) by use of the Diels–Alder reaction and subsequent transformations,[2] led us to reinvestigate the reported[3a] conversion of the lactone

(1) Supported in part by National Science Foundation Grant No. G-9486 and in part by Petroleum Research Fund Grant No. 594 A.

(2) Part II, *J. Org. Chem.*, **28**, 31 (1963).

(3) For examples see (a) R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951); (b) S. Dev, *J. Indian Chem. Soc.*, **34**, 169 (1957); (c) S. Dev and C. Rai, *ibid.*, **34**, 266 (1957).

2 to the tetrahydroindanone **3**, since the reported[3a] isolation of only a single ketonic product **3** seemed ususual in a reaction which presumably involves carbonium ion intermediates and could lead to several products.

The results of this investigation, outlined in Chart I, confirmed this suspicion since three tetrahydroindanones **1**, **3**, and **4** were produced. Although this sequence provided us with an adequate sample of the desired tetrahydroindanone **1** for characterization, the yields obtained and the complexity of the reaction mixture excluded this approach for preparative purposes.

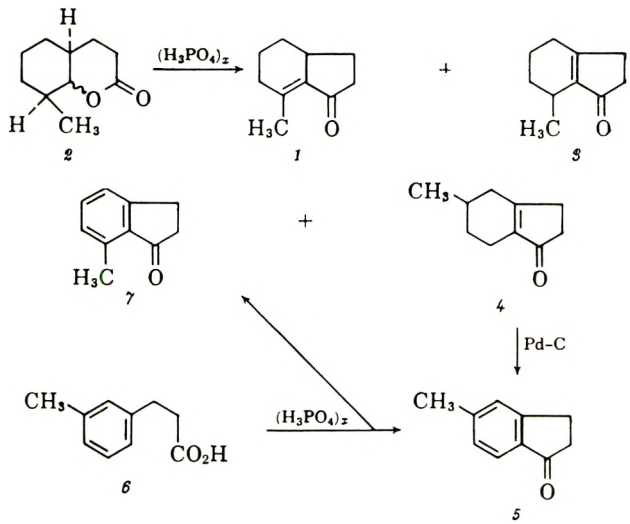


CHART I

Of incidental interest in this work was the finding that intramolecular cyclization of *m*-methylhydrocinnamic acid (**6**) does not yield a single product, 5-methylindanone (**5**), as previously reported,[4] but rather a mixture of both possible indanones **5** and **7**. Although the indanone **5** was formed in slightly larger amount, we suggest that any structure assignment based on the generalization[5] that intramolecular acylation will occur primarily *para* rather than *ortho* to a *meta*-substituent in the starting material should be made with caution.

The preparative routes employed for the lactone **2** and its isomers are outlined in Chart II. Although previous work had led us to expect only the keto acid derivative **9** from application of the Michael reaction to 2-methylcyclohexanone (**8**)[3a,6] and only the keto acid derivatives **11** and **12** by reaction of the enamine **10** with the methyl acylate,[7] the latter expectation was not realized, the ratio of product **9** to products **11** and **12** being approximately one to one. From the n.m.r. spectrum of the enamine mixture **10**, the ratio of the trisubstituted to the disubstituted enamine was estimated to be 15:85.[8] Consequently, the preference for attack at the unsubstituted position of a cyclohexanone enamine is no where near as great as had been supposed.[7,9] Of the two 2,6-disubstituted ketones **11a** and **12a** obtained from the quaternary salt **13**, the preponderant (and hence more stable) isomer has been

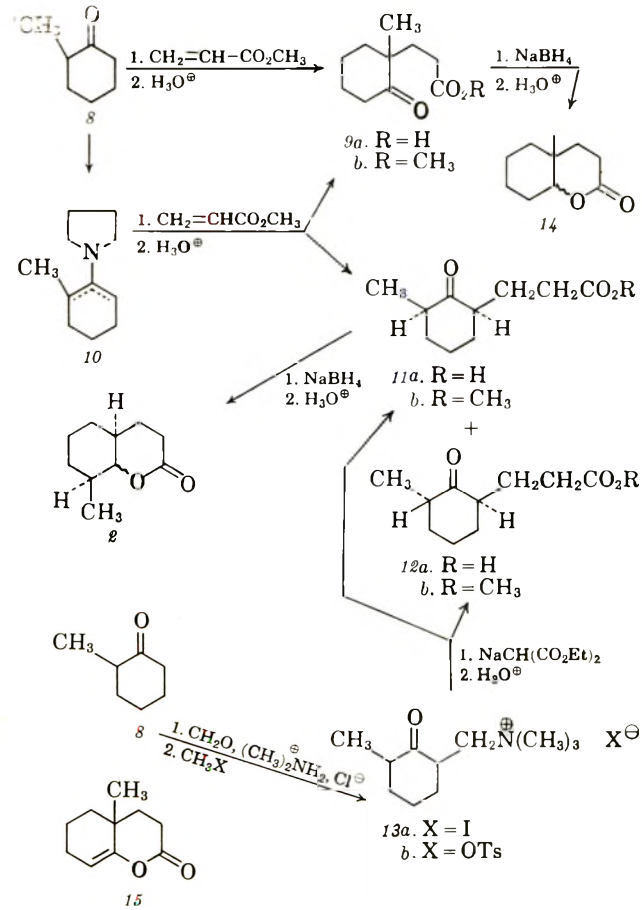


CHART II

assigned the *cis* configuration which is capable of existing in a conformation with both substituents equatorial. Reduction of each of the keto acids **9a** and **11a** yielded a mixture of stereoisomeric lactones.

Experimental[10]

β-(3-Methyl-2-oxocyclohexyl)propionic Acid Derivatives 11 and 12.—After 2-methylcyclohexanone[11] had been converted to 2-(dimethylaminomethyl)-6-methylcyclohexanone, b.p. 62–63° (0.7 mm.), $n^{25}D$ 1.4639 [lit.[3a] 71° (1.3 mm.), $n^{20}D$ 1.4650], as previously described,[3a] reaction of 45.9 g. (0.27 mole) of this Mannich base with excess (76.5 g. or 0.54 mole) of methyl iodide in 150 ml. of ether for 3 days afforded 71.2 g. (84.5%) of the crude methiodide **13a**. Extraction with methylene chloride removed the more soluble diastereoisomer **13a** which crystallized from a methylene chloride–ether mixture as white crystals, m.p. 160–163° dec. [lit.[3a] 163–164°], yield 28.2 g. (33.5%), infrared[12] 1705 cm.$^{-1}$ (C=O). The residue from the methylene chloride extraction consisted of 25.6 g. (30.5%) of the crude higher melting diastereoisomer **13a**, m.p. 190–192° dec., infrared[12] 1699 cm.$^{-1}$ (C=O). Alternatively, a solution of 78.8 g. (0.47 mole) of the Mannich base and 95.4 g. (0.51 mole) of methyl *p*-toluenesulfo-

(4) (a) J. von Braun, G. Manz, and E. Reinsch, *Ann.*, **468**, 277 (1929); (b) W. von Miller and Rohde, *Ber.*, **23**, 1887 (1890); see also Young, *Ber.*, **25**, 2102 (1892).

(5) W. S. Johnson, *Org. Reactions*, **2**, 114 (1944).

(6) (a) P. C. Dutta and N. R. Ghosh, *J. Indian Chem. Soc.*, **32**, 741 (1955). See also (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(7) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128 (1956).

(8) *Cf.* G. A. Berchtold, unpublished work.

(9) In experiments to be described elsewhere the reaction of the enamine **10** with methyl *p*-toluenesulfonate was found to produce a mixture of quaternary ammonium salts which could be rearranged thermally and subsequently hydrolyzed to a mixture of 2-methylcyclohexanone and 2,6-dimethylcyclohexanone. *Cf.* G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(10) All melting points are corrected and all boiling points are uncorrected The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted ith a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer.

(11) A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960).

(12) Determined in chloroform solution.

nate in 350 ml. of ether was allowed to stand for 6 days. After filtration to remove 130 g. (78.5%) of the crude quaternary salt **13b**, the filtrate was concentrated and allowed to stand 4 weeks. The total yield of the crude quaternary salt **13b** obtained amounted to 160.5 g. (97%), m.p. 120–145°. Fractional crystallization of a portion of the material from methylene chloride–ether mixtures separated the pure lower melting diastereoisomer **13b** as white needles, m.p. 141–142°, infrared[12] 1705 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{18}H_{29}NSO_4$: C, 60.82; H, 8.22; N, 3.94; S, 9.00. Found: C, 60.88; H, 8.28; N, 3.83; S, 9.12.

A partially purified sample of the higher melting diastereoisomer **13b** was obtained as white prisms, m.p. 178–180°, infrared 1710 cm.$^{-1}$ (C=O) [Found: C, 59.30; H, 8.32; N, 3.66; S, 8.86]. Reaction of either the crude methiodide **13a** or the crude metho-*p*-toluenesulfonate **13b** with diethyl malonate and sodium ethoxide as previously described[3a] afforded mixtures of keto esters boiling within the range 78–142° (0.2–0.4 mm.), $n^{25}D$ 1.4519–1.4672, infrared[12] 1700–1740 cm.$^{-1}$ (broad, ester and ketone C=O). After a 25.70-g. fraction of the mixture had been hydrolyzed and decarboxylated by refluxing with 300 ml. of 20% aqueous hydrochloric acid for 21 hr., appropriate manipulations separated 15.83 g. of a mixture of propionic acids **11a** and **12a** as a viscous yellow oil. A solution of this crude acid mixture in an ether–petroleum ether mixture deposited 7.93 g. of the pure *cis* acid **11a** as white prisms, m.p. 72–73° [lit. 70°,[3a] 71°,[13] 73–74°[14]], infrared[15] 2600–3200 cm.$^{-1}$ (broad, carboxyl assoc. O—H), 1710 cm.$^{-1}$ (carboxyl and ketone C=O), ultraviolet[16] maximum 282 mμ (ε 25) with ε 86 at 210 mμ. After a 500-mg. sample (2.7 mmoles) of the crystalline *cis* keto acid **11a** had been treated with an excess of ethereal diazomethane, the ethereal solution was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated. Distillation of the residue in a short-path still afforded 410 mg. (76%) of the methyl ester **11b** as a colorless liquid, b.p. 70–80° (0.005 mm.), $n^{25}D$ 1.4604, infrared[15] 1737 cm.$^{-1}$ (ester C=O) and 1710 cm.$^{-1}$ (ketone C=O), ultraviolet[16] maximum 285 mμ (ε 23) with ε 98 at 210 mμ, n.m.r.[15] singlet at 6.42 τ (3*H*, O—CH_3) and doublet (J = 7 c.p.s.) centered at 9.04 τ (3*H*, CH_3—CH<) . The material exhibits a single peak on gas chromatography[17] and a single spot on thin-layer chromatography.[18]

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.86; H, 9.01.

An 825-mg. sample (4.5 moles) of the oily keto acid mixture **11a** and **12a** left after partial separation of the crystalline keto acid **11a** was esterified with diazomethane as previously described. The resulting ester mixture **11b** and **12b**, 711 mg. (80%), b.p. 70–80° (0.5 mm.), $n^{25}D$ 1.4601, was not resolved by gas chromatography[17] but was resolved by thin-layer chromatography indicating the presence of approximately equal amounts of **11b** and **12b**. This conclusion is substantiated by the subsequently described reduction of this mixture of keto acids **11a** and **12a** with sodium borohydride. The infrared spectrum[15] of this mixture was similar but not identical with the spectrum of the pure ester **11b**. Our efforts to obtain a pure sample of either the *trans* acid **12a** or the *trans* ester **12b** were unsuccessful.

β-(1-Methyl-2-oxocyclohexyl)propionic Acid Derivatives 9.—To a solution of 40.0 g. (0.356 mole) of 2-methylcyclohexanone and the potassium *t*-butoxide, prepared from 1.16 g. (0.0207 g.-atom) of potassium, in 300 ml. of *t*-butyl alcohol was added, dropwise and with stirring under nitrogen at room temperature, 25.6 g. (0.297 mole) of methyl acrylate. During the addition, which required 30 min. the reaction mixture was kept at 30° by the intermittent use of a cooling bath. The resulting mixture was stirred for 3 hr., diluted with 2 *N* aqueous sulfuric acid, and extracted with ether. The ethereal solution was washed with aqueous sodium chloride, dried, and concentrated. Distillation of the residue afforded 33.61 g. (57%) of the crude keto ester **9b** b.p. 99–107° (0.8 mm.), $n^{25}D$ 1.4805, which was shown by gas chromatography[17] to contain no appreciable quantity of the esters **11b** and **12b**. However, the thin-layer chromatogram[18] indicated the presence of an appreciable quantity of a second component and the infrared spectum[15] of this crude product, with absorption in the 6-μ region at 1755 cm.$^{-1}$ (shoulder, enol ester C=O), 1740 cm.$^{-1}$ (ester C=O), 1705 cm.$^{-1}$ (ketone C=O), and 1675 cm.$^{-1}$ (C=C), suggests that the contaminant is the enol lactone **15**. A 32.75-g. portion of this material was stirred with 400 ml. of refluxing 20% aqueous hydrochloric acid. After the resulting mixture had been concentrated under reduced pressure, saturated with ammonium sulfate, and extracted with ether, the acidic product was extracted from the ethereal solution with aqueous sodium bicarbonate and then recovered in the usual way. Distillation of the crude acid in a short-path still afforded 27.4 g. (90%) of the crude keto acid **9a** as a colorless liquid, b.p. 140° (0.1 mm.), which crystallized on standing, m.p. 40–45°. Recrystallization from ether–petroleum ether mixtures separated 20.8 g. (68.5%) of the pure keto acid **9a** as white plates, m.p. 46–48° [lit. 48°,[3a] 49–50°[6b]], infrared[15] 2600–3200 cm.$^{-1}$ (broad, carboxyl assoc. O—H), and 1710 cm.$^{-1}$ (carboxyl and ketone C=O). A 1.00-g. sample (5.4 mmoles) of this keto acid was treated with ethereal diazomethane as previously described to yield 960 mg. (89%) of the keto ester **9b** as a colorless liquid, b.p. 85–90° (0.2 mm.), $n^{25}D$ 1.4661, infrared[16] 1740 cm.$^{-1}$ (ester C=O) and 1705 cm.$^{-1}$ (ketone C=O), ultraviolet[16] maximum at 292 mμ, (ε 29) with ε 88 at 210 mμ, n.m.r. singlet at 6.42 τ (3*H*, OCH_3) and singlet at 8.98 τ (3*H*, CH_3—C—). The material exhibits a single gas chromatographic[17] peak and a single spot on thin layer chromatography.[18]

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.25.

Samples (100 mg. or 0.5 mmole) of each of the esters **9b** and **11b** in solutions of potassium *t*-butoxide, prepared from 10 mg. (0.26 mg.-atom) of potassium and 10 ml. of *t*-butyl alcohol, were allowed to stand at room temperature for 3 hr. Neither of the recovered esters **9b** (70% recovery) or **11b** (63% recovery) contained[17,18] the other isomer, indicating that **9b** and **11b** are not interconverted under these conditions.

Reaction of the Enamine 10 with Methyl Acrylate.—The enamine **10**, prepared as previously described,[19] was obtained as a colorless liquid, b.p. 93–94° (2 mm.), $n^{25}D$ 1.5132 [lit.[19] b.p. 91–92° (5 mm.), $n^{20}D$ 1.5145]. The n.m.r. spectrum of the material (as a pure liquid) indicated the presence of 85% of the disubstituted isomer and 15% of the trisubstituted isomer as judged from integration of the triplet (J = 4 c.p.s.) centered at 5.79 τ (85% of 1*H* >C=CH—) and the doublet (J = 7 c.p.s.) centered at 8.93 τ (85% of 3*H*, CH_3—CH<). A singlet at 8.26 τ (CH_3—C=C—) is readily discernible but interference by other peaks prevents an accurate integration of this peak. A solution of 15.0 g. (0.091 mole) of the enamine **10** and 15.7 g. (0.182 mole) of methyl acrylate in 40 ml. of dioxane was refluxed under nitrogen for 66 hr. and then diluted with 8 ml. of water and refluxed for an additional 45 min. The resulting mixture was concentrated under reduced pressure and then diluted with ether and washed successively with dilute, aqueous hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride. After the resulting ethereal solution had been dried and concentrated, distillation of the residue separated 11.86 g. (66%) of a mixture of keto esters as a colorless oil, b.p. 143–145° (10 mm.), $n^{25}D$ 1.4632, which contains[17] 49% of the keto ester **9b** and 51% of the keto ester **11b** (and presumably **12b**).[20] Each of these components was collected from the gas chromatograph[17] and identified both by retention times and by comparison of the infrared spectrum of the collected sample with the spectra of previously described samples.

Reduction of the Keto Acid 9a.—To a solution of the sodium salt derived from 10.0 g. (0.0543 mole) of the keto acid **9a** in 100 ml. of water was added 765 mg. (20.2 mmoles) of sodium borohydride and the resulting solution was stirred for 19 hr. at room temperature. The resulting solution was acidified by the addition of excess hydrochloric acid and then stirred for 15 min., saturated with sodium chloride, and extracted with ether. After removal of the acidic components (0.64 g.) from the ethereal solution, the remaining ether solution was dried and concentrated. Distilla-

(13) N. N. Chatterjee and A. Bose, *J. Indian Chem. Soc.*, **18**, 196 (1941).

(14) H. Aebli and C. A. Grob, *Helv. Chim. Acta*, **40**, 2185 (1957).

(15) Determined in carbon tetrachloride solution.

(16) Determined in 95% ethanol solution.

(17) A column packed with Dow Corning silicone fluid no. 550 on ground firebrick was employed.

(18) A silica gel coating was employed.

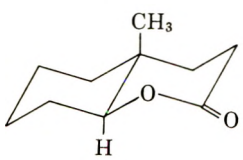
(19) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

(20) Although the presence of small amounts of the *trans* keto ester **12b** in this mixture is very probable, we have no rigorous evidence establishing its presence since esters **11b** and **12b** were not resolved by the gas chromatography columns used and esters **9b** and **12b** were not resolved by thin-layer chromatography.

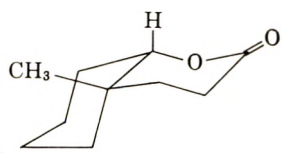
tion of the crude, neutral residue (8.26 g.) afforded 7.49 g. (82%) of a mixture of the *cis* and *trans* lactones **14** as a colorless liquid, b.p. 102–104° (0.8 mm.), $n^{25}D$ 1.4916, infrared[15] 1740 cm.$^{-1}$ (δ-lactone C=O), ultraviolet[16] absorption ε 65 at 210 mμ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.59.

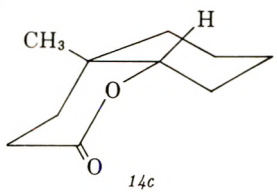
The n.m.r. spectrum[15] of the material has a broad peak centered at approximately 4.0 τ (1*H*, >C(H)–O–) and two peaks at 8.95 τ and 9.05 τ with a total area equivalent to three protons and relative areas of approximately 65% and 35%, respectively. The gas chromatograph of the lactone mixture exhibits two partially resolved peaks corresponding approximately to a 60%–40% mixture. Thus the n.m.r. peaks at 8.95 and 9.05 τ correspond to the grouping CH_3—C— in the two diastereoisomeric lactones **14**. Since the change in n.m.r. absorption for the two isomers is found in the methyl peak and not in the peak attributable to the carbinol proton,[21] conformations **14a** and **14b**, both containing axial tertiary hydrogen atoms but containing, respectively, axial and equatorial methyl groups, become most probable for the *trans* and *cis* lactones **14**. Assuming that the correlation[22] derived for angular methyl groups in the decalin system will also be applicable to the lactones **14**, we have tentatively assigned the *cis* stereochemistry **14b** (or **14c**) to the lactone isomer comprising 60–65% of the lactone mixture. The n.m.r. peak attributable to the angular methyl group in this isomer (at 8.95 τ) is at 0.10 τ lower field than the corresponding peak in the other isomer.



14a



14b

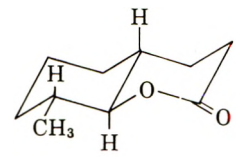


14c

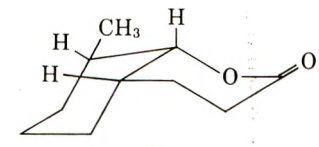
Reduction of the Keto Acid 11a.—A solution of the sodium salt derived from 7.50 g. (0.041 mole) of the keto acid **11a** and 580 mg. (0.0153 mole) of sodium borohydride in 75 ml. of water was stirred for 18 hr. at room temperature and then the mixture was worked up as previously described. The mixture of lactones **2** was collected as a colorless liquid, b.p. 87° (0.3 mm.), $n^{25}D$ 1.4855, yield 5.51 g. (80.5%). Redistillation through a 30-cm. Holtzman column gave an analytical sample, b.p. 110–111° (3 mm.), $n^{25}D$ 1.4825, infrared[15] 1735 cm.$^{-1}$ (δ-lactone C=O), ultraviolet[16] absorption ε 65 at 210 mμ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39, H, 9.59. Found: C, 71.27; H, 9.58.

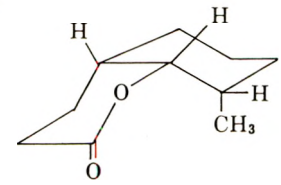
Although the gas chromatograph[17] of the product exhibits a single peak, the n.m.r. spectrum[15] is only consistent with the presence of both the *cis* (**2b**, **2c**) and *trans* (**2a**) lactones. Thus, in the region characteristic of the grouping >C(H)–O, are found a peak (half-band width 4 c.p.s.) at 5.80 τ and triplet ($J \sim 7$ c.p.s.) centered at 6.58 τ which together correspond in area to one proton. In addition two peaks (or more, splitting pattern not discernible), together attributable to the three protons of the methyl group, are found at 8.91 and 9.00 τ. The relative areas of the 5.80 peak–6.58 peak and the 8.91 peak–9.00 peak are 1 to 2. Of the two peaks attributable to the >C(H)–O grouping, the broad peak at higher field (6.58 τ) may be safely assigned to the axial proton[21] in the *trans* isomer **2a** which is *trans* and coplanar to two adjacent C—H bonds.[22] Thus, the major product (60–70% of the lactone mixture) is the *trans* isomer **2a**.



2a



2b



2c

Reduction of a 728-mg. sample of the oily mixture of the keto acids **11a** and **12a** remaining after partial separation of the pure acid **11a** by the previously described procedure yielded 434 mg. of a lactone mixture, b.p. 50–60° (0.05 mm.), $n^{25}D$ 1.4870, which exhibits two gas chromatographic peaks corresponding to the lactones **2** (first peak eluted) and a second lactone component.

Acid-catalyzed cyclization of the Lactone 2.—To 12 g. of polyphosphoric acid heated to 78 ± 2° was added, dropwise and with stirring over a 15-min. period, 1.00 g. (5.9 mmoles) of the lactone **2**. After the addition was complete, the solution was stirred for 3 hr. at 78 ± 2° and then cooled and diluted with ice water. The resulting mixture was extracted with ether and the extract was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated. Distillation of the residue in a short-path still afforded 500 mg. of a pale yellow liquid, b.p. 60–80° (0.15 mm.), containing,[17] in order of elution, the tetrahydroindanones **1** (21%), **3** (22%), and **4** (27%) as well as the starting lactone **2** (30%). A collected sample of the unsaturated ketone **3** was shown to be identical with the previously described sample[23] by comparison of retention times and the infrared, ultraviolet, and mass spectra of the two samples. A solution of 400 mg. of the mixture in 15 ml. of ether was stirred with 3.5 ml. of 10% aqueous sodium hydroxide for 1 hr. to remove the lactone **2**. After the resulting ether solution had been washed with aqueous sodium chloride, dried, and concentrated, distillation of the residue afforded 210 mg. of a mixture of the ketones **1**, **3**, and **4**, b.p. 60–70° (0.15 mm.), from which larger samples of ketones **1** and **4** were collected.[17]

After collection and distillation, the ketone **1** was obtained as a colorless liquid with infrared peaks[15] of approximately equal intensity[24] at 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1640 cm.$^{-1}$ (conj. C=C) and ultraviolet maxima[16] at 256 mμ (ε (10,400) and 330 mμ (ε 98). The n.m.r. spectrum[25] (60 Mc.) has broad complex absorption in the region 7.5 to 8.5 τ but no peaks attributable either to a vinyl hydrogen atom or to a methyl group bonded to a saturated carbon atom.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 79.71; H, 9.57; mol. wt., 150 (mass spectrum).

Collection[17] and subsequent short-path distillation separated the ketone **4** as a colorless liquid with infrared absorption[15] at 1695 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1640 cm.$^{-1}$ (conj. C=C, less intense than 1695 peak[24]) and an ultraviolet maximum at 237 mμ (ε 13,300). The n.m.r. spectrum[25] has a doublet (J = 6 c.p.s.) centered at 8.97 τ (3*H*, CH_3—CH<) and a peak at 7.58 τ (4*H*, CH_2 adjacent to C=O and CH_2 adjacent to C=C in 5-membered ring) but no peak attributable to a vinyl hydrogen atom.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 79.59, H, 9.40; mol. wt., 150 (mass spectrum).

A mixture of 90 mg. (0.6 mmole) of the ketone **4**, 25 mg. of a 30% palladium-on-carbon catalyst, and 1 ml. of *p*-cymene was refluxed under nitrogen for 66 hr. and then filtered and chromatographed on 40 g. of Woelm activity II alumina. The indanone **5**, eluted with benzene–ether mixtures, amounted to 40.6 mg. (46.5%) of white crystals, m.p. 62–65°. Recrystallization from petroleum ether afforded 23 mg. (26%) of the pure indanone **5** as

(21) An equatorial proton of this type would be expected to occur at 0.5 to 0.8 p.p.m. lower field than an axial proton. For examples and leading references see E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, No. **3**, 97 (1962).

(22) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).

(23) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).

(24) The similar intensities of these two peaks is in accord with the presence of a *cisoid* α,β-unsaturated ketone system. R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(25) Determined as a solution in deuteriochloroform.

white needles, m.p. 69–70°, which was shown to be identical with the subsequently described material by a mixed melting-point determination and by comparison of infrared and ultraviolet spectra.

5-Methylindanone (5).—β-(*m*-Tolyl)propionic acid (6), m.p. 40.5–41.5° (lit.[4b] 42–43°), was prepared from *m*-bromotoluene *via* *m*-tolualdehyde[26] and *m*-methylcinnamic acid,[27] m.p. 115–116° (lit. 111.5°,[4b] 113–114°[27b]), as previously described. To 10 g. of polyphosphoric acid heated to 78 ± 2° was added, portionwise and with stirring over a 20-min. period, 718 mg. (4.36 mmoles) of the acid 6. After the addition, the mixture was stirred at 78 ± 2° for 4.5 hr. and then cooled and diluted with ice water. The crude product, extracted with ether, was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated to leave 616 mg. (96.5%) of crude product as a yellow oil which crystallized on standing, m.p. 31–43°.[28] The thin-layer chromatogram[18] of the crude product indicated the presence of approximately equal amounts of two components, one of which has the same R_f value as 7-methylindanone (7). A 598-mg. sample of the crude product was chromatographed on 75 g. of silica gel to separate 272 mg. (43.5%) of crude 7-methylindanone (7) (eluted with 4:1 petroleum ether–ether), m.p. 51–53°, and 319 mg. (51.5%) of crude 5-methylindanone (6) (eluted with 1:1 petroleum ether–ether), m.p. 67–69°. Recrystallization from petroleum ether followed by sublimation afforded 144 mg. of pure 7-methylindanone (7) as white needles, m.p. 52.5–53.5°, identified with a previously described sample[23] by a mixed melting-point determination and comparison of infrared spectra.

Recrystallization from petroleum ether separated 229 mg. of the pure 5-methylindanone (6) as white needles, m.p. 69–70°, infrared absorption[15] at 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring), ultraviolet maxima[16] at 253 mμ (ε 15,500), 287 mμ (ε 3520), and 294 mμ (ε 3630). The sample has n.m.r. peaks[25] (60 Mc.) at 7.58 τ (3*H*, singlet, CH_3-), 7.2 to 7.5 τ (2*H*, multiplet) and 6.8 to 7.1 τ (2H multiplet), as well as peaks in the region 2.3 to 2.9 τ (3*H*, aromatic C–H).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90; mol. wt., 146. Found: C, 82.37; H, 6.95; mol. wt., 146 (mass spectrum).

(26) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

(27) The Doebner modification of the Knoevenagel reaction was employed. (a) J. R. Johnson, *Org. Reactions*, **1**, 248 (1942); (b) P. N. Agarval, K. C. Pandya and I. L. Tripath, *Proc. Indian Acad. Sci.*, **22A**, 400 (1945).

(28) The supposedly pure 5-methylindanone previously prepared by this method (ref. 4) was reported to melt at 59–60°[4a] and at 59°.[4b]

Indole Alkaloids. I. Base-catalyzed Condensations with Yohimbanones and Alloyohimbanones[1]

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Base-catalyzed condensations of yohimban-17-one (1) with magnesium methyl carbonate, ethyl formate, and ethyl oxalate afforded 17-oxoyohimban-18-carboxylic acid (2), 18-hydroxymethyleneyohimban-17-one (11), and ethyl 17-oxoyohimban-18-glyoxylate (24), respectively. Esterification of β-keto acid 2 gave methyl 17-oxoyohimban-18α-carboxylate (3) [isomeric with yohimbinone (6)] which on reduction with sodium borohydride afforded 17α-hydroxy ester 4 and 17β-hydroxy ester 5. Neither 4 nor 5 corresponded to yohimbine (7) or β-yohimbine (8), the known C-16 isomers. Treatment of 18-hydroxymethylene ketone 11 with hydroxylamine gave two isomeric isoxazoles 12 and 13. On conversion with base of isoxazole 12 to 17-oxo-18α-carbonitrile 14 and reduction of 14 with sodium borohydride, 17α-hydroxynitrile 15 and 17β-hydroxynitrile 16 were obtained. Hydrolysis of 15 followed by esterification afforded 17α-hydroxy ester 4. Similarly, 16 was converted to 17β-hydroxy ester 5. Collidine treatment of the *O*-tosylate of 17α-hydroxy ester 4 gave α,β-unsaturated ester 18, isomeric with apoyohimbine (17). These results show that carboxylation and formylation of yohimban-17-one occurred at the C-18 position. P.m.r. spectral measurements were used to confirm assignments of structure and configuration.

The chemistry of alkaloids of the β-carboline type has been studied extensively in recent years. Reserpine, one of the more complex members of this group, has been of special interest because of its stereochemical complexity and its pharmacological properties. Reserpine has substituents at positions 16, 17 and 18 in the E ring while most of the other structurally related alkaloids lack substituents at position 18. Since the C-18 trimethoxybenzoyloxy substituent of reserpine has an important influence on its pharmacological properties,[2] and since there is little known about C-18 substituted derivatives of yohimbine or its stereoisomers,[3] we became interested in a study of the introduction of activating groups, such as carboxyl and ethoxalyl, into several yohimbanes containing a keto group in the E ring. Such activating groups were considered an essential prerequisite for the selective introduction of other functional groups (*i.e.*, bromine, methyl, etc.) into the E ring.

A number of suitable E ring ketones have been prepared by transformations of known alkaloids[4] or by total synthesis.[5] However, few reactions have been reported in which these ketones have been utilized for the introduction of functional groups into the E ring. Russian workers have reported the introduction of ethoxycarbonyl[6] and formyl[7] groups at the C-16 position of yohimban-17-one (1); however, the reliability

(1) A portion of this work was presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961.

(2) R. A. Lucas, M. E. Kuehne, M. J. Ceglowski, R. L. Dziemian, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959); M. M. Robison, R. A. Lucas, H. B. MacPhillamy, W. Barrett, and A. J. Plummer, *Experientia*, **17**, 14 (1961).

(3) Oxygenation at the C-18 position of certain derivatives has been reported using microbiological techniques: S. C. Pan and F. L. Weisenborn, *J. Am. Chem. Soc.*, **80**, 4749 (1958); W. O. Godtfredsen, Y. Korsby, H. Loreck, and S. Vangedal, *Experientia*, **14**, 88 (1958).

(4) (a) B. Witkop, *Ann.*, **554**, 83 (1943); (b) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949); (c) Z. J. Vjdělek and K. Macek, *Collection Czech. Chem. Commun.*, **24**, 2493 (1959); (d) A. Le Hir and E. W. Warnhoff, *Compt. rend.*, **246**, 1564 (1958); (e) S. Kimoto, M. Okamoto, and H. Kondo, *Chem. Pharm. Bull.* (Tokyo), **7**, 650 (1959); (f) A. Le Hir, M.-M. Janot, and R. Goutarel, *Bull. soc. chim.* France, 1027 (1953); (g) R. K. Hill and K. Muench, *J. Org. Chem.*, **22**, 1276 (1957); (h) E. Wenkert, E. W. Robb, and N. V. Bringi, *J. Am. Chem. Soc.*, **79**, 6570 (1957); (i) C. F. Huebner, A. F. St. André, E. Schlittler, and A. Uffer, *ibid.*, **77**, 5725 (1955); (j) R. C. Elderfield, A. E. Hydorn, E. Schenker, and K. K. Wyckoff, *J. Org. Chem.*, **24**, 1296 (1959).

(5) (a) G. A. Swan, *J. Chem. Soc.*, 1534 (1950); (b) P. G. Philpott and A. M. Parsons, *ibid.*, 3018 (1958); (c) G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).

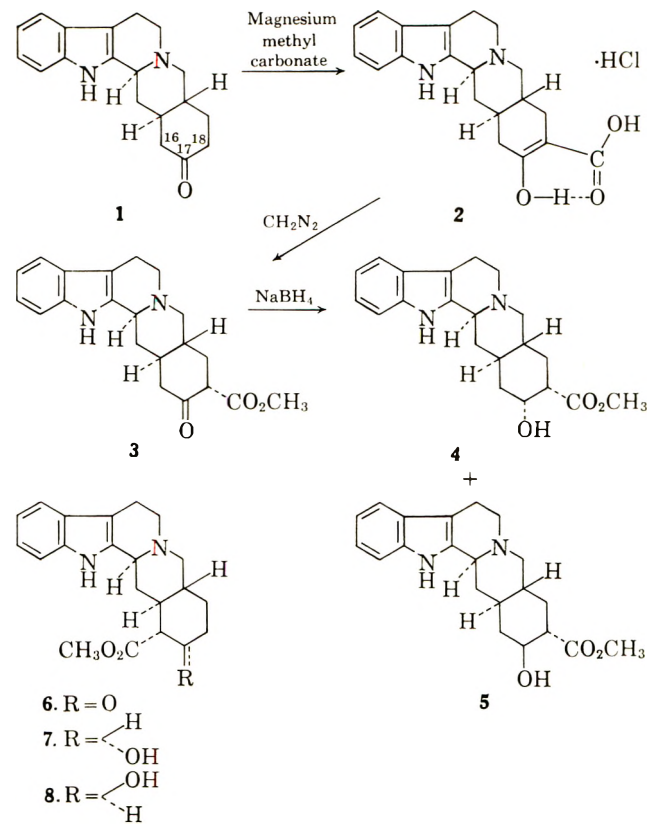
(6) L. A. Aksanova and N. A. Preobrazhenskiĭ, *Dokl. Akad. Nauk SSSR*, **117**, 81 (1957).

(7) G. S. Gusakova and N. A. Preobrazhenskiĭ, *ibid.*, **101**, 1061 (1955).

of this work has been questioned.[8,9] By analogy to results obtained with 3-keto-5α-steroids substitution at C-18 is expected, for it has been amply demonstrated that these steroids give 2-substituted derivatives in reactions (brominations, formylations, ethoxalylations) involving intermediate enol or enolate ion formation.[10] In order to ascertain the position of substitution we studied the ethoxalylation, carboxylation and formylation of yohimban-17-one.[9]

Treatment of ketone **1** with magnesium methyl carbonate (MMC)[11,12] in *N,N*-dimethylformamide, followed by hydrolysis with cold hydrochloric acid, afforded a good yield of a β-keto acid which, on the basis of its subsequent transformations, was shown to be 17-oxoyohimban-18-carboxylic acid hydrochloride (**2**). The β-keto acid was assigned the enolized chelate structure **2** on the basis of its infrared spectrum [ν_{max}^{Nujol} 1658 (s), 1619 cm.$^{-1}$ (m)]. Upon warming an aqueous solution, decarboxylation to yohimban-17-one (92%) readily occurred. On treatment with diazomethane (or *N,N'*-dicyclohexylcarbodimide and methanol[13]) methyl 17-oxoyohimban-18α-carboxylate (**3**) was formed. The infrared spectrum showed the presence of both keto and enol forms for **3** and the ultraviolet spectrum in base showed increased absorption at 289 mμ (ϵ 20,200), as anticipated for a β-keto ester which readily forms an enolate ion. Since enolization provides a convenient pathway for equilibration of the methoxycarbonyl group the more stable equatorial α-configuration was assigned. The equatorial conformation of the methoxycarbonyl group was demonstrated by the absence of change on equilibration of the ester with base. The physical properties of **3** were clearly different from those of the known non-enolic methyl 17-oxoyohimban-16α-carboxylate (**6**) (yohimbinone)[4d,e,14,15] which has an equatorial methoxycarbonyl group. The non-identity of **3** and **6** showed that substitution had indeed occurred at the C-18 position. Further proof for the position of substitution was obtained by reduction of **3** with sodium borohydride to give two epimeric 17-hydroxy esters **4** and **5**. Neither **4** nor **5** corresponded to the known C-16 isomers, yohimbine (**7**) and β-yohimbine (**8**).

The epimer **4**, m.p. 210–214° dec., was the first epimer eluted from an alumina column and was considered to have an axial C-17 hydroxyl group since axial alcohols are generally adsorbed less strongly on alumina



than equatorial alcohols. The second epimer, m.p. 142–147°, eluted from the column was assigned structure **5** with an equatorial C-17 hydroxyl group.

The p.m.r. spectra[16] (see Table I) of epimeric hydroxy esters **4** and **5**, as well as their *O*-acetates, confirmed the assignments of structure and configuration. In agreement with the general observation[17] that axial proton signals are shifted to higher field than equatorial, the equatorial C-17 proton signal of yohimbine (**7**) was observed at 5.82 τ whereas the axial C-17 proton signal of β-yohimbine (**8**) was shifted to higher field and was obscured by the methoxycarbonyl signal, thus giving a four-proton intensity peak centered at 6.27 τ. On tosylation of β-yohimbine the C-17 proton signal was shifted downfield and observed at 5.17 τ while the C-17 proton signal of yohimbine *O*-tosylate was observed at 4.78 τ. The equatorial C-17 proton signals of pseudoyohimbine and corynanthine were observed at 5.97 τ and 6.02 τ, respectively, whereas the axial C-17 proton signal of α-yohimbine (**10**) was overlapped by the methoxycarbonyl signal at 6.27 τ (four-proton intensity peak). The doublets at 5.12–5.67 τ observed in the spectra of these compounds (see Table I) measured in deuterodimethyl sulfoxide were assigned to the hydroxyl proton spin-coupled to the adjacent C-17 proton since, on addition of deuteriomethanol to solutions of yohimbine and β-yohimbine, the signals at 5.38 τ and 5.15 τ, respectively, disappeared. When dissolved in deuteriochloroform the hydroxyl signal

(8) J. E. Saxton, *Ann. Rept. Progr. Chem. (Chem. Soc. London)*, **55**, 306 (1958).

(9) After the completion of this work a report on the introduction of formyl and methoxycarbonyl groups at the C-18 position of yohimban-17-one was brought to our attention: P. D. Pacht, Ph.D. thesis, Harvard University, 1960.

(10) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959); N. A. Nelson and R. N. Schut, *ibid.*, **80**, 6630 (1958), and references contained therein.

(11) (a) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959); (b) M. Stiles, *ibid.*, **81**, 2598 (1959).

(12) The experimental details for the preparation of the reagent, MMC, were kindly supplied by Professor M. Stiles (University of Michigan).

(13) For similar esterifications with *N,N'*-dicyclohexylcarbodiimide and alcohols see L. Peyron, *Bull. soc. chim.* France, 613 (1960) and A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 2071 (1960).

(14) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959), have ascribed the non-enolic properties of yohimbinone (**6**) to the steric interactions (*peri* effect) of the C-14 hydrogen atoms and the methoxycarbonyl group in the hydrogen-bonded enol.

(15) (a) Prepared according to experimental conditions kindly supplied by Professors A. Le Hir and R. Goutarel (University of Paris) prior to publication; (b) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. soc. chim.* France, 637 (1961).

(16) P.m.r. spectra were determined with a Varian Model A-60 spectrometer in deuterated dimethyl sulfoxide. This solvent was chosen for all measurements since compounds **4**, **5**, **15**, and **16** were insufficiently soluble in deuteriochloroform. τ Values were obtained in the usual manner with tetramethylsilane as internal standard.

(17) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958); E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, No. **3**, 97 (1962); E. L. Eliel, M. H. Gianni, and Th. H. Williams, *ibid.*, No. **17**, 741 (1962).

TABLE I

PROTON MAGNETIC RESONANCE SPECTRAL MEASUREMENTS[16]

	C-17 Hydroxyl doublet (τ)	C-17 proton		Methyl singlets (τ)		
		Multiplet (τ)	Conformation[a]	CO_2CH_3	CH_3OH solvate	$OCOCH_3$
Pseudoyohimbine	5.67[b,c]	5.97	e	6.33		
Corynanthine[d]	5.12	6.02	e	6.47		
Yohimbine (**7**)	5.38[e]	5.82	e	6.27		
Yohimbine in $CDCl_3$[f]		5.68	e	6.10		
β-Yohimbine (**8**)	5.15[e]	6.27[g]	a	6.27[g]		
α-Yohimbine (**10**)	5.42	6.27[g]	a	6.27[g]		
Yohimbine *O*-tosylate		4.78	e	6.40		
β-Yohimbine *O*-tosylate		5.17[h]	a	6.35		
17α-Hydroxy ester **4**	5.37[e]	5.75	e	6.40	6.60	
17β-Hydroxy ester **5**	5.15[e]	6.38[g]	a	6.38[g]		
17α-Hydroxynitrile **15**	4.68	5.95	e			
17β-Hydroxynitrile **16**[f]	4.60	6.47[h]	a			
17α-Hydroxy ester *O*-acetate		4.40	e	6.38	6.42	8.05
17β-Hydroxy ester *O*-acetate		5.05[h]	a	6.38		8.05

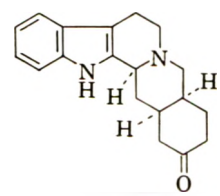
[a] a = axial, e = equatorial. [b] Multiplet of intensity equivalent to two protons; includes signal of equatorial C-3 proton. [c] After addition of CD_3OD the hydroxyl signal disappeared leaving a one-proton multiplet from the equatorial C-3 proton. [d] Measured in dimethyl sulfoxide. [e] After addition of CD_3OD this signal disappeared. [f] Determined with a Varian Model V-4300-B spectrometer operated at 56.4 Mc. [g] Axial C-17 proton signal coincident with methoxycarbonyl signal—total intensity equivalent to four protons. [h] Broad, as anticipated for an axial proton coupled with two axial and one equatorial protons.

of yohimbine was not observed. Pseudoyohimbine exhibited a two-proton multiplet centered at 5.67 τ from the coincidence of signals from the equatorial C-3 proton and the C-17 hydroxyl. On addition of deuteriomethanol the hydroxyl signal disappeared leaving a one-proton multiplet with unchanged chemical shift (equatorial C-3 proton).[18]

Hydroxy ester **4** showed a multiplet centered at 5.75 τ (equatorial C-17 proton) whereas the signal for the axial C-17 proton of hydroxy ester **5** was shifted to higher field and coincided with the methoxycarbonyl signal to produce a four-proton peak at 6.38 τ. The doublets at 5.37 τ and 5.15 τ from the hydroxyls of **4** and **5**, respectively, disappeared when the hydroxyl protons were exchanged for deuterium on addition of deuteriomethanol.

These arguments are confirmed and extended by an examination of the respective p.m.r. spectra[16] after acetylation whereupon the anticipated shifts to lower field[17,18] were observed. The *O*-acetate of **4** exhibited a signal from the equatorial C-17 proton as a multiplet centered at 4.40 τ and the *O*-acetate of **5** exhibited a signal centered at 5.05 τ from the axial C-17 proton as a broad multiplet, as anticipated for an axial proton coupled with two axial and one equatorial protons.

Carboxylation experiments with alloyohimban-17-one[4f] (**9**) using magnesium methyl carbonate were not encouraging since the isolated β-keto acid hydrochloride appeared to be unstable. Esterification with diazomethane followed by reduction with sodium borohydride gave a mixture of products which, after chromatography on alumina, afforded alloyohimban-17α-ol and a hydroxy ester fraction. The hydroxy ester fraction was a mixture of five components as shown by paper chromatography.[4c] One component had an R_f identical with that of α-yohimbine[4f,19] (**10**), suggesting that condensation occurred to some extent at C-16. Two other components had R_f's corresponding with alloyohimban-17-one and alloyohimban-17α-ol, leaving the remaining two components



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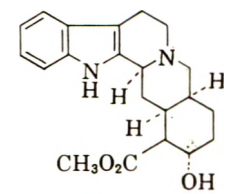

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unidentified. Carboxylation at C-18, therefore, has not been excluded. Analogies based on studies of 3-keto-5β-steroids are of little help since substitutions at C-4 and C-2 have been reported in reactions involving intermediate enol formation.[20] More definitive experiments are in progress to determine the exact nature of the substitution products.

We next directed our attention to the formylation of yohimban-17-one (**1**), where substitution at C-16 has been reported.[7] When **1** was treated with ethyl formate and sodium methoxide in either benzene or dioxane, a formylation product was obtained in 70–90% yields whose chemical properties indicated that it was 18-hydroxymethyleneyohimban-17-one (**11**) rather than the C-16 substitution product reported by the Russian workers.[7] The hydroxymethylene ketone **11** was treated with hydroxylamine hydrochloride in acetic acid to give a mixture of yohimbano[18,17*d*]isoxazole (**12**) and yohimbano[17,18*c*]-isoxazole (**13**). Treatment of the mixture with sodium methoxide in methanol at room temperature, or heating with sodium ethoxide in ethanol, afforded ketonitrile **14**,[21] along with unchanged isoxazole **13**. Conversion of hydroxymethylene ketone **11** directly to ketonitrile **14** with *O*,*N*-bis(trifluoroacetyl)hydroxylamine[22] gave a poor yield. The cyano group in **14**

(18) W. E. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961).

(19) A. Le Hir, R. Goutarel, and M.-M. Janot, *Ann. Pharm. Franc.*, **11**, 546 (1953).

(20) H. H. Inhoffen, G. Kölling, G. Koch, and I. Nebel, *Chem. Ber.*, **84**, 361 (1951); R. O. Clinton, R. L. Clark, F. W. Stoner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. Ind.* (London), 2099 (1961).

(21) For similar preparations of α-ketonitriles see K. v. Auwers, T. Bahr, and E. Frese, *Ann.*, **441**, 54 (1925); W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Am. Chem. Soc.*, **69**, 2942 (1947); G. V. Bhide, N. L. Tikotkar, and D. D. Tilak, *Tetrahedron*, **10**, 230 (1960), and references cited therein.

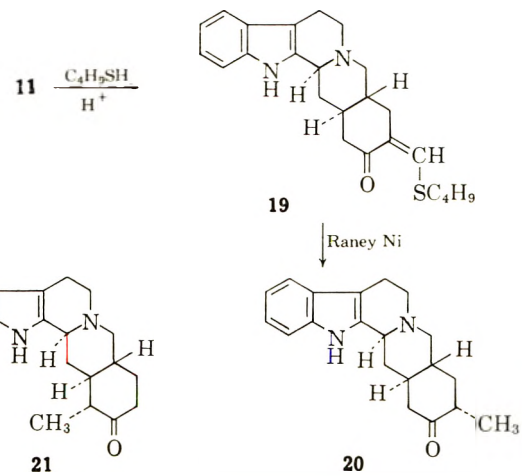
(22) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959); H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

was assigned the equatorial α-configuration by virtue of its method of preparation, for the basic reaction conditions assure equilibration of the nitrile group to the more stable α-configuration.

Reduction of ketonitrile **14** with sodium borohydride and chromatography of the product over alumina afforded two epimeric 17-hydroxynitriles. The epimer, m.p. 263–265° dec., eluted first from the column, was tentatively assigned the structure **15** with an axial hydroxyl group and the second epimer from the column, m.p. 247–250° dec., was assigned the structure **16** with an equatorial hydroxyl group. In the p.m.r. spectra[16] the equatorial C-17 proton multiplet of **15** was observed at 5.95 τ while **16** showed a broad multiplet centered at 6.47 τ. These results support the assigned structures, for the axial C-17 proton signal in **16** is shifted to higher field than the equatorial as expected.[17] Doublets from the hydroxyls were observed at 4.68 τ and 4.60 τ for **15** and **16**, respectively.

Hydrolysis of 17β-hydroxynitrile **16** with sodium hydroxide afforded a crude hydroxy acid which was esterified with diazomethane to a hydroxy ester in 41% over-all yield. The ester was identical with the 17β-hydroxy ester **5** obtained on reduction of methyl 17-oxoyohimban-18α-carboxylate (**3**) (*vide supra*). Hydrolysis of 17α-hydroxynitrile **15**, followed by esterification with diazomethane and chromatography over alumina, gave methyl yohimb-17-ene-18-carboxylate (**18**) (10% yield) and a hydroxy ester (12% yield) identical with the 17α-hydroxy ester **4** obtained on reduction of the keto ester **3**. Elimination during hydrolysis of 17α-hydroxynitrile **15** with formation of α,β-unsaturated ester **18** provides further support for the axial C-17 hydroxyl group. Collidine treatment of the *O*-tosylate of **4** also afforded the α,β-unsaturated ester **18**, isomeric with apoyohimbine (**17**).[23] In apoyohimbine the aromatic and olefinic protons were found[16] in a multiplet at 2.53–3.63 τ with the extreme high field peak centered at 3.30 τ clearly identified as the C-17 olefinic proton. The C-17 olefinic proton of **15** was found to be obscured by the absorption of the aromatic protons in the multiplet at 2.55–3.22 τ of intensity equivalent to 5 protons (1 olefinic + 4 aromatic). These results establish that the nitrile groups in **15** and **16** are at the C-18 position and, as a consequence, formylation of yohimban-17-one occurred at the C-18 position.

A second proof for the position (C-18) of the formyl group in **11** was obtained by conversion of **11** to 18α-methylyohimban-17-one (**20**), which was clearly different from 16α-methylyohimban-17-one (**21**).[4j,24] The hydroxymethylene ketone **11** was converted to 18-

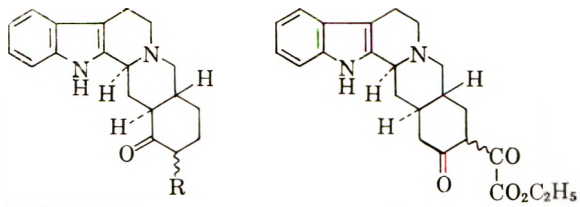


butylthiomethyleneyohimban - 17 - one (**19**) with 1-butanethiol and glacial acetic acid in the presence of anhydrous magnesium sulfate and **19** was reduced with Raney nickel[25] to give the methyl ketone **20** in good yield. Comparison of **20** with a sample of the 16α-methyl-17-ketone **21**, prepared by Oppenauer oxidation of 16-methylyohimbol,[26] served to distinguish the two compounds. Small but distinct differences were observed in the infrared spectra of the two compounds and their X-ray powder diagrams were distinctly different.

Thus base-catalyzed condensations of yohimban-17-one with magnesium methyl carbonate and ethyl formate have occurred at C-18. These results are consistent with previous work on alicyclic ketones.[10]

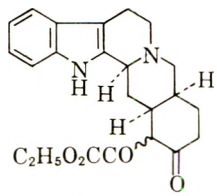
When yohimban-17-one (**1**), yohimban-16-one (**22**)[4g,h] or alloyohimban-17-one (**9**) were treated with ethyl oxalate in the presence of sodium methoxide, the corresponding glyoxylates were obtained. The ethoxalyl product from ketone **1** was assigned the structure ethyl 17-oxoyohimban-18-glyoxylate (**24**) by analogy with the carboxylation results where C-18 substitution was observed. The ability of the glyoxylate from ketone **22** to form an enolate ion in base supports the assigned ethyl 16-oxoyohimban-17-glyoxylate (**23**) structure for

(23) C. Barger and E. Field, *J. Chem. Soc.*, **123**, 1038 (1923).
(24) Z. J. Vejdělek and K. Macek, *Chem. Listy*, **52**, 2140 (1958).
(25) R. E. Ireland and J. A. Marshall, *Chem. Ind.* (London), 1534 (1960).
(26) A sample of 16-methylyohimbol for the preparation of **21** was kindly supplied by Professor R. C. Elderfield, University of Michigan.



22. C = H
23. R = $HRCO_2C_2H_5$

24



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this product. The ethoxalyl derivative from ketone 9 has been tentatively assigned the structure ethyl 17-oxoalloyohimban-16-glyoxylate (**25**). Definitive experiments however are needed to establish that substitution occurred at C-16.

The chemistry of the compounds reported is being studied and their use for the introduction of additional substituents into the E ring is being investigated.

Experimental

Unless otherwise noted all melting points were taken in sealed capillaries which were inserted in the bath at about 10–20° below the melting point. Unless otherwise noted samples were dried for analysis *in vacuo* over phosphorus pentoxide at 100° for 4–8 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin–Elmer spectrophotometer (Model 21).

17-Oxoyohimban-18-carboxylic Acid Hydrochloride (2).—A mixture of 2.0 g. (6.8 mmoles) of yohimban-17-one (1) and 25 ml. of a solution of magnesium methyl carbonate in *N,N*-dimethylformamide (*ca.* 2 *N*) was stirred and heated at 120–130° for 3 hr. under a slow stream of nitrogen. The mixture was cooled in an ice bath and added slowly to a stirred mixture of 50 g. of ice and 30 ml. of concentrated hydrochloric acid which was cooled in an ice–salt bath. The reaction flask was rinsed with a mixture of 2 g. of ice and 1 ml. of concentrated hydrochloric acid. The solid which separated was filtered and washed with 2 ml. of cold 6 *N* hydrochloric acid. After drying in the air for a short period of time and *in vacuo* over phosphorus pentoxide at room temperature for 6 hr., there was obtained 2.71 g. (98%) of **2** as tan crystals, m.p. 292–294° dec. Purification was accomplished by treating 1.91 g. of the crude product with 650 ml. of methanol, filtering through a coarse porosity sintered glass filter (some suspended solid passed through the filter) and diluting the filtrate with 600 ml. of ether. The mixture was cooled and filtered (medium porosity–sintered glass filter) to give 0.860 g. (45%) of white crystals, m.p. 314–317° dec.; ν_{max}^{Nujol} 3520, 3256, 3125, 1658 (s), 1619 (m), 1192 cm.$^{-1}$ (s); $\lambda_{max}^{CH_3OH}$ 221 mμ (ε 42,200), 270 (10,060), 281 (8,830), 289 (6,800). The sample for analysis was dried *in vacuo* over phosphorus pentoxide for 4 hr. at room temperature.

Anal. Calcd. for $C_{20}H_{22}N_2O_3 \cdot HCl \cdot 1/2\ H_2O$: C, 62.6; H, 6.30; N, 7.30; Cl, 9.24; H_2O, 2.34; CO_3, 11.5. Found: C, 62.4; H, 6.65; N, 7.41; Cl, 9.46; H_2O (K.F.), 2.06; CO_2, 10.9.

Methyl 17-Oxoyohimban-18α-carboxylate (3).—To a suspension of 0.500 g. (1.30 mmoles) of keto acid hydrochloride **2** in 50 ml. of ice-cold methanol was added 50 ml. of ice-cold ether containing diazomethane (prepared from 4.0 g. of nitrosomethylurea and 8 ml. of 40% potassium hydroxide and dried over potassium hydroxide pellets). The mixture was allowed to stand at room temperature for 10 min. and the excess diazomethane was decomposed by the dropwise addition of glacial acetic acid. The solvent was removed *in vacuo* to give 0.598 g. of a hygroscopic glass. The glass was dissolved in 15 ml. of methanol and the solution boiled while water was added dropwise until white crystals began to separate. Cooling and filtration gave 0.201 g. (42%) of white crystals, m.p. 186–188° dec. The filtrate was diluted with water to give a second crop of crystals (0.024 g., 5%). The filtrate was extracted with five 10-ml. portions of chloroform and the extracts evaporated *in vacuo* to give a glass. The glass was dissolved in 2 ml. of methanol and the solution diluted with 1 ml. of water. Cooling and filtration afforded 0.102 g. (21%) of crystals, m.p. 181–183° dec. The three crops of crystals (68%) were combined and recrystallized by dissolving in 45 ml. of methanol and diluting the solution with 3 ml. of water. Cooling and filtration gave 0.211 g. (44%) of **3** as white crystals, m.p. 186–188° dec.; $[\alpha]^{25}D$ −157° (*c* 1.00, CH_3OH), − 176° (*c* 1.10, $CHCl_3$); ν_{max}^{KBr} 3510 (w), 3379 (m), 1623 cm.$^{-1}$ (m); $\lambda_{max}^{CH_3OH}$ 225 mμ (ε 39,800), 273 (8,310), 283 (8,200), 290 (6,620); $\lambda_{max}^{0.1\ N\ NaOH}$ 225 mμ (ε 38,200), 282 (20,800), 289 (20,200); violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot 3/4\ H_2O$: C, 68.9; H, 7.02; N, 7.66; H_2O, 3.69. Found: C, 68.7; H, 6.52; N, 7.64; H_2O (K.F.), 4.95.

18-Hydroxymethyleneyohimban-17-one (11).—To a cooled mixture of 10.0 g. of yohimban-17-one (1), 10.0 g. of sodium methoxide (Mathieson), and 300 ml. of sodium–dried benzene was added 14 ml. of ethyl formate. After stirring under nitrogen at room temperature for 20 hr. the mixture was poured onto 300 g. of ice and 200 ml. of water. The organic layer was separated and washed with three 100-ml. portions of 0.1 *N* sodium hydroxide. The basic washings and aqueous layer were combined and neutralized in the cold with glacial acetic acid. Filtration afforded 9.4 g. (83%) of tan crystals, sinters to a glass at 140–147°. A second crop of crystals (1.8 g., 16%) was obtained from the mother liquors on cooling overnight. Recrystallization from methanol several times gave off-white needles, sinters to a glass at 139–142°. After drying over phosphorus pentoxide for 10 hr. the product **11** melted at 207–211° dec. (sinters to a glass at 145–148°); $[\alpha]^{25}D$ − 238° (*c* 1.03, dimethylformamide); ν_{max}^{KBr} 1603 (s), 1488 (s), 1470 (s), 1290 (s), 1031 cm.$^{-1}$ (m); $\lambda_{max}^{CH_3OH}$ 224 mμ (ε 35,300), 273 (sh.) (10,900), 284 (13,200), 290 (12,500), 314 (5,860); $\lambda_{max}^{0.1\ N\ NaOH}$ 218 mμ (ε 52,600), 284 (11,300), 290 (13,600).

Anal. Calcd. for $C_{20}H_{22}N_2O \cdot 1/2\ H_2O$: C, 72.5; H, 7.00; N, 8.45. Found: C, 72.3; H, 6.95; N, 8.84.

The following procedure was found to be more convenient for large scale runs: To a cooled mixture of 5.0 g. (17 mmoles) of yohimban-17-one (1), 5.0 g. of sodium methoxide (Mathieson), and 150 ml. of dry peroxide-free dioxane was added 7.0 ml. of ethyl formate. The mixture was stirred under nitrogen at room temperature for 21 hr. and neutralized with acetic acid. After concentration to near dryness *in vacuo*, 50 ml. of water and 25 ml. of methanol were added. Concentration and filtration gave 5.3 g. (94%) of tan crystals, m.p. 204–210° dec. (sinters to a glass at 145–154°). A 1.0-g. sample was triturated with 10 ml. of methanol to give 0.860 g. of **11** as tan crystals, m.p. 207–211° dec. (sinters to a glass at 144–148°), $[\alpha]^{25}D$ − 232° (*c* 1.3, DMF).

Yohimbano[18,17-*d*]isoxazole (12) and Yohimbano[17,18-*c*]-isoxazole (13) Hydrochlorides.—A mixture of 1.0 g. (3.0 mmoles) of hydroxymethylene ketone **11**, 0.225 g. (3.2 mmoles) of hydroxylamine hydrochloride and 15 ml. of glacial acetic acid was heated in an oil bath at 100° for 6 min. The mixture was chilled and filtered to give 0.430 g. (39%) of white needles. Recrystallization was carried out by dissolving in aqueous methanol and concentrating on a steam bath. There was obtained 0.148 g. of a mixture of **12** and **13** as white needles, m.p. 310–315° dec. (heating block), $[\alpha]^{25}D$ −132° [*c* 0.264, dimethylformamide–H_2O (1:1)].

Anal. Calcd. for $C_{20}H_{21}N_3O \cdot HCl \cdot 1/4\ H_2O$: C, 66.7; H, 6.29; N, 11.7; Cl, 9.84; H_2O, 1.25. Found: C, 66.7; H, 6.38; N, 11.9; Cl, 9.95; H_2O (K.F.), 1.96.

17-Oxoyohimban-18α-carbonitrile (14).—A mixture of 0.360 g. (1.0 mmole) of isoxazoles **12** and **13** was added to a solution of 0.115 g. of sodium in 10 ml. of ethanol. After being allowed to stand overnight the mixture was refluxed under nitrogen for 3 hr. The mixture was neutralized with glacial acetic acid, diluted with 30 ml. of water, and chilled to give 0.281 g. of tan crystals, m.p. 263–268° dec. A 0.225-g. sample was dissolved in chloroform:acetone (9:1) and chromatographed over silica gel. The product was eluted with chloroform:acetone (1:1) and crystallized from aqueous methanol to afford 0.100 g. of **14** as tan needles, m.p. 287–289° dec.; $[\alpha]^{25}D$ − 220° (*c* 1.09, pyridine); ν_{max}^{KBr} 2252, 2203, 1724 cm.$^{-1}$; $\lambda_{max}^{0.1\ N\ NaOH}$ 224 mμ (ε 37,250), 269 (14,740).

Anal. Calcd. for $C_{20}H_{21}N_3O \cdot 1/4\ H_2O$: C, 74.2; H, 6.69; N, 13.0; H_2O, 1.39. Found: C, 74.5; H, 6.69; N, 13.2; H_2O (K.F.), 1.27.

17α-Hydroxyyohimban-18α-carbonitrile (15) 17β-Hydroxyyohimban-18α-carbonitrile (16).—To a cold solution of 0.350 g. of sodium borohydride in 50 ml. of ethanol was added 2.00 g. of ketonitrile **14**. The mixture was stirred under nitrogen at room temperature for 4 hr. and then excess sodium borohydride was decomposed with acetic acid and the solvent removed *in vacuo*. The residual pale yellow solid was washed with two 50-ml. portions of chloroform and the extracts concentrated *in vacuo* to a glass (1.62 g.). The original solid was washed with water and there remained 0.220 g. of insoluble solid. The glass and the water-insoluble solid were combined and chromatographed over 125 g. of alumina (Woelm, activity III). Elution with chloroform:acetone (3:2) afforded 0.460 g. of 17α-hydroxynitrile **15** which, on crystallization from aqueous methanol, gave 0.320 g. of white needles. Recrystallization from aqueous methanol afforded white needles, m.p. 263–266° dec. (sinters 248°); $[\alpha]^{25}D$ − 66° (c 1.1, pyridine); ν_{max}^{KBr} 2252 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}N_3O \cdot 1/4\ H_2O$: C, 73.7; H, 7.27; N, 12.9. Found: C, 73.5; H, 7.28; N, 13.1.

Further elution of the column with chloroform:methanol (99:1) afforded 0.534 g. of 17β-hydroxynitrile **16** which, on crystallization from methanol, gave 0.360 g. of fluffy white needles, m.p. 247–250° dec. (sinters 245°); $[\alpha]^{25}D$ − 66° (*c* 0.92, pyridine); ν_{max}^{KBr} 2252 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}N_3O \cdot 1/4\ H_2O$: C, 73.7; H, 7.27; N, 12.9. Found: C, 73.8; H, 7.08; N, 13.1.

Methyl 17α-Hydroxyyohimban-18α-carboxylate (4) and Methyl 17β-Hydroxyyohimban-18α-carboxylate (5). Sodium Borohydride Reduction of Keto Ester 3.—To a cooled solution of 5.0 g. of sodium borohydride in 300 ml. of methanol was added 10.0 g. of keto ester **3**. The mixture was cooled and stirred under nitrogen for 1.5 hr. and carefully neutralized with acetic acid. The solvent was removed *in vacuo* and the residue partitioned between 100 ml. of chloroform and 100 ml. of 2.5% sodium bicarbonate solution. Solid separated at the interface and was removed by filtration. The organic layer was separated and the aqueous phase extracted with additional chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated *in vacuo* to give 6.1 g. of partly crystalline yellow solid. The solid was dissolved in methanol and treated twice with Darco. Concentration of the filtrate afforded a glass which was dissolved in chloroform and chromatographed over 300 g. of neutral alumina (Woelm, activity III). Elution with chloroform, evaporation of the eluate, and crystallization of the resultant solid from methanol afforded 17α-hydroxy ester **4** as colorless needles, m.p. 210–214° dec. (sinters to a glass 132–136°); $[\alpha]^{25}D$ − 65° (*c* 1.18, pyridine); ν_{max}^{KBr} 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot CH_3OH$: C, 68.4; H, 7.82; N, 7.25; O–CH_3 7.78. Found: C, 68.5; H, 7.85; N, 7.38; O–CH_3, 7.45.

In a second run 11.6 g. of keto ester **3** in 300 ml. of methanol was treated with 2.38 g. of sodium borohydride for 1 hr. Work-up of the mixture as described above gave 13.0 g. of a glass which was chromatographed over 900 g. of alumina (Woelm, activity III). Elution with chloroform and crystallization of the solid from methanol gave 0.730 g. of 17α-hydroxy ester **4**. Elution with chloroform:methanol (99:1) afforded 2.24 g. of 17β-hydroxy ester **5** as a glass. Crystallization from aqueous methanol gave off-white needles which were recrystallized from moist ethyl acetate and gave 1.50 g. of 17β-hydroxy ester **5** as off-white broken plates, m.p. 142–147°; $[\alpha]^{25}D$ − 60° (c 0.90, pyridine); ν_{max}^{KBr} 1733 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot 1/4\ H_2O$: C, 70.3; H, 7.44 N, 7.81. Found: C, 70.6; H, 7.77, N, 7.92,

Methyl 17α-Hydroxyyohimban-18α-carboxylate (4) and Methyl Yohimb-17-ene-18-carboxylate (18) from 17α-Hydroxyyohimban-18α-carbonitrile (15).—A mixture of 0.100 g. of 17α-hydroxynitrile **15**, 4.0 ml. of ethanol, 1.0 ml. of water, and 0.250 g. of sodium hydroxide was refluxed for 21 hr. The solvent was removed *in vacuo* and the residue dissolved in 5 ml. of water and brought to pH 7 with glacial acetic acid. The solid which separated was removed by filtration and washed with 3 ml. of water. After drying, there was obtained 0.090 g. of solid (crystals and glass). The solid was suspended in 10 ml. of methanol and treated with excess of an ethereal solution of diazomethane. After 10 min. the excess diazomethane was decomposed with acetic acid and the solvent removed *in vacuo*. There remained 0.092 g. of a glass which was chromatographed over neutral alumina (Woelm, activity III). Elution with chloroform afforded 0.010 g. of Δ^{17}-ester **18** which was crystallized from methanol to give white needles, m.p. 227–230° dec.; $[\alpha]^{25}D$ − 131° (*c* 0.92, $CHCl_3$); ν_{max}^{KBr} 3424 (m), 1712 (s), 1664 cm.$^{-1}$ (m). Further elution of the column with chloroform afforded 0.012 g. of 17α-hydroxy ester **4** as white needles, m.p. 206–211° dec. (sinters 150°). By comparison of infrared spectra and X-ray powder diagrams, the product was identical with the 17α-hydroxy ester **4** obtained on reduction of keto ester **3**. A mixture melting point showed no depression.

Methyl 17β-Hydroxyyohimban-18α-carboxylate (5) from 17β-Hydroxyyohimban-18α-carbonitrile (16).—A mixture of 0.092 g. of 17β-hydroxynitrile **16**, 4.0 ml. of ethanol, 1.0 ml. of water, and 0.220 g. of sodium hydroxide was refluxed for 18 hr. The mixture was concentrated to *ca.* 1.5 ml., 4.0 ml. of water was added, and the mixture was neutralized with acetic acid. Filtration gave 0.130 g. of solid which was suspended in 10 ml. of methanol and treated with excess of an ethereal solution of diazomethane. After 10 min. the excess diazomethane was decomposed with acetic acid and the solution concentrated *in vacuo* to give 0.130 g. of a glass. The glass was crystallized from aqueous methanol to give 0.030 g. of **5** as white needles, m.p. 145–148°, $[\alpha]^{25}D$ − 54° (*c* 1.0, pyridine). By comparison of infrared spectra and X-ray powder diagrams the product was identical with the 17β-hydroxy ester **5** obtained on reduction of keto ester **3**. A mixture melting point showed no depression.

Methyl Yohimb-17-ene-18-carboxylate (18) from Methyl 17α-Hydroxyyohimban-18α-carboxylate *O*-Tosylate.—A mixture of 0.386 g. (1.0 mmole) of methyl 17α-hydroxyyohimban-18α-carboxylate (**4**), 0.517 g. (3.0 mmoles) of *p*-toluenesulfonyl chloride, and 2.0 ml. of dry pyridine was allowed to stand at room temperature for 66 hr. The dark mixture was poured into a mixture of 12 g. of ice and 15 ml. of chloroform. After being allowed to stand for 2 hr. the mixture was cooled and made basic with concentrated ammonium hydroxide. The chloroform layer was separated and the aqueous layer extracted with three 25-ml. portions of chloroform. The combined extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The last traces of pyridine were removed by addition of toluene and concentration *in vacuo* to give 0.38 g. of brown crystals, m.p. 149–154°. From the infrared spectrum the product was shown to be a mixture of *O*-tosylate and α,β-unsaturated ester **18**.

A 0.100-g. sample of this mixture was heated with 1.5 ml. of 2,4,6-collidine at 160–170° for 2 hr. The mixture was cooled, diluted with 10 ml. of water, and extracted with four 10-ml. portions of chloroform. The extracts were combined, washed with 20 ml. of water containing 5 drops of concentrated ammonium hydroxide, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from aqueous methanol to give 0.044 g. of α,β-unsaturated ester **18** as brown crystals, m.p. 223–230° dec. Chromatography over neutral alumina (Woelm, activity III) with chloroform as eluant, and crystallization from methanol, gave 0.015 g. of **18** as pale pink needles, m.p. 226–230° dec.

Compound **18** was different from apoyohimbine (**17**)[23] (m.p. 247–250°) by comparison of infrared and p.m.r. spectra[16]; **18** showed a multiplet at 2.55–3.22 τ (1 olefinic + 4 aromatic protons) while apoyohimbine showed a one-proton peak at 3.30 τ (olefinic proton) clearly defined from the multiplet from the lower field aromatic protons.

Methyl 17α-Hydroxyyohimban-18α-carboxylate *O*-Acetate.—A mixture of 0.225 g. of 17α-hydroxy ester **4**, 4.0 ml. of anhydrous pyridine and 2.0 ml. of acetic anhydride was allowed to stand at room temperature for 66 hr. The dark mixture was concentrated *in vacuo* to a viscous mass which was dissolved in 10 ml. of methanol:water (1:4). The solution was cooled and made basic with concentrated ammonium hydroxide. The mixture was filtered and the solid dissolved in methanol, treated with Darco, and filtered. The filtrate was concentrated *in vacuo* to a glass and the glass crystallized from aqueous methanol to give 0.085 g. of tan crystals, m.p. 232–234° dec. Recrystallization from aqueous methanol afforded 0.050 g. of off-white crystals, m.p. 236–238° dec.; $[\alpha]^{25}D$ + 4° (*c* 0.94, pyridine; ν_{max}^{KBr} 3436, 1757, 1739 cm.$^{-1}$ (sh).

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot H_2O \cdot 1/2\ CH_3OH$: C, 65.7; H, 7.49; N, 6.51. Found: C, 65.7; H, 7.21; N, 6.36.

Methyl 17β-Hydroxyyohimban-18α-carboxylate *O*-Acetate.—A mixture of 0.250 g. of 17β-hydroxy ester **5**, 4.0 ml. of anhydrous pyridine, and 2.0 ml. of acetic anhydride was allowed to stand at room temperature for 77 hr. The dark mixture was concentrated *in vacuo* to a viscous mass which was dissolved in 10 ml. of methanol:water (1:4). The cooled solution was made basic with

ammonium hydroxide and the solid which separated was removed by filtration and washed with water. The partially dried solid was dissolved in methanol, treated with Darco, filtered, and the filtrate concentrated *in vacuo* to a brown glass (0.225 g.). Crystallization of the glass from aqueous methanol gave 0.118 g. of tan crystals, m.p. 122–125°. Recrystallization from aqueous methanol afforded 0.049 g. of tan needles, sinters 125–129°, melts slowly above 130°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot 1/4\ H_2O$: C, 69.0, H, 7.24; N, 7.06. Found: C, 68.9; N, 7.17; H, 6.99.

18-Butylthiomethyleneyohimban-17-one (19).—To a mixture of 0.663 g. (2.0 mmoles) of hydroxymethylene ketone **11**, 2.0 g. of anhydrous magnesium sulfate and 5.0 ml. of 1-butanethiol was added 10 ml. of glacial acetic acid. The mixture was stirred at room temperature for 20 hr., filtered, and the filtrate poured into cold mixture of 50 ml. of chloroform and 100 ml. of 4 *N* sodium hydroxide. The chloroform layer was separated and the aqueous layer extracted with two 50 ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give 0.66 g. of off-white crystals. Recrystallization from acetone gave, in two crops, 0.542 g. (69%) of **19** as off-white crystals, m.p. 216–219° dec. Recrystallization from ethanol and from acetone afforded off-white crystals, m.p. 219–222° dec.; $[\alpha]^{25}D$ − 164° (*c* 1.0, pyridine); ν_{max}^{KBr} 1661, 1541 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}N_2OS$: C, 73.0; H, 7.66; N, 7.10; S, 8.13. Found: C, 72.6; H, 7.89; N, 7.43; S, 8.13.

18α-Methylyohimban-17-one (20).—A mixture of *ca.* 9 g. of Raney nickel, 0.80 g. of 18-butylthiomethyleneyohimban-17-one (**19**), and 80 ml. of acetone was stirred and refluxed for 7 hr. Fresh catalyst (*ca.* 1 g.) was added and the mixture refluxed for an additional 5 hr. The mixture was filtered through Celite and the filter cake washed thoroughly with acetone. Concentration of the filtrate *in vacuo* gave 0.50 g. (83%) of off-white crystals which were chromatographed over 40 g. of alumina (Woelm, activity III). Elution with chloroform afforded 0.42 g. of white crystals which were recrystallized by dissolving in methanol–chloroform and concentrating. There was obtained 0.275 g. (46%) of **20** as white needles, m.p. 292–298° dec. Recrystallization from methanol gave white needles, m.p. 290–295° dec.; $[\alpha]^{25}D$ − 109° (*c* 1.08, pyridine, ν_{max}^{KBr} 1704 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O \cdot 1/2\ H_2O$: C, 75.7; H, 7.94; N, 8.83; C–CH_3, 4.74. Found: C, 76.1; H, 8.08; N, 9.09; C–CH_3 4.46.

By comparison of infrared spectra and X-ray powder diffraction patterns, 18α-methyl ketone **20** was found to differ significantly from 16α-methylyohimban-17-one (**21**),[4j,24] prepared by Oppenauer oxidation of 16-methylyohimbol.[26]

Ethyl 16-Oxoyohimban-17-glyoxylate (23).—A mixture of 4.71 g. (16 mmoles) of yohimban-16-one (**22**), 0.944 g. (18 mmoles) of sodium methoxide (Mathieson), 16.0 ml. of diethyl oxalate, and 200 ml. of dry benzene was stirred under nitrogen at room temperature for 20 hr. The mixture was cooled by means of an ice bath, neutralized with glacial acetic acid, and diluted with 200 ml. of chloroform. After filtration the solvent was removed *in vacuo* to give a red-brown solid. The solid was dissolved in 200 ml. of ethanol, treated with Darco, and filtered. Chilling and filtering afforded 0.490 g. of orange crystals, m.p. 208–215° dec. The filtrate was diluted with 600 ml. of water and chilled to give 2.6 g. (40%) of **23** as orange crystals, m.p. 198–200° dec. Recrystallization of a 0.200 g. sample from ethanol afforded 0.098 g. of tan crystals, m.p. 193–198° dec.; $[\alpha]^{25}D$ − 56° (*c* 0.62, DMF); violet color with ferric chloride; $\lambda_{max}^{0.1\ N\ NaOH}$ 223 mμ (ε 40,000), 283 (10,700), 290 (12,200), 318 (18,800).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 67.0; H, 6.84; N, 6.79; H_2O, 4.37. Found: C, 67.3; H, 6.64; N, 7.15; H_2O (K.F.), 2.18.

Ethyl 17-Oxoyohimban-18-glyoxylate (24).—A mixture of 0.294 g. (1.0 mmole) of yohimban-17-one (**1**), 0.059 g. (1.1 mmoles) of sodium methoxide, and 1.0 ml. (7.4 mmoles) of freshly distilled ethyl oxalate in 20 ml. of dry benzene was stirred at room temperature for 20 hr. The red-brown suspension was diluted with 500 ml. of cold anhydrous ether and filtered to give 0.346 g. (83%) of the crude sodium salt of **24**, m.p. > 350°; λ_{max}^{MeOH} 225 mμ (ε 42,700), 280 (9,330), 290 (sh) (8,320), 315 (sh) (3,240).

The salt (7.56 g.), obtained from 5.0 g. of **1**, was dissolved in 150 ml. of cold water containing a few drops of 10 *N* sodium hydroxide solution and rapidly extracted with two 100-ml. portions of ethyl acetate. The aqueous phase was separated and brought to pH 7.0 by the dropwise addition of dilute acetic acid. A voluminous precipitate formed and was separated by filtration to give 3.41 g. (51%) of **24**, m.p. 207–209° dec. The melting point was raised to 215–216° dec. by recrystallization from methanol. The product gave a brown-purple color with an alcoholic solution of ferric chloride; λ_{max}^{MeOH} 221 mμ (ε 37,200), 283 (11,800), 290 (12,600), 312 (12,300); ν_{max}^{KBr} 1718, 1710 (sh), 1704 (sh), 1610 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot 3/4\ H_2O$: C, 67.7; H, 6.79; N, 6.87; H_2O, 3.31. Found: C, 68.1; H, 6.87; N, 7.17; H_2O (K.F.) 3.25.

Ethyl 17-Oxoalloyohimban-16-glyoxylate (25).—A mixture of 0.294 g. (1.0 mmole) of alloyohimban-17-one (**9**), 0.059 g. (1.1 mmoles) of sodium methoxide, and 1.0 ml. (7.4 mmoles) of freshly distilled ethyl oxalate in 20 ml. of dry benzene was stirred at room temperature for 20 hr. under nitrogen. The orange solution was dropped slowly into 200 ml. of dry ether with magnetic stirring. After 30 min. at room temperature the suspension was filtered and the bright orange-yellow powder was washed thoroughly with ether to give 0.286 g. (69%) of sodium enolate of **25**, m.p. > 350°; red-brown color with alcoholic ferric chloride solution; λ_{max}^{MeOH} 225 mμ (ε 30,200), 280 (8,320), 290 (8,710), 314 (9,950); $\lambda_{max}^{0.1\ N\ HCl}$ 221 mμ (ε 32,400), 280 (7,760), 289 (6,920); ν_{max}^{KBr} 1614, 1678, 1716 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{25}N_2O_4Na \cdot H_2O$: C, 63.6; H, 5.80; N, 6.45; H_2O, 4.14. Found: C, 58.3; H, 5.71; N, 6.08; H_2O (K.F.), 5.32; ash, 12.9.

The crude salt (1.88 g.) was dissolved in 50 ml. of 50% aqueous methanol and passed slowly over 30 g. of Amberlite IRC-50 (H^+) resin. The first 400 ml. eluted mainly alloyohimban-17-one (**9**). The next 300 ml., as well as 200 ml. of methanol used to strip the column, contained **25**. Accordingly, the latter eluate was concentrated to a low volume *in vacuo* and the resulting brown precipitate was collected by filtration and washed extensively with water to produce 0.28 g. (9%) of a brown amorphous powder, m.p. 198–200° dec. Crystallizations from methanol produced 0.030 g. of crude **25** as tan microcrystals, m.p. 207–209° dec., $[\alpha]^{25}D$ − 162° (*c* 0.553, pyridine); λ_{max}^{MeOH} 228 mμ (ε 33,100), 284 (12,000), 292 (11,800); $\lambda_{max}^{0.1\ N\ NaOH}$ 227 mμ (ε 34,700), 284 (10,500), 291 (11,800), 314 (13,500).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 67.0; H, 6.84; N, 6.79. Found: C, 61.7; H, 5.97; N, 7.52.

Carboxylation of Alloyohimban-17-one (9).—Alloyohimban-17-one (**9**) (0.589 g., 2.0 mmoles) was suspended in 8.0 ml. of a 2.8 *M* solution of magnesium methyl carbonate in dimethylformamide, heated to 120° and stirred under dry nitrogen for 3 hr. After cooling to room temperature, the viscous mixture was poured into a chilled mixture of 4.0 ml. of concentrated hydrochloric acid and 20 g. of ice and the resulting solid was removed by filtration and washed with a little cold water. After drying overnight the crude carboxylation product as the hydrochloride weighed 0.718 g., ν_{max}^{KBr} 1661, 1718 cm.$^{-1}$. To a cold solution of 0.710 g. of the crude β-keto acid hydrochloride in 10 ml. of methanol was added 5 ml. of an ethereal solution of diazomethane prepared from 1 g. of nitrosomethylurea and 3 ml. of 40% aqueous potassium hydroxide. An immediate white precipitate appeared. After 5 min. at 5°, 2 ml. of glacial acetic acid was added and the solution was concentrated to dryness *in vacuo* with a minimum of heat to give 0.629 g. of crude β-keto ester. The product gave a brown-red color with an alcoholic solution of ferric chloride and possessed infrared bands at 1661, 1718 and 1739 (sh) cm.$^{-1}$.

To a chilled 2% solution of sodium borohydride in 25 ml. of methanol was added dropwise a solution of 0.500 g. of the crude β-keto ester in 50 ml. of cold methanol. The solution was allowed to come to room temperature while being stirred for 1 hr., a few milliliters of acetic acid were added and the solution concentrated to a small volume *in vacuo*. The resulting suspension was partitioned between water and ether and the ethereal solution was evaporated to dryness to produce 0.268 g. of an amorphous white solid. This was dissolved in chloroform and chromatographed on 30 g. of neutral alumina (Woelm, activity II), 25-ml. cuts being collected. Fractions 3 and 4 (0.0576 g.) were combined and crystallized from aqueous methanol to give 0.0202 g. of crude hydroxy ester, m.p. 113–126° dec., ν_{max} 1720 cm.$^{-1}$. The majority of the material (0.287 g.) was eluted in fractions 5–7. This material was crystallized from chloroform to give 0.095 g. of colorless needles of alloyohimban-17α-ol, m.p. 206–209° dec. (reported[27] m.p. 212–214° dec.).

(27) A. Chatterjee and S. Ghosal, *J. Indian Chem. Soc.*, **36**, 545 (1959).

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 1/6\ H_2O$: C, 76.2; H, 8.18; N, 9.36; H_2O, 1.00. Found: C, 76.5; H, 8.36; N, 9.69; H_2O (K.F.), 1.00.

The crude hydroxy ester was chromatographed on Whatman #1 paper (impregnated with an ethanolic solution of formamide and ammonium formate) in the system chloroform:benzene (saturated with formamide).[4c] Ultraviolet absorbing spots were observed at R_f = 0.06, 0.32, 0.48, 0.65 and 0.80, corresponding to alloyohimban-17α-ol (R_f = 0.05), α-yohimbine (**10**) (R_f = 0.65) and alloyohimban-17-one (**9**) (R_f = 0.82).

Acknowledgment.—We wish to express our thanks to the following: Mr. L. Brancone and his staff for elemental analyses; Mr. W. Fulmor and Dr. J. Lancaster (Central Research Division) and their staffs for spectral determinations; Mr. W. Groth for the X-ray powder diffraction measurements; Professor E. L. Eliel (University of Notre Dame) for helpful discussions on the p.m.r. spectra.

Synthesis of Isophytol

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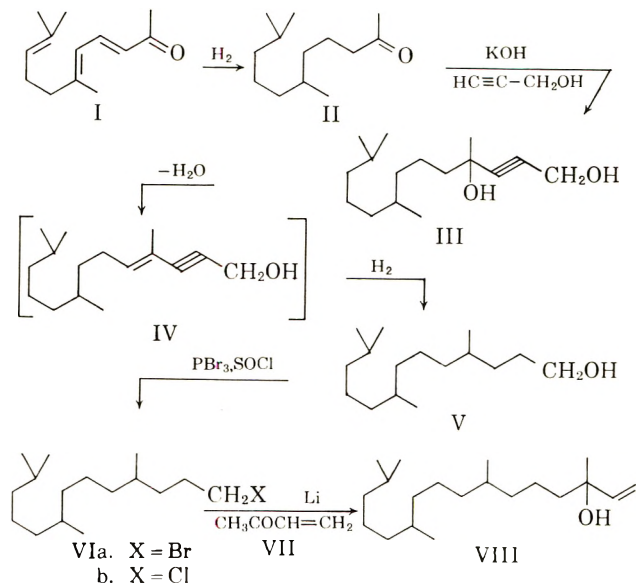
Isophytol was synthesized from pseudoionone and propargyl alcohol. The synthesis involved six steps, much fewer than the steps in other procedures. It was found in a model experiment that methyl vinyl ketone reacts with laurylmagnesium bromide to yield the 1,4-addition product, whereas the 1,2-addition product was obtained with lauryllithium. The specificity found for lauryllithium was applied for the synthesis of isophytol from 1-bromo-4,8,12-trimethyltridecane.

It has been known that tocopherols (vitamins E) are synthesized by condensation of hydroquinones with phytol[1] or its derivatives such as isophytol,[2] phytyl halides,[3,4] and phytadiene.[5] Isophytol (VIII) is a key material for the synthesis, since phytol, phytyl halides, and phytadiene can be easily derived from isophytol. A number of investigations of the synthesis of isophytol have been carried out with linalool or citral[6–14] as the starting material *via* pseudoionone. Recently, Nazarov[15] and Lukes[16] succeeded in the total synthesis of isophytol from acetylene and laevulic acid, respectively. However, these syntheses are awkward for a large scale operation, because of the many stages even from pseudoionone. A new synthesis of isophytol presented in this paper is comprised of six steps from pseudoionone (I) and propargyl alcohol. The process of the synthesis is as follows.



Hexahydropseudoionone (II) prepared from pseudoionone by hydrogenation reacted smoothly with propargyl alcohol to give 4,8,12-trimethyltridec-2-yn-1,4-diol (III) in 84% yield. The condensation was carried out in the presence of finely powdered potassium hydroxide according to Chodkiewicz.[17] 4,8,12-Trimethyltridecan-1-ol (V) was obtained in 70–75% yield from this glycol (III), by dehydration of the tertiary hydroxy group of this glycol with fused potassium hydrogen sulfate and by subsequent hydrogenation. The dehydration reaction was vigorous and completed within about ten minutes at the boiling point of xylene. The intermediate, enyne alcohol (IV), if desired, could be isolated as a pale yellow oil which, upon exposure to air, slowly polymerized to a sticky dark red material. The alcohol was highly sensitive to heat and polymerized even by careful distillation. It is, therefore, recommended that, after treating with dehydrating agent and removing the solvent, the crude product, IV, be directly hydrogenated without isolation. The reduction was smooth and quantitative in the presence of Raney nickel catalyst in ethyl alcohol to 80° under a pressure of about 140 atmospheres of hydrogen. Compound V was a colorless, stable oil, and could be converted smoothly into its bromide (VIa) and chloride (VIb) by action of phosphorus tribromide and thionyl chloride, respectively.

The final product, isophytol, may be obtained by the reaction of a metallic compound of VI with methyl

(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta.*, **21**, 309 (1938); Hoffmann-La Roche & Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U.S. Patent 2,411,968 (1946).

(2) P. Karrer and O. Isler, U.S. Patent 2,411,969 (1946); Hoffmann-La Roche & Co., Swiss Patent 208,446 (1940).

(3) P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta.*, **21**, 939 (1938).

(4) J. D. Surmatis and J. Weber, U.S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Can. Patent 530,254 (1956).

(5) L. I. Smith and H. E. Ungnale, U.S. Patent 2,421,811 (1947).

(6) F. G. Fischer and K. Löwenberg, *Ann.*, **475**, 183 (1929).

(7) P. Karrer and B. H. Ringier, *Helv. Chim. Acta*, **22**, 610 (1939).

(8) P. Karrer, A. Geiger, H. Rentschler, E. Zbinder, and A. Kugler, *ibid.*, **26**, 1741 (1943).

(9) I. K. Sarycheva, G. A. Vorobova, N. A. Kuznetsova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **28**, 647 (1958).

(10) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

(11) J. Weicht and J. Hodrová, *Chem. Listy*, **51**, 568 (1957).

(12) L. I. Smith and G. Rouault, *J. Am. Chem. Soc.*, **65**, 745 (1943).

(13) J. W. K. Burrell, L. M. Jackmann, and B. C. L. Weedon, *Proc. Chem. Soc.*, 263 (1959).

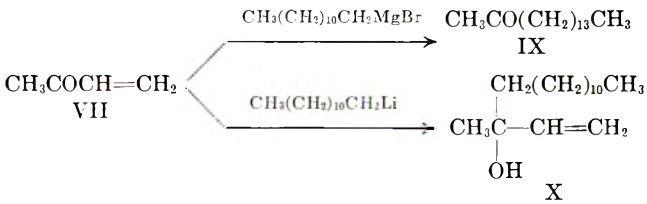
(14) V. I. Gunar and Ş. I. Zavyalov, *Dokl. Akad. Nauk SSSR*, **132**, 829 (1960).

(15) I. N. Nazarov, B. P. Gusev, and V. I. Gunar, *Zh. Obshch. Khim.*, **28**, 1444 (1958).

(16) R. Lukes and A. Zobácová, *Chem. Listy*, **51**, 330 (1957).

(17) W. Chodkiewicz, *Compt. rend.*, **240**, 1903 (1955).

vinyl ketone (VII). Smith and Sprung[10] examined the reaction of laurylmagnesium bromide with VII, and obtained no simple product owing to the polymerization of the ketone. Since no systematic study has been reported on the reaction of methyl vinyl ketone with organometallic compounds, a model experiment was carried out in the present study with laurylmagnesium bromide and lauryllithium in place of a metallic compound of VI. The reaction was conducted at low concentrations of the reactants and at the low temperature of −10° to suppress the polymerization reaction. In the reaction of methyl vinyl ketone (VII) with an organometallic compound, either 1,2- or 1,4-addition may take place and the tertiary carbinol or the saturated ketone may be obtained. 1,2-Addition is desirable for the preparation of isophytol. It was found that methyl vinyl ketone reacts with laurylmagnesium bromide to give the 1,4-addition product of hexadecan-2-one (IX) in 7.5% yield, whereas the 1,2-addition product of 3-methyl-pentadec-1-en-3-ol



(X) was obtained in 13.5% yield with lauryllithium. These products were identified by microanalysis and infrared spectrum.

These results were successfully applied to the synthesis of isophytol (VIII) from 1-halo-4,8,12-trimethyltridecane (VI) as described below. The lithium reagent could not be obtained from lithium and the chloride (VIb) by a common procedure, probably because of the long aliphatic chain in the compound VI. The reaction of lithium with the bromide VIa was also extremely difficult to start. However, the reagent was obtained when the mixture was heated to 60–65° with stirring for thirty hours in the absence of solvent. To the lithium reagent thus obtained, was added slowly methyl vinyl ketone at −10°; isophytol (VIII) was obtained in 3.9% yield (based on VIa). Isophytol was identified from the data of microanalysis, specific density, refractive index,[9,15] and infrared spectrum. The spectrum indicated the presence of tertiary hydroxy and vinyl groups. By-products of $C_{16}H_{34}$ and $C_{32}H_{66}$ were formed in the reaction. The low yield of isophytol in this final stage of the reaction may arise from the formation of these by-products in the long period of heating for the preparation of the lithium reagent.

Experimental[18]

Hexahydropseudoionone (II).—A 100-g. sample of pseudoionone (b.p. 130–133° at 7 mm., a gift from Hasegawa Perfume Co.) in 100 ml. of ethanol was hydrogenated over 6 g. of palladium–calcium carbonate (1:12) with hydrogen at atmospheric pressure and room temperature. The theoretical amount of hydrogen was absorbed in about 10 hr.: b.p. 99–104° at 4 mm., yield 96 g. (93%), $n^{20}D$ 1.4359, d^{20}_4 0.8315, (lit.,[11] b.p. 121–122° at 12 mm., $n^{20}D$ 1.4360).

4,8,12-Trimethyltridec-2-yn-1,4-diol (III).—Finely powdered potassium hydroxide (200 g., 3.6 moles) was suspended in 500 ml. of anhydrous tetrahydrofuran in a 2.0-l. three-neck flask, fitted with a stirrer, a dropping funnel, and a reflux condenser. The mixture was heated to the boiling point and then 29.0 g. (0.51 mole) of propargyl alcohol[19] was added with stirring over a period of 0.5 hr. Stirring and refluxing were continued for 3 hr. after the addition and then 99.8 g. (0.51 mole) of II in 130 ml. of tetrahydrofuran was added dropwise over a period of 2 hr. at the boiling point. The reaction mixture was stirred and refluxed for 2 hr. It was then cooled to 0° and poured in portions into a well-stirred mixture of 800 ml. of ice–water and 360 g. of concentrated sulfuric acid. The aqueous layer was extracted three times with 80 ml. of ether, and the extracts were combined with the organic layer. The resultant solution was washed with water, 5% sodium bicarbonate solution, and finally with water, and dried over anhydrous magnesium sulfate. The ether in the solution was evaporated, and the residue was distilled *in vacuo*. The product distilled was a highly viscous oil; b.p. 161–164° at 2 mm., yield 97.2 g. (84%), $n^{20}D$ 1.4717, d^{20}_4 0.9449. The infrared spectrum showed the bands of tertiary and primary hydroxy groups at 1150 cm.$^{-1}$ and at 1050 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 74.97: H, 11.71.

4,8,12-Trimethyltridec-2-yn-4-en-1-ol (IV).—A 500-ml. flask fitted with a stirrer, a dropping funnel, a thermometer, and a condenser was charged with 12 g. of fused potassium hydrogen sulfate and 150 ml. of anhydrous xylene. The bottom of the condenser was connected to a trap to collect the water formed in such a way as used in esterification. The mixture was heated to the boiling point of xylene. A solution of 25.4 g. (0.1 mole) of glycol III in 50 ml. of xylene was added to the mixture all at once with stirring. After the initial vigorous reaction had subsided, stirring was continued for 10 min. at the boiling point of xylene. The reaction mixture was then cooled with an ice bath, poured into water, and extracted with three portions, each 50 ml. of ether. The ether extract was washed with water and with 5% sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The crude product was obtained as the residue after removal of a trace of solvent under reduced pressure. The sample for analysis was distilled as a pale yellow oil at 132–135° (3 mm.), $n^{20}D$ 1.4757, d^{20}_4 0.8474.

Anal. Calcd. for $C_{16}H_{28}O$: C, 81.29: H, 11.94. Found: C, 81.03: H, 11.62.

4,8,12-Trimethyltridecan-1-ol (V).—A 13-g. sample of the crude product of IV in 40 ml. of ethanol was hydrogenated in an autoclave with 4 g. of Raney nickel catalyst under 140 atm. and 80°. Reduction was completed in 5 hr. The catalyst was separated by filtration and the saturated alcohol was distilled at 119–122° (2 mm.), yield, quantitative. Over-all yield from III to V was 70–75%, $n^{20}D$ 1.4537, d^{20}_4 0.8416.

Anal. Calcd. for $C_{16}H_{34}O$: C, 79.26: H, 14.14. Found: C, 79.00: H, 13.81.

1-Chloro-4,8,12-trimethyltridecane (VIb).—A 12.0-g. sample (0.11 mole) of thionyl chloride was added to 20 g. (0.08 mole) of V over a period of 20 min. keeping the temperature below 5°. The mixture was allowed to stand overnight at room temperature, warmed to 70–80° for 3.5 hr., poured into water, and extracted with ether. The ether extract was washed with water and 5% sodium bicarbonate solution and finally with water, and dried over calcium chloride. The product was distilled at 119–123° (1.5 mm.), yield 18.2 g. (87%), $n^{20}D$ 1.4528, d^{20}_4 0.8674.

Anal. Calcd. for $C_{16}H_{33}Cl$: C, 73.65: H, 12.75. Found: C, 73.08: H, 12.29.

1-Bromo-4,8,12-trimethyltridecane (VIa).—This substance was prepared by the method reported by Fischer[20] for the preparation of farnesyl bromide. The bromide (29.2 g.) was obtained as a pale yellowish oil from 37.3 g. (0.16 mole) of V and 40 g. (0.15 mole) of phosphorus tribromide: b.p. 130–133° at 2 mm., $n^{20}D$ 1.4620, d^{20}_4 0.9910. The infrared spectrum indicated the absence of hydroxy group.

Anal. Calcd. for $C_{16}H_{33}Br$: C, 62.88: H, 10.89. Found: C, 62.72: H, 10.72. (lit.,[10] b.p. 140–145° at 3.5 mm., $n^{25}D$ 1.4600. Found: C, 63.04: H, 11.17).

Model Experiment. (a) The Reaction of Methyl Vinyl Ketone (VII) with Laurylmagnesium Bromide.—Methyl vinyl ketone was prepared from γ-ketobutanol (78–80° at 18 mm., prepared

(18) Boiling points and melting points are uncorrected. Infrared spectra were recorded with a Shimadzu Model AR 275 spectrophotometer.

(19) Purchased from Union Carbide Co., after drying over calcium carbide, distilled; b.p. 111–113°.

(20) F. G. Fischer, *Ann.*, **464**, 69 (1928).

from acetone and formalin[21]) by dehydration with oxalic acid according to the method of Murata,[22] b.p. 80–82°. Laurylmagnesium bromide was prepared from 102.3 g. (0.41 mole) of lauryl bromide[23] and 9.9 g. (0.41 g.-atom) of magnesium in 500 ml. of anhydrous ether in a 1.0-l. three-neck flask equipped with a condenser, a stirrer, a dropping funnel, and a nitrogen inlet tube. To the solution, 19.7 g. (0.28 mole) of freshly distilled methyl vinyl ketone in 200 ml. of anhydrous ether was added under nitrogen stream with such a rate that temperature was maintained at −10°. The reaction mixture was allowed to stand overnight at room temperature. The complex was decomposed with 15% ice-cooled dilute acetic acid, and was extracted with ether. The ether extract was washed with water, saturated sodium bicarbonate solution, and water. The solvent was removed, after drying over anhydrous magnesium sulfate. The material was fractionally distilled at 4 mm. Fraction I boiled at 60–70°, fraction II at 100–108°, and fraction III at 110–120°. The residue solidified upon cooling, and crystallized from ethanol to yield 12.0 g. of tetracosan: m.p. 50.5° (lit.,[24] m.p. 51.5°).

Anal. Calcd. for $C_{24}H_{50}$: C, 85.12: H, 14.88. Found: C, 85.17: H, 14.04.

Fractions I, II, and III were redistilled. Fraction I gave 17.0 g. of *n*-dodecane boiling at 62.5–63.0° (2 mm.), $n^{20}D$ 1.4233 (lit.,[25] $n^{20}D$ 1.4209).

Anal. Calcd. for $C_{12}H_{26}$: C, 84.61: H, 15.39. Found: C, 84.85: H, 14.97.

Fraction II gave 1.5 g. of lauryl alcohol boiling at 105–107° (3 mm.) The infrared spectrum showed a band of a primary hydroxy group at 1060 cm.$^{-1}$, $n^{20}D$ 1.4405.

Anal. Calcd. for $C_{12}H_{25}O$: C, 77.35: H, 14.07. Found: C, 77.77: H, 13.82.

Fraction III, upon redistillation, gave 7.3 g. (7.5% based on lauryl bromide) of *n*-hexadecane-2-one boiling at 121–126° (4 mm.), m.p. 41° (lit., b.p. 165° at 12 mm.,[26] m.p. 43°[27]). The infrared spectrum showed a carbonyl band at 1710 cm.$^{-1}$. and the absence of hydroxy and vinyl groups.

Anal. Calcd. for $C_{16}H_3O$: C, 79.93: H, 13.42. Found: C, 79.90: H, 13.49. Semicarbazone, m.p. 124° (lit.,[26] m.p. 120°).

Anal. Calcd. for $C_{17}H_{35}ON_3$: N, 14.13. Found: N, 14.03.

(b) **The Reaction of Methyl Vinyl Ketone (VII) with Laurylithium.**—Laurylithium was prepared from 1.5 g. (0.21 g.-atom) of lithium and 20.5 g. (0.1 mole) of lauryl chloride (b.p. 100–101.5° at 3 mm., $n^{20}D$ 1.4428) by the same method as for the preparation of butyllithium.[28] Methyl vinyl ketone (7.0 g., 0.1 mole) in 70 ml. of anhydrous ether was added to the solution in the same way as in the reaction of laurylmagnesium bromide. The reaction mixture was decomposed with 15% dilute acetic acid and worked up in a usual way. The product thus obtained was distilled fractionally at 4 mm. The distillation afforded 6.5 g. of *n*-dodecane, b.p. 70–72°, $n^{20}D$ 1.4225, and 3.2 g. of 3-methylpentadec-1-en-3-ol, b.p. 127–129° in 13.5% yield (based on lauryl chloride), $n^{20}D$ 1.4521, d^{20}_4 0.8431. The infrared spectrum showed a band of tertiary hydroxy group at 1150 cm.$^{-1}$ and three bands of CH=CH_2 at 1650, 995, and 910 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 80.08; H, 13.58.

From the residue, 0.8 g. of tetracosan was obtained; m.p. 50°.

3,7,11,15-Tetramethylhexadec-2-en-3-ol (VIII) Isophytol.—No reaction occurs between the chloride, VIb, and lithium even in the absence of solvent and at 50°. A 29.0-g. sample (0.095 mole) of the bromide (VIa) and 1.5 g. (0.21 g.-atom) of lithium was heated to 60–65° in a stream of nitrogen for 30 hr. The reaction was extremely difficult to start and proceeded very slowly. An appreciable amount of lithium dissolved. After cooling and dilution with 25 ml. of anhydrous tetrahydrofuran, 13.6 g. (0.19 mole) of VII in 25 ml. of anhydrous tetrahydrofuran was slowly added to the lithium reagent with stirring so as to keep the temperature below −10°. The cooling bath was removed, and the stirring was continued until the temperature of the mixture rose to room temperature. The complex left standing overnight was decomposed with dilute acetic acid (15%) and extracted with ether. The ether extract was washed with water and dilute sodium bicarbonate solution, and again with water. After drying over anhydrous magnesium sulfate and removing the solvent, the residual oil was fractionated by distillation into three fractions Fraction I (5.9 g.) was *n*-hexadecane, boiling at 87–90° (1.5 mm.), $n^{20}D$ 1.4356, d^{20}_4 0.7757. (lit.,[29] d^{18}_4 0.7754).

Anal. Calcd. for $C_{16}H_{34}$: C, 84.86: H, 15.14. Found: C, 84.48: H, 15.04.

Fraction II (1.1 g., 3.9% based on VIa) was isophytol and boiled at 107–110° (0.01 mm.,) $n^{20}D$ 1.4571, d^{20}_4 0.8519 (lit.,[15] b.p. 125–128° at 0.06 mm., $n^{20}D$ 1.4546, d^{20}_4 0.8459). The infrared spectrum showed a band of a tertiary hydroxy group at 1150 cm.$^{-1}$ and three bands of —CH=CH_2 at 1640, 995, and 915 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.00: H, 13.60. Found: C, 81.67: H, 13.39.

Fraction III (7.2 g.) was a hydrocarbon and boiled at 180–190° (0.2 mm.), $n^{20}D$ 1.4560, d^{20}_4 0.8196.

Anal. Calcd. for $C_{32}H_{66}$: C, 85.24: H, 14.76. Found: C, 84.91: H, 14.59.

Acknowledgment.—The authors wish to express their gratitude to Hasegawa Perfume Co. for a generous gift of pseudoionone and also to Dr. Kuroiwa and the staffs of Tekkosha Co. for the measurements of infrared spectra. The authors also are grateful to Mr. T. Oonuma and Mr. T. Nakano in our laboratory for their great help in carrying out the study presented in this report.

(21) J. Murata "Synthetic Methods of Monomers," Vol. 9, Kyōritsu Publishing Co., Tokyo, 1957, p. 183.

(22) See ref. 21, p. 186.

(23) Commercial lauryl bromide was treated with concentrated sulfuric acid and distilled; b.p. 102–104° at 4 mm., $n^{20}D$ 1.4580.

(24) F. Krafft, *Ber.*, **15**, 1718 (1882).

(25) F. Krafft, *ibid.*, **15**, 1698 (1882).

(26) L. Ruzicka, H. Schinz, and M. Pfeiffer, *Helv. Chim. Acta.*, **11**, 686 (1928).

(27) F. Krafft, *Ber.*, **15**, 1705 (1882).

(28) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932).

(29) F. Krafft, *Ber.*, **15**, 1702 (1882).

The Brominative Decarboxylation of Optically Active Silver *trans*-1,2-Cyclohexanedicarboxylate

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The brominative decarboxylation (Hunsdiecker reaction) of the title compound has been found to yield optically active *trans*-1,2-dibromocyclohexane, with net inversion of configuration. The amount of optical activity varied over a wide range, but was always of the same sign. The *cis*-dibromide was not formed and was shown to be stable under the reaction conditions. A mechanistic scheme is proposed involving competitive intramolecular bromine atom transfer in a 2-bromocarboxycyclohexyl radical and some nonstereospecific mechanism, probably with a cyclohexene intermediate. The absolute configurations of the diacid and dibromide have been assigned.

Preliminary work in this laboratory[1] showed that the Hunsdiecker reaction of optically active silver *trans*-cyclobutane-1,2-dicarboxylate gave an optically active *trans*-dibromide product. This result was considered interesting in terms of its possible bearing upon the intermediacy of an olefin or bridged-bromine radical, but no information was then available on the optical purity of the product, the preferred stereochemistry (retention or inversion), or the possibility of an asymmetric induction of optical activity in the product by a path unrelated to the Hunsdiecker reaction. The present research considers these matters in some detail. The cyclobutane system was abandoned in favor of the more accessible silver cyclohexane-1,2-dicarboxylate, which has been shown by Abell[2] and confirmed by us to give only *trans*-1,2-dibromocyclohexane, with no detectable amount of *cis* product.

trans-Cyclohexane-1,2-dicarboxylic acid was prepared in 64% over-all yield by ethanolysis-esterification of commercial *cis*-hexahydrophthalic anhydride, followed by base-catalyzed epimerization to the *trans* form and saponification.[3] The acid was resolved with quinine by the method of Werner and Conrad[4] to give the dextrorotatory form in higher optical purity than has been previously obtained. Conversion of the optically active acid to its disilver salt was essentially quantitative.

Brominative decarboxylations were carried out at 0° and at 31.3° in the inverse manner (addition of silver salt to a solution of bromine in carbon tetrachloride). The specific experimental conditions, yields, and optical results for thirteen runs are summarized in Table I. The most important features of these data are the following: (1) Although the optical purities of the products varied erratically, the lower temperature clearly favored a higher optical purity. (2) The optical purity of the product was not detectably affected by a threefold increase in initial bromine concentration. (Compare especially runs 11 and 13 with runs 3–5.) (3) The rotations of products approached zero, but were always negative. (4) The yields of dibromide product were increased from 14–19% at 0° in ambient laboratory light to 39 41% by irradiation, to 36–58% by use of excess bromine, and to 26–29% by an increase in the temperature to 31.3°.

The other reaction products were esters and probably a β-lactone (infrared absorption at 1820 cm.$^{-1}$), but these were not identified or investigated beyond learning how to remove them from the dibromide.

TABLE I

SUMMARY OF THE RESULTS OF THE BROMINATIVE DECARBOXYLATIONS OF OPTICALLY ACTIVE SILVER *trans*-1,2-CYCLOHEXANEDICARBOXYLATE

Run	Temp., °C.[a]	Specific rotation (neat) of dibromide, degrees	% yield of dibromide	Specific rotation of diacid, degrees
1	31.3	− 1.77	26	+21.8
2	31.3[b]	− 4.87	29	+21.8
3	0 ± 1	−18.9	14	+21.8
4	0 ± 1	−27.0	14	+21.8
5	0 ± 1	−25.4	16.5	+21.8
6	0 ± 1[c]	−19.8	39	+20.5
7	0 ± 1[c,d]	−21.4	41	+20.5
8	0 ± 1[e]	− 8.38	19	+20.5
9	0 ± 1[e]	−10.2	14	+20.5
10	0 ± 1	−11.7	19	+20.5
11	0 ± 1[f]	−25.3	58	+21.9
12	0 ± 1[g]	−17.5	36	+21.9
13	0 ± 1[h]	−24.5	51	+21.9

[a] The reactions at 0 ± 1° were carried out for a total time of eight hours, while those at 31.3° were carried out for a total time of one hour. The additions required one hour and fifteen minutes, respectively. [b] A flashing light was the heat source in the constant temperature bath. [c] The reaction mixture was illuminated by a sun lamp at a distance of nine inches from the flask. [d] Thirty-two per cent of the starting diacid was recovered, m.p. 178–182° (original m.p. 179–182°). [e] The reaction mixture was shielded from light. [f] The reaction was carried out with three times the theoretical amount of bromine for a total of nine hours. [g] Twice the theoretical amount of bromine was added fifteen minutes before the end of the reaction; the reaction was carried out for a total of nine hours. [h] The reaction was carried out with three times the theoretical amount of bromine.

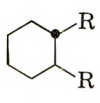
Before any interpretation of the data in Table I is presented, it would be well to consider some controls to determine whether the data can properly be interpreted solely in terms of the mechanism of the Hunsdiecker reaction. First, the optical activity of the product was shown to be activity of the dibromide and not of some impurity by identity of the infrared spectra, indices of refraction, and vapor chromatographic thermal cracking patterns of product and authentic *trans*-1,2-dibromocyclohexane; and especially by the constancy of the optical rotations in successive distillation fractions of the product. Second, it was shown that optical activity was not induced in racemic dibromide by reaction with optically active silver salt under the conditions of the Hunsdiecker reactions. Third, it was shown that the optically active dibromide

(1) D. E. Applequist and A. S. Fox, *J. Org. Chem.*, **22**, 1751 (1957).
(2) P. I. Abell, *ibid.*, **22**, 769 (1957).
(3) (a) C. C. Price and M. Schwarcz, *J. Am. Chem. Soc.*, **62**, 2891 (1940); (b) J. L. Fedrick, Ph.D. thesis, University of Illinois, 1959.
(4) A. Werner and H. E. Conrad, *Ber.*, **32**, 3046 (1899).

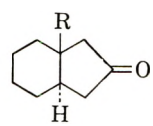
was not racemized at all by bromine in carbon tetrachloride at 31.3°, and in a Hunsdiecker reaction system (silver acetate) it was racemized to the extent of only 8.1% at 0° and 42% at 31.3°. Fourth, it was shown that *cis*-1,2-dibromocyclohexane was not isomerized to the *trans* isomer to a detectable extent under the conditions of a Hunsdiecker reaction (silver acetate), so the *trans* isomer is indeed the initial product of the reactions reported here. Fifth, it was shown that the *trans*-diacid recovered from a Hunsdiecker reaction of the active silver salt had not lost any optical activity in preparation of the silver salt or during the Hunsdiecker reaction.

A final question to be considered before specific mechanisms are proposed is that of the predominant stereochemistry (net inversion or net retention) of the reaction. Some efforts were made to determine the relative configurations of starting material and product directly by displacements on the dibromide with ammonia, azide, and cyanide, any of which might have given an inverted *trans* product which could easily be related to the diacid. The reaction with ammonia in *t*-butyl alcohol gave 3-aminocyclohexene as the only basic product.[5] Azide gave a similar result. The reaction with cyanide ion in acetonitrile or acetone gave no *trans*-1,2-cyclohexanedinitrile, which was hardly a surprising result.[6,7] However, the reaction of *trans*-dibromide with cyanide in dimethyl sulfoxide[8] gave a mixture of *cis*- and *trans*-1,2-cyclohexanedinitrile, which were separated by distillation and hydrolyzed to the corresponding acids. Unfortunately, the *trans*-diacid from optically active dibromide was racemic, possibly due to racemization in the reaction mixture after the displacement.

In view of the failure to obtain the relative configurations of diacid and dibromide directly, efforts were next directed toward the assignment of absolute configurations of both substances. The absolute configuration of (+)-*trans*-1,2-cyclohexanedicarboxylate was



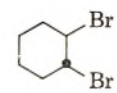
Ia. R = CO_2H
b. R = CH_2OH
c. R = CH_2OTs
d. R = CH_2CN
e. R = CH_2CO_2H



IIa. R = H
b. R = CH_3

found to be as shown in formula Ia. This assignment was accomplished by conversion of the diacid Ia ($[\alpha]^{27}D$ +21.9°) by lithium aluminum hydride reduction[9] to the glycol Ib ($[\alpha]^{27}D$ −20.2°), formation of the tosylate Ic ($[\alpha]^{28}D$ +25.0°, m.p. 109–109.7°),[10] conversion of Ic to the dinitrile Id ($[\alpha]^{25}D$ +64.7°),[11] and hydrolysis to the diacid Ie ($[\alpha]^{27}D$ +49.4°).[12] Ie had been converted to levorotatory *trans*-hexahydroindan-2-one[13] (IIa), whose absolute configuration was known from the identity of its optical rotatory dispersion curve with that of (−)-*trans*-8-methylhexahydroindan-2-one (IIb), which had been synthesized from compounds of known absolute configuration.[14]

The absolute configuration of (−)-1,2-dibromocyclohexane was assigned by comparison of its optical rotatory dispersion curve in cyclohexane with those of suitable dibromocholestanes. It was found that whereas cholestane gave a plain positive dispersion of moderate slope ($[\Phi]_{650}$ +81.4°, $[\Phi]_{300}$ +517°), both (−)-1,2-dibromocyclohexane and 2α,3β-dibromocholestane (diequatorial) gave plain negative dispersions of steeper slopes ($[\Phi]_{650}$ −28.3°, $[\Phi]_{300}$ −306° for the former, and $[\Phi]_{650}$ −118°, $[\Phi]_{300}$ −1390° for the latter). These facts by themselves suggest the configuration shown in formula III for (−)-1,2-dibromocyclohexane. In further confirmation of this assignment, the dispersion of 1α,2β-dibromocholestane (diaxial) was found to be a plain positive curve of moderate slope ($[\Phi]_{650}$ +166°, $[\Phi]_{300}$ +760°), suggesting that the fraction of III in the diaxial conformation would not have a rotation such as to reverse the assignment, a conclusion which is further confirmed by experiments described below. One unexpected observation was that 2β,3α-dibromocholestane (diaxial, opposite configuration from III) gave a plain positive dispersion ($[\Phi]_{650}$ +314°, $[\Phi]_{300}$ + 2840°) with much larger rotations and a steeper slope than either cholestane or the 1α,2β derivative, suggesting that diaxial bromines can under some conditions contribute to the rotation. The direction of that contribution in this case is, however, still in agreement with the configuration III for (−)-*trans*-1,2-dibromocyclohexane, whose rotation would then be the sum of negative contributions from both diaxial and diequatorial conformations.



III

Of particular significance is the fact that the dispersion curve of 2α,3β-dibromocholestane (diequatorial) from 300 mμ to 650 mμ is very nearly the sum of the curves for cholestane and III, provided that a weighting factor be applied to the latter curve. The weighting factor should be directly related to the optical purity of III and to the conformational equilibrium of III. Thus, a sample of III whose neat specific rotation was −21.4° was employed (next paragraph) to determine the specific rotation of the diequatorial conformer to be −41.2°. A sample whose neat rotation at 27.5° was −25.1° had a specific rotation in 2% cyclohexane solution at 27.5° of −24.4°. Since the rotatory dispersion curves were run under nearly the latter conditions (1% solutions of the neat −21.4° material in cyclohexane at 31°), molecular rotations of III at the seven wave lengths shown in the Experimental were multiplied by (41.2)(25.1)/(24.4)(21.4) = 1.98 to obtain molecular rotations of the diequatorial form. The resulting numbers were equal to 0.302 times the

(5) F. Hofmann and P. Damm, *Mitt. schles. Kohlenforschungsinst.*, **2**, 97 (1925); *Chem. Zentr.*, **1**, 2342 (1926).
(6) H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931).
(7) P. J. C. Fierens and P. Verschelden, *Bull. soc. chim. Belges*, **61**, 427 (1952).
(8) R. A. Smiley and C. Arnold, *J Org. Chem.*, **25**, 257 (1960).
(9) D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **72**, 5743 (1950).
(10) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953), had previously prepared the enantiomeric ditosylate, $[\alpha]^{21.5}D$ −24.8°, m.p. 109–110°.
(11) M. E. Ali and L. N. Owen, *ibid.*, 2111 (1953).
(12) W. Hückel, M. Sachs, J. Yantschulewitsch, and F. Nerdel, *Ann.*, **518**, 155 (1935).
(13) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 1069 (1935).
(14) (a) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); (b) P. M. Bourn and W. Klyne, *J. Chem. Soc.*, 2044 (1960).

difference between the molecular rotations of 2α,3β-dibromocholestane and cholestane at each wave length, with an average deviation of 6.2% and a maximum deviation of 9.6%. Such additivity of the curves could be expected only if the diaxial form has very little rotation or if its rotation is directly proportional to that of the diequatorial form as wave length is varied. The optical purity of the sample of III was then approximately 30%, and the maximum optical purity obtained from a Hunsdiecker reaction (Table I) was about 38%. Similar additivity of the dispersion curves was not observed for the other two dibromocholestanes, but this is perhaps not surprising in view of the possibilities for general distortion of the carbon skeleton by 1,3-diaxial interactions in these cases. The optical purities obtained by this procedure are unlikely to have more than qualitative significance, even when additivity is observed.

The conformational equilibrium of *trans*-1,2-dibromocyclohexane in solution has been studied with dipole moment measurements by Kwestroo, Meijer, and Havinga,[15] who found the substance to be 68% diaxial in carbon tetrachloride at 30° and 52% diaxial in benzene at 30°. From our observed rotations of one sample of III ($[\alpha]^{30}D$ −21.0° in CCl_4) in these solvents, one can calculate the specific rotations of the two conformers (assuming these rotations to be solvent independent) as $[\alpha]^{30}D$, axial −11.5°, and $[\alpha]^{30}D$, equatorial −41.2°. These observations and those on the dibromocholestanes (except the 2β,3α derivative) are in qualitative agreement with the empirical theory of Brewster,[16] which predicts the conformations Ia for the (+)-diacid and III for the (−)-dibromide, though the simple theory predicts no rotation for the diaxial conformer in the latter case.

Taken together, the foregoing evidence appears to provide sufficient basis for the assignment of III for the configuration of the Hunsdiecker product, which means that the reaction proceeds with net inversion of configuration.

Mechanistic Conclusions.—A considerable body of evidence may now be cited[17] in support of a mechanism for the simple Hunsdiecker reaction which consists of a free-radical chain decomposition of an intermediate acyl hypobromite. The following are probable propagation steps:

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \quad (1)$$

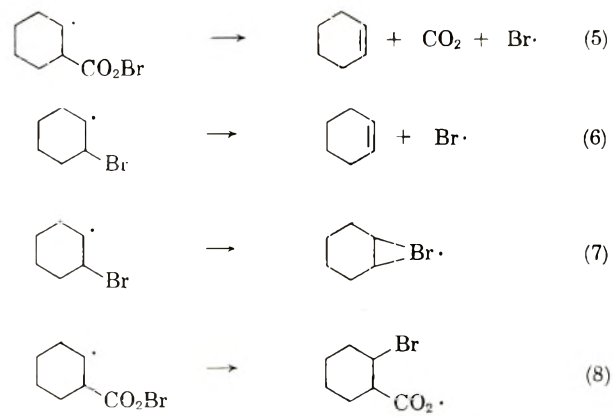
$$R\cdot + RCO_2Br \longrightarrow RBr + RCO_2\cdot \quad (2)$$

In the presence of excess bromine, the following steps probably are also involved:

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot \quad (3)$$

$$Br\cdot + RCO_2Br \longrightarrow RCO_2\cdot + Br_2 \quad (4)$$

The particular interest of the vicinal dicarboxylate system is that it could shed light upon the interactions of the neighboring functional groups and radicals involved in the mechanism, thereby confirming the mechanism shown above and/or revealing new properties of these functional groups and radicals. Several possible neighboring group involvements are shown in equations 5–8.



In order to accommodate the data of Table I and the controls described above, it is necessary to have a mechanistic scheme which includes an inversion pathway and either a retention pathway or a pathway leading to racemic product. In Chart I is presented a scheme of possibilities based upon reactions 1–8 and assuming (for the immediate discussion only) that the bishypobromite IV is an intermediate in all pathways. Decomposition of IV by reactions 9, 13, and 14, involving an intramolecular bromine atom transfer of type 8, appears to be the most reasonable mechanism for formation of inverted product III. Reactions 9–12, with steric control of entering bromine in steps 10 and 12, represent the classical Hunsdiecker mechanism (reactions 1–4) without specific neighboring group involvements, and could be expected to lead to dextrorotatory dibromide. It is felt that this pathway makes little if any contribution, since reaction 10 should be favored over 13 by increased bromine concentration, whereas a three-fold increase in initial bromine concentration (resulting in a larger ratio as the reaction proceeds) did not decrease the optical activity of the product (Table I). Furthermore, it will be noted that whereas under some conditions the activity of the product became almost nil, it always remained negative. The evidence then suggests most strongly that there is a racemate-producing mechanism in competition with 9, 13, and 14.

The most likely racemate-producing mechanisms are those which involve a cyclohexene intermediate (which would add bromine ionically under the reaction conditions) and those which involve a bridged-bromine radical, V, as an intermediate or as a transition state for racemization of the 2-bromocyclohexyl radical (VI). A strong argument against the participation of V is that its formation from VI in competition with reaction 14 would be favored by low bromine concentration, so that the failure of a threefold increase in bromine concentration to change the optical activity of product (Table I) argues against reaction 15 in the same way that it argues against 10. This result is a little surprising in view of recent demonstrations of rapid 1,2 shifts of bromine atoms and/or bridged bromine radicals by Skell, Allen, and Gilmour[18] and by Abell and Piette.[19] Particularly pertinent is the latter work, which showed by an elegant e.p.r. method that the radical from addition of bromine atom to cyclohexene in a glass at 77° K. is either the bridged

(15) W. Kwestroo, F. A. Meijer, and E. Havinga, *Rec. trav. chim.*, **73**, 717 (1954).

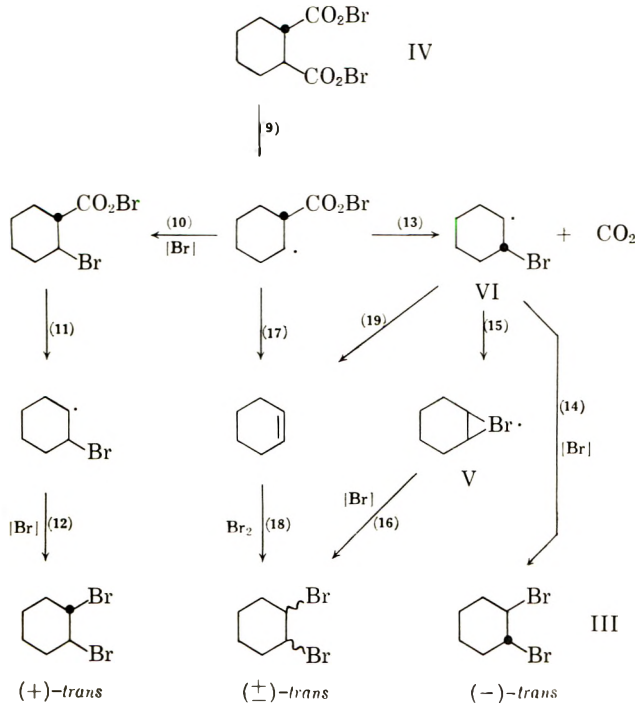
(16) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475, 5483 (1959).

(17) C. V. Wilson, *Org. Reactions*, **IX**, 332 (1957).

(18) P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.*, **83**, 504 (1961).

(19) P. I. Abell and L. H. Piette, *ibid.*, **84**, 916 (1962).

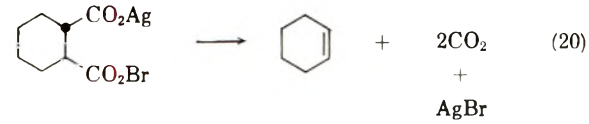
CHART I
HOMOGENEOUS FREE-RADICAL MECHANISMS



radical V or a classical 2-bromocyclohexyl radical (VI) which is racemizing by bromine migration at a rate of at least 10^7 sec.$^{-1}$ The present results certainly argue in favor of the oscillating classical structure rather than the bridged structure, a distinction which the e.p.r. studies could not make. The failure of radical VI to racemize in the present work is not inconsistent with the e.p.r. studies, since if one assumes a normal bimolecular frequency factor[20] (10^{11}) for reaction of VI with bromine (or acyl hypobromite) and a low activation energy[21] (<3 kcal.) for this process, then the lifetime of VI under the Hunsdiecker conditions would be substantially less than 10^{-7} seconds.

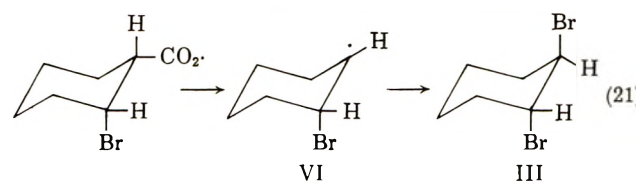
If we grant that V is not responsible for the racemic product, then we are left with paths through cyclohexene as the only obvious racemate-producing mechanisms.[22] Loss of a bromine atom from VI, though a known reaction type,[23] is ruled out in the present work again by the insensitivity of the optical yield to bromine concentration. Reaction 17 might form cyclohexene in a path whose competition with the inversion mechanism (reaction 13) would be independent of bromine concentration.

Left unsettled by the above discussion is the cause of the erratic optical yields (Table I) which while reproducible enough to establish independence of bromine concentration, were nevertheless scattered considerably more than one would expect from a simple competition of reactions 13 and 17, which should lead only to small variations in optical yield, due to slight temperature variations. A possible explanation is the formation of cyclohexene by a heterogeneous reaction,



20, which would be affected by a number of difficultly-controlled variables in experimental conditions. Although the case is good for a homogeneous decomposition of a hypobromite in most Hunsdiecker reactions[17] (the usual lack of stereospecificity and the demonstrations of metastable, silver-free solutions of acyl hypobromites being especially significant evidence), such a homogeneous pathway is not independently supported by the evidence presented here, and since nothing comparable to reaction 20 can be expected in simpler systems, the previous knowledge cannot be used to argue against it.

Although we have argued that reaction 14 must be responsible for the inverted product and that there is no significant amount of *cis*-dibromide formed, it is not possible to conclude that reaction 14 gives the *trans* product stereospecifically, unless we know the optical yield of the reaction. This was proposed to be as high as 38% by analogy with the observed molecular rotations of cholestane and 2α,3β-dibromocholestane (above). If this number is valid and since the infrared method will detect as little as 5% of the *cis*-dibromide in the *trans* product, then we can conclude that reaction 14 must be at least 85% stereospecific to give *trans* product. Such specificity is comparable with that observed in the reaction of the 1,2-dibromocyclohexyl radical with hydrogen bromide, which has been discussed by others.[24] Of the explanations which have been offered in that case, the only one which appears applicable to reaction 14 is a conformational control,[25] as shown in reaction 21. It is possible that



the diaxial arrangement is the preferred transition state for the conversion of VI to III, or that this reaction takes place by preferential axial attack before conformational equilibration of VI (which may have an energy barrier as high as 10 kcal.[26]) takes place.

Experimental[27]

trans-**1,2-Cyclohexanedicarboxylic Acid.**[3]—A mixture of 100 g. (0.65 mole) of *cis*-1,2-cyclohexanedicarboxylic anhydride (Matheson, Coleman and Bell), 100 ml. of absolute ethanol, 300 ml. of benzene, and 1 ml. of sulfuric acid was heated under

(20) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 130.

(21) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 374.

(22) Exotic possibilities, such as bromine oxidation of VI to a cyclic bromonium ion, may be written and cannot be ruled out with the evidence available, but are not discussed in detail simply because they seem not to have close analogies.

(23) Ref. 21, p. 302.

(24) Ref. 19 and papers cited therein.

(25) H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **77**, 3465 (1955).

(26) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 205.

(27) All melting points and boiling points are uncorrected unless otherwise specified. The infrared spectra were obtained with a Perkin–Elmer Infracord or a Perkin–Elmer spectrophotometer, Model 21B, both with sodium chloride optics. The nuclear magnetic resonance spectra were measured at 60 Mc. on a Varian nuclear magnetic spectrophotometer, Model V-4300 B. The optical rotatory dispersions were determined on a Rudolph recording spectropolarimeter, Model 260/655/850/810-614. Thanks are due to Dr. Max Marsh of the Eli Lilly Co. for assistance in determining the dispersions and for the use of its instrument. Experimental details not given here are to be found in the Ph.D. thesis of N. D. Werner, University of Illinois, 1962.

reflux with continuous removal of the water–benzene–ethanol azeotrope for 10 hr. The solution was then washed with 5% aqueous sodium bicarbonate and water. The solvent was removed under reduced pressure to give 122 g. (79%) of crude diethyl ester, which was added to an ethanolic solution of sodium ethoxide prepared from 5.0 g. (0.22 g.-atom) of sodium and 1.3 l. of absolute ethanol. The solution was heated at reflux overnight. An aqueous solution of 150 g. (2.68 moles) of potassium hydroxide in 1.3 l. of water was added to the cloudy yellow reaction mixture. The reaction mixture was then heated at reflux for 4 hr. The ethanol was distilled while the solution was kept at constant volume by the continuous addition of water. After most of the ethanol had been removed, the solution was filtered to remove solid impurities. The pH of the solution was adjusted to a value of approximately 2 with concentrated hydrochloric acid. The white solid was collected on a filter and washed with ice–water. The solid was dried in an oven (130°) for 3 hr. The yield of the *trans*-diacid was 71 g. (81% based upon ester), m.p. 227–229° (lit.,[3] m.p. 227–229°).

Resolution of (±)-*trans*-1,2-Cyclohexanedicarboxylic Acid.—A solution of 43 g. (0.25 mole) of (±)-*trans*-1,2-cyclohexanedicarboxylic acid in 370 ml. of 95% ethanol was heated to boiling and then added slowly (heat was evolved) to a hot solution of 162 g. (0.50 mole) of quinine in 950 ml. of 95% ethanol. The combined solution was heated to boiling and then filtered. The filter was washed with 195 ml. of hot 95% ethanol. The solution was cooled overnight and the solid was then removed by filtration to give 117 g. (95%) of a white crystalline material. After three more recrystallizations from 95% ethanol, the diastereomer was sufficiently pure to give (+)-*trans*-1,2-cyclohexanedicarboxylic acid with high optical purity. The yield of pure quinine salt was 55 g. (45% based upon isolation of one diastereomer). Fifty grams (0.089 mole) of the quinine salt was added in portions to 500 ml. of a sulfuric acid–water solution (1:4) in an ice bath. The solution was then continuously extracted with ether for 2 days. The ether was removed on a steam bath and 10.3 g. (100%) of (+)-*trans*-1,2-cyclohexanedicarboxylic acid was obtained, m.p. 183.5–185.0° (lit.,[4] m.p. 179–183°); $[\alpha]^{30}D$ in acetone +22.3° (c = 5.3) (lit.,[4] $[\alpha]^{20}D$ +18.2°).

Silver *trans*-1,2-Cyclohexanedicarboxylate.—A mixture of 20.0 g. (0.116 mole) of *trans*-1,2-cyclohexanedicarboxylic acid in 200 ml. of water was titrated with 1 *M* aqueous sodium hydroxide to a phenolphthalein end point. The solution was filtered. A solution of 40.0 g. (0.235 mole) of reagent grade silver nitrate in 200 ml. of water was added over a 25-min. period to the neutralized solution of the *trans*-diacid. The addition of the silver nitrate solution was carried out in diffuse light and the reaction mixture was stirred continuously during the addition. The white precipitate was collected on a filter and washed with water, ethanol, and ether. The silver salt was dried in a vacuum desiccator over phosphorus pentoxide for several days at room temperature. The yield was 43.6 g. (97.8%).

***trans*-1,2-Dibromocyclohexane** was prepared in the manner described by Snyder and Brooks.[28] The product boiled at 76–78° at 4.5 mm., $n^{25}D$ 1.5483 (lit.,[28] b. p. 99–103° at 16 mm., $n^{25}D$ 1.5510[2]).

Brominative Decarboxylation of Optically Active Silver *trans*-1,2-Cyclohexanedicarboxylate.—To an ice-cooled solution of 8.3 g. (0.052 mole) of bromine (dried over phosphorus pentoxide) in 200 ml. of dry carbon tetrachloride was added over a 1-hr. period 10.0 g. (0.026 mole) of dry optically active silver *trans*-1,2-cyclohexanedicarboxylate. After the addition of silver salt was completed the suspension was stirred for seven more hours at 0°. The solid was then collected on a filter and washed with carbon tetrachloride. The combined carbon tetrachloride solutions were washed with 10% aqueous sodium bisulfite solution, 10% aqueous sodium bicarbonate solution, and water. The carbon tetrachloride solution was dried over anhydrous magnesium sulfate and distilled under reduced pressure to obtain 1.30 g. of colorless distillate and 0.3 g. of a nonvolatile, gummy residue. The distillate was taken up in 10 ml. of hexane (distilled over sodium) and chromatographed on 25 g. of neutral alumina. Hexane was used as an eluent to remove the expected *trans*-1,2-dibromocyclohexane from the column. The hexane was distilled on the steam bath and the residual liquid was distilled through a modified Holzman semimicro column.[29] The distillation yielded 0.90 g. (14%) of a colorless liquid boiling at 53–55° (1.4 mm.). The infrared spectrum of this liquid was identical to that of an authentic sample of *trans*-1,2-dibromocyclohexane, $n^{21}D$ 1.5511 (lit.[2] $n^{26}D$ 1.5510); $[\alpha]^{22}D$ (neat) −27.0°. In a similar Hunsdiecker reaction the specific rotations of two consecutive distillation fractions were the same within experimental error of the polarimetric measurement. The distillation residue from one run showed intense infrared absorption at 1740 cm.$^{-1}$ and 1820 cm.$^{-1}$. A sample of the dibromide decomposed in the injection port of a gas chromatograph (at 180–250°), but the pattern of peaks thus produced was identical to that obtained from an authentic sample of *trans*-1,2-dibromocyclohexane.

A very similar procedure was used for reactions at 31.3°, the addition time being 15 min. and the total reaction time being 60 min. (see Table I).

The following analysis was obtained from a sample of (−)-*trans*-1,2-dibromocyclohexane prepared by a Hunsdiecker reaction.

Anal. Calcd. for $C_6H_{10}Br_2$: C, 29.77; H, 4.17. Found: C, 30.09; H, 4.12.

It was shown by iodimetric titration in one run at 0° that after 8.3 hr., only 40% of the theoretical bromine (or hypobromite) had been consumed. It was further found that a 38% yield of recovered diacid, with undiminished optical rotation, could be isolated from such a reaction mixture by ether extraction of the acidified aqueous washings.

Silver Acetate.—The preparation was carried out in diffuse light. A solution of 15.0 g. (0.183 mole) of reagent grade sodium acetate in 50 ml. of water was prepared. A solution of 31.0 g. (0.183 mole) of reagent grade silver nitrate in 50 ml. of water was added dropwise to the aqueous sodium acetate solution. The white precipitate was collected on a filter, washed with water, ethanol, and reagent grade ether. The silver acetate was dried in a vacuum desiccator over phosphorus pentoxide for several days at room temperature. The yield was 22.0 g. (72%).

Stability of (−)-*trans*-1,2-Dibromocyclohexane.—In an apparatus similar to that used for the above Hunsdiecker reactions, 7.8 g. (0.047 mole) of silver acetate was added over a period of 1 hr. to an ice-cooled solution of 11.2 g. (0.070 mole) of bromine (dried over phosphorus pentoxide) and 0.63 g. (0.0026 mole) of (−)-*trans*-1,2-dibromocyclohexane ($[\alpha]^{22}D$ (neat) −27.0°) in 200 ml. of dry carbon tetrachloride. The reaction mixture was stirred for an additional 7 hr., and then treated in the same manner as described for the Hunsdiecker reactions above. The yield of recovered *trans*-1,2-dibromocyclohexane was 0.35 g., $n^{22}D$ 1.5524, $[\alpha]^{22}D$ (neat) −24.8°, corresponding to 8.1% racemization. The infrared spectrum was identical with that of an authentic sample.

When the same experiment was performed at 31.3° (1 hr.) instead of 0°, a sample of dibromide with $[\alpha]^{26}D$ −6.12° gave recovered dibromide with $[\alpha]^{26}D$ −3.55° (42% racemized).

When a similar experiment was done at 31.3° (1 hr.) but without any silver acetate present, the dibromide was recovered in 82% yield with undiminished rotation.

Stability of (±)-*trans*-1,2-Dibromocyclohexane.—To 6.3 g. (0.039 mole) of (±)-*trans*-1,2-dibromocyclohexane in 200 ml. of dry carbon tetrachloride at 0° was added 5.0 g. (0.013 mole) of optically active silver *trans*-1,2-cyclohexanedicarboxylate in portions. The mixture was stirred for 8 hr. at 0° and the silver salt then collected on a filter and washed with carbon tetrachloride. The carbon tetrachloride was distilled under reduced pressure and distillation of the residual liquid through a modified Holzman semimicro column gave 5.9 g. (94%) of *trans*-1,2-dibromocyclohexane boiling at 50–52° (1.0 mm.), $n^{26}D$ 1.5489. The infrared spectrum was identical to that of an authentic sample. The recovered *trans*-1,2-dibromocyclohexane exhibited no optical rotation within experimental error.

A similar experiment conducted at 31.3° for 1 hr. gave the same result.

Stability of *cis*-1,2-Dibromocyclohexane under Conditions of the Hunsdiecker Reaction.—*cis*-1,2-Dibromocyclohexane was prepared according to a published procedure.[30] The material obtained boiled at 54–56° (0.3 mm.), $n^{28.5}D$ 1.5490 (lit.,[30b] $n^{25}D$ 1.5509).

In an apparatus similar to that used for the Hunsdiecker reactions, immersed in a constant temperature bath at 31.3°, was placed a solution of 5.5 g. (0.034 mole) of bromine (dried

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over phosphorus pentoxide) in 127 ml. of dry carbon tetrachloride. The solution was stirred for 0.5 hr. and then 1.0 g. (0.0041 mole) of *cis*-1,2-dibromocyclohexane was added over a 15-min. period. The reaction mixture was stirred for an additional 45 min. The silver bromide was collected on a filter and washed with carbon tetrachloride. The carbon tetrachloride solution was washed with 10% aqueous sodium bisulfite, 10% aqueous sodium bicarbonate, and water. The carbon tetrachloride solution was dried over sodium sulfate and distilled at reduced pressure. Distillation of the residual liquid through a modified Holzman semimicro column gave 0.92 g. of a colorless liquid, b.p. 50–60° (1.6 mm.); $n^{25}D$ 1.5635. A bromine analysis indicated that this liquid contained 69.75% bromine. A comparison of the infrared spectrum of this liquid with those of authentic *cis*-1,2-dibromocyclohexane and authentic *trans*-1,2-dibromocyclohexane showed that the spectrum of the liquid contained all the absorption maxima characteristic of the *cis*-dibromide, but none that could be ascribed definitely to the *trans*-dibromide. It was estimated that the liquid contained not more than 5% of the *trans*-dibromide, if any at all.

The Reaction of Optically Active *trans*-1,2-Dibromocyclohexane and Sodium Cyanide in Dimethyl Sulfoxide.—To a mixture of 2.4 g. (0.049 mole) of sodium cyanide (vacuum dried) and 40 ml. of dimethyl sulfoxide (passed through a column of molecular sieves, Linde Co., Type 4A, and then distilled) was added dropwise 5.0 g. (0.022 mole) of (−)-*trans*-1,2-dibromocyclohexane ($[\alpha]^{23.5}D$ neat −11.0°). The reaction mixture was heated at 85° for 10.5 hr., then poured into a saturated aqueous sodium chloride solution, and this mixture was extracted with four portions of chloroform. The chloroform solution was dried over sodium sulfate, the chloroform was removed under reduced pressure, and the residue was taken up in ether except for a small amount of brown solid which did not dissolve. The ether was removed on a steam bath and the residual liquid was distilled to give 0.96 g. of material, b.p. 105–110° (0.4 mm.). A portion of this material (0.84 g.) was chromatographed on neutral alumina, and elution with 30% benzene–hexane gave a fraction, which after evaporation of the solvent contained 0.36 g. of solid. Further elution with 30% benzene–hexane gave two more fractions which contained 0.21 g. and 0.10 g. of material, respectively. The first fraction was recrystallized from low boiling petroleum ether to give 0.21 g. of dinitrile, m.p. 47–48.5° (cor.). An infrared spectrum had an absorption maximum at 2240 $cm.^{-1}$. A 30% solution of this material in benzene exhibited no optical activity within experimental error. A suspension of 97 mg. (0.00074 mole) and 4 ml. of 2 *N* nitric acid was heated at reflux for 24 hr. After the solution had cooled, 95 mg. (76%) of *trans*-1,2-cyclohexanedicarboxylic acid precipitated, m.p. 227.9–228.7° (cor.) (lit.,[31] m.p. 227–229°). An optical rotatory dispersion curve obtained on a 2% solution in absolute ethanol indicated that the diacid possessed no optical activity within experimental error.

A reaction run in the same way on 5 g. of optically inactive dibromide was examined more carefully, and was found to yield 0.16 g. of *cis*-1,2-cyclohexanedinitrile, m.p. 62–64° (lit.,[32] m.p. 63–65°), hydrolyzable with 2 *N* nitric acid to *cis*-diacid (compared with an authentic sample) and 0.68 g. of a more volatile, lower melting, impure *trans*-dinitrile, which was hydrolyzable to nearly pure *trans*-diacid.

Reaction of Ammonia with *trans*-1,2-Dibromocyclohexane.—A solution of 3 g. (0.18 mole) of anhydrous ammonia and 7.5 g. (0.031 mole) of *trans*-1,2-dibromocyclohexane in 50 ml. of dry *t*-butyl alcohol was heated in a sealed tube for 64 hr. at 91–112°. The *t*-butyl alcohol was distilled through a packed 12-in. Vigreux column and the residual liquid was then taken up in 2 *N* hydrochloric acid and extracted with ether. The acidic aqueous solution was then made basic (pH >11) with sodium hydroxide and continuously extracted with ether for 1 week. An Ascarite drying tube protected the extraction system from carbon dioxide in the atmosphere. The ether was distilled through a packed 12-in. Vigreux column and the residual liquid was distilled through a modified Holzman semimicro column. Two colorless liquid fractions were obtained. The first fraction weighed 0.98 g., b.p. 50° (2 mm.), and the second fraction weighed 0.23 g. Vapor phase chromatography indicated that the first fraction was a pure compound while the second fraction consisted mainly (>95%) of the compound present in the first fraction. This compound, which was obtained in 40% yield, was 3-aminocyclohexene as characterized by the formation of the 2,4-dinitrophenyl derivative, which was prepared in the usual manner,[33] m.p. 107–108°.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.84; H, 4.88; N, 16.14.

A similar displacement was attempted with sodium azide in dimethyl sulfoxide solvent at 85° for 7.5 hr. The resulting organic azide was reduced without careful purification by lithium aluminum hydride in ether to obtain a small yield of amine which yielded the same 2,4-dinitrophenyl derivative, m.p. 107.5–108.5°, though satisfactory elemental analyses could not be obtained in this case.

Anal. Found: C, 55 29; H, 4.90; N, 16.59.

(−)-*trans*-1,2-Bis(hydroxymethyl)cyclohexane.—A solution of 10.0 g. (0.058 mole) of (+)-*trans*-1,2-cyclohexanedicarboxylic acid ($[\alpha]^{27}D$ +21.9°) in 220 ml. of dry ether was added to a stirred refluxing suspension of 8.8 g. (0.23 mole) of lithium aluminum hydride in 300 ml. of ether at such a rate as to maintain gentle reflux. After the addition was completed the reaction mixture was heated at reflux for 8 hr. The excess lithium aluminum hydride was then decomposed with 8.8 ml. of water (carefully), 8.8 ml. of aqueous 15% sodium hydroxide solution, and 25.4 ml. of water. The suspension was stirred for 25 min. and the solid was collected on a filter and washed with ether. The ether was evaporated on a steam bath and a clear, slightly yellow oil was obtained which crystallized slowly. The white solid was dissolved in benzene and hexane was added until the solution became slightly cloudy. The solution was placed in a −20° freezer overnight and the solid was collected on a filter and washed with hexane–benzene. The solid was air dried and 6.9 g. (82%) of (−)-*trans*-1,2-bis(hydroxymethyl)cyclohexane was obtained, m.p. 63–64°; $[\alpha]^{24}D$ (in benzene) −20.2° (c = 4.0) [lit.,[10] m.p. 61–62°; $[\alpha]^{24}D$ +21.4° (enantiomer)].

(+)-*trans*-1,2-Bis(hydroxymethyl)cyclohexane Di-*p*-toluenesulfonate.—The ditosylate was prepared in a manner similar to that described by Ali and Owen.[11] Six grams (0.039 mole) of (−)-*trans*-1,2-bis(hydroxymethyl)cyclohexane in 21.8 ml. of dry pyridine was added dropwise over 30 min. to a vigorously stirred solution of 18.0 g. (0.094 mole) of *p*-toluenesulfonyl chloride in 38 ml. of dry pyridine in an ice bath. The reaction mixture was then stirred at room temperature for 0.5 hr. and poured into an ice–water mixture. A viscous oil formed which soon crystallized. The solid was collected on a filter, washed with ice–water, and recrystallized from methanol to give 11.1 g. (65%) of the ditosylate, m.p. 109–109.7°; $[\alpha]^{28}D$ (in benzene) (+25.0° (c = 5.0) [lit.,[10] m.p. 109–110°; $[\alpha]^{21.5}D$ −24.8° (enantiomer)].

(+)-*trans*-1,2-Cyclohexanediacetonitrile was prepared in a manner similar to that described by Ali and Owen[11] for the racemic dinitrile. To a mixture of 4.6 g. (0.071 mole) of reagent grade potassium cyanide and 73 ml. of 90% ethanol was added 11.0 g. (0.0243 mole) of (+)-*trans*-1,2-bis(hydroxymethyl)-cyclohexanedi-*p*-toluenesulfonate. The mixture was heated to boiling and a clear solution was obtained. This solution was heated at reflux for 67 hr. and then concentrated at reduced pressure. The residue was taken up in saturated aqueous sodium chloride solution and extracted four times with ether. The ether solution was washed twice with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The ether was removed on a steam bath and a viscous oil which crystallized slowly was obtained. A recrystallization from benzene–hexane gave 1.8 g. of a yellow crystalline solid, m.p. 57–63°. A small amount of this solid was sublimed at 54° (0.2 mm.) to give a white solid, m.p. 62–63° (cor.) which was analyzed.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.30; H, 8.77; N, 16.94.

The benzene–hexane mother liquor was evaporated to dryness and the solid was recrystallized from ether to give 0.49 g. of a white solid, m.p. 62–63°; $[\alpha]^{25}D$ (in benzene) +64.7° (c=5.0). The total yield of (+)-*trans*-1,2-cyclohexanediacetonitrile was 58% of theoretical.

(+)-*trans*-1,2-Cyclohexanediacetic Acid.—The procedure used was similar to that described by Ali and Owen[11] for the preparation of the racemic diacid. A solution of 1.7 g. (0.011 mole)

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of (+)-*trans*-1,2-cyclohexanediacetonitrile and 30 ml. of 50% aqueous sulfuric acid solution was heated at reflux for 4 hr. When the solution cooled, solid precipitated and was collected on a funnel and washed with cold water. The solid was recrystallized from methanol to give 1.28 g. (61%) of (+)-*trans*-1,2-cyclohexanediacetic acid, m.p. 149–150°; $[\alpha]^{27}D$ (absolute ethanol) +49.4° (c=5.0) (lit.,[12,13] m.p. 152°; $[\alpha]^{19.5}D$ +48.28°).

Measurement of the Dependence of the Optical Activity of *trans*-1,2-Dibromocyclohexane on Solvent.—The measurements were made in a 1-dm. polarimeter tube which was maintained at 30.0°. The measurements were made on solutions which were prepared in the following manner: Approximately 0.2 g. of (−)-*trans*-1,2-dibromocyclohexane (weighed to four significant figures) was placed in a 2-ml. volumetric flask and diluted to the mark with the appropriate solvent. The values listed for benzene and carbon tetrachloride solutions are the results of duplicate determinations, while those listed for dioxane and absolute ethanol solutions are the results of single determinations. The benzene used was reagent grade benzene which had been distilled from sodium and the dioxane was purified by the method of Hess and Frahm.[34] The carbon tetrachloride and the absolute ethanol used were reagent grade solvents which were not purified further. The values obtained for the specific rotations in various solvents are listed in Table II.

TABLE II

SPECIFIC ROTATION OF *trans*-1,2-DIBROMOCYCLOHEXANE IN VARIOUS SOLVENTS AT 30.0°

Solvent	$[\alpha]^{30.0}D$
Benzene	−25.8°
Dioxane	−23.7
Absolute ethanol	−22.5
Carbon tetrachloride	−21.0

2-Bromocholestan-3-one was prepared from cholestanone[35] (m.p. 129.0–129.6°) by a modification of the procedure of Butenandt and Wolff.[36] Six drops of a 40% aqueous hydrogen bromide solution were added to a solution of 12.0 g. (0.031 mole) of cholestanone in 360 ml. of glacial acetic acid. A solution of 5.4 g. (0.034 mole) of bromine in 12 ml. of glacial acetic acid was added in a dropwise manner to this solution and the total solution concentrated under reduced pressure. The solid residue was recrystallized from ethanol–acetone to give 10.0 g. (69%) of 2-bromocholestan-3-one, m.p. 167–169° (lit.,[36] m.p. 169–170°).

2β,3α-Dibromocholestane was prepared from 2-bromocholestan-3-one by the method of Alt and Barton[37] in 18% over-all yield, m.p. 123.7–124.7° (lit.,[37] m.p. 123–124°). The n.m.r. spectrum had broad, overlapping low-field signals at about 274 and 283 c.p.s. from tetramethylsilane.

2α,3β-Dibromocholestane was prepared by thermal isomerization[37] of the 2β,3α isomer at 180–190°, m.p. 145–146° (lit.,[37] m.p. 144–145°). The n.m.r. spectrum had broad overlapping low-field signals at about 239 and 248 c.p.s. from tetramethylsilane.

Cholestane.—A suspension of 300 mg. (0.0008 mole) of Δ^2-cholestene dissolved in 70 ml. of reagent grade ethyl acetate and 82 mg. of platinum oxide catalyst was subjected to a hydrogen atmosphere of 35 lbs./sq. in. on a Parr shaker for 73 hr. at room temperature. The catalyst was collected on a filter and the solvent was removed under reduced pressure. The residue was chromatographed on neutral alumina and eluted with hexane. The hexane was distilled and the solid residue was recrystallized from ether–ethanol to give 212 mg. (70%) of cholestane, m.p. 79.5–80.5° (lit.,[38] m.p. 79.5–80°).

Δ^1-Cholestene.—2-Bromocholestan-3-one was converted to Δ^1-cholestenone semicarbazone by the method of Djerassi,[39] and the semicarbazone was converted to the ketone by the method of Hershberg.[40] The ketone was in turn reduced to Δ^1-cholesten-3-ol by the method of Bergmann, Kita, and Giancola,[41] and the alcohol converted to Δ^1-cholestene as described by Henbest and Wilson.[42] The over-all yield from 2-bromocholestan-3-one was 13%, m.p. 66–67° (lit.,[42] m.p. 69°).

1α,2β-Dibromocholestane was prepared by bromination of Δ^1-cholestene both by the method of Henbest and Wilson[42] (36% yield, m.p. 133–134°) and by the method of Grob and Winstein[43] (30% yield, m.p. 130–131°, no depression of mixed melting point with the former sample). The n.m.r. spectrum showed broad but clearly separated signals at 273 and 293 c.p.s. from tetramethylsilane.

Attempts to isomerize the 1α,2β-dibromide to the 1β,2α isomer by heating it to 180–190° for 7 hr. or by treatment with anhydrous zinc bromide in refluxing cyclohexane gave no isolable isomerization product, but only recovered starting material (35% and 64% yields, respectively).

Optical Rotatory Dispersion Studies.—The measurements were carried out with a Rudolph recording spectropolarimeter, and a 1-dm. polarimeter tube with quartz end plates was used for all determinations. A scanning speed of 25 min. was used except for the solvent blank, when a scanning speed of 12.5 min. was used. Duplicate determinations were made in all cases except for *trans*-1,2-dibromocyclohexane. Eastman spectro grade cyclohexane was the solvent used in all determinations and the concentrations of all solutions were approximately 1%. The determinations were carried out at a temperature range between 30 and 31°. The values listed are molecular rotations, [Φ]:

Cholestane; plain positive curve (650 mμ) +81.4; (600) +95.5; (589) +103; (500) +149; (400) +248; (350) +346; (300) +517.

2β,3α-Dibromocholestane; plain positive curve (650 mμ) +314; (600) +380; (589) +401; (500) +624; (400) +1.10 × 10^3; (350) + 1.64 × 10^3; (300) +2.84 × 10^3.

2α,3β-Dibromocholestane; plain negative curve (650 mμ) −118; (600) −138; (589) −143; (500) −246; (400) −458; (350) −749; (300) −1.39 × 10^3.

1α,2β-Dibromocholestane; plain positive curve (650 mμ) +166; (600) +198; (589) +206; (500) +306; (400) +477; (350) +621; (300) +760.

(−)-*trans*-1,2-Dibromocyclohexane; plain negative curve (650 mμ) −28.3; (600) −32.8; (589) −35.0; (500) −61.3; (400) −118; (350) −176; (300) −306.

The sample of (−)-*trans*-1,2-dibromocyclohexane used had a neat rotation (polarimeter) $[\alpha]^{26.5}D$ −21.4°. Another sample whose neat rotation was $[\alpha]^{27.5}D$ −25.1° gave a specific rotation $[\alpha]^{26.5}D$ −24.4° as a 2% solution in cyclohexane.[44]

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Mr. Josef Nemeth and his associates performed the microanalyses, Messrs. Paul McMahon and Dick Johnson and their associates supplied infrared spectra, and Mr. O. W. Norton and his associates determined the n.m.r. spectra.

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Decomposition of Tertiary Alkyl Hypochlorites[1]

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The scope of the decomposition of tertiary alkyl hypochlorites has been investigated (Table I). Decomposition proceeds by a free radical chain reaction of long chain length (Table II). Principal reactions of the intermediate alkoxy radicals are (1) fragmentation to ketone and alkyl radical and (2) intramolecular hydrogen abstraction. The relative ease of ejection of alkyl radical in the fragmentation of alkoxyl is isopropyl > ethyl > 1-norbornyl (1-bicyclo[2.2.1]heptyl) ~ methyl. Ring strain appears to be of importance in determining the direction of fragmentation—*e.g.*, in 1-isopropyl-1-cyclopentoxyl radical, rate of ring opening to the primary radical $(CH_3)_2CH—CO—(CH_2)_3—CH_2\cdot$ exceeds rate of ejection of isopropyl radical. Intramolecular hydrogen abstraction may predominate over fragmentation and occurs principally *via* "1,5" transfer of hydrogen, leading to α,δ-chlorohydrins. Subsequent cyclization renders this a convenient route to a number of substituted tetrahydrofurans. Intermolecular hydrogen abstraction from cyclohexene (solvent) competes poorly with "1,5" intramolecular hydrogen abstraction.

Alkyl hypochlorites, a class of compounds readily available from the corresponding alcohols, have been known for many years and have received attention principally as chlorinating agents[3] and oxidants.[4] Recently, attention has been directed to the thermal and photochemical decomposition of hypochlorites.[1a,5-7] The tertiary hypochlorites have been shown in a number of isolated examples to undergo decomposition to carbonyl compounds and alkyl chlorides. For a few

$$R_3C—O—Cl \longrightarrow R_2CO + RCl$$

of these cases, strong evidence exists for decomposition by a radical chain reaction.[8] This study reports the results of decomposition of a series of hypochlorites which serve to outline the scope and limitations of this degradation reaction of alcohols. Principal questions concern: (1) the generality of decomposition by a radical chain reaction, (2) the involvement of alkoxyl radicals and selectivity in fragmentation of these species, and (3) the reactions of alkoxyl radicals competitive with fragmentation, such as inter- and intramolecular hydrogen abstraction.

Results

The hypochlorites were prepared by the action of hypochlorous acid on the alcohols. The decompositions were effected thermally or photochemically in Freon 11 (trichlorofluoromethane), carbon tetrachloride, or cyclohexene. Products were isolated by gas phase chromatography. In most cases an accounting is made for 80–90% of the hypochlorite. (Decompositions in Freon 11 and in carbon tetrachloride occasionally have afforded high-boiling polyhalogenated material, believed to be products of olefin–solvent addition reactions.) The product compositions are fairly insensitive to initial concentrations of hypochlorite but optimum yields are obtained in the region 0.5–1.5 *M* under degassed and dry conditions. At high hypochlorite concentrations, an undesirable side reaction—intermolecular chlorination affording α-chloro ketones—may occur (**4**–**6**). The product data of this study are summarized in Table I.

Structural Assignments.—Identification of all of the products in Table I of known structure was made by direct comparison of infrared spectra and gas–liquid phase chromatography (g.l.p.c.) retention times with authentic samples. Of the new compounds of Table I, assignment of structure to alcohols of **3**, **11**, and **12** and to methyl 1-norbornyl ketone is based on mode of synthesis and infrared spectral data. Assignment of structure to the chlorohydrins from **8** and **9** is based on cyclization by the action of sodium hydride in ether to the corresponding tetrahydrofurans and comparison with samples made by independent routes. The structures of the olefins from **3** and **12** and the chloro olefins from **8** and **9** are based on identity with the products of dehydration of the corresponding tertiary alcohols. Assignment of the *exo*-methylene position to the double bond in the olefins from **3** and the chloro olefins from **8** and **9** is based on the strong terminal methylene absorption at 890 cm.$^{-1}$ in the infrared. The isopropylidene structure for the olefin from **12** is based on oxidation by osmium tetroxide and cleavage of the resulting diol by lead tetraacetate to give 2-norbornanone, established by direct comparison of the 2,4-dinitrophenylhydrazone derivative with an authentic sample. Assignment of structure to the chloro ketones from **5**, **6**, and **7** is based on infrared and n.m.r. data, outlined here in detail for the chloro ketone from **5**, 1-chloro-6-octanone. The analysis and infrared spectra indicate that the product is an acyclic saturated chloro ketone. The

N.m.r. of	CH_3—	—CH_2—	—$\overset{O}{\overset{\|}{C}}$—	—CH_2—	—$(CH_2)_3$—	—CH_2Cl
Description	Triplet	Quartet		Triplet	Multiplet	Triplet
tau	8.96	7.57		7.57	8.4	6.47
Approx. rel. area	3	2		2	6	2
J, c.p.s.	7.2	7.2		6.3		6.2

(1) (a) For a preliminary account of work in this area, see F. D. Greene, M. L. Savitz, H. H. Lau, F. D. Osterholtz, and W. N. Smith, *J. Am. Chem. Soc.*, **83**, 2196 (1961). (b) This work was supported by grants from the Sloan Foundation and the National Science Foundation.

(2) This paper is dedicated to the memory of Paul M. Zanet, who began the work of these laboratories on the hypochlorites.

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(5) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **83**, 2207 (1961).

(6) J. S. Mills and V. Petrow, *Chem. Ind.* (London), 946 (1961); M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2213 (1961).

(7) J. W. Wilt and J. W. Hill, *J. Org. Chem.*, **26**, 3523 (1961); E. L. Jenner, *ibid.*, **27**, 1031 (1962); B. E. Englund, U.S. Patent 2,691,682 (Oct. 12, 1954).

(8) See F. D. Greene, *J. Am. Chem. Soc.*, **81**, 2688 (1959) and references cited therein; D. B. Denney and W. F. Beach, *J. Org. Chem.*, **24**, 108 (1959).

TABLE I

PRODUCTS OF DECOMPOSITION OF TERTIARY HYPOCHLORITES

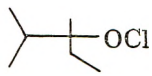
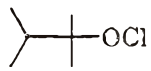
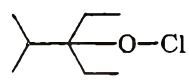
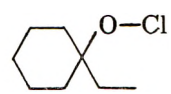
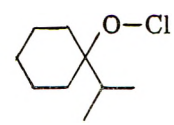
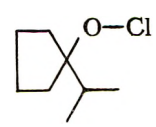
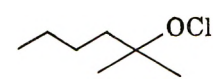
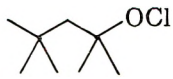
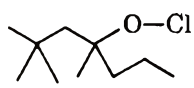
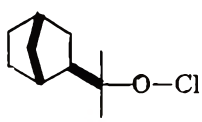
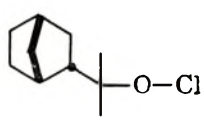
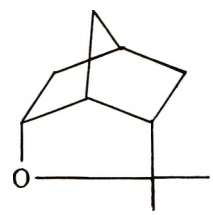
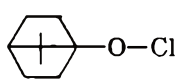
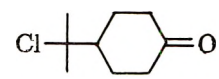
	Hypochlorite	Solvent	Products	Yield, %
(1)		CCl_4[a]	Isopropyl chloride, 2-butanone	95
			Ethyl chloride, 3-methyl-2-butanone	3
			Methyl chloride, 2-methyl-3-pentanone	<0.5[b]
(2)		CCl_4[a]	Isopropyl chloride, acetone	96
			3-Methyl-2-butanone	<0.5[b]
		$CBrCl_3$[c]	Acetone	98
			Isopropyl chloride	38
			Isopropyl bromide, CCl_4	32
		Cyclohexene[c,d]	Isopropyl chloride, acetone	80
			3-Chlorocyclohexene	2
(3)		$CFCl_3$[c]	1-Chloronorbornane, acetone	22
			Methyl 1-norbornyl ketone	5.2
			1-Isopropenylnorbornane	5
		Cyclohexene[c,d]	Dimethyl(1-norbornyl)carbinol	94
			1-Isopropenylnorbornane	3
			1-Chloronorbornane	(2)
			Norbornane	<0.5[b]
			3-Chlorocyclohexene	94
			4-Chlorocyclohexene	<3
			Cyclohexyl chloride	<0.5[b]
(4)		CCl_4[a]	3-Pentanone	84
			2-Methyl-3-pentanone	3.7
			2-Chloro-3-pentanone[e]	(3)
		CCl_4[c]		[f]
(5)		CCl_4[a]	Ethyl chloride, cyclohexanone	5
			1-Chloro-6-octanone	68
			1-Ethylcyclohexene	1
			2-Chlorocyclohexanone[e]	(1)
			1,X-Dichloro-6-octanones[e]	(5)
(6)		CCl_4[a]	Isopropyl chloride, cyclohexanone	66
			$(CH_3)_2CHCO(CH_2)_4CH_2Cl$	13.5
			2-Chlorocyclohexanone	[g]
			1-Isopropylcyclohexene	<0.5[b]
			Isopropylidenecyclohexane	<0.5[b]
(7)		$CFCl_3$[c]	$(CH_3)_2CHCO(CH_2)_3CH_2Cl$	94
			Isopropyl chloride, cyclopentanone	3.4
(8)		$CFCl_3$[c]	$CH_3CHClCH_2CH_2C(CH_3)_2OH$	55
			n-Butyl chloride, acetone	15
			Methyl chloride, 2-hexanone	<0.5[b]
		Cyclohexene[c,d]	$CH_3CHClCH_2CH_2C(CH_3)_2OH$	75
			n-Butyl chloride, acetone	14
			$CH_3CHClCH_2CH_2C(CH_3)=CH_2$	3
			2,2,5-Trimethyltetrahydrofuran	2
			3-Chlorocyclohexene	8
			4-Chlorocyclohexene	<0.5[b]
			Cyclohexyl chloride	<0.5[b]

TABLE I (*Continued*)

Hypochlorite	Solvent	Products	Yield, %
(9) 	$CFCl_3$[c]	Neopentyl chloride, acetone	55
		$(CH_3)_2C(CH_2Cl)CH_2C(CH_3)_2OH$	20
		2,2,4,4-Tetramethyltetrahydrofuran	5
		Methyl neopentyl ketone	<0.5[b]
		t-Amyl chloride	<0.5[b]
	Cyclohexene[c,d]	Neopentyl chloride, acetone	55
		$(CH_3)_2C(CH_2Cl)CH_2C(CH_3)_2OH$	25
		$(CH_3)_2C(CH_2Cl)CH_2C(CH_3)=CH_2$	4
		2,2,4,4-Tetramethyltetrahydrofuran	2
		3-Chlorocyclohexene	8
		4-Chlorocyclohexene	<0.5[b]
		Cyclohexyl chloride	<0.5[b]
	Toluene	Neopentyl chloride, acetone	50
		$(CH_3)_2C(CH_2Cl)CH_2C(CH_3)_2OH$	20
		Benzyl chloride	6
(10) 	$CFCl_3$[c]	Neopentyl chloride, 2-pentanone	25
		n-Propyl chloride, 4,4-dimethyl-2-pentanone	25
	Cyclohexene[h]	Neopentyl chloride, 2-pentanone	25
		n-Propyl chloride, 4,4-dimethyl-2-pentanone	25
		$(CH_3)_2C(CH_2Cl)CH_2C(CH_2CH_2CH_3)=CH_2$[g]	(5)
		3-Chlorocyclohexene	7
(11)  *exo*	CCl_4[c]	*exo*-Norbornyl chloride, acetone	80
		endo-Norbornyl chloride	<5
		Methyl 2-norbornyl ketone	<0.5[b]
(12)  *endo*	CCl_4[c,i]		30
		2-Isopropylidenenorbornane	7
		exo-Norbornyl chloride	3.5
		Methyl 2-norbornyl ketone	<0.5[b]
(13) 	CCl_4[a]		>95

[a] Thermal initiation at 80°. [b] Not present within the limits of detection of the analyses. [c] Weak ultraviolet initiation at 0°. [d] Initial concn. of ROCl, approx. 1.3 *M*. [e] By retention time only, tentative assignment. [f] Ratio of diethyl ketone to ethyl isopropyl ketone, 26:1. [g] By retention time and infrared spectrum, amount uncertain. [h] Violent self initiation. [i] In presence of pyridine.

appearance of only one methyl peak in the n.m.r. requires that the chlorine be attached at the remaining terminal position. The typical propionyl pattern in the n.m.r. requires the location of the chlorine at the opposite end of the chain, leading unambiguously to the structure shown. Assignment of structure to the chloro ketone from **13** is based on (a) conversion to derivatives of 4-isopropylcyclohexanone and (b) conversion to a dibenzal derivative identical in melting point with that of Wallach,[9] formed by the action of hydrochloric acid and benzaldehyde on nopinone (6,6-dimethylbicyclo[3.1.1]heptanone-2). Assignment of structure to the cyclic ether derived from **12** is based on strong absorption in the infrared at 1060 cm.$^{-1}$ and on identity with the product obtained by the action of lead tetraacetate on alcohol **12**.[10]

(9) O. Wallach, *Ann.*, **437**, 187 (1924).

(10) G. Cainelli, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959); for some additional examples of this reaction, see O. Jeger, M. Lj. Mihailović, *et al.*, *ibid.*, **44**, 186, 502 (1961), and A. Bowers, E. Denot, L. Cuéllar Ibanez, Ma. E. Carbezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

Effect of Reaction Conditions on Rate of Decomposition.—Solutions of the hypochlorites in carbon tetrachloride or in trichlorofluoromethane are stable in the dark for prolonged periods. Exposure to weak ultraviolet light, or heating of the solutions, or the addition of free radical sources effect rapid decomposition of the hypochlorites. Oxygen and *m*-dinitrobenzene markedly inhibit both the photochemical and the thermal decompositions. A lower limit of 1000 for chain length is estimated for 2,4,4-trimethyl-2-pentyl hypochlorite in toluene. Illustrative data on the effect of accelerators and inhibitors on the decomposition of this hypochlorite, **9**, are summarized in Table II. The effect of temperature on the product composition of this work has not been examined in detail other than to establish that the effect is small—*e.g.*, for case **4** the ratio of cleavage of isopropyl radical to cleavage of ethyl radical is 45 at 80°, 52 at 0°.

TABLE II

EFFECT OF REACTION CONDITIONS ON RATE OF DECOMPOSITION OF 2,4,4-TRIMETHYL-2-PENTYL HYPOCHLORITE (9)

Conditions	Solvent	Temp., °C.	Time, min.	Reaction, %
U,[a] dark	T[b]	80	800	99
U,[a] hν[c]	T[b]	0	7	99
D,[d] dark	T[b]	25	2540	<1
D,[d] AIBN[e]	T[b]	45	110	35[f]
D,[d] AIBN[g]	T[b]	45	150	25[h]
U,[a] hν[c]	F[i]	0	20	99
D,[d] hν[c]	F[i]	0	3	99
D,[d] hν, DNB[j]	F[i]	0	170	99

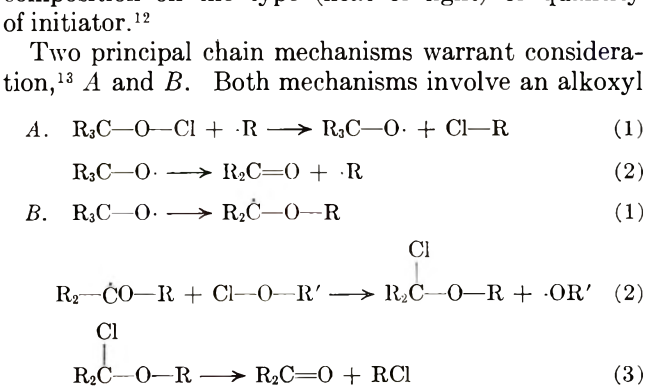
[a] Undegassed. [b] Toluene, ROCl concn., 1.15 *M*. [c] Weak irradiation with a Burton lamp. [d] Degassed. [e] Azobisisobutyronitrile, 0.0132 *M*. [f] Corresponds to a chain length of 1300 using k_1 of 0.004 hr.$^{-1}$ (ref. 3a, p. 513) for AIBN at 45° and a 20% correction for cage recombination [G. S. Hammond, C. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keyes, *J. Am. Chem. Soc.*, 82, 5394 (1960)]. [g] AIBN, 0.0056 *M*. [h] Corresponds to chain length of 1800 (see *f*). [i] $CFCl_3$, ROCl concn., 0.80 *M*. [j] *m*-Dinitrobenzene, 0.6 *M*.

Discussion

Examination of Table I reveals that the decomposition of tertiary hypochlorites varies from a clean one-product reaction to complex multiproduct reactions affording ketones, chloro ketones, chlorohydrins, olefins, alkyl halides, and tetrahydrofurans. The principal features of these decompositions will be considered with reference to the three points outlined in the introduction: (1) generality of radical chain decomposition, (2) involvement of, and selectivity in cleavage of, alkoxyl radicals, and (3) reactions of alkoxyl radicals competitive with fragmentation.

Mechanism.—Previous studies have provided evidence that *t*-butyl hypochlorite[11] and 2-methyl-3-phenyl-2-butyl hypochlorite[8] decompose by chain reactions. Kinetic data (such as illustrated in Table II) and product data of this study provide strong support that this mode of decomposition is general for the tertiary hypochlorites. (For example, relevant product data supporting a chain mechanism are the formation of both isopropyl bromide and chloride from the decomposition of dimethylisopropylcarbinyl hypochlorite, **2**, in bromotrichloromethane and the predominance of the *exo* isomer in the 2-norbornyl chloride obtained from both **11** and **12**.) That all of the products of decomposition are derived from chain reactions is indicated by the independence of product composition on the type (heat or light) or quantity of initiator.[12]

Two principal chain mechanisms warrant consideration,[13] *A* and *B*. Both mechanisms involve an alkoxyl

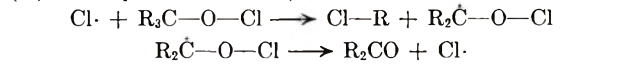


radical intermediate. In *B* this intermediate undergoes rearrangement and subsequent conversion to an α-chloro ether. The α-chloro ether might then proceed to alkyl chloride and ketone by several possible mechanisms. Although our inability to prepare the appropriate α-chloro ethers has precluded the most direct approach to evaluation of this sequence, indirect evidence may be cited against the intermediacy of α-chloro ethers. (1) Decomposition of 2,4,4-trimethyl-2-pentyl hypochlorite in toluene saturated with water[14] still affords neopentyl chloride as the major product. (2) Rearrangement of α-chloro ethers,[15] equation *B*-3, appears to require higher temperatures than those employed in the decomposition of hypochlorites. (3) A number of α-chloro ethers has been prepared by the photochemical chlorination of ethers[15-17] under illumination conditions much more intense than those needed to effect decomposition of hypochlorites. (The formation of α-chlorotetrahydrofuran in good yield by photochlorination[17] seems of particular importance to the point under discussion.) Thus, although α-chloro ethers may be involved in some hypochlorite decomposition, there is no evidence to involve them in the examples of this study; and the preferred mechanism of decomposition is that shown in sequence *A*.[18] The principal paths of reaction then available to the alkoxyl radical are fragmentation and inter- and intramolecular hydrogen abstraction.

(11) A. D. Yoffe, *Chem. Ind.* (London), 963 (1954).

(12) Exclusive of temperature dependence: The effect of temperature on the product compositions of Table I is small. Similar effects are reported in ref. 5 and 20.

(13) A third possible mechanism,



may be rejected directly for *tertiary* hypochlorites on several grounds: It leads to the wrong prediction of structure for alkyl halide from cases such as 11 and that reported in reference 8; and it ascribes a selectivity and behavior to atomic chlorine that is not in accord with other information on this species—*e.g.*, see ref. 3a, chap. 8. This type of chain may be operative when the R undergoing attack by chlorine atom is hydrogen—*i.e.*, with primary or secondary hypochlorites (unpublished work of these laboratories).

(14) α-Halo ethers are rapidly hydrolyzed: see P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 3641 (1955) and references cited therein; F. Straus and H. J. Weber, *Ann.*, **498**, 105, 128 (1932).

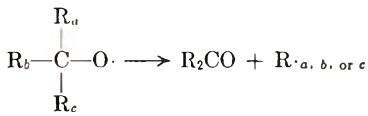
(15) (a) L. Summers, *Chem. Revs.*, **55**, 301 (1955); (b) R. K. Summerbell and D. R. Berger, *J. Am. Chem. Soc.*, **79**, 6504 (1957), **81**, 633 (1959); (c) For a study of the unimolecular decomposition of α-chloroethyl methyl ether to hydrogen chloride and methyl vinyl ether, see P. J. Thomas, *J. Chem. Soc.*, 136 (1961).

(16) H. Böhme and A. Dörries, *Ber.*, **89**, 723 (1956).

(17) H. Gross, *Angew. Chem.*, **72**, 268 (1960).

(18) Rearrangement of type *B*-1 *does* appear to occur in triarylmethoxyl radicals, ref. 3a, p. 473.

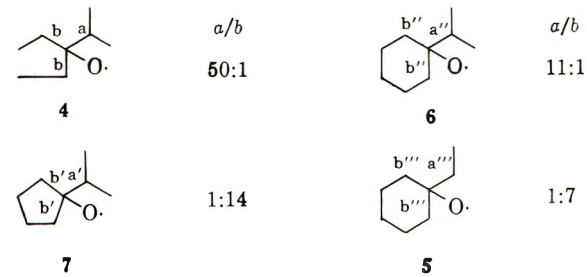
Selectivity in Fragmentation.—Examination of the cases **1, 2, 4, 8, 9, 11,** and **13** indicates that the order of increasing ease of fragmentation of alkyl groups is



methyl < primary alkyl < secondary, in confirmation of other data on alkoxyl radicals.[19,20] Rate of cleavage of a primary alkyl group exceeds rate of cleavage of methyl by factors as large as one hundred (**8, 9**). Rate of cleavage of *sec*-alkyl (isopropyl) exceeds rate of cleavage of *n*-alkyl (ethyl) by factors of thirty (case **1**) and fifty (case **4**). This order of fragmentation is in the order of increasing radical stability, increasing carbonium ion stability, or simply increasing size. Case **3** is of special interest in this connection. The 1-norbornyl group represents a group of large size but of demonstrated instability as an ion,[21] and of lower radical stability than a secondary radical.[22] In case 3, the preference for ejection of the tertiary (but bridgehead) 1-norbornyl radical *vs.* ejection of methyl is only four to one. The smallness of this ratio must be attributed either to the reluctance of cleavage of this 1-norbornyl group or to a great decrease in selectivity of *all* fragmentation paths in compound **3,** a situation that might obtain in this alkoxyl radical due to strain produced by the presence of the bulky bridgehead group. Experiments described (under *Hydrogen Atom Abstraction*) provide compelling evidence that the alkoxyl radical of **3** is longer lived than that of **2,** thereby excluding this second possibility. One concludes that a principal factor in the order of fragmentation is the stability, rather than the size, of the departing group.[23]

In the recent report of Kochi,[20] the relative intramolecular cleavage rates of *n*-alkyl groups from *t*-alkoxyl radicals at 25° are methyl (~0.003), ethyl (1.0), *n*-propyl (0.65), *n*-butyl (0.43). It was noted that a linear correlation exists between the logarithms of the relative cleavage rates for ethyl, *n*-propyl, and *n*-butyl *vs.* the corresponding carbon-hydrogen bond dissociation energies.[24] This correlation is an interesting one, but appears to be of limited application. As pointed out by the author,[20] methyl is cleaved more slowly than predicted from the correlation; and from the present work, isopropyl is cleaved more rapidly than predicted. Competition between alternative fragmentation paths may be expected to be dependent on many factors: the stability of the ejected radical and the product ketone, the importance of strain in the reactant alkoxyl radical, the degree of brokenness of the carbon–carbon bond at the transition state, the importance of ionic character in the transition state. A detailed consideration of the relative importance of these factors must await the accumulation of more data.

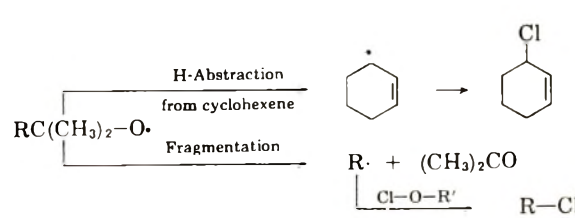
Examination of cases **4, 5, 6,** and **7** indicates the importance of ring strain in dictating the direction of cleavage. One notes a large preference for opening of a five-membered ring *vs.* ejection of ethyl (700-fold from the comparison of *b′ vs. b* in **7** and **4**, and making



the assumption that $a \cong a'$). The preference for opening a six-membered ring *vs.* ejection of ethyl is much smaller (fourfold: *b″ vs. b* in **6** and **4**). The orders are in accord with the strain associated with these rings (five-membered ring, 6 kcal. per mole; six-membered ring, 1 kcal. per mole).[25] The 700-fold preference for opening the five-membered ring corresponds to a difference in free energy of 3.5 kcal. per mole at the temperature of the experiment and suggests that a major portion of the ring strain has been released at the transition state of the ring-opening step. (As indicated above, this is based on the *assumption* that $a \cong a'$.)

Examples **5** and **6** afford an intermolecular comparison of ease of fragmentation of isopropyl *vs.* ethyl. The value, 77 to 1, is moderately close to the *intra*molecular value from case **4** of 50 to 1 for these groups.

Hydrogen Atom Abstraction.—Competition between hydrogen abstraction by the *t*-butoxyl radical *vs.* fragmentation has been employed to determine the relative reactivities of a large number of kinds of carbon–hydrogen bonds.[3] In the decomposition of hypochlorites, competition between hydrogen abstraction from a single substrate, cyclohexene, by alkoxyl radicals *vs.* fragmentation may be employed to provide an index of the relative stabilities of the alkoxyl radicals. Such an index is based on the assumption that the hydrogen abstraction reaction is independent of the structure of the alkoxyl radical. (This method was originally used in the determination of the following order of stability of alkoxyl radicals [derived from dialkyl peroxides] at 195°: methoxyl > ethoxyl > *n*-butoxyl > isopropoxyl > isobutoxyl ≅ *t*-butoxyl.)[26] The principal feature of the data of Table III is the



much greater difficulty of ejection of the 1-norbornyl radical than of the *n*-butyl, neopentyl, or isopropyl radicals—a strong indication (as pointed out above)

(19) See P. Gray and A. Williams, *Chem. Revs.*, **59,** 239 (1959); *Trans. Faraday Soc.*, **55,** 760 (1959).

(20) J. K. Kochi, *J. Am. Chem. Soc.*, **84,** 1193 (1962).

(21) See P. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83,** 2700 (1961) and references cited therein.

(22) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4,** 382 (1958).

(23) The question of the degree of ionic character to the transition state of the fragmentation reaction will be discussed in a later paper.

(24) For a thorough re-examination of bond dissociation data in simple hydrocarbons, see B. Steiner, C. F. Giese, and M. G. Inghram, *J. Chem. Phys.*, **34,** 189 (1961).

(25) V. Prelog, *Bull. soc. chim. France*, 1433 (1960).

(26) F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, *J. Am. Chem. Soc.*, **72,** 338 (1950).

TABLE III

CHAIN DECOMPOSITION OF $RC(CH_3)_2$-O—Cl IN CYCLOHEXENE

	R	C_6H_9Cl,[a] %	RCl, %
	Methyl	>95	
8	Butyl	8[b]	14[c]
9	Neopentyl	8[b]	55[d]
2	Isopropyl	2[b]	80
3	1-Norbornyl	94	(2)

[a] 3-Chlorocyclohexene (>93%) and 4-chlorocyclohexene (<7%). [b] May not be formed exclusively from R'—O. [c] Plus 78% chlorohydrin and chloro olefin (see Table I). [d] Plus 29% chlorohydrin and chloro olefin (see Table I).

that the stability, not the size, of the ejected fragment is of overriding importance in the fragmentation reaction.

As indicated by examples **8**, **9**, **10**, and **12**[27] (Table I), decomposition of hypochlorites may result in the replacement in the alkyl portion of the hypochlorite of a carbon–hydrogen bond by a carbon–halogen bond. The selectivity in point of attack—four carbon atoms removed from the oxygen atom (1,5-hydrogen abstraction)[28]—is suggestive of intramolecular attack by the alkoxyl radical. Confirmation of the intramolecular nature is provided by the unimportance of attack on cyclohexene (as solvent) relative to attack on the alkyl portion of hypochlorite (Table III, **8** and **9**). In-

tramolecular hydrogen transfer reactions have been proposed in a number of reactions. Some of the principal cases have been summarized recently by Barton and Morgan.[29]

Preliminary results reported in an independent, and more detailed, examination of intramolecular chlorination with long chain hypochlorites[5] also indicate marked preference for 1,5-hydrogen abstraction by alkoxyl radical, and considerable discrimination in the abstraction reaction between primary, secondary, and tertiary hydrogens. Chlorohydrin formation from steroidal hypochlorites has also been reported recently.[6]

Competition between Fragmentation and Intramolecular Hydrogen Abstraction.—The rate of 1,5-abstraction of secondary C-H (per hydrogen) *vs.* fragmentation of *n*-alkyl (butyl) is 2.7 to 1 (**8**). The rate of fragmentation of ethyl *vs.* isopropyl is 1 to 50 (**4**). On a purely statistical basis these data would predict that ejection of a secondary radical would outweigh abstraction of a secondary hydrogen. Example **12** shows a tenfold preference (a minimum value) for abstraction of the single available hydrogen *vs.* fragmentation to the 2-norbornyl radical. Thus the steric situation of the δ-hydrogens with respect to the alkoxyl oxygen may be of overriding importance in the competition between intramolecular hydrogen abstraction and fragmentation.

Experimental

The order of description of experiments is: (1) preparation of reactants, standards, and products, (2) preparation and decomposition of the hypochlorites, and (3) control data. Preparations and decompositions are given in the order in which they are listed in Table I. Materials obtained commercially were purified when necessary to obtain material giving a single peak on g.l.p.c. columns and agreeing with reported physical constants. The constants for such compounds are not reproduced.

(1 and 2)

2,3-Dimethyl-3-pentanol, b.p. 137–137.5°, $n^{30}D$ 1.4241 (lit.,[30] b.p. 139–140°, $n^{25}D$ 1.4262) and **2,3-dimethyl-2-butanol**, b.p. 116.2–116.7°, $n^{30}D$ 1.4121 (lit.,[31] b.p. 117.91–117.95°, $n^{25}D$ 1.4151) were prepared by standard Grignard syntheses.

(3)

Norbornane-1-carboxylic acid was prepared from *endo*-norbornanecarboxylic acid by bromination and successive catalytic hydrogenolysis.[32] The acid had m.p. of 111–112° (lit., m.p. 112–113°).

Norbornane-1-carbonyl Chloride.—A 5.6-g. sample of norcamphane-1-carboxylic acid was treated with 8 g. of thionyl chloride under nitrogen and the temperature was maintained at 30–40° until the hydrogen chloride evolution had ceased. The excess of thionyl chloride was removed at aspirator pressure and the acid chloride was distilled at 47–47.5° at 2.1 mm., yield 85%. Treatment with concentrated ammonia converted the acid chloride to *norbornane-1-carboxamide*, m.p. 233–234° (recrystallized from chloroform).

Anal. Calcd. for $C_8H_{13}NO$: C, 69.02; H, 9.41; N, 10.06. Found: C, 68.72; H, 9.55; N, 9.92.

Anhydride of Norbornane-1-carboxylic Acid.—A solution of 1.58 g. of norcamphane-1-carbonyl chloride and 20 ml. of pyridine was allowed to stand at room temperature for 4 hr. at which time a copious precipitate was present. Moist either was added and the solution was washed successively with water, 6 *N* hydrochloric acid, 2 *N* sodium carbonate, and water. After drying over anhydrous magnesium sulfate, the ether was removed *in vacuo*. Crystallization from pentane at low temperatures gave the anhydride, m.p. 73.0–74.5°.

Anal. Calcd. $C_{16}H_{22}O_3$: C, 73.24; H, 8.45. Found: C, 73.19; H, 8.55.

Methyl 1-Norbornyl Ketone.—To an ethereal solution of methylmagnesium iodide, prepared from 3.55 g. of methyl iodide and 0.6 g. of magnesium, was added 2.56 g. of anhydrous cadmium chloride.[33] The ether was evaporated at 25° under nitrogen and replaced by 40 ml. of dry benzene. A 3.2-g. sample of norbornane-1-carbonyl chloride in 20 ml. of benzene was added dropwise at room temperature. The mixture was stirred for another 2 hr. and decomposed by addition of ice-cold 2 *N* hydrochloric acid. The water layer was extracted three times with ether. The combined ether–benzene layers were washed twice with 1 *N* sodium hydrogen sulfite, twice with 1 *N* sodium hydrogen carbonate, and dried over calcium chloride. After removal of the ether and the benzene, distillation of the residue at 73–74° (11 mm.) yielded 2.2 g. of ketone (80%). Some unchanged acid chloride was removed by passing a solution of the ketone in pentane through an aluminum oxide (base-washed) column. The ketone had b.p. 194–195°, $n^{27}D$ 1.4702.

Anal. Calcd. for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 78.77, 78.70; H, 10.63, 10.42.

A sample of the ketone was converted to the **2,4-dinitrophenylhydrazone**, m.p. 121–122°.

Anal. Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.71; N, 17.60. Found: C, 56.79; H, 5.69; N, 17.46.

Methyl Norbornane-1-carboxylate.—The above acid was converted by the action of an ethereal solution of diazomethane to

(27) Assuming that the precursor of the ether from **12** is the corresponding chlorohydrin.

(28) For example **8**, a specific search was made for the product of 1,6-hydrogen abstraction. Cyclization of the chlorohydrin fraction by base failed to reveal any 2,2-dimethyltetrahydropyran within the limits of the g.l.p.c. analysis (0.5%).

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(33) D. A. Shirley, *Org. Reactions*, **VIII**, 45 (1954).

the methyl ester, b.p. 70–72° (11 mm.) [lit. 52–53° (1.8 mm.)[32]], n_D^{26} 1.4621 (lit.,[34] $n^{25}D$ 1.4633).

Dimethyl(1-norbornyl)carbinol.—To a cooled ethereal solution of methylmagnesium iodide, prepared from 20.8 g. of methyl iodide and 3.12 g. of magnesium in 40 ml. of ether under nitrogen atmosphere, was added a solution of 9.0 g. of the above ester in 10 ml. of ether over a period of 10 min. The mixture was stirred at room temperature for an additional 2 hr., and then decomposed by the addition of ice-cold saturated aqueous ammonium chloride solution. The water layer was extracted three times with ether. The combined ether layers were washed twice with 1 *N* sodium hydrogen sulfite solution, twice with 1 *N* sodium hydrogen carbonate solution, and dried over magnesium sulfate. Removal of the ether afforded a white solid, which was twice recrystallized from pentane at low temperatures, m.p. 67–68°, b.p. 57–59° at 1.6 mm., yield 89%. The alcohol is hygroscopic and should be kept in a desiccator over phosphorus pentoxide.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.59; H, 11.73.

A sample of the above alcohol was treated with an equimolar amount of phenyl isocyanate for 3 days at room temperature,[35] and then for 1 hr. at 90°. The solid obtained was filtered, recrystallized from methanol, and extracted with cold hexane to free it from *sym*-diphenylurea. This extract was evaporated and the solid was recrystallized from methanol, yielding the **phenylurethane** of the above alcohol, m.p. 157–158°.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.49; H, 8.32; N, 5.12.

1-Isopropenylnorbornane.—A 1.1-g. sample of the alcohol was distilled at atmospheric pressure in the presence of a trace of iodine. The distillate was dissolved in ether and the solution was washed twice with 1 *N* sodium bisulfite, with 1 *N* sodium hydrogen carbonate, and dried over calcium chloride. The ether was removed and the liquid was distilled at 11-mm. pressure yielding 82% of the olefin, b.p. 169–170°, $n^{31}D$ 1.4695. The gas chromatogram of the product exhibited only one peak; the infrared absorption spectrum exhibits bands at 3030, 1640, and 890 cm.$^{-1}$ (terminal methylene).

Anal. Calcd. for $C_{10}H_{16}$: C, 88.15; H, 11.84. Found: C, 88.12; H, 12.10.

Norbornane.—A solution of 0.170 g. of sublimed norbornylene in absolute methanol was added to a mixture of 0.034 g. of prereduced platinum oxide in absolute methanol. The theoretical amount of hydrogen was taken up in 15 min. The catalyst was removed by filtration and the mixture subjected to gas chromatography to determine retention time.

(4)

2-Methyl-3-ethyl-3-pentanol was prepared by the reaction of methyl isobutyrate and ethylmagnesium bromide, b.p. 62° at 18 mm., $n^{25}D$ 1.4353 (lit.,[36] b.p. 53° at 10 mm., $n^{20}D$ 1.4372).

(5)

1-Ethylcyclohexanol was prepared by the procedure of Mosher,[37] m.p. 31–35° (lit.,[38] m.p. 33°), $n^{25}D$ 1.4628 (lit.,[37] $n^{20}D$ 1.4642), m.p. of *p*-nitrobenzoate 73–74° (lit.,[39] 73–74°). Dehydration[37] afforded a mixture of 1-ethylcyclohexene and 1-ethylidenecyclohexane for use in determination of retention times on g.l.p.c.

2-Chlorocyclohexanone was prepared by a standard procedure.[40]

(6)

1-Isopropylcyclohexanol was prepared by the procedure of Mosher,[37] b.p. 60° at 1.2 mm. $n^{25}D$ 1.4659 (lit.,[37] b.p. 80° at 1.8 mm.). Dehydration[37] afforded a mixture of isopropylidenecyclohexane and 1-isopropylcyclohexene for use in determination of g.l.p.c. retention times.

(7)

1-Isopropylcyclopentanol was prepared by the Grignard reaction[41] of 1,4-dibromobutane and ethyl isobutyrate in 50% yield, b.p. 62–63° at 11 mm., $n^{25}D$ 1.4545 (lit.,[41] b.p. 53° at 6 mm., $n^{25}D$ 1.4551).

(8)

2-Methyl-2-hexanol, b.p. 141–142°, $n^{27}D$ 1.4166 (lit.,[42] b.p. 141–143°, $n^{20}D$ 1.4186) was prepared by a standard Grignard reaction.[42] Distillation of the alcohol in the presence of a trace of iodine afforded a mixture of **2-methyl-1-hexene** and **2-methyl-2-hexene**, b.p. 90–92° (lit.,[43] b.p. 94–96°). Gas chromatography indicated a predominance of the former compound, infrared band at 890 cm.$^{-1}$.

2-Methylhexane-2,5-diol.—To a cooled ethereal solution of methylmagnesium iodide, prepared from 70.5 g. (0.500 mole) of methyl iodide and 12.0 g. (0.500 g.-atom) of magnesium in 100 ml. of ether under nitrogen atmosphere was added an ethereal solution of 250 g. (0.247 mole) of γ-valerolactone over a period of 1 hr. The mixture was refluxed for an additional hour, and decomposed by the addition of an ice-cold saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with ether. The combined ether layers were washed with 10% sodium bisulfite solution, 10% sodium bicarbonate solution and water and dried over magnesium sulfate. Filtration, removal of the ether, and distillation afforded the diol as the major fraction, b.p. 106–110° at 8 mm., (lit.,[44] b.p. 121° at 14 mm.).

2,2,5-Trimethyltetrahydrofuran.—To 0.60 g. of the above diol at 90° was added an equal amount of 60% sulfuric acid. The reddish brown layer was stirred for 30 min., extracted with ether washed with sodium bicarbonate solution and water and dried over magnesium sulfate. Distillation gave 0.150 g. of 2,2,5-trimethyltetrahydrofuran, b.p. 99–102° (lit.,[44] b.p. 102–103°), infrared absorption band at 1080 cm.$^{-1}$.

2,2-Dimethyl-3,4-dihydropyran was prepared by the Diels–Alder addition of isobutylene and acrolein according to the procedure of Smith, Norton, and Ballard, b.p. 55° at 75 mm., $n^{25}D$ 1.4390 (lit.,[45] b.p. 52–58° at 100 mm., $n^{20}D$ 1.4371).

2,2-Dimethyltetrahydropyran.—A solution of the above 2,2-dimethyl-3,4-dihydropyran in petroleum ether was added to a mixture of pre-reduced platinum oxide. The theoretical amount of hydrogen was taken up in 20 min. The catalyst was removed by filtration and mixture was subjected to gas chromatography. The retention time differed from that of 2,2,5-trimethyltetrahydrofuran.[46]

(9)

2,4,4-Trimethyl-2-pentanol was prepared from the chloride by the method of Brown and Berneis[45] with the modification of a reaction time of 30 hr. at 50–55°; b.p. 57–58° at 25 mm. $n^{25}D$ 1.4860 (lit.,[47] b.p. 146–146.5°).

Neopentyl chloride was prepared from neopentyl alcohol by the procedure of Gerrard and Tolcher, $n^{25}D$ 1.4020 (lit.,[48] $n^{20}D$ 1.4048).

Methyl neopentyl ketone was prepared by potassium dichromate–sulfuric acid oxidation of diisobutylene according to the procedure of Mosher and Cox, b.p. 123–125°, $n^{25}D$ 1.4013 (lit.,[49] b.p. 124–125°, $n^{25}D$ 1.4018).

2,4,4-Trimethylpentene-1 and -2.—The acid dehydration of 2,4,4-trimethyl-2-pentanol according to the procedure of Whitmore[50] gave 2,4,4-trimethyl-1-pentene in 80% yield and 2,4,4-trimethyl-2-pentene in 20% yield, indicated by gas chromatography.

2,4,4-Trimethyl-3,5-pentanediol was prepared by heating 68 g. of freshly distilled isobutyraldehyde and 136 g. of 13.5% potassium hydroxide for 12 hr. at 50° according to the procedure of Fossek, b.p. 83–86° at 5 mm., (lit.,[51] b.p. 222–223°).

2,2,4,4-Tetramethyltetrahydrofuran.—To 20 g. of the above glycol was added an equal amount of concd. sulfuric acid. The reddish-brown layer was stirred for 30 min. at 0°, poured into twenty times the amount of ice–water, extracted with ether, and dried over magnesium sulfate. Ether was removed and distillation afforded 10.5 g. of the tetrahydrofuran, b.p. 120–122°

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(46) The gas–liquid phase chromatography columns used in this work are described in the section entitled *Decomposition of Alkyl Hypochlorites*.
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(lit.,[52] b.p. 120°) and higher boiling material. The infrared spectrum agreed with a published one.[52] The structure of 2,2,4,4-tetramethyltetrahydrofuran, previously assigned on the basis of infrared evidence, is strongly supported by the n.m.r. spectrum (four singlets of relative area 3:3:1:1 at τ of 8.91, 8.77, 8.40, and 6.6 in carbon tetrachloride).

(10)

2,2,4-Trimethyl-4-heptanol was prepared from propylmagnesium bromide and methyl neopentyl ketone according to the procedure of Moersch and Whitmore, b.p. 70–73° at 9 mm., $n^{25}D$ 1.4350 (lit.,[53] b.p. 59.6° at 7 mm., $n^{20}D$ 1.4373).

(11)

exo-**5-Norbornene-2-carboxylic Acid.**—The Diels–Alder addition of freshly distilled cyclopentadiene with methyl acrylate afforded a 71% yield of a mixture of 75% *endo*- and 25% *exo*-methyl 5-norbornene-2-carboxylate.[54,55] The mixture was isomerized by the action of sodium methoxide to a 54% *exo*–46% *endo* mixture. This mixture was hydrolyzed by aqueous sodium hydroxide and the resulting acid mixture was separated into iodo lactone, m.p. 58–59° (lit.,[56] m.p. 58–59°) and *exo* acid by the procedure of ver Nooy and Rondestvedt. Two recrystallizations from petroleum ether gave *exo* acid of m.p. 40.2–40.8° (lit.,[56] 44–45°).

Dimethyl(*exo*-norbornyl)carbinol.—A sample of the above acid was converted by diazomethane to the methyl ester, b.p. 82–83° at 15 mm. (lit.,[55] b.p. 86.5° at 17 mm.). The ester was hydrogenated in methanol at 2 atm. with platinum oxide, giving methyl *exo*-norbornanecarboxylate, b.p. 88–89° at 18 mm., $n^{25}D$ 1.4653 (lit.,[55] b.p. 84° at 15 mm., $n^{20}D$ 1.4643). To an ether solution of methylmagnesium iodide, prepared from 26 g. (0.18 mole) of methyl iodide and 4.3 g. (0.18 g.-atom) of magnesium was added an ether solution of 13.0 g. (0.094 mole) of the above ester over a period of 1 hr. The reaction mixture was heated at reflux for an additional hour, cooled, and excess Grignard reagent was decomposed by the addition of a saturated aqueous ammonium chloride solution. The ether layer was washed with 10% sodium bisulfite solution, 10% sodium bicarbonate solution, and dried over magnesium sulfate. Filtration, removal of the ether, and distillation of the residual yellow oil from potassium carbonate afforded 11.0 g. of pure dimethyl(*exo*-norbornyl)carbinol, b.p. 99–100° at 22 mm., $n^{25}D$ 1.4668.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.86; H, 11.96.

exo- and *endo*-**Norbornyl chloride** were prepared by published procedures: *exo* chloride, b.p. 59° at 20 mm., $n^{25}D$ 1.4905 (lit.,[57a] b.p. 88–89° at 74 mm.); *endo* chloride, b.p. 60–61° at 22 mm., $n^{25}D$ 1.4845 (lit.,[57b] b.p. 51–53° at 17 mm., $n^{25}D$ 1.4835).

(12)

endo-**5-Norbornene-2-carboxylic Acid.**—The Diels–Alder addition of freshly distilled cyclopentadiene to acrylic acid afforded a 60% yield of adduct, b.p. 103–106° at 2 mm., (lit.,[58] b.p. 129–130° at 13 mm.) which solidified in the receiver. Successive recrystallizations from petroleum ether afforded the pure *endo* acid, m.p. 43–44° (lit.,[56] m.p. 44–45°), mixed m.p. with *exo* acid, 32–34°.

Dimethyl(*endo*-norbornyl)carbinol.—A sample of the above acid was converted by the action of an ethereal solution of diazomethane to the methyl ester, b.p. 63–64° at 8 mm., (lit.,[55] b.p. 88–89° at 18 mm.). The ester, 16.5 g., was hydrogenated with 500 mg. of platinum oxide in 125 ml. of absolute methanol to give 15.9 g. of methyl *endo*-norbornanecarboxylate, b.p. 67–68° at 8 mm. (lit.,[55] b.p. 70° at 10 mm.). The Grignard reaction was performed as described for the *exo* carbinol giving 8.3 g. of pure dimethyl(*endo*-norbornyl)carbinol b.p. 78° at 8 mm.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.93, H, 11.45.

2-Isopropylidenenorbornane.—To a 3.8-g. sample of the *endo*-carbinol was added an equal amount of 15% sulfuric acid. The mixture was refluxed for 1 hr., extracted with ether, and dried with magnesium sulfate. Removal of ether and distillation through a small Claisen head gave 2.2 g. of colorless 2-isopropylidenenorbornane, b.p. 67° at 21 mm., infrared absorption bands at 3080 cm.$^{-1}$, 1640 cm.$^{-1}$, no band at 890 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}$: C, 88.24; H, 11.76. Found: C, 88.16; H, 11.84.

Conversion of 2-Isopropylidenenorbornane to 2-Norbornanone.—To a solution of 500 mg. (3.7 mmoles) of 2-isopropylidenenorbornane and 15 ml. of pyridine was added 1.0 g. (3.94 mmoles) of osmium tetroxide. The deep red solution was stirred magnetically for 80 min. and the pyridine was removed *via* a water aspirator. To the brown residue was added 17 ml. of 95% ethanol, 17 ml. of dried benzene, 7.0 g. of mannitol, and a solution of 7.0 g. of potassium hydroxide in 17 ml. of water and 35 ml. of ethanol.[59] After refluxing for 16 hr. the bulk of the solvent was removed with the water aspirator. The remaining mixture was extracted with ether, washed with water, and dried over magnesium sulfate. The diol was not isolated, but used immediately for oxidation with lead tetraacetate. To the above benzene solution of diol was added 1.8 g. of lead tetraacetate. The solution was stirred for 90 min. at 30°. The reaction mixture was washed with 10% potassium iodide solution and extracted with ether. The ether solution was decolorized with 10% sodium thiosulfate, washed with 10% sodium bicarbonate, water, and dried over magnesium sulfate. Some of the ether was removed on a steam bath. The rest of the solution was shaken with a solution of 1.0 g. of 2,4-dinitrophenylhydrazine in 20 ml. of 75% ethanol containing 4 ml. of concd. sulfuric acid. Removal of the solvent yielded a 2,4-dinitrophenylhydrazone which after two recrystallizations from ethanol melted at 128–129°, mixed melting point with an authentic sample, 129–130°.

Methyl 2-Norbornyl Ketone.—An *endo–exo* mixture was prepared by the procedure of Berson and Suzuki, b.p. 125–127° at 22 mm. (lit.,[60] b.p. 87° at 19 mm.).

3-Chlorocyclohexene.—A. The reaction of 12.0 g. of *t*-butyl hypochlorite, 50 ml. of cyclohexene, and 0.200 g. of benzoyl peroxide according to the procedure of Grob, Kny, and Gagneux afforded 4.3 g. of 3-chlorocyclohexene, b.p. 63–64° at 40 mm., $n^{25}D$ 1.4838, (lit.,[61] b.p. 76–78° at 80 mm., $n^{20}D$ 1.4860). Gas chromatographic analysis indicated 94% of desired product and 6% of 4-chlorocyclohexene. After two distillations, gas chromatography indicated 77.6% of the desired product and 22.4% of 4-chlorocyclohexene. Pure 3-chlorocyclohexene was obtained by gas chromatography collection. Repassage of the collected peak showed only the same peak.

B. A solution of 25 ml. (0.25 mole) of purified cyclohexene, 20.0 g. (0.15 mole) of recrystallized N-chlorosuccinimide, 38 ml. of reagent carbon tetrachloride, and 0.500 g. of benzoyl peroxide was refluxed under nitrogen and irradiated with a Westinghouse sun lamp for 14 hr. Filtration of the solution and distillation gave 2.0 g. of chlorocyclohexene mixture, b.p. 64–66° at 40 mm. which was shown to be 73% 3-chlorocyclohexene and 27% 4-chlorocyclohexene by gas chromatography.

4-Chlorocyclohexanol was prepared by the reaction of 1,4-cyclohexanediol and hydrochloric acid according to the procedure of Owens and Robins, b.p. 74–77° at 13 mm., $n^{25}D$ 1.4985 (lit.,[62] b.p. 80–85° at 5 mm., $n^{16}D$ 1.4964).

4-Chlorocyclohexene.—To a solution of 7.2 g. of 4-chlorocyclohexanol, 5.5 g. of freshly distilled pyridine, and 20 ml. of reagent chloroform was added 8.3 g. of thionyl chloride dropwise. The mixture was allowed to reflux for 1 hr. and was washed three times with water. The water was washed with ether which was combined with the chloroform and was dried over magnesium sulfate. Distillation afforded 0.32 g. of forerun, 2.2 g. of 4-chlorocyclohexene, b.p. 38–45° at 13 mm., and 0.88 g. of material, b.p. 65–68° at 13 mm. The infrared spectrum of the 4-chlorocyclohexene was identical with the spectrum of the component of shorter retention time from the reaction of *t*-butyl hypochlorite and cyclohexene.

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(13)

7,7-Dimethyl-1-norbornanol (1-apocamphanol) was prepared by the method of Hawthorne, Emmons, and McCallum,[63] m.p. 160–161° (lit.,[63] m.p. 160°).

Conversion of Alcohols to Tetrahydrofurans by the Action of Lead Tetraacetate.[10] **2,2,4,4-Tetramethyltetrahydrofuran.**—A solution of 0.500 g. of 2,4,4-trimethyl-2-pentanol and 1.0 g. of lead tetraacetate (dried at reduced pressure in a desiccator) in 25 ml. of dry benzene was refluxed for 4 days. The reaction mixture was washed with 10% potassium iodide solution (a precipitate of lead iodide formed) and the colloidal mixture was extracted with ether. The organic layers were combined, decolorized with 10% sodium thiosulfate solution, washed successively with 10% sodium bicarbonate solution and water, and dried over magnesium sulfate. The bulk of the solvent was removed through a Vigreux column; 2,2,4,4-tetramethyltetrahydrofuran was collected by gas chromatography of the residue (yield, 15%; when the reaction was stopped after 37 hr., this yield was 7.5%). The gas chromatography retention time and infrared spectrum of the ether agreed with those of an authentic sample.

When the reaction was carried out in heptane as solvent with a 4-day reflux period and work-up as described above, the products were 2,2,4,4-tetramethyltetrahydrofuran (3%), unchanged alcohol (65%), 2,4,4-trimethyl-2-pentyl acetate (5%, see below) and a mixture of heptanones (10%, assigned on the basis of the 1710-cm.$^{-1}$ band and a prominent mass spectral peak at m/e 114).

2,2,5-Trimethyltetrahydrofuran was obtained from 2-methyl-2-hexanol and lead tetraacetate in benzene in 3% yield after a 19-hr. reflux period. It was isolated by g.l.p.c. and had identical infrared spectrum and g.l.p.c. retention time with that of authentic material.

3,3-Dimethyl-2-oxatricyclo[4.2.1.0^{4,8}]nonane.—The lead tetraacetate procedure with dimethyl(*endo*-norbornyl)carbinol in benzene at reflux for 16 hr. gave a 45% conversion of alcohol to the ether. The infrared spectrum was identical to that of the product from the decomposition of the corresponding hypochlorite (12). (Combustion analysis, performed on several samples collected from gas chromatography, failed to give satisfactory data.)

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.36; H, 10.47.

2,4,4-Trimethyl-2-pentyl Acetate.—To a solution of 5.0 g. (0.038 mole) of freshly distilled 2,4,4-trimethyl-2-pentanol and 4.6 g. (0.038 mole) of freshly distilled N,N-dimethylaniline in 20 ml. of dry ether was added dropwise 3.2 g. (0.038 mole) of freshly distilled acetyl chloride.[64] The mixture was heated with a water bath for 2 hr. and a white precipitate of N,N-dimethylaniline hydrochloride formed. Water (20 ml.) was added. The mixture was extracted with ether. The ether layer was washed with 10% sulfuric acid and dried over magnesium sulfate. Filtration, removal of ether, and distillation afforded 0.65 g. of forerun, 2.50 g. of acetate, b.p. 59–61° at 13 mm., n^{25}D 1.4351.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 69.77; H, 11.67.

Preparation of Alkyl Hypochlorites.—The hypochlorites were prepared by the action of aqueous hypochlorous acid on the alcohol, neat or dissolved in carbon tetrachloride or Freon 11 (trichlorofluoromethane).

Because of the sensitivity of the hypochlorites to light the preparations and purifications were carried out in amber glass vessels or vessels otherwise protected from light. The general procedure is described in detail for example **5**.

A. Aqueous Sodium Hypochlorite.—A mixture of 160 g. (1.5 moles) of sodium carbonate, 306 g. of 70% calcium hypochlorite (1.5 moles) (Olin-Matheson H.T.H.), and 1 l. of water was stirred for 1 hr., filtered, and the filter cake was washed with 50–100 ml. of water. The yellow filtrate, approximately 2.8 *M*, was stored in the dark at 5° and was stable for many weeks.

B. 1-Ethylcyclohexyl Hypochlorite (**5**).—To 50 ml. of the aqueous hypochlorite solution, cooled to 0°, was added with stirring a solution of 6.42 g. (0.0506 mole) of 1-ethylcyclohexanol in 10 ml. of carbon tetrachloride (reagent grade) containing 5.7 ml. (0.1 mole) of glacial acetic acid. The mixture was stirred in the dark at 0° for 45 min. The layers were separated and the water layer was washed three times with 10-ml. portions of carbon tetrachloride. The combined carbon tetrachloride fractions were washed with three 10-ml. portions of 3% aqueous sodium bicarbonate, once with 10 ml. of water, and dried over magnesium sulfate at 5°; yield of hypochlorite: 85% by iodometric analysis.

Decomposition of Alkyl Hypochlorites.—The decompositions were effected under a variety of conditions (Tables I, II, and III). Light initiation (by means of a weak ultraviolet source—a Burton Ultraviolet Black Lamp, Model 1910, Burton Manufacturing Co., Santa Monica, California) was faster and usually afforded less secondary products than thermal decomposition. The procedure is described in detail for example **5**, and briefly for those cases in which decomposition of a hypochlorite represents the only mode of synthesis for new compounds obtained in this work.

A. Decomposition of 1-Ethylcyclohexyl Hypochlorite (**5**).—A 1.8 *M* solution of the hypochlorite in carbon tetrachloride prepared by the method described above was heated at reflux under nitrogen until a negative starch iodine test was obtained (8 hr.). Analysis of the solution by vapor phase chromatography [Dow–Corning Hi-Vac grease (30%) on Chromosorb P[65] (60/80 mesh)] at 135° indicated peaks (relative to carbon tetrachloride, 1.0) at 0.49, 1.0, 2.07, 2.32, 3.86, 4.75, 11.2, and a triplet from 19.3–21.8. The minor peaks at 0.49, 2.07, and 4.75 were shown by retention time to be ethyl chloride, 1-ethylcyclohexene, and 2-chlorocyclohexanone. The major peaks at 1.0, 2.32, and 3.86 were collected from a preparative-scale g.l.p.c. column and shown by comparison of infrared spectra with those of authentic samples to be pure carbon tetrachloride, cyclohexanone, and 1-ethylcyclohexanol. The 11.2 peak and the 19.3–21.8 triplet were collected; both showed strong carbonyl absorption.

A sample of the major component (the 11.2 peak) was obtained by distillation of the reaction mixture through a 30-cm. Holtzman column. The fraction of b.p. 52–53° at 0.2 mm. was shown by g.l.p.c. analysis to be the 11.2-component (over 95%). The fraction was chromatographed on Woelm activity III alumina in petroleum ether. Short path distillation of the main fraction afforded the pure chloro ketone, 1-chloro-6-octanone (infrared, 1715 cm.$^{-1}$, 790 cm.$^{-1}$; the n.m.r. spectrum is described under *Results*).

Anal. Calcd. for $C_8H_{15}ClO$: C, 59.07; H, 9.30; Cl, 21.80. Found: C, 59.00; H, 9.16; Cl, 21.93.

The 2,4-dinitrophenylhydrazone had m.p. of 100–104° (yellow form; upon cooling of the melt it is converted to orange form, m.p. 69–70°; this material is reconverted upon recrystallization from ethanol to the material of m.p. 100–104°), λ_{max} in chloroform 364 mμ (log ε 4.37).

Anal. Calcd. for $C_{14}H_{19}N_4O_4Cl$: C, 49.05; H, 5.59; Cl, 10.34. Found: C, 48.80; H, 5.48; Cl, 10.41).

B. Analysis of Product Compositions.—The yield data of Table I were obtained by gas–liquid phase chromatography analysis of solutions from decompositions obtained under degassed conditions. The columns employed for the examples of Table I were: 30% w./w. Dow–Corning Hi-Vac grease on Chromosorb P[65], 60/80 mesh (**4**, **5**, **6**); 30% w./w. Dow Corning silicone oil 550 on Chromosorb P, 80/100 mesh (before coating, the Chromosorb was soaked in 1% aqueous sodium hydroxide, then washed with water to pH 7-8, and dried) (**1**, **2**, **3**, **7**, **8**, **9**, **10**, **11**,[66] **12**); 30% w./w. γ-methyl-γ-nitropimelonitrile on Chromosorb P, 80/100 mesh, washed with aqueous sodium hydroxide before coating (**1**, **2**). The general procedure will be described in detail for case **5**.

C. Quantitative Analysis of the Products of Decomposition of 1-Ethylcyclohexyl Hypochlorite (**5**).—A 4.00-ml. sample of a 1.17 *M* solution of the hypochlorite in carbon tetrachloride was transferred to a tube with a constricted neck. The tube was degassed by three cycles of freezing, evacuating, and thawing (closed off from the vacuum source) and was then sealed *in vacuo*. The tube was heated for 10 hr. at 80°. After decomposition was complete, the tube was opened and a known amount of tetralin (retention time 8.3 relative to carbon tetrachloride 1.0 on Hi-Vac grease column) was added for use as an internal standard. In addition, a calibration mixture was prepared containing exactly known amounts of tetralin and of the major products of the decomposition in approximately the same proportions as the un-

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(64) B. Abramovitch, J. Shrives, B. Hudson, and C. Hauser, *ibid.*, **65**, 986 (1943).

(65) Johns–Manville Corporation.

(66) None of these g.l.p.c. columns resolved *exo*- and *endo*-norbornyl chloride; the analysis for the *exo*–*endo* ratio was made by use of differences in the infrared.

known. This calibration mixture was analyzed by g.l.p.c. at the same time and under the same conditions as the unknown.

A simple proportionality was set up:

$$\frac{\text{Moles tetralin}}{\text{Peak area tetralin}} = k_x \frac{\text{moles } x}{\text{area } x} = k_y \frac{\text{moles } y}{\text{area } y} = \ldots \quad (1)$$

The areas of the peaks on the chromatogram for each component of both the calibration and the unknown mixtures were determined with a planimeter. The areas from the calibration mixture and the amount of each component of the calibration mixture were substituted into equation 1 and k was thereby determined for cyclohexanone, 1-ethylcyclohexanol, and 1-chloro-6-octanone. The areas obtained from the unknown mixture, the k's, and the amount of tetralin added to the unknown were then used to calculate the amount of each component present. A k of 1.0 was used for components not in the standard mixture.

1-Chloro-7-methyl-6-octanone was obtained from the thermal decomposition of a solution of the hypochlorite (**6**) in carbon tetrachloride and collection of the chloro ketone by use of a preparative-scale g.l.p.c. column.

Anal. Calcd. for $C_{19}H_{17}ClO$: C, 61.17; H, 9.70; Cl, 20.07. Found: C, 61.11; H, 9.61; Cl, 20.19.

The n.m.r. spectrum in carbon tetrachloride at 60 Mc. showed a doublet at 9.05 τ (area, 6 protons; J, 6.5 c.p.s.), a multiplet at 8.5 τ (area, 6), a triplet superimposed on a multiplet at 7.6 τ (area, 3; J for the triplet, 7 c.p.s.), and a 1,2,1-triplet at 6.52 τ (area, 2; J, 6.5 c.p.s.).

1-Chloro-6-methyl-5-heptanone.—A 2.6-g. sample of 1-isopropylcyclopentanol in 20 ml. of carbon tetrachloride was converted to the hypochlorite (**7**) and decomposed by the slow distillation of the solvent under reduced pressure. The residual oil, 2.88 g. (principally the chloro ketone by g.l.p.c. analysis) was distilled, b.p. 101–102° at 12 mm., $n^{28}D$ 1.4419. The n.m.r. spectrum was markedly similar to that of 1-chloro-7-methyl-6-octanone, described above.

Anal. Calcd. for $C_8H_{15}ClO$: C, 59.07; H, 9.30; Cl, 21.80. Found: C, 59.06; H, 9.32; Cl, 22.35.

The **2,4-dinitrophenylhydrazone** had m.p. 83–84°.

Anal. Calcd. for $C_{14}H_{19}ClN_4O_4$: C, 49.05; H,, 5.59; Cl, 10.35; N, 16.35. Found: C, 48.74; H, 5.46; Cl, 10.35; N, 16.63.

5-Chloro-2-methyl-2-hexanol.—A 10-g. sample of 2-methyl-2-hexanol was converted to the hypochlorite (**8**) in Freon 11. The solvent was removed under reduced pressure and the pure hypochlorite was slowly added to a refluxing solution of 50 ml. of freshly distilled cyclohexene containing 0.2 g. of benzoyl peroxide. After the initial vigorous reaction, heating was continued for 30 min., solvent was removed under reduced pressure and the residue was distilled. The fraction of b.p. 78–79° at 10 mm., 4.5 g., was largely the chlorohydrin (90% by g.l.p.c. analysis). A sample was collected from a preparative-scale g.l.p.c. column.

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.81; H, 9.97; Cl, 23.59. Found: C, 55.83; H, 10.13; Cl, 23.26.

5-Chloro-2-methyl-1-hexene.—Distillation of a mixture of the above chlorohydrin and potassium hydrogen sulfate afforded the olefin b.p. 42–44° at 10 mm., infrared absorption bands at 3080 cm.$^{-1}$, 1642 cm.$^{-1}$, 890 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}Cl$: C, 63.40, H, 9.81, Cl, 26.79. Found: C, 63.81, H, 9.65, Cl, 26.71.

Conversion of 5-Chloro-2-methyl-2-hexanol to 2,2,5-Trimethyltetrahydrofuran.—A solution of 3.4 g. of the above chlorohydrin and 1.3 g. of 54% sodium hydride–mineral oil dispersion (Metal Hydrides, Inc.) in 5 ml. of ether was stirred for 2.5 hr.[67] The excess reagent was decomposed with water, the mixture was extracted with ether and distilled through a modified Claisen head to give a compound whose gas chromatography retention time and infrared spectrum were identical with authentic 2,2,5-trimethyltetrahydrofuran.

5-Chloro-2,4,4-trimethyl-2-pentanol was prepared from the corresponding hypochlorite (**9**) by the procedure described for the chlorohydrin from **8**. The chlorohydrin was principally in the fraction of b.p. 80–82° at 12 mm. A pure sample was collected from a preparative-scale g.l.p.c. column.

Anal. Calcd. for $C_8H_{17}ClO$: C, 58.36; H, 10.33; Cl, 21.58. Found: C, 58.56; H, 10.39; Cl, 21.71.

A sample of the chlorohydrin was converted to 2,2,4,4-tetramethyltetrahydrofuran by the procedure described above for the 2,2,5-derivative.

(67) A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, 2255 (1961).

5-Chloro-2,4,4-trimethyl-1-pentene.—Distillation of a mixture of the above chlorohydrin and potassium hydrogen sulfate afforded the olefin, b.p. 38–40° at 11 mm., infrared absorption bands at 3080, 1640, 890 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{15}Cl$: C, 65.51; H, 10.24; Cl, 24.23. Found: C, 65.48; H, 9.99; Cl, 23.67.

5-Chloro-4,4-dimethyl-2-propyl-1-pentene was prepared by the photochemical decomposition of hypochlorite (**10**) in Freon 11 at 0° and collection of the products by g.l.p.c. The chloro olefin structural assignment is based on infrared (3080, 1640, 890 cm.$^{-1}$) and combustion data.

Anal. Calcd. for $C_{10}H_{19}ClO$: C, 68.77; H, 10.89; Cl, 20.34. Found: C, 68.69; H, 10.95; Cl, 20.16.

4-(α-Chloroisopropyl)cyclohexanone.—A 1.5-g. sample of 7,7-dimethyl-1-norbornanol in 45 ml. of carbon tetrachloride was converted to the hypochlorite (**13**). The dried solution was diluted to 100 ml. and the bulk of the solvent was removed by distillation. Removal of the residual solvent under reduced pressure afforded 1.8 g. of the chloro ketone, m.p. 61–62°. Recrystallization from benzene–hexane gave material of m.p. 61–62°.

Anal. Calcd. for $C_9H_{15}ClO$: C, 61.88; H, 8.65; Cl, 20.29. Found: C, 61.74; H, 8.77; Cl, 20.23.

A sample of the chloro ketone was dehydrochlorinated by refluxing in quinoline. The elimination product was hydrogenated in ethanol with palladium-on-carbon catalyst, stopping after the uptake of 1 mole. The product was converted in 55% over-all yield to the 2,4-dinitrophenylhydrazone, m.p. 118–119° (reported m.p. for DNP of 4-isopropylcyclohexanone,[68] 118–119°) and to the semicarbazone, m.p. 186–187° (lit.,[68] m.p. 186–187°).

2,6-Dibenzal-4-(α-chloroisopropyl)cyclohexanone.—To a suspension of 0.45 g. (0.0026 mole) of 4-(α-chloroisopropyl)cyclohexanone in 2 ml. of concd. hydrochloric acid and 2 ml. of absolute ethanol was added 0.54 g. (0.0051 mole) of benzaldehyde. The bright yellow precipitate which formed rapidly was filtered and washed with a small amount of dilute ethanol, giving 0.88 g. (98%), m.p. 144–148°. Two recrystallizations from carbon tetrachloride raised the melting point to 148–149° (reported[9] m.p. for a chlorodibenzal derivative from nopinone, 148–149°) λ_{max} 329 mμ (log ε 4.52) in ethanol [reported[69] for 3-methyl-2,6-dibenzalcyclohexanone: λ_{max} 328 mμ (log ε 4.54) in ethanol].

Anal. Calcd. for $C_{23}H_{23}ClO$: C, 78.70; H, 6.61; Cl, 10.10. Found: C, 78.92; H, 6.73; Cl, 10.06.

A Convenient Synthesis of Neopentyl Chloride.—A mixture of 10 g. of 2,4,4-trimethyl-2-pentanol in 60 ml. of Freon 11, 180 ml. of 1.68 M sodium hypochlorite solution, and 30 ml. of acetic acid was stirred for 20 min. at 0°. The Freon layer was separated, dried over magnesium sulfate, and decomposed by weak ultraviolet light. The solution was washed with two 25-ml. portions of concd. sulfuric acid, with 25 ml. of 5% aqueous sodium bicarbonate, and dried over magnesium sulfate. Removal of the solvent afforded pure neopentyl chloride, $n^{25}D$ 1.4021 (lit.,[48] $n^{20}D$ 1.4042) in 45% yield.

Decomposition of Hypochlorites in Cyclohexene and Toluene.—The alcohols were converted to the hypochlorites either without use of solvent or in Freon 11 followed by removal of the solvent under reduced pressure and then added to the desired solvent. Product analyses were made by the methods described above.

Hazards.—The principal hazards are associated with the sensitivity of the hypochlorites to light and peroxides. Attempts to distil some of the hypochlorites have led to vigorous decomposition, but many of the hypochlorites of this work have been kept in an undiluted state in the dark at 5° for days. A second source of hazard is the unexpected reactivity of certain combinations. For example, hypochlorites **2**, **3**, **8**, and **9** may be dissolved in cyclohexene without visible reaction; addition of hypochlorite **10** to cyclohexene produces violent decomposition. Addition of this hypochlorite, cooled to −15° (the hypochlorite freezes at −70°), to cyclohexene, cooled to −70°, still results in rapid decomposition, affording the products of chain decomposition of the hypochlorite (see Table I).[70]

Effect of inhibitors and accelerators was determined by sealed tube experiments. Conditions are given in Table II. Rate of disappearance of hypochlorite was followed by iodometric analysis.

(68) M. D. Soffer and M. A. Jeunik, *J. Am. Chem. Soc.*, **77**, 1003 (1955).

(69) H. S. French and M. E. T. Holden, *ibid.*, **67**, 1239 (1945).

(70) This reactivity may be due to the formation of chain-initiating free radicals by a direct reaction between the hypochlorite and cyclohexene. For an example of this kind of reaction, see F. D. Greene, W. Adam, and J. E. Cantrill, *J. Am. Chem. Soc.*, **83**, 3461 (1961).

The Oxidation of Carboxylic Acids to Esters by Tetravalent Lead[1]

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Lead tetrasalts of aliphatic acids are oxidized by halogens to the corresponding esters and carbon dioxide in fair to good yields under anhydrous conditions. With larger amounts of halogen the chief products are alkyl halides. These methods offer advantages in cost and simplicity of procedure over the Simonini and Hunsdiecker methods in which the starting materials are silver salts. The effects of a number of variables on yields are discussed and mechanistic possibilities are considered.

The formation of esters from carboxylic acids and their derivatives under oxidative conditions has often been observed to occur. The over-all process may be represented as follows.

$$2RCOOH + (O) \longrightarrow RCOOR + CO_2 + H_2O \qquad (1)$$

The acids themselves,[3] their metal salts,[4] and the corresponding peracids and peranhydrides[5] have served as starting materials, while the anodic current (electrolysis),[6] halogens,[7] metal oxides,[8] and even aromatic ketones[9] have been used as oxidizing agents. In most cases esters were merely observed as byproducts, and their yields were not determined. In only a few cases is the process proposed as a preparative method. The most successful of these methods is the Simonini reaction.[7,10]

$$2RCOOAg + I_2 \xrightarrow{CCl_4} RCOOR + CO_2 + 2AgI \qquad (2)$$

This reaction produces yields of esters from aliphatic acids of 20–70%. It suffers from several disadvantages, however, especially in the cost and inconvenience of preparing and drying the silver salts required.

We have studied the effects of a number of different chemical oxidizing agents on carboxylic acids and their salts and have found that the reaction of halogens with lead tetrasalts provides an ester synthesis with yields comparable to those of the Simonini synthesis and with a considerably simplified procedure.

Lead tetrasalts are readily prepared from the corresponding acids by warming them with lead tetraacetate and distilling the acetic acid liberated, preferably under reduced pressure.

$$4RCOOH + Pb(CH_3COO)_4 \xrightarrow[10\ mm.]{70^\circ} 4CH_3COOH + Pb(RCOO)_4 \qquad (3)$$

A suitable inert solvent may be present during this reaction and is especially useful when the lead salt formed is high melting. Care must be taken to avoid decomposition of the lead tetrasalts by contact with moisture or by overheating (> 100°). However, for ester synthesis, they need not be isolated or further purified, and may, in fact, be used *in situ*.

The reaction between lead tetrasalts and iodine proceeds vigorously at about 100° with evolution of carbon dioxide and formation of the considerably less soluble lead disalts. It is therefore desirable to employ a solvent to moderate the reaction and to prevent caking or gelling of the reaction mixture. This solvent should boil at or above 140°, since optimum yields of ester require a further period of heating at elevated temperatures after the gas evolution has ceased. Other necessary properties of the solvent include chemical inertness to the lead salts and iodine, and physical characteristics (especially boiling point) which permit easy separation and purification of the product ester. No one solvent meets all of these qualifications in all cases. We have found *sym*-tetrachloroethane, *o*-dichlorobenzene, and mineral oil suitable at various times. Alternatively, the reaction may be run in an autoclave with or without solvents.

Yields of ester by the lead tetrasalt–iodine method depend markedly on the structure of the acid. Straight-chained aliphatic acids react quite satisfactorily, and the yields increase with the molecular weight of the acid. An acid in which the carboxyl group was attached to a secondary carbon atom (isobutyric acid) gave diminished yields, and one in which it was attached to a tertiary carbon atom (pivalic acid) gave no ester. Glutaric acid yielded the corresponding lactone in modest yield. The introduction of unsaturation in the acid has a drastic effect. Oleic acid and picolinic acid gave tars, and benzoic acid gave iodobenzene but no phenyl benzoate. An equimolar mixture of benzoic and palmitic acids gave pentadecyl ester but no phenyl ester. Table I summarizes the results obtained with a number of acids.

TABLE I

LEAD TETRASALT–IODINE SYNTHESIS OF ESTERS

Acid	Conversion, mole ester/2 moles acid
Acetic	0.20
Caproic	.34
Caprylic	.50
Lauric	.50
Palmitic	.54
Behenic	.52
Isobutyric	.18
Pivalic	.00
Glutaric	.19
Picolinic	.00
Benzoic	.00[a]
Benzoic–palmitic	.24[b]

[a] Iodobenzene, 61.5% yield based on iodine, was obtained. [b] Product consisted of pentadecyl ester and no phenyl ester.

(1) From the Ph.D. thesis of Joseph W. Wittmann, Purdue University, August, 1960.

(2) Archer–Daniels–Midland Company Research Assistant, 1957–1959; Purdue Research Foundation XR Fellow, 1959–1960.

(3) R. Bacon and R. Batt, *Chem. Ind.* (London), 1287 (1953).

(4) F. Fichter and E. Brunner, *Helv. Chim. Acta*, **12**, 573 (1929).

(5) D. Swern, *Chem. Rev.*, **45**, 1 (1949); C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., Chapman and Hall, Ltd., 1957, p. 491; H. Lau and H. Hart, *J. Am. Chem. Soc.*, **81**, 4897 (1959).

(6) H. Kolbe, *Ann.*, **69**, 257 (1849); and B. Weedon, *Quart. Rev.*, **6**, 380 (1952).

(7) C. Wilson, *Org. Reaction*, **IX**, 332 (1956); and R. Johnson and R. Ingham, *Chem. Rev.*, **56**, 219 (1956).

(8) O. Veiel, *Ann.*, **148**, 164 (1868).

(9) F. Paterno, *Atti accad. Lincei*, **24**, I, 675–675 (1915); *Gazz. chim. ital.*, **45**, I, 389–390 (1915); *Chem. Abstr.*, **9**, 3064 (1915).

(10) A. Simonini, *Monatsh.*, **13**, 337 (1892); **14**, 59 (1893).

The lead tetrasalt–iodine synthesis of esters proceeds in several steps, as is evident from the temperature effects observed. At 60–70° two moles of lead tetrasalt decolorize one mole of iodine without any other noticeable change—*i.e.*, no gas evolution or precipitation of lead disalt or lead iodide. At 85–105° the reaction mixture evolves carbon dioxide vigorously, and if worked up at this (second) stage yields approximately one mole of ester, two moles of alkyl iodide, two moles of lead disalt, and three moles of carbon dioxide, as illustrated in equation 4. The figures in parenthesis

$$2Pb(RCOO)_4 + I_2 \xrightarrow{85\text{–}105^\circ} \underset{(92\%)}{RCOOR} + \underset{(72\%)}{2RI} + \underset{(80\%)}{3CO_2} + \underset{(89\%)}{2Pb(RCOO)_2} \quad (4)$$

below each product represent the actual yields in the case of palmitic acid. A small amount of palmitic acid (9%) was regenerated. The over-all material balance was 89%.

The third stage of the reaction requires a still higher temperature and involves double decomposition between the alkyl iodide and the lead disalt, as in equation 5. In a separate run using pure lead dipalmitate and

$$Pb(RCOO)_2 + 2RI \xrightarrow{150\text{–}180^\circ} 2RCOOR + PbI_2 \quad (5)$$

pentadecyl iodide a 77% yield of pentadecyl palmitate was obtained.

Summing up equations 3, 4, and 5 we obtain equation 6 for the over-all synthesis. The figures in parentheses refer to the actual yields obtained with palmitic acid.

$$2Pb(CH_3COO)_4 + 8RCOOH + I_2 \longrightarrow \underset{(71\%)}{3RCOOR} + \underset{(80\%)}{3CO_2} + \underset{(86\%)}{Pb(RCOO)_2} + PbI_2 + 8CH_3COOH \quad (6)$$

Equation 6 indicates that two of the eight moles of starting acid are lost to ester formation through formation of the lead disalt. It seemed probable that the addition of more iodine would prevent this by reacting with the disalt to form more alkyl iodide and hence more ester. However this proved not to be the case, since iodine does not react with lead disalts. In one experiment lead dicaproate was heated with equimolar amounts of iodine in an autoclave to 260–270°. The principal organic products were caprone (35.8%) and caproic acid (17%) and no ester was obtained. Caprone is formed when lead dicaproate is heated alone to this temperature.[11] Mehta[12] has also observed that lead disalts do not react with iodine.

In further attempts to improve this ester synthesis, red lead was substituted for lead tetraacetate and bromine or chlorine for iodine. Red lead reacts with organic acids to give a mixture of lead tetrasalts and disalts. Since water is also formed and is deleterious to the subsequent reactions, it must be removed, preferably by reaction with acetic anhydride followed by vacuum distillation of the acetic acid generated. Bromine and chlorine differ from iodine in that they react

$$Pb_3O_4 + 8RCOOH + 4(CH_3CO)_2O \longrightarrow Pb(RCOO)_4 + 2Pb(RCOO)_2 + 8CH_3COOH \quad (7)$$

with lead disalts as well as with lead tetrasalts to form alkyl halides. These bromides and chlorides react with lead salts to form esters, although considerably more slowly than do iodides. Ester synthesis may therefore be completed according to the stoichiometry of equation 8. Using lauric acid and bromine, a 50% yield of undecyl laurate was obtained. With lauric acid and chlorine, a 20% yield of undecyl laurate was obtained.

$$Pb(RCOO)_4 + 2Pb(RCOO)_2 + 3Br_2 \longrightarrow 4RCOOR + 3PbBr_2 + 4CO_2 \quad (8)$$

Substantial amounts of free lauric acid (*ca.* 20 and 50% respectively), we regenerated in these reactions—more than in the reactions involving iodine (10–20%). This is doubtless one of the factors which prevent the yields of ester from being higher than they are. Other investigators have explained free acid formation in the reactions of silver salts with halogens as arising from substitution reactions, which generate hydrogen halide, which in turn reacts with the silver salt to generate free carboxylic acid.[13] A similar process may operate with the lead salt. Since the amount of free carboxylic acid formed is roughly proportional to the substitutive reactivity of the halogens employed—*i.e.*, chlorine > bromine > iodine, this seems to be a reasonable assumption. However free acid formation probably occurs by other mechanisms as well, since others have observed that merely heating lead tetrasalts in the absence of halogens generates some acid.[14]

Comparisons of the lead tetrasalt–halogen and Simonini methods of ester synthesis show that the principal advantages of the first method are in convenience and cost. The lead tetrasalts are readily prepared under anhydrous conditions and may be used without isolation or purification. Furthermore, they form homogeneous solutions in the solvents employed, while silver salts are insoluble in the solvents employed in the Simonini reaction. From the standpoint of yield the two processes seem to be similar, although published yield data on the Simonini reaction are sparse and in some cases inconsistent. Since the two processes proceed by reactions with entirely different stoichiometries, cost comparisons are best made on the basis of other reagents used per mole of acid reacted or per mole of ester formed. On this basis the lead tetraacetate–iodine process is about one third as expensive and the red lead–bromine process is about one fiftieth as expensive as the silver salt–iodine process.

A number of experiments were run in attempts to oxidize caproic acid to amyl caproate using other oxidizing agents, including: PbO_2, CrO_3, MnO_2, $K_2S_2O_8$, BaO_2, H_2O_2, and various combinations of these. In no case did the yield of ester exceed 14% (using 30% hydrogen peroxide in concd. sulfuric acid), and in most cases no more than a trace of ester was detected by odor.

Although this study has been directed primarily toward the synthesis of esters, it should be noted that the lead–halogen method may also be employed for the preparation of alkyl halides. Using larger ratios of halogens to lead salts decreases the yields of esters and increases the yields of alkyl halides. This effect is smallest in the case of iodine. When the synthesis represented by equations 7 and 8 is run with seven instead of three moles of bromine, and the reaction temperature is maintained below 140°, the yield of amyl bromide increases from 0 to 0.36 mole per mole of acid

(11) J. Kenner and F. Morton, *Ber.*, **72**, 455 (1939).

(12) T. Mehta, W. Mehta, and T. Thosar, *J. Indian Chem. Soc., Ind. Ed.*, **3**, 166 (1940).

(13) J. Cason, M. Kahn, and R. Mills, *J. Org. Chem.*, **18**, 1670 (1953).

(14) C. Hurd and P. Austin, *J. Am. Chem. Soc.*, **53**, 1543 (1931).

$$Pb_3O_4 + 8RCO_2H + 4(CH_3CO)_2O + 7Br_2 \longrightarrow 8RBr + 8CO_2 + 3PbBr_2 + 8CH_3CO_2H \quad (9)$$

(36% yield by equation 9). A yield of 92% is reported for amyl bromide in the Hunsdiecker reaction using silver caproate. However, this yield was estimated from the results of a quantitative determination of bromine on a neutral fraction of the reaction products and not by weighing an isolated purified material. The average yield reported for primary alkyl bromides is about 60%.[7] It is difficult to judge the relative merits of the two processes from a standpoint of yield using such insufficient data, but it seems probable that the silver salt method gives somewhat higher yields. On the other hand, the lead salt method is obviously more convenient to use.

The mechanism of formation of esters and alkyl halides by the Simonini and Hunsdiecker reactions cannot be considered to be thoroughly established in all details. The same is true of the lead salt method here described, but some of the facts developed are pertinent to mechanistic considerations and will be mentioned. Ester formation between alkyl halides and lead salts, as illustrated in equation 5, may well proceed by a combination of Sn1 and Sn2 processes as proposed by Kornblum[15] for reactions of alkyl halides with silver salts. However, ester formation as well as alkyl halide formation by reactions involving decarboxylation and a change in valence of lead from four to two, as illustrated in equations 4 and 8, are apparently much more complicated. It seems to us that they cannot proceed by an ionic mechanism involving formation of carbonium ion intermediates as proposed for similar reactions by Mosher,[16] since they proceed best in nonionizing solvents, the yields of ester are not improved by addition of excess carboxylate ions (from excess acid), and no olefins are formed (through loss of protons from the intermediate carbonium ion) from unbranched acids. A free radicals process also seems unlikely, since any R· radical formed might be expected to dimerize to R—R hydrocarbons to some extent, especially with minimal amounts of halogen present. To test this point we made a run with four moles of lead tetrapalmitate and one mole of iodine and found that the only hydrocarbon produced in detectable amounts was pentadecane (0.19 mole/mole of acid). We conclude that any radicals formed in these decompositions cannot be very free.

This leaves for consideration concerted and cage-type mechanisms. We are of the opinion that one of the other or both of these can best be used to explain the formation of esters, alkyl halides, and free carboxylic acids directly from lead tetrasalts. Acyl peroxides are unlikely intermediates, since it has been shown that they give low yields of esters from straight-chained aliphatic acids. Thus lauroyl peroxide gives not over a 16% yield of undecyl laurate,[17] and 4-phenylvaleryl peroxide gives only a 17.5% yield of the corresponding symmetrical ester[18] on thermal decomposition. Hence a more direct means of formation of the ester molecule seems likely. Acyl hypohalites have frequently been proposed as intermediates in the formation of alkyl halides,[7] and iodine triacyls have been shown to form in the reaction of silver carboxylates with iodine and to decompose into alkyl iodide and ester on warming.[19] Such intermediates are therefore sufficient to account for the qualitative results of the lead tetrasalt–iodine reactions, but whether they are necessary intermediates in this synthesis is not certain. Further work along these lines is now under way and will be reported in a later publication.

(15) N. Kornblum, R. Smiley, R. Blackwood, and D. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).
(16) W. Mosher and C. Kehr, *ibid.*, **75**, 3172 (1953).
(17) W. Cass, *ibid.*, **72**, 4915 (1950).
(18) D. De Tar and C. Weis, *ibid.*, **78**, 4296 (1956).

TABLE II
LEAD TETRASALTS

Acid	Solvent	M.p.	Anal. for Pb Calcd.	Anal. for Pb Found
Caproic	...	Oil	...	...
Caproic	...	Oil	...	...
Lauric	Pet. ether	61–62	20.63	20.88
Palmitic	Pet. ether	77–78	16.86	17.01
Behenic	Pet. ether	86–87	13.24	13.42
Oleic	...	Oil	...	...
Isobutyric	Pet. ether	102–103	...	...
Pivalic	Benzene	173	...	...
Benzoic	Benzene	180–181	...	...
Glutaric	Insol.	Dec.	...	...

Experimental

Preparation of Lead Tetrasalts.—Lead tetraacetate (0.25 mole) and a carboxylic acid (1.0 mole) were heated together at 60–80° and the acetic acid distilled at 10-mm. pressure as it formed. The product was pure enough for further reactions without other treatment. When the lead tetrasalt melted above 80–100° a solvent, such as 1,1,2,2-tetrachloroethane, *o*-dichlorobenzene, or mineral oil, was used to prevent caking and local superheating of the product.

In separate experiments each of the lead tetrasalts prepared was isolated, purified by recrystallization, and characterized by m.p. Those which have not previously been reported (tetralaurate and tetrabehenate) and one for which an analysis has not been reported (tetrapalmitate) were analyzed quantitatively for lead. The m.p.'s. which were above 100° occurred with decomposition and were determined fairly rapidly to avoid extensive decomposition.

Thermal Decomposition of Lead Tetracaproate.—When lead tetracaproate was heated alone in an autoclave for 1.5 hr. at 140–200°, it yielded 0.048 mole of amyl caproate per mole of starting caproic acid. Other products which formed were not identified. When heated similarly with sulfur or red phosphorus (equimolar amounts), or with barium peroxide in mineral oil to 170°, it gave no detectable amounts of amyl caproate.

Generalized Preparation of Esters. A. Lead Tetrasalts and Iodine.—To the lead tetrasalt (0.25 mole) was added solvent, about 300 ml., and iodine (0.125 mole). The stirred mixture was heated until gas evolution began and maintained at 85–105° until gas evolution ceased (about 20 min.). The temperature was then raised to 150–200° (depending on b.p.'s of solvent and alkyl iodide) for about 1 hr.

The work-up of the reaction mixture depended on the relative b.p.'s of the solvent and the ester. With higher boiling solvents the ester was distilled from the reaction mixture, washed with dilute sodium carbonate solution, dried, and fractionated through a short column. With lower boiling solvents the solvent was distilled, the residue was triturated with 300 ml. of ether, filtered to remove lead salts, the ether solution washed with sodium carbonate solution and sodium thiosulfate solution, dried, and fractionally distilled. With high boiling esters the product was not distilled but was recrystallized from a suitable solvent. Yields of esters were determined on purified materials showing correct elementary analyses, physical properties corresponding to those in the literature, and infrared spectra showing no extraneous peaks in the 4000–1600-cm.$^{-1}$ region. Only heneicosylbehenate, m.p. 72–73°, is new. It showed characteristic ester carbonyl absorption peaks at 1750–1735 cm.$^{-1}$ and no extraneous peaks.

(19) W. Oldham and A. Ubbelohde, *J. Chem. Soc.*, 368 (1941).

Anal. Calcd. for $C_{43}H_{86}O_2$: C, 81.31; H, 13.65. Found: C, 81.16; H, 13.60.

Recovery of free carboxylic acids was accomplished by acidifying the sodium carbonate wash solutions with mineral acid and distilling or recrystallizing the nonaqueous phase which separated.

B. Red Lead and Halogens.—The carboxylic acid (1.0 mole), acetic anhydride (0.54 mole), and acetic acid (20 ml.) were placed in a 1-l. three-necked flask fitted with a stirrer, a thermometer, and a Y-tube, one arm of which held a condenser and drying tube and the other arm of which held a rubber addition tube and flask containing red lead (0.125 mole). The mixture was heated to 60–80°, and the red lead was added incrementally as rapidly as it was decolorized. The Y-tube was replaced by a distilling head and condenser, and the acetic acid was removed completely at 70° under vacuum. The reaction mixture was cooled, the distilling head replaced by a reflux condenser fitted with a drying tube, and the solvent (300 ml.) and halogen (0.375 mole) were added. The stirred mixture was then heated slowly through the gas evolution period to about 200°, where it was held for 2–4 hr. or until the refluxing alkyl halide had reacted. The reaction mixture was worked up as described in procedure A. When a low boiling solvent was used it was removed by distillation before the final heating period.

When alkyl halide was the desired product, more halogen (0.875 mole) was added, and the temperature was not raised above 140°.

Reaction of Lead Tetrapalmitate with Iodine. Isolation and Material Balance of All Products.—Tetrachloroethane, 250 ml., and iodine, 20.9 g. (0.0825 mole), were added to lead tetrapalmitate, 101.2 g. (0.165 mole), prepared as described above in A. The mixture was stirred and heated to about 120° for 2 hr. During this period carbon dioxide was evolved and measured through the wet test meter, 0.198 mole (80.0%). The solvent was removed under a water aspirator, and the solid residue was extracted with several samples of benzene–methanol (70:30), totalling 750 ml. The liquid solution was titrated with a 1 *N* solution of sodium methoxide in methanol using Thymol Blue as indicator to determine the free carboxylic acid, 0.057 mole (8.6%). The precipitated sodium salt was filtered off, dried, and weighed as a check on this determination, 0.057 mole (8.6%). The remaining liquid was fractionally distilled, eventually under vacuum, to obtain pentadecyl iodide, b.p. 110–120° (0.03–0.06 mm.), m.p. 20–22°, $n^{25}D$ 1.4754, 0.118 mole (71.8%). The residue was recrystallized from acetone to obtain pure pentadecyl palmitate, m.p. 53–54°, 0.077 mole (34.1%).

Anal. Calcd. for $C_{31}H_{62}O_2$: C, 79.76; H, 13.39. Found: C, 79.47; H, 13.16.

The pentadecyl iodide was converted to pentadecylpyridinium iodide,[12] m.p. 105–106°, for further identification. The residue from the ester extraction was recrystallized from benzene to obtain pure lead dipalmitate, m.p. 112–114°, 0.146 mole (88.5%).

In an identical run the reaction mixture was heated to 200° for 15 min. after removal of the solvent. The solid residue was treated as before and the carboxylic acid content determined as 0.0062 mole (15.0%). The isolated and recrystallized pentadecyl palmitate amounted to 0.175 mole (70.6%). The inorganic residue from these extractions was boiled with 1 l. of benzene, filtered hot to obtain the lead iodide, 0.149 mole (91%). The hot benzene on cooling deposited the lead dipalmitate as a nearly white amorphous solid, which was separated by filtration and dried, 0.066 mole (80.0%).

Reaction of Lead Dipalmitate and Pentadecyl Iodide.—Lead dipalmitate, 7.32 g. (0.0102 mole), and pentadecyl iodide, 5.68 g. (0.0168 mole), were heated together at 200° for 15 min., cooled, and treated as above to obtain pentadecyl palmitate, 0.0128 mole (77.0%, based on iodide).

Reaction of Lead Dicaproate with Iodine.—Lead dicaproate, 166.3 g. (0.38 mole), and iodine, 63.5 g. (0.25 mole), were ground together, placed in a 250 ml. autoclave, and heated at 260–270° for 4 hr. After cooling, the gases were bled off through Dry Ice traps to isolate any low boiling hydrocarbons or other compounds. None was found. The remaining contents of the autoclave were distilled rapidly under vacuum, the distillate washed several times with sodium carbonate solution, dried, and redistilled to obtain caprone, b.p. 90–92° (6 mm.), $n^{25}D$ 1.4270. 23.0 g. (0.135 mole), 35.8% yield based on the dicaproate, The sodium carbonate solutions were acidified, extracted with ether, the ether solution dried and distilled to obtain caproic acid, b.p. 82–83° (3.8 mm.), $n^{20}D$ 1.4165, 15.4 g. (0.132 mole), 17.4% yield.

Reaction of Lead Dipalmitate Dibenzoate with Iodine.—Lead dipalmitate dibenzoate, prepared from a mixture of lead tetraacetate (0.120 mole), palmitic acid (0.24 mole), and benzoic acid (0.24 mole), reacted with iodine, 15.23 g. (0.06 mole), in tetrachloroethane, 170 ml., at 120° for 2 hr. The solvent was distilled under a water aspirator, and the residue heated at 250° for 15 min. The cooled solid product was extracted several times with ether, filtered from the inorganic residue, the ether solution washed several times with sodium carbonate solution, dried, and distilled to obtain a mixture of pentadecyl esters from which pentadecyl palmitate separated on treatment with cold acetone, m.p. 54–55°, 0.013 mole (21% yield based on the expectation of 1 mole of ester from each 2 moles of lead tetrasalt); identity was confirmed by a mixture m.p. with an authentic sample, 54–55°, and by comparisons of the infrared spectra. The residual ester was assumed to be pentadecyl benzoate. Hydrolysis with 5% potassium hydroxide in ethyl yielded only pentadecyl alcohol, m.p. 43–44° (from acetone), 0.045 mole (37%, based on the expectation of 1 mole of ester from each mole of tetrasalt). No phenol was found among the hydrolysis products.

Ester and Alkyl Bromide Syntheses Using Red Lead.—Red lead, 27.4 g. (0.04 mole), lauric acid, 65.0 g. (0.32 mole), acetic anhydride, 20.0 g. (0.20 mole), and acetic acid, 12 ml., reacted as in B to form the mixed lead dilaurate and tetralaurate. The solvent, tetrachloroethane, 150 ml., was added, the mixture warmed to 60°, and bromine, 19.2 g. (0.12 mole), dissolved in tetrachloroethane, 50 ml., was added dropwise over a period of 1 hr. The reaction mixture was heated at 140° until gas evolution ceased, then the solvent was distilled and the temperature of the residue was raised to 210–220° for 4 hr. The mixture was distilled under diminished pressure and the product purified as in A. Undecyl laurate, b.p. 220° (0.3 mm.), m.p. 32–33°, $n^{40}D$ 1.4400, 0.081 mole (50.0% yield) was obtained.

Anal. Calcd. for $C_{23}H_{46}O_2$: C, 77.90; H, 13.08. Found: C, 77.91; H, 12.92.

Red lead, 27.5 g. (0.04 mole), caproic acid, 37.0 g. (0.32 mole), acetic anhydride, 20.4 g. (0.20 mole), and acetic acid, 11 ml., reacted as in B. Then o-dichlorobenzene, 150 ml., was added, the mixture warmed to 60°, and bromine, 44.6 g. (0.28 mole), dissolved in *o*-dichlorobenzene, 50 ml., was added dropwise over a period of 1 hr. After gas evolution ceased, the mixture was heated at 140° for 0.5 hr. Then the product was distilled from the mixture, purified by washing with sodium carbonate solution, dried, and fractionally distilled to obtain amyl bromide, b.p. 127–128° (760 mm.), $n^{20}D$ 1.4443, 0.115 mole (36% yield).

Ortho Oxidation of 2,6-Dimethylphenol with Trifluoroperoxyacetic Acid

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Slow addition of hydrogen peroxide to a solution of 2,6-dimethylphenol and trifluoroacetic acid in methylene chloride affords primarily a product of ortho oxidation, the dimer (III) of 2,6-dimethyl-*o*-quinol (II). When the reagents are mixed together all at once, however, 2,6-dimethylbenzoquinone is the overwhelmingly predominant product. A cyclic hydrogen-bonded transition state is suggested to account for the ortho hydroxylation of 2,6-dimethylphenol with trifluoroperoxyacetic acid formed *in situ* from hydrogen peroxide and trifluoroacetic acid.

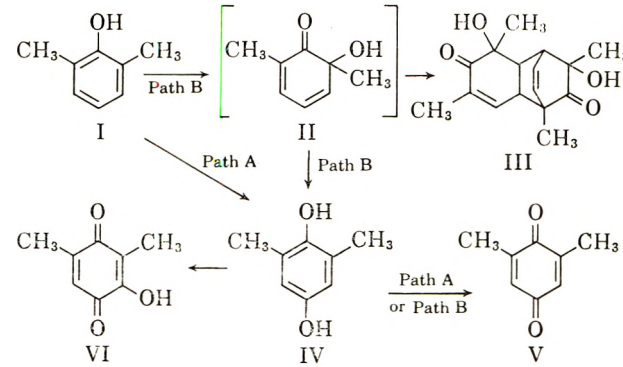
Recently, Musgrave and co-workers[1] have found that oxidation of 2,6-dimethylphenol with trifluoroperoxyacetic acid affords only one isolable product, 2,6-dimethylbenzoquinone, in 77% yield. We now wish to report that under certain conditions a different major product, resulting from ortho oxidation of the phenol, is obtained. The relative amounts of this product and 2,6-dimethylbenzoquinone formed are strongly dependent upon the concentration of oxidant.

When three molar equivalents of 50–85% hydrogen peroxide are added very slowly to a solution of 2,6-dimethylphenol (I) and one half of a molar equivalent of trifluoroacetic acid in methylene chloride solution, the major product is the compound $C_{16}H_{20}O_4$, isolated in 42% yield. 2,6-Dimethylbenzoquinone (V) is also obtained in 27% yield. When the hydrogen peroxide is added all at once, however, $C_{16}H_{20}O_4$ is obtained in 10% yield and 2,6-dimethylbenzoquinone in 60% yield. 2,6-Dimethyl-3-hydroxybenzoquinone (VI) is isolated as a minor product (3–7% yield) using either procedure.

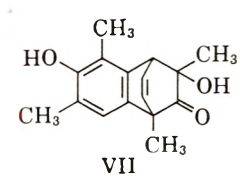
The physical and spectral properties of the compound $C_{16}H_{20}O_4$ (see Experimental) are in agreement with those reported[2] recently for the Diels–Alder dimer[3] (III) of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (II). Mixed melting point determination with an authentic specimen of III prepared by sodium periodate oxidation[2] of I confirms the identity of this product.

That acidic hydrogen peroxide is not an effective oxidant under these conditions was shown by the failure of 2,6-dimethylphenol to react with hydrogen peroxide in the presence of *p*-toluenesulfonic acid in either methylene chloride (heterogeneous) or ether (homogeneous) diluent. Slow addition of preformed trifluoroperoxyacetic acid (no free hydrogen peroxide present) to I in methylene chloride in the presence of disodium hydrogen phosphate acid scavenger affords products III, V, and VI in 40, 20, and 7% yields, respectively. Accordingly, then, trifluoroperoxyacetic acid is the active oxidizing agent involved in the formation of all three products.

In the absence of a complete kinetic study, these results are subject to several interpretations. Any effort to explain them, however, must be consistent with the following additional observations. 2,6-Dimethylhydroquinone (IV) has been shown to be a precursor to both products V (72% yield) and VI (10% yield). The dimer (III) is not transformed to V on further treatment with hydrogen peroxide and trifluoroacetic acid. The hydroxyquinone (VI) is not formed from V under the conditions of the reaction.



It appears that product V could arise from I by either of two possible paths. The first (path A) is a direct oxidative route involving the hydroquinone (IV) as a primary intermediate. The second (path B) would involve initial formation of unstable 2,6-dimethyl-*o*-quinol (II) followed by acid-catalyzed allylic rearrangement of II to IV. This 1,3-migration of hydroxyl, rendered irreversible by the driving force of aromatization, is analogous to a similar migration of fluorine encountered recently.[4] There the Diels–Alder dimer of 6-fluoro-2,6-dimethyl-2,4-cyclohexadienone was found to undergo reversal to monomer at 140° followed by hydrogen fluoride-catalyzed rearrangement to 4-fluoro-2,6-dimethylphenol. Our own efforts to carry out a similar reaction with the dimer (III) of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (II) at 145° in the presence of trifluoroacetic acid have been thwarted by the tendency of III to undergo irreversible acid-catalyzed dehydration to VII[2] (23% yield) prior to conversion to monomer.[5] 2,6-Dimethylhydroquinone (IV) could not be isolated from the complex mixture of products obtained under these conditions.



VII

Regardless of the principal path to V, the experimental results indicate that the rate equation for the

(1) R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *J. Chem. Soc.* 1804 (1959).

(2) E. Adler, J. Dahlen, and G. Westin, *Acta Chem. Scand.*, **14**, 1580 (1960).

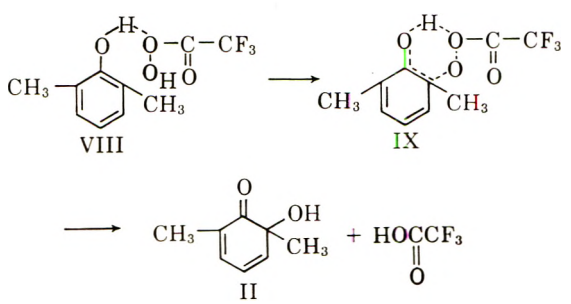
(3) A. S. Kende and P. MacGregor, *J. Am. Chem. Soc.*, **83**, 4197 (1961), have reported that this product is also formed in 22% yield when sodium 2,6-dimethylphenoxide reacts with perchloryl fluoride in dimethylformamide solution.

(4) A. S. Kende and P. MacGregor, *Chem. Ind.* (London), 460 (1962)

(5) The dimer (III) has been reported (ref. 2) to form the stable acetate of 2,6-dimethyl-*o*-quinol on refluxing (140°) with acetic anhydride and sodium acetate.

formation of V contains at least one term having a higher order in oxidizing agent than the corresponding term in the rate equation for the formation of III. Then, in the presence of a high concentration of trifluoroperoxyacetic acid, V would be expected to be the predominant product. When the concentration of oxidizing agent is very low, however, the rate of formation of V would be reduced significantly more than the rate of formation of III so that the latter becomes the major product.

It is our view that the 2,6-dimethyl-*o*-quinol (II) arises from an intermediate (VIII) in which hydrogen bonding anchors the peroxy acid in a position favorable for attack on the ortho carbon atom by the electrophilic peracid oxygen. The hydrogen bonded complex may then proceed *via* cyclic transition state IX to give product II. Analogy for IX exists in the cyclic hydrogen bonded transition state proposed by Henbest[6] to account for the selective *cis* epoxidation of 2-cyclohexenol with perbenzoic acid.



Consistent with this theory is the observation that 2,6-di-*t*-butylphenol fails to yield any 2,6-di-*t*-butyl-*o*-quinol dimer on oxidation with trifluoroperoxyacetic acid under conditions wherein III is obtained from I in moderate yield. Here, the steric requirements of the *t*-butyl groups are too great to permit hydrogen bonding[7,8] between the phenol and trifluoroperoxy acetic acid. Consequently, 2,6-di-*t*-butylbenzoquinone (70% yield) is the only product[9] isolated.

Experimental

Oxidation of 2,6-Dimethylphenol with Hydrogen Peroxide–Trifluoroacetic Acid.—Hydrogen peroxide (0.2 mole of 50–85%) was added in small portions over a 20-hr. period to a stirred solution of 2,6-dimethylphenol (12.2 g., 0.1 mole) and trifluoroacetic acid (4.0 g., 0.035 mole) in 50 ml. of methylene chloride at 25–30°. Stirring was continued at 25° for 8 hr. Then, trifluoroacetic acid (4.0 g., 0.035 mole) was added followed by hydrogen peroxide (0.1 mole of 50–85%) in small portions over a 5-hr. period. The mixture was stirred at 25° for 8 hr. and at 42° for 2–4 hr.

After dilution with methylene chloride the mixture was washed with water and extracted thrice with a 10% sodium bicarbonate solution. The wine-colored alkaline extract was washed twice with methylene chloride and the washings added to the organic solution. Drying and removal of the solvent under vacuum left 8.9–9.4 g. of yellow solid which was leeched with three 20-ml. portions of hot *n*-hexane. The pale yellow, insoluble material (5.3–5.8 g., 39–42% yield) melted at 187–190° and was recrystallized from chloroform to give white plates, m.p. 193–195° (lit., m.p. 194–196°). The melting point of an admixture with 2,6-dimethyl-*o*-quinol dimer (III), prepared by sodium periodate oxidation,[2] was undepressed; $\lambda_{max}^{CHCl_3}$ 2.88, 5.80, and 5.95 μ; λ_{max}^{EtOH} 242 mμ (ϵ 6990).

Anal. Calcd. for $C_{16}H_{20}O_4$: 69.5; H, 7.30; hydroxyl value, 0.72 $\frac{eq.}{100\ g.}$; mol. wt., 276. Found: C, 69.8; H, 7.35; hydroxyl value, 0.73 $\frac{eq.}{100\ g.}$; mol. wt., 278 (ebullioscopic).

The hexane-soluble portion was concentrated to 10 ml. and crystallized to give 3.6 g. (27% yield) of 2,6-dimethylbenzoquinone[1] (V), m.p. 70–71°.

The sodium bicarbonate extract was acidified with 20% sulfuric acid and extracted twice with methylene chloride. After drying and removal of methylene chloride the residue was sublimed to give orange crystals (0.5–1.0 g., 3–7% yield) of 2,6-dimethyl-3-hydroxybenzoquinone (VI) which melted at 101–102° (lit.[10], m.p. 103°) on recrystallization from *n*-hexane.

Anal. Calcd. for $C_8H_8O_3$: C, 63.2; H, 5.30; neut. equiv., 152. Found: C, 63.6; H, 5.45; neut. equiv., 151.

Oxidation of 2,6-Di-t-butylphenol with Hydrogen Peroxide–Trifluoroacetic Acid.—The reaction was carried out and processed in the same manner as that described for 2,6-dimethylphenol with the exception that an additional 0.035 mole of trifluoroacetic acid was added to the reaction mixture when hydrogen peroxide addition was complete. From 20.6 g. (0.1 mole) of 2,6-di-*t*-butylphenol there was obtained, after washing with sodium bicarbonate, 19 g. of a red liquid which crystallized on cooling. Recrystallization from 90% ethanol afforded 15.3 g. (70% yield) of yellow prisms, m.p. 62–63°. After sublimation and recrystallization from ethanol the 2,6-di *t*-butylbenzoquinone melted at 65–66° (lit.,[11] m.p. 65–66°).

Anal. Calcd. for $C_{14}H_{21}O_2$: C, 76.4; H, 9.10. Found: C, 76.8; H, 9.10.

Oxidation of 2,6-Dimethylhydroquinone with Hydrogen Peroxide–Trifluoroacetic Acid.—Hydrogen peroxide (0.2 mole of 85%) was added all at once to a stirred mixture of 2,6-dimethylhydroquinone (13.8 g., 0.1 mole), trifluoroacetic acid (8 g., 0.07 mole), and methylene chloride (200 ml.) at 25°. Stirring was continued at 25° for 24 hr. at which time the mixture was filtered to remove a small amount of intractable solid (m.p. >300°).

The filtrate was washed with water and extracted three times with 10% sodium bicarbonate solution. The wine-colored alkaline extract was washed twice with methylene chloride and the washings added to the organic solution. Drying and removal of the solvent under reduced pressure gave 9.8 g. (72% yield) of V, m.p. 65–68°. Recrystallization from *n*-hexane afforded yellow needles, m.p. 71–72°.

The sodium bicarbonate extract was processed in the same manner as that described for 2,6-dimethylphenol to give 1.5 g. (10% yield) of VI, m.p. 97–100°, after sublimation.

Oxidation of 2,6-Dimethylphenol with Trifluoroperoxyacetic Acid.—A solution of trifluoroperoxyacetic acid[12] (110 ml., 2.1 *M*) in methylene chloride was added dropwise over an 8-hr. period to a stirred mixture of I (12.2 g., 0.1 mole), disodium hydrogen phosphate (120 g., 0.85 mole), and methylene chloride (100 ml.) at 15–20°. Stirring was continued at 20–25° for 2 hr. at which time 98% of the peroxy acid had been consumed. Solids were collected and exhaustively washed with hot methylene chloride.

The methylene chloride solution was processed in the usual manner to afford 5.0 g. (40% yield) of crude III, m.p. 187–190°. Distillation of the hexane soluble portion gave 3.5 g., b.p. 65–80° (3 mm.), which melted at 40–55°. Analysis of the distillate by gas–liquid chromatography at 200° on a column packed with Carbowax 20 M on Fluoropak showed the presence of 2.4 g. (20% yield) of V and 1.1 g. of I.

The solids were dissolved in the sodium bicarbonate extract and the solution acidified with 20% sulfuric acid. Extraction with methylene chloride followed by sublimation afforded 1.0 g (7% yield) of VI, purified by recrystallization from hexane.

Dehydration of Dimer of 2,6-Dimethyl-*o*-quinol (III).—A solution of III (2.76 g., 0.01 mole) and trifluoroacetic acid (0.2 g.) in 60 ml. of toluene in a glass-lined sealed reactor under nitrogen was maintained at 145° for 6 hr. The mixture was

(6) H. A. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
(7) L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc., A*, **254**, 119 (1960).
(8) G. A. Harlow and D. B. Bruss, *Anal. Chem.*, **30**, 1833 (1958).
(9) This failure to observe dimer is also consistent with another interpretation whereby the initially formed oxidation product, 2,6-di-*t*-butyl-*o*-quinol, might be expected to dimerize much less readily than 2,6-dimethyl-*o*-quinol because of the steric strain introduced into the dimer by the presence of the *t*-butyl groups; see D. Y. Curtin and D. H. Dybvig, *J. Am. Chem. Soc.*, **84**, 225 (1962).
(10) J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 24 (1962).
(11) S. J. Metro, *J. Am. Chem. Soc.*, **77**, 2901 (1955).
(12) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955).

diluted with ether, washed with 10% sodium bicarbonate, and dried. Solvent was removed on a rotary evaporator under reduced pressure to give 2.3 g. of partially crystalline residue. Crystallization from toluene afforded 1.2 g. of product melting at 130–150°. Recrystallization from chloroform followed by recrystallization from ethanol gave 0.59 g. (23% yield) of VII as white plates, m.p. 170–172° (lit.,[2] m.p. 172–174°); λ_{max}^{KBr} 2.92, 5.90, 6.21, and 6.33 μ.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.01; mol. wt., 258. Found: C, 73.9; H, 6.91; mol. wt. (mass spectroscopy), 258.

The Preparation of Carbodiimides, Isocyanates, and Isothiocyanates by Metal Ion-assisted Elimination of Mercaptan[1,2]

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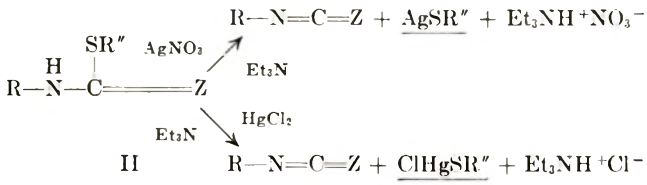
Solutions of reactive intermediates of structure I (carbodiimides, isocyanates, and isothiocyanates) which may be used for subsequent reaction without further treatment may be prepared conveniently by treating compounds of structure II with solutions of silver nitrate or mercuric chloride. An alkyl mercaptan is eliminated in the reaction as an insoluble metal mercaptide. In typical experiments, products of condensation of the intermediates with amines or alcohols were obtained in 50–100% yield.

Compounds of the general structure I, namely the carbodiimides (Z = NR′), the isocyanates (Z = O),

$$R{-}N{=}C{=}Z \qquad Z = NR', O, \text{ or } S$$

and the isothiocyanates (Z = S) are widely useful as intermediates,[3] but frequently high reactivity, instability, and/or lachrymatory properties make them difficult to handle in the isolated state.

In the present study it has been found that solutions of intermediates of type I may be prepared by heavy metal ion-assisted elimination of mercaptan from molecules of type II. The elimination is effected by treating a solution of a compound of type II with a



solution of silver nitrate or mercuric chloride in the presence of an acid acceptor. The heavy metal mercaptide is formed rapidly under mild conditions and precipitates, leaving a solution of the reactive intermediate which may be used directly for subsequent reaction. The elimination reaction is not without precedent, since strong heating is known to eliminate mercaptan from N,S-disubstituted dithiocarbamates,[4] and elimination of heavy metal sulfides from 1,3-disubstituted thioureas[3b] and dithiocarbamate salts[5] is well known. For small scale synthetic work, however, it is apparent that the new technique offers considerable convenience, since it obviates the necessity for isolating and purifying the reactive intermediate and provides optimum conditions for rapid reaction and high yields. In the discussion which follows, the elimination reaction will be considered primarily in terms of its utility as a synthetic method.

Starting materials for the synthesis of the carbodiimides are the 1,2,3-trisubstituted thiopseudoureas[6]; for the isocyanates, the N,S-disubstituted thiolcarbamates[7]; and for the isothiocyanates, the N,S-disubstituted dithiocarbamates.[8] All are prepared by well known methods. The only metal salts which have been found useful for mercaptan elimination are silver nitrate and mercuric chloride. Both are soluble in a fair number of organic solvents, react rapidly with compounds of type II, and given mercaptides insoluble in most organic solvents as long as the alkyl group which is eliminated (R″ in II) is small. Zinc chloride is also soluble in many organic solvents, but usually does not assist the elimination reaction. Acetonitrile and dimethylformamide are the best solvents for the silver nitrate reaction, and acetone, methanol, ethanol, and dimethylformamide for the mercuric chloride reaction. Though dimethyl sulfoxide is a good solvent for both metal salts, large amounts of tarry by-products are formed when it is used. As a matter of convenience, triethylamine has been used most commonly as the acid acceptor.

The elimination reaction is carried out by adding a solution of the metal salt to a solution of the substrate (II) and the acid acceptor at room temperature or below. The reaction is exothermic and sometimes requires cooling. The silver mercaptides precipitate instantly, frequently in very finely divided form. A small amount of diatomaceous earth added to the reaction mixture *before* precipitation of the silver mercaptide gives a more easily filtered solid. Formation of the mercury mercaptides is usually complete in half an hour, and they precipitate in granular form. The alkylmercaptomercuric chloride (RSHgCl) is formed, not the dimercaptide (RSHgSR).[9] When the elimination reaction is complete, carbodiimide and isothiocyanate solutions may be filtered and used directly for

(1) This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract no. DA-49-193-MD-2174.

(2) Presented in part at the Thirteenth Annual Kansas City Chemistry Conference, November 17, 1961.

(3) See, for example: (a) I. D. Morton and E. Hoggarth, "Chemistry of Carbon Compounds," Vol. IB, E. H. Rodd, ed., Elsevier Publishing Co., Amsterdam, 1952, pp. 939 and 945; (b) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); (c) J. R. Schaeffer, *Org. Chem. Bull.*, **33**, No. 2 (1961).

(4) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, p. 239.

(5) Ref. 4, p. 215.

(6) Ref. 4, Vol. I, p. 32.

(7) W. H. Schuller and C. Niemann, *J. Am. Chem. Soc.*, **75**, 3425 (1953).

(8) Ref. 4, Vol. I, p. 923.

(9) The nature of the mercury mercaptide was established by treating 1,3 diphenyl-2-n-propyl-2-thiopseudourea with mercuric chloride in acetone. *n*-Propylmercaptomercuric chloride, a compound of known[10] melting point, was obtained in 84% yield.

(10) Ref. 4, Vol. I, p. 145.

whatever subsequent reaction is desired. The more water sensitive isocyanate solutions are best treated with the condensing reagent before filtration to avoid excessive exposure to water vapor of the air.

As nearly as can be determined, yields of the reactive intermediates (I) obtained by mercaptan elimination are essentially quantitative. The yields of final products depend on the occurrence of side reactions in the second step and on the usual isolation problems, and in typical experiments have ranged from almost quantitative down to about 50%. The reactive intermediates themselves have been isolated in a few cases, but because of isolation difficulties, the yields of the intermediates were usually lower than those of secondary products derived from reaction of the same intermediates in solution.

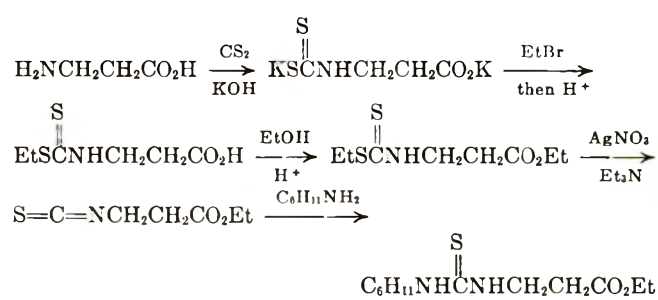
In representative experiments in the carbodiimide series (I. Z = NR'), various 2-alkyl-1,3-diphenylthiopseudoureas were treated with solutions of silver nitrate or mercuric chloride, and the resulting diphenylcarbodiimide solutions were converted to 1,3-diphenylurea (89%) by mineral acid, to 1,3-diphenylguanidine (62%) by ammonium nitrate, and to 1,2,3-triphenylguanidine (60%) by aniline hydrochloride. A solution of diisopropylcarbodiimide prepared by the action of silver nitrate in acetonitrile on 2-ethyl-1,3-diisopropylthiopseudourea gave a 60% yield of 1,3-diisopropylurea when treated with acetic acid. Isolation of diisopropylcarbodiimide from a similar preparation gave a 43% yield of distilled material.

One of the most valuable applications of carbodiimides in organic synthesis is their use as water abstractors in ester and amide preparations.[3b,c] In such reactions the carbodiimide is converted to the corresponding urea, and isolation of the ester or amide depends on a considerable solubility difference between the desired product and the urea. In situations where it is desirable to have the by-product urea *more* soluble than the ester or amide, diethylcarbodiimide is a particularly convenient condensing agent, since 1,3-diethylurea is soluble in water and many other solvents. Although diethylcarbodiimide is reported[3b] to be too unstable to store, solutions of this carbodiimide were prepared readily from 2-methyl-1,3-diethylthiopseudourea by mercaptan elimination. An acetonitrile solution gave a 64% yield of phenylacetanilide at room temperature from equimolar amounts of phenylacetic acid and aniline, and a methanol solution reacted with *p*-nitrobenzoic acid to give a 53% yield of methyl *p*-nitrobenzoate.

In view of the water sensitivity of the isocyanates (I. Z = O), no attempt was made to isolate the representatives of this class prepared by mercaptan elimination. The isocyanates were treated as rapidly as possible with amines or alcohols, and the resulting urea or urethanes were the first products isolated. In typical experiments, S-methyl N-phenylthiolcarbamate (prepared in 96% yield from aniline and methyl chlorothiolformate) was treated with silver nitrate in acetonitrile to give solutions of phenyl isocyanate. These reacted with *n*-butylamine to give 1-*n*-butyl-3-phenylurea in 82% yield (*n*-butylamine as acid acceptor), with diethylamine to give 1,1-diethyl-3-phenylurea in 82% yield (triethylamine as acid acceptor), and with dimethylamine (generated in solution from dimethylamine hydrochloride and triethylamine) to give 1,1-dimethyl-3-phenylurea in 71% yield. Treatment of S-methyl N-phenylthiolcarbamate with mercuric chloride in dry acetone gave a solution of phenyl isocyanate which reacted with cyclohexylamine to give 1-cyclohexyl-3-phenylurea in quantitative yield. *n*-Butylamine with methyl chlorothiolformate gave a crude thiolcarbamate, which, on treatment with silver nitrate in acetonitrile and then with aniline, gave 1-*n*-butyl-3-phenylurea in 78% yield. S-Methyl N-(4-ethoxycarbonyl)phenylthiolcarbamate reacted with silver nitrate in the presence of allylamine to give 1-allyl-3-(4-ethoxycarbonyl)phenylurea in 93% yield and with mercuric chloride in ethanol to give O-ethyl N-(4-ethoxycarbonylphenyl)carbamate in 94% yield.

In the isothiocyanate series (I. Z = S) the only example of a compound of type I which did not react satisfactorily in solution was encountered. Ethyl S-ethyldithiocarbamoylacetate[11] was converted readily by the action of silver nitrate in acetonitrile to ethyl isothiocyanatoacetate, which could be isolated in 60% distilled yield. However, when solutions of ethyl isothiocyanatoacetate in acetonitrile were treated with various amines in an effort to get 5-substituted 4-thiohydantoic esters, intensely colored tarry masses were obtained from which no well defined products could be isolated. An ethanol solution of ethyl isothiocyanatoacetate reacted with aniline to give a red tar from which it was possible to isolate 3-phenyl-2-thiohydantoin in 37% yield. It appears that cyclization is an almost inevitable concomitant of reactions of ethyl isothiocyanatoacetate with amines in polar solvents such as those necessary for the elimination reaction.

When cyclization was less favored, no difficulty was encountered in isolating the expected products. Crude ethyl 3-(ethyldithiocarbamoyl)propionate (from β-alanine) reacted with silver nitrate to give ethyl 3-isothiocyanatopropionate. This was isolated in 53% distilled yield and, in contrast to the isothiocyanatoacetate, gave a 64% yield of 1-cyclohexyl-3-(2-ethoxycarbonylethyl)-2-thiourea when the unpurified solution was treated with cyclohexylamine.



Isothiocyanate formation also took place readily in simple systems. S-Ethyl N-methyldithiocarbamate reacted in acetonitrile with silver nitrate to give a solution of methyl isothiocyanate, which in turn gave a 65% yield of 1-*t*-butyl-3-methyl-2-thiourea[12] with *t*-butylamine.

(11) H. Korner, *Ber.*, **41**, 1901 (1908).
(12) E. Schmidt, W. Striewsky, and F. Hitzler, *Ann.*, **560**, 222 (1948).

Experimental[13,14]

Typical experiments covering all the variations in technique employed are presented below. All products mentioned in the Discussion and not described below are known compounds, identified by agreement between their physical properties and those reported in the literature and by infrared spectra.

1,3-Diphenylguanidine.—To a solution of 6.1 g. (0.025 mole) of 2-methyl-1,3-diphenylthiopseudourea and 2.5 g. (0.025 mole) of triethylamine in 20 ml. of dimethylformamide containing 2.0 g. of suspended filter-aid was added a solution of 4.2 g. (0.025 mole) of silver nitrate in 15 ml. of dimethylformamide. The yellow precipitate was removed by suction filtration and washed with 25 ml. of dimethylformamide and then with acetone. Then 4.0 g. (0.05 mole) of ammonium nitrate was dissolved in the dimethylformamide filtrate, and the solution was held at 50–55° for 40 hr. The reaction mixture was poured into 200 ml. of water, the small amount of solid which separated was removed by filtration, and the filtrate was made strongly basic with 10% sodium hydroxide solution. The solid which came out was recovered by suction filtration and dried. The silver methyl mercaptide and filter-aid amounted to 6.1 g. (theory 5.9 g.). The 1,2-diphenylguanidine amounted to 3.3 g. (62%), m.p. 140–146°. Recrystallization from ethanol gave pure 1,2-diphenylguanidine, m.p. 148–150° (lit.,[15] m.p. 148–148.5°).

1,2-3-Triphenylguanidine.—To a solution of 6.1 g. (0.025 mole) of 2-methyl-1,3-diphenylthiopseudourea and 2.3 g. (0.025 mole) of aniline in 15 ml. of dimethylformamide was added a solution of 6.8 g. (0.025 mole) of mercuric chloride in 20 ml. of dimethylformamide. A white solid precipitated. The mixture was held at 50–55° for 40 hr., then the solid was removed by suction filtration and washed with 20 ml. of dimethylformamide. The filtrate was poured into a solution of 1.0 g. (0.025 mole) of sodium hydroxide in 200 ml. of water, and a creamy white solid separated. Addition of an aqueous solution of sodium sulfide caused a black solid to precipitate. The black and white solids were recovered by suction filtration, and the wet cake was heated with 75 ml. of 95% ethanol. The white solid went into solution; the black remained undissolved and was removed by filtration. To the filtrate was added 10 ml. of water and on cooling a white solid crystallized. After recovery by suction filtration and drying, it amounted to 3.5 g., m.p. 138–141°. Partial evaporation of the filtrate and crystallization gave another 0.8 g. of solid, m.p. 132–138°. Total recovery of 1,2,3-triphenylguanidine was 4.3 g. (60%). Two recrystallizations from ethanol gave pure material, m.p. 144–146° (lit.,[16] m.p. 144–145°).

Phenylacetanilide from Phenylacetic Acid and Aniline.—To a solution of 26.4 g. (0.20 mole) of 1,3-diethyl-2-thiourea in 100 ml. of acetone was added 35.5 g. (0.25 mole) of methyl iodide. The mixture warmed spontaneously to reflux. When the temperature had dropped back to 30° the acetone was evaporated under reduced pressure, and solid crystallized. The solid was slurried in 100 ml. of anhydrous ether, recovered by suction filtration, and dried *in vacuo*. A total of 54.5 g. (99%) of crude 1,3-diethyl-2-methylthiopseudourea iodide was recovered.

To a cold solution of 13.7 g. (0.05 mole) of the iodide in 15 ml. of water was added 20 ml. of 10% sodium hydroxide solution. The homogeneous solution was extracted with two 50-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate for 2 hr. Evaporation of the ether left 7.0 g. (96%) of crude liquid 1,3-diethyl-2-methylthiopseudourea. This was taken up in 50 ml. of acetonitrile, and 5.1 g. (0.05 mole) of triethylamine and 2.0 g. of filter-aid were added. To this solution was added a solution of 8.5 g. (0.05 mole) of silver nitrate in 20 ml. of acetonitrile. The yellow precipitate was removed by suction filtration and washed with two 25-ml. portions of acetonitrile. To the combined acetonitrile filtrate was added a solution of 5.4 g. (0.04 mole) of phenylacetic acid and 3.7 g. of aniline (0.04 mole) in 20 ml. of acetonitrile. The temperature rose rapidly from 30 to 45°, then fell slowly to room temperature. After several hours the mixture was poured into 200 ml. of ice–water, and a solid separated. It was recovered by suction filtration and dried. The dry solid amounted to 5.4 g. (64%), m.p. 113–117°. Recrystallization from 25 ml. of 95% ethanol gave 4.1 g. of pure phenylacetanilide, m.p. 115.5–117.5° (lit.,[17] m.p. 116–117°).

S-Methyl N-(4-Ethoxycarbonyl)phenylthiolcarbamate.—A solution of 41.3 g. (0.25 mole) of ethyl *p*-aminobenzoate and 25.4 g. (0.25 mole) of triethylamine in 50 ml. of acetonitrile was added with stirring and cooling to a solution of 27.4 g. (0.25 mole) of methyl chlorothiolformate in 25 ml. of acetonitrile. The mixture was allowed to stand for 1 hr., then was poured into 500 ml. of ice–water. The solid which separated was recovered by suction filtration and dried under vacuum. The crude S-methyl N-(4-ethoxycarbonyl)phenylthiolcarbamate amounted to 23.0 g. (96%), m.p. 118–122°. Recrystallization from acetonitrile gave a pure sample, m.p. 121–123°.

Anal. Calcd. for $C_{11}H_{13}O_3NS$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.27; H, 5.54; N, 5.75; S, 13.47.

1-Allyl-3-(4-ethoxycarbonyl)phenylurea.—To a solution of 9.6 g. (0.04 mole) of S-methyl N-(4-ethoxycarbonyl)phenylthiolcarbamate and 4.6 g. (0.08 mole) of allylamine in 50 ml. of acetonitrile was added a solution of 6.8 g. (0.04 mole) of silver nitrate in 15 ml. of acetonitrile. Cooling was required to hold the temperature between 30 and 40°. The yellow precipitate was recovered by suction filtration, washed with three 25-ml. portions of acetonitrile, and dried. The filtrate was evaporated to half volume and poured into 400 ml. of ice–water. The solid was recovered by suction filtration and dried. It amounted to 8.9 g., m.p. 109–120°. An additional 0.3 g. was recovered by extracting the silver methyl mercaptide with 25 ml. of boiling ethanol and pouring the filtrate into water. A portion of the product was recrystallized from ethanol to give pure 1-allyl-3-(4-ethoxycarbonyl)phenylurea, m.p. 121–122.5° (lit.,[18] m.p. 120°).

O-Ethyl N-(4-Ethoxycarbonylphenyl)carbamate.—To a solution of 9.6 g. (0.04 mole) of S-methyl N-(4-ethoxycarbonylphenyl)-thiolcarbamate and 5.1 g. (0.05 mole) of triethylamine in 75 ml. of absolute ethanol was added a solution of 10.9 g. (0.04 mole) of mercuric chloride in 40 ml. of absolute ethanol. A white solid precipitated, and the temperature rose from 30 to 50°. After 1.5 hr. the solid was recovered by suction filtration and washed with 50 ml. of ethanol. Hydrogen sulfide was bubbled through the filtrate for a few minutes; a small amount of black solid was removed by suction filtration. The filtrate was evaporated to about half volume under reduced pressure, and considerable solid crystallized. The solid was recovered by suction filtration and dried, and the filtrate was poured into 300 ml. of water. More solid separated, and was recovered by suction filtration and dried. The pure O-ethyl N-(4-ethoxycarbonylphenyl)carbamate from alcohol amounted to 3.8 g., m.p. 130–131.5° (lit.,[19] m.p. 130°, 131–132°). The less pure material from water amounted to 3.8 g., m.p. 124–126.5°. The infrared spectra of these two solids were identical. An additional 1.3 g., m.p. 130–132°, was recovered by extracting the methylmercaptomercuric chloride with 50 ml. of boiling ethanol and pouring the ethanol solution into 250 ml. of water. After this treatment the methylmercaptomercuric chloride weighed 10.8 g. (96%). The total recovery of O-ethyl N-(4-ethoxycarbonylphenyl)carbamate was 8.9 g. (94%).

Ethyl 3-Isothiocyanatopropionate.—A solution of 112.2 g. (2.0 moles) of potassium hydroxide and 89.1 g. (1.0 mole) of β-alanine in 250 ml. of water was stirred for 2.5 hr. with 76.1 g. (1.0 mole) of carbon disulfide. To the resulting homogeneous solution was added 104.7 g. (0.95 mole) of ethyl bromide, and the mixture was stirred for 3 hr. Enough heat was evolved to cause the ethyl bromide to reflux gently. A small amount of insoluble oil was removed by extraction with 100 ml. of ether, and the aqueous solution was acidified with 5 *N* hydrochloric acid. The oil which separated was extracted into 200 ml. of ether, and the ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 124.5 g. (81%) of crude 3-(S-ethyldithiocarbamoyl)propionic acid. The acid was taken up in 356 g. of absolute ethanol and 7.7 g. of *p*-toluenesulfonic acid was added. The solution was heated under reflux for 15 hr., then half the ethanol was evaporated under reduced pressure. The residue was poured into 1 l. of water, and 10% sodium carbonate solution was added until the pH was 8. The oil which separated was extracted into 150 ml. of ether, and the ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 105.6 g. (72%) of crude ethyl 3-(S-ethyldithiocarbamoyl)propionate.

A solution of 18.1 g. (0.10 mole) of this ester and 10.1 g. (0.10 mole) of triethylamine in 30 ml. of acetonitrile was treated with a

(13) All melting and boiling points are uncorrected.
(14) Microanalysis by Galbraith Laboratories, Inc., Knoxville 21, Tenn.
(15) W. J. S. Naunton, *J. Soc. Chem. Ind. Japan*, **45**, 376 T (1926).
(16) H. Tieckelmann and H. W. Post, *J. Org. Chem.*, **13**, 268 (1948).
(17) A. Reissert and A. More, *Ber.*, **39**, 3298 (1906).
(18) H. Thoms and K. Ritsert, *Ber. pharm. Ges.*, **31**, 65 (1921).
(19) (a) H. King and W. O. Murch, *J. Chem. Soc.*, **125**, 2595 (1924); (b) S. Basterfield and H. N. Wright, *J. Am. Chem. Soc.*, **48**, 2367 (1926).

solution of 17.0 g. (0.10 mole) of silver nitrate in 30 ml. of acetonitrile. The precipitate was removed by suction filtration, washed with two 10-ml. portions of acetonitrile, and dried. The dry silver ethyl mercaptide amounted to 17.0 g. (theory 16.9 g.). Most of the acetonitrile was evaporated from the filtrate, and 50 ml. of water was added to the residue. The oil which separated was extracted into two 50-ml. portions of ether, and the solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 10.5 g. (66%) of crude ethyl isothiocyanatopropionate. Distillation under reduced pressure gave 8.4 g. (53%) of purified material, b.p. 59.5–61° (0.2 mm.), $n^{27}D$ 1.4970. Redistillation gave pure ethyl 3-isothiocyanatopropionate, b.p. 58.5–60° (0.2 mm.), $n^{27}D$ 1.4983, d^{20}_4 1.114. Because the physical properties of this material did not agree well with those reported in the literature[20] [b.p. 92–94° (0.04 mm.), $n^{25}D$ 1.4904, d^{20}_4 1.132], the compound was analyzed.

(20) D. L. Garmaise, P. Schwartz, and A. F. McKay, *J. Am. Chem. Soc.*, **80**, 3332 (1958).

Anal. Calcd. for $C_6H_9O_2NS$: C, 45.26; H, 5.70; N, 8.80; S, 20.14. Found: C, 45.43; H, 5.63; N, 8.68; S, 20.39.

1-Cyclohexyl-3-(2-ethoxycarbonylethyl)-2-thiourea.—A solution of ethyl 3-isothiocyanatopropionate in 150 ml. of acetonitrile prepared as described above from 61.1 g. (0.324 mole) of ethyl 3-(S-ethyldithiocarbamoyl)propionate was treated with 32.2 g. (0.324 mole) of cyclohexylamine. The temperature rose from 27 to 76°. After 1 hr. the reaction mixture was poured into 500 ml. of cold water. An oil separated and coagulated to a solid when the mixture was neutralized with 15 ml. of 5 *N* hydrochloric acid. After recovery by suction filtration and drying, the crude 1-cyclohexyl-3-(2-ethoxycarbonylethyl)-2-thiourea amounted to 52.1 g. (64%). Two recrystallizations from 1:1 benzene–petroleum ether gave 19.9 g. of brownish solid, m.p. 53–58°. A portion was recrystallized twice more from 1:1 benzene–petroleum ether to give pure white 1-cyclohexyl-3-(2-ethoxycarbonylethyl)-2-thiourea, m.p. 56–60°.

Anal. Calcd. for $C_{12}H_{22}ON_2S$: C, 55.78; H, 8.38; N, 10.85; S, 12.41. Found: C, 55.58; H, 8.34; N, 10.69; S, 12.52.

Reactions of Dicyanoacetylene

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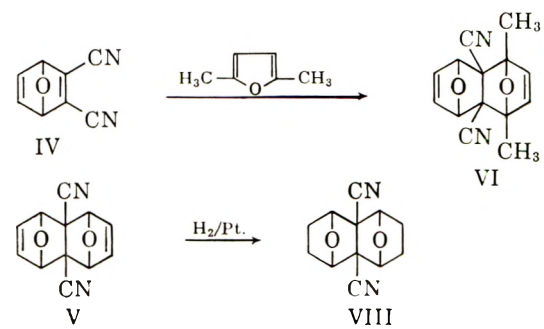
Dicyanoacetylene proved to be a highly reactive acetylenic dienophile. 1,4- Addition to durene gave the bicyclooctatriene skeleton. Other reactions with benzonitrile oxide, mercuric chloride, and diazomethane have been studied.

Literature reports on the reactivity of dicyanoacetylene (I) and its reaction products are noteworthy for their paucity. Only the addition of hydrogen chloride, ammonia, some amines,[1] and the Diels–Alder reaction with cyclopentadiene[2] have been reported. More recently it has been shown that dicyanoacetylene exhibited an exceptional reactivity as an acetylenic dienophile toward a number of 3,4-negatively substituted furan derivatives.[3] Its nature as a strong dienophile is further attested by the fact that fumaronitrile or tetracyanoethylene failed to undergo diene reaction with these 3,4-substituted furan derivatives as well in solution as in a solvent free phase.[3] Acetylene dicarboxylic acid[4] or its methyl ester[5] on the other hand may serve as a dienophile in a number of reactions, but the yields are not so good as with dicyanoacetylene. Hexafluoro-2-butyne, whose dienophilic activity was demonstrated even in the special case of 1,4- additions to benzene derivatives,[6] also underwent a facile diene reaction with 3,4-negatively disubstituted furan derivatives.[7] However, it led to an unstable adduct which underwent a retrodiene reaction as soon as it formed. In general, Diels–Alder reactions with hexafluoro-2-butyne require a higher temperature[6] than the ones with dicyanoacetylene.

The diene reaction of dicyanoacetylene with furan was of some interest because the tetracyclic system of 1,4,5,8-diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene(V) is formed with unusual ease.

The two components gave in molar ratios a mixture of the 1:1 adduct 1,4-epoxy-2,3-dicyanocyclohexa-2,5-diene (IV) and the 2:1 adduct (V). A 2:1 ratio of the starting materials led quantitatively to structure V at room temperature.



IV reacted with a second mole of furan and yielded again the tetracyclic system (V) or, with 2,5-dimethylfuran as diene, 1,4-dimethyl-4a,8a-dicyano-1,4,5,8-diepoxy-4a,5,8,8a-tetrahydronaphthalene (VI) was obtained.

The structure of all these products was supported by the n.m.r. and infrared spectra which showed them to be regular diene adducts.

1,4,5,8-Diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene (V) was hydrogenated and consumed two moles of hydrogen giving the tetrahydro derivative 1,4,5,8-diepoxy-4a,8a-dicyanodecalin (VIII).

Since the attack of the 1:1 adduct (IV) by a second mole of furan occurs at the more hindered side, the formation of these diene adducts seems governed by the strong electron-withdrawing effect of the nitrile substituents. It seems, therefore, not limited to compounds with an exceptionally low electron density at the double bond such as is found in 2,3-dicyanobenzoquinone.[8] While dicyanoacetylene yielded this tetra-

(1) (a) C. Moureu and J. C. Bongrand, *Compt. rend.*, **158**, 1092 (1920); (b) *Ann.*, **14**, 5 (1920).

(2) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

(3) C. D. Weis, *ibid.*, **27**, 3520 (1962).

(4) H. Stockmann, *ibid.*, **26**, 2025 (1961).

(5) O. Diels and S. Olsen, *J. prakt. Chem.*, **156**, 289 (1940).

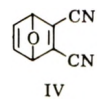
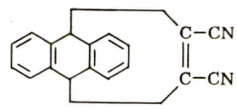
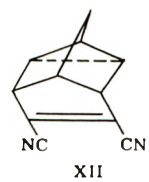
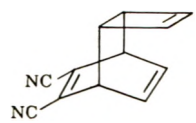
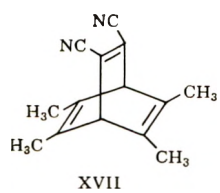
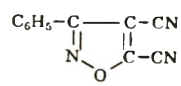
(6) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.*, **83**, 3428 (1961).

(7) C. D. Weis, *J. Org. Chem.*, **27**, 3693 (1962).

(8) H. D. Hartzler and R. E. Benson, *ibid.*, **26**, 3507 (1961).

TABLE I

THE DIELS–ALDER ADDITION OF DICYANOACETYLENE TO DIENES

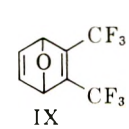
Addends	Products	Solvent	Temperature, °C.	Time	Yield, %
Furan	 IV +  V	Tetrahydrofuran	25	3 days	71 (IV) 11.5 (V)
Furan[a]	 V	Tetrahydrofuran	25	3 days	96
Anthracene	 X	None	100	1 hr.	100
1,3-Cyclohexadiene	 XI	None	0	1 hr.	93
Butadiene	 XIII	Tetrahydrofuran Benzene	100 25	5 hr. 15	94 88
Bicycloheptadiene	 XII	Tetrahydrofuran	56	6 hr.	66.5
Cyclooctatetraene	 XIV	Tetrahydrofuran	56	43 hr.	16.8
1,2,4,5-Tetramethylbenzene	 XVII	None	135	6 hr.	3.8
Benzonitrile oxide	 XVIII	Ether	33	40 hr.	81

[a] Ratio of diene to dienophile, 2:1.

cyclic structure with ease, it seems noteworthy that acetylene derivatives with substituents of less electron-withdrawing character such as acetylenedicarboxylic acid or esters yielded analogous compounds only after considerably longer reaction periods[4,5] and more drastic conditions.

A related tetracyclic system with angular cyano-substituents was formed during the reaction between dimethyl acetylenedicarboxylate and 3,4-dicyanofuran.[3] Its formation, however, required an extended reaction period at 110°.

The electron density of the substituted olefinic double bond in 2,3 - bis(trifluoromethyl) - 7 - oxabicyclo-


IX

[2.2.1]hepta-2,5-diene[7] (IX) is not sufficiently low to serve as a dienophile and lead to a tetracyclic structure.

IV decomposed on heating into furan and dicyanoacetylene, but no 3,4-dicyanofuran was observed.

The thermal decomposition of V is at least partially a retrogression of its formation. Thus, dicyanoacetylene and furan were the main products together with a small amount of IV, some unidentified product and much

tar. No 3,4-dicyanofuran was formed, as might be expected from an alternative path of the cleavage.

1,4,5,8-Diepoxy-4a,8a-dicyanodecaline (VIII) did not show any indication of undergoing a thermal cleavage.

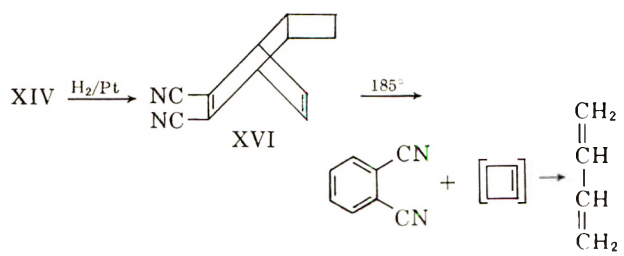
A number of Diels–Alder adducts obtained with acetylenic dienophiles are listed in Table I.

The preparation of 11,12-dicyano-9,10-dihydro-9,10-ethenoanthracene (X) has been reported earlier[9] by means of a different route. It could be heated to 400° without noticeable decomposition.

On heating, 2,3-dicyanobicyclo[2.2.2]octa-2,5-diene (XI) cleaved quantitatively into phthalonitrile and ethylene.

Bicycloheptadiene gave an adduct of the nortricyclene type, (XII) analogous to the one reported in the literature.[10,16] The retrogressive cleavage of 1,2-dicyanocyclohexadiene-1,4 (XIII) was accompanied by a considerable formation of charry products and gave phthalonitrile, traces of benzonitrile, and probably hydrogen cyanide.

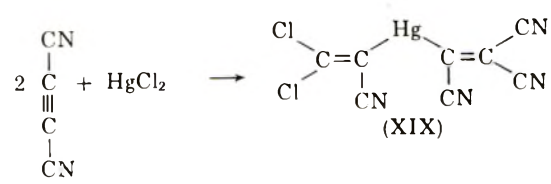
7,8-Dicyanotricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (XIV) might be assumed to have the *cis–cis* form by analogy with the structures of the addition products of cyclooctatetraene and dimethyl maleate.[11] The palladium chloride–benzonitrile complex could not be purified because of its insolubility. The retrodiene fission of 7,8 - dicyanotricyclo[4.2.2.0^{2,5}] - 3,4 - dihydrodeca-3,9-diene (XVI) obtained by partial hydrogenation of XIV, yielded phthalonitrile and as transient intermediate cyclobutene the ring of which opened under the applied experimental conditions[12] and 1,3-butadiene was isolated.



Dicyanoacetylene added 1,4 to durene to provide another example of a Diels–Alder addition of an acetylene to a substituted benzene ring[6] giving 2,3,5,6-tetramethyl-7,8-dicyanobicyclo[2.2.2]octa-2,5,7-triene (XVII). There was only a narrow temperature range in which its formation was observed.

Proof of the symmetrical structure of XVII was obtained from the nuclear magnetic resonance spectrum which contained the expected sharp bands for allylic methyl and tertiary allylic hydrogen in a 6:1 ratio of intensities. The light yellow color of XVII might be indicative of considerable overlap of the π-systems of the cyanosubstituted double bond and the methyl substituted ones.

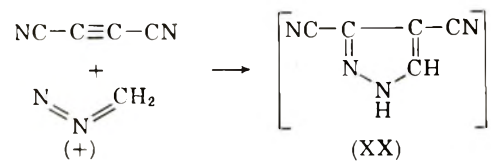
A slurry of dicyanoethylene in an aqueous mercuric chloride solution gave bis(1,2-dicyano-1-chloroethene)-mercury (XVIII). This type of reaction of acetylenes with mercuric chloride has been mentioned by Freidlina.[13]



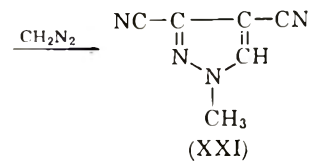
(XIX)

The reaction of dicyanoacetylene with diazomethane followed the general pattern of the Büchner pyrazole synthesis as has already been described for its reaction with diazoacetic ester.[14]

The acidity of the N-bonded hydrogen did not permit the isolation of the intermediate 3,4-dicyanopyrazole (XIX). It reacted further to yield solely N-methyldicyanopyrazole (XX). Changing the conditions—



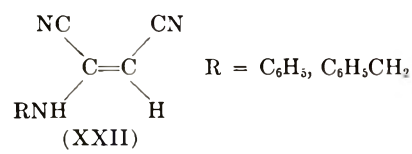
(XX)



(XXI)

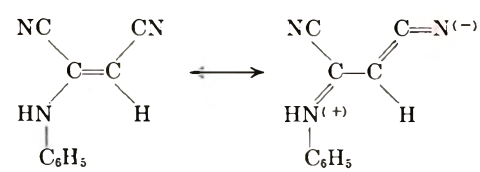
e.g., an excess of dicyanoacetylene or changing the order of addition of the two reactants gave again the N-methylated product only.

The addition of substituted amines to dicyanoacetylene has already been mentioned by Moureau and Bongrand,[1] who first isolated dicyanoacetylene. Since no characteristic data of the compounds obtained were given, some typical reactions have been included in this investigation. While aliphatic amines gave intractable tars only, aniline or benzylamine added to the acetylenic bond forming N-substituted aminomaleonitrile derivatives (XXII).



(XXII)

The infrared spectrum of XXII showed a doublet for the nitrile absorption at 4.46 and 4.53 μ. There are bands of strong intensity at 6.18 and 6.27 μ, which are believed to be due to the absorption of the ethylenic double bond and the phenyl ring, respectively. The presence of the phenyl group interferes with the assignment of NH deformation absorption. The very strong intensity of the aromatic absorption band may be indicative of resonance between the structures XXIIIa and XXIIIb.



XXIIIa XXIIIb

(9) O. Diels and W. Thiele, *Ber.*, **71**, 1173 (1938).
(10) A. T. Blomquist and Y. Meinwald, *J. Am. Chem. Soc.*, **81**, 669 (1959).
(11) M. Avram, E. Sliam, and C. D. Nenitzescu, *Ann.*, **636**, 184 (1960).
(12) W. Cooper and W. D. Walters, *J. Am. Chem. Soc.*, **80**, 4220 (1958).
(13) R. Kh. Freidlina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **14**, (1942); *Chem. Abstr.*, 3050 (1943).
(14) C. D. Weis, *J. Org. Chem.*, **27**, 3695 (1962).

Experimental

Melting points are uncorrected.

Dicyanoacetylene (I) was prepared according to the method of Blomquist and Winslow.[15]

Furan and Dicyanoacetylene. (a) Molar Ratio 1:1. 1,4-Epoxy-2,3-dicyanocyclohexadiene-2,5- (IV) and 1,4,5,8-Diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene (V).—A cold solution of dicyanoacetylene (4 g., 0.0530 mole) in tetrahydrofuran (10 ml.) was slowly added to a solution of furan (3.5 g., 0.0510 mole) in tetrahydrofuran (10 ml.). The mixture had to be cooled in ice during the addition of the furan. Then it was allowed to stand at room temperature for 3 days. The crystals which precipitated (V) were filtered off (1.26 g.) and repeatedly recrystallized from ethanol, m.p. 240° dec.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.21. Found: C, 67.92; H, 3.57; N, 13.54.

The infrared spectrum exhibited absorption bands at 4.42, 7.60, 9.42, 9.50, 10.48, 10.51, 10.77, 11.20, 11.83, 13.35, 13.60 μ.

The mother liquor from the above filtrate was evaporated to dryness and the residue (IV) (5.27 g., 71%) recrystallized from methanol–water, m.p. 112.5–113.5°.

Anal. Calcd. for $C_8H_4N_2O$: C, 66.65; H, 2.80; N, 19.63. Found: C, 67.09; H, 2.95; N, 20.03.

The infrared spectrum exhibited principal bands at 4.47, 7.88, 7.95, 9.58, 11.20, 11.75, 13.56, 13.68 μ.

IV (39.9 mg., 0.276 mmole) consumed 7.1 ml. of hydrogen (calcd. 6.95 ml.) on hydrogenation with platinum in 90% methanol. The hydrogenated compound did not give off dicyanoacetylene on heating while IV decomposes into furan and dicyanoacetylene.

(b) Molar Ratio 2:1. 1,4,5,8-Diepoxy-4a,8a-dicyano-1,4,-4a,5,8,8a-hexahydronaphthalene (V).—Furan (7 g., 0.1 mole) and dicyanoacetylene (3.5 g., 0.046 mole) were added to tetrahydrofuran (20 ml.) and kept at room temperature for 3 days. The content of the flask was evaporated to dryness and gave colorless crystals (9.4 g., 96%). A sample (2 g.) was recrystallized from dioxane, m.p. 240° dec.

The infrared spectrum was identical with the one of the previously isolated sample. Evaporation of the mother liquor left 0.1 g., the infrared spectrum of which showed the pattern of the diepoxynaphthalene system only.

1,4,5,8-Diepoxy-4a,8a-dicyanodecalin (VIII).—1,4,5,8-Diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene (V) (0.0628 g., 2.96×10^{-4} mole) was hydrogenated in methanol (90%) with palladium on charcoal and consumed 14.2 ml. of hydrogen (Calcd. 14.8 ml.). The compound was recrystallized from methanol, m.p. 205°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 67.15; H, 5.85; N, 13.19.

No dicyanoacetylene was given off on heating the compound to its decomposition point.

The infrared spectrum exhibited nitrile absorption at 4.50 μ.

1,4-Dimethyl-4a,8a-dicyano-1,4,5,8-diepoxy-4a,5,8,8a-tetrahydronaphthalene (VI).—1,4-Epoxy-2,3-dicyanocyclohexadiene (2,5) (IV) (0.5 g., 0.0347 mole) and 2,5-dimethylfuran (0.5 g., 0.0520 mole) in a solution of tetrahydrofuran (8 ml.) were kept in slight reflux for a period of 6 hr. Evaporation of the solvent left white crystals (0.8 g., 96%), which were recrystallized from methanol, m.p. 182–183°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 4.92; N, 11.66. Found: C, 70.10; H, 4.81; N, 11.36.

The Thermal Cleavage of V.—The procedure was essentially the same as described earlier.[3]

1,4,5,8-Diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene (V) (0.465 g., 0.0022 mole) was heated to 240–245° and maintained at this temperature for a period of 20 min. The dicyanoacetylene and furan formed were swept in a current of nitrogen into a small cold trap. The over-all yield was 0.33 g. A sample of the liquid phase was withdrawn and identified as furan by its infrared spectrum. The solid crystals in the top of the cold trap were mechanically removed and identified by their infrared spectrum as dicyanoacetylene. Crystals (0.069 g.) had deposited in the upper part of the decomposition tube. Recrystallization from acetonitrile gave traces of the 1:2 (V) and 0.052 g. of 1:1 (IV) adducts. Both were identified by their infrared spectrum. No 3,4-dicyanofuran could be detected. Carbonaceous residue (0.021 g.) was left.

11,12-Dicyano-9,10-dihydro-9,10-ethenoanthracene (X).—Anthracene (1.78 g., 0.010 mole) and dicyanoacetylene (0.97 g., 0.014 mole) were placed in a sealed tube and heated on a steam bath for a period of 1 hr. The crystalline reaction product was recrystallized from acetonitrile, m.p. 267–268°.

Anal. Calcd. for $C_{18}H_{10}N_2$: C, 85.03; H, 3.96; N, 11.02. Found: C, 84.77; H, 4.00; N, 10.92.

2,3-Dicyanobicyclo[2.2.2]octa-2,5-diene (XI).—Cyclohexadiene(1,3) (2 g., 0.025 mole) and dicyanoacetylene (2 g., 0.026 mole) were added to tetrahydrofuran (20 ml.). The mixture was kept in ice while the reaction took place. The solvent was evaporated after standing overnight. The solid (3.8 g., 93%) was recrystallized from methanol (charcoal) and yielded white crystals, m.p. 105°.

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.97; H, 5.16; N, 17.94. Found: C, 77.07; H, 5.22; N, 17.92.

There was no indication of any 2:1 adduct formed. The nitrile absorption appeared at 4.50 μ.

The Thermal Cleavage of 2,3-Dicyanobicyclo[2.2.2]octa-2,5-diene (XI).—(160.7 mg., 0.0010 mole) was placed in a sealed tube and kept for 15 min. at 180°. Ethylene (1.002 mmoles, calcd. 1.025 mmoles) was characterized by the infrared spectrum. Neither acetylene nor dicyanoacetylene could be detected.

The solid material (126 mg., 98%) was identified as phthalonitrile, m.p. 141°, by the mixture m.p. with an authentic sample.

2,3-Dicyanocyclohexa-2,5-diene (XIII).—Buta-1,3-diene (approximately 0.9 g., 0.0167 mole) was added to tetrahydrofuran (15 ml.) followed by dicyanoacetylene (1 g., 0.0130 mole). The mixture was placed in a sealed tube and kept in a steam bath for 5 hr. Evaporation of the solvent and subsequent sublimation at 90°, 1 mm., gave white crystals (1.61 g., 94%), m.p. 109–110°.

Anal. Calcd. for $C_8H_6N_2$: C, 73.82; H, 4.65; N, 21.53. Found: C, 73.81; H, 4.71; N, 21.26.

The nitrile absorption appeared at 4.48 μ.

A similar run in benzene as solvent was allowed to stand at room temperature for 15 hr. Crystalline material (1.5 g., 88%) was obtained, m.p. 110°. The infrared spectrum was identical with the one above.

The Thermal Cleavage of 2,3-Dicyanocyclohexa-2,5-diene (XIII).—A small sample (0.64 g.) was heated to its decomposition point and the gaseous products pumped into a cold trap. Benzonitrile could be identified by its infrared spectrum. Phthalonitrile (0.15 g.), m.p. 140–141° (mixed m.p.), was collected in the decomposition tube.

6,7-Dicyanotetracyclo[3.2.1.$1^{3,8}$.$O^{2,4}$]non-6-ene (XII).—Bicycloheptadiene (2 g., 0.0217 mole) and dicyanoacetylene (1.8 g., 0.0237 mole) were refluxed in a solution of tetrahydrofuran (15 ml.) for a period of 6 hr. The dark brown solution was evaporated to dryness. The solid residue was taken up in chloroform and filtered through aluminum oxide. Evaporation of the solvent gave a colorless crystalline material (2.43 g., 66.5%) which was recrystallized from methanol, m.p. 89°.

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.80; N, 16.66. Found: C, 78.62; H, 4.88; N, 16.27.

The infrared spectrum showed principal absorption bands at 4.51, 6.34, 7.91, 10.52, 10.72, 11.12, 12.05, 12.30, and 12.49 μ (nortricyclene bands),[16] 13.13 μ.

No hydrogen was taken up with platinum in 90% methanol and no bromine could be added to the double bond. XII did not indicate any retrodiene reaction on heating to 250°. The structure was further confirmed by the n.m.r. spectrum. There is no absorption at a field lower than 182 c.p.s. (60 Mc./sec.). Therefore there can be no olefinic hydrogen. A poorly resolved multiple peak of intensity (2) is observed at 182 c.p.s. (60 Mc./sec.) and is assigned to the *tert*-allylic hydrogen. There are two *tert*-hydrogens part of a cyclopropane ring and two secondary hydrogens on the bridge. Since the two *tert*-hydrogens are part of a cyclopropane ring, it is consistent that they are coincidentally at the same field (104 c.p.s., 60 Mc./sec.) as the bridgehead hydrogen. The remaining two peaks are assigned to the two non-equivalent bridgehead hydrogens. The one at lower field a broad ringlet at 147 c.p.s. (60 Mc./sec.) is assigned to the hydrogen adjacent to the dicyanoacetylene function and the other, a poorly resolved doublet centered at 124 c.p.s. (60 Mc./sec.) with a peak separation of 6 c.p.s. (60 Mc./sec.) is assigned to the bridgehead hydrogen which is part of the cyclopropane ring.

(15) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

(16) J. D. Roberts, E. R. Trumbull, W. Bonnett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

7,8-Dicyanotricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (XIV).—Cyclooctatetraene (10 g., 0.096 mole) and dicyanoacetylene (7.6 g., 0.1 mole) were refluxed in tetrahydrofuran (60 ml.) for a period of 43 hr. Removal of the solvent left a semisolid residue which was taken up in chloroform; after filtration through aluminum oxide, the filtrate was evaporated to dryness. Recrystallization of the slightly oily crystals (2.9 g., 16.8%) from 90% methanol (charcoal) gave almost white crystals which after sublimation at 130–140°, 1 mm., melted at 148–149°.

Anal. Calcd. for $C_{12}H_8N_2$: C, 79.97; H, 4.48; N, 15.48. Found: C, 79.85; H, 4.53; N, 15.55.

7,8-Dicyanotricyclo[4.2.2.0^{2,5}]-3,4-dihydrodeca-3,9-diene (XVI).—XIV (0.125 g., 0.0007 mole) was hydrogenated in methanol with platinum. The hydrogen uptake (17.3 ml., calcd., 17.4 ml.) was a very rapid one, but became rather slow after one mole had been consumed. Evaporation of the solvent and sublimation at 130°, 1 mm. with subsequent recrystallization from methanol afforded white crystals, m.p. 134.5–135.5°.

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.10; H, 5.54; N, 15.38. Found: C, 78.96; H, 5.66; N, 15.27.

The Retrodiene Cleavage of 7,8-Dicyanotricyclo[4.2.2.0^{2,5}]-3,4-Dihydrodeca-3,9-diene (XVI).—XVI (0.397 g., 0.00218 mole) was placed in a sealed tube and kept at 185° for a period of 40 min. The butadiene formed (46 ml., at S.T.P., 93%) showed the following characteristic data: pressure, 10 mm. at −78° (by standard high vacuum technique); lit.[17]: 10 mm. at −79.7° for 1,3-butadiene and 10 mm. at 75° for cyclobutene. Mol. wt., 53.6; calcd. 54.

The infrared spectrum was superimposable over the one of a known sample of 1,3-butadiene. No absorption belonging to cyclobutene could be detected. The solid residue (0.2742 g., 97.3%) was identified by m.p. and by infrared spectrum as phthalonitrile.

2,3,5,6-Tetramethyl-7,8-dicyanobicyclo[2.2.2]octa-2,5,7-triene (XVII).—Durene (2 g., 0.015 mole) and dicyanoacetylene (2.6 g., (0.034 mole) were placed in a sealed tube and heated to 132° (1-nitropropane as a heat exchange medium) for a period of 6 hr. The excess of dicyanoacetylene was evaporated and the semisolid residue added to methanol (10 ml.). The tarry material was well dispersed, the solution cooled in ice, and the solid (0.57 g.) filtered off. Then it was added to ether (5 ml.) and the insoluble part (0.19 g.) filtered off. Sublimation at 120–150°/1 mm. through a thin layer of glass wool gave traces of durene and 120 mg. of XVII as a light yellow sublimate, m.p. 231–232.5°.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.95; H, 6.71; N, 13.33. Found: C, 80.06; H, 6.66; N, 13.03.

The infrared spectrum showed CN absorption at 4.49 μ and a band for C=C at 6.25 μ (KBr wafer). Absorption in the ultraviolet occurred at $\lambda_{max}^{ethanol}$ 241 mμ (ϵ 5120) shoulder at 250 mμ (ϵ 4440), 358 mμ (ϵ 299).

The n.m.r. spectrum contained peaks at 107 c.p.s. (60 Mc/sec.) characteristic for allylic methyl of intensity (6), and at 256 c.p.s. (60 Mc./sec.) characteristic for tertiary allylic hydrogen of intensity (1).

4-Benzo-2,3-dicyanoisoxazole (XVIII).—Dicyanoacetylene (1.4 g., 0.018 mole) was added to an ethereal solution of benzonitrile oxide[18] (approximately 2.3 g., 0.019 mole) and refluxed for a period of 40 min. Evaporation of the solvent and recrystallization of the residue (2.92 g., 81%) from carbon tetrachloride yielded slightly yellow crystals, m.p. 84–86°.

Anal. Calcd. for $C_{11}H_5N_3O$: C, 67.69; H, 2.58; N, 21.53. Found: C, 67.64; H, 2.57; N, 21.50.

Bis(1,2-dicyano-1-chloroethene)mercury (XIX).—Dicyanoacetylene (5 g., 0.0658 mole) was added to a solution of mercuric chloride (18 g., 0.066 mole) in water (50 ml.) saturated with sodium chloride. The suspension was shaken for 20 min. with occasional cooling. The yellow precipitate (8.5 g., 61%) was filtered off, washed with water, and dried.

It was dissolved in acetone, chloroform added, and precipitation of yellow crystals, m.p. 185–190° dec., brought about by cooling the mixture in ice–water.

Anal. Calcd. for $C_8Cl_4N_4Hg$: C, 22.68; Cl, 16.73; N, 13.22; Hg, 47.35. Found: C, 22.79; Cl, 16.54; N, 13.19; Hg, 47.27.

***N*-Methyl-3,4-dicyanopyrazole (XXI).**—An ethereal solution of diazomethane was slowly added to a solution of dicyanoacetylene (3.8 g., 0.05 mole) in ether until a yellow color persisted. The temperature during the reaction was kept at about 5°. (The reaction becomes a very violent one without external cooling.) Evaporation of the solvent left a crystalline residue (6.9 g., 99%). Sublimation at 200°, 20 mm. gave white crystals, m.p. 195–196.5°. The compound is slightly soluble in boiling water.

Anal. Calcd. for $C_6H_9N_4$: C, 54.55; H, 3.05; N, 42.41. Found: C, 54.51; H, 2.88; N, 42.08.

1,2-Dicyano-1-phenylaminoethene (XXIIa).—A solution of dicyanoacetylene (1.52 g., 0.02 mole) in ether (10 ml.) was added with external cooling to a solution of aniline (1.86 g., 0.02 mole) in ether (20 ml.). It was allowed to remain at room temperature for 30 min. Evaporation of the solvent gave a tan residue (3 g., 88%). Recrystallization from chloroform yielded light yellow needles, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.93; H, 4.17; N, 24.83. Found: C, 71.01; H, 4.59; N, 24.52.

1,2-Dicyano-1-benzylaminoethene (XXIIb).—A solution of dicyanoacetylene (1.52 g., 0.02 mole) in ether (10 ml.) was added with external cooling to a solution of benzylamine (2.1 g., 0.02 mole) in ether (20 ml.). The solution remained at room temperature for 30 min. and was then evaporated to dryness. The residue (3.3 g., 92%) was dissolved in chloroform and filtered through aluminum oxide and finally recrystallized from the same solvent. The colorless crystals melted at 119–120°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.79; H, 4.91; N, 22.64.

Acknowledgment.—The author is indebted to Dr. B. C. McKusick for helpful discussions and to Dr. T. H. Regan for the n.m.r. spectra.

(17) "Handbook of Chemistry and Physics," 38th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1956–1957.

(18) F. Montforte, *Gazz. chim. ital.*, **82**, 130 (1952).

Aromatic Cyclodehydration. L. Some Bisacridizinium Systems[1]

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Starting from 2,2′- (V), 3,3′- (VI), and 4,4′-bisbromomethylbiphenyls (VII) and using the cyclization methods previously developed, the first bisacridizinium systems have been synthesized. In addition, a bis(9-acridizinium)methane (XVI) and a bis(9-acridizinium)ethane have been prepared. In contrast to the presumably planar 9,9′-bisacridizinium system, the sterically hindered 7,7′-system has an ultraviolet absorption spectrum closely resembling that of the acridizinium ion.

The current interest in the pharmacology of bisquaternary nitrogen systems, especially with regard to their application as hypotensive, ganglionic, and neuromuscular-blocking agents,[3] made it desirable to study the possibility of synthesizing some bisacridizinium

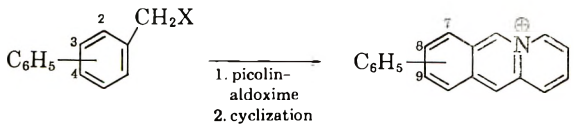
(1) For the preceding communication of this series see *J. Org. Chem.*, **26**, 4944 (1961).

(2) This research was supported by a research grant (H-2170) of the National Heart Institute of the National Institutes of Health.

(3) *E.g.*, A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3805 (1957); A. P. Phillips, *ibid.*, **79**, 5754 (1957).

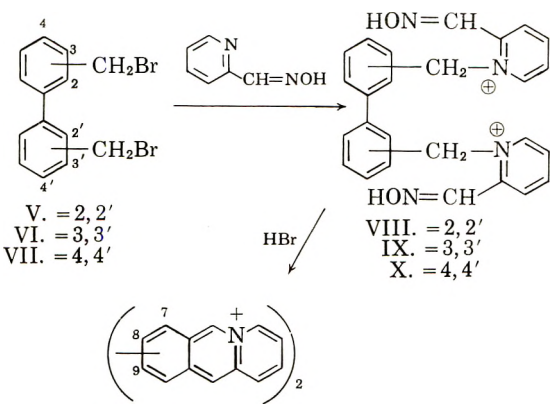
compounds. This class of diaryls has not been synthesized previously.

Since it appeared that the most logical route to the synthesis of such salts would involve cyclization of quaternary salts derived from bis(bromomethyl)-biphenyls (V–VII), model experiments were carried out using 2-bromomethyl- and 4-iodomethylbiphenyl (I and II). The hitherto unknown 7- and 9-phenylacridizinium salts were obtained without difficulty.



I. 2-C_6H_5, X = Br
II. 4-C_6H_5, X = I
III. 7-C_6H_5
IV. 9-C_6H_5

It has been shown by several workers[1–6] that biphenyl derivatives which are capable of assuming a configuration in which the rings are coplanar can transmit electronic effects across the pivot bond. It was not known whether the positive charge on the acridizinium nucleus first formed would be sufficiently transmitted to make the second cyclization impossible. The first synthesis started with 2,2′-bis(bromomethyl)-biphenyl[7] (V), selected because the expected arylacridizinium intermediate could not easily assume the coplanar position needed for transmission of electronic effects. In any event, 2,2′-bis(bromomethyl)biphenyl (V) was quaternized by reaction with two equivalents of 2-picolinaldoxime and the crude hygroscopic salt (presumably VIII) cyclized with 48% hydrobromic acid to yield a yellow-orange product having the properties expected for 7,7′-bis(acridizinium bromide).



V. = 2, 2′
VI. = 3, 3′
VII. = 4, 4′

VIII. = 2, 2′
IX. = 3, 3′
X. = 4, 4′

XI. = 7, 7′
XII. = 8, 8′
XIII. = 9, 9′

In the same way, starting from 4,4′-bis(bromomethyl)-biphenyl (VII), 9,9′-bis(acridizinium bromide) (XIII), was prepared via the intermediate quaternary salt (X). The quaternary salt (IX) from 3,3′-bis(bromomethyl)biphenyl (VI) in theory could afford 8,8′-, 8,10′-or 10,10′-bis(acridizinium bromide), on cyclization, but it seems most probable that the product which we have isolated is the 8,8′-salt.[8]

(4) M. T. O'Shaughnessy and W. H. Rodebush, *J. Am. Chem. Soc.*, **62**, 2906 (1940).

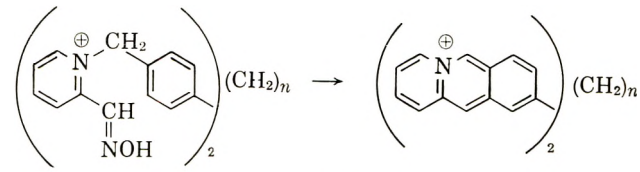
(5) E. Berliner and E. A. Blommers, *ibid.*, **73**, 2479 (1951).

(6) D. W. Sherwood and M. Calvin, *ibid.*, **64**, 1350 (1942).

(7) C. W. Muth, W. Sung, and Z. B. Papanastassiou, *ibid.*, **77**, 3393 (1955).

(8) Alkaline permanganate oxidation did not appear to yield any biphenyltetracarboxylic acid. Work is in progress on the development of a suitable general method for the degradation of acridizinium derivatives.

From 4,4′-bis(bromomethyl)diphenylmethane and 4,4′-bis(bromomethyl)bibenzyl, *via* the quaternary salts XIV and XV, 9,9′-methylenebis(acridizinium bromide) (XVI) and 9,9′-ethylenebis(acridizinium bromide) (XVII) were obtained.



XIV. $n = 1$
XV. $n = 2$

XVI. $n = 1$
XVII. $n = 2$

The ultraviolet absorption spectra of the 7,7′- and 9,9-′acridizinium salts make an interesting comparison with that of acridizinium perchlorate (Table I).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME BISACRIDIZINIUM SALTS

	Max.		Min.	
	λ, mμ	$\log_{10}\epsilon$	λ, mμ	$\log_{10}\epsilon$
Acridizinium perchlorate[a]	242	4.68	311	3.15
	361	3.99	369.5	3.88
	379.5	4.01	389.5	3.81
	399	3.93		
7,7′-bis(bromide) (XI)	244	4.93	315	3.55
	363	4.27	372	4.13
	383	4.24	392	4.14
	406	4.32		
9,9′-bis(bromide) (XIII)	243	4.74	255	4.52
	266	4.60	279	4.51
	302	4.78	307	4.76
	310	4.77	347	3.95
	366	4.15	374	4.11
	410	4.38	417	4.34
	431	4.42		

[a] Bradsher and Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

It would be expected that 7,7′-bis(acridizinium bromide) would be nonplanar, and as a result, its ultraviolet absorption spectrum would closely resemble that of the simple acridizinium ion. This is essentially true, there being only a slight bathochromic shift.

It seems probable that the 9,9′-bisacridizinium (XIII) would have no serious impediment to the achievement of planarity, and as in biphenyl[6] or the dimethochloride of γ,γ′-dipyridyl[9] the pivot bond would develop double bond character. In any case, the spectrum of the 9,9′-bisacridizinium system is more complex than that of simple acridizinium salts and shows significant absorption at higher wave lengths.

The bisacridizinium systems form an interesting new class of compounds worthy of additional study.

Experimental

All analyses were carried out by Dr. Ing. A. Schoeller, Microanalytisches Laboratorium, Kronach, Germany. The melting points were determined using the Mel-Temp apparatus and are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol using the Cary model 11 recording spectrophotometer and 1-cm. silica cells. Wave lengths are expressed in millimicrons and shoulders are designated by use of an asterisk (*).

1-(2-Biphenylmethyl)-2-oximidomethylpyridinium Bromide.—A mixture containing 2.47 g. (0.01 mole) of 2-bromomethylbi-

(9) P. Krumholz, *J. Am. Chem. Soc.*, **73**, 3487 (1951).

phenyl (I. X = Br)[10] 1.22 g. (0.01 mole) of picolinaldoxime and 1.5 ml. of N-methylpyrrolidone was heated on the steam bath in a stoppered flask for 15 min. The resinous product was triturated with ethyl acetate to effect crystallization. Recrystallization from methanol–ethyl acetate yielded 2.45 g. (66%) of colorless hexagonal platelets m.p. 167–168°.

Anal. Calcd. for $C_{19}H_{17}BrN_2O$: C, 61.81; H, 4.54; N, 7.59. Found: C, 61.76; H, 4.76; N, 7.65.

7-Phenylacridizinium Salts (III).—A solution of 1.6 g. of 1-(2-biphenylylmethyl)-2-oximidomethylpyridinium bromide in 15 ml. of 48% hydrobromic acid was refluxed. At the end of 1.5 hr. yellow crystals formed in the boiling solution and (after the mixture had been cooled) were collected, 0.78 g. The mother liquor on vacuum evaporation afforded and additional 1.0 g. The combined crude product was crystallized from methanol–ethyl acetate yielding 1.34 g. (89%) of a bright yellow powder, m.p. about 271°. The analytical sample of the bromide formed a bright yellow powder from methanol–ethyl acetate, m.p. 276–278°. The analysis indicated that the product was a double salt[11] containing hydroxylamine hydrobromide.

Anal. Calcd. for $(C_{19}H_{14}NBr)_2 \cdot NH_3OHBr$: C, 58.03; H, 4.10; N, 5.34. Found: C, 57.94; H, 4.17; N, 5.09.

The **picrate** was prepared in ethanol as bright yellow microcrystalline needle clusters, m.p. 141.5–143.5° (from ethanol); λ_{max} (log ϵ), 249 (4.79), 365 (4.45), and 386 (4.38); λ_{min} 225 (4.62), 311 (3.86), and 380 (4.37).

Anal. Calcd. for $C_{25}H_{16}N_4O_7$: C, 61.98; H, 3.33; N, 11.57. Found: C, 62.01; H, 3.39; N, 11.53.

1-(4-Biphenylylmethyl)-2-oximidomethylpyridinium Iodide.—Two grams of 4-chloromethylbiphenyl[12] was converted to crude 4-iodomethylbiphenyl, m.p. 95–96°, by the action of potassium iodide in methanol–water. The reaction of 1.24 g. of the crude iodomethylbiphenyl with 0.51 g. of 2-picolinaldoxime was carried out in 6 ml. of dimethylformamide at refrigerator temperature over a period of 8 days. Addition of ethyl acetate caused the precipitation of the yellow salt, m.p. 145–147°; yield 0.96 g. (57%). The analytical sample formed pale yellow irregular platelets from methanol–ethyl acetate, m.p. 157–158°.

Anal. Calcd. for $C_{19}H_{17}IN_2O \cdot {}^1/_4CH_3COOC_2H_5$: C, 54.88; H, 4.38; N, 6.40. Found: C, 55.26; H, 4.64; N, 6.38.

9-Phenylacridizinium (IV) Picrate.—After conversion in the usual way of 0.96 g. of 1-(4-biphenylylmethyl)-2-oximidomethylpyridinium iodide to the corresponding chloride (by the action of silver chloride) the resulting chloride was cyclized by refluxing it for 3 hrs. in 48% hydrobromic acid. Vacuum evaporation of the acid and conversion of the residue to the picrate yielded 0.81 g. (71%), m.p. 237–240°. This material crystallized from ethanol-water as bright yellow needles, m.p. 243–245°.

Anal. Calcd. for $C_{25}H_{16}N_4O_7$: C, 61.98; H. 3.33; N, 11.57. Found: C, 61.76; H, 3.31; N, 11.20.

7,7′-Bis(acridizinium Bromide) (XI).—The quaternization of 3.40 g. (0.01 mole) of 2,2′-bis(bromomethyl)biphenyl (V)[7] with 2.44 g. (0.02 mole) of 2-picolinaldoxime in 3 ml. of N-methylpyrrolidone was carried out in the usual way. The white solid (5.43 g.) obtained by trituration of the mixture with ethyl acetate, proved too hygroscopic for crystallization by conventional procedures, and was used directly in the cyclization. From 2.47 g. of the crude bromide (VIII), after 4 hr. refluxing in 48% hydrobromic acid, followed by the usual isolation procedure, 0.96 g. (40% over-all) of yellow-orange crystals of the bromide (m.p. 305° dec.) were obtained. The analytical sample was crystallized from ethanol–water as bright yellow microcrystalline parallelograms, m.p. 310° dec.

Anal. Calcd. for $C_{26}H_{18}Br_2N_2 \cdot {}^1/_2H_2O$: C, 59.22; H, 3.63; N, 5.31. Found: C, 59.41; H, 3.63; N, 5.03.

The **picrate** crystallized from acetonitrile as bright yellow irregular platelets, m.p. 248° d.

Anal. Calcd. for $C_{38}H_{22}N_8O_{14}$: C, 56.03; H, 2.72; N, 13.76. Found: C, 55.68; H, 2.67; N, 13.39.

The **perchlorate** crystallized from ethanol–water as pale yellow elongated rectangular crystals, m.p. 372° (with detonation).

Anal. Calcd. for $C_{26}H_{18}N_2Cl_2O_8$: C, 56.03; H, 3.25; N, 5.03. Found: C, 56.05; H, 3.18; N, 5.05.

3,3′-Bis(1-methylene-2-oximidomethylpyridinium Picrate)-biphenyl (IX).—The quaternization of 3.40 g. of 3,3′-bis(bromomethyl)biphenyl (VI)[13] was carried out essentially as in the case of the isomer (V) except that all heating was avoided. When the contents of the flask became solid, ethyl acetate was added and the bromide collected. The yield was 5.5 g. (94%), m.p. 187–190°. The best sample crystallized from methanol–ethyl acetate as colorless microcrystalline needle clusters, m.p. 205–207°, but was not of analytical purity.

The **picrate** crystallized from ethanol as well defined bright yellow needles, m.p. 119–121°.

Anal. Calcd. for $C_{38}H_{28}N_{10}O_{16} \cdot {}^1/_2C_2H_5OH$: C, 51.83; H, 3.46; N, 15.51. Found: C, 51.63; H, 3.40; N, 15.52.

8,8′(?)-Bis(acridizinium Bromide).—The cyclization of 2 g. of the crude bromide (IX) was carried out in the usual way (5 hr.) yielding 0.56 g. (32%) of yellow solid, m.p. above 375°. The analytical sample was crystallized from ethanol–water as a yellow microcrystalline powder, m.p. above 380°, λ_{max} (log ϵ) 242 (4.70) 318–326* (3.95), 3.67 (4.26), 380* (4.18), 397* (3.60); λ_{min} 331 (3.94).

Anal. Calcd. for $C_{26}H_{25}Br_2N_2 \cdot {}^1/_2\ H_2O$: C, 59.22; H, 3.63; N, 5.31. Found: C, 59.21; H, 3.83; N, 5.69.

The **picrate** was obtained from acetonitrile as a yellow microcrystalline powder, m.p. >400°.

Anal. Calcd. for $C_{38}H_{22}N_8O_{14} \cdot H_2O$: C, 54.81; H, 2.90; N, 13.46. Found: C, 54.51; H, 3.24; N, 13.39.

The **perchlorate** crystallized from acetonitrile as a pale yellow microcrystalline powder, m.p. above 390°.

Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_8$: C, 56.03; H, 3.25; N, 5.03. Found: C, 56.39; H, 3.50; N, 5.29.

4,4′-Bis(1-methylene-2-oximidomethylpyridinium Picrate)-biphenyl (X).—The quaternization of 3.40 g. of 4,4′-bis(bromomethyl)biphenyl (VII)[14] with picolinaldoxime was carried out in dimethylformamide. Trituration of the reaction mixture with ethyl acetate yielded 5 g. of a hygroscopic solid (presumably the bromide of X) suitable for further reactions.

The **picrate** was crystallized from ethanol as a bright yellow microcrystalline powder, m.p. 197–198°.

Anal. Calcd. for $C_{38}H_{28}N_{10}O_{16}$: C, 51.82; H, 3.20; N, 15.91. Found: C, 52.06; H, 3.43; N, 15.47.

The **perchlorate** was crystallized from methanol–ethyl acetate as a cream-colored microcrystalline powder, m.p. 198–200°.

Anal. Calcd. for $C_{26}H_{24}Cl_2N_4O_{10} \cdot {}^1/_2CH_3COOC_2H_5$: C, 51.00; H, 4.28; N, 8.50. Found: C, 50.94; H, 4.30; N, 8.72.

9,9′-Bis(acridizinium Bromide) (XIII).—The cyclization of 2.7 g. of the bromide (X) in the usual way afforded 1.0 g. (37%) of orange product, m.p. above 390°. The analytical sample crystallized from ethanol–water as aggregates of flat orange needles, m.p. above 390°.

Anal. Calcd. for $C_{26}H_{18}Br_2N_2 \cdot {}^1/_2H_2O$: C, 59.22; H, 3.63; N, 5.31. Found: C, 59.30; H, 3.85; N, 5.12.

The **perchlorate** crystallized from acetonitrile as a bright yellow powder, m.p. above 390° d.

Anal. Calcd. for $C_{26}H_{18}N_2Cl_2O_8$: C, 56.03; H, 3.25; N, 5.03. Found: C, 56.44; H, 3.54; N, 4.95.

4,4′-Bis(1-methylene-2-oximidomethylpyridinium Bromide)-diphenylmethane (XIV).—The quaternization of 2-picolinaldoxime by 4,4′-bis(bromomethyl)diphenylmethane[15] was carried out in N-methylpyrrolidone at steam bath temperature. Worked up as usual it afforded 5.0 g. of crude bromide (XIV) suitable for further reactions. The analytical sample crystallized from ethanol–ethyl acetate as a colorless microcrystalline powder, m.p. 202–203° dec.

Anal. Calcd. for $C_{27}H_{26}Br_2N_4O_2 \cdot {}^1/_2H_2O$: C, 54.12; H, 4.70; N, 9.02. Found: C, 54.40; H, 4.61; N, 8.86.

9,9′-Methylenebis(acridizinium Bromide).—The crude quaternary salt (XIV) obtained from 1.77 g. of 4,4′-bis(bromomethyl) diphenylmethane was cyclized in hydrobromic acid by heating the solution overnight at steam bath temperature. A total of 1.08 g. (41%) of product, m.p. 289° dec., was recovered. The analytical sample crystallized from ethanol–water as yellow needle clusters, m.p. 289° dec., λ_{max} (log ϵ), 244 (4.96), 250* (4.93), 277* (4.74), 362 (4.42), 374 (4.50), and 394 (4.41); λ_{min} 318 (3.72), 366 (4.38), 385 (4.29).

Anal. Calcd. for $C_{27}H_{20}Br_2N_2$: C, 60.92; H, 3.79; N, 5.26. Found: C, 60.75; H, 4.13; N, 5.54.

The **picrate** crystallized from ethanol–water as bright yellow felted needles, m.p. 247–248°.

(10) J. von Braun and G. Manz, *Ann.*, **468**, 258 (1929).

(11) A forthcoming publication will discuss some earlier observations on double salt formation in the acridizinium series.

(12) J. von Braun, G. Irmisch, and J. Nelles, *Ber.*, **66**, 1471 (1933).

(13) W. Werner, *J. Org. Chem.*, **17**, 523 (1952).

(14) D. D. Reynolds and K. R. Dunham, U. S. Patent 2,789,971; *cf.*, *Chem. Abstr.*, **51**, 14814b (1957).

(15) H. Steinberg and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5388 (1952).

Anal. Calcd. for $C_{39}H_{24}N_8O_{14}\cdot{}^1/_2C_2H_5OH$: C, 56.41; H, 3.20; N, 13.16. Found: C, 56.50; H, 3.11; N, 12.71.

4,4′-Bis(1-methylene-2-oximidomethylpyridinium Picrate)-bibenzyl (XV).—The quaternization of picolinic aldoxime with 4,4′-bis(bromomethyl)bibenzyl[16] was carried out in N-methylpyrrolidone in the usual way. A portion of the crude product was converted to the picrate which formed a bright yellow powder from ethanol, m.p. 130–131°.

(16) J. L. R. Williams and K. R. Dunham, U. S. Patent 2,843,567; *cf.*, *Chem. Abstr.*, **52**, 16798h (1958).

Anal. Calcd. for $C_{40}H_{28}N_{10}O_{16}\cdot C_2H_5OH$: C, 53.05; H, 3.60; N, 14.73. Found: C, 52.75; H, 3.50; N, 14.41.

9,9′-Ethylenebis(acridizinium Bromide) (XVII).—The cyclization of 2.5 g. of the crude bromide (XV) was carried out as in the case of the homolog (XIV). The product consisted of 1.1 g. (40%) of small bright orange needles from ethanol–water, m.p. above 390°, λ_{max} (log ϵ), 245 (4.79), 252 (4.80), 362 (4.52), 376 (4.20), 393 (4.26), and 395* (4.12); λ_{min}, 249 (4.78), 314 (3.34), 368 (4.17), and 388 (4.03).

Anal. Calcd. for $C_{28}H_{22}Br_2N_2$: C, 61.56; H, 4.06; N, 5.13. Found: C, 61.37; H, 4.11; N, 5.41.

Aromatic Cyclodehydration. LI.[1] Phenanthridizinium Derivatives Bearing a Carboxyethyl Group

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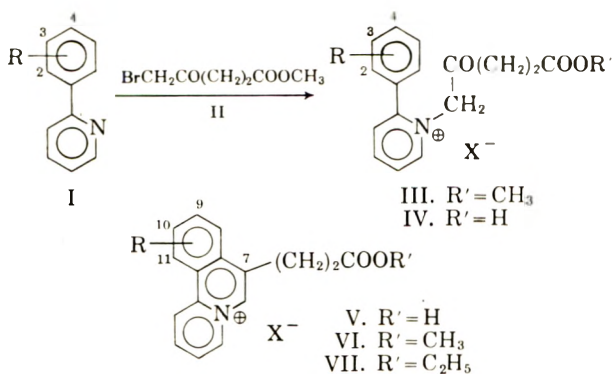
The quaternary salt formed by the reaction of methyl δ-bromolevulinate with 2-phenylpyridine may be cyclized to afford the 7-(β-carboxyethyl)benzo[*a*]quinolizinium ion. The synthesis was extended to two of the 2-tolylpyridines.

Analogy suggests that any extensive application of phenanthridizinium[3] salts in medicinal chemistry will require that there be one or more functional groups in addition to the quaternary nitrogen. To date, fully aromatic phenanthridizinium salts bearing a methoxyl[4] or hydroxyl[3] group have been prepared, but with the exception of the 1,2,3,4-tetracarbomethoxyphenanthridizinium ion reported by Diels and co-workers[5,6] it appears that no derivatives having functional groups have been synthesized. The present communication describes some experiments directed toward the introduction of the carboxyl or a carboxylalkyl group into the 7-position of the phenanthridizinium nucleus.



It seemed probable that the carboxyl function could be introduced into the phenanthridizinium nucleus by quaternization of a 2-phenylpyridine with a suitable ω-bromoketo ester, $BrCH_2CO(CH_2)nCOOR$ followed by cyclization. Preliminary attempts at quaternization using ethyl bromopyruvate[7] (n = 0) were unsuccessful, the major product being the hydrobromide of the base I. The next higher homolog, γ-bromoacetoacetic ester (n = 1) was not studied since it seemed obvious that in boiling mineral acid, rapid hydrolysis and decarboxylation of the quaternary salt would occur. The next higher homolog, methyl δ-bromolevulinate (II. n = 2) is easily obtained[8] and quaternizes readily with 2-phenyl- and 2-tolylpyridines (I) to afford ether-insoluble liquid salts (III). The crude salts were not purified, but used directly in the cyclization reaction. Cyclization in boiling hydrobromic acid proved slower (6–16 days) than was the case with the simple 1-acetonyl-2-arylpyridinium salts (2–3 days) studied earlier.[9] In nearly all cyclization attempts, uncyclized keto acid (IV) was recovered along with the product (V). Where the methyl group was in the *ortho* position of the phenyl ring (I. R = 2-CH_3), no cyclization product was detected, even after a reflux period of fifteen days, 39% of starting material being recovered as uncyclized keto acid (IV. R = 2-CH_3). This was not too surprising since the methyl at the 2-position impedes the achievement of the coplanarity essential for cyclization. The related 1-acetonyl-2-(*o*-tolyl)pyridinium salt cyclized in only 9% yield under the conditions which produced a 71% yield from the *p*-tolyl analog.[9]

The 7-(β-carboxyethyl)phenanthridizinium (V) perchlorates melted above 200° and showed the characteristic instability toward alkali. Efforts to prepare the zwitterion either by addition of potassium hydroxide to an alcoholic solution of the perchlorate or by action of silver oxide on the bromide yielded unstable products which showed the characteristic carboxylate anion absorption at 1575 cm.$^{-1}$, but were not analytically pure. Esterification of the new acids (V) in absolute methanol (hydrogen chloride catalyst) occurred in good yield. In one case (V. R = 9-CH_3) esterification was likewise brought about *via* the acid chloride, which was formed as a milky suspension by stirring a suspension of the acid in carbon tetrachloride with oxalyl chloride at room temperature. If the resulting milky suspension

(1) For the preceding communication of this series see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 78 (1963).

(2) Taken from part of a dissertation submitted by N. L. Y. in partial fulfillment of the requirements for the Ph.D. degree, Duke University. This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(3) The name phenanthridizinium has been proposed [C. K. Bradsher and K. B. Moser, *J. Am. Chem. Soc.*, **81**, 1941 (1959)] as a simpler alternative to the *Chem. Abstr.* designation, benzo[*a*]quinolizinium.

(4) L. E. Beavers, Ph.D. dissertation, Duke University, 1955.

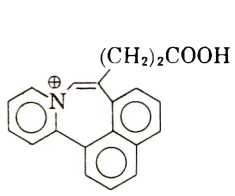
(5) O. Diels and J. Harms, *Ann.*, **525**, 73 (1936).

(6) O. Diels and K. Alder, *ibid.*, **498**, 16 (1932).

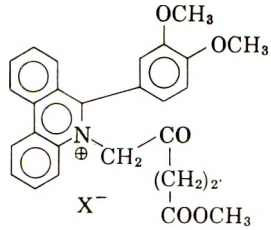
(7) C. F. Ward, *J. Chem. Soc.*, **123**, 2207 (1923).

(8) H. Dannenberg and S. Läufer, *Ber.*, **89**, 2242 (1956).

(9) C. K. Bradsher and K. B. Moser, *J. Am. Chem. Soc.*, **81**, 1941 (1959).



VIII



IX

was stirred with methanol or ethanol, the expected ester was formed.

When 2-(1-naphthyl)pyridine[10] was quaternized with methyl δ-bromolevulinate, and the crude salt cyclized, it afforded a yellow powder in 24% yield. The ultraviolet absorption spectrum of this new substance suggests that, as in the case of simpler analogs,[11] cyclization has occurred into the alpha position of the naphthalene ring to form a new seven-membered ring (VIII) rather than into the beta position to form a six-membered ring.

The quaternization product (IX), obtained by the reaction of 6 - (3,4 - dimethoxyphenyl)phenanthridine with methyl α-bromolevulinate, when heated with hydrochloric acid underwent cleavage rather than cyclization.

Experimental

All analyses were carried out by Dr. Ing. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, Germany. The melting points were determined with the Mel-Temp apparatus and are uncorrected. The ultraviolet absorption spectra were determined in 95% ethanol using 1-cm. silica cells in the Cary Model 11 recording spectrophotometer.

7-(β-Carboxyethyl)phenanthridizinium (V. R = H) Perchlorate.—An intimate mixture of 2.95 g. (0.019 mole) of 2-phenylpyridine[12] with 4.09 g. (0.019 mole) of methyl δ-bromolevulinate[8] (II) in a 50-ml. glass-stoppered round-bottomed flask was gently heated on the steam bath until the mixture formed a golden brown resin on cooling. The resin was washed thoroughly with ether and then dissolved in 30 ml. of 48% hydrobromic acid. The solution was heated without a condenser until the temperature reached 125° and then refluxed for 16 days. The dark-colored solution was filtered to remove some of the decomposition products and the filtrate evaporated *in vacuo*. The residue was dissolved in 75 ml. of water, the solution treated with Norit, filtered, and again evaporated *in vacuo*. The residue was dissolved in 20 ml. of water, the solution filtered and treated with 9 ml. of 23% perchloric acid. On cooling, 4.84 g. of a tan product precipitated and was collected. Recrystallization of the crude material from hot water yielded 2.3 g. (34.5%) of small light tan needles, m.p. 239–240°, λ_{max} (log ϵ), 225 (4.32), 238 (4.40), 269 (4.30), 282 (4.34), 326 (3.67), 340 (3.94), and 355 mμ (4.06).

Anal. Calcd. for $C_{16}H_{14}ClNO_6$: C, 54.64; H, 4.01; N, 3.98. Found: C, 54.65; H, 4.03; N, 4.10.

A second fraction which separated from the solution on standing proved to be **1-(2-keto-4-carboxybutyl)-2-phenylpyridinium (IV. R = H) perchlorate.** It was recrystallized from water as elongated rectangles m.p. 202–204°.

Anal. Calcd. for $C_{16}H_{16}ClNO_7$: C, 51.98; H, 4.34; N, 3.79. Found: C, 52.00; H, 4.43; N, 3.95.

7-(β-Carbomethoxyethyl)phenanthridizinium (VI. R = H) perchlorate was prepared in 96% yield by refluxing the free acid (V) overnight with methanol saturated with hydrogen chloride, m.p. 188–190°. The analytical sample was recrystallized from methanol as aggregates of flat needles, m.p. 189.5–190.5°.

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.41; N, 3.83. Found: C, 55.97; H, 4.24; N, 4.10.

7-(β-Carboxyethyl)-9-methylphenanthridizinium (V. R = 9-CH_3) Perchlorate.—Starting with 4.06 g. of 2-(*p*-tolyl)pyridine[13] and following the procedure for (V. R = H), except that refluxing in acid was stopped after 6 days, a 54% yield of nearly colorless, long, well formed prisms was obtained by crystallization from hot water, m.p. 233–234°, λ_{max} (log ϵ), 228 (4.42), 242 (4.44), 274 (4.48), 325 (3.84), 340 (4.07), and 355 mμ (4.20); λ_{min} 232 (4.36), 256 (4.33), 318 (3.76), 330 (3.77), and 347 (3.83).

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.42; N, 3.83. Found: C, 55.88; H, 4.69; N, 3.92.

From the mother liquor 1.23 g. of **1-(2-keto-4-carboxybutyl)-2-(*p*-tolyl)pyridinium (IV. R = 4-CH_3) perchlorate** was obtained as colorless microcrystalline aggregates, m.p. 163–165°.

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.20; H, 4.73; N, 3.65. Found: C, 53.12; H, 4.67; N, 3.55.

7-(β-Carbomethoxyethyl)-9-methylphenanthridizinium (VI. R = 9-CH_3) Perchlorate. (a) **By Fischer Esterification.**—Esterification of V (R = 9-CH_3) in the usual way afforded 77% yield of product, m.p. 175–178°. The analytical sample crystallized from methanol as colorless hexagonal platelets, m.p. 173–175°.

(b) ***Via* the Acid Chloride.**—To a suspension of 200 mg. of the free acid (V. R = 9-CH_3) in 20 ml. of dry carbon tetrachloride 0.3 ml. of oxalyl chloride was added and the mixture stirred overnight. To the resulting milky suspension 25 ml. of anhydrous methanol was added and stirring continued for 5 hr. The solvents were vacuum-evaporated and the residue washed with ether. Once recrystallized from methanol it afforded colorless platelets, m.p. 174–175°. The melting point was not depressed when the substance was mixed with the product from procedure a.

Anal. Calcd. for $C_{18}H_{18}ClNO_6$: C, 56.92; H, 4.78; N, 3.69. Found (procedure a): C, 56.97; H, 4.91; N, 3.84.

7-(β-Carboethoxyethyl)-9-methylphenanthridizinium (VII. R = 9-CH_3) perchlorate was prepared *via* the acid chloride essentially as described for the lower homolog (VI. R = 9-CH_3) except that the crude acid chloride was stirred with absolute ethanol for 24 hr., yield 88%, m.p. 157–161°. The analytical sample was crystallized from ethanol as colorless needle clusters, m.p. 165–167°.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.71; H, 5.01; N, 3.71.

7-(β-Carboxyethyl)-10-methylphenanthridizinium (V. R = 10-CH_3) Salts.—Starting with 4.06 g. of 2-(*m*-tolyl)pyridine[13] (I. R = 3-CH_3), and following the 6-day cyclization procedure, it was found that before perchloric acid could be added, the bromide crystallized from 20 ml. of water affording 3.75 g. (45%) of felted needles, m.p. 244–248°. The analytical sample crystallized from water as nearly colorless needles, m.p. 250–251°.

Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.06. Found: C, 58.74; H, 4.56; N, 4.08.

The mother liquor was treated with dilute perchloric acid and the resulting brown precipitate crystallized from ethanol–water (Norit), affording 1.16 g. of the perchlorate, m.p. 202–205°. The analytical sample formed slender colorless needles from ethanol–water, m.p. 219–221°, λ_{max} (log ϵ), 228 (4.38), 243 (4.54), 263 (4.35), 285 (4.39), 332*[14] (3.56), 347 (3.97), and 362 mμ (4.11); λ_{min} 229 (4.36), 256 (4.33), 271 (4.32), 322 (3.54), and 353 (3.87).

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.83; H, 4.38; N, 4.01.

The methyl ester (VI. R = 10-CH_3) of the perchlorate, prepared by direct esterification afforded colorless crystals, m.p. 196–198°, in 77% yield. The analytical sample crystallized from methanol as colorless well formed needles, m.p. 197–199°.

Anal. Calcd. for $C_{18}H_{18}NClO_6$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.64; H, 4.59; N, 3.82.

1-(2-Keto-4-carboxybutyl)-2-(*o*-tolyl)pyridinium (IV. R = 2-CH_3) Perchlorate.—Starting with 4.06 g. of 2-(*o*-tolyl)pyridine[9] (I. R = 2-CH_3) and carrying out the usual quaternization procedure followed by 15 days refluxing in hydrobromic acid 3.6 g. of tan-colored crystals was precipitated as the perchlorate, m.p. 159–168°. Recrystallized from water it formed colorless rectangular platelets, m.p. 170–171°.

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.20; H, 4.72; N, 3.65. Found: C, 53.52; H, 4.57; N, 3.70.

(10) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(11) C. K. Bradsher and J. W. McDonald, *J. Org. Chem.*, **27**, 4482 (1962).

(12) J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

(13) J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Am. Chem. Soc.*, **74**, 2667 (1952).

(14) The asterisk (*) is used to denote a shoulder.

7-Methylbenzo[1,m]morphanthridizinium[15] (VIII) Perchlorate.—The quaternization of 2.05 g. of 2-(1-naphthyl)pyridine[10] was carried out as usual, and the crude salt cyclized by refluxing it for 100 hr. with hydrobromic acid. The product was isolated as the perchlorate and crystallized from ethanol as a bright yellow powder, m.p. 205–210°, yield 1.01 g. (24%). The analytical sample was crystallized from ethanol–water as a yellow microcrystalline powder, m.p. 214°, λ_{max} (log ϵ), 242 (4.69), 291 (4.30), and 380 mμ (3.88); λ_{min} 265 (4.05) and 344 (3.51).

Anal. Calcd. for $C_{20}H_{16}ClNO_6$: C, 59.78; H, 4.01; N, 3.49. Found: C, 60.13; H, 4.36; N, 3.54.

5-(2-Keto-4-carbomethoxybutyl)-6-(3,4-dimethoxyphenyl)-phenanthridinium (IX) Perchlorate.—The quaternization of 1.57 g. of 6-(3,4-dimethoxyphenyl)phenanthridine[16] with 1.05 g. of methyl α-bromolevulinate (II) was carried out in 5 ml. of N-methylpyrrolidone by heating on the steam bath for about 3 hr. The solution was cooled and ether added until the solution was turbid. In the refrigerator, 1.4 g. (51%) of yellow crystals was deposited from the solution, m.p. 146–160°. Recrystallization from ethanol gave bright yellow crystals, m.p. 170–171°. A sample, converted to the perchlorate for analysis, formed a yellow microcrystalline powder, m.p. 193–195°.

Anal. Calcd. for $C_{27}H_{26}NClO_9$: C, 59.62; H, 4.82; N, 2.58. Found: C, 59.52; H, 4.66; N, 2.97.

The bromide IX was dissolved in 25 ml. of concentrated hydrochloric acid, 5 ml. of ethanol added, and the mixture refluxed for 4.5 hr. On cooling, a yellow microcrystalline powder precipitated, and was recrystallized from ethanol–ether, m.p. 123°. This substance showed no significant absorption in the carbonyl region of the infrared spectrum, and analysis indicated that the product was 6-(3,4-dimethoxyphenyl)phenanthridine hydrochloride.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.15; N, 3.98. Found: C, 72.01; H, 5.03; N, 4.05.

(15) The name morphanthridizinium has been proposed [K. B. Moser and C. K. Bradsher, *J. Am. Chem. Soc.*, **81**, 2547 (1959)] for the pyro[1,2-*a*]-benzo[*d*]-3*H*-azepinium system.

(16) P. Mamalis and V. Petrow, *J. Chem. Soc.*, 703 (1950).

Aromatic Cyclodehydration. LII.[1] Carbonyl Derivatives as Intermediates in the Acridizinium Synthesis

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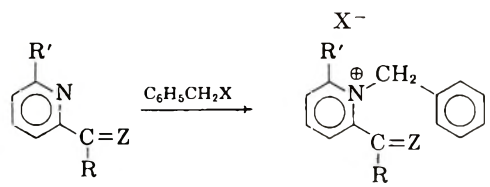
Received August 17, 1962

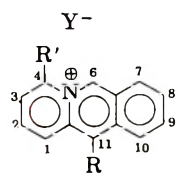
A search has been made for a picolinaldehyde derivative which might offer more advantage in the synthesis of acridizinium salts than does picolinaldoxime. The new 2-(1,3-dioxolan-2-yl)pyridine is superior to any known picolinaldehyde derivative in both the yield and quality of the acridizinium salt produced. Similarly, the dioxolan from 6-methyl-2-picolinaldehyde afforded the 4-methylacridizinium ion while that prepared from 2-acetylpyridine gave improved yields of 11-methylacridizinium salts.

The first synthesis of the acridizinium ion VII[3] involved the quaternization of 2-picolinaldehyde (I. Z = O) with benzyl bromide, followed by the acid-catalyzed cyclization of the crude salt (IV. Z = O). More recently,[4] it was shown that the unstable aldehyde (I. Z = O) could be replaced by the oxime (I. Z = NOH), with beneficial results.



I. R = R′ = H
II. R = CH_3, R′ = H
III. R = H, R′ = CH_3

IV. R = R′ = H
V. R = CH_3, R′ = H
VI. R = H, R′ = CH_3



VII. R = R′ = H
VIII. R = CH_3, R′ = H
IX. R = H, R′ = CH_3

Although the new procedure proved extremely useful,[5] there remained unsolved problems. One problem involved the rather low yield usually obtained in the cyclization of ketoximes (II. Z = NOH), and another, the complete failure of 6-methyl-2-aldoximinopyridine (III. Z = NOH) in the synthesis. A third, but minor problem, was the difficulty in the separation of the acridizinium ion from the hydroxylamine salt released in the cyclization reaction.

It seemed probable that a study of carbonyl derivatives other than the oxime might provide an intermediate which would be superior to the oxime in at least some respects. A number of derivatives related to the oxime (I. Z = NOH) were examined. The most successful of these was the semicarbazone (I. R = $NNHCONH_2$), which could be quaternized with benzyl bromide to afford a salt (IV. Z = $NNHCONH_2$) (68% yield), which when cyclized in hydrobromic acid, and then converted to the perchlorate, afforded a 47% yield of the acridizinium ion (VII). The yields, although fairly good, are inferior to those obtained with the oxime, in both the quaternization and cyclization steps, and separation of the acridizinium ion from the semicarbazide salts is tedious and accompanied by losses. The semicarbazone (III. Z = $NNHCONH_2$) of 6-methylpicolinaldehyde failed completely in the quaternization reaction with benzyl bromide. When the thiosemicarbazone (I. Z = $NNHCSNH_2$) was used, quaternization of the pyridine nitrogen[6] evidently did not occur, for the crude reaction product with benzyl bromide yielded no acridizinium ion on heating with

(1) For the preceding communication of this series see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 81 (1963).

(2) This research was supported by a research grant (CY-5509) of the National Cancer Institute of the National Institutes of Health.

(3) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(4) C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

(5) *E.g.*, C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960); C. K. Bradsher and T. W. G. Solomons, *ibid.*, **82**, 1808 (1960); C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

(6) It has been observed that reaction of thiosemicarbazones with α-chloro ketones occurs readily at the sulfur atom, J. McLean and F. J. Wilson, *J. Chem. Soc.*, 556 (1937).

hydrobromic acid. Other analogs (I) of the oxime which were tried proved to be uniformly unsatisfactory. These included the phenylhydrazone (Z = $NNHC_6H_5$), and the azine.

As a clear departure from the imino derivatives (I. Z = N—X) the new dioxolan acetal [I. Z = (—$OCH_2)_2$] was prepared. Despite the well known instability of picolinaldehyde, yields as high as 80% were obtained for the preparation of the cyclic acetal. This acetal [I. Z = (—$OCH_2)_2$] readily forms a well defined quaternary salt (92% yield) with benzyl bromide, and cyclization of the salt [IV. Z = (—$OCH_2)_2$] in hydrobromic acid affords the acridizinium ion VII in 95% yield. Less satisfactory results (65% yield) were obtained when the ring closure was carried out in liquid hydrogen fluoride or sulfuric acid (40%). Further, cyclization of the quaternary salt [IV. Z = (—$OCH_2)_2$] in polyphosphoric acid occurred in 77% yield. By comparison, the usefulness of polyphosphoric acid in the cyclization of free aldehydes (IV. Z = O) or oximes (IV. Z = NOH) in this series is very limited.

The dioxolan acetal [III. Z = $(OCH_2)_2$] of 6-methylpicolinaldehyde can be prepared in 63% yield. Quaternization of the acetal with benzyl bromide (1 month) yielded the crude salt as an oil which could not be crystallized. Cyclization of the oil in hydrobromic acid afforded 4-methylacridizinium bromide (IX. Y = Br) in 9% yield.

It has already been demonstrated that 11-methylacridizinium (VIII) salts may be synthesized by cyclization of the quaternary salt (V) obtained by the reaction of benzyl bromide with 2-acetylpyridine (II. Z = O)[7] or its oxime (II. Z = NOH).[4] The dioxolan ketal [II. Z = $(OCH_2)_2$] may be quaternized and cyclized to 11-methylacridizinium perchlorate in an overall yield of 35%. While this yield is not high, it compares favorably with those obtained *via* the ketone (3%) or oxime (18%).

It has been recognized for some time[8] that the reaction of an alkyl halide with a tertiary amine is facilitated by the presence of a polar solvent. It is important also that the solvent not react with the alkyl halide being used. It has been reported[9] that benzyl bromide reacts at a significant rate with dimethylformamide even at room temperature. In a publication dealing with the kinetics of quaternization, Coleman and Fuoss[10] pointed out that tetramethylene sulfone has a high dielectric constant (42) and "does not involve side reactions such as appear with nitrobenzene and dimethylformamide." Our observations lend further support to that statement. In tetramethylene sulfone (sulfolane) as a reaction medium, we have been able to obtain, in good yield and in crystalline form, quaternary salts which merely formed colored oils when the reaction was carried out in other solvents.

Experimental

Except as noted, all analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. All melting points were determined in capillaries in the Mel-Temp apparatus, and, like the boiling points, are uncorrected. Melting points determined in sealed tubes are indicated by the abbreviation (s.t.). All ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. quartz cells with the Cary Model 14 spectrophotometer. The asterisk (*) is used to denote a shoulder.

1-Benzyl-2-formylpyridinium Bromide Semicarbazone (IV. Z = $NNHCONH_2$, X = Br).—A solution containing 2.45 g. of picolinaldehyde semicarbazone[11] and 2 ml. of benzyl bromide in 10 ml. of dimethylformamide was allowed to react in the dark for 4 days at room temperature. At the end of this period the mixture was triturated with ether, cooled, and collected. The yellow crystals were recrystallized from methanol, affording material, m.p. 165–168° dec. (s.t.), satisfactory for the cyclization reaction; yield 3.45 g. (68%).

An analytical sample, prepared by recrystallization from methanol, yielded white granules m.p. 196–197° (with evolution of gas and formation of a green liquid). The crystals yellowed on standing overnight and the melting point declined to about 192°.

Anal. Calcd. for $C_{14}H_{15}BrN_4O \cdot {}^3/_4H_2O$: C, 48.56; H, 4.74; N, 16.09. Found: C, 48.22; H, 4.81; N, 16.20.

The perchlorate formed fine colorless needles, m.p. 207–208.5° (with gas evolution and decomposition), which turned yellow on standing.

Anal. Calcd. for $C_{14}H_{15}ClN_4O_5$: C, 47.45; H, 4.23; N, 15.82. Found: C, 47.13; H, 4.26; N, 15.71.

Cyclization of the Semicarbazone (IV. Z = $NNHCONH_2$, X = Br) of 1-Benzyl-2-formylpyridinium Bromide.—Two grams of the salt (IV. Z = $NNHCONH_2$, X = Br) was dissolved in 10 ml. of 48% hydrobromic acid and the mixture heated on the steam bath for 8 hr. The acid was removed under vacuum (aspirator) and the residue crystallized from ethanol–ether. The resulting crude bromide (1.2 g., m.p. 181–195°) was dissolved in water and treated with perchloric acid. The resulting precipitate was crystallized from methanol–ethyl acetate as yellow prisms, m.p. 203–205°; yield 0.80 g. (47%). The product gave no melting point depression with an authentic sample[3] of acridizinium (VII) perchlorate.

2-(1,3-Dioxolan-2-yl)pyridine [I. Z = (O—$CH_2)_2$].[12]—A solution containing 21.4 g. (0.2 mole) of picolinaldehyde, 24 ml. (0.4 mole) of ethylene glycol, 10 g. of *p*-toluenesulfonic acid, and 300 ml. of benzene was refluxed for 64 hr., in an apparatus provided with a modified Dean–Stark water separator. The reaction mixture was then poured into concentrated sodium carbonate solution and the benzene layer separated. The water layer was extracted four times with benzene, then the combined benzene layers were washed once with water and dried over anhydrous magnesium sulfate. The benzene was evaporated, and the residue was vacuum distilled; yield 21.45 g. (71%), b.p. 122° (4 mm.), $n^{25}D$ 1.5225.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.05; H, 6.01; N, 9.25.

1-Benzyl-2-(1,3-dioxolan-2-yl)pyridinium [IV. Z = (O—CH_2—$)_2$] Bromide.—A solution containing 3.0 g. (0.02 mole) of 2-(1,3-dioxolan-2-yl)pyridine, and 2.5 ml. (0.021 mole) of benzyl bromide in 5 ml. of tetramethylene sulfone was allowed to stand for 4 days in a stoppered flask at room temperature. The viscous oil was triturated with several 50-ml. portions of ethyl acetate and the residue crystallized from methanol–ethyl acetate as colorless crystals, m.p. 102–104°; yield 6.0 g. (93%). The analytical sample consisted of colorless, blunt needles, m.p. 106–107°.

Anal. Calcd. for $C_{15}H_{16}BrNO_2 \cdot H_2O$: C, 52.94; H, 5.29; N, 4.11. Found: C, 53.05; H, 5.07; N, 4.46.

The perchlorate crystallized from methanol–ethyl acetate as colorless needles, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{16}ClNO_6$: C, 52.78; H, 4.69; N, 4.10. Found: C, 52.73; H, 4.53; N, 4.22.

Cyclization of 1-Benzyl-2-(1,3-dioxolan-2-yl)pyridinium Bromide to Acridizinium VII Salts. (a) In Hydrobromic Acid.—A solution containing 1.0 g. (0.0031 mole) of 1-benzyl-2-(1,3-dioxolan-2-yl)pyridinium bromide in 5 ml. of 48% hydrobromic acid was refluxed for 11 hr. The hydrobromic acid was removed under vacuum (aspirator), and the residue was dissolved in ethanol. The acridizinium bromide crystallized from the chilled flask as bright yellow needles, m.p. 244–244.5° (lit.,[3] 239–240°);

(7) C. K. Bradsher and T. W. G. Solomons, *J. Org. Chem.*, **24**, 589 (1959).

(8) *E.g.*, N. Menschutkin, *Z. physik. Chem.* (Leipzig), **6**, 41 (1890); H. v. Halban, *ibid.*, **84**, 129 (1913); R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 1573 (1937).

(9) N. Kornblum and R. K. Blackwell, *J. Am. Chem. Soc.*, **78**, 4037 (1956).

(10) B. D. Coleman and R. M. Fuoss, *ibid.*, **77**, 5472 (1955).

(11) G. Lenart, *Ber.*, **47**, 808 (1914).

(12) *Cf.*, S. Sugasawa and M. Kirisawa, *Pharm. Bull.* (Tokyo), **3**, 190 (1955); *Chem. Abstr.*, **50**, 9415h (1956).

yield 0.76 g. (95%). The infrared spectrum was identical with that of an authentic sample.[3]

(b) **In Hydrogen Fluoride.**—In a polyethylene bottle was placed 3.2 g. (0.01 mole) of the bromide [IV. Z = $(OCH_2)_2$] and a Teflon-coated magnetic stirring bar. Approximately 50 ml. of liquid hydrogen fluoride was added, and the mixture stirred magnetically for 1 hr. The mixture was allowed to remain in the hood until the hydrogen fluoride had evaporated. The residue was dissolved in 100 ml. of water and evaporated to dryness under reduced pressure (aspirator). The residue was dissolved in 250 ml. of methanol and passed through an Amberlite 401 anion exchange column loaded with bromide. The acridizinium bromide isolated from the eluate was less pure than that obtained in the hydrobromic acid cyclization; yield 1.71 g. (65%), m.p. 230–233°.

(c) **In Sulfuric Acid.**—A solution containing 3.22 g. (0.01 mole) of the bromide [IV. Z = $(OCH_2)_2$] in 30 ml. of concentrated sulfuric acid was stirred at 80–90° for 3 hr. The cooled solution was slowly poured with stirring into 300 ml. of cold ether (−10°). The yellow precipitate was collected on a sintered-glass funnel and then dissolved in 5 ml. of water. Addition of 35% perchloric acid caused the precipitation of acridizinium perchlorate which was purified by crystallization from methanol–ethyl acetate; yield 1.12 g. (40%), m.p. 205–206° (lit.,[3] 205–206°).

(d) **In Polyphosphoric Acid.**—The bromide [1.60 g.; IV. Z = $(OCH_2)_2$] was stirred for 4 hr. at 70–80° with 30 g. of p lyphosphoric acid. The mixture was cooled to room temperature and diluted by the addition of about 60 g. of ice. To the resulting solution 35% perchloric acid was added dropwise until further addition caused no further precipitation. The resulting acridizinium perchlorate was collected; yield 1.08 g. (77%), m.p. 197–200°. A sample was recrystallized from methanol–ethyl acetate as light yellow prisms, m.p. 205–206° (lit.,[3] 205–206.2°). It gave no mixed melting point depression with an authentic sample.

2-(1,3-Dioxolan-2-yl)6-methylpyridine [III. Z = $(O—CH_2—)_2$] was prepared starting with 6-methyl-2-picolinaldehyde (III. Z = O) and following the procedure used in the preparation of the lower homolog [I. Z = $(O—CH_2—)_2$] except that 3 molecular equivalents of ethylene glycol were used as well as a correspondingly greater quantity of benzene; yield 63%, b.p. 121–126° (6 mm.), $n^{25}D$ 1.5200.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.54.

4-Methylacridizinium Bromide (IX. Y = Br).—A solution containing 4.95 g. (0.03 mole) of 2-(1,3-dioxolan-2-yl)-6-methylpyridine and 3.6 ml. (0.031 mole) of benzyl bromide was dissolved in 4 ml. of tetramethylene sulfone and the mixture allowed to stand for 1 month at room temperature. The addition of 100 ml. of ethyl acetate precipitated an oil which was washed with two other portions of ethyl acetate. The resulting oil, which could not be obtained in a crystalline form, was dissolved in hydrobromic acid, and refluxed for 3 hr. The acid was removed in the usual way, and the yellow residue crystallized from methanol–ethyl acetate; yield 0.73 g. (9%), m.p. 233–239°. The analytical sample formed fine yellow needles from the same solvents, m.p. 245–246°; λ_{max} (log ϵ), 200 (4.38), 243 (4.52), 250* (4.50), 364 (3.91), 381 (3.91), 400 (3.81); λ_{min} 214 (4.11), 313 (3.07), 372.5 (3.80), 391 (3.70).

Anal. Calcd. for $C_{14}H_{12}BrN \cdot {}^1/_2H_2O$: C, 59.38; H, 4.63; N, 4.95. Found: C, 59.45; H, 4.63; N, 5.12.

The perchlorate was obtained from methanol–ethyl acetate as bright yellow platelets, m.p. 180–180.5°.

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.23; H, 4.11; N, 4.76. Found[13]: C, 57.35; H, 4.03; N, 4.80.

The picrate crystallized from methanol–ethyl acetate as yellow needles, m.p. 199.5–201° (lit.,[4] 230–233°).[14]

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found[13]: C, 56.62; H, 3.87; N, 13.24.

2-(2-Methyl[1,3]dioxolan-2-yl)pyridine [II. Z = $(O—CH_2—)_2$].—The reaction of ethylene glycol (110 ml.) with 72.6 g. of 2-acetylpyridine (II. Z = O) was carried out essentially as in the case of the isomeric acetal [III. Z = $(O—CH_2)_2$]. The product was purified by vacuum distillation, b.p. 120–130° (12 mm.); yield 85.3 g. (86%). A sample was redistilled in a spinning band column at 6.2 mm. b.p. 106°, $n^{27}D$ 1.5093.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.76; H, 6.71; N, 8.54.

11-Methylacridizinium (VIII) Perchlorate.—The quaternization of 3.30 g. of 2-(2-methyl[1,3]dioxolan-2-yl)pyridine by reaction of 2.6 ml. of benzyl bromide in the presence of 4 ml. of dry tetramethylene sulfone was carried out at 64° in a sealed flask (5 days). The resulting viscous yellow oil was washed repeatedly with ethyl acetate and the solvent removed *in vacuo* on the steam bath. The residual oil was stirred for 15 hr. in polyphosphoric acid at 120–130°. The cooled reaction mixture was diluted by adding about 100 g. of ice. The diluted mixture was heated on the steam bath and filtered. To the cold filtrate, 35% perchloric acid was added. The precipitated 11-methylacridizinium perchlorate was recrystallized from methanol–ethyl acetate; yield 2.02 g. (35%), m.p. 237–238°. Recrystallized, it melted at 240–241° and was shown to be identical with a sample obtained *via* the ketone (reported, m.p. 243–244.5°).[7]

(13) Analysis by Dr. C. Daessle, Montreal, P. Q., Canada.

(14) The compound, prepared earlier (ref. 4) and reported to be 4-methylacridizinium picrate, has been shown (by actual comparison of samples) to be acridizinium picrate, m.p. 238–239°. In view of the fact that only a 2.5% yield of a very crude product was obtained in the earlier work, it seems probable that the acridizinium picrate was derived from a small amount of picolinaldehyde present as an impurity in the 6-methylpicolinaldehyde.

Reaction of Cyanuric Acid with Epoxides

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Tris(2-hydroxyethyl) isocyanurate (Ib) of 95–99% purity was prepared in 98–100% yields by the uncatalyzed reaction of cyanuric acid (Ia) with ethylene oxide in dimethylformamide or dimethylacetamide. Adjustment of the molar ratio of ethylene oxide to Ia permitted preparation of mixtures of mono- (Id), bis- (Ic), and tris(2-hydroxyethyl) isocyanurates (Ib) ranging from 99% tris at a ratio of 3.1, to 97% bis at 2.0, to 31.5% mono–68.5% bis at 1.0. The uncatalyzed reaction of Ia with propylene oxide in dimethylformamide gave quantitative yields of bis–tris mixtures containing 93–95% tris(2-hydroxypropyl) isocyanurate (Ig). Tris(2-hydroxyalkyl) isocyanurates are subject to decomposition to 2-oxazolidones (II) by bases generated during the reaction but this decomposition can be prevented by avoiding an excess of alkylene oxide. A mechanism for the decomposition is proposed. Ia reacted with styrene oxide to give a mixture of *N*-mono[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N'*,*N''*-bis(2-hydroxy-2-phenylethyl) isocyanurate (Ii), and *N*,*N'*-bis[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N''*-mono(2-hydroxy-2-phenylethyl) isocyanurate (Ij).

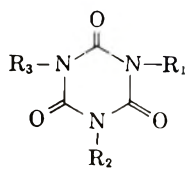
Epichlorohydrin is apparently the first epoxide described to react with cyanuric acid (Ia) to give an hydroxyalkyl isocyanurate believed to be substantially all tris(2-hydroxy-3-chloropropyl) isocyanurate.[1] The reaction was conducted at 100–120° in epichlorohydrin and dioxane in the presence of a variety of base catalysts. An earlier patent[2] discloses the general reaction of epoxides with Ia at 150–200° in the presence of base

(1) H. G. Cooke, Jr., U.S. Patent 2,809,942 (1957).

(2) W. P. Ericks, U.S. Patent 2,381,121 (1945).

catalysts but without providing examples. Tris(2-hydroxyethyl) isocyanurate (Ib) has recently been reported to have been prepared from Ia and ethylene oxide both by a heterogeneous reaction in benzene at 110–130° and seven to eleven atmospheres catalyzed by dimethylaniline,[3] and in dimethylformamide solution at 135–140° and atmospheric pressure catalyzed by sodium hydroxide.[4] More recently a report[5] of inability to prepare Ib in isolable form from reaction of Ia with ethylene oxide in dimethylformamide has appeared.

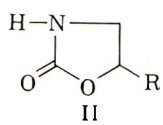
We have found that Ia reacts with ethylene oxide in dimethylformamide or dimethylacetamide solution at 100° and one atmosphere pressure gage in the absence of added catalyst to give tris-, bis-, or monobis-(2-hydroxyethyl) isocyanurate mixtures in close to quantitative yields by varying the ethylene oxide to Ia molar ratio. The reactions of several epoxides with Ia were investigated including ethylene, propylene, octylene, and styrene oxides. The following 2-hydroxyalkyl isocyanurates (I) were prepared:



I

Ia. R_1, R_2, R_3 = —H (cyanuric acid)
b. R_1, R_2, R_3 = —CH_2CH_2OH
c. R_1, R_2 = —CH_2CH_2OH, R_3 = —H
d. R_1 = —CH_2CH_2OH, R_2, R_3 = —H
e. R_1, R_2, R_3 = —$CH_2CH_2OC(O)CH_3$
f. R_1, R_2 = —CH_2CH_2—OCH_2OH; R_3 = —CH_2CH_2OH
g. R_1, R_2, R_3 = —$CH_2CH(OH)CH_3$
h. R_1, R_2 = —$CH_2CH(OH)CH_3$; R_3 = —H
i. R_1, R_2 = —$CH_2CH(OH)C_6H_5$; R_3 = —$CH_2CH(C_6H_5)OCH_2CH(OH)C_6H_5$
j. R_1 = —$CH_2CH(OH)C_6H_5$; R_2, R_3 = —$CH_2CH(C_6H_5)OCH_2CH(OH)C_6H_5$
k. R_1, R_2 = —H; R_3 = —C(O)OH (postulated only)

Both Ib and Ig were transformed to 2-oxazolidones (II) on heating in alkaline dimethylformamide solution.



II

IIa. R = —H
b. R = —CH_3

2-Oxazolidone (IIa) has previously been reported to be formed from Ib by vacuum pyrolysis[4] and on heating in dimethylformamide solution at 150–155°.[5]

In the reaction of ethylene oxide with Ia at an ethylene oxide–Ia molar ratio of 3.1 and 100° under autogenous pressure up to 790 mm., reaction was complete in from 4.5 to 7.5 hours. At a dimethylformamide–ethylene oxide molar ratio of 6.3–6.9, runs 2–5, Table I, crude products, isolated by vacuum stripping, were mixtures of Ib and Ic containing from 94.9 to 99.3% Ib. Yields were 98% or better. A comparison of runs 6, 7, and 8 with runs 2–5 shows the effect of decreasing the dimethylformamide–ethylene oxide molar ratio from over 6 to 2.2 while maintaining the ethylene oxide–Ia ratio at 3.1. In runs 6 and 7 as the reaction proceeded, the pressure decreased to a minimum and then began to increase (see Table I). Alkaline vapor (dimethylamine) was present over the alkaline solutions (pH 9) at the end of the reactions. The products isolated by the standard technique contained 66.2 and 24.8% 2-oxazolidone (IIa). In run 8, the solution at the end was also alkaline (pH 9) but there was little or no alkaline vapor. 2-Oxazolidone formation was avoided by neutralizing the mixture to pH 7 with sulfuric acid before stripping. That dimethylformamide functions as a base catalyst is suggested by the results of run 9 in which the addition of 0.2 mole of sodium bisulfate per mole of Ia effectively prevented hydroxyethylation.

Reduction of the ethylene oxide–Ia ratio to 3.00, run 10, Table I, resulted in a quantitative yield of product containing 20.9% Ic and 79.1% Ib. Reduction of the ratio to 2.00 and 1.75, runs 11, 12, 13, 14, and 15, Table I, resulted in quantitative yields of products containing 97.0 to 100.0% Ic with the balance Id or Ib. In run 12, the addition of triethylamine amounting to 1 mole % of Ia did not change the product composition appreciably. Further reduction in the ethylene oxide–Ia ratio to 1.50 and 1.00 gave Ic–Id mixtures containing 82.7% Ic at a ratio of 1.50 and 68.5% Ic at 1.00. Table II summarizes the relations among ethylene oxide–Ia ratio, % of Ia reacting, and product composition. It is of interest that no Ia remained unchanged at ethylene oxide–Ia ratios of 2.00 or higher but that only 57% of Ia reacted at an ethylene oxide–Ia ratio of 1.00, and only 80% at 1.50 ratio.

An increase in the ethylene oxide–Ia ratio to 4.0, run 1, Table I, gave a quantitative yield of product containing 89.4% Ib and 10.6% 2-oxazolidone showing the effect of excess ethylene oxide on 2-oxazolidone formation.

Hydroxyethylation of Ia proceeded more slowly in dimethylacetamide than in dimethylformamide in the absence of added catalyst at 100° and at an ethylene oxide–Ia molar ratio of 3.1. Hydroxyethylations in dimethylpropionamide and di-*n*-butylacetamide required a base catalyst to attain reaction rates comparable to those obtained in dimethylformamide and dimethylacetamide in the absence of added catalyst. With 2 mole % triethylamine added as catalyst, 100.0 and 92.7% yields of Ic–Ib mixtures containing 96.9 and 92.5% Ib were obtained. See Table III for a comparison of these four *N*,*N*-dialkylamides as reaction media.

The formation of an alkaline gas (dimethylamine), an alkaline solution, and 2-oxazolidone during the hydroxyethylation of Ia in dimethylformamide at an ethylene oxide–Ia molar ratio of 3.1, which was especially pronounced at the lower dimethylformamide–ethylene oxide molar ratios, may be explained by the following interpretation: Ia and dimethylformamide react on heating to liberate dimethylamine suggesting that dimethylformamide can function as a base to liberate cyanurate ion ($Ia^{\ominus}$) from Ia which can then attack dimethylformamide to liberate dimethylamine and a formyl derivative of Ia (Ik) (steps 1 and 2).

(3) G. B. Tal'kovskii, S. L. Lifina, A. A. Potashnik, and V. N. Chernetskii, U.S.S.R. Patent 118,042 (1959); *Chem. Abstr.*, **53**, 21673e (1959).

(4) T. C. Frazier, E. D. Little, and B. E. Lloyd, *J. Org. Chem.*, **25**, 1944 (1960).

(5) A. A. Savigh and H. Ulrich, *J. Chem. Soc.*, 3148 (1961).

TABLE I

HYDROXYETHYLATION OF CYANURIC ACID BY ETHYLENE OXIDE IN DIMETHYLFORMAMIDE[a]

Run no.	Molar ratios: Ethylene oxide/ cyanuric acid	Molar ratios: Dimethyl-formamide/ ethylene oxide	Reaction time, hr.	Pressure range (mm.) Min.	Pressure range (mm.) Final	Final pH	Description	N, %	Product composition Id[c]	Product composition Ic[d]	Product composition Ib[e]	Product composition IIa[f]	Yield,[b] %
1	4.0	6.9	4.0	220	220	8–9	Solid	..	0.0	0.0	89.4	10.6	102.8
2	3.1	6.7	4.5	0	0	7	Solid	..	.0	5.1	94.9	0.0	99.2
3	3.1	6.9	6.2	0	0	7	Solid	16.2	.0	3.9	96.1	.0	99.9
4	3.1	6.9	5.0	13	13	7–8	Solid	..	.0	5.0	95.0	.0	99.4
5	3.1	6.3	7.5	10	150	8–9	Solid	16.0	.0	0.7	99.3	.0	98.2
6	3.1	2.2	5.5	115	140	9	Solid–sirup	..	.0	.0	33.8	66.2	99.3
7[g]	3.1	2.2	4.8	75	212	9	Solid–sirup	..	.0	.0	75.2	24.8	101.7
8[h]	3.1	2.2	4.9	30	30	9	Solid	15.6	.0	3.6	96.4	0.0	104.8
9[i]	3.1	2.2	3.0	410	410	6–7	...	..	..	...	..	..	...
10	3.0	6.9	4.5	0	0	7	Solid–sirup	..	.0	20.9	79.1	.0	99.9
11	2.0	6.9	3.0	0	0	7	Solid–sirup	19.5	3.0	97.0	0.0	.0	103.8
12[j]	2.0	6.9	5.0	0	0	7	Sirup	19.3	0.0	98.5	1.5	.0	99.0
13	2.0	3.5	1.8	0	0	7	Sirup	19.5	3.0	97.0	0.0	.0	103.3
14	2.0	3.3	3.5	0	0	7	Sirup	19.5	3.0	97.0	.0	.0	101.7
15	1.75	6.9	3.8	0	0	7	Sirup	19.3	0.0	100.0	.0	.0	102.6
16	1.50	6.9	2.0	0	0	7	Sirup	20.2	17.3	82.7	.0	.0	103.5
17	1.00	6.9	3.3	0	0	7	Sirup	20.9	31.5	68.5	.0	.0	105.3

[a] Hydroxyethylations of from 0.2 to 2.8 moles of Ia at 100° with no added catalyst under autogenous pressure. Maximum pressures ranged from 695 to 795 mm. [b] Based on indicated composition and Ia charged except in runs 15, 16, and 17 where yields are based on Ia consumed; run 15, 86.0%; 16, 80.2%; 17, 57.3% consumed. [c] Mono(2-hydroxyethyl) isocyanurate (Id) was assumed to be absent in runs 1–10 based on the high ethylene oxide–Ia ratios used and low acidities found; in runs 11–17, Id–Ic compositions are based on nitrogen contents. [d] Bis(2-hydroxyethyl) isocyanurate (Ic) was determined by alkalimetric titration in runs 1–10; in runs 11–17, Ic content is based on nitrogen content. [e] Tris(2-hydroxyethyl) isocyanurate (Ib) was determined by difference. [f] 2-Oxazolidone (IIa) was determined by infrared analysis. [g] The gas responsible for at least part of the final system pressure was demonstrated to be dimethylamine through the *p*-toluenesulfonyl derivative m.p. 79°. [h] Reaction mixture was neutralized to pH 7 before vacuum stripping. [i] Sodium bisulfate (20 mole % of Ia) was added to the reaction mixture before hydroxyethylation to scavenge any base formed. [j] Triethylamine (1 mole % of Ia) was added as a base catalyst.

TABLE II

EFFECT OF ETHYLENE OXIDE–CYANURIC ACID MOLAR RATIO ON PER CENT OF CYANURIC ACID REACTING AND PRODUCT COMPOSITION

Run no.	Ethylene oxide/Ia molar ratio	Cyanuric acid reacting, %	Product composition, %: Id[a]	Ic[b]	Ib[c]	IIa
14	1.00	57.3	31.5	68.5	0.0	0.0
13	1.50	80.2	17.3	82.7	.0	.0
12	1.75	86.0	0.0	100.0	.0	.0
11	2.00	100.0	3.0	97.0	.0	.0
10	3.00	100.0	0.0	20.9	79.1	.0
4	3.10	100.0	.0	0.7	99.3	.0
1	4.00	100.0	.0	0.0	89.4	10.6

[a] Mono(2-hydroxyethyl) isocyanurate (Id). [b] Bis(2-hydroxyethyl)isocyanurate (Ic). [c] Tris (2-hydroxyethyl) isocyanurate (Ib).

$$Ia + HC(O)N(CH_3)_2 \rightleftharpoons Ia^{\ominus} + HC(OH)=\overset{\oplus}{N}(CH_3)_2 \quad (1)$$

$$Ia^{\ominus} + HC(O)N(CH_3) \longrightarrow Ik + {}^{\ominus}{:}\ddot{N}(CH_3)_2 \quad (2)$$

$$HC(OH)=\overset{\oplus}{N}(CH_3)_2 \qquad \underbrace{HC(OH)=\overset{\oplus}{N}(CH_3)_2}$$
$$HN(CH_3)_2 + HC(O)N(CH_3)_2$$

In the presence of ethylene oxide the cyanurate ion ($Ia^{\ominus}$) reacts preferentially with ethylene oxide, which is shown in step 3.

$$Ia^{\ominus} + \overbrace{CH_2CH_2O} \longrightarrow \underbrace{Id^{\ominus} + HC(OH)=\overset{+}{N}(CH_3)_2} \quad (3)$$
$$HC(OH)=\overset{\oplus}{N}(CH_3)_2 \qquad Id + HC(O)N(CH_3)_2$$

When Ia has been converted to Ib, any excess ethylene oxide may react with dimethylformamide to give an inner quaternary ammonium hydroxide (III) (step 4).

TABLE III

HYDROXYETHYLATION OF CYANURIC ACID WITH ETHYLENE OXIDE. COMPARISON OF SEVERAL *N,N*-DIALKYLAMIDES AS REACTION MEDIA[a]

$R_1C(O)N(R_2)_2$: R_1	R_2	Reaction time, hr.	Pressure range, mm.: Max.	Min.	Final	Final pH	M.p., °C.	N, %	Product composition[b]: Ic[d]	Ib[e]	Yield,[c] %
H—	CH_3—	4.9	790	30	30	9	95–131	15.6	3.6	96.4	104.8
CH_3—	CH_3—	6.0	803	128	128	8	113–131	16.1	5.2	94.8	100.4
CH_3CH_2—	CH_3—	3.4	750	105	105	8	127–134	15.8	3.1	96.9	100.0
CH_3—	$CH_3CH_2CH_2CH_2$—	8.0	760	0	0	7	120–130	16.4	7.5	92.5	92.7[f]

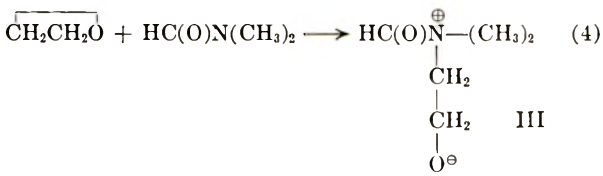
[a] Hydroxyethylations of 0.2-mole quantities of Ia at 100° under autogenous pressure. The reactant molar ratios were: ethylene oxide/Ia, 3.1; amide/ethylene oxide, 2.2. Hydroxyethylation proceeded readily in dimethylformamide and dimethylacetamide without added catalyst but a catalyst (triethylamine, triethylamine/Ia molar ratio 0.02) was required with both dimethylpropionamide and di-*n*-butylacetamide. [b] 2-Oxazolidone was absent in all cases. [c] Based on indicated composition and Ia charged. [d] Bis(2-hydroxyethyl) isocyanurate (Ic) as determined by alkalimetric titration. [e] Tris(2-hydroxyethyl) isocyanurate (Ib) obtained by difference. [f] A product recovery of 28.8% was obtained by collecting product insoluble in di-*n*-butylacetamide and vacuum stripping. This fraction contained 1.0% Ic, 99.0% Ib, m.p. 129.5 to 135.0.

TABLE IV

HYDROXYPROPYLATION OF CYANURIC ACID WITH PROPYLENE OXIDE IN DIMETHYLFORMAMIDE[a]

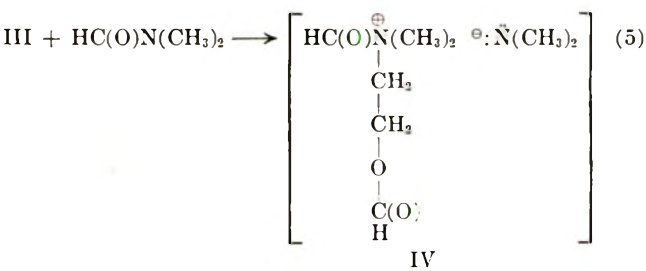
Run no.	Ia, moles	Reaction time, hr.	Pressure range, mm. Max.	Min.	Final	Description	OH, %[b] Calcd.	Found	N, %[b] Calcd.	Found	Composition, % Ib[c]	Ig[d]	IIb[e]	Yield,[f] %
1	0.201	8.5	800	205	290	Sirup	16.78	15.6	13.91	14.0	1.8	80.5	17.7	91.3[g]
2	.600	3.9	800	290	400	Glass	16.63	15.4	14.08	14.2	6.9	93.1	0.0	101.1
3	.600	3.9	775	200	280	Glass	16.63	15.6	14.08	14.2	6.9	93.1	.0	101.1

[a] Hydroxypropylations at 115–125° with no added catalyst under autogenous pressure. The reactant molar ratios were: propylene oxide/Ia, 3.1; dimethylformamide/propylene oxide, 2.2. The final reaction mixture pH values were all 8–9. [b] The calculated OH and N values are based on the indicated product compositions. [c] Bis(2-hydroxypropyl) isocyanurate (Ih) as determined by alkalimetric titration. [d] Tris(2-hydroxypropyl) isocyanurate (Ig) obtained by difference. [e] 5-Methyl-2-oxazolidone (IIb) as determined by chemical method. [f] Based on indicated composition and Ia charged. [g] Low recovery due to loss of some 5-methyl-2-oxazolidone during vacuum stripping. A sample of liquid distillate collected during the end of the stripping contained 95.8% 5-methyl-2-oxazolidone.



(4)

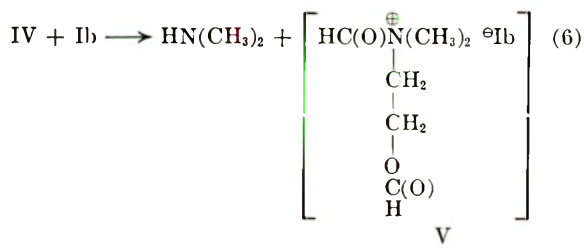
Step 4 does not proceed unless Ib is present presumably to supply protons required in step 6 and to increase solvent polarity. Dimethylformamide (2.02 moles) and ethylene oxide (0.196 mole) at a 10.3 molar ratio heated at 100° in the absence of Ib in a closed system for eight hours did not become alkaline to thymol blue. III is a strong base and should be capable of reacting with dimethylformamide, with the displacement of a dimethylamine anion, to form a quaternary ammonium salt (IV).



(5)

IV

The salt IV should react readily with Ib to liberate dimethylamine and the quaternary salt V.



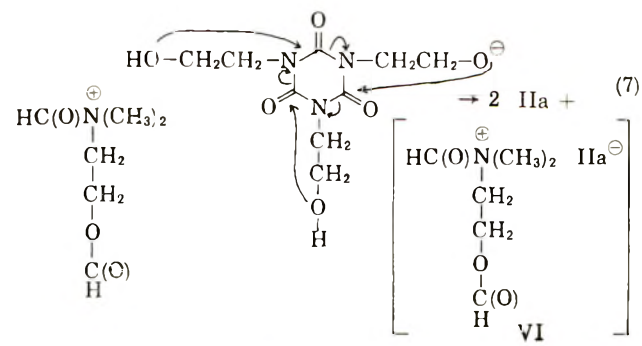
(6)

V

It is presumed that V will readily decompose to 2-oxazolidone (IIa) and the quaternary salt VI *via* a concerted internal displacement.

The increase in pH of the reaction medium under the above defined conditions may be due to varying concentrations of III, IV, V, and VI (step 7).

Ib was readily acetylated to tris(2-acetoxyethyl) isocyanurate (Ie) a low melting solid by acetic anhydride in ethyl acetate with 72% perchloric acid as catalyst.[8] Methylolation of Ib with 37% formaldehyde gave *N*,*N*′-bis(2-hydroxymethoxyethyl)-*N*″-mono-(2-hydroxyethyl) isocyanurate (If) a viscous water-soluble sirup.



(7)

VI

Propylene oxide reacted smoothly with Ia in dimethylformamide in the absence of added catalyst at 115–125° and at a propylene oxide – Ia ratio of 3.1 to give quantitative yields of mixtures of bis(2-hydroxypropyl) isocyanurate (Ih) and tris(2-hydroxypropyl) isocyanurate (Ig) containing 93.1% Ig. By stopping the reaction before the solution pH exceeded 8 and while the mixture still contained a few per cent of Ih partial degradation of Ig to 5-methyl-2-oxazolidone was effectively eliminated. See Table IV for a summary of the reactions of propylene oxide with Ia.

Ia failed to react with octylene oxide at an octylene oxide–Ia molar ratio of 15 in the presence of dimethylaniline (3 mole % based on Ia) during a 12.5-hr. period at 156°. Failure to react may have been due to the low 1,2-epoxide content (15%) of the octylene oxide used.

Reaction of Ia with styrene oxide (styrene oxide–Ia molar ratio 15) at 192° with dimethylaniline catalyst gave an 81% yield of a mixture containing 81% *N*-mono[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N*′,*N*″-bis(2-hydroxy-2-phenylethyl) isocyanurate (Ii) and 19% *N*,*N*′-bis[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N*″-mono(2-hydroxy-2-phenylethyl) isocyanurate (Ij), a light yellow low melting solid.

Experimental[6]

Materials.—Cyanuric acid (Ia) from FMC plant production was recrystallized from water and dried at 130° to give an anhydrous product of over 99.5% purity as determined by potentiometric titration with correction for ammelide as determined by an ultraviolet method. Ethylene oxide of 99.7% min. purity was used as received from Olin Matheson Chemical Corp. Propylene oxide, b.p. 34–35°, was obtained from Matheson Coleman and Bell Division. Octylene oxide, 85% 2,3- and 15% 1,2-epoxide, b.p. 156°, was from Chemicals and Plastics Division of FMC Corp. Styrene oxide, b.p. 74–76° (10 mm.), was from Matheson Coleman and Bell Division. 2-Oxazolidone, m.p. 89–90°, and 5-methyl-2-oxazolidone, b.p. 111–113°, (1 mm.),

(6) Melting points reported are uncorrected.

$n^{20}D$ 1.4593, were prepared by the method of Bell, Jr., and Malkemus.[7]

Analytical.—All samples were analyzed for nitrogen by a Kjeldahl method. Carbon and hydrogen analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. 2-Oxazolidone was determined by an infrared method in dimethylformamide solution using the characteristic absorption bands at 10.45 and 10.90 μ. The presence of mono-, bis-, and tris(2-hydroxyethyl) isocyanurate did not interfere with the quantitative determination. 5-Methyl-2-oxazolidone was determined by a chemical method: A 0.2-g. sample is dissolved in 50 ml. of 0.1 *N* sodium hydroxide and titrated with 0.1 *N* silver nitrate to a faint turbid yellow end point. One gram of 5-methyl-2-oxazolidone = (ml. $AgNO_3$)(N_{AgNO_3}) (0.606) where 0.606 is the milliequivalent based on the stoichiometry: one Ag ≡ six 5-methyl-2-oxazolidone. Recoveries ranging from 95 to 105% were obtained on 5-methyl-2-oxazolidone, b.p. 111–113° (1 mm.).

Compositions containing largely Ib or 2-oxazolidone were analyzed for Ic by alkalimetric titration to the thymol blue end point. Reported compositions are based on nitrogen content, acidity, and 2-oxazolidone content. This analytical scheme does not always allow one to distinguish between products of ring hydroxyl and side chain hydroxyl hydroxyalkylations. It is least satisfactory for compositions containing large concentrations of Id and Ic. For this case, the concentrations were estimated from the nitrogen content. Infrared was found unsuitable for analyzing mixtures of Id, Ic, and Ib. The hydroxyl content of Ib and Ig was determined by the method of Fritz and Schenk.[8]

Tris(2-hydroxyethyl) Isocyanurate (Ib) (Run 5).—To 3928 ml. of dimethylformamide in a 5-l., one-necked, 24/40 S.T. joint, round-bottomed flask equipped with a magnetic stirrer, electric heating mantle, and 760-mm. mercury manometer was added 357.6 g. (2.77 moles) of Ia and 378.4 g. (8.59 moles) of ethylene oxide. The system was closed and heated to 100° with good agitation. The maximum pressure attained was 775 mm., the minimum 10 mm. and the final pressure after 7.5 hr. of reaction was 150 mm. The resulting reaction mixture was a clear liquid having a pH of 8–9. The crude product was isolated by vacuum stripping to constant weight at 100° and 2 mm. It was a white solid weighing 707.8 g. (yield 98%). The crude melted at 112–129° and contained 0.0% 2-oxazolidone and acidity equivalent to 0.7% Ic.

Anal. Calcd. for $C_9H_{15}N_3O_6$: N, 16.09; OH, 19.53. Found: N, 16.00; OH, 18.70.

Acetone extraction of the crude product at room temperature (2 ml./g.) gave a 91.1% recovery of product, m.p. 127.4–134.0°. Recrystallization of the acetone-extracted product from diethyl maleate (9 ml./g.) gave an 84.7% recovery of colorless crystals, m.p. 134.0–135.4° (lit.,[3,4] m.p. 134–136°). The over-all recovery of pure Ib based on Ia was 75.5%.

Anal. Calcd. for $C_9H_{15}N_3O_6$: C, 41.39; H, 5.79; N, 16.09; OH, 19.53. Found: C, 41.66; H, 5.88; N, 15.90; OH, 19.28.

An infrared scan of the recrystallized product showed it to contain hydroxyl groups and the isocyanurate ring. The sample was free of polyoxyethylene.

Tris(2-acetoxyethyl) Isocyanurate (Ie).—Ie was prepared by acetylating Ib with acetic anhydride in ethyl acetate with 72% perchloric acid as catalyst. The crude product isolated by vacuum stripping was a water-insoluble, petroleum ether-insoluble sirup readily soluble in glacial acetic acid, ethyl alcohol, chloroform, and acetone. On stirring the sirup vigorously with heptane at room temperature and vacuum drying a white granular solid, m.p. 59.5–62.0°, was obtained.

Anal. Calcd. for $C_{15}H_{21}N_3O_9$: C, 46.53; H, 5.47; N, 10.85. Found: C, 46.68; H, 5.56; N, 10.83.

***N*-Mono(2-hydroxyethyl)-*N'*,*N''*-bis(2-hydroxymethoxyethyl) Isocyanurate (If).**—A solution of Ib (7.83 g., 0.030 mole) in 7.33 g. (0.090 mole) of 37% formaldehyde was vacuum stripped at 100° and 2 mm. to give 9.59 g. of a clear, colorless, viscous water-soluble sirup (yield 99.5%).

Anal. Calcd. for $C_{11}H_{19}N_3O_8$: C, 41.11; H, 5.96; N, 13.08. Found: C, 40.82; H, 5.96; N, 13.23.

Bis(2-hydroxyethyl) Isocyanurate (Ic) (Run 14).—To 296 ml. of dimethylformamide (4.05 moles) in a reactor similar to that used for preparing Ib except of 1-l. capacity, was added 79.1 g. (0.61 mole) of Ia and 54.0 g. (1.23 moles) of ethylene oxide. The system was closed and heated to 100° with good agitation. The maximum pressure attained was 760 mm., the minimum 0 mm. The final pressure after 3.5 hr. was 0 mm. The resulting reaction mixture was a clear liquid having a pH of 7. Vacuum stripping to constant weight at 100° and 2 mm. gave 134.6 g. of a clear sirup containing 0.0% 2-oxazolidone.

Anal. Calcd. for Ic $C_7H_{11}N_3O_6$: N, 19.35; Id $C_6H_7N_3O_4$: N, 24.28. Found: N, 19.5.

The composition of the crude product estimated from the nitrogen content is 3.0% Id and 97.0% Ic. The yield based on the indicated composition and Ia charged is 101.7%.

Tris(2-hydroxypropyl) Isocyanurate (Ig).—Ia was hydroxypropylated in dimethylformamide solution at 115–125° in the absence of an added catalyst with the propylene oxide/Ia molar ratio at 3.1 and the dimethylformamide/propylene oxide molar ratio at 2.2. The procedure was similar to that used in the hydroxyethylations except that the propylene oxide was added in four portions and each portion allowed to react before adding the next so as to avoid exceeding 1-atm. pressure. About 4 hr. were required for reaction. The crude products were neutralized to a pH of 7 with 1 *N* sulfuric acid before stripping to minimize oxazolidone formation. The products were analyzed for hydroxyl, nitrogen, acidity, and 5-methyl-2-oxazolidone. See Table IV.

***N*-Mono[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N'*,*N''*-bis(2-hydroxy-2-phenylethyl) Isocyanurate (Ii)-*N*,*N'*-bis-2-(2-hydroxy - 2 - phenylethoxy) - 2 - phenylethyl - *N''* - mono(2-hydroxy-2-phenylethyl) Isocyanurate (Ij) Mixture.**—Ia (6.46 g., 0.050 mole), 94.5 ml. (0.750 mole) of styrene oxide and 0.2 ml. (0.0016 mole) of dimethylaniline were mixed and refluxed (192°) for 1 hr. The resulting solution was dissolved in methyl alcohol and extracted with heptane to remove excess styrene oxide and the sirup vacuum stripped at 95° to give 26.4 g. (yield 81%) of viscous sirup. Further purification was obtained by precipitating from carbon tetrachloride solution with heptane. A light yellow water-insoluble neutral solid was obtained m.p. 56–74°. The wide melting range suggests that the product is a mixture. The composition as estimated from elemental analysis is 81.2% Ii and 18.8% Ij.

Anal. Calcd. for $C_{36.5}H_{36.5}N_3O_{8.5}$: C, 67.08; H, 5.64; N, 6.44. Found: C, 66.57; H, 5.85; N, 6.40.

Acknowledgment.—The author thanks Mr. Herman Adelman and his staff for the infrared analyses and Mr. Arthur Zaleski for help with the experimental work.

(7) J. B. Bell, Jr., and J. D. Malkemus, U.S. Patent 2,755,286 (1956).
(8) J. S. Fritz and G. H. Schenk, *Anal. Chem.*, **31**, 1808 (1959).

A New Synthesis of Cyclic Ketones[1]

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Cyclopentanone, cyclohexanone, and cycloheptanone have been obtained by reaction of the appropriate ω-iodo esters **3** with triphenylphosphine followed by treatment of the phosphonium salts **4** with base and subsequent hydrolysis of the ylids **6**. Reaction of the ylid **6b** with peracetic acid produced adipic acid and triphenylphosphine oxide.

The successful acylation of alkylidenetriphenylphosphoranes (Wittig reagents) with esters, thioesters, and acid chlorides[2] suggested that the intramolecular application of this reaction, like the intramolecular reaction of a Wittig reagent with an aldehyde or ketone,[3] might provide a useful route to cyclic ketones. The results of our exploration of this idea are summarized in Chart I,

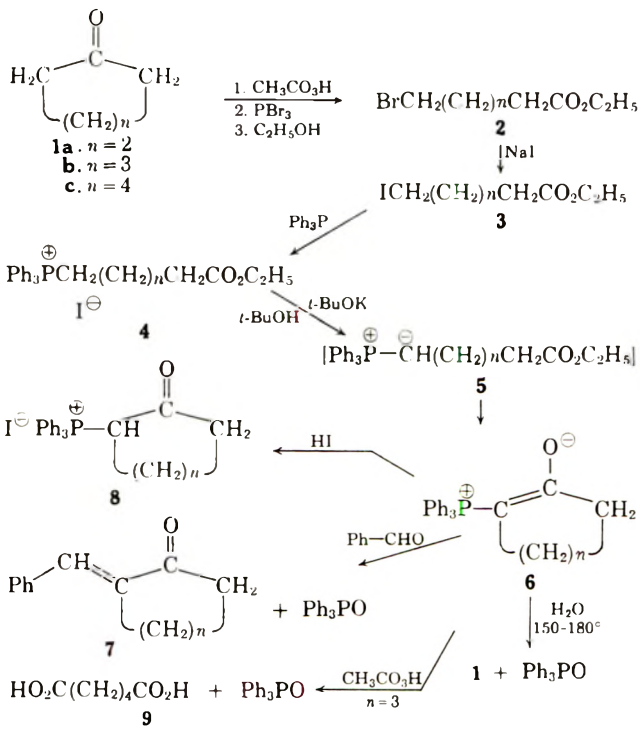
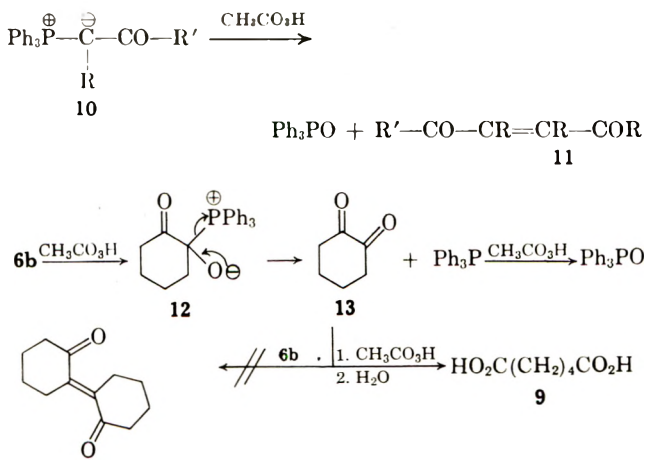


Chart I

wherein the ring closure step (*i.e.*, **5**→**6**) may be considered mechanistically comparable to a Dieckman condensation.[4] Subsequent hydrolytic cleavage[5] furnished the appropriate ketones. A noteworthy by-product of this study is a ready preparative route for the α-ketocycloalkylidenetriphenylphosphoranes **6** which are not accessible[6,7] *via* the reaction of the α-halocycloalkanones with triphenylphosphine. The formation of the *trans*-2-benzylidenecycloalkanones **7** from reaction of the ylids with benzaldehyde is in agreement with the expected stereochemical course of Wittig reactions involving relatively stable phosphorus ylids.[8] The ylid **6b** (or its conjugate acid) was found to undergo a rapid reaction with three molar equivalents of peracetic acid to form adipic acid (**9**) and triphenylphosphine oxide. Since attempts to intercept possible intermediates in this oxidative cleavage by use of less than a stoichiometric quantity of peracid led only to the isolation of **6**, **9**, and triphenylphosphine oxide, we conclude that the first step in this oxidation is rate determining. In the light of the reported[9] conversions of acyclic phosphoranes **10** to diketo ethylene derivatives **11** by reaction with one molar equivalent of peracetic acid, it seems probable that both reactions involve formation and cleavage of the alkoxide—*e.g.*, **12**—to form an α-diketone—*e.g.* **13**. In the case reported here the diketone **13** is apparently sufficiently reactive that it is intercepted by peracetic acid to form an anhydride more rapidly than it reacts with an additional molecule of the ylid **6**.



Experimental[10]

The ω-Halo Esters 2 and 3.—Following the general procedures previously summarized,[11] each of the ketones **1** was allowed to react with peracetic acid in refluxing chloroform. The crude

(1) This research has been supported by Grant No. RG-8761 from the National Institutes of Health and Grant No. 594-A from the Petroleum Research Fund.

(2) (a) H. J. Bestmann, *Tetrahedron Letters*, No. **4**, 7 (1960); (b) H. J. Bestmann and B. Arnason, *ibid.*, No. **14**, 455 (1961); (c) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961); (d) S. T. D. Gough and S. Trippett, *ibid.*, 2333 (1962).

(3) (a) T. I. Bieber and E. H. Eisman, *J. Org. Chem.*, **27**, 678 (1962); (b) C. E. Griffin, K. R. Martin, and B. E. Douglas, *ibid.*, **27**, 1627 (1962).

(4) C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, **1**, 266 (1942).

(5) (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957); (b) R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **45**, 1137 (1962); (c) α-Ketoalkylidene triphenylphosphoranes have also been reductively cleaved with zinc and acetic acid (ref. 2c).

(6) (a) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

(7) (a) I. J. Borowitz and L. I. Grossman, *Tetrahedron Letters*, No. **11**, 471 (1962); (b) H. Hoffmann and H. J. Diehr, *ibid.*, No. **13**, 583 (1962).

(8) H. O. House and G. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

(9) D. B. Denny and L. C. Smith, *J. Am. Chem. Soc.*, **82**, 2396 (1960).

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined on a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954).

lactones produced were heated on a steam bath with excess phosphorus tribromide[12] for 12 hr. and then treated with ethanol to produce the bromo esters **2** in over-all yields ranging from 53 to 95%. Each of the esters exhibited a single peak on gas chromatography[13] and had infrared and n.m.r. absorption consistent with the assigned structure. Reaction of the bromo esters **2** with sodium iodide in acetone produced the iodo esters **3** in yields ranging from 89 to 97%.

The Phosphonium Salts 4.—A solution of 21 g. (0.078 mole) of the iodo ester **3b** and 21 g. (0.080 mole) of triphenylphosphine in 150 ml. of benzene was refluxed for 12 hr. and then cooled. The benzene solution was decanted from the crude salt **4** which had separated as a pale yellow oil and the residual oil was extracted with three 100-ml. portions of boiling benzene. The residual oil was heated to 100° under reduced pressure for 1 hr. to leave 42.5 g. (100%) of the crude salt **4b** whose thin-layer chromatogram[14] showed only one spot and indicated the absence of either starting material. The product, which gave an immediate precipitate with methanolic silver nitrate, has infrared absorption[15] at 1722 cm.$^{-1}$ (ester C=O) with n.m.r. absorption[16] in the region 2.0–2.5 τ (15*H*, aryl C—H), a quadruplet (J = 7 c.p.s.) centered at 5.93 τ (2*H*) with a triplet (J = 7 c.p.s.) at 8.79 τ (3*H*) attributable to an ethoxyl function, a very broad peak centered at 6.35 τ (2*H*, $\overset{\oplus}{\text{—P—}}\text{CH}_2\text{—}$), and a triplet ($J$ = 6 c.p.s.) at 7.74 τ (2*H*, $\text{—CH}_2\text{—CO—}$) and broad absorption in the region 8.0–8.6 τ (6*H*, $\text{—CH}_2\text{—}$).

Similarly, reaction of 50.2 g. (0.194 mole) of the iodo ester **3a** with 52.4 g. (0.20 mole) of triphenylphosphine in 300 ml. of benzene followed by the previously described purification procedure yielded 98 g. (97%) of the crude salt **4a** as a pale yellow oil which showed only a single spot (not starting materials) on thin-layer chromatography[14] and has infrared absorption[15] at 1722 cm.$^{-1}$ (ester C=O) with n.m.r. absorption[16] in the region 2.0–2.5 τ (aryl C—H) with a quadruplet (J = 7 c.p.s.) at 5.95 τ and a triplet (J = 7 c.p.s.) at 8.82 τ (OCH_2CH_3) as well as broad absorption at about 6.3 τ ($\overset{\oplus}{\text{—P—}}\text{CH}_2$) and broad absorption in the region 7.5–8.4 τ.

The same procedure employing 57 g. (0.20 mole) of the iodo ester **3c**, 53 g. (0.20 mole) of triphenylphosphine, and 200 ml. of benzene yielded 90 g. (90%) of the crude salt **4c** as a colorless oil which exhibits a single spot on thin-layer chromatography[14] and has infrared absorption[15] at 1720 cm.$^{-1}$ (ester C=O) and n.m.r. absorption[15] in the region 1.9–2.5 τ (aryl C—H), a broad band centered at about 6.3 τ ($\overset{\oplus}{\text{—P—}}\text{CH}_2$), broad absorption in the region 7.4–8.6 τ and a quadruplet (J = 7 c.p.s.) at 5.84 τ with a triplet (J = 7 c.p.s.) at 8.75 τ (OCH_2CH_3).

α-Ketocyclohexylidenetriphenylphosphorane (6b).—A solution of 42 g. (0.078 mole) of the salt **4b** in 300 ml. of *t*-butyl alcohol was placed in a flask fitted with a Soxhlet extractor containing 3.4 g. (0.085 g.-atom) of potassium.[17] The mixture was refluxed, with stirring and conversion of the potassium to the potassium alkoxide, for 12 hr. After the reaction mixture had been concentrated under reduced pressure and partitioned between water and chloroform, the chloroform solution was dried and diluted with ethyl acetate to precipitate 22.1 g. (79%) of the ylid **6b** as yellow prisms, m.p. 243–245°. Recrystallization from an ethyl acetate–chloroform mixture raised the melting point to 245–247° (sealed capillary). The product has infrared absorption[15] at 1507 cm.$^{-1}$[18] with intense end absorption (ϵ 5,200 at 210 mμ) and a shoulder with no distinct maxima in the region 250–280 mμ of the ultraviolet.[19] The material has complex n.m.r. absorption in regions 2.0–3.0 τ (aryl C—H) and 7.5–8.5 τ (aliphatic C—H) with no other absorption.

Anal. Calcd. for $C_{24}H_{23}PO$: C, 80.34; H, 6.47. Found: C, 80.03; H, 6.47.

To a solution of 1.72 g. (5 mmoles) of the ylid **6b** in 25 ml. of boiling methanol containing a few crystals of sodium bisulfite was added 1.4 ml. (10 mmoles) of hydriodic acid. The solution was cooled and filtered to separate 1.98 g. (81%) of the iodide **8b** as yellow crystals, m.p. 235–240° dec. Repeated attempts to purify the salt **8b** resulted in conversion back to the ylid **6b**. The crude salt **8b** has infrared absorption[15] at 1698 cm.$^{-1}$ (C=C).

A solution of 7.168 g. (0.020 mole) of the ylid **6b** and 2.12 g. (0.020 mole) of benzaldehyde in 50 ml. of benzene was refluxed for 24 hr. and then concentrated under reduced pressure. Distillation of the residue (125° at 0.3 mm.) and subsequent recrystallization from pentane afforded 3.41 g. (91.5%) of benzalcyclohexanone (**7b**), m.p. 54–55°, identified with an authentic sample[20] by a mixed melting-point determination and comparison of infrared spectra.

A mixture of 3.560 g. (0.01 mole) of the ylid **6b**, 1.470 g. of *o*-dichlorobenzene (as an internal standard), and 12 ml. of a 2:1 (by volume) ethanol–water mixture containing a small amount of sodium hydroxide to bring the pH of the mixture to 10–11 was heated to 150° in a sealed tube for 3 days. After the reaction mixture had been partitioned between chloroform and water, the chloroform solution was distilled. Gas chromatographic analysis[13] of the distillate indicated a quantitative yield of cyclohexanone (**1b**). A portion of the distillate was converted to cyclohexanone 2,4-dinitrophenylhydrazine, m.p. 159–160°, identified by a mixed melting-point determination. Sublimation (200° at 0.3 mm.) of the residue from the hydrolysis mixture separated 2.35 g. (85%) of triphenylphosphine oxide, m.p. 154–156°.

α-Ketocyclopentylidenetriphenylphosphorane (6a).—Reaction of 98 g. (0.188 mole) of the phosphonium salt **4a** with 8.5 g. (0.21 g.-atom) of potassium and 250 ml. of *t*-butyl alcohol as previously described was followed by acidification of the crude product with 20 ml. (0.24 mole) of concentrated hydrochloric acid and concentration. The residue was partitioned between water and methylene chloride and the methylene chloride phase was dried, concentrated, and diluted with ethyl acetate to separate 70 g. of crude phosphonium salt. A solution of this salt in ethanol was made basic with aqueous sodium hydroxide and concentrated to precipitate 54.5 g. (84%) of the ylid **6a** as pale yellow crystals, m.p. 243–245° dec. (sealed capillary). This product, whose decomposition point was not altered by recrystallization from aqueous ethanol or a methylene chloride–ethyl acetate mixture, has infrared absorption[15] at 1545 cm.$^{-1}$[18] with ultraviolet[19] end absorption (ϵ 5200 at 210 mμ) and a shoulder in the region 250–280 mμ.

Anal. Calcd. for $C_{23}H_{21}PO$: C, 80.21; H, 6.15. Found: C, 80.14; H, 6.04.

A 3.58-g. sample of the ylid **6a** was converted to the 4.79 g. of the iodide **8a** as colorless needles, m.p. 243–254° dec. Recrystallization from methanol separated the pure salt **8a**, m.p. 245–248° dec., with infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O).

Anal. Calcd. for $C_{23}H_{22}IPO$: C, 58.49; H, 4.70; I, 26.87. Found: C, 58.75; H, 4.86; I, 26.87.

Reaction of 6.848 g. (0.02 mole) of the ylid **6a** with 2.12 g. (0.02 mole) of benzaldehyde in 50 ml. of benzene as previously described afforded 5.35 g. (96.5%) of triphenylphosphine oxide, m.p. 155–156°, and 3.26 g. (95%) of benzalcyclopentanone (**7a**), m.p. 67–69°, identified with an authentic sample[20] by comparison of infrared spectra.

Hydrolysis of a 3.24-g. (0.01 mole) sample of the ylid **6a** employing 1.265 g. of *o*-chlorotoluene (as an internal standard) and 12 ml. of 2:1 (by volume) ethanol–water (adjusted to *p*H 10–11) at 180° for 3 days afforded 2.52 g. (92%) of triphenylphosphine oxide, m.p. 153.7–155°. The calculated[13] yield of cyclopentanone (**1a**) was 93%. A portion of the volatile product was converted to cyclopentanone 2,4-dinitrophenylhydrazone, m.p. 145–145.5°, identified by a mixed melting-point determination.

α-Ketocycloheptylidenetriphenylphosphorane (6c).—Reaction of 90 g. (0.18 mole) of the phosphonium salt **4c** with 6.9 g. (0.17 g.-atom) of potassium and 250 ml. of *t*-butyl alcohol as described in the previous case afforded 32.8 g. (52%) of the crude ylid **6c**, m.p. 210–216°. Recrystallization from an ethyl acetate–methylene chloride mixture separated 26.8 g. (41%) of the pure ylid, m.p. 205–208°, with infrared absorption[15] at 1508 cm.$^{-1}$[18] and ultraviolet[19] end absorption (ϵ 3,900 at 210 mμ) with a series of maxima (ϵ 770–460) in the region 250–280 mμ.

(12) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(13) A column packed with Dow-Corning silicone fluid, no. 710, suspended on ground firebrick was employed.

(14) A Silica Gel coating was employed with a 1:1 (by volume) mixture of methanol and ethyl acetate as the solvent system.

(15) Determined in chloroform solution.

(16) Determined in deuteriochloroform.

(17) An attempt to achieve cyclization with ethanolic sodium ethoxide was unsuccessful, the bulk of the starting material being recovered.

(18) α-Ketoalkylidene ylids are reported (ref. 5a) to have infrared absorption in the region 1515–1530 cm.$^{-1}$ with ultraviolet maxima in the region 268–288 mμ.

(19) Determined in 95% ethanol.

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

Anal. Calcd. for $C_{25}H_{25}PO$: C, 80.62; H, 6.77. Found: C, 80.40; H, 6.68.

A 3.75-g. sample of the ylid **6c** gave 4.95 g. (98%) of the iodide **8c** as yellow prisms from methanol, m.p. 206–208°, dec., with infrared absorption at 1695 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{25}H_{26}IPO$: C, 60.01; H, 5.24; I, 25.36. Found: C, 59.72; H, 5.11; I, 25.63.

From the reaction of 7.410 g. (0.02 mole) of the ylid **6c** with 2.12 g. (0.02 mole) of benzaldehyde in 50 ml. of benzene was isolated 4.10 g. (74%) of triphenylphosphine oxide, m.p. 154–156°, and 3.08 g. (82.5%) of benzalcycloheptanone (**7c**), b.p. 200° (0.5 mm.), in a short-path still. Recrystallization gave 2.66 g. (71%) of the pure benzylidene derivative **7c**, m.p. 37–39°, identified with an authentic sample[20] by comparison of infrared spectra.

Hydrolysis of 3.7052 g. (0.01 mole) of the ylid **6c** in the presence of 1.265 g. of *o*-chlorotoluene (as an internal standard) and 12 ml. of 2:1 ethanol–water at 160° for 3 days produced 2.48 g. (84%) of triphenylphosphine oxide, m.p. 154.5–156°. The calculated yield of cycloheptanone (**1c**) was 90%; a portion of the volatile product was converted to cycloheptanone 2,4-dinitrophenylhydrazone, m.p. 147.5–148°, identified by a mixed melting-point determination.

Reaction of the Ylid 6b with Peracetic Acid.—To a cold (0°) solution of 3.44 g. (0.01 mole) of the ylid **6b** in 50 ml. of methanol was added, dropwise and with stirring, a solution containing from 0.01 to 0.04 mole of peracetic acid in a mixture (1:1 by volume) of methanol and methylene chloride. The resulting mixture was stirred for 1.5 hr. at 0° and then concentrated under reduced pressure and partitioned between methylene chloride and sodium bicarbonate. The adipic acid, recovered from the bicarbonate solution in the usual way, was recrystallized from an acetone–methylene chloride mixture to give the pure acid (**9**), m.p. 151–153°, identified by a mixed melting-point determination. Concentration of the methylene chloride solution followed by extraction with ether separated the unchanged ylid **6b** (recrystallized from an ethyl acetate–methylene chloride mixture, m.p. 243–245° dec.) and triphenylphosphine oxide (recrystallized from an acetone–pentane mixture, m.p. 152–156°). The yields as a function of quantity of peracid used are summarized in Table I.

TABLE I

REACTION OF 0.01 MOLE OF THE YLID 6b WITH PERACETIC ACID

Peracetic acid, mole	Ylid **6b**, %	Ph_3PO, %	Acid **9**, %
0.01	54	..	20
0.02	35	36	33.5
0.03	..	75	66
0.04	..	88	71

C-6 Hydroxylated Steroids. IV.[1] 6-Hydroxylated 17α-Acetoxyprogesterone, 17α-Acetoxy-6-methylprogesterone, and Related Compounds

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The preparation of the 6α- and 6β-hydroxy derivatives of 17α-acetoxyprogesterone and 17α-acetoxy-6-methylprogesterone by a variety of methods is described. Certain transformations (dehydrogenation, elimination, and isomerization) of these C-6 oxygenated steroids have been studied.

Our interest in the various methods for the synthesis of steroids containing a 6-hydroxyl group has been centered about the study of the conversion of Δ^4-3-ones to the corresponding 6-hydroxy-Δ^4-3-ones.[2-4] In this paper we wish to report on the preparation of a number of 6-hydroxy compounds related to 17α-acetoxyprogesterone and 17α-acetoxy-6-methylprogesterone.

We have previously demonstrated a general utility for the preparation of 6-hydroxy-Δ^4-3-ones through the reaction of $\Delta^{3,5}$-enol ethers with peracid.[1] Accordingly, when 17α-acetoxy-3-methoxypregna-3,5-dien-20-one (II) was oxidized with monoperphthalic acid there were isolated by chromatography two crystalline fractions. The less polar material was readily identified as 17α-acetoxy-6β-hydroxypregn-4-ene-3,20-dione (III). The second fraction isolated in much smaller yield proved to be 17α-acetoxy-6α-hydroxypregn-4-ene-3,20-dione (IV).[5] As in other series we have studied, a mixture of the 6-hydroxylated compounds is encountered with the β-epimer predominating.[1]

When the 6β,17α-diacetate V was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone,[6] there was obtained 6β,17α-diacetoxypregna-1,4-diene-3,20-dione (VI). Under the vigorous reaction conditions required for 1,2-dehydrogenation, protection of the 6-hydroxyl group was mandatory.[7] Selective hydrolysis of VI afforded 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII). The latter was converted into its crude 6-mesylate, which on attempted recrystallization led to the formation of the $\Delta^{1,4,6}$-trienone VIII.[8] Chromic acid oxidation of VII yielded the $\Delta^{1,4}$-3,6-dione IX with an ultraviolet absorption maximum at 250 mμ (ε 14,800). Under basic conditions it exhibited a more intense maximum at 253 mμ (ε 18,000) and a second broad maximum centered at 393 mμ (ε 9650).[9]

The preparation of 6-hydroxy-6-methyl compounds was also undertaken and was approached through a number of pathways. Peracid attack on 3,17α-diacetoxy-6-methylpregna-3,5-dien-20-one (X)[10] was selected for one study. When an ethereal solution of the latter

(1) Previous paper in this series, *J. Org. Chem.*, **27**, 4046 (1962).

(2) S. Bernstein, W. S. Allen, C. E. Linden, and J. Clemente, *J. Am. Chem. Soc.*, **77**, 6612 (1955).

(3) S. Bernstein and R. Littell, *J. Org. Chem.*, **25**, 313 (1960).

(4) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *ibid.*, **26**, 974 (1961).

(5) (a) The 6β-hydroxy compound III has been previously prepared by acetic acid opening of the appropriate 5α,6α-epoxide and subsequent hydrolysis [R. Sciaky, *Gazz. chim. ital.*, **91**, 545 (1961)]; and (b) through the reaction of peracid on the corresponding $\Delta^{3,5}$-enol acetate [H. Mori, *Chem. Pharm. Bull. Japan*, **9**, 328 (1961)]. The 6α-hydroxy compound IV has been obtained by epimerization of the 6β-acetoxy derivative IV followed by 6-deacetylation (ref. 5a).

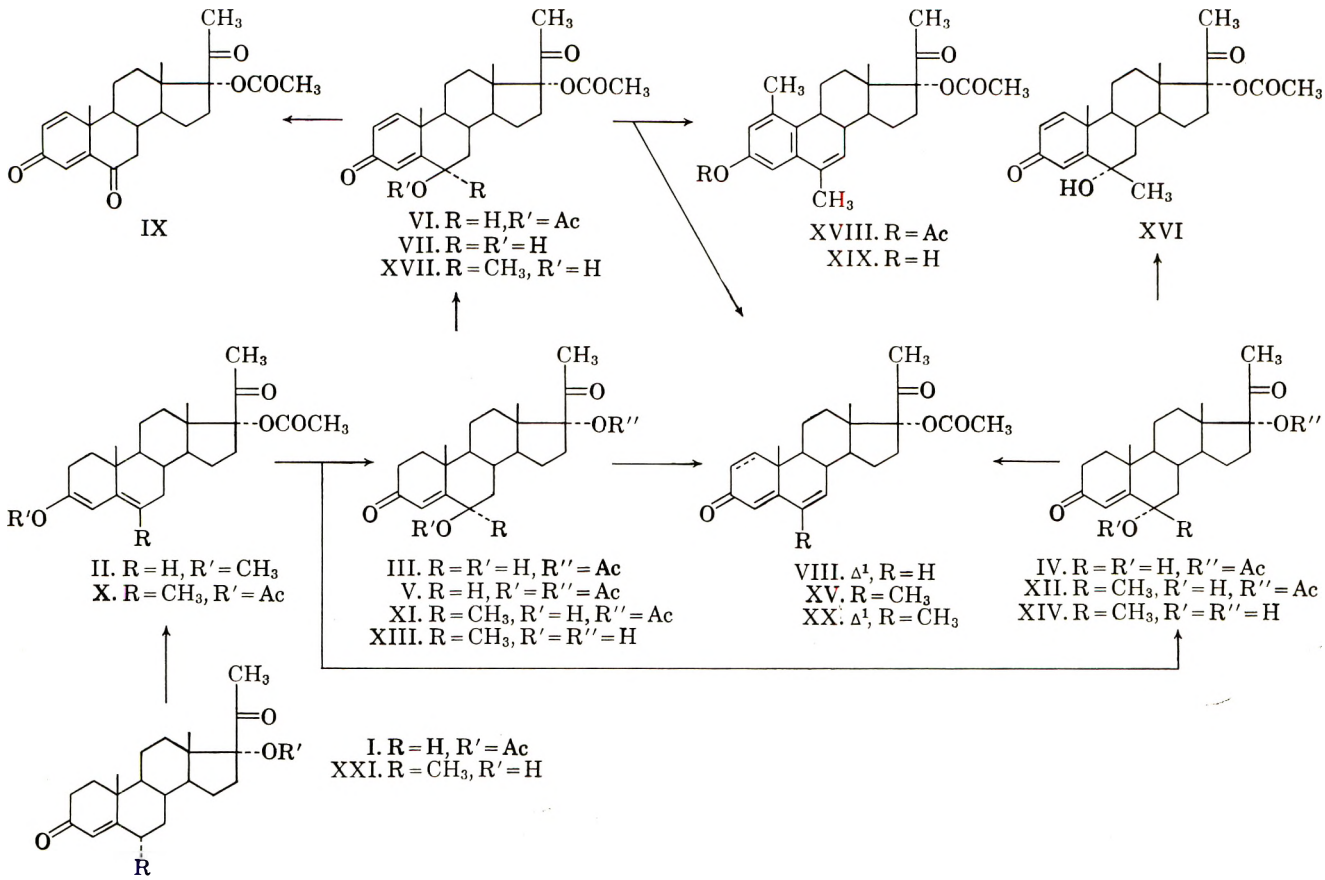
(6) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(7) Although the selective oxidation of Δ^4-3β,6β-diols to 6β-hydroxy-Δ^4-3-one by the quinone reagent has been successfully executed [D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. **9**, 14 (1960)] the conditions used were considerably milder than those employed here for 1,2-dehydrogenation.

(8) W. Hiersemann, E. Kaspar, and U. Kerb, U.S. Patent 2,962,510 (November 29, 1961).

(9) In the cholesterol series, this chromophore [λ_{max} 251 mμ (ε 14,800)] has been generated by quinone oxidation of the Δ^4-3,6-dione; D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, 29 (1962).

(10) H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959).



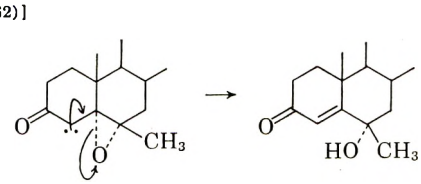
was refluxed with monoperphthalic acid, subsequent chromatography provided two crystalline fractions. The less polar component was identified as 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI) because it exhibited an ultraviolet absorption maximum at 238 mμ (ϵ 13,300) and a characteristically broad and irregular absorption maximum near 1660 cm.$^{-1}$ in the infrared. In addition, the infrared spectrum showed diminished absorption for the double bond in the 1615-cm.$^{-1}$ region, also encountered with other 6β-hydroxy-Δ^4-3-ones.[11] The second more polar fraction eluted was 17α-acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII).[12,13] This epimer exhibited an absorption maximum at 243 mμ (ϵ 14,100) which could be attributed to the 6α-hydroxy-Δ^4-3-one system and showed a sharp Δ^4-3-one infrared absorption band at 1667 cm.$^{-1}$. Although these compounds possess an additional methyl group at C-6, their ultraviolet spectra paralleled the desmethyl series except for a small bathochromic effect probably attributable to the 6-methyl group. Hydrolysis of the 17-acetate function in XI and XII was accomplished with refluxing potassium hydroxide giving rise to the respective diols XIII and XIV. The presence of the 6-methyl group in each case prevents formation of the 3,5-enolate which would effect isomerization of the 6-hydroxy-Δ^4-3-one to the 3,6-dione.[14]

A direct structural assignment of the 6-hydroxy-6-methyl epimers was accomplished by chemical means. Refluxing the 6β-hydroxy-6α-methyl epimer XI in acetic acid led to the formation of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (XV),[10] while similar treatment of the 6α-hydroxy-6β-methyl compound resulted in recovery of starting material. Since the 6β-hydroxyl group possesses the axial conformation, elimination tends to proceed under milder conditions than for the equatorial 6α-epimers.[15] The 6-methyl-$\Delta^{4,6}$-3-one XV was obtained from both epimers by employing acetic acid-*p*-toluenesulfonic acid.

The reaction of XII with 2,3-dichloro-5,6-dicyanobenzoquinone gave 17α-acetoxy-6α-hydroxy-6β-methylpregna-1,4-diene-3,20-dione (XVI) in approximately 50% yield. A similar reaction with XIII afforded 17α-acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII) in 75% yield. The tertiary nature of the C-6 hydroxyl group presented no complications during quinone oxidation. When the dienone XVII was allowed to stand at room temperature with acetic anhydride–*p*-toluenesulfonic acid, two compounds were obtained on chromatography of the reaction mixture. The initial material eluted was assigned the structure

(11) These observations are based on the experience of this laboratory with related compounds.

(12) Attack of peracid on a 6-methyl-$\Delta^{3,5}$-enol acetate system has recently been reported [B. Ellis, S. P. Hall, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 22 (1962)]. They report only the isolation of the 6β-hydroxy epimer in their series. These authors have observed the formation of the 6α-hydIoxy-6β-methyl epimer as arising from base treatment of a 5α,6α-epoxy-6β-methyl-3-one system. A similar finding as illustrated below has recently been made [J. Iriate, J. N. Shoolery, and C. Djerassi, *J. Org. Chem.*, **27**, 1139 (1962)]



(13) Of interest is the 6β/6α ratio (1.25) observed in this experiment. Whereas ratios of 5 to 10 are normally encountered in oxidation of $\Delta^{3,5}$-enol ethers or enol acetates, the effect of the 6-methyl group and/or more vigorous reaction conditions have raised the yield of the 6α-hydroxy epimer appreciably.

(14) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(15) This selectivity has been observed recently in this laboratory.

3,17α-diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XVIII). Spectral data were in agreement with the proposed structure and quite similar to those reported for the 1,6-dimethylestra-1,3,5(10),6-tetraene system.[9] Selective hydrolysis of the 3-acetate was achieved thus affording 17α-acetoxy-3-hydroxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XIX). The second fraction eluted was easily identified through its ultraviolet absorption spectrum as 17α-acetoxy-6-methylpregna-1,4,6-triene-3,20-dione (XX).[10]

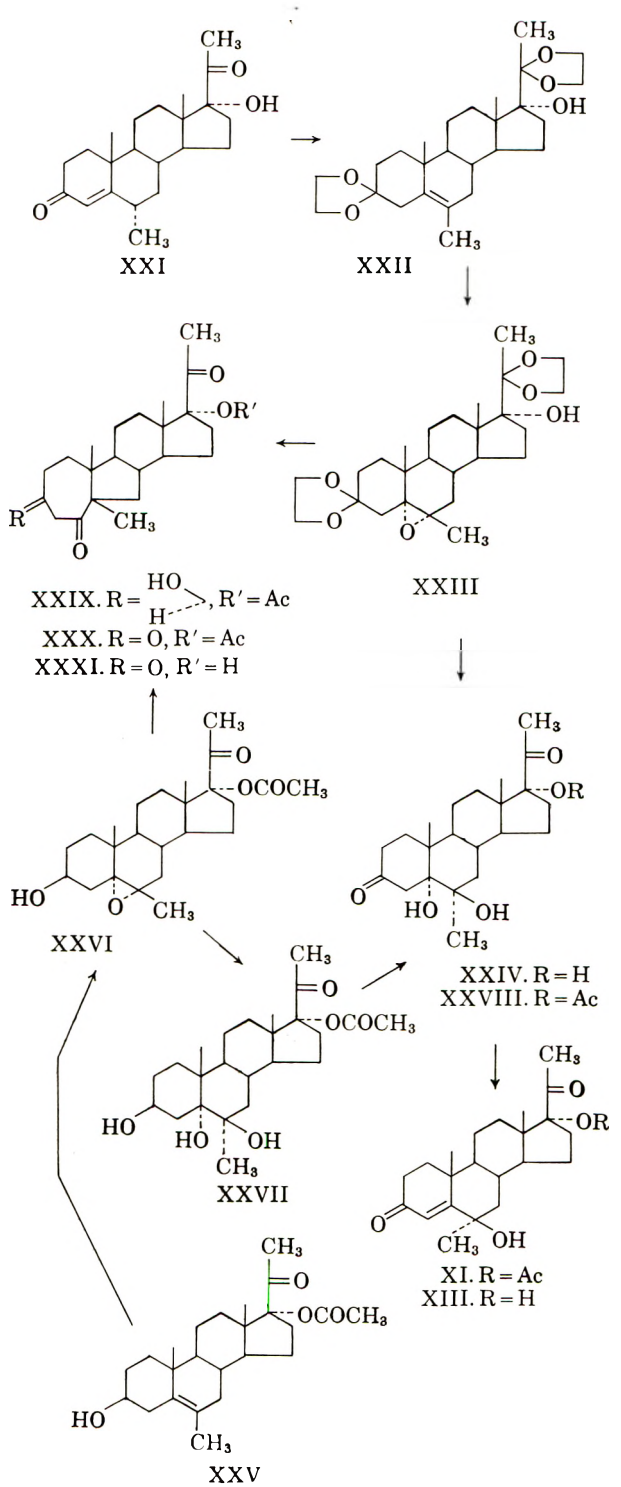
The conditions employed in this reaction were less severe than those normally used to effect dienone–phenol rearrangements. In simple $\Delta^{1,4}$-3-ones, the rearranged products have been shown to be 1-hydroxy-4-methyl and 3-hydroxy-1-methyl aromatic ring A compounds.[9,16] When the rearrangement conditions were applied to $\Delta^{1,4,6}$-3-ones, the products have been characterized as the 3-hydroxy-1-methyl-6-dehydro aromatic ring A compounds. In the 6-methyl series, a report confirmed the rearrangement to the corresponding 1,6-dimethyl compound.[9] The isolation of both XVIII and XX suggested that the initial step is an elimination reaction leading to the trienone, which was then partially rearranged to the aromatic product.[17]

A more general approach for the introduction of a second substituent into the 6-position of a 6-methyl steroid was formulated on the preparation of the 5α,6α-epoxy-6β-methyl unit. At the time, literature information from the 6-methylcholesterol series confirmed the possibility of the proposed epoxidation of the Δ^5-6-methyl grouping and demonstrated a normal *trans* opening of the epoxide.[18] Since both the 6α-methyl-Δ^4-3-one and 3β-hydroxy-Δ^5-6-methyl steroids were available, a sequence of reactions from each substrate was pursued.

The ketalization of 17α-hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI) afforded the bisketal XXII in excellent yield. Epoxidation of this material with monoperphthalic acid under refluxing conditions gave the desired 5α,6α-epoxy-6β-methyl unit. Assignment of configuration to the epoxide was based solely on the 6-methylcholesterol series mentioned above.[19] The reaction of the bisketal epoxide XXIII with aqueous perchloric acid led to 5α,6β,17α-trihydroxy-6α-methylpregnane-3,20-dione (XXIV). Epoxide opening was accompanied by removal of the two ketal groupings.[3] Base treatment to effect β-elimination yielded the desired diol XIII identical in all respects to the compound prepared by the hydrolysis of XI reported above.

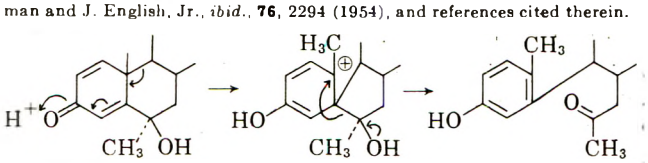
The epoxidation of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one (XXV) with monoperphthalic acid under reflux gave a compound assigned the structure 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI) on the basis of the evidence cited previously. Aqueous perchloric acid treatment led to the expected *trans* opening of the epoxide and compound XXVII. Chromic acid oxidation of the triol produced XXVIII which on treatment with anhydrous hydrogen chloride gave 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI), identical to one of the compounds isolated from peracid treatment of the enol acetate X and which had been assigned the 6β-hydroxy confirmation.

Chemical support for the assignment of the 5α,6α-orientation to the epoxide grouping in XXVI was obtained indirectly. In an attempt to introduce a fluorine



(16) (a) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, **75**, 3159 (1953); (b) R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

(17) Had the dienone–phenol rearrangement taken place prior to the elimination reaction, one might also expect the formation of seco products of the following type, suggestive of the acid cleavage of 1,3-glycols; H. E. Zimmerman and J. English, Jr., *ibid.*, **76**, 2294 (1954), and references cited therein.



(18) M. Shiota, *Nippon Kagaku Zasshi*, **75**, 1217 (1954); **76**, 1272 (1956); **77**, 778 (1956). *Chem. Abstr.*, **51**, 17969 (1957); **52**, 416, 417 (1958).

(19) A report on the reinvestigation of the 6-methylcholesterol work [M. Davis and G. H. R. Summers, *J. Chem. Soc.*, 4707 (1960)] has shown that the β-epoxide is also formed but only to a minor extent.

atom at C-6, the reaction of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI) with anhydrous hydrogen fluoride and boron trifluoride etherate was studied. In each case the same fluorine-free product was isolated. On the basis of the reported isomerization of 5α,6α-epoxy-6β-methyl steroids to A-homo-B-nor compounds,[20] the structure assigned to this material was 17α-acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX). Chromic acid oxidation provided the 3,4a,20-trione XXX. The intense ultraviolet absorption maximum [$\lambda_{max}^{MeOH + Base}$ 300 mμ (ε 18,000)] exhibited on addition of base, confirmed the positioning of both oxygen functions in ring-A and in a 1,3-relationship.[21] Further support for the structure of the trione XXX has been supplied by n.m.r. data. The five methyl groups could be located as follows: C-21 (δ 2.16), C-19 (δ 1.20), C-18 (δ 0.62), C-5 (δ 0.94),[22] C-17 acetyl methyl (δ 2.07). In addition, the only other prominent peak in the spectrum was found centered at 3.62 δ as a doublet having 2-c.p.s. splitting. This peak, intergrating for two hydrogens, has been assigned to the methylene hydrogens at C-4.

An identical ring expansion was observed in the 3,20-bisketal series. When 5α,6α-epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII) was treated with 72% perchloric acid in acetone, there was obtained 17α-hydroxy-5β-methyl-A-homo-B-norpregnane-3,4a,-20-trione (XXXI) in contrast to the normal epoxide opening observed with 1.5 *N* aqueous perchloric acid.

NOTE ADDED IN PROOF. R. Sciaky and A. Consonni [*Gazz. chim. ital.*, **92**, 547 (1962)] have recently reported the preparation of III and IV by a similar oxidation of the enol acetate X with monoperphthalic acid.

Experimental

Melting points are uncorrected. The ultraviolet spectra were determined as indicated in 2% Methyl Cellosolve–methanol and in basic methanol. The expression basic methanol refers to a solution of the steroid (20 γ/ml.) in 1 part of 20% Methyl Cellosolve–methanol and 9 parts of 0.1 *N* sodium hydroxide solution. The infrared absorption spectra were determined in potassium bromide disks. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption, optical rotation, and nuclear magnetic resonance data. We wish also to thank Louis M. Brancone and associate for the analyses. Petroleum ether refers to the fraction, b.p. 60–70°.

17α-Acetoxy-3-methoxypregna-3,5-dien-20-one (II).—Concentrated sulfuric acid (0.1 ml.) was added to the suspension resulting from the addition of 17α-acetoxypregn-4-ene-3,20-dione (I, 2.0 g.) to a solution consisting of dioxane (15 ml.), trimethyl orthoformate (15 ml.) and absolute methanol (0.1 ml.). The reaction mixture became homogeneous in 5 min. and was allowed to stand an additional 15 min. at room temperature when pyridine (2.0 ml.) was added and the solution was poured into water. The collected solid was crystallized from aqueous methanol to give the desired enol ether II (2.1 g.). A portion of the material was crystallized several times from methanol, m.p. 195–198°, $[\alpha]^{25}D$ −135° (1% pyridine in chloroform); λ_{max} 239 mμ (ε 21,000); ν_{max} 1745, 1720, 1660, 1637, 1252, and 1172 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.51): C, 74.57; H, 8.87. Found: C, 74.19; H, 8.96.

17α-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione and 17α-Acetoxy-6α-hydroxypregn-4-ene-3,20-dione (III and IV).—A solution of 17α-acetoxy-3-methoxypregna-3,5-dien-20-one (II, 2.0 g.) in ether (130 ml.) was treated with 0.684 *N* monoperphthalic acid in ether solution (15.2 ml.). After standing at room temperature in the dark for 18 hr., the precipitated crystalline solid was separated to yield 0.745 g., m.p. 238–243°. This material was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. After an initial small quantity of 17α-acetoxypregn-4-ene-3,20-dione (I), there was obtained two crystalline fractions. The material eluted with 3% acetone–methylene chloride (3 × 50 ml.), 4% acetone–methylene chloride (4 × 50 ml.), and 5% acetone–methylene chloride (4 × 50 ml.) proved to be the 6β-hydroxy epimer III, which after crystallization from acetone–petroleum ether afforded the product (0.327 g.), m.p. 245–246°, $[\alpha]^{25}D$ +14° (chloroform); λ_{max} 236 mμ (ε 15,500); ν_{max} 3440, 1740, 1680 (sh), 1658, 1260, 1250, and 1227 cm.$^{-1}$; lit.,[5b] m.p. 239–243°, $[\alpha]^{20}D$ +7°; λ_{max}^{EtOH} 238 mμ.

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.20; H, 8.62.

The second fraction eluted with the later 7% acetone–methylene chloride (3 × 50 ml.), 10% acetone–methylene chloride (4 × 50 ml.), and the early 15% acetone–methylene chloride (3 × 50 ml.) fractions was crystallized from acetone–petroleum ether and was shown to be the 6α-hydroxy epimer IV, m.p. 254–255°, $[\alpha]^{25}D$ +55° (chloroform): λ_{max} 239 mμ (ε 15,400); ν_{max} 3520, 3450 (sh), 1712, 1664, 1282, 1267, and 1250 cm.$^{-1}$; lit.,[5a] m.p. 244–246°, $[\alpha]D$ +75°; λ_{max} 241 mμ (ε 14,700).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.40; H, 8.69.

The initial reaction mixture (crystalline phase removed) was diluted with methylene chloride and washed with a saturated aqueous sodium bicarbonate solution followed by a saturated saline solution. The evaporation of this dried solution provided a glass which was chromatographed in a manner similar to that described above. An additional quantity of the 6β-hydroxy epimer III (0.325 g.) was obtained with the 3, 4, and 5% acetone fractions. No subsequent fractions containing the pure 6α-hydroxy epimer could be isolated, although paper strip chromatography indicated these fractions contained a mixture of the α- and β-hydroxy epimers.

6β,17α-Diacetoxypregn-4-ene-3,20-dione (V).—17α-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione (III, 0.5 g.) was dissolved in a solution of acetic anhydride (2.0 ml.) and pyridine (4.0 ml.). After standing at room temperature for approximately 24 hr., the reaction mixture was poured into water. The collected solid was crystallized from acetone–petroleum ether and provided the diacetate (0.47 g., m.p. 245–248°); $[\alpha]^{25}D$ +28° (chloroform); λ_{max} 235 mμ (ε 14,800); ν_{max} 1740, 1714, 1693, 1252, and 1238 cm.$^{-1}$; lit.,[5b] m.p. 243–245°, $[\alpha]^{20}D$ +22°; λ_{max}^{EtOH} 236 mμ.

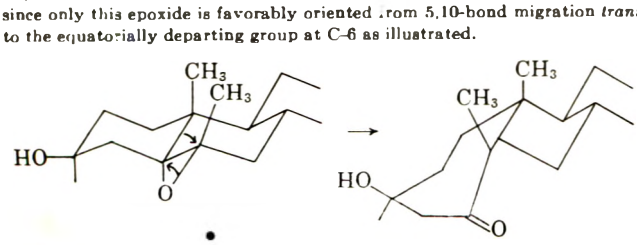
6β,17α-Diacetoxypregna-1,4-diene-3,20-dione (VI).—A solution of 6β,17α-diacetoxypregn-4-ene-3,20-dione (V, 0.82 g.) and 2,3-dichloro-4,6-dicyanobenzoquinone (0.65 g.) in dry dioxane (20 ml.) was refluxed for 20 hr. and then cooled. The precipitated hydroquinone was removed by filtration and the filtrate was evaporated. The resultant glass was dissolved in methylene chloride (250 ml.) and passed through a short magnesium silicate column to remove colored impurities. Additional methylene chloride (250 ml.) was then passed through the column. Evaporation and crystallization of the residue from acetone–petroleum ether afforded 0.371 g., m.p. 252–254°, $[\alpha]^{25}D$ −13° (chloroform); λ_{max} 243 mμ (ε 17,800); ν_{max} 1742, 1712, 1670, 1635, 1256, and 1229 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_6$ (428.51): C, 70.07; H, 7.53. Found: C, 69.75; H, 7.79.

17α-Acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII).—Nitrogen was bubbled through a solution of 6β,17α-diacetoxypregna-1,4-diene-3,20-dione (VI, 0.35 g.) in methanol (50 ml.). To the purged solution was added a 10% aqueous potassium carbonate solution (2.5 ml.) and the nitrogen stream was continued for 45 min. Acetic acid was added dropwise to neutralize the reaction mixture and then most of the methanol was evaporated at reduced pressure. The reaction mixture was poured into water and after filtration provided VII (0.30 g.), m.p. 194–195°. Crystallization from acetone–petroleum ether gave 0.243

(20) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4657 (1960).

(21) The α-configuration assigned to the epoxide is thereby supported since only this epoxide is favorably oriented from 5,10-bond migration *trans* to the equatorially departing group at C-6 as illustrated.



(22) Assignment of the signals to the C-19 and C-5 methyl groups may well be reversed.

g., m.p. 224–225°, $[\alpha]^{25}D$ −45° (pyridine); λ_{max} 243 mμ (ε 17,200); ν_{max} 3330, 1740, 1684, 1618, 1262, and 1252 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.73; H, 8.20.

17α-Acetoxypregna-1,4,6-triene-3,20-dione (VIII).—A solution of 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII, 0.2 g.) dissolved in dry pyridine (1.5 ml.) at 5° was treated with methane–sulfonyl chloride (120 mg.), and the mixture was allowed to stand at room temperature for 20 hr. It was then poured into water and the precipitated material collected, 0.173 g., m.p. 105–130°. Because the material could not be recrystallized from acetone–petroleum ether or aqueous methanol, it was chromatographed on a synthetic magnesium silicate. The crystalline fractions obtained from the late 10% acetone–petroleum ether (4 × 20 ml.) and early 12% acetone–petroleum ether, (2 × 20 ml.) fractions were combined and crystallized from acetone–petroleum ether to give VIII (30 mg.); m.p. 195–196°, $[\alpha]^{25}D$ −33° (chloroform); λ_{max} 220, 255, and 298 mμ (ε 12,550, 9600, and 12,650); ν_{max} 1743, 1728, 1667, 1612, 1590, 1260, and 1250 cm.$^{-1}$; lit.,[8] m.p. 192–192.5°; λ_{max}221, 259, and 296 mμ (ε 11,025, 9790, and 12,830).

17α-Acetoxypregna-1,4-diene-3,6,20-trione (IX).—Dropwise addition of 8 *N* chromic acid in 8 *N* sulfuric acid to a solution of 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII, 150 mg.) was continued until the yellow color of the oxidizing agent persisted then methanol was added to decompose the excess reagent. The reaction mixture was filtered and the filtrate evaporated. The residue was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The material eluted with the late 2% acetone–methylene chloride (3 × 25 ml.) and the early 5% acetone–methylene chloride (2 × 25 ml.) fractions was crystallized from acetone–petroleum ether to give IX (85 mg.), m.p. 220–201°, $[\alpha]^{25}D$ −135° (chloroform); λ_{max} 250 mμ (ε 14,800); $\lambda_{max}^{Basic\ MeOH}$ 253 mμ (ε 18,000), 393 mμ (ε 9650); ν_{max} 1748, 1723, 1712, 1667, 1630, 1252, and 1227 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_5$ (384.45): C, 71.85; H, 7.34. Found: C, 71.91; H, 7.48.

3,17α-Diacetoxy-6-methylpregna-3,5-dien-20-one (X).—17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI, 10.0 g.) was added to acetic anhydride (60 ml.), and *p*-toluenesulfonic acid monohydrate (1.0 g.). The reaction mixture was heated on a steam bath for 1 hr., cooled, and poured into water. The solid was collected and crystallized from methanol to give X (9.0 g.); m.p. 162–165°, $[\alpha]^{25}D$ −132° (chloroform); λ_{max} 243 mμ (ε 16,400); ν_{max} 1770, 1740, 1720, 1670, 1640, 1250, and 1216 cm.$^{-1}$; lit.,[10] m.p. 160–162°; $[\alpha]D$ −146°; λ_{max}^{EtOH} 244 mμ (ε 19,950).

17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione and 17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XI and XII).—3,17α-Diacetoxy-6-methylpregna-3,5-dien-20-one (X, 2.0 g.) was dissolved in ether (100 ml.) and refluxed for 3.5 hr. with ethereal 0.62 *N* monoperphthalic acid (16 ml.). The solution was cooled and washed with a dilute sodium bicarbonate solution and then with a saturated saline solution. The dried solution was evaporated to give an oil which was chromatographed on a synthetic magnesium silicate (65 g.).

The crystalline material eluted with the 15% acetone–petroleum ether fractions (5 × 100 ml.) was combined and crystallized from acetone–petroleum ether to give XI (0.435 g.), m.p. 218–224°. After two more crystallizations from the same solvent pair, there was isolated the 6β-hydroxy epimer XI (0.281 g.), m.p. 226–228°; $[\alpha]^{25}D$ ±0° (chloroform); λ_{max} 238 mμ (ε 13,300); ν_{max} 3430, 1742, 1725, 1662, 1267, and 1257 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 70.40; H, 8.78.

A second fraction eluted by the late 20% acetone–petroleum ether (4 × 100 ml.) and the early 30% acetone–petroleum ether (2 × 100 ml.) fractions was collected. Crystallization from acetone–petroleum ether afforded the 6α-hydroxy epimer XII (0.343 g.), m.p. 240–243°. Crystallization from the same solvent pair raised the m.p. to 245–247°; ν_{max} 3490, 1740, 1723, 1667, 1613, 1269, 1258, 1235, and 1222 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 70.75, 70.65; H, 9.29, 9.00.

6β,17α-Dihydroxy-6α-methylpregn-4-ene-3,20-dione (XIII).—17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 50 mg.) was dissolved in methanol (20 ml.) and then 2.5% methanolic potassium hydroxide (0.25 ml.) was added. The solution was refluxed for 1 hr. under nitrogen. The reaction mixture was neutralized with acetic acid and poured into water. Extraction of the aqueous solution with methylene chloride and evaporation gave a solid, m.p. 238–258°. Crystallization from acetone–petroleum ether gave the diol XIII (23 mg.), m.p. 266–270°; $[\alpha]^{26}D$ ±0° (chloroform); λ_{max} 237 mμ (ε 13,100); ν_{max} 3450, 1712 (sh.), 1698, and 1610 cm.$^{-1}$. This material was identical to the diol prepared by the procedure described below.

6α,17α-Dihydroxy-6β-methylpregn-4-ene-3,20-dione (XIV).—A solution of 17α-acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.1 g.) in methanol (10 ml.) and 2.5% methanolic potassium hydroxide (0.5 ml.) was refluxed 1 hr. under nitrogen. After being neutralized with acetic acid, the reaction mixture was concentrated at reduced pressure and then poured into water. The solid was collected and crystallized several times from acetone–petroleum ether to give the pure diol (32 mg.), 238–243°, raised to 245–247° when dried *in vacuo* at 80° for 12 hr., $[\alpha]^{25}D$ +51° (chloroform); λ_{max} 242 mμ (ε 14,600); ν_{max} 3420, 1703, 1665, 1612, and 1230 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.46; H, 9.06. Found: C, 72.40; H, 9.17.

17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (XV).—A. 17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.25 g.) was dissolved in a solution of acetic acid (10 ml.), acetic anhydride (2.5 ml.) and *p*-toluenesulfonic acid monohydrate (0.25 g.). After standing overnight at room temperature, the reaction mixture was poured into water and filtered. Crystallization of this material from acetone–petroleum ether gave the dienone XV (0.182 g.); m.p. 215–216°; $[\alpha]^{25}D$ +8° (chloroform); λ_{max} 289 mμ (ε 24,200); ν_{max} 1742, 1722, 1675, 1640, 1592, 1268, and 1250 cm.$^{-1}$, lit.,[10] m.p. 218–220°; $[\alpha]D$ +11°; λ_{max}^{EtOH} 289 mμ (ε 24,000).

B. 17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XII, 50 mg.) was dissolved in acetic acid (5 ml.) and refluxed for 1 hr. The reaction mixture was cooled, poured into water, and the solid collected (25 mg.), m.p. 199–205°. Crystallization from acetone–petroleum ether gave the dienone, m.p. 205–211°. This was identical to material isolated by method A.

C. A solution of 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 0.25 g.) in acetic anhydride (2.5 ml.), acetic acid (10 ml.), and *p*-toluenesulfonic acid monohydrate (0.25 g.) was allowed to stand at room temperature for 17 hr. The reaction mixture was poured into water and filtered. Crystallization of this material gave 0.181 g., m.p. 209–213°, identical to the compound isolated by method A.

17α-Acetoxy-6α-hydroxy-6β-methylpregna-1,4-diene-3,20-dione (XVI).—17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.3 g.) was dissolved in dry dioxane (25 ml.) and to this solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.3 g.). The reaction mixture was refluxed for 20 hr., cooled and the hydroquinone separated by filtration. The filtrate was evaporated and the residue was dissolved in ethyl acetate. This solution was washed with water, cold 1% sodium hydroxide solution, and saturated saline solution, dried, and evaporated. The residue was crystallized from acetone–petroleum ether to give 0.165 g., m.p. 271–273°. After two more crystallizations it had m.p. 282–284°; $[\alpha]^{25}D$ −7° (chloroform); λ_{max} 245 mμ (ε 15,400); ν_{max} 3460, 1732 (broad), 1667, 1227, 1255, and 1230 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 71.63; H, 7.75.

17α-Acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII).—A solution of 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 1.5 g.) in dioxane (15 ml.) was refluxed with 2,3-dichloro-5,6-dicyanobenzoquinone (1.06 g.) for 72 hr. and cooled. The precipitated hydroquinone was collected and the filtrate evaporated. The residue was dissolved in ether and washed with water, cold 1% aqueous sodium hydroxide solution, and saturated saline solution. After being dried, the ether extract was evaporated to give a crystalline residue which was recrystallized from acetone–petroleum ether affording 0.945 g., m.p. 239–241°; $[\alpha]^{25}D$ −30° (chloroform); λ_{max} 244 mμ (ε 18,200); ν_{max} 3500, 1740, 1718, 1669, 1638, 1262, and 1252 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 71.65; H, 8.34.

3,17α-Diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one and 17α-Acetoxy-6-methylpregna-1,4,6-triene-3,20-dione (XVIII and XX).—A mixture of 17α-acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII, 0.3 g.), acetic anhydride (10 ml.), and *p*-toluenesulfonic acid monohydrate (0.25 g.) was allowed to stand at room temperature for 20 hr. It was then poured into water and filtered to give a solid (0.29 g.)

which was dissolved in a minimum amount of benzene and chromatographed on a synthetic magnesium silicate. The material eluted with the last 2% acetone–petroleum ether fraction (25 ml.) and with the 3% acetone–petroleum ether (6 × 25 ml.) fractions was combined and crystallized from aqueous methanol to give 0.105 g., m.p. 148–150°. Another crystallization raised the m.p. to 149–151°; $[\alpha]^{25}D$ −111° (chloroform); λ_{max} 222, 228, and 265 mμ (ε 31,000, 28,300, and 8900); $\lambda_{max}^{Basic\ MeOH}$ 238 and 322 mμ (ε 34,300 and 2460); ν_{max} 1780, 1750, 1605, 1267, 1256 (sh), and 1215 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{32}O_5$ (424.52): C, 73.56; H, 7.60. Found: C, 73.16; H, 7.76.

On further development of the column there was obtained a second crystalline fraction eluted in later 7% acetone–petroleum ether (3 × 25 ml.) and the 10% acetone–petroleum ether (6 × 25 ml.) fractions. Crystallization of this combined material from acetone–petroleum ether gave 70 mg., m.p. 206–208°. Another crystallization raised the m.p. 213–215°; $[\alpha]^{25}D$ −29° (chloroform); λ_{max} 227, 252, and 304 mμ (ε 14,700, 11,200, and 9600); ν_{max} 1742, 1722 (sh), 1667, 1620, 1590, 1267, and 1251 cm.$^{-1}$; lit.,[10] m.p. 225–227°; $[\alpha]D$ −38°; λ_{max}^{EtOH} 228, 253, and 304 mμ (ε 13,000, 11,700, and 9120).

Anal. Calcd. for $C_{24}H_{30}O_4 \cdot {}^1/_2C_3H_6O$: C, 74.42; H, 8.08. Found: C, 74.25, 74.41; H, 8.22, 8.31.

17α-Acetoxy-3-hydroxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XIX).—3,17α-Diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XVIII, 60 mg.) in methanol (10 ml.). Nitrogen was bubbled through the mixture and then 10% aqueous potassium carbonate (0.5 ml.) was added. The nitrogen stream was continued for 45 min. and then the solution was neutralized with acetic acid. The solvents were partially removed *in vacuo* and the mixture was filtered to give 40 mg., m.p. 240–245°. After two crystallizations from acetone–petroleum ether there was obtained 32 mg., m.p. 251–252°; $[\alpha]^{30}D$ −92° (chloroform); λ_{max} 225, 265, 275, and 305 mμ (ε 27,700, 7400, 6100, and 2140); $\lambda_{max}^{Basic\ MeOH}$ 237 and 322 mμ (ε 29,900 and 2200); ν_{max} 3450, 1728, 1718 (sh), 1612, 1590, 1280, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 74.98, 74.82; H, 8.38, 8.13.

3,20-Bisethylenedioxy-6-methylpregn-5-en-17α-ol (XXII).—17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI, 1.1 g.) was dissolved in a solution of benzene (50 ml.) and ethylene glycol (3.0 ml.). After the addition of *p*-toluenesulfonic acid (10 mg.), the reaction mixture was refluxed with constant water removal for 24 hr., cooled, and then washed with aqueous sodium bicarbonate and water. Evaporation of the dried extract gave the bisketal (1.2 g.) as a white crystalline solid, m.p. 213–218°. Repeated crystallizations from methanol raised the m.p. to 224–226°; ν_{max} 3560, 3500, 1465, 1375, 1265, 1185, 1100, 1073, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5 \cdot C_3H_6O$: C, 70.98; H, 9.45. Found: C, 71.23, 71.14; H, 9.26, 9.49.

5α,6α-Epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII).—A solution of 3,20-bisethylenedioxy-6-methylpregn-5-en-17α-ol (XXII, 1.0 g.) was dissolved in methylene chloride (100 ml.) and refluxed with an ethereal 0.62 *N* monoperphthalic acid solution (10 ml.) for 3 hr. and then allowed to remain at room temperature overnight. The reaction mixture was washed with an aqueous sodium bicarbonate solution, water, and then dried. Evaporation of the solvent left a white solid (0.44 g.), m.p. 259–262°. After crystallization from acetone–petroleum ether, the product melted at 265–267°; $[\alpha]^{25}D$ +6° (dioxane); ν_{max} 3600, 3450, 2960, 1465, 1368, 1362, 1178, 1105, 1085, 1070, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_6$ (448.58): C, 69.61; H, 8.99. Found: C, 69.84; H, 9.36.

5α,6β,17α-Trihydroxy-6α-methylpregnane-3,20-dione (XXIV).—To a suspension of 5α,6α-epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII, 0.1 g.) in acetone (4 ml.) was added a 1.5 *N* aqueous perchloric acid solution (0.4 ml.). The reaction mixture was shaken to dissolve suspended material and then the solution was allowed to remain at room temperature for 2 hr. It was then neutralized with excess aqueous sodium bicarbonate. Evaporation of the organic extract afforded the triol XXIV (80 mg.), m.p. 220–235°. Repeated crystallization of this material from ethanol–petroleum ether (90–100°) gave XXIV (21 mg.), m.p. 243–246°; ν_{max} 3460, 2980, 1705, 1460, 1385, 1310, 1215, 1135, and 1085 cm.$^{-1}$; $[\alpha]^{25}D$ −21° (chloroform).

Anal. Calcd. for $C_{22}H_{34}O_5 \cdot {}^1/_2H_2O$: C, 68.18; H, 9.10. Found: C, 68.91, 68.78; H, 9.55, 9.04.

6β,17α-Dihydroxy-6α-methylpregn-4-ene-3,20-dione (XIII).—A. Methanolic potassium hydroxide (2.5%—1.0 ml.) was added to a solution of 5α,6β,17α-trihydroxy-6α-methylpregnane-3,20-dione (XXIV, 224 mg.) in methanol (10 ml.). After being refluxed for 1 hr. the solution was cooled, neutralized with acetic acid, and concentrated almost to dryness. The addition of water to the residue gave the diol XIII which was separated and dried, 165 mg., m.p. 266–270°. Repeated crystallization from acetone–petroleum ether raised the melting point to 270–271°; λ_{max} 237–238 mμ (ε 13,800); ν_{max} 3500, 2930, 1700, 1680, 1610, 1380, 1360, 1230, 1145, 1125, and 1075 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.46; H, 9.06. Found: C, 72.32, 72.06; H, 9.17, 8.77.

B. A solution of 17α-acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,20-dione (XXVIII, 128 mg.) in methanol (5 ml.) was refluxed for 1 hr. with methanolic potassium hydroxide (2.5%—0.5 ml.). The product was isolated as above and on crystallization there was obtained XIII (25 mg.), m.p. 271–274°. This was identical to the material prepared by procedure A.

17α-Acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI).—To a solution of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one (XXV, 0.5 g.) in methylene chloride (50 ml.) was added 0.62 *N* monoperphthalic acid–ether solution (5.0 ml.) and the mixture was refluxed for 2 hr., cooled, and washed with a saturated sodium bicarbonate solution and water. The dried ether extract was evaporated leaving a gum which became crystalline on trituration with ether. Crystallization from acetone–petroleum ether gave the epoxide XXVI (409 mg.), m.p. 204–207°; $[\alpha]^{25}D$ −48° (chloroform); ν_{max} 3460, 2960, 1740, 1445, 1380, 1255, 1082, 1055, and 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$ (404.53): C, 71.25; H, 8.97. Found: C, 70.96; H, 9.28.

17α-Acetoxy-3β,5α,6β-trihydroxy-6α-methylpregnan-20-one (XXVII).—Perchloric acid (1.5 N—5.0 ml.) was added to a solution of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI, 1.5 g.) in acetone (60 ml.). After 2 hr. at room temperature, the solution was neutralized with an aqueous sodium bicarbonate solution, and the organic solvent was removed by distillation *in vacuo*. Water was added to the resultant residue and the solid was collected by filtration. After being washed thoroughly with water, the material was dried to give the triol XXVII (1.7 g.), m.p. 220–230°. The melting point was raised to 241–243° after several crystallizations from acetone–petroleum ether; $[\alpha]^{25}D$ −51° (chloroform); ν_{max} 3400, 2925, 1710, 1450, 1375, 1260, 1145, and 1075 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_6 \cdot C_3H_6O$: C, 67.47; H, 9.23. Found: C, 66.93, 67.20; H, 9.26, 9.35.

17α-Acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,20-dione (XXVIII).—17α-Acetoxy-3β,5α-6β-trihydroxy-6α-methylpregnan-20-one (XXVII, 1.0 g.) was dissolved in reagent acetone (distilled from potassium permanganate) (100 ml.). Under a nitrogen atmosphere, 8 *N* chromic acid in 8 *N* sulfuric acid (1.3 ml.) was added to the above solution. The oxidation was allowed to proceed for 2 min., the mixture was poured into water, and the acetone removed at reduced pressure. The resulting white solid was collected, washed with water, and dried to give XXVIII (0.74 g.), m.p. 247–250°. Crystallization from acetone–petroleum ether raised the melting point to 250–252°; $[\alpha]^{25}D$ −9° (chloroform); ν_{max} 3450, 2930, 1712, 1375, 1263, 1140, and 1078 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6 \cdot C_3H_6O$: C, 67.75; H, 8.85. Found: C, 68.27, 67.86, 67.56; H, 9.09, 9.03, 8.83.

17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI).—A stream of dry hydrogen chloride was passed through a solution of 17α-acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,-20-dione (XXVIII, 0.2 g.) in methylene chloride (50 ml.) maintained at 5°. After 75 min. the excess hydrogen chloride was removed by a stream of nitrogen bubbled through the reaction mixture. The methylene chloride solution was washed with an aqueous sodium bicarbonate solution and with water. After drying, evaporation of the solvent *in vacuo* gave a crystalline residue (112 mg.), m.p. 188–190°. Repeated crystallizaton from acetone–petroleum ether afforded XI (47 mg.), m.p. 216–217° dec.; $[\alpha]^{25}D$ +1° (chloroform); λ_{max} 235 mμ (ε 14,400); ν_{max} 3440, 2960, 1740, 1660, 1615, 1370, 1260, 1250, 1145, 1120, and 1078 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 69.97, 70.76, 70.05; H, 8.81, 8.95, 8.40.

17α-Acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX).—A. A solution of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI, 0.3 g.) in methylene chloride (5 ml.) was cooled to −60° and to this was added a cooled solution (−60°) of tetrahydrofuran (1.1 ml.), methylene chloride (0.5 ml.), and anhydrous hydrogen fluoride (0.8 ml.). After being kept at −5° for 5 hr., the solution was poured carefully into a saturated sodium bicarbonate solution. The organic phase was separated, and the aqueous layer was extracted with methylene chloride. The combined organic solutions were washed with water and dried. Evaporation left an amorphous residue which was dissolved in a small amount of benzene and added to a column of synthetic magnesium silicate (12 g.). Elution with 3% acetone–petroleum ether gave a crude crystalline material. Crystallization from acetone–petroleum ether yielded XXIX (118 mg.), m.p. 189–190°. This melting point was raised to 194–196° by several crystallizations, λ_{max} none; $[\alpha]^{25}D$ −30° (chloroform); ν_{max} 3350, 2940, 1730, 1695, 1445, 1370, 1255, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$ (406.54): C, 71.25; H, 8.97. Found: C, 70.66; H, 9.33.

B. Boron trifluoride in ether (20 ml.) was added to a solution of XXVI (1.9 g.) in ether (100 ml.) and benzene (100 ml.). After 18 hr. the solution was neutralized with saturated sodium bicarbonate solution. The organic phase was separated, washed with water, and dried. Evaporation of the solvent afforded a gum which was dissolved in anhydrous ether and seeded with material obtained from procedure A above. In this manner a crystalline product (1.2 g.) was obtained, m.p. 174–184°. Crystallization from acetone–petroleum ether gave XXIX (0.62 g.), m.p. 195–197°, identical to the product obtained by procedure A.

17α-Acetoxy-5β-methyl-A-homo-B-norpregnane-3,4a,20-trione (XXX).—To a solution of 17α-acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX, 0.1 g.) in reagent acetone (distilled from potassium permanganate) (2 ml.) was added 8 *N* chromic acid in 8 *N* sulfuric acid dropwise until the orange color of the oxidizing agent persisted. The solution was poured into water and filtered. Two crystallizations of the solid from acetone–petroleum ether provided XXX (55 mg.), m.p. 239–240°; $[\alpha]^{25}D$ −104° (chloroform); $\lambda_{max}^{Basic\ MeOH}$ 300 mμ (ε 18,100); ν_{max} 1740, 1720, 1700, 1262, and 1248 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.46; H, 8.64.

17α-Hydroxy-5β-methyl-A-homo B-norpregnane-3,4a,20-trione (XXXI).—5α,6α - Epoxy - 3,20 - bisethylenedioxy - 6β - methylpregnan - 17α - ol (XXIII, 0.2 g.) was suspended in acetone (8 ml.) and 72% perchloric acid (2 drops) was added. Solution was effected immediately. The mixture after 2 hr. at room temperature was treated with dilute sodium bicarbonate solution, and the solid which separated was collected by filtration and washed with water. This material was crystallized several times from acetone–water to give XXXI (30 mg.), m.p. 194–196°; $[\alpha]^{25}D$ −124° (chloroform); $\lambda_{max}^{Basic\ MeOH}$ 300 mμ (ε 18,600); ν_{max} 3460, 2970, 1720, 1695, 1390, 1355, 1200, and 1080 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4$ (360.48): C, 73.30; H, 8.95. Found: C, 73.17; H, 9.33.

Synthesis of α-Amino-γ-hydroxy Acids: γ,γ′-Dihydroxyvaline

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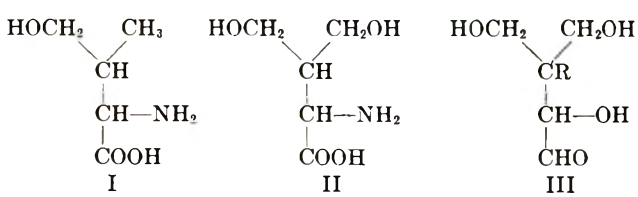
γ-Hydroxyvaline (I) and γ,γ′-dihydroxyvaline (II) have been prepared by a modified Erlenmeyer synthesis. The geometry of the intermediate azlactones IVb and IVc and of the corresponding benzoylamino acrylic esters VIIb and VIIc has been determined.

Until a few years ago, homoserine was the only α-amino-γ-hydroxy acid known with certainty to occur in Nature. Recently, however, a prodigious number of such compounds has been detected, both in free form and as peptide constituents and their chemistry has been the subject of considerable study.[1]

We wish to describe a simple synthetic method leading to α-amino acids with chain branching in the beta position and carrying hydroxyl groups in one or both of the gamma positions. The method offers an alternate synthesis for γ-hydroxyvaline (I), recently isolated from crowngall tumors of *Kalanchoe daigremontiana* and synthesized from α-chloro-β-methyl-γ-butyrolactone.[2] More importantly, however, it has permitted us to prepare a new, otherwise difficulty accessible amino acid, γ,γ′-dihydroxyvaline (II). Although this compound has not been found to occur naturally, closely related structures like the sugars cordicepose and apiose (III. R = H and OH respectively) have been isolated,[3] and the role of γ,γ′-dihydroxyvaline itself as a possible biogenetic precursor of the antibiotic Cephalosporin C has been discussed.[4] The method of synthesis is based on the observation that the Erlenmeyer azlactone synthesis, although seldom practicable with ketones,[5] can be successfully extended to the acetates of α-hydroxy and α,α′-dihydroxy ketones by applying the modified conditions of Baltazzi and Robinson.[5c] Thus, by using equimolecular amounts of ketone and hippuric acid, three moles of acetic anhydride, lead(II) acetate as a base, and tetrahydrofuran as the solvent, the azlactones IV are formed in practical yields, readily isolable by crystallization.[6]



The exocyclic double bond in compounds IV can be hydrogenated (palladium–charcoal, dioxane) to give the "dihydro," azlactones V with little or no hydrogenolysis of the allylic acetate groups and the azlactones hydrolyzed with hydrochloric acid to the aminohydroxy acid lactone hydrochlorides VI, which can then be converted to the free amino acids by treatment with ammonia.

(1) For reviews, see Th. Wieland, *Angew. Chem.*, **72**, 892 (1960); H. Musso, *ibid.*, **68**, 313 (1956); A. I. Virtanen, *ibid.*, **67**, 381 (1955).

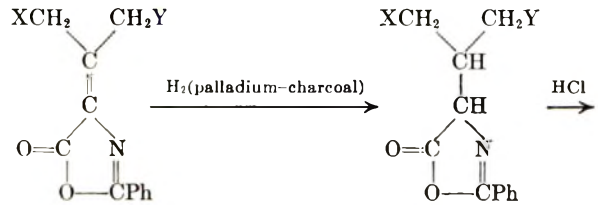
(2) J. K. Pollard, E. Sondheimer, and F. C. Steward, *Nature*, **182**, 1356 (1958).

(3) W. G. Overend, M. Stacey in "Advances in Carbohydrate Chemistry," Vol. 8, Academic Press Inc., New York, N. Y., 1953, p. 52; C. S. Hudson, *ibid.*, Vol. 4, 1949, p. 57.

(4) E. P. Abraham and G. F. Newton, *Biochem. J.*, **79**, 377 (1961).

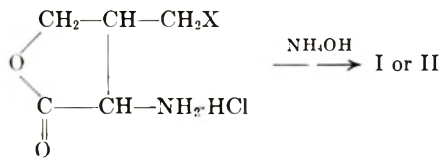
(5) (a) H. E. Carter, *Org. Reactions*, **III**, 206 (1946); (b) J. W. Cornforth in "Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 730 ff; (c) E. Baltazzi and R. Robinson, *Chem. Ind.* (London), 191 (1954).

(6) Substitution of 2-phenyl-2-oxazolin-5-one [J. M. Stewart and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 5336 (1956)] for hippuric acid did not improve the yields.

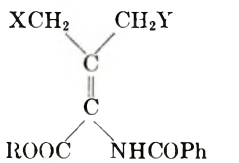


IVa. X = Y = H
IVb. X = H, Y = AcO
IVc. X = AcO, Y = H
IVd. X = Y = AcO

V. X = H or AcO
Y = H or AcO



VIa. X = H
VIb. X = OH



VIIa. X = Y = H, R = CH_3
VIIb. X = H, Y = AcO, R = CH_3
VIIc. X = AcO, Y = H, R = CH_3
VIId. X = Y = AcO, R = CH_3
VIIe. X = MeO, Y = AcO, R = CH_3
VIIf. X = Y = AcO, R = C_2H_5
VIIg. X = Y = AcO, R = H

It is interesting to note that in contrast to the azlactones IV, the substituted acrylic acids and esters VII undergo only hydrogenolysis to give the known α-benzamido-β,β-dimethylacrylic acid (ester VIIa), the double bond of which resists hydrogenation under the conditions used.

In the condensation of acetol acetate with hippuric acid both geometrical isomers IVb and IVc are formed and can be separated by fractional crystallization. Their geometry will be discussed below. On catalytic hydrogenation both IVb and IVc yield what appear to be identical mixtures of the diastereomeric dihydro azlactones V (X = H, Y = AcO), and the γ-hydroxyvaline I obtained on hydrolysis of V is likewise a mixture of diastereomers similar in melting point to the product described by Pollard, Sondheimer, and Steward.[2]

The new amino acid, γ,γ′-dihydroxyvaline (II), obtained on acid hydrolysis of the azlactone V (X = Y = AcO) followed by ion exchange chromatography, crystallized readily as the lactone hydrochloride VI (X = OH), which could be converted with ammonia into the likewise crystalline D,L-amino acid. Resolution of the latter was achieved by incubating the lithium salt of its *N*-chloroacetyl derivative with hog kidney acylase and separating the dechloroacetylated L-acid from the *N*-chloroacetyl-D-derivative by ion exchange methods. The specific rotations observed were $[\alpha]^{24}D$ −12.2° for the L-acid and +13.7° for the D acid (c = 1–2, freshly prepared solutions in 0.1 *N* potassium bicarbonate). Table I contains paper chromatographic data obtained in three systems.

The precise geometry of the *cis-trans* isomeric azlactones IVb and IVc and of the acrylic esters VIIb and VIIc has been determined by n.m.r. spectroscopy on the basis of the elegant work of Jackman.[7] Comparing the position of the C-methyl signals in the acrylic ester VIIa

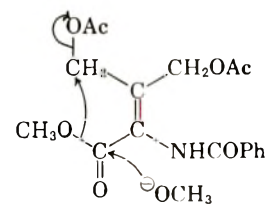
TABLE I

$R_{alanine}$-VALUES FOR γ-HYDROXYVALINE AND γ,γ′-DIHYDROXYVALINE[a]

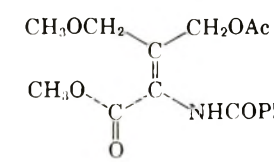
	n-BuOH–AcOH–H_2O 4:1:1	65% pyridine	95% ethanol
γ-Hydroxyvaline	0.95	1.21	1.36
γ-Hydroxyvaline lactone			2.72
γ,γ′-Dihydroxyvaline	0.55	1.10	0.69
γ,γ′-Dihydroxyvaline lactone	1.18	1.46	2.64

[a] Descending, Whatman paper no. 1, solvent front traveled 40 cm. Spots detected by ninhydrin.

with those of methyl β,β-dimethylacrylate (Table II) we find almost complete correspondence indicating that the α-benzoylamino group exerts no greater effect on the C-methyl groups than the α-proton. This confirms the view readily gained from inspection of molecular models that the most stable conformations are those in which the benzoyl group points away from the *cis*-β-methyl group. Since the C-methyl signal in methyl β,β-dimethylacrylate appearing at lower field (τ = 7.88) has been assigned to the more shielded methyl group *cis* to the carbomethoxy group, the same assignment is made in the case of VIIa. For similar reasons, the methylene protons of the β-acetoxymethylene group in VIId appearing at lower field are assigned the *cis*, those at higher field the *trans* structure with respect to the carbomethoxy group. Inspection of the τ values for the methyl and methylene group in VIIb and VIIc now permits the assignments shown in Table II. The agreement between the signals of each of the two methyl groups in VIIa and the corresponding signals in VIIb and VIIc are particularly striking. Chemical confirmation of the above assignments was possible with the aid of a product obtained from IVd by brief heating in methanol in the presence of potassium acetate. The structure VIIe assigned to this compound is most satisfactorily rationalized as arising from the intermediate VIId by an intramolecular substitution reac-



VIId



VIIe

tion involving the carbomethoxy and acetoxymethylene groups *cis* to each other. The n.m.r. spectrum, as expected, shows the *trans*-acetoxymethylene group at higher field and a new signal (τ = 5.83) for the *cis*-methoxymethylene group.

The spectra of the corresponding azlactones IVa–IVd do not show the pronounced differences for the *cis* and *trans* methyl and methylene signals seen with the acrylic esters VIIa–VIId, although the differences are in the same direction. Moreover, these signals appear at lower field. This is ascribed to greater shielding of these protons due to the cisoid nature of the α,β-unsaturated carbonyl system in the azlactones—the car-

(7) L. M. Jackman: "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 58, 121.

TABLE II

METHYLENE AND METHYL PROTON MAGNETIC RESONANCE SIGNALS OF AZLACTONES IV AND SUBSTITUTED ACRYLIC ESTERS VII[a]

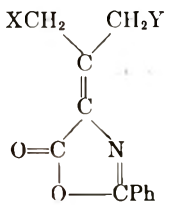
	$AcOCH_2-C=$		$MeOCH_2-C=$		$-COOCH_3$	$CH_3OCH_2-C=$	CH_3COO-		$CH_3-C=$	
IVa									7.61	7.67
IVb		4.76					7.85		7.60	
IVc	4.65							7.90		7.67
IVd	4.60	4.70					7.85	7.90		
Methyl β,β-dimethyl-acrylate					6.30				7.88	8.16
VIIa					6.30				7.85	8.15
VIIb		5.35			6.20			7.95	7.86	
VIIc	4.88				6.22		7.90			8.10
VIId	5.05	5.26			6.15		7.85	7.90		
VIIe		5.22		5.83	6.15	6.62		7.84		

[a] Spectra taken at 60 Mc. (Varian A-60 n.m.r. spectrometer) in deuteriochloroform solutions with tetramethylsilane as internal standard. Signal positions are given in τ values.

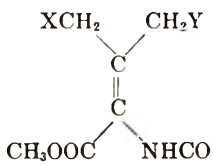
TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED AZLACTONES[a] AND METHYL BENZAMIDO ACRYLATES[b]

(Absorption maxima, mμ; log ε values in brackets)



X = Y = H	Sh 321 (4.17)	310 (4.38)	298 (4.37)	244 (4.08)	235 (4.08)	Sh 232 (4.06)	224 (4.04)
X = H, Y = AcO	Sh 323 (4.19)	306 (4.28)		244 (4.07)	236 (4.07)	Sh 230 (4.03)	225 (4.00)
X = AcO, Y = H	Sh 323 (4.21)	306 (4.37)		245 (4.06)	237 (4.07)	Sh 232 (4.05)	
X = Y = AcO		308 (4.29)		245 (3.99)	237 (4.03)		



X = Y = H	226 (4.15)		
X = H, Y = AcO	231 (4.20)	Sh 250	
X = AcO, Y = H	230 (4.23)		
X = Y = AcO	244 (4.13)	235 (4.15)	
X = MeO, Y = AcO	251 (4.14)	233 (4.17)	

[a] In cyclohexane solution. [b] In ethanol solution.

bonyl group being directed towards these protons—as compared to the *s-trans* conformation prevalent in the acrylic esters, and to the closeness of the anisotropic N=C grouping in the azlactones in place of the benzoylamino group in the esters.

The ultraviolet absorption maxima of the azlactones IV and esters VII are summarized in Table III. While no correlation with the geometrical isomerism can be made, attention is drawn to the increasing simplicity of the azlactone spectra with the increasing number of acetoxy substituents, which may be related to the strongly decreased ability of the acetoxymethylene groups to enter into hyperconjugation with the extended conjugated system, thereby increasing the number of relatively low energy excited states.

Experimental

2-Phenyl-4-(2-acetoxy-1-methylethylidene)-2-oxazolin-5-one (IVb and IVc).—A mixture of 35.90 g. of hippuric acid (0.20 mole), 27.80 g. of acetol acetate (0.24 mole), and 32.50 g. of anhydrous lead(II) acetate (0.10 mole) in 60.10 g. of acetic anhydride (0.60 mole) and 460 ml. of peroxide free tetrahydrofuran was heated under reflux for 16 hr. in a nitrogen atmosphere. After cooling, the mixture was filtered and evaporated to dryness *in vacuo*. The residue was taken up in 700 ml. of benzene and treated with hydrogen sulfide for 5 min. at 10°. The filtered solution was again evaporated to a slowly crystallizing mixture of the geometrical isomers IVb and IVc (40.32 g. or 78%). After short boiling with 50 ml. of isopropyl alcohol, 11.32 g. (22%) of isomer IVb crystallized (m.p. 98–101°) in the form of yellow needles. The analytical sample, obtained after three recrystallizations from diisopropyl ether, melted at 101–102°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.77; H, 5.21; N, 5.14.

The isopropyl alcohol mother liquor of IVb was concentrated *in vacuo* until it weighed 53 g. On cooling, 5.31 g. (10%) of isomer IVc separated (m.p. 76–79°). Two recrystallizations from diisopropyl ether yielded the pure compound in form of yellow needles: m.p. 81.5–82°. Mixed m.p. with IVb: 66–90°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.91; H, 5.08; N, 5.62.

The infrared absorption spectra of the isomers (KBr) showed differences in the fingerprint region and had the following more important common bands: IVb: 5.57 (oxazolone C=O), 5.76, 8.01 (acetate) and 5.97 μ (oxazolone C=N); IVc: 5.60, 5.74, 8.03 and 5.98 μ.

γ-Hydroxyvaline (I).—To a solution of 825 mg. (3.18 mmoles) of 2-phenyl-4-(2-acetoxy-1-methylethylidene)-2-oxazolin-5-one (IVb, m.p. 100–101°) in 15 ml. of peroxide free dioxane there was added 225 mg. of prehydrogenated palladium-on-charcoal (5%) catalyst and the mixture was stirred in hydrogen atmosphere at room temperature. After the uptake of 1 mole of hydrogen (135 min., 80 ml. at 21°/760 mm. saturated with dioxane), the hydrogenation was stopped and the filtered solution evaporated to give 915 mg. of a pale yellow oil. The infrared absorption spectrum (neat) indicated the formation of the "dihydro" azlactone V (5.47 μ, oxazolone C=O; 5.74, 8.13 μ, acetate) and the presence of some unhydrogenated "unsaturated" azlactone (weak band at 5.58 μ). Hydrogenation of the isomer IVc proceeded in the same way and yielded an oil with its infrared absorption spectrum indistinguishable from that described above.

The crude, oily V (860 mg.) was heated under reflux with a mixture of 6 ml. of concentrated hydrochloric acid and 4 ml. of water for 3.5 hr. and left in the refrigerator (+8°) overnight. The mixture was then filtered from 345 mg. (94%) of benzoic acid and evaporated to dryness *in vacuo*. The residual glass (488 mg.) was dissolved in 5 ml. of water and passed through a column of Amberlite IR 120 (H^+ form, 8 ml. resin). The column was washed with 50 ml. of water. The amino acid was obtained by

elution with 15 ml. of 1.5 *N* aqueous ammonia, boiling the eluate until the ammonia had escaped, and by evaporation of the aqueous solution *in vacuo*. The white crystalline residue (303 mg. 76%, m.p. 206–209°) was recrystallized for analysis from water–ethanol (m.p. 208–209° dec., reported[2] 209–211°).[8]

Anal. Calcd. for $C_5H_{11}O_3N$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.17; H, 8.50; N, 10.55.

2-Phenyl-4-(2-acetoxy-1-acetoxymethylethylidene)-2-oxazolin-5-one (IVd). (a)—A mixture of 5.37 g. of hippuric acid (30 mmoles), 6.25 g. of diacetoxyacetone (prepared from dihydroxyacetone according to H. O. L. Fischer and L. Feldmann[9]), 4.86 g. (15 mmoles) of anhydrous lead(II) acetate, 9.20 g. (90 mmoles) of acetic anhydride, and 100 ml. of peroxide free tetrahydrofuran was stirred and heated under reflux for 20 hr. in an atmosphere of nitrogen. The filtered mixture was then evaporated *in vacuo*, and the residue dissolved in 50 ml. of benzene and treated with hydrogen sulfide for 5 min. at 10°. The filtered red solution on evaporation gave 11.89 g. of a slowly crystallizing oil, from which, on trituration with 30 ml. of *t*-butyl alcohol, 4.02 g. (41.4%) of the oxazolone IVd could be separated (m.p. 125–128°). Two recrystallizations from *t*-butyl alcohol and benzene–hexane, respectively, raised the melting point to 130.5–131° (yellow needles); λ_{max}^{KBr} 5.56 μ (oxazolone C=O); 5.75, 8.00–8.10 μ (acetates); 5.94 μ (oxazolone C=N).

(b) A mixture of 18.75 g. of diacetoxyacetone[9] (108 mmoles), 14.50 g. of 2-phenyl-2-oxazolin-5-one[7] (90 mmoles), 13.20 g. lead-(II) acetate (40.5 mmoles), 20 ml. of acetic anhydride (181 mmoles), and 300 ml. of peroxide free tetrahydrofuran gave, after 12 hr. refluxing in nitrogen atmosphere and a work-up similar to that described under a, 10.86 g. (38%) of the azlactone (IVd) with m.p. 129–130°.

DL-γ,γ′-Dihydroxyvaline (II).—A solution of 6.30 g. (20 mmoles) of 2-phenyl-4-(2-acetoxy-1-acetoxymethylethylidene)-2-oxazolin-5-one (IVd) in 90 ml. of peroxide free dioxane was hydrogenated in a Parr hydrogenation apparatus at room temperature in the presence of 0.30 g. of 5% palladium on carbon catalyst. The hydrogenation was interrupted after uptake of 20 mmoles of hydrogen (54 min.) and the filtered solution evaporated to give 6.27 g. of an oil. On treatment with 6.0 ml. of cold isopropyl alcohol, 0.65 g. of starting material crystallized and was removed by filtration. The oil obtained by evaporation of the mother liquor (5.45 g.) consisted of the "dihydro" azlactone (V. X = Y = AcO), as indicated by its infrared absorption spectrum: bands at 5.44 μ ("dihydro" azlactone C=O), 5.70, 8.10–8.15 μ (acetates), 6.03 μ ("dihydro" azlactone C = N). Bands characteristic for the starting material (5.56, 5.94 μ) were virtually absent.

A solution of 5.44 g. of the above oil (17 mmoles) was heated under reflux with 28 ml. of 5 *N* hydrochloric acid for 20 hr. On cooling, 1.87 g. (90%) of benzoic acid crystallized and was removed by filtration. The filtrate was evaporated *in vacuo* to remove hydrochloric acid and then redissolved in 50 ml. of water. The solution was passed through a 9-ml. column of Amberlite IR 120 resin (H^+ form, 1.9 meq./ml.) which was subsequently washed with 300 ml. of water and finally eluted with 100 ml. of 1.5 *N* aqueous ammonia. Evaporation of the ammonia eluate yielded 1.29 g. of a dark oil, which was heated with 7.5 ml. of 5 *N* hydrochloric acid and 0.50 g. of Darco for 10 min. The filtered solution gave on evaporation 1.81 g. (57%) of the diastereomers of **γ,γ′-dihydroxyvaline lactone hydrochloride** (VI. X = OH). Recrystallization from 36 ml. of ethanol–ethyl acetate 2:1 gave 0.82 g. of white needles, m.p. 192–195° dec.

Anal. Calcd. for $C_5H_9NO_3 \cdot HCl$: C, 35.83; H, 6.01; N, 8.36; Cl, 21.16. Found: C, 35.92; H, 6.09; N, 8.24; Cl, 21.59.

A second crop (0.26 g., m.p. 176–184°) crystallized on standing from the mother liquor. The infrared absorption spectra showed two sharply resolved lactone absorption bands λ_{max}^{Nujol} 5.54, 5.60 μ.

A solution of 830 mg. (5.30 mmoles) of the lactone hydrochloride in 150 ml. of water was passed through a weakly basic anion exchange column (40 ml., Amberlite IR 4B, OH^- form, 2.5 meq./ml.) in 3 hr. The column was washed with 50 ml. of water and to the combined solutions there was added 50 ml. of concentrated aqueous ammonia. After boiling for 1 hr., the solution was evaporated to dryness *in vacuo* to yield 490 mg. (62%) of an oil, which solidified on treatment with aqueous acetone to white crystals of m.p. 160–168°. After two recrystallizations from water–acetone (1:3 v./v.) the pure **DL-γ,γ′-dihydroxyvaline** (306.6 mg., 39%) melted at 169–170°.

Anal. Calcd. for $C_5H_{11}NO_4$: C, 40.26; H, 7.43; N, 9.39. Found: C, 40.24; H, 7.43; N, 9.24.

Resolution of DL-γ,γ′-Dihydroxyvaline.—A solution of 3.035 g. (18.1 mmoles) of DL-γ,γ′-dihydroxyvaline lactone hydrochloride (VI. X = OH) in 25 ml. of water was placed in a Beckman Automatic Titrator (Model K), in which an efficient vibration mixer replaced the stirrer. Upon setting the pH dial to 8.5, the titrator added 5.30 ml. of 3.56 *N* sodium hydroxide solution (18.8 mmoles, NaOH). The solution was then cooled and, under strong vibration, 6.20 g. (36.2 mmoles) of chloroacetic anhydride was added in ten equal portions over a period of 1 hr. Simultaneously, the titrator added 15.25 ml. of 3.56 *N* sodium hydroxide solution (54.3 mmoles, NaOH). After one more hour of vibration at room temperature, the solution was acidified to pH 1.5 by the addition of 4.0 ml. of concentrated hydrochloric acid and extracted with ethyl acetate (twelve 10-ml. portions). Evaporation of the dried ethyl acetate solution yielded an oil, from which most of the chloroacetic acid was eliminated by successive extractions with hot hexane (five 10-ml. portions) and high vacuum drying over solid potassium hydroxide. The residue consisted of 2.55 g. (50%) of crude **α-chloroacetamino-β-chloroacetoxymethyl-γ-butyrolactone**, which remained a viscous oil. λ_{max}^{neat} 2.92, 5.63–5.70, 5.99, 6.48, 6.52 and 8.45 μ.

Anal. Calcd. for $C_9H_{11}NO_5Cl_2$: C, 38.04; H, 3.90; Cl, 24.95; N, 4.93. Found: C, 38.64; H, 4.66; Cl, 22.93; N, 4.64.

A 2.37-g. sample (8.4 mmoles) of the above oil was vibrated in 50 ml. of water and by setting the pH dial of the autotitrator to 9.0, an 1.835 *N* lithium hydroxide solution was automatically added. The base uptake virtually stopped after addition of 8.30 ml. (15.3 mmoles LiOH; 180 min. at room temperature) and a clear solution resulted. After dilution to 180 ml. and adjusting the pH to 8.0, 60 mg. of hog kidney acylase powder (Nutrition Biochemical Corporation, Cleveland, Ohio) was added and the mixture kept at 38° ± 1° for 90 hr. The enzyme was then eliminated by stirring the solution (pH 6) with 1.0 g. of "Darco" for 1 hr. at room temperature and the filtered solution was evaporated *in vacuo* to yield 2.36 g. of an oil. The latter was redissolved in 25 ml. of water and passed through a column of Amberlite IR 120 cation exchange resin (H^+ form, 1.9 meq./ml., 20 ml.). The column was washed with 250 ml. of water and the combined solutions were evaporated *in vacuo* to yield 1.417 g. of an oil, from which the **D-γ,γ′-dihydroxyvaline** was obtained after hydrolysis with boiling 5 *N* hydrochloric acid (25 ml., 20 hr.) followed by adsorption on Amberlite IR 120 resin (20 ml. H^+ form) and elution with 1.5 *N* aqueous ammonia. Evaporation of the ammonia eluate gave 240 mg. (39% based on the dichloroacetyl lactone) of an oil, which soon solidified. After one recrystallization from water–acetone 1:3 v./v., colorless needles of m.p. 168–172° were obtained.

The **L-γ,γ′-dihydroxyvaline** was eluted from the first column with 1.5 *N* aqueous ammonia (250 ml.). The 454 mg. of oily product, obtained on evaporation, solidified on treatment with acetone. Recrystallization from water–acetone 1:3 yielded colorless needles, m.p. 174.5–175°.

The specific rotations of the D and L acids, measured on freshly prepared solutions in 0.1 *N* potassium hydrogen carbonate, were $[\alpha]_D$ +13.7° and $[\alpha]_D$ −12.2°, respectively (c was 1.90 and 1.49 respectively).

Methyl α-Benzamido-β-acetoxymethylisocrotonate (VIIb).—To a solution of 120.4 mg. of the azlactone IVb in 10 ml. of anhydrous methanol was added 0.01 ml. of concentrated sulfuric acid. After 30 min. heating under reflux, the cooled mixture was poured onto 25 ml. of ice cold 2% sodium bicarbonate solution and extracted with chloroform. The solid obtained after evaporation of the chloroform solution (97.7 mg., m.p. 106.5–109) was twice recrystallized from methylene chloride–hexane to yield needles of m.p. 110–111°. λ_{max}^{KBr} 3.05, 5.76, 5.98, 6.57, 7.50, and 8.10 μ.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; methoxy, 10.63. Found: C, 62.07; H, 5.53; N, 4.71; methoxy, 10.50.

Methyl α-Benzamido-β-acetoxymethylcrotonate (VIIc).—A solution of 184.9 mg. of the azlactone IVc in 10 ml. of anhydrous methanol was treated with 0.01 ml. of concentrated sulfuric acid and heated under reflux for 30 min. The mixture was then poured into 25 ml. of ice cold 2% sodium bicarbonate solution and

(8) The γ-hydroxyvaline thus obtained contained traces of valine, as revealed by paper chromatography. In ref. 2, a simple ion exchange process for the purification of hydroxyvaline is described, which can be applied here if the presence of traces of valine is disturbing.

(9) H. O. L. Fischer and L. Feldmann, *Ber.*, **62B**, 854 (1929).

extracted with chloroform. Evaporation of the chloroform solution yielded 187.7 mg. of solid material, which after three recrystallizations from methylene chloride–diisopropyl ether furnished 102 mg. of white needles of m.p. 106.5–107°. Sublimation at 105°/0.003 mm. raised the m.p. to 109.5–110°. Mixed m.p. with VIIb: 85–100°. λ_{max}^{KBr} 3.07, 5.71, 5.78, 6.06, 6.59, 7.60, and 8.13 μ.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; methoxy, 10.63. Found: C, 61.61; H, 6.04; N, 4.85; methoxy, 10.92.

Methyl α-Benzamido-β,β-di-acetoxymethylacrylate (VIId).—A solution of 4.05 g. (12.75 mmoles) of the azlactone IVd in 100 ml. of anhydrous methanol was heated under reflux for 48 hr. Evaporation gave an oil (4.30 g.), from which 2.29 g. (52%) of crystals of m.p. 97–102° could be separated by trituration with ether. Recrystallization from methylene chloride–diisopropyl ether raised the m.p. to 105–106°. λ_{max}^{KBr} 3.08, 5.73–5.76, 6.04, 6.59, and 7.50 μ.

Anal. Calcd. for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01; methoxy, 8.88; acetyl, 24.60. Found: C, 58.45; H, 5.77; N, 4.00; methoxy, 9.14; acetyl, 25.18.

The ethanolysis product (VIIf) obtained in an analogous manner, had a melting point of 106.5–107°.

α-Benzamido-β,β-diacetoxymethylacrylic Acid (VIIg).—A solution of 500 mg. (1.58 mmoles) of the azlactone IVd in 20 ml. of 50% aqueous dioxane was heated under reflux for 30 min. On evaporation, a crystalline residue was obtained which on recrystallization from water yielded 465 mg. of the acid (m.p. 129–130°). The analytical sample obtained after two recrystallizations from ethyl acetate–hexane melted at 135–135.5°. λ_{max}^{KBr} 2.06, 3.35–3.85, 5.72, 5.86, 6.00, 6.05, 6.63, 6.72, 8.06, and 8.23 μ.

Methyl α-Benzamido-β-acetoxymethyl-γ-methoxyisocrotonate (VIIe).—A mixture of 3.17 g. (10.0 mmoles) of the azlactone IVd and 0.98 g. (10.0 mmoles) of anhydrous potassium acetate in 50 ml. of anhydrous methanol was heated under reflux for 30 min. The residue obtained after evaporation *in vacuo* was thoroughly extracted with benzene to yield 3.56 g. of a light yellow oil, which was subsequently chromatographed on 158 g. of neutral alumina (Woelm, activity II). The first oily fractions obtained on elution with benzene and benzene–ether (9:1) solidified on standing (510 mg., m.p. 88–96°) and gave on recrystallization from chloroform-hexane white needles of m.p. 100–101°. λ_{max}^{Nujol} 3.05, 5.76, 5.83, 5.99, 6.07, 6.60, 6.74, 7.53, 8.10, 8.20, 9.25, and 9.35 μ.

Anal. Calcd. for $C_{16}H_{19}NO_6$: C, 59.80; H, 5.96; N, 4.36; methoxy, 19.30. Found: C, 59.61; H, 5.69; N, 4.27; methoxy, 19.08.

Elution of the column with chloroform–methanol (9:1) yielded 1.013 g. (84%) of benzamide of m.p. 115–120°.

Methyl α-Benzamido-β,β-dimethylacrylate (VIIa).—A solution of 151.5 mg. (0.435 mmole) of methyl α-benzamido-β,β-di-acetoxymethylacrylate (VIId) in 5 ml. of methanol was stirred with 50 mg. of prehydrogenated 5% palladium–charcoal catalyst (Baker) in an atmosphere of hydrogen. After an uptake of 0.885 mmoles of hydrogen (15 min. at room temperature), no more gas was consumed. Evaporation of the filtered solution gave 103.2 mg. (100%) of a solid, which on sublimation at 110°/0.005 mm yielded crystals of m.p. 137–137.5°, undepressed by an authentic specimen[6] of methyl α-benzamido-β,β-dimethylacrylate. The infrared absorption spectra (KBr pellets) were superimposable. Similar results were obtained when dioxane was used as a solvent, with the exception that hydrogenation proceeded more slowly.

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Lactones Derived from 3-(17β-Hydroxysteroid-16β-yl)propionic Acids

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A series of steroid delta lactones was prepared for comparison with the previously described gamma lactones. The 3β,17β-diacetoxy-5α-androstan-16β-ylacetic acid, the corresponding 5-unsaturated compound and 3,17β-diacetoxy-1,3,5(10)-estratrien-16β-ylacetic acid were converted by the Arndt–Eistert method into the corresponding propionic acids, which in turn yielded the desired lactones.

As a part of a continuing study of ring D modified steroidal hormones, we are reporting several new lactones having a three-carbon side chain structure at position 16 of the androstane and estrane nuclei. The 16β-acetic acids of the androstane[1] and estrane[2] series described earlier served as intermediates in this work.

The 3β,17β-diacetoxy-5α-androstan-16β-ylacetic acid (I)[1] was converted to its acid chloride II, which in turn was allowed to react with diazomethane to yield the diazo ketone III. The treatment of III with silver oxide in methanolic solution led to the isolation of methyl 3-(3β,17β-diacetoxy-5α-androstan-16β-yl)propionate (IV) in variable yields. The alkaline hydrolysis of the latter (IV) and subsequent acidification of the reaction mixture gave the dihydroxy acid V which was converted to 3-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid lactone (VI) at elevated temperature. The lactone VI was further characterized as the 3-acetate VII.

In order to overcome the erratic yields first encountered in the Arndt–Eistert rearrangement of the diazo ketone III, the latter was treated in benzyl alcohol and 2,4,6-trimethylpyridine at elevated temperature.[3] The resulting intermediate was hydrolyzed and finally subjected to pyrolysis to give the desired lactone VI in reproducible yields.

When VI was oxidized in a two-phase system,[4] 3-(17β-hydroxy-3-oxo-5α-androstan-16β-yl)propionic acid lactone (VIII) was obtained. From the latter (VIII) 3-(17β-hydroxy-3-oxo-1,4-androstadien-16β-yl) propionic acid lactone (IX) was prepared by bromination followed by the elimination of the elements of hydrogen bromide.[5]

In a similar manner the available 3β,17β-diacetoxy-5-androsten-16β-ylacetic acid (X)[1] was converted to the acid chloride XI, which gave rise to the diazo ketone XII. This intermediate (XII) was subjected to the Arndt–Eistert rearrangement under the conditions recommended by Wilds and Meader[3] and the crude inter-

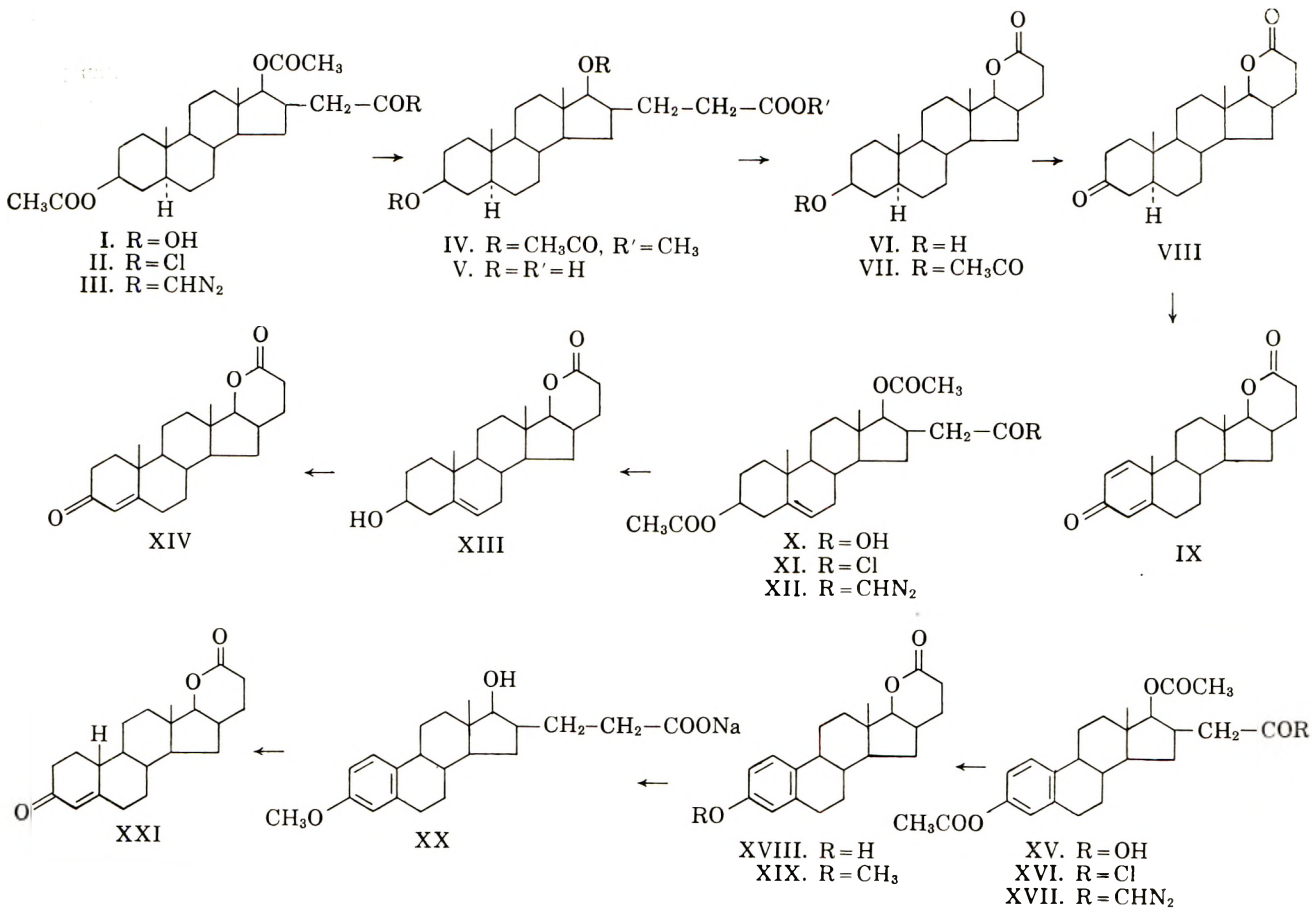
(1) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961).

(2) P. Kurath and W. Cole, *ibid.*, **26**, 4592 (1961).

(3) A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948). We wish to express our thanks to Dr. C. Hummel Winestock for calling attention to this work.

(4) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 139.

(5) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. soc. chim. France*, 366 (1958). P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, **43**, 523 (1960).



mediate was treated as in the case of the corresponding saturated compound above to give, in good yield, 3-(3β,17β-dihydroxy-5-androsten-16β-yl) propionic acid lactone (XIII). The oxidation of XIII under acidic conditions[6] led to the isolation of 3-(17β-hydroxy-3-oxo-4-androsten-16β-yl)propionic acid lactone (XIV).

For the δ-lactones in the estrane series, 3,17β-diacetoxy-1,3,5(10)-estratrien-16β-ylacetic acid (XV)[2] served as starting material. Its acid chloride XVI was converted via the diazo ketone XVII to 3-[3,17β-dihydroxy-1,3,5(10)-estratrien-16β-yl]propionic acid lactone (XVIII), using procedures analogous to those outlined above for the androstane series. The 3-methyl ether XIX was prepared from the crude Arndt–Eistert hydrolysis product or from the phenolic lactone XVIII in the usual manner with dimethyl sulfate in an alkaline solution followed by pyrolysis of the crude intermediate. Treatment of the methoxylactone XIX with sodium hydroxide gave rise to sodium 3-[17β-hydroxy-3-methoxy-1,3,5(10)-estratrien-16β-yl]propionate (XX) and the latter (XX) was subjected to a Birch reduction[7] under typical conditions.[8] The crude intermediate from the Birch reduction was treated with acid and the product heated to yield the desired 3-(17β-hydroxy-3-oxo-4-estren-16β-yl)propionic acid lactone (XXI).

Several of the lactones—*e.g.*, VI, XIII, and XVIII—were obtained after a pyrolysis step. It appeared desirable to investigate if any of the asymmetric centers were changed during this treatment. The mild alkaline hydrolysis of 3-(3β,17β-dihydroxy-5α-androstan-16β-yl) propionic acid lactone (VI) followed by acidification of the reaction mixture gave 3-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid (V) in good yield. It was thus demonstrated that the stereochemistry at C-16 and/or C-17 was not altered during the pyrolysis procedure employed for the lactonization of V to VI. The stereochemical relationship of the lactones described in this paper was demonstrated by comparison of their optical rotations. A positive shift (Δ M_D +297° to +362°) in molecular rotation caused by the 17β-hydroxy-16β-ylpropionic acid lactone structure, as compared with the parent 17β-hydroxy steroid having no substituent at C-16, is observed. The molecular rotation differences are presented in Table I.

Experimental[9]

Methyl 3-(3β,17β-Diacetoxy-5α-androstan-16β-yl)propionate (IV).—A mixture of 5.48 g. of 3β,17β-diacetoxy-5α-androstan-16β-ylacetic acid (I), 2.3 ml. of thionyl chloride, 3 drops of pyridine, and 124 ml. of anhydrous ether was allowed to stand at room temperature with occasional swirling for 3 hr.[10] The reaction mixture was freed from a small amount of insoluble residue by filtration. The solvent was evaporated to leave a residue of 5.763 g. of crude acid chloride II, m.p. 147–149°, $\lambda_{max}^{CHCl_3}$ 5.55 μ, 5.77 μ, 8.05 μ.

The above prepared crude acid chloride II was dissolved in 120 ml. of methylene chloride and added over a period of 15 min. to an ice cold solution of diazomethane, made from 20.5 g. of N-nitrosomethylurea, and 85 ml. of 40% potassium hydroxide solution in 430 ml. of methylene chloride,[11] according to the ex-

(6) P. L. Julian, W. Cole, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945).

(7) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).

(8) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

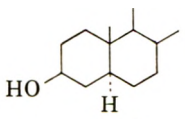
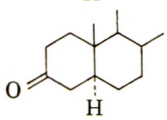
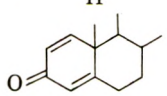
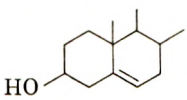
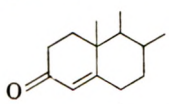
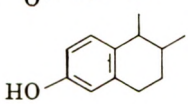
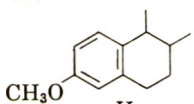
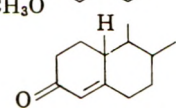
(9) The melting points are uncorrected and were determined on a Fisher–Johns melting point apparatus unless stated otherwise. The optical rotations were measured in a 1-dm. tube in chloroform solution unless stated otherwise. The values have a limit of error of ±2°. The infrared spectra were recorded on a Perkin–Elmer infrared spectrophotometer, Model 21.

(10) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945).

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

TABLE I

COMPARISON OF MOLECULAR ROTATIONS

Partial structure	OH	O	ΔMD
	+12°[a]	+333°[c]	+321° (ethanol, chloroform)
	+87°[a]	+397°[c]	+310° (chloroform)
	+63°[a]	+425°[c]	+362° (chloroform)
	−160°[a]	+138°[c]	+298° (chloroform)
	+340°[a]	+637°[c]	+297° (chloroform)
	+215°[a]	+523°[c]	+308° (dioxane)
	+220°[a]	+517°[c]	+297° (chloroform)
	+151°[b]	+473°[c]	+322° (chloroform)

[a] J.-P. Mathieu and A. Petit, "Pouvoir Rotatoire Naturel, I. Stéroïdes," Masson et Cie., Paris, 1956. [b] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953). [c] See Experimental.

perimental procedure of Wettstein.[12] The resulting solution was left at room temperature for 3 hr., concentrated to about 150 ml., and filtered. Complete removal of the solvent gave a residue of 5.925 g. of crude, partly crystalline diazo ketone III, $\lambda_{max}^{CHCl_3}$ 4.75 μ, 5.78 μ, 6.10 μ, 8.03 μ.

The reaction mixture obtained by dissolving the above prepared diazo ketone III in 330 ml. of methyl alcohol with the addition of 0.80 g. of freshly precipitated silver oxide was stirred under reflux for 30 min. An additional 0.34 g. of silver oxide was added to the suspension during the next 15 min., and stirring and refluxing was continued for 30 min. Finally the reaction mixture was kept at room temperature for 2 hr.[13] The addition of 2.3 g. of activated carbon was followed by warming on the steam bath for 20 min. The solid was removed by filtration of the hot suspension through a short column of silica gel. Evaporation of the solvent left 4.902 g. of brown oil. This was purified by chromatography on 200 g. of alumina of grade III. From the petroleum ether–benzene (1:1) eluates[14] a total of 2.026 g. of crude methyl ester IV was obtained. The compound was recrystallized from petroleum ether to give 1.128 g. of the desired methyl 3-(3β,17β-diacetoxy-5α-androstan-16β-yl)propionate (IV), m.p. 95–96°. A second crop of 0.305 g. melted at 91–93°. The over-all yield from I was 24% in this experiment.[15]

A sample was recrystallized for analysis, m.p. 100–101°, $[\alpha]^{25}D$ +9° (c, 1.13); $\lambda_{max}^{CHCl_3}$ 5.81 μ, 8.02 μ.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.21; H, 8.97.

From the later chromatographic fractions no clean product could be obtained even after repeated chromatography.

3-(3β,17β-Dihydroxy-5α-androstan-16β-yl)propionic Acid (V).—The mixture of 1.006 g. of IV, 1.34 g. of potassium hydroxide pellets, 50 ml. of methyl alcohol, and 5 ml. of water was refluxed for 2 hr. Distilled water (130 ml.) was added and the solution was concentrated to about 70 ml. The resulting suspension was diluted with 150 ml. of water, warmed on the steam bath, and acidified with 100 ml. of 2 *N* hydrochloric acid. The acidic suspension was warmed for 20 min. and allowed to cool. The precipitate was collected on a filter, washed with several small amounts of water and dried at 75° under reduced pressure overnight. Recrystallization of the crude acid from acetone yielded 0.591 g. (75%) of the hydroxy acid V, m.p. 199–200°, resolidification at 204–208°, second melting at 236–238°.

A sample was recrystallized for analysis, m.p. 205–206°, resolidification at 210 and second m.p. 237–239°; $[\alpha]^{23}D$ +9° (c, 0.677 dioxane); λ_{max}^{KBr} 3.00 μ, 3.75–4.5 μ, 5.86 μ.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.30; H, 10.02.

3-(3β,17β-Dihydroxy-5α-androstan-16β-yl)propionic Acid Lactone (VI). A. From the Dihydroxy Acid V.—The dihydroxy acid V was sublimed at 200° ± 10° under high vacuum. The lactone VI was recrystallized from acetone to a constant m.p. 239–240°; $[\alpha]^{24}D$ +96° (c, 1.024); λ_{max}^{Nujol} 2.96 μ, 5.73 μ, 5.85 μ; $\lambda_{max}^{pyridine}$ 5.77 μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.90. Found: C, 76.38; H, 9.83.

B. Without Isolation of the Dihydroxy Acid V; Using the Procedure of Wilds and Meader.[3]—The solution of the crude diazo ketone III, prepared from 3.075 g. of 3β,17β-diacetoxy-5α-androstan-16β-ylacetic acid (I) as described above, in 20 ml. of 2,4,6-trimethylpyridine and 20 ml. of benzyl alcohol in an atmosphere of nitrogen was immersed in an oil bath heated to 190°. The mixture was allowed to react for 10 min. and then left to cool. Ether was added and the solution was washed with 2 *N* hydrochloric acid and water, dried, and evaporated. The residue was dissolved in 80 ml. of methyl alcohol and 20 ml. of water and refluxed for 2 hr. with 4.0 g. of potassium hydroxide. The alkaline solution was diluted with 500 ml. of water and extracted with ether, the ether solution was extracted with several portions of 0.2 *N* sodium hydroxide solution and water and then discarded. The alkaline phase was made acidic by the addition of 10% hydrochloric acid and warmed on the steam bath for a short time. After the suspension cooled, the precipitate was collected on a filter, washed with several small amounts of water and dried at 75° under reduced pressure. Sublimation of the product at 200° ± 10° under high vacuum and two recrystallizations from acetone gave 0.959 g. (39% based on I) of 3-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid lactone (VI), m.p. 236–237°. From the mother liquors a second crop of 0.216 g., m.p. 228–230°, was obtained.

A sample was recrystallized to a constant m.p. 239–240°; $[\alpha]^{25}D$ +96° (c, 1.022); λ_{max}^{KBr} 2.93 μ, 5.73 μ, 5.85 μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.90. Found: C, 76.14; H, 10.00.

The products from preparations A and B are identical.

3-(3β-Acetoxy-17β-hydroxy-5α-androstan-16β-yl)propionic Acid Lactone (VII).—A mixture of 0.060 g. of VI, 2 ml. of acetic anhydride and 4 ml. of pyridine was allowed to stand at room temperature overnight. The solvents were evaporated under reduced pressure and an ether solution of the crystalline residue was washed with 2 *N* hydrochloric acid, 0.2 *N* sodium hydroxide solution, and water. The ether solution was dried and evaporated, and the residue was recrystallized from acetone–petroleum ether to give 0.056 g. (83%) of the acetate VII, m.p. 198–199°.

Further recrystallization gave an analytical sample, m.p. 201–202°; $[\alpha]^{23}D$ +75° (c, 1.023); $\lambda_{max}^{CHCl_3}$ 5.81 μ, 8.00 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.98; H, 9.32.

3-(17β-Hydroxy-3-oxo-5α-androstan-16β-yl)propionic Acid Lactone (VIII).—To the cooled and stirred mixture of 0.86 g. of sodium dichromate, 1.2 ml. of concentrated sulfuric acid, 0.6 ml. of acetic acid, 3.7 ml. of water, and 28 ml. of benzene was added 0.578 g. of the lactone VI. The reaction mixture was kept immersed in an ice bath for 20 min. and then stirred at room temperature for 16 hr.[4] The mixture was diluted with 200 ml. of benzene; the water layer was separated and extracted with two

(12) A. Wettstein, *Helv. Chim. Acta*, **24**, 311 (1941).

(13) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(14) The petroleum ether fraction boiling at 90–100° was used in this work.

(15) This represents one of the better yields; other experiments gave only 10–20% yield.

200-ml. portions of benzene. The benzene extract was washed with water, dried, and evaporated to leave a residue of 0.551 g. of crystalline material. Recrystallization from acetone–petroleum ether gave 0.430 g. (75%) of the desired compound VIII, m.p. 241–243°. A second crop amounted to 0.052 g., m.p. 221–223°.

The analytical sample melted at 243–244°; $[\alpha]^{24}D$ +115° (*c*, 1.014); $\lambda_{max}^{CHCl_3}$ 5.80 μ, 5.85 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.71; H, 9.37. Found: C, 76.61; H, 9.42.

3-(17β-Hydroxy-3-oxo-1,4-androstadien-16β-yl)propionic Acid Lactone (IX).—A solution of the lactone VIII (0.673 g.) in 20 ml. of acetic acid was treated with 1.02 g. of 30% hydrogen bromide in acetic acid and then with 0.68 g. of bromine in 3 ml. of acetic acid with swirling at about 18° for 5 min.; 3 ml. of acetic acid was added and the reaction mixture was allowed to stand at room temperature for 30 min. with occasional swirling. After the addition of 80 ml. of water, the precipitate was collected on a filter, washed with several small amounts of water, and dissolved in 200 ml. of benzene. The benzene solution was washed with water and evaporated to dryness at 40° under reduced pressure. The crude dibromide (1.086 g.) was dissolved in 23 ml. of dimethylformamide and added, with stirring, to 0.98 g. of lithium bromide and 0.98 g. of lithium carbonate at 95°, under nitrogen, and the mixture was stirred overnight.[5] The cooled reaction mixture was diluted with 70 ml. of distilled water and 17.5 ml. of 2*N* hydrochloric acid and then extracted with three 120-ml. portions of methylene chloride. The organic phase was washed to neutrality with water, dried and evaporated to leave a residue of 0.762 g. of crude oily material, which was purified by chromatography on 45 g. of silica gel. From the benzene–ether (1:1) and ether eluates a total of 0.455 g. of IX was obtained. Recrystallization from acetone–petroleum ether gave 0.353 g. (53%) of the desired compound IX, m.p. 200–201°. After sublimation at 210° and recrystallization from acetone–petroleum ether, 0.163 g. of product, m.p. 204–205°, was isolated.

An analytical sample melted at 206–207°; $[\alpha]^{24}D$ +125° (*c*, 1.032); $\lambda_{max}^{CH_3OH}$ 243 mμ (ε 16,500); $\lambda_{max}^{CHCl_3}$ 5.79 μ, 6.02 μ, 6.16 μ, 6.23 μ.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.31.

3-(3β,17β-Dihydroxy-5-androsten-16β-yl)propionic Acid Lactone (XIII).—The acid chloride XI (4.015 g., m.p. 143–145°) was prepared from 3.90 g. of 3β,17β-diacetoxy-5-androsten-16β-ylacetic acid (X), 1.8 ml. of thionyl chloride, and 1 drop of pyridine in 100 ml. of ether.[10] The crude intermediate XI was converted to the diazo ketone XII (4.19 g., m.p. 225–235° dec.; $\lambda_{max}^{CHCl_3}$ 4.76 μ, 5.79 μ, 6.10 μ, 8.04 μ) in methylene chloride solution with diazomethane according to the procedure of Wettstein.[12] A mixture of the crude diazo ketone XII, 30 ml. of 2,4,6-trimethylpyridine, and 30 ml. of benzyl alcohol was immersed into an oil bath at 200° for 10 min. according to the procedure of Wilds and Meader,[3] and worked up as in the preparation of VI. The reaction product was sublimed at 220° under high vacuum and recrystallized from acetone to give 1.735 g. (56%) of 3-(3β,17β-dihydroxy-5-androsten-16β-yl) propionic acid lactone (XIII), m.p. 259–260°. A second crop of 0.409 g. of less pure product, m.p. 252–253°, was obtained from the mother liquors.

An analytical sample melted at 259–260°; $[\alpha]^{23}D$ +40° (*c*, 0.988); $\lambda_{max}^{CHCl_3}$ 2.77 μ, 2.90 μ, 5.81μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.71; H, 9.37. Found: C, 76.43; H, 9.44.

3-(17β-Hydroxy-3-oxo-4-androsten-16β-yl)propionic Acid Lactone (XIV).—The solution of 1.88 g. of the lactone XIII in 80 ml. of glacial acetic acid was treated successively with 0.80 g. of bromine in 8 ml. of glacial acetic acid, 0.73 g. of chromic anhydride in 1.5 ml. of water and 11 ml. of acetic acid for 2 hr. Chromous chloride solution (80 ml., 1 *N*) was added and the solution was allowed to stand under nitrogen for 2 hr.[6] The reaction mixture was diluted with 700 ml. of distilled water and the precipitate was separated by filtration and washed with several small portions of water. The product was dried at 75° *in vacuo* overnight and recrystallized from acetone–petroleum ether and then from acetone to yield 0.724 g. of the desired lactone XIV, m.p. 241–242°. A second crop of 0.581 g. melted at 235–240°. The yield amounts to 70%.

A part of the first crop was sublimed and recrystallized from acetone–petroleum ether; m.p. 244–245°; $[\alpha]^{24}D$ +186° (*c*, 1.14); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,300); $\lambda_{max}^{CHCl_3}$ 5.81 μ, 6.01 μ, 6.18 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.20; H, 8.87.

3-[3,17β-Dihydroxy-1,3,5(10)-estratrien-16β-yl]propionic Acid Lactone (XVIII).—The acid XV (3.18 g.) was allowed to react with 1.5 ml. of thionyl chloride and 1 drop of pyridine in 150 ml. of ether[10] to yield 3.40 g. of the crude acid chloride XVI, m.p. 124–126°; $\lambda_{max}^{CHCl_3}$ 5.67 μ, 5.77 μ, 6.24 μ, 6.34 μ, 6.72 μ. The 3,17β-diacetoxy-1,3,5(10)-estratrien-16β-ylacetic acid chloride (XVI) was added to a solution of diazomethane in methylene chloride[13] to give, after workup, 3.71 g. of the diazo ketone XVII, m.p. 126–128° dec.; $\lambda_{max}^{CHCl_3}$ 4.76 μ, 5.78 μ, 6.10 μ, 6.72 μ.

The diazo ketone XVII prepared above was treated in 22.5 ml. of 2,4,6-trimethylpyridine and 22.5 ml. of benzyl alcohol at 200° for 15 min. under nitrogen[3] and worked up as described above in the case of the corresponding compounds in the androstane series. The reaction product was pyrolyzed at 200° under high vacuum for 12 hr. and purified by chromatography on 150 g. of silica gel. The eluates with benzene–ether (1:1), ether, and ether–acetone (9:1, 8:2) gave, after evaporation of the solvent, 1.289 g. of the crude lactone XVIII. After two recrystallizations from acetone 0.651 g. (26% based on XV) of the desired 3-[3,17β-dihydroxy-1,3,5(10)-estratrien-16β-yl]propionic acid lactone (XVIII) was isolated; this compound decomposed above 320°.

A sample was recrystallized twice more for analysis; decomposition point above 320°; $[\alpha]^{23}D$ +160° (c, 0.55 dioxane); $\lambda_{min}^{CH_3OH}$ 248 mμ (ε 80); $\lambda_{max}^{CH_3OH}$ 280 mμ (ε 2,600); $\lambda_{max}^{CHCl_3}$ 3.03 μ, 5.88 μ, 6.18 μ, 6.31 μ, 6.68 μ.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.49; H, 8.06.

3-[17β-Hydroxy-3-methoxy-1,3,5(10)-estratrien-16β-yl]propionic Acid Lactone (XIX).—The crude hydrolysis product of the Arndt-Eistert rearrangement (2.17 g.), made from 3.15 g. of XV as indicated above, was dissolved in 58 ml. of methyl alcohol and 58 ml. of water in the presence of 1.86 g. of sodium hydroxide pellets and warmed to 50°. To this mixture was added with stirring 4 ml. of dimethyl sulfate in 4.5 ml. of methyl alcohol over a period of 15 min.[6] The dropping funnel was rinsed with 4.5 ml. of methyl alcohol and the reaction mixture was stirred at 50° for 3 hr. The resulting suspension was stirred for 2 hr. at room temperature and was allowed to stand overnight. Sodium hydroxide pellets (0.40 g.) were added and the mixture was refluxed for 2 hr. The resulting slurry was diluted with 580 ml. of water and made acidic with 60 ml. of 5 *N* sulfuric acid. The acidic mixture was warmed on the steam bath for 40 min. and allowed to cool. The solid was collected on a filter, washed with water, dried at 75° under reduced pressure, and pyrolyzed at 210° for 24 hr. The compound was purified by chromatography[17] on 220 g. of silica gel. The residues from the benzene–ether (9:1) eluates gave, after sublimation at 220° under high vacuum and subsequent recrystallization from acetone–petroleum ether, 1.114 g. (43% based on XV) of the methoxylactone XIX, m.p. 224–226°.

A sample was recrystallized for analysis; m.p. 224–225°; $[\alpha]^{24}D$ +152° (c, 1.05); $\lambda_{max}^{CHCl_3}$ 5.80 μ, 6.21 μ, 6.35 μ, 6.67 μ.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.51; H, 8.43.

The same compound XIX was obtained from the phenolic lactone XVIII on similar treatment.

Sodium 3-[17β-Hydroxy-3-methoxy-1,3,5(10)-estratrien-16β-yl]propionate (XX).—A mixture of 2.309 g. of the lactone XIX and 17 ml. of a 2 *N* aqueous sodium hydroxide solution in 130 ml. of methyl alcohol was refluxed gently on the steam bath for 30 min. The solution was diluted with 140 ml. of water and concentrated under reduced pressure to about 150 ml. The suspension was warmed on the steam bath for 40 min. and allowed to cool. The crystalline compound was collected on a filter and washed with 130 ml. of ice cold water. The sodium salt XX amounted to 2.532 g. (98%), carbonization at 230–233° (capillary).

3-(17β-Hydroxy-3-oxo-4-estren-16β-yl)propionic Acid Lactone (XXI).—A suspension of 2.53 g. of the sodium salt XX in 40 ml. of *t*-butyl alcohol and 40 ml. of tetrahydrofuran was diluted to about 400 ml. with liquid ammonia. The reaction mixture was cooled in a Dry Ice–acetone bath and 1.62 g. of lithium wire was added in small pieces to the stirred solution over a period of 15 min.[8] After 4 hr. 0.25 g. more of the lithium wire was added. Fifteen minutes later 7.5 ml. of anhydrous ethyl alcohol was added

(16) O. Schindler, *Helv. Chim. Acta*, **43**, 754 (1960).

(17) We express our thanks to Mr. Michael H. Evans for technical assistance in this experiment.

with stirring and continued cooling. This was followed by the addition of a second 7.5-ml. portion of ethyl alcohol 25 min. later. The cooling bath was removed and the ammonia was allowed to evaporate in a stream of nitrogen.

The reaction mixture was diluted with 450 ml. of distilled water, brought to pH 5 by the addition of 600 ml. of 1 *N* oxalic acid, and extracted with 800 ml. of ether. The water phase was separated and extracted with two successive portions of 400 ml. of ether. The ether extracts were washed with water, combined, dried, and evaporated to leave a solid residue weighing 2.55 g. A mixture of this crude Birch reduction product, 24 ml. of 2 *N* hydrochloric acid, and 12 ml. of water in 120 ml. of methyl alcohol was warmed to a gentle reflux for 40 min. After the addition of 35 ml. of 2 *N* sodium hydroxide solution the reaction mixture was warmed for an additional 15 min. under nitrogen. This was followed by the addition of 250 ml. of water and concentration of the suspension to about 200 ml. under vacuum. The slurry was made acidic by the addition of 100 ml. of 10% hydrochloric acid, warmed on the steam bath for 15 min., and allowed to cool. The precipitate was collected on a filter, washed with several small amounts of water and dried overnight at 60° under reduced pressure to leave 2.25 g. of a mixture, m.p. 166–182°. The above product was pyrolyzed at 220° under high vacuum for 60 hr. and the reaction product was purified by chromatography[17] on 220 g. of silica gel. The benzene–ether (8:2) eluates gave, after evaporation of the solvent and recrystallization from acetone–petroleum ether, 0.364 g. (16%) of unreduced methoxylactone XIX, m.p. 223–225° (identified by mixed melting point determination and comparison of the infrared spectrum with that of a reference sample of XIX).

The residues from the ether and ether–acetone (9:1) eluates yielded 1.281 g. of impure 3-(17β-hydroxy-3-oxo-4-estren-16β-yl)-propionic acid lactone (XXI). The compound was recrystallized from acetone–petroleum ether to yield 0.669 g. of the lactone XXI, m.p. 218–220°. A second crop amounted to 0.133 g., m.p. 215–218°, bringing the yield to 37%.

A part of the first crop was sublimed under high vacuum and recrystallized from acetone–petroleum ether to a constant melting point of 223–224°. The sample had $[\alpha]^{26}D$ +144° (*c*, 1.117); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,400) $\lambda_{max}^{CHCl_3}$ 5.80 μ, 6.02 μ, 6.18 μ.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.88; H, 8.88.

Potassium Carbonate Hydrolysis of 3-(3β,17β-Dihydroxy-5α-androstan-16β-yl)propionic Acid Lactone (VI).[17]—A mixture of 0.346 g. of the lactone VI, 0.26 g. of potassium carbonate, 2.6 ml. of water, and 21 ml. of methyl alcohol was swirled to obtain a solution and allowed to stand at room temperature for 60 hr. The addition of 25 ml. of water was followed by concentration of the suspension to about 25 ml. under reduced pressure at room temperature. The resulting slurry was made acidic with 30 ml. of 10% hydrochloric acid; the precipitate was collected on a filter, washed with several small amounts of water, and dried at 60° under reduced pressure overnight. The compound was recrystallized from acetone to give 0.273 g. (75%) of the dihydroxy acid V, m.p. 196–197°, resolidification at 200°, and second melting at 224–227°.

A sample was recrystallized to a constant melting point of 202–203°, resolidification at 208–210°, and second melting point at 235–238°. The compound dried at 65° had $[\alpha]D^{25}$ +8° (*c*, 0.588 dioxane); λ_{max}^{KBr} 3.00 μ, 3.75–4.5 μ, 5.86 μ.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.33; H, 9.78.

The above compound was identical to a reference sample of 3-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid (V).

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The Kinetics of the Silver Metal-catalyzed Cannizzaro Reaction[1]

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The kinetics of the silver metal-catalyzed Cannizzaro reaction of benzaldehyde and sodium hydroxide in 50% aqueous ethanol has been measured, and it has been found that the order of the reaction varies from initially first order in benzaldehyde to zero order in the latter stages of the reaction, that the reaction is linearly dependent on the amount of silver metal catalyst used, is zero order in sodium hydroxide, and apparently takes place on the catalyst surface. The rate constant for the first 7–12% of reaction at 30° was found to be 4.9 ± 0.3 × 10^{-3} $min.^{-1}$ on the basis of 20 mg. of silver per 100 ml. of solution, and a k_Hk_D rate factor of 6.8 ± 0.5 measured with benzaldehyde-α-d_1. Benzyl benzoate could not be detected among the reaction products, although it was shown that the ester is saponified at a slower rate than the rate of formation of products from the reaction. A mechanism has been proposed which is consistent with the results and all known facts.

The Cannizzaro reaction is the disproportionation of two aldehyde molecules to form the corresponding carboxylate anion and alcohol in the presence of alkali. It has been previously reported that the rate for this reaction with benzaldehyde, as well as with many of its derivatives, was second order in aldehyde and first order in base.[3] Strong evidence has been furnished that a hydride transfer occurs between two aldehyde groups and that a hydrogen transfer from solvent to aldehyde is not involved.[4,5] Thus, when a Cannizzaro reaction was carried out with benzaldehyde in deuterium oxide solution, it was found that the resulting benzyl alcohol contained no deuterium atom bonded to carbon.[4,5] Furthermore, when benzaldehyde-α-d_1 was caused to dismutate in the presence of base, benzyl alcohol-α,α-d_2 ($C_6H_5CD_2OH$) was formed. Evidence that the hydride transfer takes place in the rate-determining step is that a k_H/k_D value of 1.8 has been found for the disproportionation of benzaldehyde.[6] A reaction scheme frequently proposed is

$$C_6H_5CHO + OH^- \underset{}{\overset{\text{fast}}{\rightleftharpoons}} C_6H_5-\underset{O^-}{\underset{|}{C}}H-OH$$

$$C_6H_5-\underset{O^-}{\underset{|}{C}}H-OH + C_6H_5CHO \xrightarrow{\text{slow}} C_6H_5CO_2H + C_6H_5CH_2O^-$$

$$C_6H_5CO_2H + C_6H_5CH_2O^- \xrightarrow{\text{fast}} C_6H_5CO_2^- + C_6H_5CH_2OH$$

(1) From the Ph.D. thesis of D. R. L., University of Connecticut, 1962. The complete compilation of the experiments can be found in this thesis. Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 20Q.

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(3) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 259.

(4) H. Fredenhagen and K. F. Bonhoeffer, *Z. physik Chem.*, **181A**, 379 (1938).

(5) C. R. Hauser, P. J. Hamrick, Jr., and A. F. Stewart, *J. Org. Chem.*, **21**, 260 (1956).

Benzyl benzoate has been found to be an isolable product under certain reaction conditions.[7]

It has been reported that the presence of silver causes the dismutation of benzaldehyde to occur at an accelerated rate and that *o*- and *p*-hydroxybenzaldehydes which do not undergo the Cannizzaro reaction under normal conditions,[8] do so in the presence of an active silver catalyst to form the corresponding acid and alcohol products.[9,10] The silver by complexing apparently changes the electronic nature of the hydroxyaldehyde.

It has also been observed that the presence of an alcohol has no apparent effect on the mechanism of the Cannizzaro reaction.[11]

Results

To establish a set of conditions under which the silver metal-catalyzed Cannizzaro reaction would proceed at a reasonable and readily followed rate and to determine the contribution made to the reaction products, if any, by a noncatalyzed reaction, a number of exploratory experiments (1–21)[1] some of which are summarized in Table I, were carried out. In addition, it was necessary to find an effective silver catalyst, and for this purpose three different silver preparations (no. 1–3) were tested in those initial experiments carried out in the presence of a catalyst. Some of the exploratory experiments were conducted in an effort to determine the reaction order. All Cannizzaro reactions were carried out with benzaldehyde and sodium hydroxide in 50% (by weight) aqueous ethanol, and it was found that equimolar quantities of alcohol and acid were produced.

TABLE I
EXPLORATORY EXPERIMENTS

No.[a]	Solvent, ml.	C_6H_5CHO, mole	NaOH, mole	Silver,[b] g.	Temp., °C.	Time, min.	Per cent completion
6	69	0.197	0.0292	3.15[c]	82.5	1230	0
8	90	.0883	.0907	..	75	300	75
9	90	.0885	.0910	5.18[d]	75	60	100
17	100[e]	.0203	.00872	0.244	27	120	80
18	100[e]	.0192	.00825	.2004	30	180	77
19	90[e]	.0995	.00710	.1998	30	120	87
20	100[e]	.0194	.00900	.1003	30	395	35

[a] Samples were removed at various times from all reaction mixtures. [b] Silver no. 3 unless noted otherwise. [c] Silver no. 1. [d] Silver no. 2. [e] All or in part as sodium hydroxide solution.

A limiting set of conditions of temperature and concentrations, below which no reaction of any kind takes place, was provided by experiment 6, for which no reaction occurred. Experiment 6, furthermore, was conducted in the presence of silver catalyst no. 1, which was thus proved to be ineffective. In experiment 9, carried out with catalyst no. 2, the reaction was brought to completion in less than one fifth the time required to bring about 75% reaction in experiment 8, which was carried out under similar conditions but in the absence of catalyst. Thus it was established that catalysis of the Cannizzaro reaction by metallic silver, under the conditions of experiment 9 at least, was possible. The effectiveness of silver catalyst no. 3 was tested in experiment 17 under conditions such that no noncatalyzed reaction was possible. This catalyst was effective in bringing about approximately 40 and 80% reaction after one and two hours, respectively. In addition, experiment 17 provided a set of conditions under which the reaction appeared to proceed at a reasonable and readily followed rate. Because it was desirable to carry out the reactions at a relatively low temperature, and yet, one which could be controlled conveniently, 30° was chosen as the reaction temperature for all subsequent experiments. Benzyl benzoate was occasionally looked for in the gas chromatographic analyses of these experiments and was always found to be absent.

Silver catalyst no. 3 was used in experiments 18–20 which were carried out in an effort to determine the order of the reaction. The results of experiment 18 indicated that, under the reaction conditions, the rate was initially rapid (72% reaction occurring during the first 90-min. period), and that it changed to a slow constant value in the latter stages (5% additional reaction occurring during the second 90-min. period). Similar results were observed for experiment 19 in which 70% of the reaction took place within the first 30 min. and 17% took place within the following 90 min. The slow constant reaction rate was made manifest in experiment 20 in which it was brought about at an earlier stage of the reaction by using less silver catalyst, for it was observed that the rate was virtually constant after 22% reaction (120 min.) and that only 13% additional reaction occurred within the 275-min. period which followed.

From the results of the last three experiments, it was apparent that the order of the reaction under study changed from a value, thus far undetermined, to zero order (the slow reaction rate). An attempt was made to determine the initial order of the reaction, with the data collected from experiments 19 and 20, by conventional methods which included the method of isolation, the differential method (both graphically and by calculation), the time required to complete a given fraction of the reaction, and the method of integration.[12] The results of these determinations indicated that the reaction order changed greatly with time, but were otherwise meaningless since no agreement could be found among values obtained from the various methods.

The necessity of investigating the initial stages of the reaction more closely became apparent. The principal problems involved in studying this area were the rapidity of the reaction and the consequent difficulty in making accurate measurements. For the purpose of determining the initial order of the reaction a modification of the differential method[13] was devised. The method is dependent on the fact that the rate of a reaction of a given order is linearly dependent on the concentration of reactant raised to a power of the given order, $dx/dt = kc^n$, where dx/dt is the rate of formation of products at a given time, c is the concentration of reactant at a given time, k is the proportionality con-

(6) K. B. Wiberg, *J. Am. Chem. Soc.*, **76**, 5371 (1954).
(7) T. A. Geissman, *Org. Reactions*, **II**, 94 (1944).
(8) G. I. Kudryavtsev and E. A. Shilov, *Dokl. Akad. Nauk SSSR*, **64**, 73 (1949); *Chem. Abstr.*, **43**, 4651 (1951).
(9) I. A. Pearl, *J. Am. Chem. Soc.*, **67**, 1628 (1945).
(10) I. A. Pearl, *J. Org. Chem.*, **12**, 89 (1947).
(11) M. S. Kharasch, and R. H. Snyder, *ibid.*, **14**, 819 (1949).
(12) S. Glasstone, "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., Princeton, N. J., 1946, p. 1066.
(13) Ref. 12, p. 1067.

stant, and n is the order of reaction with respect to the reactant. For two different concentrations, $(dx/dt)_1 = kc_1^n$ and $(dx/dt)_2 = kc_2^n$, and the proportionality constants are calculated from these equations with different values of n. The value of n which best correlates the data, as determined by calculation of the constant k, is selected as the correct order of the reaction with respect to the reactant varied.

Experiments 22–25[1] were carried out with the intention of determining the initial order of the reaction by the above-described method. The amount of one of the reagents was varied from one reaction to another (within a given set of experiments) in the following ratios: The amount of silver was varied in a ratio of 1:4.00 (five experiments). The amount of silver was varied in a ratio of 1:2.00 (two experiments). The amount of benzaldehyde was varied in a ratio of 1:1.85 (three experiments), and the amount of sodium hydroxide was varied in a ratio of 1:2.00 (three experiments). The value of dx/dt was approximately determined by measuring $\Delta x/\Delta t$ within the first few per cent of reaction, and a proportionality constant was calculated for each set of experiments. Thus, the proportionality constants were found for those sets of experiments in which the amount of silver was varied, when calculated from conversion rate/mg. Ag ($4.0 \pm 0.1 \times 10^{-6}$ mole $C_6H_5CO_2H$/min. × mg. Ag), and for the set of experiments in which the amount of benzaldehyde was varied, when calculated from conversion rate/mole C_6H_5CHO ($8.1 \pm 0.1 \times 10^{-3}$ mole $C_6H_5CO_2H$/min. × mole C_6H_5CHO). A constant conversion rate ($2.30 \pm 0.04 \times 10^{-4}$ mole $C_6H_5CO_2$/min.) was observed for the set of experiments in which the amount of sodium hydroxide was varied. The results indicated that the reaction rate is linearly dependent on the amounts of silver catalyst and benzaldehyde and that it is independent of sodium hydroxide concentration.

Because it had been found that an average of 0.3% benzoic acid was contained in the samples of benzaldehyde used, it was of interest to determine if a small additional amount of benzoic acid affected the results. Thus experiment 26A, Table II, was carried out for comparison with experiment 26B, which contained benzoic acid in a ratio to benzaldehyde of about 1:100, but which otherwise was run under the same conditions. A negligible difference between the results of the experiments was observed. Although precautionary measures were taken, exposure of benzaldehyde samples to the atmosphere could not be completely avoided. To determine if such exposure affected the results, experiment 27A was carried out for comparison with experiment 27B, which was run with a sample of benzaldehyde, aerated immediately before use, but which otherwise was run under the same conditions. Virtually no difference was observed in the results of these experiments.

TABLE II

EXPERIMENTS TO INVESTIGATE POSSIBLE COMPLICATING FACTORS[a]

No.	C_6H_5CHO, mole × 10^2	NaOH, mole × 10^2	Silver,[b] mg.	Time, min.	Yield $C_6H_5CO_2H$, mole × 10^2
26A	1.83	0.454	40.0	3	0.0630
26B[c]	1.83	.456	40.0	3	.0600
27A	1.83	.459	40.0	3	.0471
27B	1.83[d]	.459	40.0	3	.0468
28–29[e]	1.07	2.60	..	5	.00047
101	1.07	2.60	20.0	5	.049

[a] All reaction mixtures contained 100 ml. of solvent. [b] Silver no. 5. [c] Benzoic acid (4.1×10^{-5} mole) added. [d] Benzaldehyde taken from 5-ml. sample aerated (10 min. at 4.7 ml./min.) immediately before use. [e] Contained silver oxide (4.7×10^{-6} mole).

Since there existed the possibility that catalysis was due to silver oxide contained in the silver metal samples, it was of interest to test the catalytic property of the oxide. Thus experiments 28 and 29 contained no silver but instead contained silver oxide in an amount equivalent to that which would be contained in a 20.0-mg. sample of silver, 5% of which was in the form of the oxide. The amount of benzoic acid produced, as determined by titration, was stoichiometrically equivalent to that expected from the oxidation of benzaldehyde by the silver oxide and less than 1/100 of that which was produced under the same conditions (experiment 101) with 20.0 mg. of silver metal.

Experiments 37–100 are summarized in Table III where the amounts of reactants and catalyst were varied among these reactions by the following ratios: silver, 5.0; benzaldehyde, 3.4; and sodium hydroxide, 4.6. The ratios of the reactants and catalyst with each other were varied as follows: benzaldehyde–sodium hydroxide, 1.1:4.0; silver (g.)–sodium hydroxide (mole), 2.2:10; and silver (g.)–benzaldehyde (mole), 0.11:0.49. Conversion rates ($\Delta C_6H_5CO_2H/\Delta t$) were measured and were found to be essentially identical when placed on the same molar basis of benzaldehyde to the first power and when corrected to the same amount of silver catalyst. A proportionality constant was thus obtained, in the manner previously described, for the differential method of determining reaction

TABLE III

EXPERIMENTS TO ESTABLISH REACTION ORDER AND CORRESPONDING RATE CONSTANTS[a]

No.	C_6H_5CHO, mole × 10^2	NaOH, mole × 10^2	Silver, mg.	Time, min.	Rate constant,[b] $min.^{-1}$ × 10^3
37	1.95	0.975	50.0[c]	2	4.5
38	1.95	.488	50.0[c]	2	5.1
39	2.03	.970	100.0[d]	2	4.9
40	1.83	.920	40.0[d]	1.5	4.5
41	1.83	.920	20.0[d]	3	4.8
42–43	1.83	.458	40.0[d]	3	4.3 ± 0.0
44	1.83	.458	20.0[d]	6	4.7
45, 47	1.83	.454	40.0	3	4.5 ± 0.1
46	1.83	.454	20.0	3	5.6
48–49	1.83	.456	40.0	3	5.0
50[e]	1.83	.456	40.0	3	4.9
51, 53	1.83	.459	40.0	3	4.4 ± 0.1
52	0.99	.459	40.0	5.55	5.5
54	.99	.459	40.0	4.33	5.5
55–57	1.07	.105	20.0	5[f]	4.9 ± 0.3
58–67	1.07	.052	20.0	5	5.1 ± 0.3
68–78	0.592	.052	20.0	8	4.7 ± 0.2
79–81	.816	.0523	20.0	6	4.8 ± 0.2
82–89	1.35	.0523	20.0	4	4.6 ± 0.2
90–94	0.592	.104	20.0	5	5.2 ± 0.2
95–100	.592	.207	20.0	5	5.4 ± 0.3

[a] All reaction mixtures contained 100 ml. of solvent and silver no. 5 unless noted otherwise. [b] $\Delta C_6H_5CO_2H/\Delta t \times C_6H_5CHO$; based on 20.0 mg. silver. [c] Silver no. 3. [d] Silver no. 4. [e] Benzoic acid (4.1×10^{-5} mole) added. [f] Time for one run was 2.5 min.

order, which is the reaction rate constant for the reaction with a given amount of catalyst. It should be noted that although experiments 37 and 38 contained silver no. 3, experiments 39–44 silver no. 4 and experiments 45–100 silver no. 5, their rate constants are essentially the same.

The average reaction rate constant for experiments 37–100 (64 experiments as described in Table III) was found to be $4.9 \pm 0.3 \times 10^{-3}$ min.$^{-1}$, based on reactions run to 7–12% conversion.

Experiments 101–104[1] were carried out under identical conditions and contained sodium hydroxide in a concentration higher than that of any of the other experiments for which a reaction rate constant was calculated. The average rate constant for these four reactions was abnormally high (9.6×10^{-3} min.$^{-1}$), and it was apparent that a different reaction begins to take place at this concentration.

Because benzyl benzoate could not be detected among the reaction products, it was of interest to determine the fate of the ester under the conditions of the reaction. Thus, benzyl benzoate, in an amount equivalent to that which could be produced from benzaldehyde after 5% reaction, was allowed to undergo saponification under Cannizzaro reaction conditions for the period of time required for benzaldehyde to undergo 5% reaction. Complete saponification of the ester would be expected if it were an intermediate in this reaction. However, only 10% saponification was found to have occurred in two identical experiments.

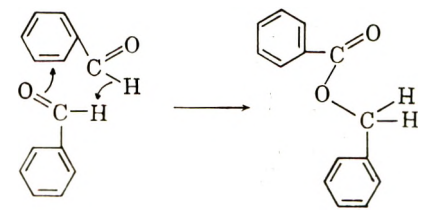
Cannizzaro reactions were carried out, on a scale one half that normally used, in deuterated solvent, to the extent of 13, 25, and 71% reaction of benzaldehyde. Infrared analysis showed that no exchange had taken place between the deuterium of the solvent and the carbonyl hydrogen of benzaldehyde. Cannizzaro reactions were also carried out with benzaldehyde-α-d_1 and their conversion rates were measured. The average reaction rate constant, k_D, from three identical experiments was $7.2 \pm 0.3 \times 10^{-4}$ min.$^{-1}$, and benzyl alcohol-α,α-d_2 was isolated and identified. Compared to the average reaction rate constant, k_D, obtained from experiments 37–100, the k_H/k_D value of this reaction was found to be 6.8 ± 0.5. A method for the determination of the k_H/k_D rate factor by a competitive reaction of benzaldehyde and benzaldehyde-α-d_1 was considered; however, due to the complexity of the reaction, it was found to be inapplicable.

Discussion

This investigation has provided information from which a reasonable mechanism may be proposed for the silver metal-catalyzed Cannizzaro reaction of benzaldehyde and sodium hydroxide. A comprehensive explanation of the following results must be incorporated in such a mechanism. The rate of the dismutation reaction is linearly dependent on the amount of catalyst used, is initially first order in benzaldehyde and zero order in base, and is zero order over-all in the latter stages. In addition, a k_H/k_D rate factor of 6.8 was found for benzaldehyde and benzaldehyde-α-d_1. Benzyl benzoate is not a detectable product in this Cannizzaro reaction, although the ester is saponified at a much slower rate than if it were formed under the reaction conditions. There is a direct hydride transfer.

From the large k_H/k_D value it can be stated with reasonable certainty that the rate-determining step of reaction must include the breaking of the carbonyl C—H bond. The results pertaining to benzyl benzoate eliminate any mechanism in which the ester is postulated as an intermediate and in which it is saponified on the catalyst surface at a rate slower than its rate of adsorption. These results also eliminate any mechanism in which benzyl benzoate is postulated as an intermediate and in which it is saponified at a rate slower than its rate of desorption from the catalyst surface.

Mechanisms which can be eliminated on kinetic grounds are as follows: 1. A four-center type disproportionation of two benzaldehyde molecules on the



catalyst to form benzyl benzoate which involves: (a) a sparsely covered catalyst surface, for this would be expected to give second-order kinetics, and (b) an almost completely covered catalyst surface, for this would be expected to result in zero-order kinetics throughout.

2. The formation of benzyl benzoate in the slow step from the intermediate $(C_6H_5—\overset{OH}{\overset{|}{C}}H—O—\overset{O}{\overset{|}{C}}H—C_6H_5)^-$ adsorbed on the catalyst surface, which is, (a) sparsely covered by the intermediate, for this situation would be expected to give third-order kinetics, and (b) almost completely covered by the intermediate, for this would be expected to give zero-order kinetics throughout.

Another possibility which must be considered is that the mechanism includes the slow formation of benzyl benzoate on the catalyst, and the subsequent saponification of the ester at a faster rate than that of its adsorption. Thus, it would appear that a conflict is avoided with the results pertaining to benzyl benzoate. Such mechanisms are as follows.

3. The formation of benzyl benzoate by a four-center type disproportionation (see above) between a free molecule of benzaldehyde and one which is adsorbed on the catalyst, the surface of which is almost completely covered with benzaldehyde.

4. An equilibrium in which the intermediate $(C_6H_5—\overset{OH}{\overset{|}{C}}H—O—\overset{O}{\overset{|}{C}}H—C_6H_5)^-$ is formed on the catalyst from free benzaldehyde and hydroxylated benzaldehyde adsorbed on, and almost completely covering, the surface of the catalyst, and the subsequent formation of benzyl benzoate from this intermediate by an intramolecular hydride transfer and displacement of hydroxyl ion.

One objection to mechanism 3 is that if it were possible, it appears to be less probable than mechanism 1b, where both reacting molecules are on the catalyst surface. An objection to mechanism 4 is that there are no

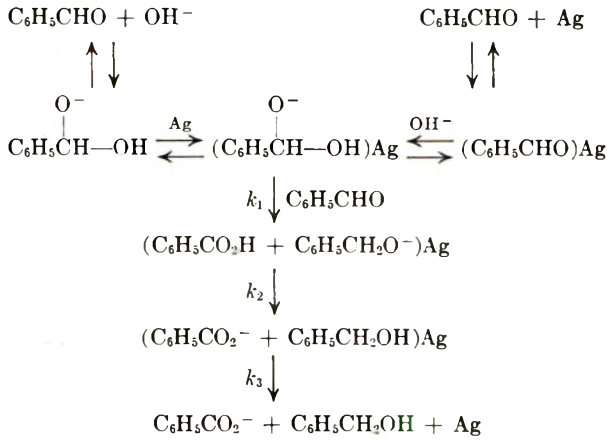


Fig. 1.—Proposed reaction mechanism for the silver metal-catalyzed Cannizzaro reaction of benzaldehyde.

known instances in which a hydride ion displaces a hydroxide ion from a saturated carbon atom.[14]

The extent to which a solute is adsorbed is principally dependent on the available amount of adsorbent. The adsorption is almost invariably reversible and an equilibrium is rapidly established depending on the concentration of solute and the amount of adsorbent.[15] The saponification experiments with benzyl benzoate were set up such that the concentration of the ester and the quantity of available catalyst were extremely high by comparison to the situation required in mechanisms 3 and 4. Both mechanisms depend on a very rapid adsorption of solutes in order for the catalyst surface to be almost completely covered with reactant. To postulate, at the same time, that benzyl benzoate is adsorbed at a very slow rate and that the results pertaining to benzyl benzoate do not apply, is unreasonable.

A mechanism can be proposed which is completely consistent with the results of the kinetic studies of the silver metal-catalyzed Cannizzaro reaction and the other available data and is outlined in Fig. 1.

The initial step is the rapid formation, and/or adsorption, of hydroxylated benzaldehyde on the catalyst, the surface of which rapidly becomes almost completely covered. The rate-determining step, k_1, involves a hydride transfer to free benzaldehyde from the hydroxylated species on the catalyst, which initially is in almost constant supply. Thus, the requirement that the reaction initially be first order in benzaldehyde is fulfilled. The final products, benzoate ion and benzyl alcohol, are formed rapidly in the next step, k_2, from benzoic acid and benzylate ion, followed by the slow desorption, k_3, of the products from the catalyst surface. The rate constant of desorption, k_3, being slightly smaller than that of the hydride transfer, k_1, eventually becomes the controlling factor of the reaction.

The k_H/k_D value of 6.8 found for the silver metal-catalyzed reaction is rather high compared to the value of 1.8[6] found for the noncatalyzed reaction and indicates that the mechanisms of the two reactions are different. The suggestion has been made that the reaction is free radical in nature, there are too few facts which support this contention. The relatively high k_H/k_D rate factor found for the catalyzed reaction suggests a large amount of bond breaking in the transition state of the reaction.

(14) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 548.
(15) Ref. 12, p. 1216.

Experimental

Reagents.—The following were used without purification: ethanol (Commercial Solvents Corp.), sodium hydroxide (Baker and Adamson, reagent), benzyl benzoate (R. Gesell, Inc., $n^{21}D$ 1.5682), silver nitrate, sodium bisulfite (J. T. Baker Chemical Co.), silver oxide (Merck & Co.), benzil (Fairmount Chemical Co., Inc., m.p. 96–96.5°), lithium aluminum deuteride (Metal Hydrides, 98.4%), and deuterium oxide (General Dynamics Corp., 99.5%).

The following was distilled through a 30-in. silvered column packed with glass helices: chloroform (Baker and Adamson, b.p. 60.5°, $n^{18}D$ 1.4470).

Purification of Benzaldehyde.—Benzaldehyde (Fisher Scientific Co.) was converted to its sodium bisulfite addition compound which was washed with 95% ethanol. The addition compound was decomposed with 10% sodium hydroxide solution; the benzaldehyde was separated, washed with distilled water, and dried over sodium sulfate in a nitrogen atmosphere immediately before being distilled (at pressures ranging from 5–18 mm.) through a 12-in. silvered column equipped with a tantalum wire spiral. Nitrogen was the only gas present in the system. The benzaldehyde was distilled directly into 1-oz. brown bottles. The bottles were stored under nitrogen in the dark and usually were used within 2 months. Benzaldehyde was never used from a bottle which had been opened more than 5 hr. previously. The average amount of benzoic acid (analyzed by titration) in the benzaldehyde samples used was 0.3%.

Silver Metal Catalyst Preparations.—(1) A solution of silver nitrate (12.5 g., 0.0745 mole) in water (50 ml.) at 54° was slowly added to a solution containing water (100 ml.), sodium hydroxide (16.1 g., 0.403 mole), benzaldehyde (9.2 g., 0.087 mole), and absolute ethanol (60 ml.) at 41° and stirred by a magnetic stirring bar. The maximum temperature on mixing was 51°. The resulting dark, powder-like solid (7.5 g.) was separated by filtration while hot and washed with water and absolute ethanol.

(2) A solution of silver nitrate (18.1 g., 0.106 mole) in water (50 ml.) at 60° was slowly added to a solution containing water (150 ml.), sodium hydroxide (25.1 g., 0.628 mole), benzaldehyde (15.5 g., 0.146 mole), and absolute ethanol (85 ml.) at 60° and stirred by a magnetic stirring bar. The maximum temperature on mixing was 78°. The resulting fluffy, metallic-like solid (10.5 g.) was separated by filtration while hot and washed with water and absolute ethanol.

(3) The procedure followed, and the amounts of materials used in this preparation were the same as the previous one. Stirring was accomplished with a mechanical stirrer. The maximum temperature on mixing was 76°. The silver was separated while hot and washed with water and absolute ethanol. The fluffy, metallic-like solid (10.6 g.) that was isolated was clumped in small aggregates, and a slurry of the material in water was stirred by a mechanical stirrer to break up the aggregates.

(4) A solution of silver nitrate (36.2 g., 0.213 mole) in water (100 ml.) at 61° was slowly added to a solution containing water (300 ml.), sodium hydroxide (50.2 g., 1.26 moles), benzaldehyde (31.0 g., 0.292 mole), and absolute ethanol (170 ml.) at 61° and stirred by a mechanical stirrer. The maximum temperature on mixing was 73°. The resulting dark gray powder (23.0 g.) was separated and washed with water and absolute ethanol. A test for silver ion indicated the presence of an appreciable amount of silver oxide and thus the process was repeated.

The silver previously prepared (shifted through a no. 80 wire mesh) and benzaldehyde (22.6 g., 0.213 mole) were added to a solution of sodium hydroxide (8.52 g., 0.213 mole) in 50% (by weight) aqueous ethanol (250 ml.), at room temperature, and stirred by a mechanical stirrer. An exothermic reaction immediately resulted and stirring was allowed to continue for 3.5 hr. The resulting light gray powder (23.0 g.) was filtered and washed with water and absolute ethanol. A test for silver ion indicated that a slight amount of silver oxide was present. The silver was passed through a no. 80 wire mesh, washed with concentrated ammonium hydroxide, distilled water, and absolute ethanol, and dried in a vacuum desiccator.

(5) The bulk of the previously prepared silver was washed with concentrated ammonium hydroxide, distilled water, and absolute ethanol. The washed silver was then placed in a vacuum desic-

TABLE IV

PRECISION OF AMOUNT BENZALDEHYDE DELIVERED BY SYRINGE

C_6H_5CHO, mole × 10^2	Standard deviation, %	Number of determinations
1.83	0.6	6
0.99	3.7	9
1.07	0.7	15
0.592	1.6	5
1.95	0.7	6
0.816	.6	6
1.35	1.8	6
2.03 (pipet)	0.9	6

cator which was flushed with nitrogen and the silver was allowed to dry overnight under vacuum. This amount of silver was sufficient for all kinetic runs.

Methods of Analysis.—(1) Studies were made to determine the feasibility of following the reactions spectrophotometrically and potentiometrically. The results indicated, however, that these methods were impractical.

(2) The method of analyzing for products with gas chromatography was investigated and found to be useful. The method consisted in the occasional sampling of the reaction mixture, immediate extraction of each sample with an organic solvent, and analysis of the organic layer for benzyl alcohol with a gas chromatograph (Aerograph Master A-100, Wilkens Instrument and Research, Inc., equipped with a 10-mv. Varian recorder an a 10-ft. Ucon, polar column. Conditions: temp. 154–208°, pressure 7.5–14 p.s.i., filament current 200 ma.). The method was employed to follow experiments 6, 8, 9, and 17–19.

(3) Experiments 20, and 25A–25C were analyzed by isolation and titration of the benzoic acid formed after a given time. The method was found to be inconvenient because of the number of operations involved.

(4) The method employed in the analysis of experiments 18, 37, and 38 involved the isolation and subsequent weighing of the benzoic acid formed in the reaction when the reaction was quenched after a given time. Although this method was considered to be good, it was believed that a method more convenient and, possibly, more accurate could be found.

(5) The method of titration of benzoic acid was the method which was finally settled upon and was employed in the heretofore unmentioned analyses of Cannizzaro reactions. The method consisted in quenching the reaction after a given time with excess hydrochloric acid solution followed by immediate back-titration with standard sodium hydroxide to the phenolphthalein end point. Excess acid (hydrochloric acid and benzoic acid not formed in the reaction) was determined by titrating standards containing the requisite amounts of solvent, sodium hydroxide, hydrochloric acid, and benzaldehyde. In some cases the standard did not contain benzaldehyde, and the amount of benzoic acid in the benzaldehyde sample was determined separately as a check on the latter. The precision was determined, by titrating standards, before each reaction and was always found to be well within 1%.

Kinetic Procedures for Cannizzaro Reactions.—Experiments 6, 8, 9, and 17–20, were carried out in a 250-ml. two-neck flask equipped with a thermometer well and a reflux condenser. One neck of the flask was covered with a gum rubber cap. Fifty per cent (by weight) aqueous ethanol, sodium hydroxide, and silver were placed in the flask, brought to thermal equilibrium, and placed under an inert atmosphere maintained with nitrogen or argon and a mercury bubbler. Benzaldehyde, the amount of which was measured by weight difference, was transferred to the flask by means of a hypodermic syringe. The reaction mixtures were stirred by a magnetic stirring bar. In the case of experiments 6, 8, 9, and 17 the temperature was controlled, when not at reflux temperature, by a Thermocap relay, and, in the case of all remaining experiments by means of a large water bath, the temperature of which was controlled by an Electronic relay. Temperature control by the latter method was found to result in a temperature variation of ±0.05° as compared to ±1° with the former method. Samples (1.00 ml.) were removed from the reaction mixture at various times through the gum rubber cap with a hypodermic syringe, except in the case of experiment 20. Samples were removed from the latter reaction mixture by means of a 1.0-ml. pipet through a gum rubber cap specially prepared for its entrance. In the case of all reactions containing silver, stirring had been stopped 2 min. prior to each sampling.

Experiments 22–29 and 35–100, were carried out in 250-ml. flasks. Into the reaction flask was placed a solution of sodium hydroxide in 50% (by weight) aqueous ethanol (100 ml.) and the silver catalyst. The system was brought to thermal equilibrium and an inert atmosphere was obtained with nitrogen and a mercury bubbler. Constant temperature was maintained with the large water bath, the temperature of which was controlled by an Electronic relay, and the mixture was stirred by a magnetic stirring bar. In the case of experiments 25, 37, and 38, benzaldehyde was measured and transferred to the reaction flask with a pipet. In the case of all the remaining experiments this transfer was accomplished with a hypodermic syringe. After a given time the reactions were quenched with hydrochloric acid solution and analyzed. The data from all these kinetic experiments are reported in a previous section.

Saponification of Benzyl Benzoate.—(1) Into a 250-ml. flask was placed a solution of sodium hydroxide in 50% aqueous ethanol (0.0520 *M*, 100.0 ml.) and silver (20.0 mg., no. 5). The system was flushed with nitrogen and brought to thermal equilibrium. Benzyl benzoate (0.00571 mole) was injected into the reaction flask with a hypodermic syringe. The temperature was maintained at 30° with the water bath, and the mixture was stirred by a magnetic stirring bar. After 10 min. the reaction was quenched with a slight excess of hydrochloric acid solution and immediately back-titrated to determine the amount of benzoic acid produced. Thus it was found that 11.7% saponification had occurred.

(2) This reaction was a duplication of the preceding one with the exception that 2.6×10^{-4} mole of benzyl benzoate was brought into reaction for 5 min. Ten per cent saponification was found to have occurred.

(3) This reaction was a duplication of the preceding one. Ten per cent saponification was found to have occurred.

Exchange Tests in Deuterated Solvent.—The solvent, 96.7% deuterated, was prepared by mixing ethanol-O-*d* (prepared from sodium ethoxide and deuterium oxide) and deuterium oxide in the molar ratio, 1:2.55, calculated for 50% (by weight) aqueous ethanol. The requisite amount of sodium hydroxide was dissolved in the solvent to make the solution 0.052 *M*.

Into a 100-ml. flask was placed a solution of sodium hydroxide in the deuterated solvent (0.052 *M*, 50 ml.) and silver (10.0 mg., no. 5). The system was flushed with nitrogen, brought to thermal equilibrium, and benzaldehyde (0.0063 mole) added to the reaction mixture. The temperature was maintained at 30° with the water bath and the mixture was stirred by a magnetic stirring bar. The reaction was quenched with hydrochloric acid and the mixture immediately added to an ice-cold solution of 2,4-dinitrophenylhydrazine. Benzaldehyde 2,4-dinitrophenylhydrazone was isolated and weighed. Three identical runs were made having reaction times of 10 min., 2 hr., and 9.25 hr. in which benzaldehyde was found to have undergone 13, 25, and 71% conversion, respectively. Analysis of the recovered 2,4-dinitrophenylhydrazone by infrared (Perkin–Elmer Model 21) with the band at 12.54 μ indicated that virtually no exchange had occurred in any of the runs.

Cannizzaro Reaction of Benzaldehyde-α-d_1.—Into a 250-ml. flask was placed a solution of sodium hydroxide in 50% aqueous ethanol (0.051 *M*, 100.0 ml.) and silver (20.0 mg., no. 5). The system was deaerated with nitrogen, brought to thermal equilibrium, and benzaldehyde-α-d_1 (0.0059 mole, b.p. 50.5–51.0° at 5 mm.), previously prepared after the manner of Wiberg,[6] added to the reaction mixture. The temperature was maintained at 30° with the water bath and the mixture was stirred by a magnetic stirring bar. The reaction was quenched with excess hydrochloric acid after 56 min. and immediately back-titrated with standard base to determine the amount of benzoic acid formed in the reaction. The reaction was run in triplicate and the yields of benzoic acid were found to be, 2.56×10^{-4}, 2.30×10^{-4}, and 2.36×10^{-4} mole. The benzyl alcohol was isolated by gas chromatography and mass spectrographic analysis indicated the benzyl alcohol to be greater than 98% α,α-dideuterated.

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The Synthesis of Highly Fluorinated Compounds by Use of Potassium Fluoride in Polar Solvents

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Fluorination of highly chlorinated compounds of three or more carbon atoms by the action of potassium fluoride in polar solvents—*e.g.*, N-methyl-2-pyrrolidone—has been found to give fair to excellent yields of highly fluorinated products. Dechlorination and dehydrochlorination of the substrate appear to be first steps in the mechanism, often followed by addition of the elements of hydrogen fluoride, and finally replacement by fluorine of all but highly hindered chlorine atoms. For example, the three-carbon substrates octachloropropane, heptachloropropane, and hexachloropropane yield $CF_3CCl_2CF_3$, $CF_3CHClCF_3$, and $CF_3CH_2CF_3$, in mixtures of varying proportions that can be controlled to some degree by choice of conditions. Hexachlorobutadiene yields the new fluoroölefins *cis*- and *trans*-$CF_3CH{=}CFCF_3$. Cyclic compounds are particularly responsive to this technique—*e.g.*, perfluorocyclopentene is obtained in high yield from perchlorocyclopentene.

The synthesis of organic compounds containing isolated fluorine atoms by the action of anhydrous potassium fluoride on compounds having suitably reactive chlorine atoms has long been known.[1] Glycol solvents have often been used,[2] and more recently the polar amide solvents have been employed, often in more complex exchange reactions.[3] Henne and Sedlak[4] recently showed that vinylic chlorine atoms can be replaced with fluorine by the action of potassium fluoride in polar solvents if they are flanked by highly fluorinated structures. Miller[5] and co-workers have postulated nucleophilic substitution of vinylic chlorine atoms by potassium fluoride in formamide, although the existence of the direct substitution products was obscured by the fact that only saturated hydrogen fluoride addition products could be isolated under the conditions employed.

We have now found, in a study of new routes to highly fluorinated organic compounds, that wholesale replacement of chlorine in highly chlorinated compounds of more than two carbon atoms can be readily accomplished with reactive alkali fluorides in certain polar solvents. Among the most useful solvents are N-methyl-2-pyrrolidone and dimethyl sulfone. The reactions have been carried out at about 200° in ordinary open glass laboratory equipment and are so rapid that even starting materials boiling substantially lower than the reaction mixture can be successfully converted to highly fluorinated products.

Results and Discussion

One- and Two-carbon Compounds.—The reactions of one- and two-carbon compounds were not found to yield useful quantities of fluorinated products, although the observations made with these substrates are helpful in understanding the reaction mechanisms involved in systems of this sort. Table I summarizes the reactions observed.

TABLE I

REACTIONS OF CHLORINATED ONE- AND TWO-CARBON COMPOUNDS WITH KF IN N-METHYL-2-PYRROLIDONE[a]

Starting material	Products	Yield, %
One-carbon compound		
CCl_4	$CHCl_3$	53
	CHF_3	Minor
Two-carbon compounds		
CCl_3CCl_3	$CCl_2{=}CCl_2$	54–80
$CHCl_2CCl_3$	$CCl_2{=}CCl_2$	65
$CCl_2{=}CCl_2$	CF_3CHCl_2	5
$CHCl{=}CCl_2$	$CCl{\equiv}CCl$	?
	$CHF{=}CCl_2$	15
	$CHF{=}CClF$	?
$CH_2{=}CHCl$	$CH{\equiv}CH$	?

[a] Where yields are indicated as minor or in question, identification was qualitative, based on infrared absorption spectra.

The data of Table I show that solvent attack on chlorocarbon substrates is an important step in reactions in this system. The reduction of carbon tetrachloride to chloroform and the dechlorination of hexachloroethane to tetrachloroethylene suggest that abstraction of the elements of chlorine by the solvent is involved. N-Methylpyrrolidone alone converted hexachloroethane to tetrachloroethylene in 40% yield, although the yield was as high as 80% when potassium fluoride was also present. In the latter case the inorganic salts isolated from the reaction mixture contained substantial amounts of potassium bifluoride. Apparently abstracted chlorine can react with a solvent proton to yield hydrogen chloride, which then reacts with potassium fluoride to give hydrogen fluoride. This hydrogen fluoride can add to olefinic bonds as shown by Fried and Miller[3c] and as will be discussed later. The fate of the solvent involved in this reaction has not been determined.

(1) A. L. Henne, *Org. Reactions*, **II**, 49 (1944).

(2) (a) F. W. Hoffman, *J. Org. Chem.*, **15**, 425 (1950); (b) F. L. M. Pattison and J. J. Norman, *J. Am. Chem. Soc.*, **79**, 2311 (1957), and other papers in this series.

(3) (a) I. Blank, Br. Patent 727,768 (April 6, 1955); (b) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956); (c) J. Fried and W. T. Miller, Jr., *ibid.*, **81**, 2078 (1959).

(4) (a) A. L. Henne and J. Sedlak, Abstracts of Papers, 138th National Meeting of the American Chemical Society, New York, N. Y., September 11–16, 1960; (b) A. L. Henne, U. S. Patent 3,024,290, (March 6, 1962).

(5) W. T. Miller, J. Fried, and H. Goldwhite, *J. Am. Chem. Soc.*, **82**, 3091 (1960).

(6) Made by sulfur tetrafluoride treatment of choranil.

Dehydrochlorination can occur when the structure of the substrate is suitable, as shown by the conversion of pentachloroethane to tetrachloroethylene, of trichloroethylene to dichloroacetylene, and of vinyl chloride to acetylene. This was also seen in the conversion of hexachlorocyclohexane to 1,2,4-trichlorobenzene in 84% yield by the system potassium fluoride/N-methylpyrrolidone.

This ability of the system to attack chlorinated compounds with abstraction of the elements of chlorine and hydrogen chloride, while not leading to useful products in one- and two-carbon compounds, has made possible a variety of remarkable conversions with higher chlorocarbons. Reactions observed with open chain three- to six-carbon compounds are summarized in the following sections.

Compounds from the Three-carbon Series.—The most extensively examined group of reactants was the three-carbon compounds containing six or more chlorine atoms. The interplay of all of the reactions observed in one- and two-carbon compounds can be clearly seen in the product pattern obtained from the chlorinated propanes and propenes, as illustrated in Fig. 1. For purposes of discussion, these can be conveniently considered as members of three groups—*i.e.*, Group A, octachloropropane; group B, the heptachloropropanes and hexachloropropene; and group C, the hexachloropropanes and pentachloropropenes. Observed reactions are indicated by solid arrows, and hypothetical intermediate steps are shown by broken arrows.

The most highly chlorinated substrate, octachloropropane (A), gave 2,2-dichlorohexafluoropropane (I) as the major product in yields of about 60%, with minor amounts of a mixture of low-boiling partially fluorinated propanes and propenes (II), and a very small yield of 2,2-dihydrohexafluoropropane (III). The least chlorinated group, the hexachloropropanes and pentachloropropene (C), gave III as the major product in yields of about 20%, with smaller amounts of Group II compounds. The hypothetical tetrachloroallene appears to be the common intermediate through which the group C compounds yield III. Group B, the heptachloropropanes and their dehydrochlorination product, hexachloropropene, gave a mixture of all products I, II, and III. These reactions can be rationalized as involving an interrelated series of chlorination, dechlorination, dehydrochlorination, and hydrofluorination steps followed by ultimate displacement of terminal chlorine atoms by fluorine. Both SN2 and SN2′ displacements may be involved. I can be assumed to be the normal product from A, II from B, and III from C.

Formation of both I and III from hexachloropropene can be visualized as resulting from dechlorination to the hypothetical tetrachloroallene, leading to III, and addition of the elements of chlorine thus made available to part of the propene, yielding A. A then gives I on fluorination. This hypothesis was strengthened by carrying out the reaction of hexachloropropene in the presence of an excess of a compound known to be dechlorinated by this system—*i.e.*, hexachloroethane. I became the exclusive product from hexachloropropene under these conditions. The formation of Group II and III compounds was completely suppressed when the reaction of octachloropropane (A) was carried out in the

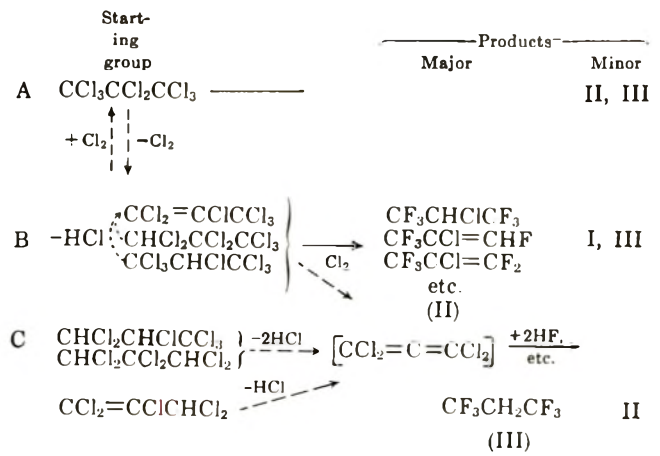


Fig. 1.—Fluorination products of three-carbon chloro-compounds.

presence of hexachloroethane. The relatively poor yields obtained from group C compounds probably result from losses due to degradation and resinification of the highly unsaturated intermediates that are involved in these cases.

Products from Four-carbon Compounds.—The most interesting conversion in this group, as shown in Table II, was the synthesis in good yield of 2-H-heptafluorobutene from hexachlorobutadiene. This reaction appears first to involve the 1,2-addition of one mole of hydrogen fluoride derived from initial attack of solvent and potassium fluoride on the chloro compound. A series of SN2′ displacements of chlorine by fluorine follows in the fashion seen by Fried and Miller[3c] in their studies of the replacement of Cl by F in the propene series. The observed heptafluorobutene is the end product of such a series of reactions. Once initi-

TABLE II

REACTIONS OF FOUR-CARBON COMPOUNDS WITH KF IN N-METHYL-2-PYRROLIDONE

Starting material	Major products	Yield, %
$CCl_2=CClCCl=CCl_2$	$CF_3CH=CFCF_3$	65
$CCl_3CCl=CClCCl_3$	$CF_3CH=CFCF_3$	20
$CF_3CCl_2CCl_2CF_3$	$CF_3CClFCClFCF_3$	70
	$CF_3CF=CFCF_3$	Minor
$CF_3CClFCCl_2CF_3$	$CF_3CCl=CFCF_3$	Minor

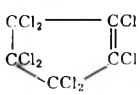
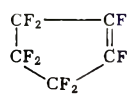
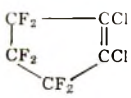
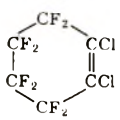
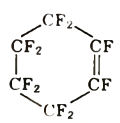
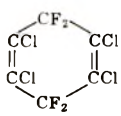
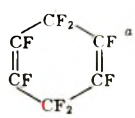
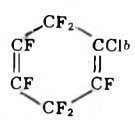
ated, this series of displacements tends strongly to go to completion. When the reaction was carried out at lower temperatures—*e.g.*, 150–160°, yields of the heptafluorobutene were small and a large proportion of the hexachlorobutadiene was recovered unchanged. Compounds of an intermediate degree of fluorine substitution were not obtained in any significant amount.

Cyclic Compounds.—The rapid and complete conversion of perchlorocyclopentene to its perfluoro analog is perhaps the most surprising reaction observed in the system potassium fluoride/N-methylpyrrolidone. 1,2-Dichlorohexafluorocyclopentene, the normal product of antimony fluoride treatment of the perchloro compound, gave the same product, as shown in Table III. This is striking evidence of the desirability of operating in an open system, in view of Henne's[4a] observation that replacement of the second chlorine is slow when the reaction is carried out in a closed system. The analogous reactions were observed with 1,2,4,5-tetrachlorotetrafluorocyclohexadiene-1,4[6] and 1,2-dichloroocta-

fluorocyclohexene.[7] Products from the diene were a mixture of isomers, and this reaction has been studied in detail by Dr. W. H. Powell of the Organic Chemicals Department of our company as will be reported in a separate communication. Hexachlorocyclopentadiene, on the other hand, yielded only intractable resinous products, even though analysis of the reaction mixtures showed that a high proportion of the chlorine had been displaced. Under forcing conditions—*i.e.*, 240° in dimethyl sulfone—a small yield of perfluorocyclopentene was obtained from the diene. This undoubtedly resulted from partial chlorination of the diene to perchlorocyclopentene with chlorine abstracted from a portion of the substrate, as in the case of hexachloropropene, and constitutes further evidence for the mechanisms proposed in the three-carbon series. The conversion of hexachlorocyclopentadiene to perfluorocyclopentene could probably be carried out in good yield in the presence of a chlorine source, although this has not been attempted.

TABLE III

REACTIONS OF CHLORINATED CYCLIC COMPOUNDS WITH KF IN N-METHYL-2-PYRROLIDONE

Starting material	Product	Yield, %
		72
	same	76
		71
	 [a]	~10
	 [b]	~10
C_6Cl_6	*sym*-$C_6Cl_3F_3$	23
	$C_6Cl_2F_4$	34
	C_6ClF_5	Small

[a] B.p. 56–59°, $n^{20}D$ 1.3132. Single infrared double bond band at 5.68 μ. [b] B.p. 86–89°, $n^{20}D$ 1.3562. Two infrared double bond bands at 5.59, 5.82 μ.

Hexachlorobenzene was converted to *sym*-trichlorotrifluorobenzene, m.p. 57–61°, by the action of potassium fluoride in polar solvents in earlier work by Finger and co-workers.[3b] We have found this is also the major product in the system potassium fluoride/N-methylpyrrolidone, although significant amounts of dichlorotetrafluorobenzene and a small yield of chloropentafluorobenzene, identified from its infrared absorption spectrum, were also obtained. Yields indicated in Table III are those obtained by retreating all fluid fractions from an initial fluorination of hexachlorobenzene. It was not possible to push the reaction all the way to hexafluorobenzene.

(7) E. T. McBee, P. A. Wiseman, and G. B. Bachman, *Ind. Eng. Chem.*, **39**, 415 (1947).

Choice of Solvent.—Mixtures of potassium fluoride with any of a wide variety of polar solvents were found to attack chlorocarbons with more or less complete conversion of chlorine to water-soluble chloride form. Table IV lists the solvents tested in order of apparent reactivity in attacking hexachloropropene. In these scouting experiments, no attempt was made to isolate and identify products other than chloride ion. Thus, although many solvents were found to be active for this type of reaction, N-methylpyrrolidone was preferred because of its stability at the required temperature, its high boiling point, its low volatility, and its ready availability. Dimethyl sulfone, while not among those solvents tested in the series of Table IV, appears to be essentially equivalent in action to the pyrrolidone. Its principal disadvantage is that it is a solid at room temperature.

TABLE IV

REACTION OF HEXACHLOROPROPENE WITH POTASSIUM FLUORIDE IN POLAR SOLVENTS

Solvent	Temp., °C.	Time, hr.	Cl displaced, %
Formamide	150	1	71
N-Methylacetamide	150	1	61
N-Methylformamide	100	1	20
Ethylene carbonate	140–180	2	61
Tetramethylene sulfone	150	2	43
Dimethylformamide	145	4	54
N-Methylpyrrolidone	100	3	13
N-Methylpyrrolidone	190–200	3	80
Dimethylacetamide	100	3	11
Nitroethane	114	5	12
α-Butyrolactone	150	2	26
Acetylacetone	140	1	19
Ethyl acetoacetate	150	1	19
Cyclohexanone	160	4	15
Nitropropane	130	4	7
Diglyme	164	4	7
Acetonylacetone	150	1	5
Acetonitrile	82	4½	<1
Nitrobenzene	200	2	<1

Experimental

General Procedure.—Reactions were carried out in three-necked glass flasks fitted with stirrer, thermometer, gas inlet, and a Claisen still head carrying a dropping funnel for addition of the chlorocarbon. The receiver was vented to traps cooled in Dry Ice for collection of low boiling products. In some cases it was found convenient to use a cold finger condenser cooled with Dry Ice, on which volatile products condensed and were collected in a graduated cylinder also so cooled, thus making it possible to observe the course of product formation.

Reagent grade anhydrous potassium fluoride was dried at least two hours in a 150° vacuum oven. N-Methylpyrrolidone was redistilled before use. In the usual procedure, a 100% excess of potassium fluoride over the theoretical requirement was used, although as little as a 20% excess was found adequate in those reactions that were studied in detail. Potassium fluoride has a solubility of about 3% in N-methylpyrrolidone at 190–200°.[8] Salt and solvent were brought to 195°, a gentle flow of dry nitrogen introduced to carry over volatile products, and the chlorocarbon added over a 1–3 hr. period. If the chlorocarbon was a solid, it was added as a concentrated solution in the solvent. If the reactant had a low boiling point—*e.g.*, 1,2-dichlorohexafluorocyclopentene, b.p. 90°, a short length of tubing or a short water-cooled condenser was inserted below the Claisen head to reflux the reactant. Optimum results were in general not obtained at temperatures below 190°.

(8) H. L. Jackson, private communication.

Products were distilled in appropriate spinning band stills and characterized by refractive index, infrared absorption spectroscopy, and n.m.r. spectroscopy. Most of the compounds prepared in this work are well characterized in the literature. The preparation and characterization of those which are new are described here.

Synthesis of 2,2-Dichlorohexafluoropropane.—Three hundred and twenty grams (1 mole) of octachloropropane in 400 ml. of N-methyl-2-pyrrolidone was added over 2.5 hr. to a stirred mixture of 522 g. (9 moles) of anhydrous potassium fluoride and 1250 ml. of N-methyl-2-pyrrolidone at 195°. Product distilled as the octachloropropane was added, and its formation was complete 0.5 hr. after addition was finished. There were obtained 151.7 g. (69%) of crude $CF_3Cl_2CF_3$. Residual solvent was distilled and reused in a second run of the same size to give a total of 316 g. of product. This was distilled to yield 35 g. of foreshot, b.p. 24–31°, a main cut at 31–34°, and a small residue. Redistillation of the product gave b.p. 32.2–33.6°, m.p. 3°, $n^{20}D$ 1.3032. The n.m.r. absorption spectrum agreed with the symmetrical structure suggested by the high melting point. Analysis of such a low boiling compound is difficult, but the results agreed fairly well with this composition. Calcd. for $C_3Cl_2F_6$: C, 16.25; Cl, 32.4; F, 51.4; Found, C, 17.45; Cl, 31.5; F, 49.4. Infrared absorption bands were seen at 7.85 and 8.05 μ (C–F), 10.62 and 10.98 μ (C–Cl), and 14.13 μ (CF_3).

Synthesis of 2-H-Heptafluoro-2-butene.—Two hundred and sixty-one grams (1 mole) of hexachlorobutadiene was added to 522 g. of potassium fluoride in 1500 ml. of N-methyl-2-pyrrolidone as above. Yield of low boiling product was 114 g. (65%). On distillation this boiled almost entirely in the range 8.5–15°. After storage in a stainless steel cylinder for about a month, on redistillation this product was found to boil sharply at 7–8°, with only a small tail at 8–10°. Vapor phase chromatography analysis of the main cut showed it to be 95.3% one component, with an adjacent second component accounting for 2.3% of the whole. Infrared and n.m.r. studies agreed with the structure $CF_3CH{=}CFCF_3$, and it is assumed that the *trans* form is the major product, with some higher boiling *cis* form that tends to isomerize to *trans* on standing. Infrared bands were seen at 3.38 μ (C—H), 5.68 μ (C=CF), 7.10, 7.31, 8.18, and 8.35 μ (C—F), 11.55 μ (?), and 13.55 μ (CF_3). In the 40-Mc. n.m.r. spectrum, using CF_3COOH as the standard, doublets at +39 c.p.s. and +620 c.p.s. accounted for two different CF_3 groups, the doubling being attributed to *cis-trans* isomerism. A single fluorine atom was indicated by a peak at −1682 c.p.s.

Additional Observations.—Potassium fluoride is the most practical salt for this reaction, although cesium fluoride was found at least as effective, and rubidium fluoride would undoubtedly also be active. Potassium bifluoride was active but very corrosive in glass equipment. Sodium fluoride showed little activity, as all workers in this field have found. With mixtures of potassium and sodium fluoride, the yield of product could be accounted for entirely by the potassium salt, in agreement with the observation of Finger.[3b] Micropulverization of the salt seemed to help in the sense that less tar formation occurred, but yields were not significantly improved. Addition of glass beads to give a grinding action on the salt made little difference in yields. Addition of various agents in an effort to catalyze the reaction was ineffective, although it was found that those which could be expected to interfere with the chlorine-solvent interaction—*e.g.*, zinc oxide—prevented the reaction entirely.

Determination of the amount of chlorine ion formed was made by filtering precipitated salts from the reaction mixture, washing with acetone, and dissolving them to a known volume in water. An aliquot was then titrated for chloride ion. The presence of substantial amounts of potassium acid fluoride was frequently indicated by the strongly acidic nature of this salt solution, which was neutralized with potassium carbonate to prevent attack on the glass equipment used.

The reactions with the lower boiling chloroethylenes were carried out in a Hastelloy rocker bomb.

Conclusions

The combination of anhydrous potassium fluoride with stable polar solvents, of which N-methyl-2-pyrrolidone is the most convenient, has been found to be an exceedingly powerful agent for the synthesis of highly fluorinated organic compounds from highly chlorinated starting materials. Frequently, more extensive conversions can be accomplished in simple glass equipment with this system than with difficultly handled fluorination systems such as hydrogen fluoride and antimony halides. The reactions that occur in potassium fluoride systems are complex and often result in formation of products with a substantially different structure from that of the starting materials, although in special cases, as in the cyclopentenes, displacement of chlorine by fluorine appears to be straightforward. This latter case may, of course, involve intermediate stages of hydrofluorination and dehydrochlorination that are not apparent from the over-all result. It should be pointed out that displacement of a single chlorine atom by fluorine is readily accomplished by this technique. N-Octyl chloride gave an excellent yield of the corresponding fluoride when treated by the procedure described under Experimental.

These systems give most useful results with compounds in the three- to six-carbon range. One- and two-carbon compounds have not given useful yields of fluorocarbons, and larger compounds are likely to be degraded or to yield complex mixtures. Perchloro-1,5-hexadiene, for example, gave the same products as the hexachloropropanes. A cleavage at the 3,4-position seems to be followed by reaction steps again suggesting the hypothetical tetrachloroallene as an intermediate. Many of the products obtained are of synthetic interest, and a variety of useful conversions to second-stage products can be visualized.

Acknowledgment.—This work was initiated on the strength of a suggestion by Prof. A. L. Henne that potassium fluoride in polar solvents should be expected to accomplish unusual displacements of chlorine by fluorine. Helpful discussions with Dr. R. G. Arnold, Dr. P. A. Roussel, and Prof. J. D. Roberts are also gratefully acknowledged. The interest of Dr. W. H. Powell in this reaction and his further studies of it will be reported in another paper. N.m.r. spectra and interpretations were kindly carried out by Dr. T. E. Beukelman of the Organic Chemicals Department of the Du Pont Company.

The Synthesis of New Heterocyclic Compounds from 3,4-Dichlorocoumarins

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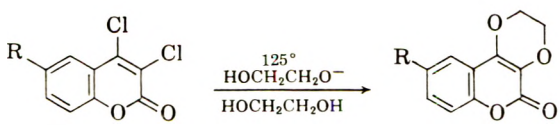
By reaction of 3,4-dichlorocoumarin and 3,4,6-trichlorocoumarin with difunctional reagents, several new heterocyclic types of compounds, having a heterocyclic ring fused at the 3,4-position of the coumarin nucleus, have been prepared for the first time.

On treatment with nucleophilic reagents, each of the chlorine atoms in 3,4-dichlorocoumarins is replaced, that in the 4-position considerably more easily than that in the 3-position.[3] Because of this behavior, the synthesis of compounds containing an additional heterocyclic ring fused to the 3,4-positions of the coumarin nucleus seemed possible. This objective was of interest because compounds having physiological activity might be produced since the coumarin ring system is present in several active compounds; *e.g.*, warfarin,[4] novobiocin,[5] and Dicumarol.[6]

In general, the construction of a new heterocyclic ring onto the 3,4-position of a coumarin was envisioned by causing a difunctional reagent to displace the 4-chlorine atom. The resulting 3-chloro-4-substituted coumarins could then be cyclized by an intramolecular displacement reaction to yield 3,4-heterocyclic coumarins. This objective has been attained by treating 3,4-dichlorocoumarin and 3,4,6-trichlorocoumarin[7] with ethylene glycol, catechol, 2-ethanolamine, and *o*-aminophenol. However, with ethylenediamine, *o*-phenylenediamine, butyramidine, guanidine, triphenylguanidine, thiourea, sodium α-sodioacetate,[8] and sodium α-sodiophenylacetate[9] none of the expected cyclic products was obtained. In general, the cyclization reactions, even in the successful cases, did not take place as easily as expected.

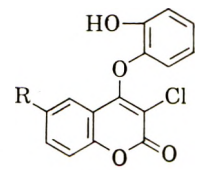
The reaction of 3,4-dichlorocoumarin (Ia) and 3,4,6-trichlorocoumarin (Ib) with ethylene glycol containing sodium 2-hydroxyethoxide yielded directly 2,3-dihydro-5H-*p*-dioxino[2,3-*c*][1]benzopyran-5-one (IIa) and the 9-chloro analog IIb. Because of the good yields obtained, no attempts were made to prepare the intermediate 3-chloro-4-β-hydroxyethyl ethers.



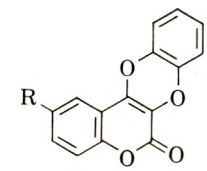
Ia. R = H
b. R = Cl

IIa, IIb

In similar experiments using the monoanion of catechol in excess molten (110°) catechol or in N-methyl-2-pyrrolidone (NMP) the monoethers, IIIa and IIIb, were obtained in excellent yields. However, cyclization of IIIb to 2-chloro-6H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one, IVb preceeded with difficulty and we were unable to obtain IVa from IIIa.

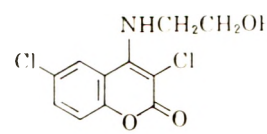


IIIa, b

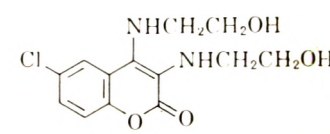


IVb

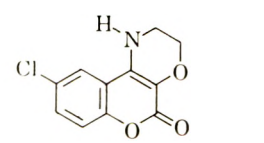
When Ib was treated with two equivalents of ethanolamine in refluxing methanol, 3,6-dichloro-4-(2-hydroxyethylamino)coumarin (V) was obtained in 80% yield. When Ib was treated with excess ethanolamine at 80°, 6-chloro-3,4-bis(2-hydroxyethylamino)-coumarin (VI) was obtained in 72% yield. The cyclization of V to 9-chloro-2,3-dihydro[1]benzopyrano-[3,4-*b*][1,4]oxazin-5(1H)-one (VII) by heating the sodium salt of V in tetrahydrofuran went in 87% yield. However, when sodium isopropoxide in isopropyl alcohol was used, V was converted into 6-chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (VIII) in 90% yield.[10]



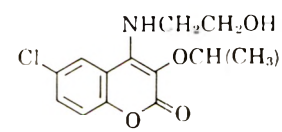
V



VI

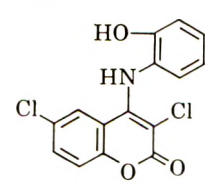


VII

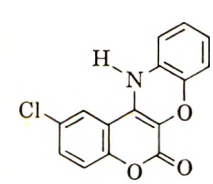


VIII

Similarly, Ib could be treated with *o*-aminophenol to yield 3,6-dichloro-4-(*o*-hydroxyanilino)coumarin (IX), and the latter could be cyclized to 2-chloro-(1)benzopyrano[3,4-*b*][1,4]benzoxazin-6(12H)-one (X).



IX



X

(1) This work was supported by a grant, RG-7450, from the U. S. Public Health Service, and formed part of the Ph.D. thesis of C. Y. Perry, Ohio State University, 1962.

(2) Sinclair Oil Company Fellow 1961–1962.

(3) M. S. Newman and S. Schiff, *J. Am. Chem. Soc.*, **81**, 2266 (1959).

(4) M. W. Schein, *Public Health Rept.* (U. S.), **65**, 368 (1950).

(5) E. A. Keazka, F. J. Wolf, F. P. Rathe, and K. Folkers, *J. Am. Chem. Soc.*, **77**, 6404 (1955).

(6) L. J. Audus and J. H. Quastel, *Nature*, **159**, 320 (1947).

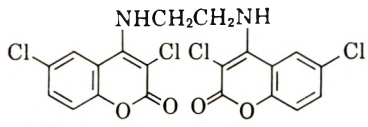
(7) The trichlorocoumarin was often used in preference to 3,4-dichlorocoumarin because (a) it was prepared more easily in higher yield and (b) the yields of reaction products were somewhat higher in general.

(8) Obtained through the courtesy of Dr. Rex Closson, The Ethyl Corp., Detroit, Mich.

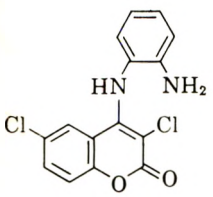
(9) Prepared as described by C. R. Hauser and R. B. Meyer, *J. Org. Chem.*, **26**, 3183 (1961).

(10) The reason for this unexpected result is under study now.

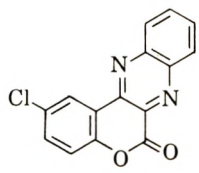
When Ib was treated with two equivalents of ethylendiamine in methanol a 35% yield of N,N′-bis(3,6-dichloro-4-coumarinyl)ethylenediamine (XI), was obtained. All attempts to prepare a monoethylenediamine product failed as did attempts to prepare a piperazine derivative. With *o*-phenylenediamine, Ib reacted to give 81% of 4-(*o*-aminoanilino)-3,6-dichlorocoumarin (XII), which could be cyclized in small yield to 2-chloro - 6H - (1)benzopyrano[3,4, - *b*]quinoxaline - 6-one (XIII) by heating in pyridine at 110–115°. If manganese dioxide[11] were present, the yield was increased to 70%.



XI

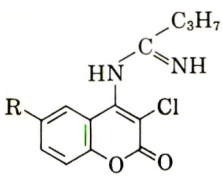


XII

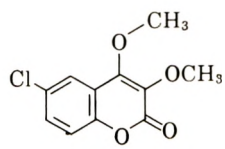


XIII

In an attempt to obtain a five-membered heterocyclic ring fused to the 3,4-positions of the coumarin nucleus, Ia and Ib reacted with *n*-butyramidine. The only products obtained, however, were N-(3-chloro-4-coumarinyl)butyramidine[12] (XIVa) and the corresponding 3,6-dichloro derivative (XIVb). Attempts at cyclization of XIVa,b failed. Ib was recovered unchanged after heating with *o*-aminopyridine in NMP at 100°.

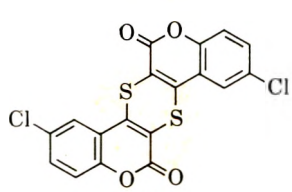


XIVa, b



XV

When Ib was treated with thiourea in methanol, a high melting (>450°) extremely insoluble compound was obtained in almost quantitative yield. Because of its great insolubility in all common reagents no further work was done with this compound which is most likely 2,9-dichloro-6H,13H-*p*-dithiino[2,3-*c*:5,6-*c*′]bis[1]benzopyrane-6,13-dione (XVI).[13]



XVI

When Ib was treated with guanidine in refluxing methanol, 6-chloro-3,4-dimethoxycoumarin (XV) was obtained. This was compared with an authentic sample prepared from Ib and sodium methoxide in methanol. On heating Ib with guanidine in diglyme (diethylene glycol dimethyl ether) at 98° a compound was obtained which has not been identified, but it is not any obvious reaction product. When Ib was heated with triphenylguanidine in diglyme at 100°, Ib was recovered unchanged.

Attempts to react Ib with ammonia, sodium amide, sodium α-sodioacetate,[14] sodium α-sodiophenylacetate,[15] sodiomalonic ester, ethoxymagnesium malonic ester,[16] urea, and sodium or potassium fluoride (NMP—100°) were unsuccessful. Either Ib was recovered unchanged or tars were obtained.

The amino alcohols V and VI were unique in that the former formed only the O-acetyl and the latter the bis-O-acetyl derivative on treatment with acetic anhydride or acetyl chloride in the presence of a tertiary amine. Normally, if amino alcohols form monoacetates, it is an N-acyl derivative.[17] We were unable to prepare a diacetate of V or a tetraacetate of VI. In further experiments 4-β-hydroxyethylaminocoumarin (XVII), β-O-toluidinoethanol, (XVIII), and 3,6-dichloro-4-propylaminocoumarin (XIX) were submitted to acetylation procedures. The fact that XVII formed only an O-monoacetyl derivative shows that the presence of a chlorine in position 3 of the coumarin nucleus is not the deciding factor in the formation of mono-O-acetyl derivatives in this class of compound. The fact that XVIII formed a diacetyl derivative shows that the steric hindrance provided by an *ortho* methyl group is not sufficient to prevent formation of the expected diacetyl derivative. The fact that XIX did not form an acetyl derivative in refluxing acetic anhydride shows that the hydroxy group on the 2-hydroxyethyl group is not responsible for the failure to N-acylate.

Both n.m.r.[18] and infrared analyses are consistent with the formulas of the monoacetate of V and diacetate of VI in which the NH group is present. This evidence rules out tautomeric structures which would remove the hydrogen on the nitrogen.

The fact that the unusual O-acetyl derivatives abovementioned really had free NH groups was determined in two ways: (a) they were basic and (b) they had a carbonyl absorption in the 6.00–6.14-μ (1667–1630-cm.$^{-1}$) region. Whenever there is no hydrogen on the nitrogen in the 4-position of the coumarin nucleus, the coumarin carbonyl groups absorption is in the 5.7–5.9-μ (1775–1695-cm.$^{-1}$) region. The reason for the inability to form N-acetyl derivatives of V, VI, and XIX

(11) Prepared as described by J. Attenburrow, *J. Chem. Soc.*, 1094 (1952). If the manganese dioxide were omitted, the yield of XIII dropped to 25–30% as oxidation–reduction processes occurred.

(12) The alternate structure with N=C—NH$_2$ cannot be ruled out. The n.m.r. analysis was not conclusive. We are indebted to Dr. G. Fraenkel for this determination.

(13) An isomeric structure in which the right-hand coumarin system is reversed can also be written.

(14) Obtained through the courtesy of Dr. Rex Closson, The Ethyl Corp., Detroit, Mich., whom we thank.

(15) Prepared as described by C. R. Hauser and R. B. Meyer, *J. Org. Chem.*, **26**, 3183 (1961).

(16) Prepared as described by K. Meyer and H. Bloch, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 637.

(17) For example, see G. Fodor and J. Kiss, *J. Am. Chem. Soc.*, **72**, 3495 (1950), and references therein.

(18) We thank Dr. G. Fraenkel for this analysis.

under normal conditions may be tied up with the fact that these compounds are vinylogous amides.[19]

Experimental[20]

9-Chloro-2,3-dihydro-5H-*p*-dioxino[2,3-*c*][1]benzopyran-5-one (IIb).—To the solution made by treating 1.33 g. of sodium with 50 ml. of ethylene glycol was added 7.25 g. of 3,4,6-trichlorocoumarin.[3] The solution was rapidly heated to 125°, held at 115–125° for 1 hr. and poured onto 150 g. of ice. The resulting white solid was recrystallized from benzene (*ca.* 75 ml.) to yield 5.63 g. (81%) of IIb, m.p. 201–203° (5.80 μ, 1725 cm.$^{-1}$). Several recrystallizations from benzene gave the analytical sample, m.p. 202–203°.

Anal. Calcd. for $C_{11}H_7ClO_4$: C, 55.4; H, 3.0; Cl, 14.9. Found: C, 55.6; H, 3.1; Cl, 14.7.

2,3-Dihydro-5H-*p*-dioxino[2,3-c][1]benzopyran-5-one (IIa).—As above, 3,4-dichlorocoumarin[3] reacted with the sodium salt of ethylene glycol to give IIa, m.p. 162–163° (5.88 μ, 1701 cm.$^{-1}$), in 63% yield. The analytical sample melted at 163–164°.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.9. Found: C, 64.4; H, 3.8.

3,6-Dichloro-4-(*o*-hydroxyphenoxy)coumarin (IIIb).—To a solution made by treating 0.12 g. of sodium in 5 g. of molten (110°) catechol was added 1.25 g. of 3,4,6-trichlorocoumarin. The solution was held at 110–115° for 15 min., cooled, and poured into 50 ml. of ice–water. The resulting white solid was recrystallized from 15 ml. of ethanol to yield 1.46 g. (95%) of IIIb, m.p. 174–176° (5.87 μ, 1706 cm.$^{-1}$). Several recrystallizations from ethanol gave the analytical sample, m.p. 176–177°.

Anal. Calcd. for $C_{15}H_8Cl_2O_4$: C, 55.7; H, 2.5; Cl, 21.9. Found: C, 56.0; H, 2.8; Cl, 21.9.

3-Chloro-4-(*o*-hydroxyphenoxy)coumarin (IIIa).—To a solution of 8 g. of catechol in 30 ml. of NMP was added 0.23 g. of sodium. The resulting solution was stirred for 15 min. and 2.15 g. of 3,4-dichlorocoumarin was added. The solution was heated to 110°, held at 110–115° for 15 min., cooled, and poured into 100 ml. of cold water. The resulting white solid was recrystallized by dissolving in 20 ml. of hot methanol and adding water to turbidity. The yield of IIIa, m.p. 159–162° (5.89 μ, 1699 cm.$^{-1}$), was 2.30 g. (80%). Several recrystallizations of IIIa from methanol–water gave the analytical sample, m.p. 160–162°.

Anal. Calcd. for $C_{15}H_9ClO_4$: C, 62.4; H, 3.1; Cl, 12.3. Found: C, 62.1; H, 3.0; Cl, 12.3.

2-Chloro-6H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one (IVb).—To a solution of 6 g. of catechol in 20 ml. of NMP was added 0.46 g. of sodium. The solution was stirred for 15 min. and 2.50 g. of 3,4,6-trichlorocoumarin was added. The resulting solution was heated to 150°, held at 145–150° for 80 min., cooled, and poured into 100 ml. of cold water. The resulting orange-white solid was recrystallized from acetone (*ca.* 25 ml.) to yield 1.23 g. (43%) of VI, m.p. 220–222° (5.80 μ, 1725 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 222–223°.

Anal. Calcd. for $C_{15}H_7ClO_4$: C, 62.9; H, 2.5; Cl, 12.4. Found: C, 63.2; H, 2.5; Cl, 12.1.

Any large deviation from the specified reaction temperature and time leads to a lowering of the yield of IVb as does the use of molten catechol or dimethylformamide as solvent. If IIIb is used in the above experiment, the yield of IVb is no better.

Several attempts to prepare 6-H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one (IVa) from 3,4-dichlorocoumarin by similar procedures gave only tars.

3,6-Dichloro-4-(2-hydroxyethylamino)coumarin (V).—A solution of 1.22 g. of ethanolamine in 10 ml. of absolute methanol was added to a refluxing solution of 2.50 g. of Ib in 25 ml. of absolute methanol. The solution was refluxed an additional 45 min. and concentrated to dryness under reduced pressure. The resulting white solid was washed with 50 ml. of water and recrystallized from methanol (*ca.* 20 ml.) to yield 2.18 g. (80%) of V, m.p. 197–199° (6.08 μ, 1643 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 198.0–199.5°.

Anal. Calcd. for $C_{11}H_9Cl_2NO_3$: C, 48.2; H, 3.3; Cl, 25.8; N, 5.1. Found: C, 48.3; H, 3.5; Cl, 25.9; N, 4.9.

4-(2-Acetoxyethylamino)-3,6-dichlorocoumarin.—A solution of 5.48 g. of V and 0.1 g. of fused sodium acetate in 10 ml. of acetic anhydride was refluxed for 3 hr. and cooled to 2°. The white needles which formed were collected by filtration, washed with 50 ml. of dry ether, and dried to yield 5.66 g. (92%) of the acetate, m.p. 159–162° (5.84 μ, 1715 cm.$^{-1}$) (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from 95% ethanol (*ca.* 25 ml.) gave the analytical sample, m.p. 160–162°.

Anal. Calcd. for $C_{13}H_{11}Cl_2NO_4$: C, 49.5; H, 3.5; Cl, 22.4; N, 4.4. Found: C, 49.8; H, 3.8; Cl, 22.4; N, 4.6.

This acetate would not react with a mixture of acetyl chloride and 2,6-lutidine. It formed a hydrochloride (not analyzed).

3,4-Bis(2-hydroxyethylamino)-6-chlorocoumarin (VI).—To 40 ml. of ethanolamine maintained at a temperature of 75–80° was added, over a period of 30 min., 25 g. of 3,4,5-trichlorocoumarin. The solution was maintained at a temperature of 75–80° for an additional 45 min., cooled, and poured into 300 ml. of cold water. The resulting white solid was filtered, washed with 100 ml. of water, and recrystallized from acetone (*ca.* 50 ml.) to yield 21.5 g. (72%) of VI, m.p. 150–152° (6.14 μ, 1629 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 151–152°.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_4$: C, 52.3; H, 5.1; Cl, 11.9; N, 9.4. Found: C, 52.5; H, 5.0; Cl, 11.6; N, 9.6.

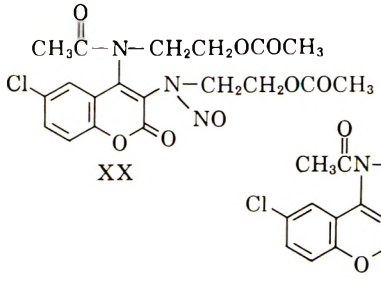
3,4-Bis(2-acetoxyethylamino)-6-chlorocoumarin.—A solution of 2.99 g. of VI and 0.1 g. of fused sodium acetate in 20 ml. of acetic anhydride was refluxed for 2 hr., cooled, and poured into 100 ml. of cold water. The pH was adjusted to about 7.5 by the addition of potassium carbonate and the resulting white solid was filtered, washed with 50 ml. of water, and recrystallized from acetone (*ca.* 15 ml.) to yield 3.65 g. (95%) of the diacetate, m.p. 92–94° (5.80 μ, 1725 cm.$^{-1}$), (6.10 μ, 1638 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 93.0–94.5°.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_6$: C, 53.3; H, 5.0; Cl, 9.2; N, 7.3. Found: C, 53.0; H, 5.1; Cl, 8.9; N, 7.0.

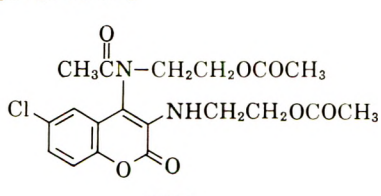
This amine did not react with a mixture of acetyl chloride and 2,6-lutidine or with phosgene in 2,6-lutidine. This amine (1.0 g.) was dissolved in a minimum of benzene (*ca.* 10 ml.) and treated with excess anhydrous hydrogen chloride. The resulting white precipitate was filtered and dried to give 1.0 g. (85%) of the hydrochloride (not analyzed). The infrared band assigned to the NH_2^+ absorption occurred at 3.60 μ, 2785 cm.$^{-1}$.

3-(2-Acetoxyethylnitrosoamino)-4-(2-acetoxyethylacetamido)-6-chlorocoumarin (XX).—A stirred mixture of 5.74 g. (0.015 mole) of the diacetate of VI and 4.0 g. of fused sodium acetate in 20 ml. of acetic anhydride and 10 ml. of glacial acetic acid was cooled to 2°. To the mixture was added over a period of 30 min. a solution of 1.12 g. of nitrosyl chloride in 4 ml. of acetic anhydride. During the addition the temperature was maintained at 5–8°. The resulting solution was held at 12–15° for 30 min. and poured into 150 ml. of cold water. The resulting yellow solid was filtered, washed with 100 ml. of water and recrystallized from methanol (*ca.* 20 ml.) to yield 6.35 g. (93%) of XX, m.p. 83–85° (5.79 μ, 1729 cm.$^{-1}$) (5.89 μ, 1700 cm.$^{-1}$) (6.00 μ,

(19) This suggestion was made by a referee. We had considered this possibility but because of the basicity of the compounds wondered how much the principle of vinylogy is responsible for the facts. In one case, an N-acetyl derivative was formed. The stability of this N-acetyl group shows that lack of stability is not the reason for failure to form N-acetyl compounds. When the di-O-acetate of VI was treated with nitrosyl chloride in acetic anhydride, XX was obtained. Denitrosation of XX yielded XXI. The structure XXI was assigned to this compound because of the infrared band at 5.83 μ (2727 cm.$^{-1}$) characteristic of coumarins not having an NH group in the 4-position.



XX



XXI

(20) All melting points are uncorrected. Melting points above 200° were taken in a heated aluminum block. All microanalyses by Schwarzkopf Laboratory, Woodside, N. Y. Infrared spectra were taken on a Baird Associates spectrophotometer, Model B. Only strong carbonyl bands are listed. Assistance in naming several compounds was provided by Mr. Don Walker of *Chemical Abstracts*, whom we thank.

1667 cm.$^{-1}$). The product gave a positive Liebermann nitroso test.[21] Several recrystallizations from methanol gave the analytical sample, m.p. 84.8–85.8°.

Anal. Calcd. for $C_{19}H_{20}ClN_3O_8$: C, 50.3; H, 4.4; Cl, 7.8; N, 9.3. Found: C, 50.5; H, 4.5; Cl, 7.6; N, 9.6.

3-(2-Acetoxyethylamino)-4-(acetoxyethylacetamido)-6-chlorocoumarin (XXI).—A solution of 4.54 g. of XX in 25 ml. of xylene was heated on a steam bath until gas evolution ceased (*ca.* 45 min.). The xylene was removed under reduced pressure and the resulting solid was recrystallized from absolute methanol (*ca.* 5 ml.) to yield 3.89 g. (91%) of XXI, m.p. 90–92° (5.79 μ, 1728 cm.$^{-1}$) (5.83 μ, 1718 cm.$^{-1}$) (6.00 μ, 1667 cm.$^{-1}$). The product gave a negative Liebermann nitroso test. Several recrystallizations from methanol gave the analytical sample, m.p. 91.5–93.0°.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_7$: C, 53.8; H, 5.0; Cl, 8.3; N, 6.6. Found: C, 53.7; H, 5.0; Cl, 8.2; N, 6.3.

This amine would not react with refluxing acetic anhydride.

9-Chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (VII).—To a refluxing solution of 5.48 g. of V in 250 ml. of dry tetrahydrofuran was added, over a period of 30 min., 0.87 g. of a 53% suspension of sodium hydride in mineral oil.[22] A white precipitate formed during the addition. The mixture was refluxed an additional 45 min. and cooled. Methanol (2 ml.) was added to destroy any unchanged sodium hydride. The solvent was removed under reduced pressure and the resulting white solid was washed with 50 ml. of water and recrystallized from N,N-dimethylacetamide (*ca.* 40 ml.) to yield 4.10 g. (87%) of VII, m.p. 311–315° (6.08 μ, 1643 cm.$^{-1}$). Several recrystallizations from dimethylacetamide gave the analytical sample, m.p. 313–316°.

Anal. Calcd. for $C_{11}H_8ClNO_3$: C, 55.8; H, 3.4; Cl, 14.9; N, 5.9. Found: C, 55.8; H, 3.3; Cl, 15.2; N, 6.2.

This amine would not react with refluxing acetic anhydride (sodium acetate or pyridine catalyst) or with a mixture of acetyl chloride and 2,6-lutidine.

6-Chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (VIII).—To a refluxing solution of 2.74 g. of V in 60 ml. of isopropyl alcohol was added over a period of 30 min. a solution of 0.23 g. of sodium in 100 ml. of isopropyl alcohol. The solution was refluxed an additional 30 min. and the isopropyl alcohol was removed under reduced pressure. The resulting white solid was washed with 50 ml. of water and extracted with 150 ml. of refluxing 95% ethanol. The insoluble material was filtered and dried to yield 0.4 g. (2%) of VII, m.p. 310–314°. The filtrate was concentrated to about 30 ml., cooled, and filtered to yield 2.69 g. (90%) of VIII, m.p. 122–123° (6.14 μ, 1631 cm.$^{-1}$). Several recrystallizations from 95% ethanol gave the analytical sample, m.p. 122–123°.

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.5; H, 5.4; Cl, 11.9; N, 4.7. Found: C, 56.3; H, 5.7; Cl, 11.8; N, 4.8.

3,6-Dichloro-4-(*o*-hydroxyanilino)coumarin (IX).—A solution of 5.00 g. of Ib and 6.00 g. of *o*-aminophenol in 20 ml. of NMP was heated at 95–99° for 30 min., cooled, and poured into 600 ml. of cold water. The resulting solid was filtered and dissolved in 350 ml. of hot methanol. Water was added to turbidity. The solid which crystallized on cooling was filtered and dried to yield 5.79 g. (90%) of IX, m.p. 241–243° (6.03 μ, 1660 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 241–243°. IX is soluble in 5% aqueous sodium hydroxide and gives a positive ferric chloride test.

Anal. Calcd. for $C_{15}H_9Cl_2NO_3$: Cl, 22.0. Found: Cl, 21.8.

2-Chloro-[1]benzopyrano[3,4-*b*]benzoxazin-6(12H)-one, (X).—To a solution of 6.44 g. of IX in 20 ml. of NMP was added 0.87 g. of a 53% dispersion of sodium hydride in mineral oil.[22] The resulting solution was heated at 135–140° for 30 min., cooled, and poured into 200 ml. of cold water. The resulting rust color solid was recrystallized from tetrahydrofuran (*ca.* 70 ml.) to yield 3.20 g. (56%) of X, m.p. 347–350° (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from tetrahydrofuran gave the analytical sample, m.p. 349–352°.

Anal. Calcd. for $C_{15}H_8ClNO_3$: C, 63.1; H, 2.8; Cl, 12.4; N, 4.9. Found: C, 62.9; H, 3.1; Cl, 12.1; N, 4.6.

N,N′-Bis(3,6-dichloro-4-coumarinyl)ethylenediamine (XI).—To a stirred slurry of 7.50 g. of Ib in 150 ml. of absolute methanol maintained at a temperature of 2–3° was added, over a period of 10 min., 3.60 g. of ethylenediamine. The temperature was maintained at 2–3° for an additional 45 min. at which time solution was complete. The solution was allowed to warm up and was stirred at 24–28° for 12 hr. A white precipitate appeared after about 1 hr. and was quite heavy after 12 hr. The precipitate was filtered, washed with 25 ml. of cold methanol, and dried to yield 2.54 g. (35%) of XI, m.p. 340–344° (6.01 μ, 1664 cm.$^{-1}$). Only tar could be recovered from the methanol mother liquor. Several recrystallizations from dimethylacetamide (*ca.* 40 ml.) gave the analytical sample, m.p. 345–346°.

Anal. Calcd. for $C_{20}H_{12}Cl_6N_2O_4$: C, 49.5; H, 2.5; Cl, 29.1; N, 5.8. Found: C, 49.8; H, 2.8; Cl, 29.0; N, 5.5.

4-(*o*-Aminoanilino)-3,6-dichlorocoumarin (XII).—A solution of 3.00 g. of Ib and 3.00 g. of *o*-phenylenediamine in 15 ml. of NMP was heated on a steam bath for 10 min. The solution was diluted with 500 ml. of cold water and the resulting yellow solid was washed with 200 ml. of hot water and recrystallized from benzene (*ca.* 300 ml., dissolves slowly) to yield 3.13 g. (81%) of XII, m.p. 199–201° (6.02 μ, 1662 cm.$^{-1}$). Several recrystallizations from benzene gave the analytical sample, m.p. 200–202°.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O_2$: C, 56.2; H, 3.1; Cl, 22.1; N, 8.8. Found: C, 56.3; H, 3.4; Cl, 21.8; N, 8.8.

2-Chloro-6H-[1]benzopyrano[3,4-*b*]quinoxalin-6-one (XIII).—A mixture of 2.1 g. of XII, 4.0 g. of manganese dioxide,[23] 10 ml. of NMP, and 25 ml. of pyridine was heated with stirring at 110–115° for 90 min. The manganese dioxide was removed by filtration and washed ten times with 30 ml. portions of pyridine. The combined organic fraction was concentrated to about 60 ml. under reduced pressure and diluted with 300 ml. of cold water. The resulting yellow solid was washed with water and recrystallized from glacial acetic acid (*ca.* 75 ml.) to yield 1.40 g. (70%) of XIII, m.p. 320–323° (5.77 μ, 1733 cm.$^{-1}$). Several recrystallizations from acetic acid gave the analytical sample, m.p. 323–324°.

Anal. Calcd. for $C_{15}H_7ClN_2O$: C, 63.8; H, 2.5; Cl, 12.6; N, 9.9. Found: C, 63.6; H, 2.5; Cl, 12.6; N, 9.7.

N-(3,6-Dichloro-4-coumarinyl)butyramidine (XIVb).—To a stirred solution of 3.69 g. of butyramidine hydrochloride[24] in 125 ml. of absolute methanol was added 7.5 ml. of methanol which contained 0.03 mole of sodium methoxide. A fine precipitate of sodium chloride was formed. The mixture was cooled to 2° and 2.50 g. of Ib was added. The mixture was stirred at 2–3° 45 min. at 28–31° for 90 min., and at reflux for 90 min. Methanol was distilled until the reaction mixture volume was about 25 ml. Water (*ca.* 75 ml.) was added over a 15-min. period with stirring. The resulting white solid was filtered, washed with 25 ml. of water, and recrystallized from methanol (*ca.* 5 ml.) to yield 2.40 g. (80%) of XIVb, m.p. 154–156° (6.00 μ, 1667 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 155–156°.

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.3; H, 4.1; Cl, 23.6; N, 9.4. Found: C, 52.2; H, 4.2; Cl, 23.8; N, 9.2.

Note that the molar ratio of butyramidine to coumarin was 3. This was intended as cyclization of XIVb was expected. However, the cyclization did not occur.

N-(3-Chloro-4 coumarinyl)butyramidine (XIVa).—As above, reacted with butyramidine to give XIVa, m.p. 115–118° (6.04 μ, 1658 cm.$^{-1}$), in 67% yield. The analytical sample melted at 119–121°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: C, 59.0; H, 5.0; Cl, 13.4; N, 10.6. Found: C, 59.1; H, 5.0; Cl, 13.2; N, 10.5.

5-Chloro-3,4-dimethoxycoumarin (XV).—To a solution made by treating 0.46 g. of sodium with 40 ml. of absolute methanol was added 2.50 g. of Ib. The solution was refluxed for 1 hr. and the methanol was then removed under reduced pressure. The resulting white solid was washed with 30 ml. of water and recrystallized from absolute methanol (*ca.* 25 ml.) to yield 1.78 g. (74%) of XV, m.p. 100–102° (5.82 μ, 1720 cm.$^{-1}$). Several recrystallizations of I from methanol gave the analytical sample m.p. 101–102°.

Anal. Calcd. for $C_{11}H_9ClO_4$: C, 55.0; H, 3.8; Cl, 14.8. Found: C, 55.1; H, 4.0; Cl, 14.8.

To a solution of 3.66 g. of guanidine nitrate in 50 ml. of methanol was added an equivalent of sodium methoxide in methanol (10 ml.). After stirring at room temperature for 5 min., 2.50 g. of Ib was added and the reaction mixture was held at reflux for 3

(21) A. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p. 649.

(22) Obtained from Metal Hydrides, Inc., Beverly, Mass.

(23) Prepared from potassium permanganate and manganese sulfate by the procedure of J. Attenburrow, *J. Chem. Soc.*, 1094 (1952). The manganese dioxide used was about 2 months old.

(24) Purchased from Winthrop Laboratories, New York 18, N. Y.

hr. The methanol was removed under reduced pressure and the solid remaining was washed with water. Recrystallization from methanol afforded 1.2 g. (50%) of XV, m.p. and mixed m.p. with authentic sample, 101–102°.

2,9-Dichloro-6H,13H-*p*-dithiino[2,3-*c*:5,6-*c'*]bis[1]benzopyrane-6,13-dione (XVI).—A solution of 2.50 g. of Ib and 2.28 g. of thiourea in 125 ml. of absolute methanol was refluxed for 5 hr. A yellow precipitate formed after about 20 min. and became progressively heavier. The yellow solid was filtered from the hot methanol, washed with hot methanol (*ca.* 100 ml.), washed with water (*ca.* 100 ml.), and dried to yield 1.98 g. (94%) of XVI, m.p. > 450° (5.88 μ, 1770 cm.$^{-1}$). The material could not be satisfactorily recrystallized from any of the solvents tried nor could it be sublimed under vacuum. The analytical sample was obtained by extracting 0.5 g. with 200 ml. of boiling methanol and sending the residue for analysis.

Anal. Calcd. for $C_{18}H_6Cl_2O_4S_2$: C, 51.3; H, 1.4; Cl, 16.8; S, 15.2. Found: C, 51.0, 51.1; H, 2.0, 1.8; Cl, 16.7; S, 15.3.

4-(β-Hydroxyethylamino)coumarin (XVII).—A solution of 1.80 g. of 4-chlorocoumarin[25] and 1.22 g. of ethanolamine in 40 ml. of absolute methanol was refluxed for 45 min. The methanol was removed under reduced pressure and the resulting solid was washed with 30 ml. of water and recrystallized from methanol (*ca.* 15 ml.) to yield 1.50 g. (74%) of XVII, m.p. 171–173° (6.00 μ, 1643 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 172.5–174.0°.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.5; H, 5.4; N, 6.8. Found: C, 64.8; H, 5.7; N, 7.0.

A solution of 1.02 g. of XVII and 0.05 g. of fused sodium acetate in 5 ml. of acetic anhydride was refluxed for 2 hr., cooled, and poured into 40 ml. of cold water. The pH was adjusted to about 7.3 by the addition of potassium carbonate and the resulting white solid was filtered, washed with 75 ml. of water, and recrystallized from methanol (*ca.* 10 ml.) to yield 1.12 g. (90%) of 4-(β-acetoxyethylamino)coumarin, m.p. 161–163° (5.84 μ, 1716 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 162–163°.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.3; H, 5.3; N, 5.7. Found: C, 63.5; H, 5.5; N, 6.0.

N-(2-Acetoxyethyl)-N-acetyl-*o*-toluidine (XXII).—A solution of 100 g. of β-*o*-toluidinoethanol[26] (XVIII) and 0.1 g. of fused sodium acetate in 100 ml. of acetic anhydride was refluxed for 1 hr., cooled, and poured into 500 ml. of cold water. The pH was adjusted to about 7.5 by the addition of potassium carbonate. The mixture was extracted twice with 100 ml. of benzene. The combined benzene extract was washed twice with 50 ml. of water and once with 50 ml. of a saturated aqueous sodium chloride solution. The benzene was removed under reduced pressure. Two distillations of the residual oil gave 10.5 g. (68%) of XXII, b.p. 150–153° (4 mm.), $n^{24}D$ 1.5138 (5.78 μ, 1730 cm.$^{-}$) (6.02 μ, 1661 cm.$^{-1}$).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0. Found: C, 66.4; H, 7.4; N, 6.0.

3,6-Dichloro-4-(*n*-propylamino)coumarin (XIX).—A stirred slurry of 2.50 g. of Ib in 25 ml. of absolute methanol was cooled to 2° and to it was added 1.18 g. of *n*-propylamine. The stirring was continued and the temperature was maintained at 2–3° for 1 hr. at which point solution was complete, at 24–26° for 2 hr., and at 40–50° for 3 hr. The methanol was removed under reduced pressure and the resulting white solid was washed with 25 ml. of water and recrystallized from absolute methanol (*ca.* 25 ml.) to yield 2.63 g. (97%) of XIX, m.p. 189–190° (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 189.6–190.2°.

Anal. Calcd. for $C_{12}H_{11}Cl_2NO_2$; C, 53.0; H, 4.1; Cl, 26.0; N, 5.1. Found: C, 53.3; H, 4.3; Cl, 25.8; N, 5.1.

All attempts to prepare the bis-*n*-propylamino compound failed. When XIX was treated with two equivalents of *n*-propylamine in methanol or NMP it was recovered unchanged. Then XIX was added to excess *n*-propylamine at 2° only tars were isolated. When XIX was treated with refluxing acetic anhydride (sodium acetate catalyst), it was recovered unchanged.

(25) Prepared from 4-hydroxycoumarin (Aldrich Chemical Co., Milwaukee, Wis.) by the procedure of D. P. Spalding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 5338 (1950).

(26) Purchased from Distillation Products Industries, Rochester 3, N. Y.

Isolation, Identification, and Synthesis of Components of a "Styrene Dimer Fraction"

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The following components were isolated and identified in a "styrene dimer fraction" obtained by refluxing styrene with a small amount of sulfur: 1,3-diphenylpropane (I), *cis*-1,3-diphenyl-2-butene (IV), 2,4-diphenyl-1-butene (III), and *trans*-1,3-diphenyl-2-butene (V). This paper illustrates the utility of the combination of mass, infrared, n.m.r., and ultraviolet spectrometry in the identification of small amounts of organic compounds isolated by gas chromatography.

A "styrene dimer fraction" was obtained by refluxing 104 g. (1.00 mole) of freshly distilled styrene and 0.32 g. (0.010 mole) of sulfur for three hours at 143–150° (pot temperature) under nitrogen. Distillation at 0.2 mm. through a Vigreux column (8 in. × 1 in.) at 0.2 mm. gave 3.9 g. of a "dimer fraction" (head temperature 80–135°). We are concerned here with the isolation, identification, and synthesis of the components of this mixture. Results of a continuing study[1] of styrene dimerization will be presented elsewhere.

Four pure components were isolated by gas chromatography. The initial separation was made on a DC-710 silicone substrate; each of the three initial cuts was subjected to further separation on a QF1–0065 fluorosilicone substrate. Heart cuts on the latter substrate were taken until each of the four components isolated appeared to be chromatographically homogeneous on both substrates. Tentative identification was made by mass, infrared, nuclear magnetic resonance, and ultraviolet spectrometry, and by derivatization when indicated. Comparison of spectral characteristics and gas chromatographic behavior with those of authentic samples afforded conclusive identification. The components are numbered in order of elution from the DC-710 silicone column.

(1) F. R. Mayo, Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

Identification

Component No. 1.—Components no. 1 and no. 2 were eluted together from the DC710 silicone column and were separated by repeated passes on the QF1–0065 fluorosilicone column. On the latter column, component no. 2 preceded component no. 1.

A mass spectrum of component no. 1 showed a mass 208 peak (styrene dimer molecular weight is 208) whose intensity was 4% of the base peak, mass 92, which is a common benzyl rearrangement peak. The benzyl ion peak (91) was 57%; an unexpected peak at mass 196 (intensity 49%) was also present. The infrared spectrum showed more methylene absorption at 3.42 μ compared with the other components, and the n.m.r. spectrum effectively ruled out any styrene dimer structure we could write, including olefins, cyclobutanes, tetralins, or indanes. The n.m.r. spectrum showed 10 protons at τ 2.91, 4 protons as a slightly distorted triplet at τ 7.41, and 2 protons as a quintet (with some second-order perturbation) at τ 8.1. The answer quickly became apparent, once we assumed the mass 208 peak to be an impurity and took mass 196 as the parent peak. The parent +1 peak was 16.3% of the parent peak and the parent +2 peak was 1.26% of the parent peak. These values give an excellent fit for the calculated values[2,3] for empirical formula $C_{15}H_{16}$. With this information available, the n.m.r. spectrum spells out 1,3-diphenylpropane (I). Comparison with an authentic sample confirmed this identification.

$$C_6H_5CH_2CH_2CH_2C_6H_5$$
I

Though in retrospect the picture seems clear, considerable confusion ensued when chromic acid oxidation of component no. 1 yielded the same product obtained on oxidation of component no. 3; the product was β-phenylpropiophenone (II). Marion[4] pointed out that chromic acid oxidation of 1,3-diphenylpropane (I) gave a good yield of β-phenylpropiophenone (II). Marion also noted that Staudinger[5] obtained β-phenylpropiophenone (II) on oxidation of a "styrene dimer

$$C_6H_5CH_2CH_2\overset{\overset{O}{\|}}{C}C_6H_5$$
II

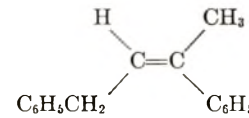
fraction" from pyrolysis of polystyrene. On this basis, Staudinger assumed the presence of 2,4-diphenyl-1-butene (III) in his "styrene dimer fraction." Marion

$$C_6H_5CH_2CH_2\overset{\overset{CH_2}{\|}}{C}C_6H_5$$
III

suggested that Staudinger's precursor was, in fact, 1,3-diphenylpropane (I) rather than 2,4-diphenyl-1-butene (III).

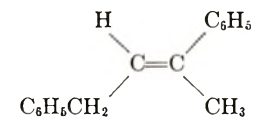
The presence of 1,3-diphenylpropane (I) in our "styrene dimer fraction" can be attributed to pyrolysis, during distillation, of the considerable amount of polystyrene present.

Component No. 2 and Component No. 4.—Component no. 2, a minor component, was separated, as noted above, from component no. 1 on the fluorosilicone column. The infrared spectrum showed two strong bands in the 13–14.5-μ region, characteristic of the C—H bending vibrations of monosubstituted benzene rings. The aliphatic C—H stretching band at 3.45 μ was weaker than the aromatic and olefin C—H stretching band at 3.32 μ. There was no sign of a C=C absorption in the 6.0–6.2-μ region nor could any band be definitely assigned to an olefinic C—H bending vibration. The n.m.r. spectrum was more informative. It showed ten aromatic protons at τ 2.85 and 2.93, one olefinic proton (triplet) at τ 4.42, two aliphatic protons (doublet) at τ 6.74, and three aliphatic protons (singlet) at τ 7.93. Under the circumstances, it is difficult to write any structure other than 1,3-diphenyl-2-butene (IV). The ultraviolet spec-



IV

trum showed benzenoid absorption in the 265–275-mμ region and a shoulder at 230 mμ (ϵ 7350). Comparison of the n.m.r. and ultraviolet spectra with those of component no. 4 permitted assignment of the *cis* structure to component no. 2, and the *trans* structure to component no. 4 (V).



V

Component no. 4 gave infrared and n.m.r. spectra very similar to those of component no. 2. The n.m.r. spectrum of component no. 4 showed ten aromatic protons at τ 2.85, one olefinic proton (triplet) at τ 4.08, two aliphatic protons (doublet) at τ 6.50, and three aliphatic protons (singlet) at τ 7.88. The significant downfield shift to τ 4.08 of the olefinic proton in component no. 4, compared with its position (τ 4.42) in component no. 2, permitted tentative assignment of structures; the phenyl ring of the *trans* configuration (V) accounts for the extra deshielding of the olefinic proton. The assignments were confirmed by the longer wave length absorption band in the ultraviolet spectrum of component no. 4 ($\lambda_{max}^{95\%\ EtOH}$ 245 mμ, ϵ 8250); this, presumably, is a consequence of less steric interference with coplanarity in the *trans* form.

The spectra of components 2 and 4 were identical with those of synthesized samples of IV and V.

Component No. 3.—The infrared spectrum of component no. 3, the major component, showed a C=C stretching absorption at 6.14 μ of medium intensity, and a fairly strong C—H bending absorption at 11.16 μ, characteristic of 2,2-disubstituted olefins ($R_2C{=}CH_2$). The n.m.r. spectrum showed 10 aromatic protons at τ 2.85 and 2.93, one olefinic proton (doublet with J of about 2 c.p.s.) at τ 4.84, one olefinic proton (poorly resolved doublet) at τ 5.05, and 4 aliphatic protons (sharp singlet) at τ 7.31.

The n.m.r. spectrum presented an impasse. As mentioned above, component no. 3 gave β-phenylpropiophenone (II) on oxidation. The mass spectrum supported the empirical formula $C_{16}H_{16}$: parent 208, 24% of base, parent + 1, 17.5% of parent (Calcd. 17.5%), impurity at parent + 2, base 91. The structure we were forced to write, 2,4-diphenyl-1-butene (III), would be expected to show two triplets for the

(2) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960.

(3) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," J. Wiley and Sons, Inc, New York, N. Y., in press. Table of Isotope Abundance Values reproduced with the kind permission of Dr. Beynon.

(4) L. Marion, *Can. J. Res.*, **16B**, 213 (1938).

(5) H. Staudinger and A. Steinhofer, *Ann.*, **517**, 35 (1935).

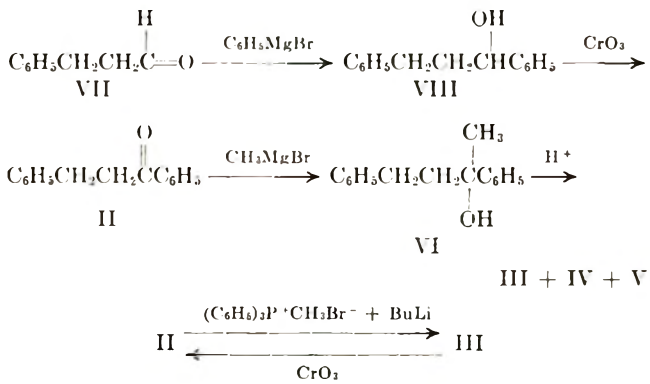
—CH_2CH_2— moiety or at least a broad partially split peak if the chemical shifts were similar. The singlet at τ 7.31 remained sharp with no sign of splitting on the 100-Mc. n.m.r. instrument. Apparently the chemical shifts of the two methylene groups are identical within present-day limits of resolution. An authentic sample of 2,4-diphenyl-1-butene (III) gave identical n.m.r. and infrared spectra.

To our knowledge, 2,4-diphenyl-1-butene (III) has not been previously identified in a styrene dimer fraction. Its significance as a major component in the present fraction will be described as part of the broad study of styrene dimerization.

Synthesis

An authentic sample of 1,3-diphenylpropane (I) was prepared by Clemmensen reduction of 1,3-diphenyl-2-propanone. The infrared and n.m.r. spectra and the gas chromatographic behavior of the synthetic product were identical with those properties of component no. 1.

The following sequence was carried out to furnish samples for comparison with components no. 2, 3, and 4.



Dehydration of 2,4-diphenyl-2-hydroxybutane (VI) gave a crude mixture of olefins which gave three peaks on gas chromatography on QF1–0065 fluorosilicone substrate. These peaks coincided precisely with the peaks of components no. 2, 3, and 4 of the "styrene dimer fraction." Infrared and n.m.r. spectra of the fractions isolated by gas chromatography of the dehydration mixture were identical with the spectra of the corresponding components isolated from the styrene dimer mixture.

Chromic acid oxidation of 2,4-diphenyl-1-butene (III) gave β-phenylpropiophenone (II). An unequivocal synthesis of 2,4-diphenyl-1-butene (III) was effected by reaction of β-phenylpropiophenone (II) with triphenylmethylphosphonium bromide (Wittig synthesis). The susceptibility to air oxidation of 2,4-diphenyl-1-butene (III), noted by Marion,[4] was confirmed; the infrared spectrum of a month-old sample showed diminution of the bands at 6.14 and 11.16 μ and appearance of an aromatic C=O band at 5.93 μ.

Experimental

Gas chromatography was carried out on a Wilkens Aerograph instrument. Infrared spectra were obtained on a Perkin–Elmer 221 instrument; n.m.r. spectra on a Varian HR-60; ultraviolet spectra on a Cary Model 14M; and mass spectra on a Consolidated Electrodynamics Corp. Model 21-103C.

Components no. 1 and 2 were eluted in 15 min., component no. 3 in 20 min., and component no. 4 in 30 min. under the following conditions: 30 λ sample, 30% DC710 silicone oil (Dow Corning) on firebrick, 6 ft. × 1/4 in. copper tubing, temperature 210°, helium flowrate 30 ml./min. The area ratios were 1:8:2.5 for components no. 1 and 2, component no. 3, and component no. 4, respectively.

Component no. 1 (elution time 17 min.) was separated from component no. 2 (elution time 15.5 min.) under the following conditions: 20 λ sample, 30% QFI-0065 fluorosilicone oil (Dow Corning) on Chromosorb W, 5 ft. × 1/4 in. copper tubing, temperature 155°, helium flow rate 40 ml./min. The ratio was 10 (component no. 1):1 (component no. 2). The elution times on the fluorosilicone column under the same conditions for components no. 3 and 4 were 22 and 32 min., respectively.

1,3-Diphenylpropane (I).—Clemmensen reduction[6] of 1,3-diphenyl-2-propanone (Eastman) gave 1,3-diphenylpropane (I) in 80% yield; b.p. 92°/0.15 mm. (lit.,[4] 124°/2 mm.); infrared (film); μ 3.33 (m), 3.43 (m), 3.51 (w), 6.25 (m), 6.67 (m), 9.24 (w), 9.70 (w), 11.06 (w), 13.45 (s), 14.35 (s); n.m.r. (CCl_4): τ 2.91 (singlet, 10), 7.41 (triplet, 4), 8.1 (perturbed quintet, 2).

1,3-Diphenyl-1-propanol (VIII).—The Grignard reagent, prepared from 2.43 g. of sublimed magnesium turnings and 15.7 g. of bromobenzene (0.1 mole) in dry ether, was added slowly to 13.4 g. (0.1 moles) of hydrocinnamaldehyde (Eastman), and the mixture was refluxed for 3 hr. ater was added, and the separated ether layer was washed with dilute hydrochloric acid and with water, then dried. The dried ether solution was evaporated on the steam bath. The residue was used directly in the next step.

β-Phenylpropiophenone (II).—The crude carbinol (VIII) was added portionwise over a period of 1 hr. to a warm (40°) chromic acid solution (50 g. of sodium dichromate dihydrate, 20 ml. of concentrated sulfuric acid, 400 ml. of water). The solution was allowed to stand at room temperature for 1 hr., cooled in an ice bath and extracted with ether. The ether solution was dried, and the ether was removed by distillation. The light tan solid residue (17 g.) was recrystallized from petroleum ether (b.p. 30–65°); the off-white product melted at 69–71° (lit.,[7] m.p. 73°); 2,4-dinitrophenylhydrazone (recrystallized from ethanol–water) 166–168° (lit., m.p. 142–144°,[8] 166°,[9] 186.6–187.2°[10]).

2,4-Diphenyl-2-hydroxybutane (VI).—A solution of 2.1 g. (0.01 mole) of β-phenylpropiophenone in 50 ml. of ether was added over a period of 20 min. to a refluxing solution of 0.015 mole of methylmagnesium iodide in 100 ml. of ether. Refluxing was continued for another 20 min. The mixture was cooled; water was added dropwise; the mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was dried and evaporated. The crude residue was used directly in the next step.

Dehydration of 2,4-Diphenyl-2-hydroxybutane (VI).—A mixture of 1.16 g. (0.00515 mole) of the crude carbinol (VI) and 25 ml. of 50% sulfuric acid was heated on the steam bath for 15 min. The reaction mixture was cooled, diluted with 50 ml. of water, and extracted with ether. Drying and evaporation of the ether solution gave 0.88 g. (82% yield) of a crude mixture of olefins. An infrared spectrum showed no hydroxyl band. The crude olefin mixture was chromatographed on a fluorosilicone column as described above. The three peaks obtained coincided with the peaks of components no. 2, 3, and 4 of the "styrene dimer fraction"; the area ratios were 1.7:1:7.3, respectively.

Olefin Mixture. A. *cis*-1,3-Diphenyl-2-butene (IV).—The compound that was eluted in 15.5 min. on the fluorosilicone column gave the following spectra. Infrared (film): μ 3.29 (shoulder), 3.32 (w), 3.45 (w), 3.51 (shoulder), 6.25 (w), 6.68 (m), 6.87 (w), 6.96 (w), 7.30 (w), 9.15 (w), 9.32 (w), 9.73 (w), 10.95 (w), 13.12 (m), 14.35 (s); n.m.r. (CCl_4): τ 2.85 and 2.93 (10), 4.42 (triplet, 1), 6.74 (doublet, 2), 7.93 (singlet, 3); ultraviolet (95% ethanol): 230 mμ (ϵ 7350), 266 mμ (ϵ 2600), 273 mμ (ϵ 1838).

(6) E. Clemmensen, *Ber.*, **47**, 681 (1914).

(7) R. Adams, J. W. Keon, and R. L. Shriner, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 101.

(8) L. F. Chelpanova, and Z. V. Printseva, *Zh. Obsch. Khim.*, **23**, 1135 (1953); *Chem. Abstr.*, **47**, 12211a (1953).

(9) J. Frederick, J. Dippy, and R. L. Lewis, *Rec. trav. chim.*, **56**, 1000 (1937); *Chem. Abstr.*, **32**, 5215 (1938).

(10) M. Romero and J. Romo, *Bol. inst. quim. univ. nal. auton. Mex.*, **4**, 3 (1952); *Chem. Abstr.*, **47**, 10498a (1953).

B. 2,4-Diphenyl-1-butene (III).—The compound that was eluted in 22 min. on the fluorosilicone column gave the following spectra. Infrared (film): μ 3.28 (shoulder), 3.32 (w), 3.42 (w), 3.50 (shoulder), 6.14 (m), 6.24 (w), 6.67 (w), 6.86 (m), 9.30 (w), 9.70 (w), 11.16 (m), 12.87 (m), 13.40 (m), 14.35 (s); n.m.r. (CCl_4): τ 2.85 and 2.93 (10), 4.84 (doublet, 1, J = 2 c.p.s.), 5.05 (partially resolved doublet, 1), 7.31 (singlet, 4).

C. *trans*-1,3-Diphenyl-2-butene (V).—The compound that was eluted in 32 min. on the fluorosilicone column gave the following spectra. Infrared (film) μ 3.28 (shoulder), 3.30 (w), 3.43 (w), 6.25 (w), 6.68 (m), 6.87 (m), 7.25 (w), 9.32 (w), 9.47 (w), 9.71 (w), 13.25 (s), 13.50 (shoulder), 14.40 (s); n.m.r. (CCl_4): τ 2.85 (multiplet, 10), 4.08 (triplet, 1), 6.50 (doublet, 2), 7.88 (singlet, 3); ultraviolet (95% ethanol): 245 mμ (ϵ 8250), 273 mμ (ϵ 3750 sh).

2,4-Diphenyl-1-butene (III) (Wittig Synthesis[11]).—A suspension of triphenylmethylphosphonium bromide (Beacon Chemical Industries) (1.43 g., 0.004 mole) in a solution of 0.320 g. (0.005 mole) of *n*-butyllithium in 25 ml. of ether was stirred at 25° under nitrogen for 2 hr. To the solution which was effected during this period, was added 0.84 g. (0.004 mole) of β-phenylpropiophenone (II); stirring was continued at 25° for another 0.5 hr. Dry tetrahydrofuran (50 ml.) was added, the ether removed by distillation, and the solution was refluxed for 4 hr. The tetrahydrofuran was distilled at 20 mm., and the residue was triturated with six 40-ml. portions of pentane. Removal of the pentane left 0.68 g. of a colorless oil. Chromatography on the fluorosilicone column at 190° and 40 ml. min. gave a major peak at 9 min. and a small peak (starting ketone, 5% of the major peak) at 21 min. The infrared and n.m.r. spectra of the compound represented by the major peak were identical with those obtained from component no. 3 of the "styrene dimer fraction," and from the second fraction of the chromatographed olefinic dehydration mixture.

(11) S. Trippett, "Advances in Organic Chemistry," Vol. I, Interscience Publishers, New York, N. Y., 1960, p. 83.

Anal. Calcd. for $C_{16}H_{16}$ (208.29): C, 92.26; H, 7.74. Found: C, 92.38; H, 8.03.

Oxidation of Component No. 1.—To a solution of 10 mg. of component no. 1 in 0.5 ml. of glacial acetic acid held at 70°, was added, portionwise, 50 mg. of chromic anhydride over a period of 45 min. The mixture was cooled and extracted with ether which then was washed with 10% sodium hydroxide solution, dried, and evaporated. The residue in 0.2 ml. of hexane was placed on an alumina column (Merck, acid-washed, 0.5 g. in a 4-mm. tube) and eluted with hexane. The hexane solution was concentrated to 0.2 ml., cooled to −30°, and filtered. A 4-mg. crop of crystals was obtained, m.p. 70–73° (lit.,[7] m.p. for β-phenylpropiophenone 73°). Admixture with an authentic sample (II) did not depress the melting point; infrared (melt): 5.92 μ (C=O).

Oxidation of Component No. 3.—A 2% aqueous solution of potassium permanganate was added dropwise over a period of 2 hr. to 10 mg. of component 3 on a steam bath until the permanganate color persisted. The mixture was extracted with ether, and the ether solution was dried and evaporated. The residue was treated with 2,4-dinitrophenylhydrazine. Three recrystallizations of the product from ethanol–water gave the 2,4-dinitrophenylhydrazine, m.p. 162–164.5°, whose identity was proved by mixed melting point with an authentic sample of β-phenylpropiophenone 2,4-dinitrophenylhydrazone and by comparison of the infrared spectra.

Acknowledgment.—The work described is part of a broad study of styrene dimerization by Dr. F. R. Mayo who furnished the fraction described. The authors are indebted to Mr. Norman Bhacca of Varian Associates for the 100-Mc. n.m.r. spectrum, and to Dr. S. A. Fuqua of Stanford Research Institute for many helpful discussions of n.m.r. spectra. The n.m.r. and mass spectra were run at Stanford Research Institute by Mr. W. R. Anderson, Jr., and Mrs. L. Peters, respectively.

The Metalation of Methyl(disubstituted)phosphine Oxides and Their Subsequent Reactions

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A series of phosphine oxides containing an additional carboxy, hydroxy, carbonyl, or phosphinyl group was prepared by reaction of the lithium metalated methyl(disubstituted)phosphine oxide with the appropriate reagent. The physical data and the infrared frequencies of the main functional groups are reported.

Bis(disubstituted phosphinyl)methanes, $R_2P(O)CH_2P(O)R_2$, appear to be more effective extractants for various metal ions than the monophosphine oxides.[1] It was found desirable to study the effect of substitution of other functional groups for one of the phosphinyl groups on the extractability of metal ions.

Use was made of the acidic nature of the hydrogen atom of a methylene group adjacent to the P—O group of a phosphine oxide to introduce functional groups such as carboxy, hydroxy, and carbonyl into the molecule.[2–6] Di-*n*-hexylmethylphosphine oxide and methyldiphenylphosphine oxide were first metalated with *n*-butyllithium and the resulting intermediate was treated with the various types of compounds listed below to give the indicated product. The method also can be used to prepare bis(disubstituted phosphinyl)methanes (equation 5).

$$R_2P(O)CH_2Li + CO_2 \longrightarrow \xrightarrow{H^+} R_2P(O)CH_2CO_2H \quad (1)$$

$$R_2P(O)CH_2Li + R'CHO \longrightarrow \xrightarrow{H^+} R_2P(O)CH_2C(OH)HR' \quad (2)$$

$$R_2P(O)CH_2Li + R_2'CO \longrightarrow \xrightarrow{H^+} R_2P(O)CH_2C(OH)R_2' \quad (3)$$

$$R_2P(O)CH_2Li + R'CO_2Et \longrightarrow R_2P(O)CH_2C(O)R' \quad (4)$$

$$R_2P(O)CH_2Li + R_2'P(O)Cl \longrightarrow R_2P(O)CH_2P(O)R_2' \quad (5)$$

Although the lithium salts of the methyl(disubstituted)phosphine oxides were not isolated, they were formed in at least 60–70% yield as indicated by the recovery of the carboxymethyl(disubstituted)phosphine oxides.

(1) K. E. Burke, J. J. Richard, H. Sakurai, J. W. O'Laughlin, and C. V. Banks, 138th National Meeting of the American Chemical Society, Abstracts, p. 13-B; *Chem. Eng. News*, p. 57, (September 19, 1960).

(2) L. Horner, H. Hoffmann, and H. G. Wippel, *Ber.*, **91**, 61 (1958).

(3) L. Horner, H. Hoffmann, H. Wippel, and G. Klahre, *ibid.*, **92**, 2499 (1959).

(4) F. Hein and H. Hecker, *ibid.*, **93**, 1339 (1960).

(5) L. Horner, H. Hoffmann, and V. G. Toscano, *ibid.*, **95**, 536 (1962).

(6) L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. G. Toscano, *ibid.*, **95**, 581 (1962).

TABLE I

PREPARATION AND PROPERTIES OF SOME PHOSPHINE OXIDES

	Compound	Yield, %	B.p. °C.	B.p. Mm.	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
1.	$(C_6H_{13})_2P(O)CH_2CO_2H$	67				60.84	60.82	10.57	10.80	11.21	11.11
2.	$(C_6H_5)_2P(O)CH_2CO_2Na$	63				59.58	59.61	4.29	4.38	10.98	11.25
3.	$(C_6H_5)_2P(O)CH_2CO_2H$[a,b]				145–146						
4.	$(C_6H_{13})_2P(O)CH_2CO_2CH_3$	50	168	0.3		62.04	61.61	10.76	10.81	10.67	10.90
5.	$(C_6H_{13})_2P(O)CH_2C(OH)(C_2H_5)_2$	46	158–168	.1		67.88	67.82	12.34	12.22	9.71	9.70
6.	$(C_6H_5)_2P(O)CH_2C(OH)(C_2H_5)_2$	61			114–116	71.50	71.55	7.67	7.72	10.24	10.15
7.	$(C_6H_{13})_2P(O)CH_2C(OH)(C_6H_5)_2$	49			82–83	75.33	75.76	9.48	9.57	7.47	7.39
8.	$(C_6H_5)_2P(O)CH_2C(OH)(C_6H_5)_2$	81			192–193	78.37	78.84	5.82	5.85	7.77	7.75
9.	$(C_6H_{13})_2P(O)CH_2CH(OH)(C_6H_5)$	50	220	.15		70.97	71.29	10.42	10.48	9.15	9.11
10.	$(C_6H_{13})_2P(O)CH{=}CH(C_6H_5)$	10	205–210	.15		74.96	75.08	10.38	10.45	9.67	9.56
11.	$(C_6H_5)_2P(O)CH_2CH(OH)(C_6H_5)$	31			141–142	74.75	74.70	5.65	5.94	9.61	9.69
12.	$(C_6H_{13})_2P(O)CH_2C(OH)(C_6H_5)CH_3$	51	207	.18	83–84	71.55	71.50	10.59	10.76	8.79	8.92
13.	$(C_6H_{13})_2P(O)CH_2CH(OH)CH_3$	44	165–170	.20		65.18	65.10	12.03	11.84	11.21	11.01
14.	$(C_6H_{13})_2P(O)CH_2CH(OH)C_3H_7$	33	175	.25		67.03	67.25	12.25	12.22	10.18	9.97
15.	$(C_6H_5)_2P(O)CH_2P(O)(C_8H_{17})_2$	25			96–97	71.28	71.00	9.50	9.48	12.68	12.66
16.	$(C_6H_{13})_2P(O)CH_2C(O)CH_3$	30	137–144	.10		65.66	65.47	11.39	11.44	11.29	11.32
17.	$(C_6H_{13})_2P(O)CH_2C(O)C_6H_5$	33	182–187	.05		71.39	71.28	9.89	9.74	9.21	9.27
18.	$(C_6H_5)_2P(O)CH_2C(O)C_6H_5$[c]	40			139–140	74.97	74.99	5.35	5.43	9.67	9.61
19.	$(C_6H_{13})_2P(O)CH_2P(O)(C_6H_{13})_2$[d]	35	225–235	.23							
20.	$(C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2$[e]	25			178–180						

[a] Calcd.: equiv. wt., 260. Found: equiv. wt., 259. [b] Reported[11] m.p. 142–144°. [c] Reported[13] m.p. 140–140.5°. [d] Reported[10] b.p. 218–223° at 0.2 mm. [e] Reported[10] m.p. 180–182°.

The β-hydroxyphosphine oxides, as opposed to the α-hydroxyphosphine oxides which decompose into starting material when heated to their melting points or when dried at 100°,[7] are thermally stable. Di-*n*-hexyl(2-hydroxy-2-phenylethyl)phosphine oxide, however, partially dehydrates upon distillation. Distillation also causes the carboxymethyl(disubstituted)phosphine oxides to decarboxylate.

The infrared data would seem to indicate that the β-hydroxyphosphine oxides are intramolecularly hydrogen bonded as are the α-hydroxyphosphine oxides.[8] The hydroxy band is shifted an average of only 70 cm.$^{-1}$ on going from solid or liquid state into solution in carbon tetrachloride (1% by weight) and further dilution produced no further shift.

Initial studies by reversed-phase chromatography indicate that several of these compounds may possess desirable characteristics as extractants for metal ions. A systematic study of their properties as extractants will be made in the future.

Experimental

Methyldiphenylphosphine Oxide[9] and Di-*n*-hexylmethylphosphine Oxide.[10]—Most of di-*n*-hexylmethylphosphine oxide used in the following experiments was obtained as a by-product from the synthesis of bis(di-*n*-hexylphosphinyl)methane,[10] but can be prepared in 70% yield by the synthesis listed below. One mole of diethyl hydrogen phosphite was added to 3 moles of the Grignard reagent (*n*-hexyl or phenyl) at such a rate to maintain steady reflux. The mixture was refluxed for an additional 3 hr., at which time a mole of methyl bromide dissolved in anhydrous ether was added. The mixture was refluxed overnight, hydrolyzed, and the phases separated. Di-*n*-hexylmethylphosphine oxide was obtained in 70% yield upon distillation of the organic phase, b.p. 130–135° at 0.2 mm. Methyldiphenylphosphine oxide[9] was obtained upon evaporation of the aqueous phase (pH 6) after removal of the magnesium hydroxide by filtration or centrifugation (pH 12). The methyldiphenylphosphine oxide separated as an oil and was extracted into hot benzene from which it crystallized on cooling. A 50% yield was obtained, m.p. 108–109°.

Lithium Salts of Di-*n*-hexylmethylphosphine Oxide (I) and Methyldiphenylphosphine Oxide (II).—*n*-Butyllithium (0.1 mole) dissolved in hexane was added to 0.1 mole of methyl(disubstituted)phosphine oxide dissolved in 300 ml. of anhydrous ether in a 500-ml. three-necked flask equipped with stirrer, dropping funnel, and reflux condenser. The mixture was refluxed for 4 hr. and used in the reactions below. An inert atmosphere was maintained throughout the reactions.

Carboxymethyldi-*n*-hexylphosphine Oxide and Carboxymethyldiphenylphosphine Oxide.—The lithium salt, I or II, was poured with stirring onto a slurry of Dry Ice and ether. The ether was evaporated and the residue was dissolved in dilute base. This solution was acidified and the carboxymethyldi-*n*-hexylphosphine oxide was purified by reextracting into ether. The purification process was repeated a second time and gave almost complete removal of the unreacted starting material. Carboxymethyldiphenylphosphine oxide, upon acidification, separated into a third phase. The desired phase was separated and the sodium salt precipitated by the addition of a small amount of concentrated aqueous sodium hydroxide. The sodium salt was recrystallized from acetone. Acidification of the sodium salt with dilute hydrochloric acid gave the acid.[11]

Di-*n*-hexyl(methoxycarbonylmethyl)phosphine Oxide.—Carboxymethyldi-*n*-hexylphosphine oxide was esterified using methyl alcohol in the usual manner. Sapon. equiv.—calcd.: 290.4; found: 289.1.

β-Hydroxyphosphine Oxides.—The appropriate ketone or aldehyde (0.1 mole) dissolved in 50 ml. of anhydrous ether was added to the lithium salt, I or II. The mixture was refluxed for 4 hr., cooled, and hydrolyzed with 3% hydrochloric acid. The phases were separated and the ether phase was washed with two small portions of water. The ether was evaporated and the residue was either recrystallized or vacuum distilled.

(2-Ethyl-2-hydroxybutyl)di-*n*-hexylphosphine oxide and (2-ethyl-2-hydroxybutyl)diphenylphosphine oxide were prepared by the reaction of 3-pentanone with I and II, respectively. The aryl compound was recrystallized from ether.

Di-*n*-hexyl(2-hydroxy-2,2-diphenylethyl)phosphine oxide and (2-hydroxy-2,2-diphenylethyl)diphenylphosphine oxide were prepared by the reaction of benzophenone and I and II, respectively. After removal of the unchanged di-*n*-hexylmethylphosphine oxide by vacuum distillation, the hexyl compound was re-

(7) R. C. Miller, C. D. Miller, W. Rogers, Jr., and L. Hamilton, *J. Am. Chem. Soc.*, **79**, 424 (1957).

(8) C. D. Miller, R. C. Miller, and W. Rogers, Jr., *ibid.*, **80**, 1562 (1958).

(9) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 115.

(10) J. J. Richard, K. E. Burke, J. W. O'Laughlin, and C. V. Banks, *J. Am. Chem. Soc.*, **83**, 1722 (1961).

(11) K. Issleib and G. Thomas, *Ber.*, **94**, 2244 (1961).

crystallized from petroleum ether (b.p. 65–110°). The tetraphenyl compound precipitated from the reaction mixture upon hydrolysis. It was filtered and recrystallized from benzene.

Di-*n*-hexyl(2-hydroxy-2-phenylethyl)phosphine oxide and 2-(hydroxy-2-phenylethyl)diphenylphosphine oxide were prepared by the reaction of benzaldehyde and I and II, respectively. The *n*-hexyl compound dehydrated upon distillation giving di-*n*-hexylstyrylphosphine oxide. If the ether solution is extracted with base prior to distillation, the dehydration product is held to approximately 10% of the total yield. The aryl compound was purified by recrystallization from benzene.

Di-*n*-hexyl (2-hydroxy-2-phenylpropyl)phosphine oxide, di-*n*-hexyl(2-hydroxy-*n*-propyl)phosphine oxide, and di-*n*-hexyl-(2-hydroxy-*n*-pentyl)phosphine oxide were prepared by the reaction of I with acetophenone, acetaldehyde, and butyraldehyde, respectively.

The disubstituted phosphinyl chlorides used in the following preparations were prepared by the method of Kosolapoff.[12]

Bis(di-*n*-hexylphosphinyl)methane[10] was prepared by the reaction of di-*n*-hexylphosphinyl chloride, b.p. 160–163° at 1 mm., and I. The reaction mixture was refluxed for 4 hr., hydrolyzed, extracted with 5% sodium hydroxide and water, and vacuum distilled.

Bis(diphenylphosphinyl)methane[10] was prepared by the reaction of diphenylphosphinyl chloride and II. The product is very insoluble in the reaction media and precipitated as a sticky residue at the bottom of the flask. The liquid was decanted from the residue which was then dissolved in hot benzene from which it crystallized on cooling.

[(Di-*n*-octylphosphinyl)(diphenylphosphinyl)]methane was prepared by the reaction of di-*n*-octylphosphinyl chloride, b.p. 190° at 0.1 mm., and II. The reaction mixture, after having been refluxed for 4 hr., was hydrolyzed with 3% hydrochloric acid, the layers were separated, and the organic layer was extracted with 5% sodium hydroxide and water several times to remove the methyldiphenylphosphine oxide and di-*n*-octylphosphinic acid. Purification was by recrystallization from petroleum ether (b.p. 65–110°).

Di-*n*-hexylphenacylphosphine oxide and acetonyldi-*n*-hexylphosphine oxide were prepared by the reaction of I with ethyl benzoate and ethyl acetate, respectively. The phenacyl compound was isolated and purified by recrystallization from ether–petroleum ether (b.p. 30–60°) at −80° or vacuum distillation and the acetonyl compound was vacuum distilled.

(12) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 3950 (1959).

TABLE II

PHOSPHORYL, HYDROXYL, AND CARBONYL FREQUENCIES OF SOME PHOSPHINE OXIDES

Compound	P—O, cm.⁻¹ Solid or liquid	P—O, cm.⁻¹ 1% solution in CCl_4	OH, cm.⁻¹ Solid or liquid	OH, cm.⁻¹ 1% solution in CCl_4	C=O, cm.⁻¹ Solid or liquid
1[a]	1110		2500		1715
2	1186				1612 and 1360
3	1170				1715
4	1162				1135
5	1142	1168	3330	3430	
6	1163	1182	3420	3470	
7	1133	1150	3260	3330	
8	1162	1177	3380	3380	
9	1147	1150	3230	3280	
10	1159				
11	1174	1185	3270	3440	
12	1143	1168	3300	3380	
13	1142	1157	3280	3330	
14	1142	1157	3280	3380	
15	1186				
16	1170				1710
17	1173				1680
18	1177				1670
19	1164				
20	1190				
21[b]	1150				
22[c]	1168				

[a] See Table I. [b] Di-*n*-hexylmethylphosphine oxide. [c] Methyldiphenylphosphine oxide.

Phenacyldiphenylphosphine oxide[13] was prepared by treating ethyl benzoate and II. It was recrystallized from acetone.

Physical properties, yields, and analytical data for the compounds prepared are compiled in Table I. Those features of the infrared spectra used in confirming assigned structures are listed in Table II. The spectra described here were obtained with a Perkin–Elmer Model 21 double beam instrument. Liquid samples and low melting solids were scanned as capillary films while the higher melting solid samples were scanned as potassium bromide pellets. The hydroxy-containing phosphine oxides were also scanned in 1% by weight solution of carbon tetrachloride.

(13) M. Saunders and G. Burchman, *Tetrahedron Letters*, **1**, 8 (1959).

Synthesis of Nitro-olefins from Olefin Dinitrogen Tetroxide Adducts[1]

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A convenient synthesis has been developed for the direct conversion of 1-octadecene into 1-nitro-1-octadecene and of cyclooctene into 1-nitrocyclooctene in 80% and 95% yields, respectively. The reaction involves addition of the olefin and oxygen to an ethereal solution of dinitrogen tetroxide and subsequent elimination of nitrous and nitric acids from the adducts with triethylamine. Elimination reactions of the independently synthesized intermediates of the addition were studied with several bases. The dependence of the product composition on the amount of oxygen used in the dinitrogen tetroxide–olefin reaction was investigated by quantitative infrared analysis, and the relative rates of elimination were determined. The results led to a nitro-olefin synthesis from a 1-olefin making isolation of any intermediate unnecessary.

Addition of pure dinitrogen tetroxide and oxygen to 1-olefins in ether or ester-type solvents has been shown[2–4] to give dinitro, I, nitro nitrite, II, nitro nitrate, III, and nitro ketone, IV, compounds as the major products.

$$RCH{=}CH_2 \xrightarrow{N_2O_4} \underset{\displaystyle X}{RCHCH_2NO_2} + \underset{\displaystyle O}{RCCH_2NO_2}\quad IV$$

(I. X = NO_2)
(II. X = ONO)
(III. X = ONO_2)

Oxygen is responsible for the formation of III[2] and IV[3,4]; both are formed at the expense of I. The unstable nitro nitrite, II, is isolated as nitro alcohol V

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) H. Baldock, N. Levy, and C. W. Scaife, *J. Chem. Soc.*, 2627 (1949), and previous papers.

(3) T. E. Stevens, *J. Am. Chem. Soc.*, **81**, 3593 (1959).

(4) T. E. Stevens, *Chem. Ind.* (London), **38**, 499 (1960).

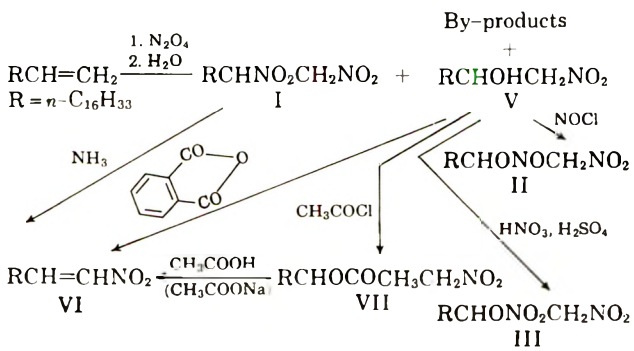
(X = OH) after hydrolysis of the crude nitration mixture.[2]

The products of dinitrogen tetroxide–olefin addition have been converted to 1-nitro-olefin by various methods—*e.g.*, acetylation of the nitro alcohol, V, and elimination of acetic acid with potassium carbonate,[5,6] dehydration of the nitro alcohol with phthalic anhydride[7] or potassium hydrogen sulfate,[8] or base-catalyzed elimination of nitrous and nitric acid, from dinitro compounds and nitro nitrates, respectively.[2] The stability of the product nitro-olefins to bases depends on the structure of the nitro-olefin—*e.g.*, 1-nitro-2-methylpropene is stable to sodium hydroxide[9] while nitroethylene polymerizes already with water. The routes known to lead from 1-olefins to 1-nitro-olefins require separation of the dinitrogen tetroxide–olefin reaction products, since either the dinitro compound or the nitro alcohol is used as starting material. In the case of higher 1-olefins, this separation is difficult[10,11];—*e.g.*, pure 1,2-dinitrooctadecane could not be isolated from a dinitrogen tetroxide-1-octadecene reaction mixture.[11]

The objective of this work was to develop a direct method of converting olefins into 1-nitro-olefins. 1-Octadecene and cycloöctene were chosen as prototypes. Treatment of the crude dinitrogen tetroxide–octadecene reaction mixture with ammonia in either anhydrous or wet ether—or urea and dioxane—elimination conditions, which were shown to be successful for converting 2,4,4-trimethyl-1-pentene to 1-nitro-2,4,4-trimethyl-1-pentene,[2] led to only small amounts of 1-nitro-1-octadecene. Therefore, the individual components of the 1-octadecene–dinitrogen tetroxide reaction mixture were prepared and the elimination reactions of the pure components studied in detail with different bases.

Results and Discussion

The pure compounds were synthesized as indicated in the following scheme:



Addition of dinitrogen tetroxide to 1-octadecene,[10] hydrolysis, and subsequent fractional crystallization gave pure 1-nitro-2-octadecanol,[10] V, and 1,2-dinitrooctadecane, I, of > 90% purity; infrared spectra and elemental analyses of I proved the complete absence of V and 1-nitro-2-octadecyl nitrate, III, and the presence of less than 10% 1-nitro-1-octadecene, VI; the latter did not interfere with the elimination studies. The nitrate ester, III, of 1-nitro-2-octadecanol was obtained by esterification of V with nitric and sulfuric acids in the presence of urea. The nitrite ester, II, of the same alcohol was synthesized by reaction of V with nitrosyl chloride and pyridine in ether. As reported previously,[2] nitrite esters of this type are thermally unstable; and attempts to isolate them failed. Our infrared investigations, however, showed that an ether solution of II was stable at −80° and contained at least 88% of pure II; the major impurity was V (8%) and did not interfere in the elimination studies. Pure VI was prepared by dehydrating V with phthalic anhydride and purified by chromatography on silicic acid. Elimination of nitrous acid from I with ammonia in ether[10] or treatment of 1-nitro-2-octadecyl acetate, VII, with acetic acid and sodium acetate followed by chromatography also led to pure VI.

In dinitrogen tetroxide–olefin reactions the nitro nitrite, II, represents a major portion of the yield. The hitherto undescribed elimination of nitrous acid from II to give VI proceeded in variable yield depending on the base used; in each case the primary elimination product was VI rather than 2-(1-octadecenyl) nitrite, since the infrared spectra of the crude elimination products never showed any terminal methylene absorption. Although no kinetic study was made, infrared analyses of reactants and products at various reaction times allowed a comparison of relative rates. The relative rates of elimination of nitrous acid from I and II and nitric acid from III to give VI were found to be I > III > II; for instance, with pyridine as both solvent and base the elimination reactions gave half lives of one minute for I, two minutes for III, and fifteen minutes for II at room temperature.

The rate of elimination of nitric acid from III being greater than that of nitrous acid from II is explained by NO_3^- being a better leaving group than NO_2^-. Since NO_3^- is a weaker base than NO_2^-, these rate observations are analogous to those in displacement reactions.[12] The fact that I eliminates nitrous acid faster than II is due to the easier breaking of a C—N bond compared with a C—O bond.[13]

Since ether is the best solvent for the dinitrogen tetroxide addition reaction, an elimination reaction in the same solvent is preferred. Compounds I and III give excellent yields of VI using different bases in ether solvent. However, the elimination of nitrous acid from II proceeds in variable yields of VI depending on the base used. This is due to a combination of two major factors: (1) the variable stability of VI to nucleophilic attack by different bases; and (2) the slow rate of elimination of nitrous acid from II. This point is illustrated further in the Experimental, which shows some data on eliminations with ammonia and triethylamine as bases. The rate of elimination of nitrous acid from II with ammonia as base overlaps with the rate of subsequent reaction of VI and, therefore, a decreased yield of VI is obtained. This subsequent reaction of the nitro-olefin can be addition of the base or nitro compound[14] or base catalyzed polymerization of VI.

(5) E. Schmidt and G. Rutz, *Ber.*, **61**, 2142 (1928).
(6) H. Schwartz and G. Nelles, U.S. Patent 2,257,980 (October 7, 1941).
(7) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).
(8) H. Wieland and E. Sakellarios, *Ber.*, **52**, 898 (1919).
(9) N. Levy, C. W. Scaife, and A. E. W. Smith, *J. Chem. Soc.*, 52 (1948).
(10) C. R. Porter and B. Wood, *J. Inst. Petrol.*, **38**, 877 (1952).
(11) C. R. Porter and B. Wood, *ibid.*, **37**, 388 (1951).
(12) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1956, p. 164.
(13) L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd ed., D. C. Heath and Company, Boston, Mass., 1957, p. 1111.
(14) C. W. Scaife and A. E. Wilder-Smith, *J. Chem. Soc.*, 1474 (1947).

Since the nitro nitrite is a major product in any dinitrogen tetroxide–olefin reaction, it was necessary to find a base which shows a faster rate of elimination but less tendency to attack VI. Triethylamine is a stronger and, therefore, faster eliminating base than ammonia. With triethylamine the important elimination of nitrous acid from II proceeds in an over 90% yield in fifteen minutes. The fact that VI is more stable to triethylamine than to ammonia can be attributed to the greater steric requirements of triethylamine for nucleophilic attack. The conditions of run 7, Table III, are the preferred ones to convert a crude dinitrogen tetroxide–1-octadecene reaction product to VI. With the knowledge of the optimum elimination behavior of I, II, and III, the dinitrogen tetroxide–olefin reaction was studied to maximize their formation at the expense of nitro ketone, nitronitroso compounds and nitro alcohol, V (Table I).

TABLE I

REACTIONS OF 1-OCTADECENE AND DINITROGEN TETROXIDE WITH SUBSEQUENT TRIETHYLAMINE TREATMENT OF THE CRUDE NITRATION SOLUTIONS[a]

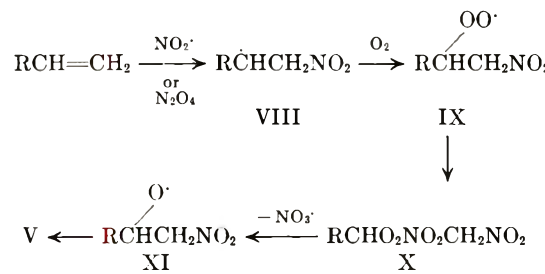
Run	O_2[b]/olefin (moles)	Mole % composition of crude dinitrogen tetroxide–olefin reaction solution[a] I	II	III	V[d]	Carbonyl compound[e]	Mole % yield of V after hydrolysis	Mole % yield of VI after elimination[f]
1	N_2	42	21	0	11	0	..	59
2	1/7	[c]	..	..	..	Large amount	..	61
3	1/50	45	39	6	..	0	44	75
4	1/150	45	36	7	13	Trace	49	77

[a] The amount of ether was chosen so that the concentration of nitro compounds after quantitative reaction of the olefin would be 33% for runs 1 and 2 and 50% for runs 3 and 4. [b] In run 1 nitrogen was used as carrier gas for the dinitrogen tetroxide; in runs 2, 3, and 4, the ether solvent was saturated with oxygen before the reaction was started. The ratios of oxygen to olefin given represent the amount run through the solution during the reaction. [c] Not analyzed. [d] The values are based on the assumption that the OH absorption is due to nitro alcohol V exclusively. [e] Presumably α-nitro ketone IV.[3,4] [f] The values are calculated as per cent of theory based on starting olefin.

In all runs the dinitrogen tetroxide was kept in slight excess during the addition. With small amounts of oxygen, the sum of the desired products (I, II, and III) accounted for about 90% of the starting olefin. If, however, oxygen is replaced by nitrogen, I and II constitute only 63% based on starting olefin, and the reaction is accompanied by green and blue coloration. The color effect also occurred to a much smaller extent in runs 3 and 4. It is presumably due to the formation of nitronitroso compounds[2] formed by addition of dinitrogen trioxide. Increasing the amount of oxygen during the reaction above the level used in run 3 again results in a decreased yield of the sum of I, II, and III (run 2). A carbonyl compound, presumably α-nitro ketone[3,4] IV, is a major by-product. A reliable check of the spectrally determined product composition is the amount of VI found after elimination with triethylamine. Runs 3 and 4 also show that a small amount of oxygen keeps the formation of nitronitroso compounds at a low level and yet does not generate more than a trace of carbonyl compound. The conditions of addition of run 4 are the preferred ones for the synthesis of VI from 1-octadecene.

An interesting observation in the addition of dinitrogen tetroxide is the formation of hydroxyl-containing compounds before hydrolysis. Aliquots of the dinitrogen tetroxide–olefin reaction mixtures of runs 3 and 4 were subjected to hydrolysis, and the products were analyzed for nitro alcohol, V. In both runs the amounts of nitro alcohol, V, formed after hydrolysis were larger than the amounts of nitro nitrite, II, observed in the original reaction solution. The nitro nitrate, III, does not hydrolyze under these conditions. In addition, the crude dinitrogen tetroxide–olefin reaction mixture showed infrared bands in the OH region; and the intensity of this absorption band was unchanged after elimination with triethylamine. The likely conclusion from these observations is that some nitro alcohol, V, may be formed during the addition of dinitrogen tetroxide to the olefin. In fact, if one attributes the total absorbance of OH observed in the crude dinitrogen tetroxide–olefin reaction solution of run 4 to V, the calculated amount of V corresponds to the difference between II found in the crude dinitrogen tetroxide–olefin reaction solution and V determined after hydrolysis; however, other OH-containing compounds such as hydroperoxides and oximes may conceivably be present in small amounts.

The presence of nitro alcohol, V, or some other hydroxylated compounds can be accommodated by an extension of an already suggested[3] reaction scheme.



The formation of I and II has been shown to proceed by a free radical mechanism[15–19] and a direct interaction of oxygen with the initially formed nitroalkyl radical VIII to give a nitroperoxy radical IX or nitroperoxy nitrate X has been suggested[3] to explain the products of the reaction of dinitrogen tetroxide with stilbene, styrene, and camphene. The hydroxyl containing compounds, which we observed, could then be formed by hydrogen abstraction by IX to give hydroperoxide or by cleavage of X to the nitroalkoxy radical XI, which could form V by hydrogen abstraction or by disproportionation to IV and V. The nitrate ester III could be formed from XI by reaction of the latter with nitrogen dioxide. The observed hydroxyl absorption in the dinitrogen tetroxide–1-octadecene reaction with nitrogen could be due to oxime formation; the latter is conceivable from the known[2] addition of dinitrogen trioxide to the olefin which occurs in the absence of oxygen.

(15) H. Shechter and F. Conrad, *J. Am. Chem. Soc.*, **75**, 5610 (1953).
(16) H. Shechter, F. Conrad, A. L. Daulton, and R. B. Kaplan, *ibid.*, **74**, 3052 (1952).
(17) H. Shechter and D. E. Ley, *Chem. Ind.* (London), **33**, 535 (1955).
(18) T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, **80**, 338 (1958).
(19) J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958).

The results obtained with 1-octadecene were applied to cycloöctene. 2-Nitrocyclo-octyl nitrite was found to eliminate nitrous acid at a slower rate than II. In spite of using an oxygen–olefin ratio of 1:30 during the dinitrogen tetroxide–cyclo öctene reaction, no trace of carbonyl compound was produced. Treatment of the crude dinitrogen tetroxide–cyclo öctene reaction solution with a threefold molar excess of triethylamine gave a 96% yield of 1-nitrocycloöctene which indicates the greater stability of the latter to nucleophilic attack compared with VI.

Experimental

Melting points are uncorrected.

Analytical Technique.—The Perkin–Elmer Infracord spectrophotometer, accurate to ± 0.03 μ, served for the quantitative determination of all nitro compounds. Since an excellent paper on the infrared study of nitro compounds is available,[20] only the data necessary for quantitative analyses are given here. For most problems the internal ratio method[21] was applied for determining mole percentages. With several compounds the extinction coefficient ε was determined to check the ratio method. Most measurements were made in carbon tetrachloride, using 0.1-mm. sodium chloride cells.

The CH_2-deformation absorption at about 3.40 μ served as the internal standard for all compounds. Table II summarizes the infrared data of the pure compounds. The analytical absorption bands chosen are sharp and show practically no overlap with bands due to other compounds present in the mixtures. Mixtures of pure nitro alcohol V with pure nitro-olefin VI

TABLE II

INFRARED DATA OF PURE NITRO COMPOUNDS

Compound	Analytical wave length, λ_A μ	Assignment	$\lambda\epsilon_{A\mu}{}^a/\epsilon_{3.40\,\mu}$	$\epsilon_{\lambda A}{}^c$ l./cm.^{1}-mole^{-1}	Accuracy, ± %
VI	6.55	$-CH{=}CHNO_2$	0.86	6.30×10^2	3
V	6.44	$-CH_2NO_2$	0.66	5.51×10^2	3
V	2.78	—OH	..	3.30×10	3
III	6.10	$-ONO_2$	1.10	...	5
II	5.95	—ONO	0.47[b]	...	5
1-Nitrocyclooctene	6.59	HC=CNO$_2$	3.12	...	3

[a] Ratio of extinction coefficient at the analytical wave length to that at 3.40 μ. [b] Extrapolated from an 88% pure product. [c] $\epsilon_{\lambda A}$ = extinction coefficient at the analytical wave lengths.

were prepared, and a straight line working curve was obtained for each compound by plotting the ratio of the extinction coefficients against the composition. A spectrally determined ratio of $\epsilon_{\lambda A_\mu}/\epsilon_{3.40\mu}$ in a crude mixture allows the calculation of the amount of the particular compound in mole per cent. For the analyses of mixtures, the concentrations were adjusted in such a way that the strongest analytical absorbance is $\leqq 0.7$ and the weakest analytical absorbance is $\geqq 0.2$. The determination of the nitro alcohol, V, in a mixture with other saturated nitro compounds was based on the free OH absorption band at 2.78 μ; hydrogen-bonding does not disturb the determination at a concentration of 0.01–0.1 mole/l. This was shown by the constancy of the extinction coefficient of the 2.78 μ band in that range of concentrations. The free OH analyses were carried out in a 1.3-mm. calcium fluoride cell because of the smaller extinction coefficient (compare Table II).

For the analysis of a crude dinitrogen tetroxide–olefin reaction solution (compare Table I), an aliquot was injected into dry carbon tetrachloride and the ether displaced at reduced pressure. When the necessary concentration was approximately reached, the amounts of nitro nitrite, II, and nitro nitrate, III, were determined by the ratio method (Table II). The exact concentration of this solution was calculated from the known extinction coefficient at 3.40 μ—*e.g.*, $\epsilon_{3.40\mu}$ for I is 8.04×10^2 l./mole^{-1}-cm.$^{-1}$) and the free OH absorption at 2.78 μ then served for the calculation of the amount of nitro alcohol, V. The content of dinitro compound I in a crude nitration solution could not be determined directly because of lack of appropriate analytical absorption bands. However, run 8 (Table III) shows how the sum of I, II, and III can be converted into nitro-olefin, VI, in 94% yield; an aliquot of the crude dinitrogen tetroxide–olefin reaction mixture was treated with an equal amount (by weight) of triethylamine for 2–3 min., worked up as usual and analyzed for nitro-olefin. With the analyses of II and III by the ratio method, the amount of I was calculated by difference. The method includes the very probable assumption that no dinitro-olefin-yielding species are contained in the crude dinitrogen tetroxide–olefin reaction mixture. Isolated nitro-olefin yields confirmed these analyses.

1 Nitro-2-octadecyl Nitrate (III).—A mixture of 10.2 g. (32.4 mmoles) of 1-nitro-2-octadecanol, 100 ml. of *n*-hexane, 20 ml. of 70% nitric acid (boiled with 2 g. of urea before use), and 40 ml. of concentrated sulfuric acid was stirred for 4.5 hr. at about 30° and then poured on 20 g. of ice. After extraction with ether, washing of the ethereal solution with water, sodium bicarbonate solution, and again with water, the ether was evaporated and the water was removed by azeotropic distillation with benzene. The remaining 11.60 g. (theory 11.66 g.) of yellow oil gave 11.0 g. (94% yield) of a white solid (m.p. 28–29°) after chromatography on silicic acid with *n*-hexane eluent.

Anal. Calcd. for $C_{18}H_{36}O_5N_2$: C, 59.97; H, 10.07. Found: C, 60.48; H, 10.32.

Additional proof for the purity of III is the formation of almost pure VI in quantitative yield after reaction with pyridine.

1-Nitro-2-octadecyl Nitrite (II).—To 1.5 g. (21 mmoles) of nitrosyl chloride, dissolved in 25 ml. of dry ether, 2.7 g. (27 mmoles) of pyridine, dissolved in 5 ml. of dry ether, was added; a yellow solid precipitated. To this mixture a solution of 5.08 g. (16 mmoles) of 96% pure (quantitative infrared) 1-nitro-2-octadecanol in 35 ml. of dry ether was added at −15° to −10° during 15 min. After distilling the excess nitrosyl chloride *in vacuo* (with added ether) the pyridine hydrochloride was filtered off and washed with ether. The ethereal filtrate of II was kept at −80° to avoid thermal decomposition. An aliquot of the solution was analyzed for unchanged nitro alcohol V by displacing the ether with carbon tetrachloride; the infrared analysis showed that 8% unchanged nitro alcohol was present. That this solution contained at least 88% (100% minus 8% minus 4%) of 1-nitro-2-octadecyl nitrite, II, was shown by the fact that quantitative elimination of nitrous acid using a 150-fold molar excess of triethylamine for 3 min. gave 87% of 1-nitro-1-octadecene VI plus 8% nitro alcohol V, confirming the presence of the latter amount in the original solution. The infrared spectrum showed an analytical absorption at 5.95 μ due to the ONO group, which is present in crude dinitrogen tetroxide–olefin reaction products. The 88% pure product allows an extrapolated ratio of $\epsilon_{5.95\,\mu}/\epsilon_{3.40\,\mu}$ of 0.46–0.48 for the pure compound.

1-Nitro-2-octadecanol, V, and 1,2-Dinitroöctadecane I.—1-Nitro-2-octadecanol was prepared as described by Porter and Wood,[10] m.p. 55–56° (reported in 55°). Fractional crystallization of the mother liquor residue from alcohol gave, contrary to the previous report,[10] an almost pure dinitro compound, I. The product contained less than 10% of 1-nitro-1-octadecene, VI, (infrared) and no trace of nitro alcohol, V, and nitro nitrate, III (m.p. 40.5–41.5°).

Anal. Calcd. for $C_{18}H_{36}O_4N_2$: C, 62.75; H, 10.53; N, 8.13. Found: C, 63.05; H, 10.62; N, 7.82.

The purity of the product was further proved by obtaining nitro-olefin in 95% yield by reaction with ammonia.

1-Nitro-1-octadecene VI. (a) *Via* **Dinitrogen Tetroxide Addition (Run 4, Table I).**—Streams of dry oxygen and 99.5% pure nitrogen tetroxide (Matheson Company) were combined and slowly run through a phosphorus pentoxide tube. Dinitrogen tetroxide was condensed in a graduated trap. The reactor was a 4-necked flask equipped with a stirrer, dropping funnel, Dry Ice condenser, thermometer, and a fritted gas inlet at its bottom. The system was protected from moisture with phosphorus pentoxide drying tubes. With the aid of an oxygen stream, 28.89 g. (0.314 mole) of dinitrogen tetroxide was distilled from the graduated trap into the reactor which contained 100 ml. of oxygen saturated dry ether. 1-Octadecene (75.65 g., 0.30 mole)

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

(21) S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

which was 95% pure was added to this solution over a 40-min. period at 9–11° while running a total amount of 2 mmoles (flow meter) of oxygen into the mixture and stirring vigorously. The reaction mixture was maintained at 20° for 35 min. About 3% of the product was removed for analytical purposes and dry ether added to the remainder to give a total volume of 800 ml. During 5 min. of vigorous stirring, 60.8 g. (0.6 mole) of triethylamine was added at 4–10°; the mixture was kept at 22–24° for 0.5 hr. and 200 ml. of 2 *N* sulfuric acid was added at 10–20° while stirring with cooling. The mixture was extracted with ether and the ethereal solution washed with sodium bicarbonate solution and water. The ether and water were vacuum evaporated; and the residue (88.22 g.) was chromatographed on silicic acid with hexane eluent, yielding 65.95 g. (77% yield) of 96–100% spectrally pure 1-nitro-1-octadecene, m.p. 32.0–33.5°. An analytically pure sample melted at 34.5–35°, m.p. reported[10]: 38°.

Anal. Calcd. for $C_{18}H_{35}NO_2$: C, 72.67; H, 11.86; N, 4.71. Found: C, 72.91; H, 11.85; N, 4.47.

The hydrolysis of an aliquot of the crude dinitrogen tetroxide–olefin reaction product for the nitroalcohol determination was carried out by stirring the ethereal reaction mixture with an excess of 2*N* sulfuric acid for 4 hr. at 23°. The hydrolysis mixture was extracted with ether, worked up as described for the synthesis of V[10] and analyzed for V.

(b) *Via* **Dehydration of Nitro alcohol.**—A mixture of 2.00 g. (6.35 mmoles) of 1-nitro-2-octadecanol and 1.88 g. (12.7 mmoles) of phthalic anhydride was heated for 70 min. at 175–180°. The dark reaction product was extracted with hexane and the solution chromatographed on silicic acid, yielding 0.93 g. (52%) of 1-nitro-1-octadecene, m.p. 30–34°. The structure was confirmed by its infrared spectrum.

TABLE III

ELIMINATION REACTIONS

Run	Base	Starting material	Reaction time, min.	Mole % yield or recovery of VI
1	NH_3	VI	120	80[c]
2	$N(C_2H_5)_3$	VI	120	95
3	NH_3	II[a]	120	60[c]
4	$N(C_2H_5)_3$	II[a]	15	92
5	NH_3	III	30	80[c]
6	NH_3	I[b]	15	95
7	$N(C_2H_5)_3$	2II[a] 3I[b]	34	94
8	$N(C_2H_5)_3$	2II[a] 3I[b]	2.5	94

[a] The starting material consists of 88% II, 8% V, and 4% other impurities. [b] The starting material contains less than 10% of VI. [c] The major by-products were saturated nitro compounds.

In the experiments with triethylamine, concentrations of 6–12% of nitro compounds in ether (except run 8: 2%) and mole ratios of triethylamine to nitro compounds of 1–2 (except run 8: 150) were used. In the elimination reactions with ammonia 0.2–0.3 mmole of the starting material was dissolved in 1 ml. of ether. After addition of 3–4 ml. of 1% aqueous ammonia, containing about 2 mmoles of ammonia, at 23°, the heterogeneous mixture was shaken at intervals. The reactions with both bases were quenched with dilute sulfuric acid or aqueous ammonium chloride solution at the times given, and the aqueous phase was extracted with ether several times; the combined ethereal solutions were washed with sodium bicarbonate and water, the ether and water were evaporated *in vacuo*, and infrared spectra of the crude products were calculated for nitro-olefin content by the ratio method. The yields of nitro-olefin given in Table III represent mole % nitro-olefin content of the isolated crude yields, which were at least 95%. In several runs, the recovery from work-up was quantitative; and the crude product melted only 2° lower than an analytically pure sample of VI.

1-Nitrocycloöctene.—Cycloöctene (44.40 g., 0.40 mole), which contained 4.6% cycloöctane, was added to a solution of 39.28 g. (0.427 mole) of dinitrogen tetroxide in 150 ml. of dry ether over a 24-min. period at 9–12° while bubbling 13 mmoles of oxygen through the solution. After addition of 25 ml. of ether and stirring of the yellow solution for 0.5 hr. at 10°, 121 g. (1.2 moles) of triethylamine was added at 4–12°. The mixture was kept at 24° for 0.5 hr., cooled to 3°, diluted with 150 ml. of ether, and quenched with 1.2 moles of acetic acid dissolved in 200 ml. of water. After work-up as described for 1-nitro-1-octadecene and removal of the cycloöctane *in vacuo*, 61.0 g. of yellow oil remained. Pure 1-nitrocycloöctene was obtained by chromatography on silicic acid and subsequent distillation, b.p. 60°/0.2 mm., $n^{20}D$ 1.5116; infrared data are given in Table II. The infrared analysis of the crude oil showed that the yield of 1-nitrocycloöctene in this reaction was 96%. A slow decomposition with simultaneous precipitation of a solid occurred upon standing for several weeks at 23°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.27; N, 8.80.

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The Formation of a Chromanone and Fluoro Ketones in the Reaction of Diazo Ketones with Boron Trifluoride

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The reaction of 1-diazo-3-(*o*-anisyl)-2-propanone with boron trifluoride or a catalytic amount of sulfuric acid gives 3-chromanone as the major product; with other acids mainly open-chain products are formed. Other diazo ketones with boron trifluoride in ether give mixtures of an ethoxy ketone and a fluoro ketone.

The normal reaction of a diazo ketone with an acid (HX) to give a substituted methyl ketone (equation 1) is frequently subverted by the formation of cyclic products when a nucleophilic center is present at an α' or β' position (equation 2). Four-membered heterocyclic ketones are obtained from

$$RCOCHN_2 + HX \longrightarrow RCOCH_2X + N_2 \quad (1)$$

$$\begin{bmatrix} COCHN_2 \\ ZR(H) \end{bmatrix} + HX \rightarrow \begin{bmatrix} COCH_2 \\ Z \end{bmatrix} + R(H)X + N_2 \quad (2)$$

α'-hydroxydiazo ketones[2,3] or 3-diazoacetylpyrazolines[4,5] on treatment with acetic acid or mineral acids. Open-chain products are not obtained in the latter reaction, even on addition of excess nucleophile (X^-)[5]; the pronounced tendency for cyclization is unusual in the formation of a four-membered ring. The facile formation of a five-membered ring by this process has

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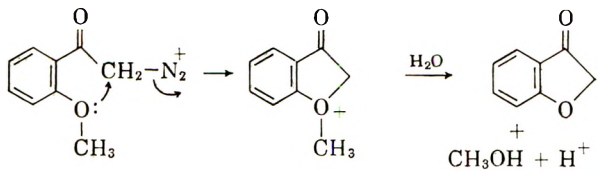
been observed most often in the reactions of *o*-substituted diazoacetophenones, which lead to coumaranones in high yields.[6-8] Only catalytic amounts of acid are required in the conversion of *o*-methoxy-ω-diazoacetophenone to coumaranone, since the proton is recovered when methanol is split off by solvolysis of the oxonium intermediate.[8]



Formation of a six-membered ring is less common. A recent example is provided by the work of Bhati,[9] who obtained isochromanediones from the reaction of *o*-diazoacetylbenzoic acids with hydriodic acid. It has been suggested[10] that the conversion of *o*-nitrodiazoacetophenone to N-hydroxyisatin[11] may proceed by initial formation of a six-membered oxazine intermediate. However, in the attempted ring closure of 1-diazo-3-(*o*-anisyl)-2-propanone (I) to 3-chromanone (VI) with hydrochloric or hydrobromic acids only the open-chain products, 1-chloro- and 1-bromo-3-(*o*-anisyl)-2-propanone, were isolated.[7]

In order to define further the scope of these cyclization reactions, particularly with respect to the formation of larger heterocyclic rings, we first reinvestigated the reactions of 1-diazo-3-(*o*-anisyl)-2-propanone (I) with other acids. In line with the earlier work, ethereal acetic acid gave only the open-chain product. The acetoxymethyl ketone Va was characterized by infrared and n.m.r. spectra and the formation of the 2,4-dinitrophenylosazone. In the reaction of I with one equivalent of concentrated sulfuric acid in ether solution, the major product (19%) was a solid which on hydrolysis liberated sulfate ion and the hydroxymethyl ketone Vc, and was thus the dialkyl sulfate Vb. A similar reaction was previously noted by Newman and Beal,[12] who obtained a solid sulfate from the reaction of 1-diazo-4-phenyl-2-butanone with concentrated sulfuric acid.

A minor liquid compound from the reaction with concentrated sulfuric acid was obtained in larger amounts, together with the hydroxy ketone Vc, when I was treated with a catalytic amount of sulfuric acid in aqueous dioxane, and was virtually the only product isolated in the reaction of I with 1.5 moles of boron trifluoride in ether. The infrared spectrum (5.78 μ) and the proton n.m.r. spectrum (three peaks at 3.10 τ, 5.68 τ, and 6.48 τ in the ratio 2:1:1, corresponding to four aromatic protons and two unsplit methylene groups) indicated that this compound was the desired 3-chromanone (VI); and this was confirmed by the correspondence in properties and derivatives with those previously reported for material made in another way.[7] The identification of this compound in the other reaction mixtures was established by peak enhancement in the vapor phase chromatograms.

The yields of 3-chromanone in the four reactions, as estimated by quantitative vapor phase chromatography on a silicone column after initial distillation, are summarized in Table I. In all the reactions a substantial amount of undistillable tar was present, and the reported yields may be somewhat lower than those actually present in the crude products.

TABLE I

Acid	Equivalent ratio acid/diazo ketone	Solvent	Yield, % Chromanone	Yield, % Open-chain product
Acetic	3.4	Ether	..	42
Sulfuric	1.0	Ether	4	19
Sulfuric	0.04	Aqueous dioxane	15	45
BF_3	1.5	Ether	35	..

In contrast to the lower homolog, *o*-methoxydiazoacetophenone, which under all acid conditions studied gives only the cyclic product, the reactions of the diazo ketone show an interesting balance between the competing paths (equations 1 and 2). The mechanisms involved in the reactions of diazocarbonyl compounds with acids have been discussed by Huisgen,[13] who distinguished the "catalytic reaction" (equation 3) in which the products are independent of the nucleophilic species present, and the "stoichiometric reaction" (equation 4) in which the nature and concentration of the nucleophile play a commanding role.[14]

$$RCOCHN_2 + H^+ \longrightarrow RCOCH_2^+ + N_2 \xrightarrow{H_2O} RCOCH_2OH + H^+ \quad (3)$$

$$RCOCHN_2 + HA \longrightarrow RCOCH_2A + N_2 \quad (4)$$

The conditions employed in the reaction of I with dilute sulfuric acid were chosen to correspond to the catalytic reaction (equation 3), while the reactions with glacial acetic acid and concentrated sulfuric acid quite evidently corresponded to equation 4. In the latter reactions the results are in accord with the relative nucleophilic capabilities of acetate ion and bisulfate ion. With the very weakly nucleophilic bisulfate ion, participation of the neighboring methoxy group becomes a significant reaction; in acetic acid no more than a trace of the chromanone was produced. Cyclization clearly becomes much more important under the catalytic conditions, even though nucleophilic solvent is available. This is consistent with the view that the stoichiometric reactions, in solvents of lower dielectric strength, involve a rather closely associated ion pair III, in which competition of a neighboring group is less favorable than in the solvated diazonium ion II. The reaction of I with boron trifluoride etherate represents essentially the limiting case, in which no effective nucleophile is present, and thus ring closure is the only reaction observed. The formation of the cyclic ether VI must involve the oxonium ion IV in the reactions with sulfuric acid, or the oxonium fluoroborate

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VII in the case of boron trifluoride, followed by nucleophilic attack at the methyl group. The hydroxy ketone Vc is probably derived by hydrolysis of the oxonium ion IV, since the anchimerically assisted conversion of the diazonium ion II to the IV would be expected to be faster than direct solvolysis of II.

The success of the cyclization reaction of I with boron trifluoride encouraged us to attempt the preparation of benzoxepanone from the next higher homolog. A diazo ketone was prepared in the usual way from *o*-methoxyhydrocinnamoyl chloride and was treated without isolation with boron trifluoride etherate. Only a very small amount of volatile product could be distilled from the dark reaction mixture. The proton n.m.r. spectrum of the major component in the distillate contained, among other peaks, a 2-proton doublet at 5.45 τ with J = 47 c.p.s. This feature clearly indicated the presence of the $COCH_2F$ grouping,[15] and analysis of the 2,4-dinitrophenylhydrazone confirmed the composition of 1-fluoro-4-(*o*-anisyl)-2-butanone. There was no indication of the formation of the seven-membered cyclic ether.

Although kinetic data have not been obtained, it seems quite plain from the product data in this and previous work[6-8] that the importance of *o*-methoxy participation of this reaction falls off sharply in the order of ring size 5 > 6 ≫ 7. This is entirely consistent with the order observed in the solvolysis of ω-methoxy bromobenzenesulfonates.[16] It must be noted, however, that in the latter solvolyses, anchimeric assistance is negligible when a four-membered ring is involved—*e.g.*, 3-methoxypropyl brosylate; while in the diazo ketone reactions, formation of a four-membered ring is quite favorable, as mentioned above, and substantial rate enhancement due to an α'-substituent has been observed in one case of four-membered ring formation.[5]

The unexpected isolation of a fluoro ketone in this reaction prompted the examination of the reactions of the two unsubstituted phenyl diazo ketones VIII and IX with boron trifluoride. These reactions were also of interest from the standpoint of possible cyclization to an indanone[17] and a tetralone,[18] respectively, both of which have been observed in other cases.

In both reactions, two products were obtained in approximately equal amounts (20–30% yields). The lower-boiling products contained fluorine and showed the characteristic n.m.r. splitting with a J value of 47 c.p.s. for α-fluoro ketones. The structures of the fluoro ketones were established as X and XI by conversion to the corresponding methyl ketones. Prolonged refluxing with sodium iodide in acetone led to the iodo ketones, which were then reduced with concentrated hydriodic acid; phenylacetone and 4-phenyl-2-butanone were characterized as the dinitrophenylhydrazones.

The presence of a doublet in the proton n.m.r. spectrum of 1-fluoro-2-phenyl-2-propanone at 6.33, with J = 3.2 c.p.s. for methylene alpha to phenyl and carbonyl, is interesting since it demonstrates spin-spin splitting of hydrogen by fluorine separated by four bonds. This type of long-range splitting has been observed in the C-19 methyl signal of 6-fluoro steroids.[19] The F^{19} n.m.r. spectrum[20] of 1-fluoro-3-phenyl-2-propanone showed a triplet further split into triplets, with J values of 47 and 3.2 c.p.s., respectively. This confirms the four-bond spin-spin splitting of this fluoro ketone.

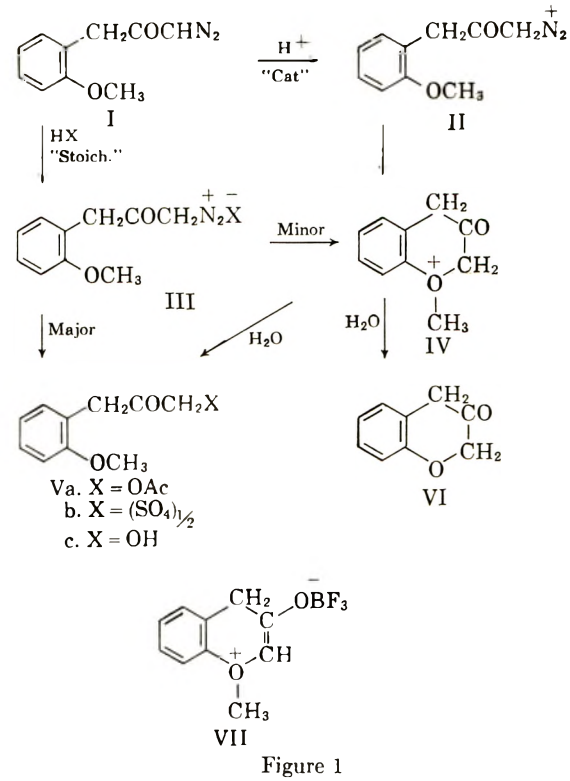

Figure 1

The higher-boiling fractions in each case were also ketonic, and the proton n.m.r. spectra and analyses indicated that they were the ethoxy ketones XII and XIII. Traces of other components were present in the v.p.c. tracings of both reaction mixtures, but no other compounds were identified.

$$C_6H_5(CH_2)_nCOCHN_2 + BF_3 \xrightarrow{EtOEt} C_6H_5(CH_2)_nCOCH_2F$$

VIII. $n = 1$ X. $n = 1$
IX. $n = 2$ XI. $n = 2$

$$C_6H_5(CH_2)_nCOCH_2OEt$$

XII. $n = 1$
XIII. $n = 2$

The formation of these products reveals two hitherto unrecognized paths in the reactions of diazo ketones with boron trifluoride. The formation of α-alkoxy ketones in the reaction of diazo ketones with alcoholic boron trifluoride was reported some years ago by Newman and Beal,[12] and represents a useful preparative method; but the reaction with boron trifluoride etherate was reported to give only tars. Very recently, the formation of an indanone has been observed with boron trifluoride in ether when two additional phenyl substituents are present in the α'-position.[17] After our work was completed, the reaction of diazoacetophenone with boron trifluoride in ether was reported to lead to a bisphenacyldiazonium–boron trifluoride

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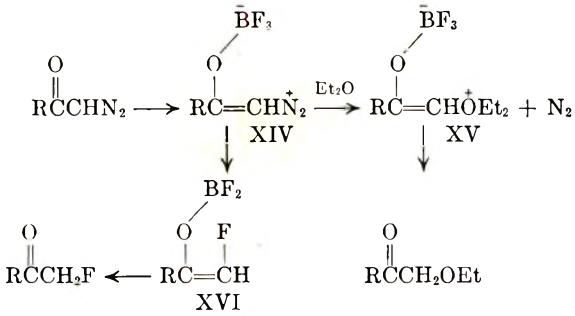

Figure 2

complex by loss of one mole of nitrogen, followed by a second condensation to an azobisfuran in unspecified yield.[21]

The course of the reaction of the diazo ketones VIII and IX is interpreted as indicated in Figure 2. Nucleophilic attack by ether at the diazo carbon of XIV would lead to the oxonium ion XV and subsequently to the ethoxy ketone, a path typical of the cleavage of ethers with powerful electrophiles. The detachment of a fluoride nucleophile in the production of the fluoroketones through XVI is reminiscent of the formation of boron difluoride chelates of 1,3-dicarbonyl compounds.[22] A very similar reaction involving the transfer of fluoride ion from boron to carbon has been observed[23] in the formation of fluorohydrins from steroidal epoxides.[24]

Experimental

1-Acetoxy-3-(*o*-anisyl)-2-propanone (Va).—*o*-Methoxyphenylacetyl chloride was prepared in 86% yield from *o*-methoxyphenylacetic acid[25] by refluxing for 30 min. with thionyl chloride, b.p. 105–110° (0.70 mm.)

A solution of 1 diazo-3-(*o*-anisyl)-2-propanone[8] (I) was obtained by addition of 7.36 g. (0.04 mole) of the acid chloride to an excess (0.16 mole) of diazomethane in ether.[26] After standing for 2 days, 10 ml. of glacial acetic acid was added and the solution was stored for another day. Evaporation of the ether and rapid distillation through a small Vigreux column at 0.50 mm. afforded four fractions: b.p. (1) 125–130°, 2.50 g.; (2) 132–139°, 0.7 g.; (3) 139–153°, 0.5 g.; and (4) 153–180°, 0.4 g. Vapor phase chromatography[27] of fraction 1 showed a major component (80%) and two unidentified minor peaks with shorter retention times. Fractions 2 and 3 were homogeneous by vapor phase chromatography and the single component corresponded to the major peak of 1. From the area under the peaks and the weight of the fractions, the yield of Va was estimated as 42%. Fraction 2, used for infrared spectrum[28] (and n.m.r.), showed strong absorption bands at 5.70 and 5.83 μ (C=O) and at (7.8–8.2 μ (ester and Ar—O—R). The proton n.m.r. spectrum[29] (20% deuteriochloroform) showed a multiplet at 2.73 τ and singlets at 5.31, 6.25, 6.35, and 7.93 τ with relative intensities 5:2:3:2:3, corresponding to C_6H_5, —$COCH_2O$—, CH_3O—, Ar—CH_2CO— and —$COCH_3$, respectively.

Fraction 2 was converted to the semicarbazone (69% yield), m.p. 147–148°, after recrystallization from methanol.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.65; H, 6.03; N, 15.07.

Fraction 1 was converted to the 2,4-dinitrophenylosazone, m.p. 259–260°, after recrystallization from acetic acid.

Anal. Calcd. for $C_{22}H_{18}N_8O_8$: C, 49.07; H, 3.37. Found: C, 49.57; H, 3.55.

3-Chromanone (VI) and 1-Hydroxy-3-(*o*-anisyl)-2-propanone (Vc).—1-Diazo-3(*o*-anisyl)-2-propanone (I) was prepared from 0.01 mole of the acid chloride. After evaporation of the ether, I was dissolved in 40 ml. of dioxane and 100 ml. of water. Twenty-one milliliters of 0.192 *N* sulfuric acid (0.004 eq.) was added to this solution over a 5-min. period with stirring. After a period of 20 hr., 0.079 mole of nitrogen had been collected over water and the rate of gas evolution was negligible. The dioxane was evaporated and the residue extracted with ether. After drying, the ether was evaporated and the product distilled at 0.5 mm. to give four fractions: b.p. (1) 82°, 0.51 g.; (2) 90–112°, 1.29 g.; (3) 113–118°, 2.63 g.; and (4) 114°, 0.38 g.

On the silicone column, fraction 1 gave one sharp peak with a shoulder; the major component was identified as 3-chromanone (15% yield) by conversion to the semicarbazone (48% yield), m.p. 188–189° after recrystallization from methanol (lit.,[7] m.p. 188.5°).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.55; H, 5.40; N, 20.48. Found: C, 58.21; H, 5.15; N, 20.28.

The infrared spectrum of VI contained bands at 5.78 μ (C=O), 8.00 μ (Ar—O—R), and 9.52 μ (R—O—R). There was also a weak band at 2.87 μ, suggesting contamination by the hydroxy compound Vc. The proton n.m.r. spectrum (20% deuteriochloroform) showed a multiplet at 3.10 τ and singlets at 5.68 and 6.48 τ, relative intensities 2:1:1, corresponding to aryl, —$COCH_2O$—R and $ArCH_2CO$ protons, respectively. There were also two minor peaks; one at 6.20 τ was apparently due to methoxy, representing 10% of Vc as an impurity.

Fraction 3 showed two peaks by gas chromatography. The major component with longer retention time was characterized as 1-hydroxy-3-(*o*-anisyl)-2-propanone as follows. Oxidation with periodic acid indicated 80% purity. The infrared spectrum showed strong absorption at 2.85 μ (OH); 5.80 μ (C=O); and 8.00 μ (Ar—O—R). The proton n.m.r. spectrum (20% deuteriochloroform) showed a multiplet at 3.10 τ and single peaks at 5.74, 6.23, 6.33, and 6.72 τ, relative intensities 4:2:3:2:1; corresponding to aryl, —$COCH_2OH$, —OCH_3, $ArCH_2CO$—, and OH, respectively. The alcohol was further characterized by conversion to the 2,4-dinitrophenylosazone whose infrared spectrum was identical with that of the 2,4-dinitrophenylosazone from Va. The yield of Vc was estimated to be 19% from vapor phase chromatography peak area. The minor component in fraction 3 was proved to be VI by peak enhancement.[30]

Di(*o*-anisyl)-β-ketopropyl sulfate (Vb).—To an ether solution of I from 0.04 mole of the acid chloride was added 2.04 g. (0.04 equiv.) of concd. sulfuric acid. Some tar was formed which was insoluble in both water and ether. The ether solution was washed twice with water, dried over anhydrous sodium sulfate, and evaporated. Benzene was added and evaporated to remove the last traces of water. The solid was filtered and recrystallized from benzene to give 1.62 g. (19% yield) of white crystals of Vb, m.p. 113°.

Anal. Calcd. for $C_{20}H_{22}SO_8$: C, 56.87; H, 5.25. Found: C, 56.84; H, 5.19.

The mother liquor was evaporated and distilled at 0.5 mm.: b.p. (1) 83–87°, 0.43 g.; (2) 100–104°, 0.34 g. Fraction 1 showed two peaks of nearly equal area on vapor phase chromatography with two peaks of nearly equal area on vapor phase chromatography with 10-ft. silicone column. The peak with shorter retention time proved to be 3-chromanone by peak enhancement. Fraction 1 yielded a semicarbazone (40% yield), m.p. 181–183°, after three recrystallizations from methanol, whose infrared spectrum was identical with that of the semicarbazone of VI.

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(24) The possibility that the fluoro ketones arise by reaction with hydrogen fluoride formed by hydrolysis of boron trifluoride with ambient moisture seems remote. The liberation of fluoride ion from the strong acid HBF_3OH is slow, and, if this were the pathway, the α-hydroxy ketone, rather than the fluoro ketone, would be expected.

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(27) The chromatograms were obtained with a 10-ft. column packed with GE-SF96 silicone suspended on firebrick, using a Wilkens Aerograph Master A-100 instrument; we appreciate the helpful advice of Mr. N. Heindel on vapor phase chromatography.

(28) The infrared spectra were determined with a Baird Model B recording spectrometer fitted with a sodium chloride prism.

(29) N.m.r. spectra were obtained at 60 Mc. with Varian A-60 instrument; we are grateful for helpful discussions of the data with Dr. H. C. Beachell.

(30) Fraction 1 from boron trifluoride reaction was used as authentic VI for peak enhancement.

Fraction 2 gave three peaks with gas chromatography. The first peak (second largest area) had the shortest retention time, the same as 3-chromanone; the second peak (largest area) was unidentified; the third peak was a minor one. The second peak represented approximately a 10% yield of the unidentified product. Fraction 2 formed a semicarbazone in very low yield, whose infrared spectrum was identical with that of the semicarbazone of 1-hydroxy-3-(*o*-anisyl)-2-propanone. The yield of 3-chromanone was estimated as 4% by vapor phase chromatography.

Hydrolysis of Di(*o*-anisyl)-β-ketopropylsulfate.—One gram of Vb was refluxed with 1 ml. of concd. hydrochloric acid and 10 ml. of water for 5 hr. on the steam bath. The product was extracted with ether and distilled. Gas chromatography of the distillate showed a major peak corresponding to Vc and some minor peaks caused by rearrangement of the α-hydroxy ketone.

3-Chromanone (VI) Using Boron Trifluoride Etherate.—To 4.32 g. (0.03 mole) of boron trifluoride etherate[31] dissolved in 100 ml. of anhydrous ether was added a solution of I (prepared from 0.02 mole of acid chloride without isolation) in 10 ml. of anhydrous ether; nitrogen was rapidly evolved. The ether layer was washed with water, dried, and evaporated. Benzene was added and evaporated to complete the drying. The residue was distilled at 0.50 mm.: b.p. (1) 84–88°, 1.04 g.; (2) 88–113°, 0.13 g.; (3) 113–116°, 0.41 g.; (4) residue, 0.43 g. Fraction 1 was shown to be homogeneous by gas chromatography and yielded a semicarbazone (78% yield), m.p. 183–185°, identical by infrared spectrum with the semicarbazone of 3-chromanone. The yield of VI was 35%. Fraction 3 showed four peaks, one of which proved to be VI; another corresponded to 1-hydroxy-3-(*o*-anisyl)-2-propanone (Vc) by peak enhancement.[32] The estimated yield of Vc was 2%.

1-Fluoro-4-(*o*-anisyl)-2-butanone.—β-(*o*-Anisyl)propionyl chloride, b.p. 110° (0.75 mm.), was prepared in 80% yield by treatment of *o*-methoxyhydrocinnamic acid (m.p. 88–89°) with thionyl chloride. An ether solution of 1-diazo-4-(*o*-anisyl)-2-butanone was prepared, without isolation of the diazo ketone, by addition of 19.8 g. (0.10 mole) of β-(*o*-anisyl)propionyl chloride to 0.04 mole of diazomethane. To 14.2 g. (0.10 mole) of boron trifluoride etherate in 225 ml. of anhydrous ether was added rapidly the diazo ketone in 85 ml. of anhydrous ether at ice bath temperature. After the usual 2-hr. period of standing at room temperature, the product was worked up as in previous experiments to yield two fractions boiling at 0.8 mm.: b.p. (1) 116–121°, 0.76 g.; (2) 122–134°, 1.44 g.

The infrared spectrum of fraction 1 had bands at 5.72 and 5.78 μ (C=O); 8.00 μ (Ar—O—R); 9.47 and 9.64 μ (C—F). The proton n.m.r. spectrum (20% carbon tetrachloride) showed a multiplet at 3.08 τ for aromatic protons; a doublet at 5.45 τ, with J = 47 c.p.s. for methylene between carbonyl and fluorine; a singlet at 6.32 τ for methoxy, and a multiplet at 7.25 τ for the two methylenes between phenyl and carbonyl. The relative intensities were 4:2:3:4, respectively. There were a few very small peaks, one of them, a triplet, was recognized as the methyl of the ethyl group at 8.88 τ, representing 10% of 1-ethoxy-4-(*o*-anisyl)-2-butanone as impurity. Fraction 1 afforded a 2,4-dinitrophenylhydrazone, m.p. 148–149°.

Anal. Calcd. for $C_{17}H_{17}N_4FO_6$: C, 54.25; H, 4.57; F, 5.05. Found: C, 54.47; H, 4.52; F, 3.98.

1-Fluoro-3-phenyl-2-propanone (X) and 1-Ethoxy-3-phenyl-2-propanone (XII).—1-Diazo-3-phenyl-2-propanone (VII) was prepared by addition of 46.5 g. (0.30 mole) of phenylacetyl chloride to an excess (0.80 mole) of diazomethane in ether. After standing for a day, the ether was evaporated to yield the diazo ketone, m.p. 43–44°.[33] The diazo ketone was dissolved in 250 ml. of anhydrous ether and added in 3 min. to 42.6 g. (0.30 mole) of boron trifluoride etherate in 675 ml. of anhydrous ether at ice bath temperature. Nitrogen evolution was very rapid. Two hours later, the ether solution was washed with water, with sodium carbonate solution, and again with water. Three fractional distillations through a small Vigreux column at 2 mm. gave three fractions: b.p. (1) 97–99°, 6.70 g.; (2) 99–120°, 6.80 g.; (3) 120–122°, 8.90 g. Before analysis these fractions were combined with the corresponding fractions of another run and fractionally distilled twice more. Fraction 1 gave a positive test for fluorine on sodium fusion and a negative test with periodic acid. The infrared spectrum showed bands at 5.70 and 5.76 μ (C=O); 9.48 and 9.64 μ (C—F). Before running the n.m.r., fraction 1 was further purified by preparative vapor chromatography on a 5-ft. silicone-on-Chromosorb column at 220°. The proton n.m.r. spectrum (20% carbon tetrachloride) showed a multiplet at 2.90 τ for aromatic protons, a doublet at 5.39 τ, with J = 47 c.p.s. for methylene between carbonyl and fluorine, and a doublet at 6.33 τ, with J = 3.2 c.p.s. for methylene *alpha* to phenyl and carbonyl. The relative intensities were 5:2:2. The two preparations yielded 1-fluoro-3-phenyl 2-propanone (X) in 22.5 and 23.4% yield, respectively. Further characterization of fraction 1 involved conversion to the 2,4-dinitrophenylhydrazone, m.p. 96–97°.

Anal. Calcd. for $C_{15}H_{13}N_4FO_4$: C, 54.22; H, 3.94; F, 5.72. Found: C, 54.56; H, 4.40; F, 5.55.

Conversion of X to phenylacetone was accomplished by refluxing 200 mg. of fraction 1 with 5 ml. of 15% sodium iodide in acetone for 48 hr. The acetone was evaporated and the residue treated with 50 ml. of chloroform and 10 ml. of 57% hydriodic acid. After washing the chloroform solution with saturated potassium iodide solution and dilute sodium thiosulfate solution, the solvent was evaporated, and the residue was converted to 201 mg. (47% yield) of the 2,4-dinitrophenylhydrazone, m.p. 147–148°; mixed melting point with the derivative of authentic phenylacetone was not depressed.

Fraction 3 was characterized as 1-ethoxy-3-phenyl-2-propanone (XII) by infrared spectrum 5.75 μ (C=O); 8.95 μ (R—O—R). The proton n.m.r. spectrum (20% deuteriochloroform) showed a multiplet at 2.80 τ for aromatic protons; a singlet at 5.98 τ for methylene alpha to phenyl and carbonyl; a singlet at 6.30 τ for methylene between carbonyl and ether oxygen; a quadruplet at 6.55 τ, with J = 7 c.p.s. for methylene of ethyl group; and a triplet at 8.82 τ, with J = 7 c.p.s. for methyl of ethyl group. The relative intensities were 5:2:2:2:3:. Fraction 3 formed a 2,4-dinitrophenylhydrazone, m.p. 133–134°.

Anal. Calcd. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 57.22; H, 5.40; N, 15.48.

The yield of XII was 23.1% and 31.9% for the two preparations.

1-Fluoro-4-phenyl-2-butanone (XI) and 1-Ethoxy-4-phenyl-2-butanone (XIII).—1-Diazo-4-phenyl-2-butanone[34] (IX) from 0.30 mole of hydrocinnamoyl chloride was added without isolation to 0.3 mole of boron trifluoride etherate and the product worked up as in the previous experiment. Three fractional distillations at 2 mm. gave three fractions: (1) b.p. 102–110°, 7.1 g.; (2) 110–128°, 1.8 g.; (3) 128–134°, 8.5 g.

Fraction 1 was redistilled and the center cut passed through a 5-ft. silicone preparative column. The infrared spectrum of this purified sample showed bands at 5.75 μ (C=O) and 9.47 μ (C—F). The proton n.m.r. spectrum (neat) was consistent with 1-fluoro-4-phenyl-2-butanone. There was a doublet in 5–6 τ range for methylene between carbonyl and fluorine, with J = 47 c.p.s. Fraction 1 yielded a 2,4-dinitrophenylhydrazone, m.p. 146–148°.

Anal. Calcd. for $C_{16}H_{15}N_4FO_4$: C, 55.49; H, 4.56; N, 16.17; F, 5.49. Found: C, 55.38; H, 4.44; N, 16.02; F, 6.03.

The yield of XI was 16.2%. The structure of XI was further proved by conversion to the 2,4-dinitrophenylhydrazone of 4-phenyl-2-butanone (45% yield), m.p. 123–125° (lit.,[35] 128.5–129°), following the procedure of the previous experiment.

Fraction 3 had absorption bands at 5.80 μ (C=O); 9.00 μ (R—O—R). The proton n.m.r. spectrum was consistent with 1-ethoxy-4-phenyl-2-butanone (yield 16.2%). The 2,4-dinitrophenylhydrazone melted at 115–117°.

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.33; H, 5.67; N, 14.90.

(31) The boron trifluoride etherate was distilled just prior to use, b.p. 126°.

(32) Fraction 3 from the water dioxane run was used for peak enhancement of Vc.

(33) H. Naga Shima, N. Ninoi, and T. Hanada, *J. Pharm. Soc. Japan*, **75**, 438 (1955).

(34) L. Birkofer, *Ber.*, **80**, 83 (1947).

(35) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

The Structure of Amidoximes. II.[1] Oxamidoxime

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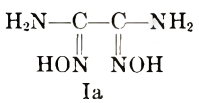
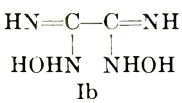
The two isomers of oxamidoxime described in the literature are shown to be identical. Infrared and proton n.m.r. evidence permits the assignment of the diaminoglyoxime structure to this compound and an analogous structure to ethyl aminoöximinoacetate.

Oxamidoxime (I) has been prepared from cyanogen and hydroxylamine,[2] by ammonolysis of dichloroglyoxime diacetate,[3] from dibromofuroxan and ammonia,[4] and by the reaction of dithioöxamide with hydroxylamine.[5] It is claimed[3] that the products from the first two methods are different compounds, yield different diacetates and should be regarded as isomers Ia and Ib.



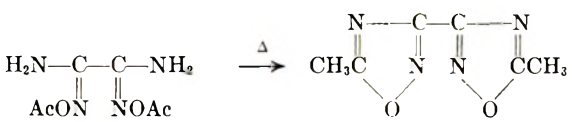
Ia



Ib

Since unsubstituted amidoximes usually exist in only one form,[6] the preparation of I has been reinvestigated.

The products from the two reactions[2,3] have been found to be identical as judged by infrared and ultraviolet absorption spectra and paper chromatography. Acetylation of I yields a diacetate II which decomposes on melting to the known 5,5′-dimethyl-3,3′-bi-1,2,4-oxadiazole (III).[2] The discrepancy in the decomposi-



II. M.p. 193–194° dec.

III. M.p. 165–167°

tion points for different preparations of I[2,3] and the corresponding diacetates is probably due to different rates of heating or methods of determining melting points.

All modern structural evidence for unsubstituted amidoximes (RCN_2H_2OH) is based on infrared absorption spectra and the various investigators agree that a single structure is present rather than a mixture of isomers. The observed absorption bands have been assigned to O—H and N—H stretching and deformation and C=N and N—O stretching.[1,6–10] The differences which may be expected in the spectra of the two possible isomers are comparable with the differences between C=N stretching frequencies of oximes and imines, N—H stretching or deformation in amines, imines, and hydroxylamines, and O—H as well as N—O stretching in oximes and hydroxylamines. In some examples these differences have been observed to be small,[11–13] the frequencies are dependent on the substituents,[10–12] and few hydroxylamines with strictly comparable structures have been available. The structural assignments are therefore subject to some uncertainty.

In the case of oxamidoxime (I) and its derivatives a clear distinction between structures Ia and Ib on the basis of infrared absorption spectra is difficult for similar reasons. The diagnostic value of the C=N stretching frequencies has been impaired by later findings[10] and the C=N band shifts on salt formation[1] (Table I) may be due to electronic influences. The previously assigned structures[1] are therefore open to question.

In order to determine the structure for oxamidoxime (I), proton n.m.r. spectra have been determined for I, its diacetate (II), and for ethyl aminooximinoacetate (IV).[1] The only solvent which was suitable for this investigation was dimethylformamide (DMF). The assignment of the resonance at −10.00 p.p.m. to the hydroxyl proton in I is unambiguous. The observed chemical shift is identical to that of the C=N—OH proton resonance in propionaldoxime.[14] Additional evidence is provided by the disappearance of the resonance on addition of a few per cent of water. This disappearance is due to the expected rapid chemical exchange of the water protons with those of the amidoxime hydroxyls. A new resonance which reflects the averaged chemical shifts at the two positions occurs at −4.07 p.p.m. Only one additional resonance has been observed (−5.32 p.p.m.; −5.34 p.p.m. on addition of water). It is considerably broader than the hydroxyl resonance as is characteristic for protons attached to nitrogen (due to the shortened nuclear spin relaxation times induced by the large quadrupole moment of the nitrogen nucleus). The assignment of this line to N—H is strengthened by the similarity of the observed chemical shift to those usually found for amide protons. The ratio of NH to OH intensities is 2:1 giving evidence for structure Ia. For the diacetate (II) the NH_2 proton resonance is again observed (−6.50 p.p.m.). The OH line is missing, as expected, and instead the spectrum exhibits a CH_3 resonance (−2.09 p.p.m.) near the position of the DMF methyl proton resonances. The observed ratio of CH_3 to NH_2 intensities is 3:2. In the case of the ester (IV) the CH_2 (−4.2 p.p.m.) and CH_3 (−1.63 p.p.m.) assignments are unambiguous

(1) Paper I, H. E. Ungnade and L. W. Kissinger, *J. Org. Chem.*, **23**, 1794 (1958). This work was performed under the auspices of the U. S. Atomic Energy Commission.

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(4) H. Wieland, *ibid.*, **42**, 4192 (1909).

(5) (a) G. A. Pearse, Jr., and R. T. Pflaum, *J. Am. Chem. Soc.*, **81**, 6505 (1959); (b) J. Ephraim, *Ber.*, **22**, 2305 (1889).

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(11) G. Duyckaerts, *Bull. soc. roy. sci. Liége*, **21**, 196 (1952).

(12) J. Fabian, M. Legrand, and P. Poirier, *Bull. soc. chim. France*, **10**, 1499 (1956).

(13) L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **25**, 1471 (1960).

(14) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

TABLE I

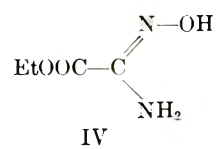
INFRARED ABSORPTION BANDS OF OXIMINO COMPOUNDS

Compound	Solvent	N—H[a] (N—D)	N—H[a] (N—D)	O—H[a] (O—D)	C=O	C=N	N—H	O—H (O—D)	C—O—C	N—O
Glyoxime	KBr			3.18 s		6.06 w		7.87 s		10.50 s
disodium salt	KBr					(6.16 m)[i]				9.95 s
diacetate	KBr				5.63 s[b]	6.17 m			8.47 s	10.85 s[c]
Oxamidoxime	KBr	2.91 s	3.01 s	3.13 s		6.06 s	6.33 s	6.98 m		10.71 s
	DMF	sh 2.88 m	3.02 s	3.12 m			6.39 m			10.70 s
disodium salt	KBr					6.33 m	6.49 m			10.35 s
diacetate	KBr	2.91 s	3.01 s		5.68 s	6.21 s	[d]		8.32 s	10.54 s[e]
	DMF	sh 2.88 m	3.01 s		5.66 s	6.17 m	[d]		8.30 s	10.62 m
	Py	2.88 m	3.02 s		5.65 s	6.13 s	[d]		8.35 s	(10.65 m)[e]
	Dioxan				5.64 s	6.14 s	[d]			
Et aminooximinoacetate	KBr	2.89 m	2.97 m	3.18 m	5.80 s	5.99 s	6.37 m	6.92 m[f]	8.11 s	10.28 s
	DMF	2.88 m	3.02 m		(5.80 m)[i]		6.35 m		8.22 s	10.45 m
Glyoxime-d_2	KBr[g]			4.18 m		6.10 m		9.33 m		
Oxamidoxime-d_2[j]	KBr	2.92 m	3.85 m[h]	4.08 m		6.16 s	6.45 m[f]	9.29 m		10.99 s

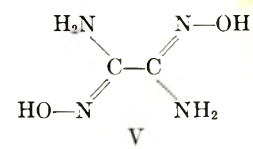
[a] Hydrogen-bonded stretching bands, *cf.* ref. 6. [b] Calcd. for acetone, *O*-acetyloxime, $\lambda_{C=O}$ 5.64 [M. Horak and O. Exner, *Chem. listy*, **52**, 1451 (1958)]. Found for purified acetone, *O*-acetyloxime ($n^{25}D$ 1.4340) $\lambda_{C=O}^{liq}$ 5.64, $\lambda_{C=N}$ 6.03, λ_{C-O-C} 8.27, λ_{N-O} 10.76, other bands at 9.98, and 11.40 μ. [c] Additional bands were found at 10.01 and 11.07 μ. [d] Fused band. [e] Additional bands occur at 9.93 and 10.95 μ. [f] Tentative assignment. [g] E. Borello and M. Colombo, *Gazz. chim. ital.*, **87**, 615 (1957). [h] The shift in the N—H bands indicates that some deuterium exchange occurred in the amino groups. [i] Values in parentheses occur where solvents or hydrates absorb. [j] Prepared according to ref. 16.

because these resonances exhibit characteristic spin-spin splittings. The NH and OH resonances occur at −5.6 p.p.m. and −10.0 p.p.m., respectively. The measured intensity ratios are: CH_2:NH_2 = 1:1 and OH:NH_2 = 1:2. The intensity ratios show that all N—H protons have been accounted for. Hence, structure Ib would be possible only if the chemical shifts of the protons associated with the two nitrogen atoms were accidentally the same in all three compounds. It has been pointed out[15] that rapid chemical exchange of non-equivalent protons in tautomeric compounds can also result in n.m.r. spectra in which these protons appear to be equivalent. This objection does not apply in the present case. The effect of adding water to I in DMF solution demonstrates the ease with which the hydroxyl protons exchange; no such effect is observed for the NH_2 resonance. The observation of separate NH_2 and OH proton resonances also argues strongly against rapid exchange of NH_2 protons. In view of the ease with which the OH protons participate in exchange it is certain that any exchange involving NH_2 protons would also involve the hydroxyls. If this were the case, only one resonance would be observed for all three protons. The possibility of accidental equivalence of the NH chemical shifts (in all three compounds investigated) if structure Ib were correct is felt to be extremely remote. Hence, only aminooximino structures corresponding to Ia can be assigned to compounds I, II, and IV in DMF solution. Furthermore, the absence of any resonances not assigned to structure Ia argues strongly that these compounds exist predominantly in one form. In view of the similarity of the infrared spectra for these compounds in DMF, other solvents, and in the solid state, it is believed that these structures are generally valid for unsubstituted amidoximes.

Since the ultraviolet spectrum for I is quite similar to those of glyoxime and dimethylglyoxime, an *anti*-structure and s-*trans* configuration is indicated for the compound.[16] This is further confirmed by the absence of a doublet in the C=N stretching region. It is felt therefore that on the basis of the present evidence the properties of I are best explained by the structure V, in which both amino and oximino groups are further involved in hydrogen bonds.



IV



V

Experimental[17]

Oxamidoxime (I).—Hydroxylamine hydrochloride (27.80 g., 0.4 mole) in 30 ml. of water was added to a solution of sodium hydroxide (16.00 g., 0.4 mole) in 64 ml. of water. The solution was cooled to 0° and treated with a slow stream of cyanogen gas. Successive precipitates were filtered with suction and dried until the amounts became quite small. During this time the originally neutral solution became acid. The average yield of crude product from several runs was 20.2 g. (85%). Aqueous solutions of oxamidoxime were chromatographed on Whatman no. 3 filter paper with water and the dried strips were sprayed with alcoholic *p*-benzoquinone. R_f values of crude and crystallized product were 0.69 and 0.70. A small spot with R_f 0.89 disappeared after crystallization. Oxamidoxime was soluble in dioxane, DMF, pyridine, and water and could be crystallized from the latter two solvents. The crystallized product was analytically pure and chromatographically uniform and gave capillary decomposition points of 192–197°. On the Dennis bar all crystallized preparations melted at 210° dec., lit. m.p. 196°,[2,4] 198°,[5b,18] 202°,[19] and 203°.[5a] The ultraviolet absorption spectrum, $\lambda_{max}^{H_2O}$ 233 mμ (log ϵ 4.03), was in good agreement with the literature value.[5a] Potentiometric titration of the compound with 0.1 *N* sodium hydroxide at 26.5° under nitrogen gave a pK_a of 10.62.[20]

Anal. Calcd. for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44. Found: C, 20.11, 20.30; H, 5.51, 5.30; N, 47.05, 47.67.

Oxamidoxime was recovered unchanged when the aqueous solution of the disodium salt was carefully acidified with aqueous acetic acid.

(15) A. R. Katritzky and A. J. Waring, *Chem. Ind.*, (London) 695 (1962).

(16) H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron*, in press.

(17) Microanalyses by M. Naranjo. Capillary melting points were determined with a copper block at a heating rate of 1° per min. [H. E. Ungnade, E. A. Igel, and B. B. Brixner, *Anal. Chem.*, **31**, 1432 (1959)] and with a Dennis bar; ultraviolet absorption spectra with a Beckman DK-2 instrument and infrared spectra with a Perkin–Elmer Model 21 spectrophotometer.

(18) J. Ephraim, *Ber.*, **22**, 2305 (1889).

(19) J. Houben and E. Schmidt, *ibid.*, **46**, 3616 (1913).

(20) Potentiometric titrations by J. F. Baytos of this laboratory. For pK_a values of other glyoximes see ref. 16.

A sample of I, prepared by ammonolysis of dichloroglyoxime diacetate (m.p. 161–162°),[3] was identical in melting behavior and infrared spectra. It had $\lambda_{max}^{H_2O}$ 233 mμ (log ε 4.03) and R_f 0.69.

Anal. Calcd. for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44. Found: C, 20.64, 20.29; H, 5.35, 5.24; N, 46.89.

Oxamidoxime gave blue-green solutions with aqueous nickel salts from which the yellow-orange nickel derivative was precipitated by addition of little dilute ammonia or pyridine.[21] Aqueous I was oxidized by aqueous or alcoholic solutions of *p*-benzoquinone with formation of dark-colored products. The reaction with molar equivalents of *p*-benzoquinone leads to destruction of a small portion of I; the remainder was unchanged. Both nickel salts and quinone solutions were used as spray reagents for the paper chromatography of I.

Oxamidoxime Diacetate (II).—An exothermic reaction occurred when I was added to excess boiling acetic anhydride. The mixture was shaken and allowed to cool. Filtering the colorless solid with suction, washing and drying gave 99% of pure diacetate, m.p. 193–194° dec., remelt 165–167°. Its solubility in pyridine at 25° was 2 g. per 100 ml. From dioxan the diacetate crystallized in colorless leaflets, m.p. 193–194°. The corresponding melting points on the Dennis bar were 229° dec., lit. m.p. 184–187°,[2] 206°,[3] 212°.[3]

Anal. Calcd. for $C_6H_{10}N_4O_4$: C, 35.65; H, 4.98; N, 27.72. Found: C, 35.62, 35.40; H, 5.22, 4.96; N, 27.52, 27.55.

Oxamidoxime Disodium Salt.—Oxamidoxime (0.118 g., 0.001 mole) was only partially soluble in 10 ml. of ethanol containing sodium ethoxide (0.002 mole). It was dissolved by adding water (5 ml.). Evaporation of the solution at 0.3 mm. gave 0.22 g. of solvated salt. The anhydrous salt obtained by heating at 100° proved to be very hygroscopic and was not obtained analytically pure.

Anal. Calcd. for $C_2H_4N_4Na_2O_2$: Na, 28.38. Found: Na, 29.69.

Glyoxime diacetate, prepared by acetylation of glyoxime with acetic anhydride, melted at 120–121°, lit. m.p. 120°,[22] 126°.[23]

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.87; H, 4.68; N, 16.28. Found: C, 42.11; H, 4.96; N, 16.25.

Glyoxime, Disodium Salt.—Glyoxime (0.088 g., 0.001 mole) was dissolved in a solution of sodium (0.0460 g., 0.002 mole) in 10 ml. of ethanol. Evaporation at 0.3 mm. gave 0.11 g. of hygroscopic sodium salt which was analyzed as the hydrate.

Anal. Calcd. for $C_2H_2N_2Na_2O_2 \cdot 1.5H_2O$: C, 15.10; H, 3.16; N, 17.62. Found: C, 14.83; H, 2.61; N, 18.07.

N.m.r. Spectra. All proton n.m.r. spectra were obtained at 56.4 Mc./sec. and 28°. Because of the low solubilities, the most prominent resonances in all cases are those of DMF.

Other solvents, including acetone, water, carbon tetrachloride, dioxane, and pyridine, were tried. In all cases, however, the solubilities were insufficient or the solvent spectrum interfered with that of the oximes. Chemical shifts are given in parts per million. The internal reference substance in this study was tetramethylsilane, the chemical shift of which was taken as 0.00 p.p.m. Relative concentrations of protons were determined by electronic integration techniques. All concentration ratios quoted in the discussion have been rounded to the nearest simple ratio of integral numbers. In all cases the measured values were within ±5% of the reported values.

(21) L. Tschugaef and J. Surenjanz, *Ber.*, **40**, 181 (1907); M. Kuras, *Mikrochim. Acta*, **32**, 192 (1944); R. Pallaud, *Chim. anal.*, **33**, 239 (1951); further references are found in A. E. C. Research and Development Report ISC-794.

(22) B. Lach, *Ber.*, **17**, 1573 (1884).

(23) A. Hantzsch, *ibid.*, **25**, 708 (1892).

Halogenation of Estrone and Derivatives[1]

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Received May 23, 1962

The halogenation of estrone and certain of its analogs has been investigated. Bromination, even with excess bromine, resulted only in substitution of the aromatic ring. Chlorination using sulfuryl chloride, chlorine, or N-chlorosuccinimide gave 10-chlorodien-3-one derivatives with chlorine substitution in rings A and D. Mixtures of different products, separable by chromatography, were obtained in all experiments. While substitution of the 2-position in estrone by halogen or nitro groups precluded chlorination in the 4-position, a similar substitution at carbon 4 did not interfere with the entrance of chlorine into the 2-position.

An observation made in this laboratory[2] that tumor growth in animals was inhibited by certain pentacyclic terpenoid methylene quinones such as pristimerin[3] led us to attempt the preparation of such structures from steroidal estrogens. Oxidation of estrone and similar estrogens with lead tetraacetate resulted in dienone–quinols with a hydroxyl group in the 10-position.[4] However, attempts to convert these substances into $\Delta^{9,10}$-methylene quinones by eliminating the 10-hydroxyl group as water were unsuccessful. Consequently, we decided to study the elimination of hydrogen halide from 10-halogenated estrogens. It was thought that the latter compounds would be formed by a reaction comparable to the action of bromine on *para*-substituted phenols.[5] While such work was in progress in this laboratory, Mukawa[6] reported that isocyanuric chloride converted estradiol 17-acetate (A-III) into 2,4,10β-trichloro-17-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-I) and Mills, *et al.*,[7] obtained a number of 10β-chloro-$\Delta^{1,4}$-estradien-3-one derivatives by the action of N-chlorosuccinimide on aromatic steroids. These authors assigned the beta configuration to the halogen in the 10-position.

We began the present investigation by repeating Woodward's work[8] on the bromination of estradiol (A-II) with N-bromoacetamide. Even with a large excess of the same or other brominating agents only 2,4-dibromoestradiol (A-VI) was isolated by direct crystallization, though a small amount of 2,4-dibromoestrone (A-V) which was not found by Woodward, was separated from the crude reaction product using Girard's reagent. In agreement with Woodward, no dienone formation was observed. Similarly, estrone gave only 4-bromoestrone (A-IV) and 2,4-dibromoestrone (A-V), depending upon the amount of bro-

(1) Supported by Grant No. 4550 from the U. S. Public Health Service, National Cancer Institute, Institutional Grant No. EIN-56 from the American Cancer Society and a grant from the Massachusetts Division of the American Cancer Society.

(2) E. Schwenk, to be published in *Arzneimittel-Forsch*, **12**, 1143 (1962).

(3) R. Harada, H. Kakisawa, S. Kobayashi, M. Musya, K. Nakanishi, and Y. Takahashi, *Tetrahedron Letters*, **17**, 603 (1962).

(4) A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

(5) D. Auwers and R. Rapp, *Ann.*, **302**, 153 (1898); *Zincke Th. Ber.*, **28**, 3125 (1895).

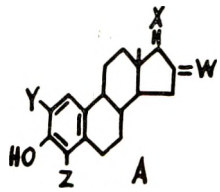
(6) F. Mukawa, *Tetrahedron Letters*, **14**, 17 (1959).

(7) J. S. Mills, T. Barrera, E. Olivares, and H. Garcia, *J. Am. Chem. Soc.*, **82**, 5882 (1960).

(8) R. B. Woodward, *ibid.*, **62**, 1625 (1940).

minating agent used, while estradiol 17-acetate (A-III) gave 2,4-dibromoestradiol 17-acetate (A-VII). We did not find any of the 16-bromo compound reported by Inhoffen[9] to be formed by the bromination of estrone acetate.

Our search for a useful halogenating agent was successful with the finding that either sulfuryl chloride in large excess or a solution of chlorine in chloroform converted both estrone and estradiol 17-acetate into dienone derivatives in good yield. The reaction took a similar course with estrone or estradiol using N-chlorsuccinimide but not with N-chloroacetamide as the chlorinating agent.



A

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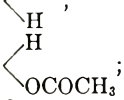
III. X =  ; Y = Z = H; W = H_2

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V. X = O; Y = Z = Br; W = H_2

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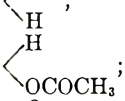
VII. X =  ; Y = Z = Br; W = H_2

VIII. X = O; Y = Cl; Z = H; W = H_2

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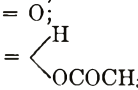
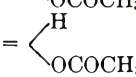
X. X = O; Y = Z = Cl; W = H_2

XI. X =  ; Y = H; Z = Cl; W = H_2

XII. X =  ; Y = Z = Cl; W = H_2

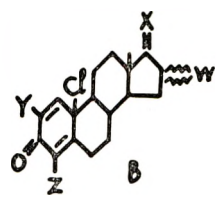
XIII. X = O; Y = NO_2; Z = H; W = H_2

XIV. X = O; Y = H; Z = NO_2; W = H_2

XV. X = O; Y = NH_2; Z = H; W = H_2

XVI. X = O; Y = Cl; Z = NH_2; W = H_2

XVII. X = O; Y = Z = Cl; W = Cl_2



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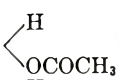
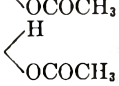
I. X =  ; Y = Z = Cl; W = H_2

II. X =  ; Y = Z = Br; W = H_2

III. X = O; Y = Z = Cl; W = 

IV. X = O; Y = Z = Cl; W = Cl_2

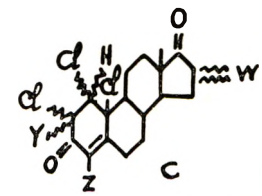
V. X = O; Y = Cl; Z = H; W = 

VI. X = O; Y = Z = Br; W = 

VII. X = O; Y = Cl; Z = NO_2; W = Cl_2

VIII. X = O; Y = Cl; Z = NO_2; W = 

IX. X = O; Y = H; Z = NO_2; W = 



C

I. Y = H; Z = H; W = 

II. Y = H; Z = Cl; W =

III. Y = NO_2; Z = H; W = Cl_2

IV. Y = NO_2; Z = H; W =

V. Y = Cl; Z = NO_2; W =

An amount of chlorinating agent slightly in excess of one mole gave resins whose infrared spectra suggested the presence of a dienone structure. In the case of estrone, chromatography of the crude reaction mixture gave only 4-chloroestrone (A-IX). Repeated recrystallization of a similar chlorination product from estradiol 17-acetate gave 4-chloro-estradiol 17-acetate (A-XI) as the sole crystalline product. This substance was identified by alkaline hydrolysis and subsequent oxidation to 4-chloroestrone, an authentic sample of which was obtained by demethylation of 4-chloroestrone methyl ether.[10] For comparison, 2-chloroestrone was also prepared similarly.

Mukawa[6] also isolated A-XI but did not establish the position of the chlorine atom. The 17-acetoxy-10β-chloro-$\Delta^{1,4}$-estradien-3-one from which he obtained this substance could not be found in our reaction products.

When estradiol 17-acetate was treated with 3.6 moles of chlorine in chloroform solution or with a large excess of sulfuryl chloride which also served as the solvent, the principal reaction product was found to be 2,4,10β-trichloro-17-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-I). Contrary to Mukawa's[6] observation, reduction of this compound with zinc dust and acetic acid gave 2,4-dichloroestradiol 17-acetate (A-XII), in good yield. Similar chlorination experiments with estradiol gave intractable resins.

A more complicated course of reaction was observed in the chlorination of estrone, which when allowed to react with a large excess of sulfuryl chloride for four hours gave a product readily isolated in solid form. Its infrared spectrum showed a split band in the carbonyl region suggesting the presence of a mixture of compounds of dienone character. Several components could be isolated by chromatography on silica gel. One of these was shown by analysis to be a tetrachloroenone with an absorption at 247 mμ in the ultraviolet and was reduced by zinc and acetic aicd to give estrone. Another chlorination product isolated was a pentachloroenone which absorbed in the ultraviolet at 266 mμ and upon reduction gave 4-chloroestrone, identified

(9) H. H. Inhoffen (to Schering A.G.), German Patent 720015; *Chem. Abstr.*, **37**, 2520 (1943).

(10) H. J. Thomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959).

by comparison with an authentic sample. These findings suggest that in both substances four chlorine atoms are in positions which allow reductive elimination with nascent hydrogen. Of these, two are accounted for by chlorine atoms in 10β- and 16ξ-positions. In the infrared spectrum the band of the 17-keto group was indeed displaced to 1753 and 1754 cm.$^{-1}$, respectively, under the influence of the 16-chloro atom. The n.m.r. spectrum of the tetrachloro compound displayed a peak at τ 4.008 (C=CH in 4), and peaks at τ 5.150 and 5.500 (C(H)(Cl) in 1 and in 16). In the n.m.r. spectrum of the pentachloro compound there was no indication of a proton on the 4-position but only peaks at τ 5.178 and 5.520 representing C(H)(Cl) in the 1- and 16-positions were found. The two chlorine atoms which were readily eliminated by reduction must necessarily be *ortho* to each other. As indicated by the n.m.r. spectra they can be only in positions 1 and 2 but not in 4 and 5 of ring . This assumption is supported by the fact that after reduction of the pentachloro product, the remaining fifth chlorine atom was found to be in the 4-position where a double bond protects it from reductive elimination. Accordingly, the substances are considered to be 1ξ,2ξ,10β,16ξ-tetrachloro-Δ^4-estrene-3,17-dione (C-I), giving estrone with zinc and acetic acid, and 1ξ,2ξ,4,10β,16ξ-pentachloro-Δ^4-estrene-3,17-dione (C-II), which was reduced to 4-chloroestrone. When chlorination of estrone was extended to twenty hours, chromatography of the crude reaction product on silica gel gave three well defined substances. The first two eluted from the column were a tetrachloro- and a pentachlorodienone. Their properties and their analytical composition characterized them as different from C-I and C-II. Their infrared spectra particularly were significantly different, showing 17-keto bands at 1760 and 1771 cm.$^{-1}$, respectively. This suggests that in the pentachloro compound the 17-keto group is vicinal to two chlorine atoms at carbon 16. In C-I and C-II the 17-keto band usually found around 1740 cm.$^{-1}$ was shifted by 14 units to 1753 and 1754 cm.$^{-1}$ by the presence of one *ortho* chlorine atom. In the new pentachloro compound another shift of 17 units is superimposed on this by the second chlorine atom at C-16.[11] Unfortunately the amount of substance was too small to permit reduction of the new pentachloro derivative with zinc and acetic acid. The substance is tentatively formulated as 2,4,10β,16,16′-pentachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IV). The principal reaction product, a tetrachloro compound, and the third substance which analysis showed to be a trichlorodienedione, were identical with the products obtained from the chlorination of 2,4-dichloroestrone and 2-chloroestrone, respectively, using excess sulfuryl chloride as described below. From these latter two reactions we were able to isolate as the main products, 2,4,10β,16ξ-tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) and 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V) so cleanly that recrystallization without chromatography sufficed to obtain them in pure form.

These formulations are supported by the n.m.r. spectra. The tetrachloro compound showed peaks at τ 2.667 (C=CH in 1), 5.550 and 5.617 (C(H)(Cl) in 16), 8.958 (CH_3 in 18), while the trichloro compound had τ 3.825 (C=CH in 4), 5.542 and 5.625 (C(H)(Cl) in 16), and 8.958 (CH_3 in 18).

For further confirmation, the crude reaction product resulting from treatment of estrone with excess sulfuryl chloride was reduced directly with zinc and acetic acid and the product chromatographed. 2,4-Dichloroestrone, 4-chloroestrone, and estrone were isolated. These must be derived from B-III and B-IV, and from C-I and C-II, respectively. Surprisingly, both 2,4-dichloro- and 4-chloroestrone were converted to the same tetrachloro compound (B-III), by excess sulfuryl chloride, while 2-chloroestrone gave exclusively 2,10β,-16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V).

Although no 2-chloroestrone was found by chromatography, the isolation of 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V), in the foregoing experiment suggested that it might also have been formed as an intermediate, and it was thought that dilution of the reactants would favor such a reaction. When estrone at a dilution of 0.2% in chloroform was treated with excess sulfuryl chloride, a resin was formed whose infrared spectrum showed dienone character. Chromatography on silica gel gave only one crystalline substance which was a chlorinated phenol and was not identical with any of the chlorinated estrones described above. It was also different from 16α-chloroestrone.[12,13] Analysis showed the new compound to be a tetrachloroestrone. The infrared spectrum had a 17-keto band at 1760 cm.$^{-1}$, which together with a band at 800 cm.$^{-1}$, characteristic for >C(Cl)(Cl), suggests that the compound is 2,4,16,16′-tetrachloroestrone. The resinous fractions, when reduced with zinc and acetic acid, gave only 4-chloroestrone and estrone by chromatography. No 2-chloroestrone was found.

Chlorination of estrone with 4.8 moles of chlorine in chloroform or with 4 moles of N-chlorosuccinimide gave results similar to those obtained from the sulfuryl chloride reaction.

The chlorination reactions take a simpler course when the 2,4-dibromo derivatives of estrone (A-V), or of estradiol acetate (A-VII), are submitted to the action of excess sulfuryl chloride.

We obtained 90% yields of 2,4-dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI), and 2,4-dibromo - 10β - chloro - 17 - acetoxy - $\Delta^{1,4}$ - estradien-3-one (B-II), respectively. Upon reduction with zinc and acetic acid both reverted to the starting materials.

A very complex course of the reaction was observed in the treatment of 2-nitro- or 4-nitroestrone with excess sulfuryl chloride, while 2,4-dinitroestrone did not react even when boiled with this agent. From 2-nitroestrone, two substances were obtained by chromatography of the crude reaction product on silica. The principal product was tetrachlorinated together with

(11) Compare: N Tosho and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961).

(12) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958).

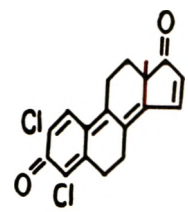
(13) The authors are grateful to Dr. G. P. Mueller of G. D. Searle & Co. for a sample of this compound.

a lesser amount of a pentachloro compound. When either the crude reaction mixture or the tetrachloro-derivative was reduced with zinc and acetic acid, only the chlorine-free 2-aminoestrone was isolated. All chlorine atoms in the two compounds must therefore be in positions from which they are easily eliminated by nascent hydrogen. The infrared spectrum of the pentachloro substance showed the 17-keto band at 1773 cm.$^{-1}$ suggesting substitution with two chlorine atoms at the 16-position. In the tetrachloro compound this band was found at 1759 cm.$^{-1}$ corresponding to one chlorine atom at carbon 16. The placement of the 3-keto bands at 1706 and 1692 cm.$^{-1}$, respectively, attests to *ortho* substitution of this group by a chlorine atom and the nitro group. The elimination of the remaining two chlorine atoms by reduction requires them to be at carbons 1 and 2 or at 4 and 5. The n.m.r. spectra were found to answer this question, showing peaks at τ 4.016 and 4.008 for a proton in the 4-position and τ 4.858 and 4.870 for a $C\langle^{H}_{Cl}$ grouping at carbon 1. Accordingly, the two substances are formulated as 2-nitro,1ξ,2ξ,10β,16ξ-tetrachloro-Δ^4-estrene-3,17-dione (C-IV) and 2-nitro,1ξ,2ξ,10β,16,16′-pentachloro-Δ^4-estrene-3,17-dione (C-III).

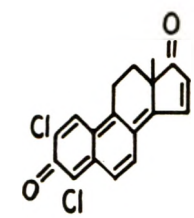
Chromatography of the crude product formed from 4-nitroestrone with excess sulfuryl chloride gave four compounds not all of which could be identified completely because of the small yields of purified material. The first substance off the column showed an analysis nearly that of a pentachloro nitroderivative. Its infrared spectrum had the 17-keto band at 1754 cm.$^{-1}$ with the 3-keto band at the unusually high value of 1711 cm.$^{-1}$. The n.m.r. spectrum located one chlorine atom as $C\langle^{H}_{Cl}$ at carbon 16 (τ 5.550) and another at carbon 1 (τ 5.250). The high absorption for the 3-keto group in the infrared suggests a substitution of two chlorine atoms at carbon 2. In all probability the substance is 1ξ,2,2′,10β,16ξ-pentachloro-4-nitro-Δ^4-estrene-3,17-dione (C-V). The second substance gave the analysis of a tetrachloro compound. It showed the 17-keto band of the infrared at 1770 cm.$^{-1}$, corresponding to a 16,16′-dichloro compound, while the 3-keto band at 1692 cm.$^{-1}$ indicated the substitution of a chlorine atom at carbon 2. The substance is formulated as 2,10β,16,16′-tetrachloro-4-nitro-Δ^{1,4}-estradiene-3,17-dione (B-VII). The third compound was a trichloro derivative with the infrared spectrum showing keto bands at 1759 cm.$^{-1}$ (17-keto, 16-chloro) and 1692 cm.$^{-1}$ (3-keto, Δ^{1,4}-2-chloro-4-nitro). The n.m.r. spectrum with τ 2.667 (C=CH in 1) and τ 5.567 and 5.633 ($C\langle^{H}_{Cl}$ in 16) indicates an agreement between the two spectra with the formulation as 2,10β,16ξ-trichloro-4-nitro-Δ^{1,4}-estradiene-3,17-dione (B-VIII). The last substance to be eluted from the column was a dichloro derivative whose n.m.r. spectrum showed only one chlorine atom as $C\langle^{H}_{Cl}$ in 16. It is formulated as 10β,16ξ-dichloro-4-nitro-Δ^{1,4}-estradiene-3,17-dione (B-IX).

Upon reduction with zinc and acetic acid of the crude chlorination product of 4-nitroestrone or of the crude trichloro fraction separated from the column, a chloro-amino estrone was isolated which gave an orange diazo oxide upon diazotization. Reduction with hypophosphorous acid produced 2-chloroestrone, which was identified by comparison with the same substance prepared from 2-aminoestrone methyl ether. The chlorine atom must, therefore, be in the 2-position. Accordingly, the compound is formulated as 2-chloro-4-aminoestrone, in agreement with its analysis, thus supporting the formulation of the products derived from the chlorination of 4-nitroestrone.

Some preliminary attempts[14] were made to eliminate hydrogen chloride from some of the compounds described, but only treatment with dimethylformamide and lithium chloride[7] gave a new compound. Thus from 2,4-dibromo-10β,16ξ-dichloro-Δ^{1,4}-estradiene-3,17-dione (B-VI) a deep blue substance was produced which gave red solutions in organic solvents. Analysis suggested the presence of five or six double bonds and showed that the bromine atoms had been exchanged for chlorine atoms. A similar reaction was observed only recently by Diassi, *et al.*[15] The analysis allows a preliminary formulation of the substance as 2,4-dichloro - Δ$^{1,4,8(14),9(10),15}$ - estrapentaene - 3,17 - dione (D) or 2,4 - dichloro - Δ$^{1,4,6,8(14),9(10),15}$-estrahexaene-3,17-dione (E). Dehydrohalogenation of B-I in the same manner afforded an orange substance which was not obtained in pure form.



D



E

It is interesting to consider the difference between our experiment and the course of the dehydrohalogenation carried out by Mills, *et al.*[7] Their starting material had no substitution in the 2- and 4-positions and the newly formed 9(10) double bond shifted to 9(11) while the molecule reverted to its initial aromatic structure. In our case, 2,4-substitution seems to stabilize the 9(10) double bond, which then together with that at 15(16) may cause dehydrogenation at 8(14) and possibly also at 6(7). The deep color of the compound, unprecedented for a steroid derivative, is in agreement with such a conjugated double bond system. A similar accumulation of double bonds was suggested by Roberts[16] for purpurogenone, a deep red methylene-quinone.

Our experiments show that bromination of the phenolic steroids is a straightforward process. In agreement with Zincke's assumption[5] that in *p*-cresol bromine first substitutes the positions *ortho* to the hydroxyl before *para* substitution takes place, we find that bromine substitutes in estrone only one or both *ortho* positions, while even excess bromine does not attack the position *para* to the hydroxy group, possibly because

(14) The senior author has retired from active laboratory work and the dehydrohalogenation experiments which must be considered as preliminary will not be continued by him.

(15) P. Diassi, J. Fried, M. Palmere, and E. F. Sabo, *J. Am. Chem. Soc.*, **83**, 4249 (1961).

(16) J. C. Roberts, Antibiotics and Mold Metabolites, Symposium, Special Publications No. 5 of the Chemical Society, London, 1956, p. 36 ff.

of steric hindrance. The action of chlorinating reagents on extrone (A-I) and estradiol acetate (A-III) is much more complex. With only about one mole of chlorine substitution apparently occurs mainly in the 10β-position with concomitant conversion of the aromatic ring to a quinolic system, possibly through a carbanion as suggested by Mills, *et al.*[7] Such 10β-monochlorodien-3-ones could not be isolated in our work, but were obtained by Mukawa[6] and by Mills, *et al.*[7] They may rearrange to the 4-chloro derivative thus reverting to the aromatic structure. Aromatic substitution on carbon 2 also occurs, although only to a small degree. Excess chlorinating reagents, however, give largely 2,4-dichloro substitution with A-I and exclusively so with A-III. The formation of tetra- and pentachloro compounds C-I and C-II from A-I is difficult to understand. It is possible that in this case 4-monochloro- and 2,4-dichlorodienone derivatives are the first reaction products and that subsequently the Δ^1-double bond (but surprisingly not Δ^4) is saturated by the addition of chlorine in a manner similar to that observed by Kirk, *et al.*,[17] in the case of Δ^4-cholesten-3-one.

It is interesting to consider that in the aromatic steroids studied, halogenation prefers the 4- over the 2-position, while in the case of estrone, nitration affords nearly equal yields of 2- and 4-nitro estrone. The Mannich reaction, however, as Patton[18] has shown, substitutes in the 2-position exclusively, with no further reaction in position-4 even with a large excess of reagents. Similarly, in the present work, 2-chloro- or 2-nitroestrone react with an excess of sulfuryl chloride to give only 10β,16ξ-dichloro derivatives without substitution in the 4-position, while 4-chloro- and 4-nitroestrone are both substituted by chlorine at the 2-carbon atom.

Experimental[19]

4-Bromoestrone (A-IV).—Estrone (540 mg.) was dissolved in 50 ml. of absolute ethanol and 300 mg. of N-bromoacetamide added. After standing overnight the reaction mixture was diluted with water and the product was filtered and washed with water. Recrystallization from chloroform–methanol gave 400 mg. of material, m.p. 281–283°. Repeated recrystallization from the same solvents gave an analytical sample with melting point unchanged, $[\alpha]^{23}D$ +147° (*c* 0.7), λ_{max} 231 (319), 282 (2234), 299 (2340); ν_{max} 3452 (arom, OH), 2980, 2916 (C—H), 1739 (17-keto), 1598, 1480, (arom. C=C), 812 (1,2,3,4 arom. subst.), 792 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{21}O_2Br$: C, 61.90; H, 6.06; Br, 22.88. Found: C, 61.90; H, 6.06; Br, 23.07.

Methylation of this compound with methyl iodide gave 4-bromoestrone-3-methyl ether, m.p. 289°, with infrared identical to that of authentic material.[20]

2,4-Dibromoestrone (A-V) and 2,4-Dibromoestradiol (A-VI) from the Bromination of Estradiol (A-II).—The crude product (2.65 g. m.p. 212–215°) obtained according to Woodward[8] and 2 g. of Girard's reagent T were dissolved in 50 ml. of absolute ethanol containing 10% acetic acid and refluxed for 45 min. The reaction mixture was diluted with water and thoroughly extracted with ether. The extracts were then repeatedly washed with water and the combined water layers acidified with hydrochloric acid and again extracted with ether. After drying with magnesium sulfate and evaporation of the ether, the semicrystalline residue was recrystallized from methanol and gave 125 mg. (3%) of white crystals, m.p. 235–237°. Repeated crystallization from the same solvent gave an analytical sample of 2,4-dibromoestrone, A-V, m.p. 235–237°, $[\alpha]^{23}D$ +63° (c 0.5); λ_{max} 230 (4070), 285 (2900), 293 (3206); ν_{max} 3332 (arom. OH), 2987. 2911 (C—H), 1731 (17-keto), 1551, 1486 (arom. C=C), 873 (1,2,3,4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2Br_2$: C, 50.49; H, 4.71; Br, 37.33. Found: C, 50.63; H, 4.64; Br, 37.33.

The original ether extract from the Girard reagent separation was dried over sodium carbonate, evaporated, and recrystallized from methanol to give 2.34 g. of the known 2,4-dibromoestradiol, A-VII, m.p. 214–215°. 2,4-Dibromoestrone was also obtained from estrone using N-bromoacetamide in ethanol or with bromine in acetic acid or in chloroform. Reduction of 2,4-dibromoestrone with sodium borohydride in methanol gave 2,4-dibromoestradiol (A-VI).

2,4-Dibromoestradiol 17β-Acetate (A-VII) by Acetylation of A-VI.—2,4-Dibromoestradiol (500 mg.) was dissolved in 25 ml. of glacial acetic acid and refluxed for 4 hr. after which the acetic acid was distilled under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with water, potassium bicarbonate, and water. After drying the ethyl acetate solution over magnesium sulfate and distillation of the solvent, the product was recrystallized from methanol and weighed 320 mg. (62%), m.p. 185–187°. The analytical sample was obtained from methanol–chloroform, $[\alpha]^{23}D$ +30.5° (*c* 1.7); λ_{max} 292 (3250), 285 (2500); ν_{max} 3437 (arom. OH), 2932, 2867 (C—H), 1733 (acetate C=O), 1467 (CH_2), 1247 (acetate CO stretch), 880 (1,2,3,4,5 arom. subst.), cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3Br_2$: C, 50.87; H, 5.12; Br, 33.84. Found: C, 51.14; H, 5.07; Br, 35.02.

The same 2,4-dibromoestradiol 17-acetate was obtained from the bromination of estradiol 17-acetate with bromine in chloroform solution.

Anal. Calcd. for $C_{20}H_{24}O_3Br_2$: C, 50.87; H, 5.12; Br, 33.84. Found: C, 50.84; H, 5.39; Br, 33.78.

4-Chloroestradiol 17β-Acetate (A-XI).—A solution of 942 mg. of estradiol 17β-acetate (A-III) in 15 ml. of chloroform was agitated magnetically while 445 mg. (1.1 moles) of sulfuryl chloride in chloroform was added dropwise. After 2 hr. the reaction mixture was washed with 10% potassium bicarbonate solution and with water, dried over magnesium sulfate, and evaporated under reduced pressure. The infrared spectrum of the partly crystalline residue showed the disappearance of the hydroxyl band and the development of a band at 1666 cm.$^{-1}$ characteristic of a 1,4-dien-3-one system of about the same intensity as the acetate carbonyl. However, repeated crystallization from chloroform–methanol afforded 250 mg. (24%) of white crystals, m.p. 254–254.5°, $[\alpha]^{24}D$ +31.3° (*c* 2.4), ν_{max} 3525 (arom. OH), 3025 (C—C), 2950 (C—H), 1720 (acetate C=O), 1617, 1579, 1502 (arom. C=C), 1445 (CH_2) 1278 (acetate CO stretch) 801 (1,2,3,4 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}O_3Cl$: C, 68.86; H, 7.22; Cl, 10.16. Found: C, 68.27; H, 7.11; Cl, 10.29.

That this material was 4-chloroestradiol 17β-acetate (A-XI) was shown by correlating it with 4-chloroestrone, as described in the following section. Chromatography of another batch on a silica column again gave the aromatic 4-chloro derivative, A-XI, as the only crystallized product.

4-Chloroestrone (A-IX) from A-XI.—The chlorination was repeated and the isolated material was dried by azeotropic distillation with benzene. The product (yield 93%) had an infrared spectrum identical with that of the substance obtained in the first experiment. A 348-mg. portion was refluxed overnight in 50 ml. of a 4% solution of ethanolic sodium hydroxide containing 5 ml. of water. The solvent was distilled under reduced pressure until precipitation started, and the slurry was then poured into water, filtered, and washed on the filter with water. The infrared spectrum showed the disappearance of the characteristic acetate bands and the appearance of a second hydroxyl band. The crude product was oxidized directly by dissolving it in 100 ml. of reagent grade acetone and adding 2 ml. of an aqueous 8 *N* chromium trioxide solution. After stirring for 30 min. the solvent was partially removed under reduced pressure at 25° and the product precipitated with water. Recrystallization from chloroform gave

(17) D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 627, 1184 (1956).

(18) T. L. Patton, *J. Org. Chem.*, **25**, 2148 (1960); *ibid.*, **26**, 1677 (1961).

(19) All melting points were observed on a Fischer hot stage and are uncorrected. Rotations were determined in chloroform solution. All ultraviolet spectra were made in methanol solution using a Cary Model 11 spectrophotometer. The infrared spectra for the chromatograms were taken with potassium bromide planchets on a Perkin-Elmer Infracord spectrophotometer, while the final infrared spectra were obtained with potassium bromide planchets on a Beckman infrared instrument. N.m.r. spectra were obtained with a Varian Associates HR60 spectrophotometer.

(20) Kindly supplied by Dr. J. P. Horwitz, Detroit Institute of Cancer Research, Detroit, Mich.

195 mg. (54%), m.p. 272–274°. Mixed melting point and infrared spectrum showed the substance to be identical to authentic 4-chloroestrone.

4-Chloroestrone (A-IX) from 4-Chloroestrone-3-methyl Ether.—A 900-mg. sample of the latter compound, prepared according to Thomson, *et al.*,[10] was dissolved in 2.5 ml. of glacial acetic acid, and 2.5 ml. of 48% aqueous hydrobromic acid was added. After refluxing for 2 hr. the reaction mixture was poured into water, extracted with chloroform, washed with potassium bicarbonate and water, and dried over sodium sulfate. The solvent was removed under reduced pressure. Chromatography of the tarry residue gave only oils which could not be induced to crystallize. The combined fractions were sublimed at 240° and 150–200-μ pressure. The white sublimate was recrystallized from chloroform and afforded 340 mg. (40%) of material, m.p. 273–275°, $[\alpha]^{23}D$ +112° (*c* 1.0) λ_{max} 285 (2470), ν_{max} 3444 (arom. OH), 2961, 2896 (C—H), 1737 (17-keto), 1598, 1484 (C=C), 1373 (—CH_3), 821 (1,2,3,4 arom. subst.).

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.31; H, 6.85; Cl, 11.80.

2-Chloroestrone (A-VIII) from 2-Chloroestrone Methyl Ether.[10]—The conditions of this experiment were the same as those described for the preparation of the 4-chloro isomer. After crystallization from chloroform–methanol there was obtained a small yield of a white substance, m.p. 223–224.5°, $[\alpha]^{23}D$ +162° (*c* 0.12) λ_{max} 227 (6100), 285 (1967), 294 (1706); ν_{max} 3369 (arom. OH), 2957, 2888 (C—H), 1738 (17-keto), 1611, 1496 (C=C), 1378 (—CH_3), 1208 (C—O stretch phenol), 886 (1,2,-4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.67; H, 6.92; Cl, 11.63.

2-Chloroestrone (A-VIII) from 4-Nitroestrone (A-XIV).—A somewhat better yield was obtained when 3 g. of 4-nitroestrone was chlorinated with 30 ml. of sulfuryl chloride and worked up as described in a later section of this paper. The crude material was dissolved in 30 ml. of warm acetic acid and 1.5 g. of zinc dust was added over a 1.5-hr. period. The reaction mixture was filtered and the zinc residue washed with acetic acid. The washes were combined with the filtrate, chloroform was added, and the mixture was neutralized with bicarbonate solution and finally washed with water. The solvent layer was dried with sodium sulfate and distilled to a crude residue which was dissolved in 480 ml. of water containing 6 ml. of sulfuric acid and filtered. The cooled filtrate was diazotized with 650 mg. of sodium nitrite. An orange diazo oxide precipitated which was filtered and washed with water. It was then suspended in 60 ml. of 50% hypophosphorous acid, stirred for 2 days at room temperature, and finally heated for 0.5 hr. The insoluble material was filtered, dried, and sublimed *in vacuo*. Finally, it was recrystallized several times from chloroform–methanol to give 320 mg. of 2-chloroestrone identical in melting point and infrared spectrum with that described above.

2,4-10β-Trichloro-17β-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-I).—Estradiol 17β-acetate (A-II) (3 g.) was suspended in 15 ml. of sulfuryl chloride. After 2 min. solution was complete and the reaction mixture was poured into water and stirred to decompose the sulfuryl chloride. The resultant slurry was extracted with chloroform and washed with 10% potassium bicarbonate solution and with water. After drying over sodium carbonate the chloroform was evaporated under reduced pressure to a small volume. Further evaporation at atmospheric pressure with concomitant addition of methanol afforded 2.63 g. (64%) of product. An analytical sample was prepared by repeated crystallization from chloroform–methanol, m.p. 201–202°, $[\alpha]^{23}D$ +10.8° (*c* 4.2), λ_{max} 260 mμ (16,000) ν_{max} 2982, 2885 (C—H), 1731 (acetate C=O), 1690 (3-keto), 1605 (C=C), 1248 (acetate), 895 cm.$^{-1}$. N.m.r.: τ 2.658 (C=CH in 1), 5.358, 5.475 (17α-H), 7.917 (CH_3 in acetyl), 9.050 (CH_3 in 18).

Anal. Calcd. for $C_{20}H_{23}O_3Cl_3$: C, 57.50; H, 5.55; Cl, 25.46. Found: C, 57.87; H, 5.77; Cl, 25.23.

Reaction of estradiol 17β-acetate in chloroform with 3.3 moles of chlorine in a 2% chloroform solution gave again B-I in excellent yield.

Anal. Calcd. for $C_{20}H_{23}O_3Cl_3$: C, 57.50; H, 5.85; Cl, 25.46. Found: C, 57.00; H, 5.46; Cl, 26.08.

2,4-Dichloroestradiol 17β-Acetate (A-XII) by Reduction of B-I.—A solution of 100 mg. of B-I in 10 ml. of acetic acid was refluxed for 10 min. with 250 mg. of zinc dust, after which an additional 250 mg. of zinc dust was added and reflux continued for 15 min. The clear solution was decanted into ice–water and the zinc residue washed with acetic acid by decantation and finally with acetone. The washes were combined and added to the ice–water. The precipitate was collected by filtration and washed with water. Two recrystallizations from acetone–water gave 63 mg. of 2,4-dichloroestradiol-17β-acetate, m.p. 199–200°, $[\alpha]^{25}D$ +40° (c 0.75), λ_{max} 230 (10280), 284 (2730), 290 (2636), ν_{max} 3434 (arom. OH), 1730 (acetate C=O), 1566 (C=C arom.), 1379 (C—CH_3), 1269 (acetate CO stretch), 1190 (phenol CO stretch), 869 (1,2,3,4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3Cl_2$: C, 62.67; H, 6.31; Cl, 18.50. Found: C, 62.56; H, 6.30; Cl, 18.18.

1ξ,2ξ,10β,16ξ-Tetrachloro-Δ^4-estrene-3,17-dione (C-I) and 1ξ,2ξ,4,10β,16ξ-Pentachloro-Δ^4-estrene-3,17-dione (C-II) by Reaction of A-I with Excess Sulfuryl Chloride, First Experiment.—Estrone (2 g.) was magnetically agitated with 10 ml. of sulfuryl chloride. Aliquots were removed periodically and after 4 hr. the infrared spectra showed no further change. The reaction mixture was then poured into water, agitated until the sulfuryl chloride had decomposed, and the solid material was washed on the filter with 10% potassium bicarbonate solution and with water. The infrared spectrum showed a split band in the carbonyl region. Since crystallization failed to separate the components the material was chromatographed on a silica gel column. Elution with benzene in small portions gave 30 semicrystalline fractions ranging in ultraviolet absorption from 266 to 259 mμ. The column was then stripped with ethyl acetate and the material thus obtained crystallized to give 370 mg. of C-I. Several recrystallizations from chloroform–methanol afforded an analytical sample, m.p. 243–245° dec., $[\alpha]^{25}D$ +141° (*c* 0.92), λ_{max} 247 mμ (13500), ν_{max} 2961, 2875 (C—H), 1754 (17-keto, 16-chloro), 1695 (3-keto, 2-chloro-Δ^4), 894 cm.$^{-1}$. N.m.r.: τ 4.008 (C=CH in 4), 5.150 and 5.500 (C(H)Cl in 1 and 16), 8.967 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{20}O_2Cl_4$: C, 52.71; H, 4.92; Cl, 34.57. Found: C, 52.23; H, 4.70; Cl, 34.72.

The fractions with ultraviolet absorption above 258 mμ were combined (930 mg.) and rechromatographed on silica gel. Elution with 3:1 benzene–hexane gave 200 mg. of material which absorbed in the ultraviolet between 266 and 264 mμ. Subsequent eluates ranged down to 248 mμ. The first fractions were combined and recrystallized several times to give 84 mg. of C-II, m.p. 217–219° dec., λ_{max} 266 mμ (10,700), ν_{max} 2955, 2870 (C—H), 1753 (17-keto, 16-chloro), 1706 (3-keto, 2-chloro, Δ^4), 1582 (C=C), 928 cm.$^{-1}$. N.m.r.: τ 5.178 (C(H)Cl in 1), 5.520 (C(H)Cl in 16), 8.986 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_2Cl_5$: C, 48.63; H, 4.31; Cl, 39.87. Found: C, 49.30; H, 4.59; Cl, 39.41.

Zinc–Acetic Acid Reduction of C-I.—Following the procedure described for reduction of B-I, 100 mg. of C-I gave 68 mg. of estrone which after two recrystallizations had a m.p. of 257–259°. Mixed melting point and infrared spectra were identical with that of authentic estrone.

Zinc–Acetic Acid Reduction of C-II.—Following the above procedure, 30 mg. of C-II gave 11 mg. of 4-chloroestrone as shown by mixed melting point and infrared spectra.

2,4,10β,16,16'-Pentachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IV) from A-I with Excess Sulfuryl Chloride, Second Experiment.—Estrone (2 g.) was dissolved in 15 ml. of sulfuryl chloride and left overnight for 20 hr. at room temperature in darkness in a flask protected from moisture by a calcium chloride tube. The solution was poured into ice and water and stirred until all sulfuryl chloride had decomposed. The reaction product, a white powder, was filtered, washed with water, and ground with 10% potassium bicarbonate solution in a mortar, again filtered, washed neutral with water, and then dried over phosphorus pentoxide *in vacuo;* yield, 3.3 g. This material was dissolved in benzene and chromatographed on 150 g. of silica. Four fractions were taken: one each of 1.8 g. and 0.32 g. with benzene, one of 0.64 g. with benzene–ether (9:1), and 0.14 g. with ether. Each fraction was dissolved in benzene–hexane (50:50) and again put on a silica column but elution was started with benzene–hexane (50:50) and continued with mixtures containing 70, 72.5, 75, and 100% benzene. Finally, benzene–ether mixtures containing 2.5, 5, and 10% ether were used. Using infrared spectra as a guide, corresponding fractions were combined and recrystal-

lized from benzene–hexane mixtures. Three main fractions were obtained in this way which gave good analyses though the yields were very small for in some cases ten recrystallizations were necessary. The compound from fraction I is formulated as 2,4,10β,16,16′-pentachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IV), m.p. 197–198°, $[\alpha]^{24}D$ +47° (*c* 1.48), λ_{max} 258 (16720), ν_{max} 2961, 2887 (C—H), 1771, (17-keto,16,16′-dichloro), 1687 (3-keto, $\Delta^{1,4}$-2,4-dichloro), 1592 (C=C), 1452 (CH_2) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{17}O_2Cl_5$: C, 48.85; H, 3.87; Cl, 40.05. Found: C, 48.88; H, 3.96; Cl, 39.68.

The product from fraction II had an infrared spectrum and properties identical with that of the later described 2,4,10β,16ξ-tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) as confirmed by analysis. The n.m.r. spectrum supports this formulation, with peaks at τ 2.700 (C=CH in 1), 5.520 (C(H)Cl in 16).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.70; 53.11; H, 4.92; 4.51; Cl, 34.58, 34.37.

Fraction III material showed an infrared spectrum and properties identical with that of the later described 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione, as confirmed by analysis.

Anal. Calcd. for $C_{18}H_{19}O_2Cl_3$: C, 57.85; H, 5.12; Cl, 28.46. Found: C, 57.97, 57.72; H, 4.86, 5.13; Cl, 29.09.

In the above experiment in which the reaction was extended for 20 hr., the tetra- and pentachloro compounds, C-I and C-II, isolated in the first experiment (4 hr.), could not be found. However when the experiment was repeated and again worked up after only 4.5 hr., C-I and C-II were identified as well as B-III and B-IV.

4-Chloroestrone (A-IX) and 2,4-Dichloroestrone (A-X) from Estrone.—Estrone (1.5 g.) was dissolved in 7.5 ml. of sulfuryl chloride left for 20 hr. in the dark and the reaction mixture was treated as described above. After drying of the product over phosphorus pentoxide *in vacuo*, the yield was 1.45 g. The substance was dissolved in 50 ml. of acetic acid and reduced by refluxing with 20 g. of zinc dust, added in portions during 1 hr. After another hour of refluxing, the solution was decanted into ice and water and the residue was extracted with small amounts of acetic acid and of acetone which were added to the ice–water mixture. The precipitate was filtered and washed with water. After drying over phosphorus pentoxide, there was obtained 1.3 g. of a buff-colored powder. This was dissolved in benzene and adsorbed on a column of 150 g. of silica gel prepared with benzene. Elution with 10% chloroform in benzene gave a crystalline material A (425 mg.) which was followed by another crystalline substance B (490 mg.) when the chloroform in the eluent was raised to 20%. Finally, a third crystalline compound C (160 mg.) was obtained using the same concentration of chloroform. Each of the three substances was three times recrystallized from benzene–hexane and then from acetone–water. Compound A was 2,4-dichloroestrone, m.p. 212–213°, $[\alpha]^{25}D$ +129° (*c* 0.73) λ_{max} 284 (2933), 292 (3000), ν_{max} 3335 (arom. OH), 2961, 2906 (C—H), 1730 (17-keto), 1557, 1473 (arom. C=C), 872 (arom. 1,2,3,4,5 subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2Cl_2$: C, 63.73; H, 5.94; Cl, 20.90. Found: C, 63.98; H, 6.07; Cl, 20.70.

Compound B was identical in all its properties with 4-monochloroestrone, A-IX.

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.81; H, 7.03; Cl, 11.71.

The third substance, C, was unchanged estrone.

2,10β,16ξ-Trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V) from 2-Chloroestrone (A-VIII).—2-Chloroestrone (200 mg.) was dissolved in 5 ml. of sulfuryl chloride and after standing 6 hr. at room temperature, poured with stirring into ice and water. The solid material was filtered, washed with water, ground with sodium bicarbonate solution and again filtered and washed thoroughly with water. Drying over phosphorus pentoxide *in vacuo* gave 180 mg. (73%). After three crystallizations from benzene–pentane the substance melted at 203°, $[\alpha]^{25}D$ +22.7 (*c* 0.74), λ_{max} 252 mμ (13,250) ν_{max} 2966, 2896 (C—H), 1762 (17-keto-16-chloro), 1675 (3-keto-$\Delta^{1,4}$-2-chloro) cm.$^{-1}$. N.m.r.: τ 3.825 (C=CH in 4), 5.542 and 5.625 (C(H)Cl in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_2Cl_4$: C, 57.85; H, 5.12; Cl, 28.46. Found: C, 57.88; H, 5.38; Cl, 28.71.

2,4,10β,16ξ-Tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) from 2,4-Dichloroestrone (A-X).—A 100-mg. sample of 2,4-dichloroestrone was dissolved in 5 ml. of sulfuryl chloride and left in the dark for 6 hr. The reaction mixture was decomposed with ice and water under stirring and the white powder which resulted was filtered, washed with water, and then treated as before with 10% potassium bicarbonate solution, and water. It was dried over phosphorus pentoxide *in vacuo* and recrystallized from benzene–hexane. Three crystallizations gave needles, m.p. 189–191°, $[\alpha]^{25}D$ +50 (*c* 0.62), λ_{max} 258 mμ (13,400), ν_{max} 2961, 2886 (C—H), 1760 (17-keto, 16-chloro), 1688 (3-keto-$\Delta^{1,4}$-2,4-dichloro) cm.$^{-1}$ N.m.r.: τ 2.667 (C=CH in 1), 5.550 and 5.617 (C(H)Cl in 16), 8.985 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.77, 52.92; H, 4.64, 4.67; Cl, 34.64, 34.40.

2,4,10β,16ξ-Tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) from 4-Chloroestrone (A-IX).—4-Chloroestrone (200 mg.) was dissolved in 2 ml. of sulfuryl chloride and after 6 hr. in the dark, the reaction mixture was worked up as in the preceding experiment. Several recrystallizations from benzene–hexane gave analytical material with analysis, properties, and infrared spectrum identical with those of B-III in the foregoing experiment.

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.92; H, 4.65; Cl, 34.70.

2,4,16,16′-Tetrachloroestrone (A-XVII).—One gram of estrone was dissolved in 400 ml. of chloroform and a solution of 5 g. of sulfuryl chloride in 100 ml. of chloroform was added with stirring. The solution, which evolved gas, was held at room temperature for 20 hr. and then washed with water, 10% potassium bicarbonate solution, and again with water, and dried with anhydrous sodium sulfate. After evaporation of the solvent a resin was obtained whose infrared spectrum showed dienone character. Elution with benzene from a column of silica gel gave a crystalline substance which after four recrystallizations from benzene–hexane was obtained in glass-like colorless plates. They became opaque at 100°, softened at 178°, and melted at 180–182°, $[\alpha]^{25}D$ +142° (*c* 1.0), λ_{max} 230 inflection (8562), 283 (2362), 292 (2509), ν_{max} 3494 (phenol-OH), 3095, 3046, (arom. CH), 1766 (17-keto, 16,16′-dichloro), 1590 1574, (arom. C=C) and 1170 (phenol C—O) cm.$^{-1}$. The compound is formulated as 2,4,16,16′-tetrachloroestrone.

Anal. Calcd. for $C_{18}H_{19}O_2Cl_4$: C, 52.84; H, 4.68; Cl, 34.66. Found: C, 52.97; H, 4.52; Cl, 34.85.

All eluates from the column were combined and reduced with zinc and acetic acid. The material which was isolated was chromatographed on a silica gel column and eluted with benzene and increasing amounts of chloroform. Only 4-chloroestrone could be obtained in crystalline form.

2,4-Dibromo-10β-chloro-17β-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-II).—2,4-Dibromoestradiol 17β-acetate (1 g.) was suspended in 2 ml. of sulfuryl chloride and dissolved completely after 30 min. The reaction mixture was poured into water and agitated magnetically to decompose the excess sulfuryl chloride. The slurry was then extracted with methylene chloride and the extract was washed successively with water, 10% potassium bicarbonate solution, and water. After drying over magnesium sulfate the solvent was removed under reduced pressure and the product was crystallized twice from methylene chloride–methanol, to give 930 mg. (87%) of white crystals, m.p. 195–197°. Repeated crystallization gave an analytical sample, m.p. 197–198°, $[\alpha]^{23}D$ +9.1° (*c* 4.4) λ_{max} 271 (16,900), ν_{max} 2942, 2877 (C—H), 1730 (acetate C=O), 1678 (3-keto, $\Delta^{1,4}$, 2,4-dibromo), 1596 (C=C), 1373 (C—CH_3), 1243 (acetate CO stretch) cm.$^{-1}$. N.m.r.: τ 2.425 (C=CH in 1), 5.400, 5.517 (17α-H), 7.950 (CH_3 in acetyl) 9.092 (CH_3 in 18).

Anal. Calcd. for $C_{20}H_{23}O_3ClBr_2$: C, 47.41; H, 4.58; Cl, 7.00; Br, 31.54. Found: C, 47.56; H, 4.56; Cl, 7.08; Br, 31.93.

Reduction of B-II.—To a solution of 100 mg. of B-II in 5 ml. of warm glacial acetic acid was added 400 mg. of zinc dust. The reaction was terminated after 20 min., and the reaction mixture was worked up as before. The residual pale yellow oil solidified and after two recrystallizations from chloroform–methanol gave 51 mg. (57%) of material with mixed melting point and infrared spectrum identical with authentic 2,4-dibromoestradiol 17β-acetate.

2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI) from 2,4-Dibromoestrone (A-V) with Sulfuryl Chloride.—A slurry of 1.3 g. of 2,4-dibromoestrone in 10 ml. of sulfuryl chloride was allowed to stand at room temperature. After 4.5 hr. solution was complete and the reaction mixture was poured into

water and stirred until the sulfuryl chloride had decomposed. The solid was filtered and ground in a mortar with bicarbonate solution. After filtration, the product was thoroughly washed with water and dried *in vacuo* over phosphorus pentoxide. The yield was 1.6 g. (92%). The analytical sample prepared by recrystallization from benzene–hexane melted at 197–198° dec. $[\alpha]^{23}D$ +19° (*c* 0.05), λ_{max} 271 (17,000) ν_{max} 1760 (17-keto, 16 chloro), 1678 (3-keto, $\Delta^{1,4}$,2,4-dibromo) 1590, 1451, 1386, 1205, 1030, 990, 931, 885, 853, 726, 691 cm.$^{-1}$. N.m.r.: τ 2.408 (C=CH in 1), 5.533 (C(H)Cl in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_2Br_2$: C, 43.49; H, 3.65; Cl, 14.26; Br, 32.15. Found: C, 44.22; H, 3.88; Cl, 14.55; Br, 32.79.

2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI) from 2,4-Dibromoestrone with Chlorine.—A slurry of 800 mg. of dibromoestrone in 10 ml. of chloroform was treated with 13.5 ml. of 2.1% chlorine solution in chloroform and left in the dark for 4 hr. The final solution was diluted with ether and washed successively with water, potassium bicarbonate, and water. After drying with sodium sulfate, the solvent was removed under reduced pressure. The yellow residue was triturated with ether and after recrystallization from benzene–hexane gave white crystals identical with B-VI, prepared in the previous experiment.

Anal. Calcd. for $C_{18}H_{18}O_2Cl_2Br_2$: C, 43.49; H, 3.65; Cl, 14.26; Br, 32.15. Found: C, 43.40; H, 3.64; Cl, 14.30; Br, 32.24.

Reduction of B-VI with zinc dust and acetic acid gave 2,4-dibromoestrone identical with authentic material.

1ξ,2ξ,10β,16,16′-Pentachloro-2-nitro-Δ^4-estrene-3,17-dione (C-III) and 1ξ,2ξ,10β,16ξ-Tetrachloro-2-nitro-Δ^4-estrene-3,17-dione (C-IV) by Chlorination of 2-Nitroestrone A-XIII.—To a 2-g. portion of 2-nitroestrone was added 15 ml. of sulfuryl chloride and the yellow solution which soon formed was left at room temperature in the dark for 20 hr. It was decomposed with ice and water under vigorous stirring until the reaction product became solid. This was filtered, ground in a mortar with 10% potassium bicarbonate solution and then with water. After drying over phosphorus pentoxide *in vacuo* 2.5 g. of a yellowish powder resulted which was put on a silica column prepared with benzene–hexane (1:1). Using infrared spectra as a guide the column was eluted with increasing benzene concentrations in the benzene–hexane mixture and then with benzene–ether mixtures. The latter gave oily material but two crystalline fractions resulted with benzene–hexane (1:1 and 5:1) and with benzene alone. They were both repeatedly recrystallized from benzene–hexane. The less polar substance gave slightly yellowish white needles, m.p. 182–184° dec., $[\alpha]^{28}D$ +120° (*c* 0.78), λ_{max} 241 (8766), 243 (9640), 252 (11,101); ν_{max} 3123, 3073 (C(H)Cl), 3031 (=CH), 1773 (17-keto, 16,16′-dichloro), 1706 (3-keto-2-nitro-2-chloro-Δ^4), 1630, (C=C), 1574 (C—NO_2), 800 (C(H)Cl), 681 (C—Cl_2) cm.$^{-1}$. N.m.r.: τ 4.008, (C=CH in 4), 4.70 (C(H)Cl in 1), 8.825 (C—CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_5$: C, 44.16; H, 3.71; N, 2.86; Cl, 36.20. Found: C, 44.56; H, 3.99; N, 2.70; Cl, 36.43.

This substance may be formulated as 1ξ,2ξ,10β,16,16′-pentachloro-2-nitro-Δ^4-estrene-3,17-dione (C-III).

The more polar substance also formed slightly yellowish needles, m.p. 186–187°, $[\alpha]^{25}D$ +127° (*c* 0.97), λ_{max} 242 (24,444), 253 (27,777); ν_{max} 3082 (C(H)Cl), 1759 (17-keto,16-chloro), 1692 (3-keto, 2-nitro, 2-chloro, Δ^4), 1612 (C=C), 1548 (C—NO_2) cm.$^{-1}$. N.m.r.: τ 4.016 (C=CH in 4), 4.858 (C(H)Cl in 1), 5.586 and 5.653 (C(H)Cl in 16), 9.000 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}NO_4Cl_4$: C, 47.50; H, 4.21; N, 3.08; Cl, 31.16. Found: C, 47.10, 47.68; H, 4.02, 4.10; N, 3.02, 3.24; Cl, 31.53, 30.98.

The structure of this substance is 1ξ,2ξ,10β,16ξ-tetrachloro-2-nitro-Δ^4-estrene-3,17-dione (C-IV).

2-Aminoestrone (A-XV) by Reduction of the Chlorination Product of 2-Nitroestrone (A-XIII).—Reduction of the crude chlorination product or of the isolated tetrachloro compound with zinc and acetic acid was carried out on the water bath and the acetic acid solution was decanted after 0.5 hr. from any unused zinc. It was diluted with water, neutralized with bicarbonate, and extracted with chloroform. The residue left after evaporation of the solvent was taken up in a solution of oxalic acid, which after filtration from resinous material was neutralized with potassium bicarbonate solution. Thereupon the amino compound precipitated as a white crystalline powder which was filtered, washed, and then dried over phosphorus pentoxide *in vacuo*. The substance gave a negative Beilstein reaction and its infrared spectrum was identical with that of a sample prepared by reduction of 2-nitroestrone.[10] Both samples showed no melting point, but decomposed over 280°. The analytical sample was recrystallized from acetone–water.

Anal. Calcd. for $C_{18}H_{23}NO_2{}^1/_2H_2O$: C, 73.44; H, 8.22; N, 4.76. Found: C, 74.07, 73.95; H, 7.99, 8.23; N, 4.35, 4.55.

Chlorination of 4-Nitroestrone (A-XIV) with Sulfuryl Chloride.—Two experiments with 1 g. and 1.6 g. of 4-nitroestrone were carried out. The nitro steroid was suspended in 10 and 16 ml. sulfuryl chloride, respectively, and left in the dark for 20 hr., during which time both experiments formed a yellow solution. This was decomposed with ice and water and worked up as before. There was obtained 1.2 and 2.1 g. of a buff powder. It was chromatographed on silica columns with benzene in the first and benzene–hexane (1:1) in the second experiment. Elution was made in the second case with increasing benzene concentrations while only benzene was used in the first experiment. Separation of the fractions was controlled by changes in the infrared spectra.

Corresponding fractions were combined. They contained oily material which was eliminated by trituration with ether before recrystallization. The first experiment gave three fractions weighing 430, 210, and 340 mg. and the second gave four fractions weighing 330, 430, 620, and 450 mg. All fractions were recrystallized repeatedly from benzene–hexane and benzene–pentane mixtures. Dark brown material remained on the column and the crude fractions when not immediately recrystallized slowly became yellow and oily.

1ξ,2,2′,10β,16ξ-Pentachloro-4-nitro-Δ^4-estrene-3,17-dione (C-V).—White needles, m.p. 217–218°, $[\alpha]^{25}D$ +139° (*c* 0.59), λ_{max} 264 (13,000) ν_{max} 2956, 2886 (C—H), 1754 (17-keto, 16-chloro), 1711 (3-keto, 2,2′-dichloro, Δ^4-4-nitro), 1632, 1581 (C=C), 1550 (C—NO_2), 1449 (CH_2), 1379 (C—CH_3) cm.$^{-1}$. N.m.r.: τ 5.250 (C(H)Cl in 1), 5.550 (C(H)Cl in 16), 8.986 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_5+{}^1/_2C_6H_6$: C, 47.70; H, 4.00; N, 2.65; Cl, 33.54. Found: C, 48.72; H, 4.07; N, 2.47, 2.95; Cl, 33.95, 32.23.

2,10β,16,16′-Tetrachloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VIII).—White needles, m.p. 206–208°, ν_{max} 3082 (C(H)Cl), 2966, 2885 (C—H), 1770 (17-keto, 16,16′-dichloro), 1692 (3-keto, $\Delta^{1,4}$-2-chloro-4-nitro), 1611 (C=C), 1547 (C—NO_2), 801 (C=Cl_2) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{19}NO_4Cl_3$ + 1/2C_6H_6: C, 51.14; H, 4.29; N, 2.83; Cl, 28.75. Found: C, 51.84; H, 4.33; N, 2.68; Cl, 28.33.

2,10β,16ξ-Trichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VIII).—White needles, m.p. 208° dec., $[\alpha]^{25}D$ +14° (c 0.87), λ_{max} 242 (9035), 254 (10,619), ν_{max} 3082 (C(H)Cl), 2956, 2911 (C—H), 1759 (17-keto, 16-chloro), 1692 (3-keto, $\Delta^{1,4}$-2-chloro-4-nitro), 1612 (C=C), 1548 (C—NO_2) cm.$^{-1}$. N.m.r.: τ 2.667 (C=CH in 1), 5.56, 5.633 (C(H)Cl in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_3$: C, 51.65; H, 4.33; N, 3.35; Cl, 25.40. Found: C, 51.51; H, 3.88; N, 3.30; Cl, 26.80.

10β,16ξ-Dichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IX).—Square plates, m.p. 192–195°, $[\alpha]^{21}D$ +47° (*c* 0.46), λ_{max} 242 (14,600), ν_{max} 2996, 2911 (C—H), 1765 (17-keto, 16-chloro), 1690 (3-keto, $\Delta^{1,4}$-4-nitro), 1621 (C=C), 1547 (C—NO_2) cm.$^{-1}$.

N.m.r.: τ 2.750, 2.938 (C=CH in 1), 3.645, 3.825 (C=CH in 2), 5.608 (C<H/Cl in 16), 8.996 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_4NCl_2$: C, 56.28; H, 4.98; N, 3.64; Cl, 18.46. Found: C, 56.12; H, 4.90; H, 3.59; Cl, 18.54.

2-Chloro-4-aminoestrone (A-XVI).—The residue from the second benzene eluate (150 mg.) in the foregoing experiment was dissolved on the water bath in 7 ml. of acetic acid and 1 g. of zinc dust was added in small portions over a 0.5-hr. period. After further heating for 0.5 hr. under stirring, the solution was decanted and the zinc residue was washed with a small amount of acetic acid and with acetone. The combined solution and washes were neutralized with potassium bicarbonate solution and extracted with chloroform. After washing with water the solvent was distilled *in vacuo* and the brown oily residue was dissolved in water containing 200 mg. of oxalic acid. The hot solution was filtered and neutralized with 10% potassium bicarbonate solution. A white crystalline precipitate was obtained, which was filtered, washed well with water, and then dried *in vacuo* over phosphorus pentoxide. Several recrystallizations were necessary from benzene–hexane to obtain pure material, m.p. 218–222°. In a similar experiment, elimination of the amino group by diazotization gave 2-chloroestrone as reported above. This substance, therefore, must be 2-chloro-4-aminoestrone as confirmed by analysis.

Anal. Calcd. for $C_{18}H_{22}NO_2Cl + {}^1/_2C_6H_6$: C, 70.26; H, 7.02; N, 3.92; Cl, 9.87. Found: C, 70.48; H, 7.41; N, 4.42; Cl, 9.23.

Dehydrogenation of 2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,5}$-estradiene-3,17-dione (B-VI).—To 1 g. of B-VI in 20 ml. dimethylformamide was added 2 g. of lithium chloride and the solution was refluxed for 5.5 hr. It soon became red and finally, dark purple. It was poured into ice and water, to which 2 g. of potassium acetate had been added. The blue precipitate was filtered and washed well with water, then dissolved in methanol, and again precipitated as before. This procedure was repeated twice with methanol and three times with acetone as solvent. The last mother liquor was almost colorless. After washing well with water the deep blue powder was dried over phosphorus pentoxide *in vacuo*. It was easily soluble with a deep red color in the usual organic solvents from which it was precipitated by the addition of either pentane or hexane. No way of crystallizing the substance could be found; yield 100 mg., m.p. 116–118°, λ_{max} 224 (27,276), 236 (12,727), 258 (14,090), ν_{max} 3445 (H_2O), 2961 (C—H), 1751 (17-keto, Δ^{15}), 1702 (3-keto-$\Delta^{1,4}$-2,4-dichloro), 1620 (C=C) cm.$^{-1}$. N.m.r.: τ 3.875, 4.675 (C=CH in 1 and 6?), 6.108, 7.116, 7.645, 8.811, 8.953 (CH_3 in 18), 9.253.

Anal. Calcd. for $C_{18}H_{12}O_2Cl_2 + {}^1/_2C_3H_6O + H_2O$: C, 61.91; H, 4.53; Cl, 18.75; for $C_{18}H_{14}O_2Cl_2 + {}^1/_2C_3H_6O + H_2O$: C, 61.53; H, 5.03; Cl, 18.63. Found: C, 61.17; H, 4.88; Cl, 18.59.

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The Autoxidation of Nonvicinal Glycols Ester Formation *via* Cyclic Ethers and Their Peroxides

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Nonvicinal glycols can be readily autoxidized to the keto alcohols; they give high peroxide yields comparable to those obtainable from simpler secondary alcohols when the carbinol groups are separated by more than four carbon atoms. In the case of the 2,5-hexane- and 2,6-heptanediols, the formation of keto alcohols is accompanied by a significant production of 2-acetoxybutanes and -pentanes. The origins of these esters have been traced to a peroxide-consuming reaction sequence proceeding from cyclic hemiketal through tetrahydrofuran or pyran peroxides to the final ester cleavage products. This sequence is supported by syntheses and degradation studies of some cyclic ether peroxides. By analogy with 2,5-dimethylhexane, 2,5-hexanediol might have been expected to be autoxidized by intramolecular peroxy radical attack to the diketone, this reaction occurs to only a minor extent, if at all.

The autoxidation of simple secondary alcohols produces ketones and peroxide as major products and hydrocarbons with two equivalent tertiary hydrogens such as 2,4-dimethylpentane undergo intramolecular oxidation of the order of 90+% to yield principally the 2,4-dihydroperoxide. In contrast, 2,4-pentanediol[1] shows neither high peroxide yields nor evidence of intramolecular oxidation. It was concluded in the latter case that the reactivity of the intermediate peroxy radical was attenuated by internal hydrogen bonding and that the oxidation involved a considerably modified reaction chain.

The effect of interposing additional methylenes between the carbinol groups has now been studied by autoxidizing 2,5-, 2,6-, 2,7-, and 2,8-dihydroxyalkanes. Although Milas, Peeler, and Mageli[2] did not report ring opening by carbon–carbon bond cleavage in their studies of the vapor phase pyrolyses of tetrahydropyran hydroperoxide and *t*-butyl tetrahydropyran peroxide in glass wool packed tubes, such cleavages are postulated here to explain aliphatic ester formation from diols. Accordingly, certain tetrahydrofuran and -pyran peroxides have been synthesized and thermally degraded.

(1) F. F. Rust and E. A. Youngman, *J. Org. Chem.*, **27**, 3778 (1962).

(2) N. A. Milas, R. L. Peeler, Jr., and O. L. Mageli, *J. Am. Chem. Soc.*, **76**, 2322 (1954).

Experimental

Materials.—Unless otherwise noted heart cuts from fractionation through a Piros-Glover spinning band column were used.

2,5-Hexanediol was prepared by hydrogenation of 2,5-hexanedione in isopropyl alcohol over nickel. The yield of product with b.p. 88°/1 mm. and $n^{20}D$ 1.4470–1.4473 was about 90%.

2-Methyl-2,5-hexanediol was prepared from γ-valerolactone and methyl magnesium bromide; b.p. 107°/4 mm., $n^{19.7}D$ 1.4500. On standing, this material solidified, m.p. 36–37°.

Anal. Calcd. for $C_6H_{14}O_2$: C, 63.6; H, 12.2. Found: C, 63.5; H, 12.2.

5-Methyl-5-hydroxyhexan-2-one was prepared by oxidation of the glycol with chromic anhydride; b.p. 72–73°/13 mm., $n^{20}D$ 1.4361; 2,4-dinitrophenylhydrazone, m.p. 106–107°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.5; H, 10.8. Found: C, 64.3; H, 10.8.

Anal. Calcd. for $C_{13}H_{18}O_5N_4$: C, 50.4; H, 5.8; N, 18.0. Found: C, 50.1; H, 5.9; N, 18.4.

2,5-Dimethyl-2,5-hexanediol was obtained by reduction of Air Reduction Co. 2,5-dimethyl-2,5-hexynediol in isopropyl alcohol over nickel and recrystallization from isopropyl alcohol followed by vacuum drying, m.p. 86.5–87.0°.

2,6-Heptanediol was obtained from glutaraldehyde and methylmagnesium bromide (56–59% yield); b.p. 101°/3 mm.; $n^{20.8}D$ 1.4515. A heart cut had b.p. 110.5°/4 mm., $n^{20}D$ 1.4512.

2,7-Octanediol was obtained from 1,4-dibromobutane and acetaldehyde *via* the Grignard reagent in 33% yield of crude product, b.p. 110°/2 mm., $n^{20}D$ 1.4529. A heart cut had b.p. 113.5/2 mm., $n^{20}D$ 1.4539.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.73; H, 12.33.

2,8-Nonanediol was prepared by a Grignard synthesis from 1,5-dibromopentane and acetaldehyde. The yield of crude product, b.p. 100–104°/3 mm., was about 25%. Careful rectification afforded material with b.p. 115°/5 mm. or 100°/2 mm.; $n^{20}D$ 1.4522–1.4540. The product was still pale yellow and therefore not completely pure.

Dihydropyran.—Eastman Kodak Co. practical grade. Redistilled heart cut; b.p. 84°, $n^{20}D$ 1.4413.

Isopropyl alcohol, Shell Chemical Co., was dried over calcium hydride and distilled just before use; a heart cut was taken.

***t*-Butyl alcohol**, Shell Chemical Co., was dried over calcium hydride and redistilled before use. A middle cut with b.p. 83.5° was taken.

Hydrogen peroxide was commercial 30% stabilized and 90%.

4-Methyl-2-pentanol, Shell Chemical Co., $n^{20}D$ 1.4113, was used without further purification.

2,5-Dimethylfuran, Eastman Kodak (White Label), was used as such.

Tetrahydrofuran (du Pont) was distilled through a 120-cm. column packed with glass beads; b.p. 88°, $n^{20}D$ 1.4210. Prior to distillation, it was washed with ferrous sulfate solution.

2-*t*-Butylperoxytetrahydropyran.—Using the method of Milas,[2] 69–81% yields of the subject peroxide were obtained from 85% by weight *t*-butyl hydroperoxide and dihydropyran; b.p. 37–38°/~1 mm., $n^{20}D$ 1.4360–1.4372.

Anal. Calcd. for $C_9O_3H_{18}$: C, 62.0; H, 10.4. Found: C, 61.5; H, 10.3.

2-Hydroperoxytetrahydropyran.[2]—This hydroperoxide was prepared at 0° from dihydropyran and 50% hydrogen peroxide (molar ratio of 1:3) in the presence of a catalytic amount of sulfuric acid. The crude hydroperoxide was used as such.

2,5-Dimethyltetrahydrofuran.—2,5-Dimethylfuran was hydrogenated over nickel at 125° and 1000 p.s.i.g. hydrogen. A 74% yield of product, b.p. 91°, $n^{20}D$ 1.4033, was obtained. There was a higher boiling unidentified residue.

The glycols were oxidized in a closed system comprised of a Pyrex reactor, an all-glass pump, a hydraulically pressured steel oxygen reservoir fitted with a sight gage, and Dry Ice-cooled traps in the system immediately following the reactor and the reservoir. Oxygen at 35 p.s.i.g. was circulated through the glycols at 115–120°. The oxygen consumption was measured at constant pressure by following the rising water level in the calibrated reservoir.

The peroxide in the product was determined iodimetrically by reduction with acidified (acetic acid) potassium iodide in isopropyl alcohol solution under reflux for 5 min.

Oxidations and Reactions

Oxidation of 2,5-Hexanediol.—2,5-Hexanediol (400 cc., 375 g., 3.18 moles) containing 14 p.p.m. of phosphoric acid was oxidized at 120° and 35 p.s.i.g. oxygen. Oxygen uptake began after an induction period of about 2.5 hr. After six more hours 0.36 mole of oxygen had been taken up (0.113 mole/mole glycol). The product contained 0.026 mole of peroxide (7.2% yield) and functional group analyses showed the presence of 0.0065, 0.234 and 0.306 equivalents of acid, ester, and aldehyde or ketone carbonyl, respectively, and 0.695 mole of water. The gases from the oxidation contained only traces of carbon monoxide, carbon dioxide, and olefins.

A portion of the crude oxidation product was treated with 2,4-dinitrophenylhydrazine reagent and the mixed derivatives chromatographed on silica gel.

A minor, strongly adsorbed band was taken from the top of the column and the derivative dissolved and crystallized from ethyl acetate. Mixed melting point and elemental analysis showed it to be a derivative of 2,5-hexanedione.

Anal. Calcd. for $C_{18}H_{20}O_8N_8$: C, 45.6; H, 3.8; N, 23.6. Found: C, 45.7; H, 4.1; N, 23.4.

The major band was eluted, concentrated, and crystallized from ethanol–water. Elemental analysis of this derivative melting at 111–112° showed it to be the 2,4-dinitrophenylhydrazone derivative of 5-hydroxy-2-hexanone. Thus, the major product is the hydroxy ketone.

Anal. Calcd. for $C_{12}H_{16}O_5N_4$: C, 48.7; H, 5.4; N, 18.9. Found: C, 48.5; H, 5.4; N, 19.0.

The remaining crude product was distilled to remove all products boiling lower than the glycol. After drying, this material was fractionated and a substantial fraction (16.3 g.) of b.p. 112–113° ($n^{20}D$ 1.3883) was unequivocally identified by infrared spectrum and ester value (0.831 eq./100 g.; calcd. 0.86 eq./100 g.) as 2-butyl acetate. Yield (moles/mole oxygen consumed) of 2-butyl acetate was 39%.

Oxidation of 2-Methyl-2,5-hexanediol.—Oxidation of this glycol (376 g., 2.85 moles) proceeded smoothly at 120° and 35 p.s.i.g. in a well conditioned reactor without added phosphoric acid. After an induction period of about 2 hr., 0.24 mole of oxygen (0.085 mole/mole glycol) was taken up in 5 hr. The total peroxide content was 0.026 mole (10.7% yield).

The greatly preponderant carbonyl compound produced was 5-methyl-5-hydroxy-2-hexanone as shown by quantitative precipitation of 2,4-dinitrophenylhydrazones and chromatography over silica gel (m.p. and m.m.p. with authentic derivative was 106–107°).

The product was concentrated at reduced pressure, the low boiling materials were separated from water, dried, and redistilled through a Piros-Glover column. *t*-Amyl acetate (4 g., 0.03 mole) was obtained (b.p. 124°, $n^{20}D$ 1.3993). Infrared spectra of the product and an authentic sample were indistinguishable.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8; ester value, 0.769 eq./100 g. Found: C, 64.6; H, 11.3; ester value, 0.755 eq./100 g.

Oxidation of 2,6-Heptanediol.—Oxidation of the glycol (289 g., 2.3 moles) proceeded readily at 120° and 35 p.s.i.g. oxygen without added phosphoric acid. After an induction period of about 1 hr., 0.263 mole of oxygen (0.11 mole/mole glycol) was taken up in 14 hr. The total peroxide content was 0.0103 mole (3.9% yield). Gas analysis (Orsat) indicated only traces of carbon monoxide and carbon dioxide. Products with boiling points below that of 2,6-heptanediol were collected at 6 mm., separated from water, dried, and redistilled through a Piros-Glover spinning band column (micro). Although great difficulty was encountered due to dehydration, two constant boiling fractions were obtained.

The first, b.p. 120°, $n^{20}D$ 1.4388, 4.3 g., appeared to be largely 2,6-dimethyl-3,4-dihydro-2H pyran.

Anal. Calcd. for $C_7H_{12}O$: C, 74.9; H, 10.7. Found: C, 73.5; H, 10.8.

The 2,4-dinitrophenylhydrazone of 6-hydroxy-2-heptanone was obtained in good yield, m.p. 96–96.5°.

Anal. Calcd. for $C_{13}H_{18}O_5N_4$: C, 50.3; H, 5.8; N, 18.1. Found: C, 50.2; H, 6.3; N, 18.2.

We conclude that the second fraction, b.p. 130°, $n^{20}D$ 1.4052, 3.9 g., was a mixture of 2-pentyl acetate and 2,6-dimethyl-3,4-dihydro-2*H*-pyran.

Anal. Calcd. for an 80.9–19.2% mixture of ester and pyran: C, 66.7; H, 10.8; ester value, 0.622. Found: C, 66.2; H, 10.8; ester value, 0.622.

The material yielded the same 2,4-dinitrophenylhydrazone as fraction 1. Authentic 2-pentyl acetate, b.p. 134°, $n^{20}D$ 1.3967, was prepared; the alcohol portion was converted to a 3,5-dinitrobenzoate (m.p. 61°). The melting point was undepressed on mixing with the same derivative from the oxidation product.

Only trace amounts of carbonyl products other than 6-hydroxy-2-heptanone (or 2,6-dimethyldihydropyran) were produced in the oxidation of 2,6-heptanediol. This was shown by quantitative preparation of 2,4-dinitrophenylhydrazones from the bulk oxidation product followed by chromatography on silica gel. The preponderant product ($\geq$ 90%) had m.p. 96–97° (m.p. undepressed by the analyzed derivative of 6-hydroxy-2-heptanone). No evidence was found for the diketone, 2,6-heptanedione, or 3-methylcyclohexenone which is readily derived from it.

Oxidation of 2,7-Octanediol.—This diol (47.5 g., 0.33 mole) was oxidized at 118°. After 16 hr., 0.0615 mole of oxygen had been absorbed. Peroxide titration showed that a 13.8% peroxide yield, based on consumed oxygen, had been obtained.

Oxidation of 2,8-Nonanediol.—A 98.5-g. (0.655 mole) quantity of 2,8 nonanediol was oxidized in the usual way at 120°. After 17 hr., 0.042 mole of oxygen had been absorbed. The peroxide titration on the product showed a 60% yield of peroxide.

Reaction of Hydrogen Peroxide with Glycols and Alcohols.—Pyrex reaction tubes (1.5 × 10 cm. with necks of 5-mm. tubing) were cleaned with fuming nitric acid (1 to 2 days at room temperature) and 90% hydrogen peroxide (1 day) with repeated rinsing with distilled water between and after treatments. Finally the tubes filled with distilled water were heated at 100° for about 6 hr. Tubes were used repeatedly after this treatment and reproducibility of results was satisfactory.

Solutions were made up by weighing 30% hydrogen peroxide and the alcohol or glycol into 100-cc. volumetric flasks (cleaned in the same manner as the tubes and containing redistilled *t*-butyl alcohol). The solutions were then made up with *t*-butyl alcohol to be 1.0 *M* in hydrogen peroxide and 1.5 or 3.0 *M* in glycol or alcohol. About 5 cc. of solution was then pipetted into the reaction tubes. The solutions were frozen in isopropyl alcohol–Dry Ice, sealed and placed in a 120° bath for the desired length of time (usually 21 hr.). Analyses before and after heating gave the per cent hydrogen peroxide unchanged. Table I presents the results. The reference compounds, isopropyl alcohol, 5-methyl-5-hydroxy-2-hexanone, and dihydropyran are included for comparison.

TABLE I

REACTION OF HYDROGEN PEROXIDE WITH GLYCOLS[a]

Substrate	% H_2O_2 unchanged
Dihydropyran	0
5-Methyl-5-hydroxy-2-hexanone	0
2-Methyl 2,5-hexanediol	5.0
2,5-Hexanediol	13.0
2,6-Heptanediol	16.0 ± 0.5
2,7-Octanediol	22.5 ± 1.0
Isopropyl alcohol (3.0 mole/l.)	30.5 ± 1.0
2,4-Pentanediol[b]	35.7 ± 2.2
2,5-Dimethyl-2,5-hexanediol	73.0 ± 3.5
t-Butyl alcohol	73.0 ± 2.0

[a] H_2O_2: 1 mole/l. Glycol: 1.5 mole/l. Temperature: 120°. Solvent: *t*-butyl alcohol. Reaction time: 21 hr. [b] Ref. 1.

Table II is a compilation of some products of glycol–peroxide interaction.

TABLE II

PRODUCTS OF GLYCOL–H_2O_2 REACTIONS[a]

Glycol	Products by analyses: mole/mole H_2O_2 Ester	Acid	Carbonyl	Remarks
2,5-Hexanediol	0.32	0.12	0.34	0.21 mole 2-butanol + 2-butyl acetate
2,5-Hexanediol-H$^+$	0.27	0.12	0.34	0.18 mole 2-butanol + 2-butyl acetate
2-Methyl 2,5-hexanediol	0.28	0.26	0.28	>0.14 mole *t*-butyl alcohol + *t*-butyl acetate
2,6-Heptanediol	0.30	0.16	0.29	2-pentanol + 2-pentyl acetate
2,6-Heptanediol-H$^+$	0.30	0.18	0.25	2-pentanol + 2-pentyl acetate
2,7-Octanediol	0.12	0.17	0.49	0.04 mole 2-hexanol + 2-hexyl acetate
2,4-Pentanediol	0.11	0.20	0.141	No 2-propanol or isopropyl acetate
1,4-Pentanediol-H$^+$	0.13	0.16	0.46	No 2-propanol or isopropyl acetate

[a] Temperature, 100°. H_2O_2: glycol, 1.0:1.5.

Reaction of Hydrogen Peroxide and 2,5-Hexanediol at 120°.—Hydrogen peroxide (39 g. 90% H_2O_2,[3] 1.03 moles) was added to stirred 2,5 hexanediol (180 g., 1.5 moles) which had been heated to 120°. The peroxide was added over 15 min. to control the temperature. After 1 hr. at 120°, the peroxide value was 13% of the original. After an additional 2 hr. reflux (112°), reaction was essentially complete. Analyses showed the presence of 0.0445 equiv. total acid, 0.340 equiv. total ester, and 0.326 equiv. total carbonyl.

Rectification afforded 2-butyl acetate (0.214 mole) and small amounts of impure 2,5-hexanedione and a fraction, b.p. 89–91°/10 mm., $n^{20.8}$D 1.4273, $C_6H_{12.1}O_{2.86}$. Infrared analysis showed the presence of hydroxyl and ester carbonyl groups. The material could be a mixture of 1,3-butanediol monoacetates (4.8 g., 0.036 moles calcd. as monoacetate).

Oxidation of 2,5-Dimethyltetrahydrofuran.—The furan was readily oxidized at 80° by oxygen at 35 p.s.i.g.; a 12% conversion being realized in about 75 min. The oxidation product was concentrated by removal of unchanged starting material through a 12-inch Vigreux column at about 10 mm. Iodometric analysis showed that no peroxide decomposition occurred during oxidation or concentration. The concentrate contained 66% by weight peroxide.

Oxidation of Tetrahydropyran.—In contrast to the behavior of the 2,5-dimethyltetrahydrofuran, the oxidation of purified tetrahydropyran occurred very slowly at 82° (< 0.07 mole of oxygen was absorbed in 15 hr. at 35 p.s.i.g. oxygen; peroxide yield of 53% by iodometric analysis). At 115 ± 2°, an appreciable rate of oxidation (~ 1% conv./hr.) occurred, but the reaction was accompanied by extensive peroxide decomposition. Oxidation was stopped after an uptake of 0.43 mole of oxygen (~ 14% conv.); analyses indicated a 55% yield of formate and a 28% yield of hydroperoxide. Although no attempt was made to isolate and characterize the products completely, the high formate yield is clearly indicative of the carbon–carbon cleavage resulting from decomposition of 2-hydroperoxytetrahydropyran and the 2-tetrahydro*pyranoxy* radical to a formate ester radical.

Thermal Decomposition of 2-Hydroperoxy-2,5-dimethyltetrahydrofuran in 4-Methyl-2-pentanol.—The peroxide (40.0 g. of the 66.0% by weight concentrate; 0.20 mole) in 4-methyl-2-pentanol (200 cc.; 162 g.; peroxide:solvent ratio, 0.20:1.59) was decomposed by simply heating the solution while removing low boiling products through a 12-in. helices-packed column. After 105 min. (kettle temperature 125–131°), the head temperature reached 131°, the solvent boiling point. Distillation was continued until the residue amounted to 21.0 g. The lower boiling products and the concentrate were then redistilled through a Piros-Glover spinning band column. There was obtained 17.8 g. of 2-butyl acetate which represented a 76% yield based upon the peroxide (identification *vide supra*).

Thermal Decomposition of 2-*t*-Butylperoxytetrahydropyran.—The decomposition of 2-*t*-butylperoxytetrahydropyran in the various solvents (4-methyl-2-pentanol, di-*n*-butyl ether and tri-*n*-butylamine) was effected by heating the peroxide in the given solvent and distilling the low boiling products as formed, utilizing a 20-cm. helices-packed column attached to the reaction kettle (e.g., the kettle temperature varied from 125° to 133° with 4-methyl-2-pentanol; 0.20 mole of peroxide:1.57 mole of solvent). After the refractive index of the distillate reached that of the solvent, the total distillate was refractionated in the Piros-Glover column.

n-Butyl formate was isolated and identified by physical properties, ester value, and comparison of its infrared spectrum with that of an authentic sample. Typical physical properties of the isolated *n*-butyl formate samples were b.p. 106–108°, n^{20}D 1.3887–1.3892, ester values of 0.91 to 0.93 eq./100 g. (theory for $C_5H_{10}O_2$ = 0.98 eq./100 g.); (lit.,[4] b.p. 106.6°, n^{20}D 1.3894). Saponification mixtures were demonstrated to give positive tests for formate. *n*-Butyl formate yields were 39%, 44% and ~ 19%, respectively in 4-methyl-2-pentanol, di-*n*-butyl ether and tri-*n*-butylamine (solvent:peroxide molar ratio ≥ 5.4:1).

Reaction of Ferrous Sulfate with 2-Hydroperoxytetrahydropyran.—A solution of 0.25 mole ferrous sulfate heptahydrate in 250 ml. of water was added slowly with stirring to a solution of 0.25 mole of 2-hydroperoxytetrahydropyran in a mixture of 50 ml. of *t*-butyl alcohol and 150 ml. of water at 0–5° (addition time ~ 1 hr.).

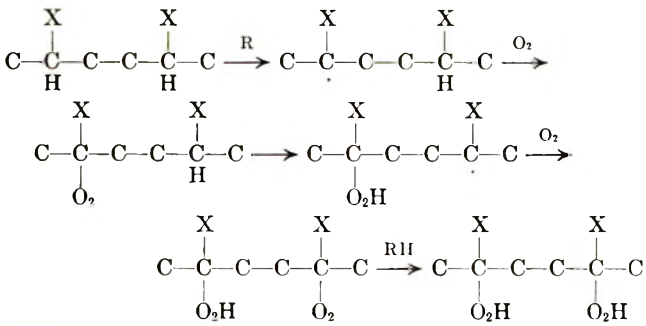
The reaction mixture was subjected to liquid–liquid extraction with ether, dried over magnesium sulfate, and distilled. Fraction 1 (b.p. 105–110°, n^{20}D 1.3887) was shown to be principally *n*-butyl formate. Fraction 2 (b.p. 100–106°/1 mm., n^{20}D 1.4410) was shown to be 1,8-octanediformate: calcd. for $C_{10}H_{18}O_4$: C, 59.5; H, 8.9. Found: C, 60.0; H, 9.1. The 1,8-octanediformate was further characterized by conversion to 1,8-octanediol by ester exchange in methanol followed by recrystallization from aqueous methanol, m.p. and m. m.p. 59–60°.

(3) Caution in use is strongly indicated.

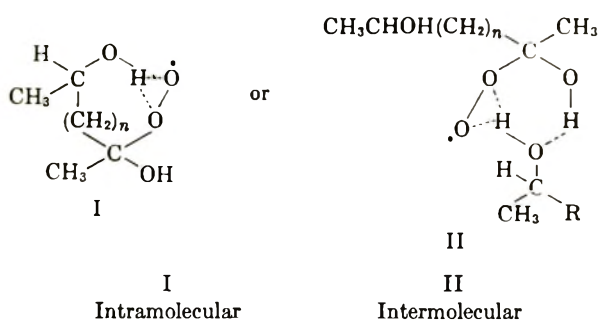
(4) E. H. Huntress and I. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, New York, N. Y., 1949, p. 302.

Discussion

In the autoxidation of 2,4-pentanediol the abnormally low peroxide yield and the absence of intramolecular oxidation was ascribed to intramolecular hydrogen bonding of the intermediate peroxy radical.[1] Hydrogen-bonded peroxy radicals must also be affecting the course of reaction in 2,5-hexanediol and to a lesser extent other hydroxy containing molecules. Certainly if no perturbing effects were present, the mechanism of oxidation for 2,5-dimethylhexane and 2,5-hydroxyhexane should be parallel.



When X = CH_3 the preceding sequence of reactions takes place at 100–150° with considerable facility. If, however, one or both CH_3 groups is replaced by —OH, *e.g.*, 5-methyl-2-hexanol or 2,5-dihydroxyhexane, intramolecular reaction is effectively eliminated. This altered reactivity of the peroxy radical is assumed to be a consequence of hydrogen bonding,[1] *e.g.*,



I
Intramolecular

II
Intermolecular

It would seem reasonable that the intramolecular form I should be decreasingly significant and II increasingly so as n increases. As discussed in the previous paper[1] intramolecularly hydrogen-bonded peroxy radicals (I) are of increased stability and, as a consequence of increased steady state concentration, should result in increased frequency of radical–radical interaction and low peroxide yields. Low peroxide yields are, in fact, observed in the autoxidation of 2,4-pentanediol and still lower yields are found for the 2,5-, 2,6-, and 2,7-alkanediols (Fig. 1). In these latter cases, however, low yields are additionally, and probably more importantly, a consequence of peroxide consuming reactions leading to ester formation.

The formation of 2-butyl acetate by autoxidation is concluded to occur as shown in col. 2.

In the sequence shown step c leads to peroxide formation, but steps f and g result in its consumption.

In like fashion that part of the 2,6-heptanediol which autoxidizes through a tetrahydropyran intermediate produces 2-acetoxypentane. The same general reaction sequence explains the appearance of *t*-amyl acetate during the oxidation of 2-methyl-2,5-hexanediol.

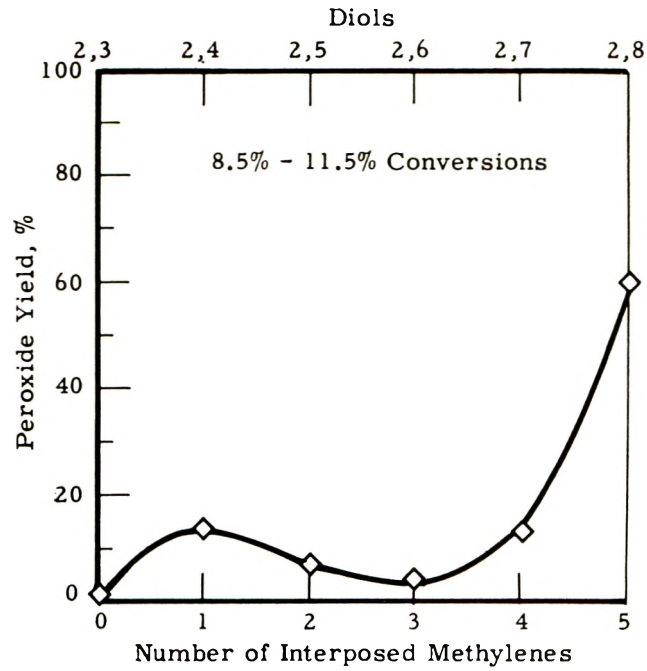
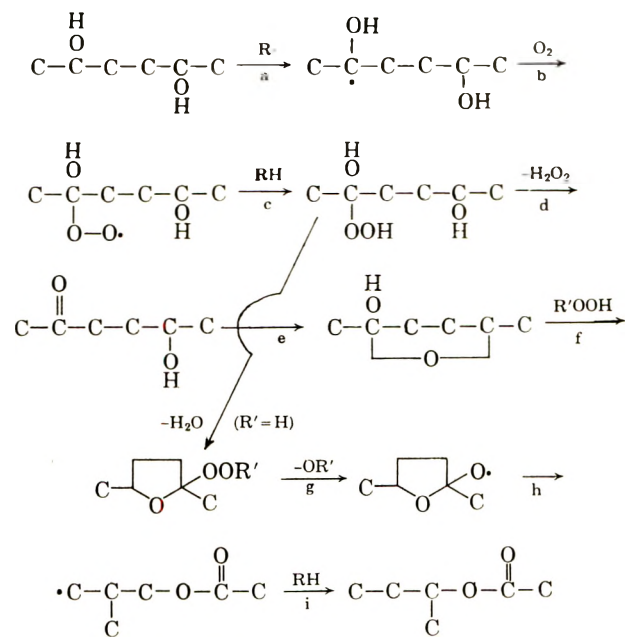


Fig. 1.—The autoxidation of straight chain glycols. Peroxide yield as a function of the number of carbon atoms between carbinol groups.



The autoxidation mechanism for ester formation from 2,5- and 2,6-diols suggests that improved yields of hydrogen peroxide would be obtained if the carbinol groups of the diol were separated sufficiently to minimize cyclic ether formation.

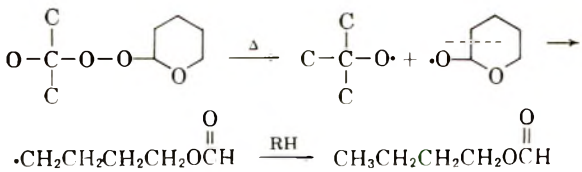
Obviously, as the carbinol groups are further separated, interaction between these polar groups or their reaction intermediates becomes more difficult. Fig. 1 shows that after 2,6-heptanediol there is an increase in peroxide yield in the autoxidation of 2,7-octanediol.[5] Finally, in the case of 2,8-nonanediol intramolecular effects have become so small that peroxide yields approach those obtainable from simple secondary alcohols.

(5) Although only a peroxide determination was made in this instance, one of the oxidation products, when hydrogen peroxide was the chosen oxidant, was 2-acetoxyhexane. Thus, hemiketal formation seems able to contribute to low peroxide yields in this example as well.

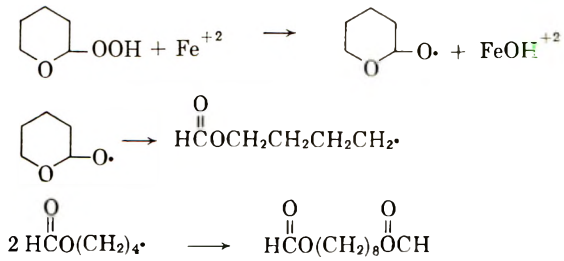
In order to validate further the ester forming steps in the mechanism which require carbon–carbon bond cleavage of a cyclic ether peroxide, the 2-hydroperoxide derivative of 2,5 - dimethyltetrahydrofuran was prepared by autoxidation and decomposed by heating in methyl isobutyl carbinol. The 76% yield of *sec*-butyl acetate supports postulated steps g, h, and i in the reaction sequence.

The methylisobutylcarbinol solvent served as the hydrogen donor to the radicals generated in the decomposition and 0.65 mole of methyl isobutyl ketone per mole of *sec*-butyl acetate formed was actually isolated.

A demonstration that the tetrahydropyran ring can also cleave was shown by the isolation of 39% and 44% yields of *n*-butyl formate when 2-*t*-butylperoxytetrahydropyran was decomposed in methylisobutylcarbinol and di-*n*-butyl ether, respectively. δ-Valerolactone was also produced in *ca.* 15% yield. The extensive ring cleavage observed in the autoxidation of tetrahydropyran is consistent with the same cleavage pattern.



When 2-hydroperoxytetrahydropyran is decomposed by an equivalent amount of ferrous ion in the absence of hydrogen donor—*i.e.*, in aqueous solution, the most important reaction of the intermediate oxy radical is, again, carbon-carbon bond scission with formation of the butyl formate radical. The final product, 1,8-octanediformate has been produced in 50 to 60% yield based on input peroxide. Less important products are *n*-butyl formate and δ-valerolactone[2] in 13 and 3% yields, respectively. This is in distinct contrast with previous descriptions of this system[2] where the major products were reported to be δ-valerolactone and 2-hydroxytetrahydropyran.



Although the actual yields of peroxide are low when 2,5- and 2,6-diols are oxidized, hydroperoxide or hydrogen peroxide is required by the proposed scheme of reaction. Experiments in which hydrogen peroxide replaces oxygen as the oxidizer do, in fact, lead to essentially the same products (Table II). It is further significant that the rate of hydrogen peroxide consumption is greatest in the presence of precisely those glycols, or keto alcohols, where the formation of cyclic hemiketals is most favored (Table I).

Reactions of Methyl-substituted 1,4-Epoxy-1,4-dihydronaphthalenes

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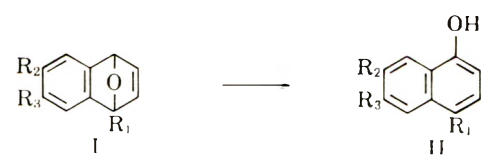
Disruption of the epoxide ring in methyl-substituted 1,4-epoxy-1,4-dihydronaphthalenes by alcohols and a little acid gives alkyl-substituted 1-naphthols when one of the alpha positions contains a hydrogen atom. However, if both the 1- and 4-positions contain methyl groups, the products are substituted 2-naphthols or their derivatives. Furthermore, if the 2- and 3-positions are also occupied by alkyl groups, compounds are formed containing the alkoxymethyl group in the alpha position. Intermolecular condensations also occur under anhydrous conditions.

It has been reported[1] that 1,4-epoxy-1,4-dihydronaphthalene is isomerized nearly quantitatively to 1-naphthol by reaction with methanol containing a little hydrochloric acid. During the course of our work[2] on the synthesis of methyl-substituted anthracenes, a number of methyl-substituted 1,4-epoxy-1,4-dihydronaphthalenes (I) were prepared. The isomerization and other reactions of some of these compounds have now been studied and are reported in this paper.

The first compounds of type I investigated were those in which the 1- and/or 4-positions were occupied by hydrogen. In these cases a little hydrochloric acid in methanol readily caused isomerization to the methyl-substituted 1-naphthols (II) as follows:



Compound no.	R_1	R_2	R_3	Reference
IIa	CH_3	H	H	3
b	H	CH_3	CH_3	4
c	H	CH_3	H	5
d	H	H	CH_3	6

Note: Compounds IIc and d are isomers obtained from the same epoxide.

This method, then, is a fairly convenient one for preparing methyl-substituted 1-naphthols, some of which are otherwise very difficult to prepare.

Naturally the question arose as to what occurs if both the 1- and 4-positions are occupied by methyl or other groups. Such compounds, because of the

(1) G. Wittig and L. Pohmer, *Ber.*, **89**, 1349 (1956).
(2) E. Wolthuis, *J. Org. Chem.*, **26**, 2215 (1961).
(3) E. Wenkert and T. Stevens, *J. Am. Chem. Soc.*, **78**, 5627 (1956).
(4) E. Coulson, *J. Chem. Soc.*, 1305 (1938).
(5) J. Corran and W. Whalley, *ibid.*, 4719 (1958).
(6) G. DiModica and S. Tira, *Ann. chim.* (Rome), **46**, 838 (1956).

electron-release effect of these groups, should be very susceptible to ring opening, but cannot form 1-naphthols. It was found that these compounds react vigorously with methanol containing a little hydrochloric acid, and that interesting rearrangements take place.

The first such compound to be studied was 1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (III), prepared as reported previously.[2] This compound can be distilled without decomposition at 108–110°/16 mm., a fact not known at the time of the earlier report. In methanol solution, III reacted vigorously with a few drops of concentrated hydrochloric acid, and on cooling, a crystalline product was obtained. Analyses of this product indicate it to be 2-methoxy-1,4-dimethylnaphthalene (IV), identical with that reported,[7] and prepared by methylation of the corresponding naphthol which, in turn, was obtained from desmotroposantonous acid. Further proof of the structure of IV was obtained by its hydrolysis to the known naphthol (V) and the conversion of the latter to 2-acetoxy-1,4-dimethylnaphthalene. Spectral data were found to agree with structure IV.

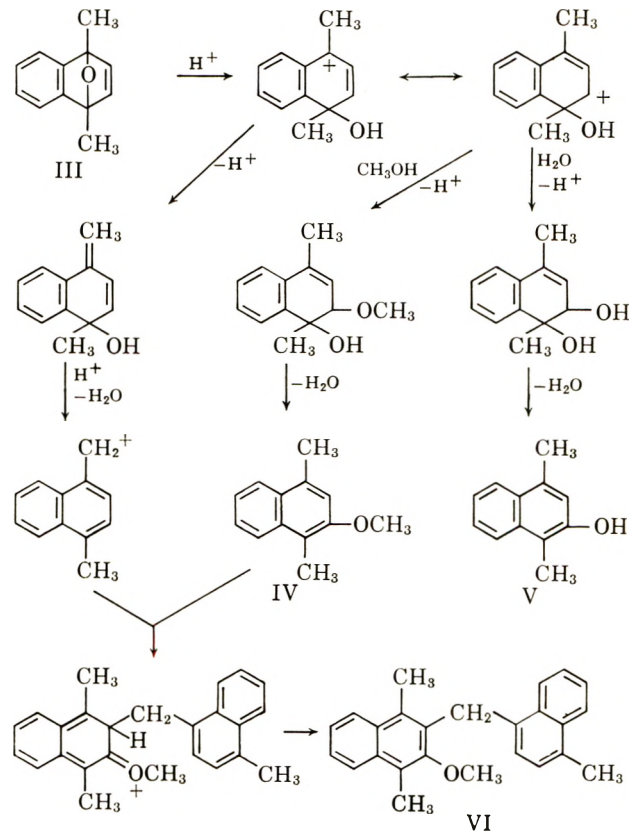
After removal of IV from the reaction mixture, the methanolic liquors contained still other products. One of these, found in small quantity, proved to be the naphthol, V. The other major product, a new compound, was finally assigned the structure VI, which agrees well with all analytical and spectral data, and which was also synthesized by condensing IV with 1-methyl-4-chloromethylnaphthalene.

Having established the fact that reaction of III with methanol and hydrochloric acid gives at least three different products, further studies showed that the relative amounts of these can be varied considerably by altering the reaction conditions. It seemed reasonable that the naphthol, V, should predominate if the reaction were carried out in the presence of more water, and this proved to be correct. With dilute hydrochloric acid alone, III gave up to 69% of V and no IV or VI. The yield of V became progressively lower as the amount of methanol in the reaction mixture was increased, while at the same time the yield of IV increased. High yields of VI were obtained only under anhydrous conditions, such as by reaction in dry methanol with dry hydrogen chloride. In this way III gave about 61% of VI and 26% of IV with only a trace of V.

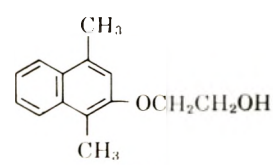
The reactions cited indicate that disruption of the epoxide ring in III results in substitution in the 2-position of the naphthalene ring. The reaction apparently is proton-activated since III is not at all affected by alkalies, and can even be recovered unchanged after boiling with aqueous alkali. It appears likely that the oxygen of the methoxyl or hydroxyl groups is derived from the solvent, but this is still to be determined experimentally.

Although compound VI was at first suspected to be a methyl-substituted dinaphthyl ether, the latter was synthesized by a zinc chloride dehydration of V and found to be other than VI. Spectral and analytical data clearly indicate the structure as shown, apparently the product of a secondary reaction between IV and a carbonium ion intermediate involving the alpha methyl group. On the theory that the intermediate might be 1-methyl-4-chloromethylnaphthalene, attempts were made to isolate this compound from the reaction mixture after a brief reaction of III with dry hydrogen chloride in methanol or hexane. All such attempts failed, but active chlorine was detected by alcoholic silver nitrate after all hydrogen chloride had been removed. That the chloride may be the active intermediate is supported by the facts that (1) it does react with IV to give VI, and (2) the corresponding chloride, X, was isolated when the tetramethyl epoxide (VIII) reacted with dry hydrogen chloride in methanol.

The following mechanism is suggested to account for the formation of IV, V, and VI.



Obviously other alcohols than methanol should also react with III to form comparable 2-alkoxynaphthalenes. Reaction of III with ethylene glycol and a little concentrated hydrochloric acid readily gave the product, VII, in good yield. Although it had been anticipated that both alcoholic functions of ethylene glycol might react to give the dinaphthyl ether of glycol, our experiment produced the mono ether as indicated by the presence of an active hydrogen in the product. Further confirmation of the structure of VII came from analytical and spectral analyses. Its formation can be explained as above for IV.



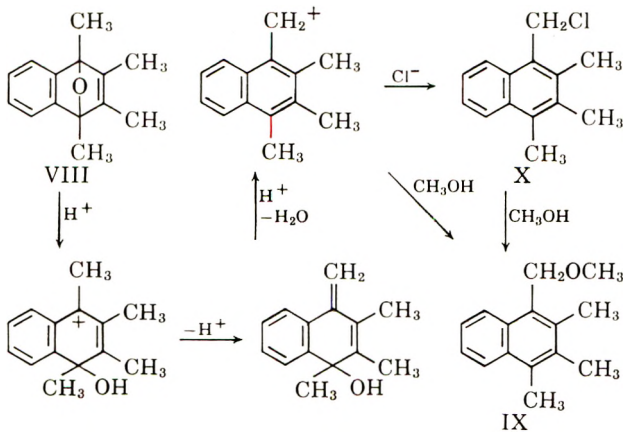
VII

In view of the products obtained from III, it was interesting to see what would happen if the 2- and 3-positions were blocked to prevent the formation of the 2-naphthol derivatives. Accordingly, 1,2,3,4-tetramethyl-1,4-epoxy-1,4-dihydronaphthalene (VIII)

(7) S. Cannizzaro and A. Carnelutti, *Gazz. chim. ital.*, **12**, 407 (1882).

was prepared by a procedure similar to that used to make III. The required 2,3,4,5-tetramethylfuran was prepared by reaction of 3,4-dimethyl-2,5-hexanedione with acetic anhydride.[8] The latter, in turn, was prepared most successfully by reaction of 2-butanone with lead dioxide.[9] Compound VIII reacted readily with methanol and a little concentrated hydrochloric acid to give a 78% yield of 1-methoxymethyl-2,3,4-trimethylnaphthalene (IX). This structure was deduced from elementary analysis, methoxyl determination, and spectral data. The position of the methoxymethyl group was not fixed by these data, but was determined by the fact that compound IX was obtained by reaction of methanol on the previously reported[10] 1-(chloromethyl)-2,3,4-trimethylnaphthalene (X). The latter was obtained in good yield from the epoxide VIII upon reaction with dry hydrogen chloride in methanol, ethanol, or hexane.

It seems likely that IX is formed by the following series of reactions:



The chloride, X, could be isolated only when anhydrous conditions prevailed. It reacted readily with methanol to give IX, and with ethanol to give 1-(ethoxymethyl)-2,3,4-trimethylnaphthalene (XI). All attempts to hydrolyze it to the corresponding alcohol failed, however. Alkaline hydrolysis of X invariably gave a compound to which we have assigned the structure of the ether, bis[2,3,4-trimethylnaphthyl-(1)-methyl] ether (XII). Simply boiling X with water also gave this ether instead of the expected alcohol. Apparently the alcohol, if formed at all, is very easily dehydrated to the ether. Such behavior also has been reported[11] for a similar compound, namely, 1-(chloromethyl)-4-methylnaphthalene.

Attempts to make the alcohol from X by indirect methods also failed. For example, X reacted with lead or silver acetate to form the acetate, which was then hydrolyzed with alkali, but the product again was the ether, XII.

One other epoxide was made for study of its reactions, 1,4-dimethyl-2,3-diethyl-1,4-epoxy-1,4-dihydronaphthalene (XV). It was made by condensation of benzyne with 2,5-dimethyl-3,4-diethylfuran (XIV), which was prepared from 3,4-diethyl-2,5-hexanedione (XIII). The latter was derived from 2-pentanone by oxidation with lead dioxide. The behavior of the epoxide (XV) was not studied extensively, but we report in the Experimental what has been done with it.

(8) R. Gaertner and R. Tonkyn, *J. Am. Chem. Soc.*, **73**, 58 (1951).
(9) A. Wolf, German Patent 876237 (1953).
(10) C. L. Hewett, *J. Chem. Soc.*, 293 (1940).
(11) G. Lock and R. Schneider, *Ber.*, **91**, 1770 (1958).

Experimental[12]

4-Methyl-1-naphthol (IIa).—1-Methyl-1,4-epoxy-1,4-dihydronaphthalene[2] 0.791 g. (5 mmoles) was dissolved in a warm mixture of 5 ml. methanol and 1 ml. of water, 3 ml. of concentrated hydrochloric acid was added, and the mixture was boiled under reflux 15 min. After removal of the methanol, the residue was dissolved in 20 ml. of water and 0.3 g. of sodium hydroxide. The warm solution was filtered with carbon and the filtrate acidified to precipitate the product. Filtration, washing, and drying gave 0.700 g. (88%) of IIa, m.p. 78–80°. Recrystallization from ligroin gave 0.620 g., m.p. 82–83° (lit.,[3] 83–84°).

6,7-Dimethyl-1-naphthol (IIb).—6,7-Dimethyl-1,4-epoxy-1,4-dihydronaphthalene,[2] 1.722 g. (10 mmoles), was dissolved in 20 ml. of warm methanol, 2 drops of concentrated hydrochloric acid was added, and the mixture refluxed 10 min. After removal of the methanol, the residue was extracted with hot, dilute sodium hydroxide solution, clarified with carbon, and filtered. The filtrate was acidified, cooled, and filtered, and the residue dried to give 1.22 g. (71%), m.p. 138.5–139.5°. Recrystallization of a part of it from benzene–petroleum ether gave m.p. 139–139.5° (lit.,[4] 140°).

6(and 7)-Methyl-1-naphthol (IIc and d).—6-Methyl-1,4-epoxy-1,4-dihydronaphthalene,[2] 0.700 g. (4.4 mmoles), in 10 ml. of warm methanol was treated with 2 drops of concentrated hydrochloric acid and refluxed for 10 min. The solvent was removed and the residue was dissolved in warm hexane, decolorized with carbon, filtered, and cooled thoroughly. Filtration and washing of the crystals gave 0.340 g. (49%) of IIc, m.p. 102–105°. One recrystallization from hexane gave m.p. 105–107° (lit.,[5] 111°), but it was not further purified. The liquors from the first crop of crystals were evaporated to dryness, the residue was extracted with hot, dilute sodium hydroxide solution, clarified with carbon, and the clear filtrate acidified to give 0.100 g. (14%) of IId, m.p. 80–83°, not further purified (lit.,[6] m.p. 83°).

1,4-Dimethyl-2-methoxynaphthalene (IV).—1,4-Dimethyl-1,4-epoxy-1,4-dihydronaphthalene (III),[2] 1.502 g. (8.73 mmoles), was dissolved in 15 ml. of methanol, heated to boiling, and 10 drops of concentrated hydrochloric acid were added. A vigorous reaction ensued, after which the mixture was held at reflux for 0.5 hr. and then cooled overnight in a refrigerator. Filtration and washing with cold methanol gave 0.422 g. (26%) of crystals, m.p. 66–67.5°. The filtrate was evaporated to dryness, the residue taken up in hexane and put through a column of alumina. The first fractions through the column contained another 0.487 g. (30%) of IV, m.p. 66.5–66.8°. Recrystallization from methanol gave m.p. 68.4–68.8° (lit.,[7] 68°). Further elution with hexane containing 5% methanol gave 0.267 g. of a semisolid fraction which was recrystallized twice from methanol to give 0.125 g. of VI, m.p. 152–153°. The alumina retained a fraction, fluorescing strongly in the ultraviolet, which was extracted with boiling methanol to give a very small amount of the naphthol, V, m.p. 132–133°.

Anal. of IV. Calcd. for $C_{13}H_{14}O$(186.2): C, 83.83; H, 7.58; OMe, 16.63; mol. wt., 186. Found: C, 83.92; H, 7.51; OMe, 16.58; mol. wt. (Rast), 180.

Ultraviolet spectrum in C_6H_{12}: λ_{max} mμ (log ε): 235.5 (4.96), 288 (3.84), 300 (3.81), 327 (3.53), 337 (3.50), 342 (3.55). Infrared spectrum showed a broad absorption at 1200–1300 cm.$^{-1}$ indicative of an ether.

1,4-Dimethyl-2-naphthol (V).—A 0.294-g. sample (1.71 mmoles) of III was heated for 5 min. at 90–100° with 10 ml. of water and 2 drops of concentrated hydrochloric acid. The mixture became cloudy at once and an oil separated which solidified on cooling. Extraction of the solid with warm, dilute sodium hydroxide solution, clarification with carbon, and acidification of the clear filtrate gave 0.202 g. (69%) of V, m.p. 130–132°. Recrystallization from ligroin gave m.p. 133–133.5° (lit.,[7] 135–136°). Upon

(12) The authors are grateful to Dr. J. L. Johnson and his staff at the Upjohn Co., Kalamazoo, Mich., for determining all spectra reported herewith, and especially to Dr. G. Slomp for assistance in interpreting the n.m.r. spectra. All melting and boiling points are uncorrected. N.m.r. spectra were observed on Varian A-60 and DP-60 spectrometers operating at 60 Mc. on solutions of the samples in chloroform. The spectra were calibrated in c.p.s. downfield from internal tetramethylsilane.

acetylation there was obtained 2-acetoxy-1,4-dimethylnaphthalene, m.p. 76–77°, from methanol (lit.,[7] 77–78°).

1-(4-Methylnaphthyl)-2-(3-methoxy-1,4-dimethyl)naphthylmethane (VI). Method A.—Dry hydrogen chloride was passed into a boiling solution of 1.056 g. (6.1 mmoles) of III in 15 ml. of dry methanol for 1.5 hr. The solution turned brown and a precipitate formed. After refrigeration overnight, the precipitate was filtered off, washed with cold methanol, and dried to give 0.552 g. (53%) of VI, m.p. 144–148°. Recrystallization from hexane gave colorless needles, m.p. 152.5–153°. The liquors were evaporated to dryness below 100° and the residue extracted with hexane to give another 0.100 g. (10%), m.p. 145–148°.

Anal. of pure product. Calcd. for $C_{25}H_{24}O$ (340.4): C, 88.20; H, 7.11; OMe, 9.1. Found: C, 88.17; H, 7.19; OMe, 9.0.

Ultraviolet spectrum in ethanol; λ_{max} mμ (log ϵ): 226.5 (4.90), 239 (4.89), 279 sh (4.11), 289 (4.20), 299 sh (4.08), 314 sh (3.40), 331 (3.41), 344 (3.38). Infrared spectrum showed bands due to aromatic ether at 1000–1050 and 1200–1300 cm.$^{-1}$. N.m.r. spectrum indicated 4 kinds of H: 3 singlets at 149, 155, and 159 c.p.s. due to 3 similar aromatic Me groups, a singlet at 231 c.p.s. (arom. OMe), a singlet at 273 c.p.s. (CH_2) and 5 kinds of absorptions at 422–490 c.p.s. (10 aromatic H atoms).

Method B.—A 0.30-g. sample (1.63 mmoles) of IV, 0.32 g. of 1-chloromethyl-4-methylnaphthalene, and 2.2 g. of anhydrous zinc chloride were heated for 4 hr. at reflux temperature in 25 ml. of dry toluene. After excess zinc chloride had been removed by filtration, the filtrate was evaporated to dryness, the residue taken up in hexane, the solution clarified with carbon and evaporated to give 0.27 g. (48%) of VI, m.p. 146–148°; after recrystallization from hexane, m.p. 151.2–152.2°. A mixed melting point with VI obtained by method A showed no depression, and the spectra were identical in every detail.

2-(1,4-Dimethyl-2-naphthoxy)ethanol (VII).—A 1.047-g. sample (6.1 mmoles) of III was dissolved in 25 ml. of ethylene glycol. Two drops of concentrated hydrochloric acid were added, whereupon the temperature rose 5°. The mixture was refluxed 15 min., cooled, and 25 ml. of 1% aqueous sodium hydroxide was added. Upon cooling, the product separated, was filtered off, washed twice with water, and then dried to give 1.05 g. (80%) of VII, m.p. 98–99.5°. Recrystallization from benzene gave 0.92 g., m.p. 102.8–103.0°. The alkaline filtrate (above) had a blue-green fluorescence, but on acidification gave only a trace of the naphthol, V.

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.3): C, 77.75; H, 7.46. Found: C, 78.03; H, 7.37.

Ultraviolet spectrum in ethanol, λ_{max} mμ (log ϵ): 214 sh (4.32), 234 (4.81), 265 sh (3.41), 277.5 sh (3.65), 286.5 (3.76), 297 (3.69), 326 (3.34), 338 sh (3.30). Infrared spectrum showed strong bands at 1200–1300 (aryl C—O) and 3200 cm.$^{-1}$ (OH). N.m.r. spectrum: 149 and 154 c.p.s. due to two aromatic Me groups, a singlet shifting to 166 c.p.s. on dilution (OH hydrogen), 240 c.p.s. (two CH_2 groups), 421 c.p.s. (one aromatic H), 444 and 473 c.p.s. (four adjacent aromatic H).

3,4-Dimethyl-2,5-hexanedione.—Butanone, 300 g., and lead dioxide, 100 g., were heated for 23 hr. at 78° under reflux. The mixture was filtered and the filtrate dried over calcium chloride and fractionated. After unchanged butanone had been distilled the product, 23.3 g. (39%), distilled at 101–107°/34 mm. (lit.,[9] 90–105°/18 mm.), n^{20}D 1.430.

2,3,4,5-Tetramethylfuran.—3,4-Dimethyl-2,5-hexanedione, 71 g., acetic anhydride, 59 g., and anhydrous zinc chloride 6 g., were heated slowly to reflux temperature and then held there for 3 hr. After addition of 200 ml. of 6 *N* aqueous sodium hydroxide, the product was removed by steam distillation and extracted from the distillate with ether. The extract was dried over calcium chloride, the ether removed, and the product distilled to give 30 g. (49%) at 65–70°/42 mm. (lit.,[8] 92.5–94°).

1,2,3,4-Tetramethyl-1,4-epoxy-1,4-dihydronaphthalene (VIII). Method A.—*n*-Butyllithium in ether, 120 ml. of 0.95 *N*, was added to a flask previously evacuated and filled with pure nitrogen, and cooled to −65°. There was added 35.6 g. of 2,3,4,5-tetramethylfuran, and then 23.6 g. (0.1 mole) of *o*-dibromobenzene during 40 min. at −65 to −60°. The mixture was allowed to warm to 0°, and 200 ml. of water was added. The layers were separated, the aqueous layer was washed twice with ether, the washes were added to the ether layer which was then washed twice with water and dried over potassium carbonate. The ether and unchanged tetramethylfuran (24.6 g.) were removed by distillation, and the oily residue was taken up in hexane and cooled to give 10.0 g. (50%) of VIII, m.p. 41–46°. Recrystallization from hexane gave m.p. 45.6–46°.

Method B.—Magnesium turnings, 5.4 g. (0.22 g.-atom), and 20 ml. of dry tetrahydrofuran were added to a flask, previously evacuated and filled with dry nitrogen. 1-Fluoro-2-bromobenzene, 35.0 g. (0.20 mole), was dissolved in 50 ml. of tetrahydrofuran, and 3–5 ml. of this solution was added to the flask to start the reaction, keeping the temperature below 40°. 2,3,4,5-Tetramethylfuran, 33.7 g. (0.272 mole), in 20 ml. of tetrahydrofuran was then added, after which the remainder of the fluorobromobenzene solution was added during about 0.5 hr. at 35–40°. After reaction had ceased, the mixture was stirred 2–3 hr. more and allowed to stand 5–6 hr. There was added a solution of ammonium chloride, 100 g. in 350 ml. water, made alkaline with ammonium hydroxide, the layers were separated, the aqueous layer was washed with ether and the washes were added to the tetrahydrofuran layer. The entire extract was then washed with 0.1 *N* ammonium hydroxide, 400 ml., separated, and dried over potassium carbonate. The ether and tetrahydrofuran were removed by distillation, and further vacuum distillation gave 5.1 g. of tetramethylfuran and then 29.5 g. (74%) of VIII distilling at 130–132.5°/16 mm. Recrystallization from hexane gave 24.8 g. (62%), m.p. 44–46°.

Anal. of pure compd. Calcd. for $C_{14}H_{16}O$ (200.3): C, 83.96; H, 8.05. Found: C, 84.06; H, 8.09.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ϵ): 247.5 (283), 258.5 (2.84), 265 (2.90), 272.5 (2.99), 279 (2.93). Infrared bands were prominent at 1250–1300 (—C—O—C—) and 680–880 cm.$^{-1}$ (Ar C—H deformation).

1-(Methoxymethyl)-2,3,4-trimethylnaphthalene (IX). Method A.—A 0.50-g. sample (2.5 mmoles) of VIII was dissolved in 10 ml. of warm methanol, and 3 drops of concentrated hydrochloric acid was added. The solution turned light red in color, was refluxed 20 min. and then cooled at 0° several hours. The crystals were filtered off and washed with cold methanol. Additional product was obtained from the liquors by evaporation and cooling; total yield: 0.42 g. (78%), m.p. 75.5–76.2°, not increased on recrystallization.

Method B.—A 0.20-g. sample of X was dissolved in 3 ml. of boiling methanol. Upon cooling thoroughly, there was obtained a quantitative yield of IX, m.p. 72–75.5°. Recrystallization from methanol gave m.p. 75.5–76.2°.

Anal. Calcd. for $C_{15}H_{18}O$ (214.3): C, 84.06; H, 8.47; OMe, 14.48. Found: C, 84.30; H, 8.44; OMe, 14.42.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ϵ): 228 sh (4.82), 233 (4.95), 280 (3.77), 290 (3.83), 300 sh (3.69), 320 sh (2.70), 324 (2.67). A strong infrared absorption at 1050–1100 cm.$^{-1}$ indicated the —C—O—Me group. N.m.r.: 144, 149, and 157 c.p.s. due to 3 similar aromatic Me groups, 208 c.p.s. (aliphatic OMe), 295 (CH_2), 443 and 483 c.p.s. (four adjacent aromatic hydrogens).

1-(Chloromethyl)-2,3,4-trimethylnaphthalene (X).—Dry hydrogen chloride was passed through a solution of 3.0 g. (1.495 mmoles) of VIII in 30 ml. of dry methanol for 20 min. The solution turned very dark. After cooling thoroughly, the product was filtered off and washed with cold methanol; yield: 2.6 g. (79%). Recrystallization from hexane gave 2.1 g. (64%), m.p. 94.5–95.5° (lit.,[10] 94–95°).

This reaction was also run in other solvents with the yields: hexane, 65.4%; ethanol, 59.4%.

Anal. Calcd. for $C_{14}H_{15}Cl$ (218.73): Cl, 16.21. Found: Cl, 16.03.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ϵ): 229 sh (4.83), 233 (4.93), 291 (3.85), 326 sh (2.81).

1-(Ethoxymethyl)-2,3,4-trimethylnaphthalene (XI). Method A.—Using the procedure of method A for IX except substituting ethanol for methanol, 0.50 g. of VIII gave 0.45 g. (79%), m.p. 52–55°. Recrystallization from ethanol gave 0.27 g. (47%), m.p. 58.2–58.8°.

Method B.—Substituting ethanol for methanol in method B for IX, 0.65 g. of X gave 0.55 g. (81%), m.p. 55–56.5°, not further purified.

Anal. of pure XI: Calcd. for $C_{16}H_{20}O$ (228.34): C, 84.16; H, 8.83. Found: C, 84.10; H, 8.76.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ϵ): 228 sh (4.83), 233 (4.96), 282 sh (3.79), 290 (3.84), 300 sh (3.70). Infrared absorptions at 1065 (CH_2O) and 1100 (—C—O—C—) cm.$^{-1}$.

Bis[2,3,4-trimethylnaphthyl-(1)-methyl] Ether (XII).—A solution of 1.8 g. (8.23 mmoles) of X in 30 ml. of 30% potassium hydroxide was refluxed for 2 hr. After dilution and cooling, the

solid product was filtered off and washed free of alkali; yield: 1.4 g. crude. Two recrystallizations from ethanol gave 0.75 g., m.p. 190–190.5°. The liquors were evaporated to dryness, the residue was dissolved in hexane and run through a column of alumina to give, first, 0.11 g. of a compound not yet identified, m.p. 57–58°, and then 0.32 g., m.p. 189–90°. The total yield of XII was 1.07 g. (68%); mol. wt. (Rast), 396 (calcd. 382).

Anal. Calcd. for $C_{28}H_{30}O$ (382.52): C, 87.91; H, 7.91. Found: C, 86.72; H, 7.89.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ε): 228 (5.11), 233 (5.13), 283 sh (4.08), 292 (4.16), 301 sh (4.06). Infrared absorption shows a broad band at 1000–1100 cm.$^{-1}$ indicating the —C—O—C— group. N.m.r.: 143, 148, and 157 c.p.s. due to six methyl groups; 307 c.p.s. (two CH_2 groups); 436–490 c.p.s. (eight aromatic hydrogen atoms).

3,4-Diethyl-2,5-hexanedione (XIII).—A 400-g. sample (4.64 moles) of 2-pentanone and lead dioxide, 530 g. (2.22 moles), were heated together at reflux temperature for 27 hr. The lead oxide was removed by filtration and washed with ether. The filtrate and washings were dried over calcium chloride and distilled to give 10 g. of recovered pentanone and then 50.7 g. (13.4%) of XIII, b.p. 112–115°/20 mm., $n^{20}D$ 1.446.

Anal. Calcd. for $C_{10}H_{18}O_2$ (170.24): C, 70.57; H, 10.55. Found: C, 72.18; H, 10.81.

2,5-Dimethyl-3,4-diethylfuran (XIV).—A 93.0-g. sample (0.546 mole) of XIII, 70 g. (0.69 mole) of acetic anhydride, and 7.0 g. of anhydrous zinc chloride were warmed together slowly until an exothermic reaction began. The reaction was moderated by cooling with water, and finally the mixture was heated at reflux temperature for 3 hr. (A shorter time may be desirable, since charring seemed to increase with time.) After making alkaline by addition of 50 ml. of 40% sodium hydroxide, the furan was distilled with steam. The layers in the distillate were separated, the aqueous layer was extracted with ether and the extract added to the crude furan layer. After drying over calcium chloride, vacuum distillation gave 40.2 g. (48.5%) of XIV, b.p. 67–69°/17 mm., $n^{20}D$ 1.458.

Anal. Calcd. for $C_{10}H_{16}O$ (152.23): C, 78.89; H, 10.60. Found: C, 77.93; H, 10.48.

1,4-Dimethyl-2,3-diethyl-1,4-epoxy-1,4-dihydronaphthalene (XV).—Using method B described above for the preparation of VIII, 36.4 g. of XIV gave 26.2 g. (57.5%) of XV, b.p. 152–154°/18 mm. Recrystallization from hexane gave 22.5 g. (49.4%) of XV, m.p. 50–52°. Another recrystallization gave m.p. 51.6–52.3°.

Anal. Calcd. for $C_{16}H_{20}O$ (228.32): C, 84.20; H, 8.76. Found: C, 84.16; H, 8.76.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ε): 250 (2.89), 265 (2.92), 272.5 (3.00), 280 (2.92). Infrared absorptions at 1250–1300 (—C—O—C—) and 680–880 cm.$^{-1}$ (Ar C—H deformation).

1-Chloromethyl)-4-methyl-2,3-diethylnaphthalene (XVI).—Dry hydrogen chloride was passed into a solution of 2.08 g. (8.76 mmoles) of XV in 30 ml. dry methanol. After 20 min. the solution, now dark in color, was refrigerated, the crystals were filtered off and washed with cold methanol; yield: 1.8 g. (84.5%). Recrystallization from hexane gave 1.2 g. (56.4%) of pure XVI, m.p. 72.5–73°.

Anal. Calcd. for $C_{16}H_{19}Cl$: Cl, 14.32. Found: Cl, 13.85.

Ultraviolet spectrum in ethanol: λ_{max} mμ (log ε): 230 sh (4.80), 235.5 (4.98), 293 (3.86), 329 sh (2.87).

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Catalytic Hydrogenation of α,β-Unsaturated Ketones. III. The Effect of Quantity and Type of Catalysts[1,2]

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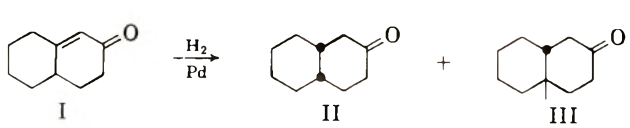
The relative amounts of *cis*- and *trans*-β-decalone obtained on hydrogenation of $\Delta^{1,9}$-octalone-2 using varying amounts of 10% palladium–charcoal catalyst has been determined in acidic, basic, and neutral media. In all cases, a sharp change in the per cent of *cis* isomer formed was observed at a palladium–substrate ratio of 1:100. This corresponded to the point of inflection of the rate *vs.* quantity of catalyst curve. The effect of platinum and rhodium as catalysts was also determined.

In line with other work on the hydrogenation of α,β-unsaturated ketones,[1] it was considered important to study the effect of the quantity of catalyst on the stereospecificity of the reaction. To do this a series of hydrogenations of $\Delta^{1,9}$-octalone-2 (I) using a wide variety of catalyst–substrate ratios were run. The amounts of *cis*-β-decalone (II) obtained in acidic, basic and neutral medium hydrogenations using different weights of 10% palladium on charcoal to hydrogenate 250 milligrams of I are shown in Fig. 1. It is of interest to note that the stereospecificity in acid medium shows a maximum at a palladium–octalone ratio of 1:100 while in neutral and basic media a minimum in the percent of II obtained occurs at the same point.



I II III

(1) Part II in this series; R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

(2) Support for this work by the National Institutes of Health through Research Grant RG9696 from the Division of General Medical Sciences, U. S. Public Health Service, is gratefully acknowledged.

Fig. 2 shows the per cent of II obtained using fifty milligrams each of different percentages of palladium on charcoal in the hydrogenation of I. The results shown here are not so clear as those in Fig. 1. Young and Hartung have stated that varying the metal to carrier ratio of palladium-on-charcoal catalysts can also vary the number of palladium atoms in a given cluster, the spacing between these clusters and, possibly, even the crystalline lattice structure of the metal as well.[3] It is possible, then, that the activity of the catalyst as well as its stereospecificity could be effected by changing any of these variables. In the case where the weight of catalyst was varied the metal to carrier ratio remained constant and the above mentioned variables were eliminated. The following discussion will concern itself only with this latter type of system.

The rates of the various reactions are shown in Fig. 3. These rates represent the volume of hydrogen taken up in the time between five and fifteen minutes after the initiation of the reaction keeping the hydrogen pressure and the stirring rate constant. The re-

(3) J. G. Young and W. H. Hartung, *J. Org. Chem.*, **18**, 1659 (1953).

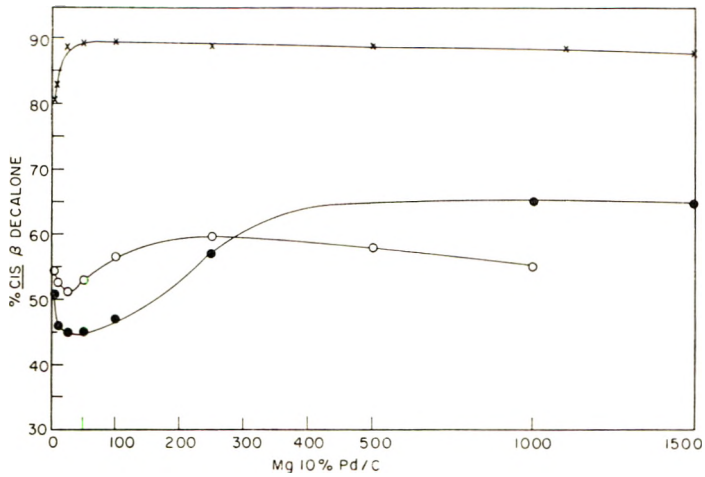


Fig. 1.—Per cent of *cis*-β-decalone formed on hydrogenation of 250 mg. of $\Delta^{1,9}$ octalone-2 with varying weights of 10% palladium–charcoal as the catalyst.

x Acidic medium
○ Basic medium
● Neutral medium

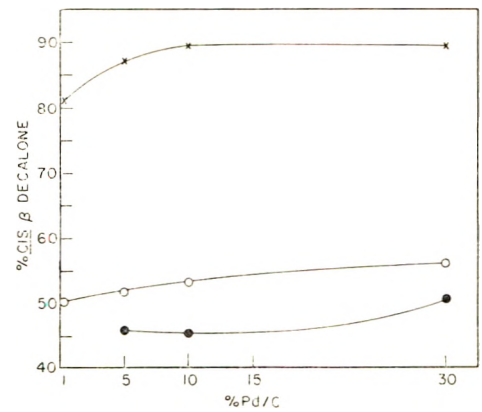


Fig. 2.—Per cent of *cis*-β-decalone formed on hydrogenation of 250 mg. of $\Delta^{1,9}$-octalone-2 with 50 mg. of varying percentages of palladium–charcoal as the catalyst.

x Acidic medium
○ Basic medium
● Neutral medium

actions were run at room temperature which was 20° ± 2° over the entire sequence of reactions. Even though these measurements were crude, they give approximately the same shape curve as that reported by Watt[4] for the hydrogenation of allyl alcohol using varying quantities of palladium. He reports a transition in the curve corresponding to 20 mg. of palladium catalyst with 1 ml. of allyl alcohol in 11 ml. of neutral solution. Csuros[5] and Erdey-Grúz and Szabó[6] also mention a dependency of the rate of hydrogenation on the quantity of palladium catalyst used. They observed, however, both a minimum and a maximum in the velocity–quantity of catalyst curve. The position of these minima and maxima were particular to the compound being hydrogenated. No such curves corresponding to hydrogenation in acidic or basic medium could be found in the literature. It should be noted that in all three rate curves, the point of transition corresponds to the point of maximum or minimum formation *cis*-β-decalane as shown in Fig. 1.

From examination of the neutral curves of Fig. 1 and Fig. 3, it appears that the hydrogen availability to the catalyst surface is the primary factor involved, particularly in those instances above the inflection point. This concept was proven by Watt[4] and used recently by House to explain similar data.[7]

Examination of molecular models of I shows that the difference between the steric hindrance to *cis* and *trans* adsorption is very slight with the *trans* adsorption being somewhat more favored. Thus, one can say that as the amount of catalyst increases above the inflection point, the amount of hydrogen available is spread over a larger surface area of catalyst, decreasing the probability of interaction with I. This permits equilibration between the *cis* and *trans* half-hydrogenated states (IV and V)[8] or the *cis* and *trans* adsorbed octalone thus resulting in decreased stereospecificity of the reaction. This same concept can be used to

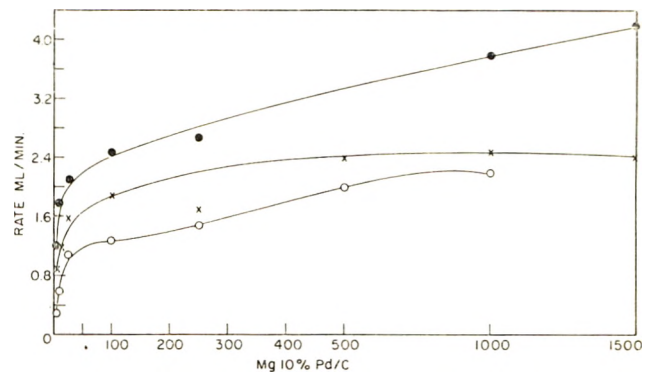


Fig. 3.—Rate of hydrogen uptake on hydrogenation of 250 mg. of $\Delta^{1,9}$-octalone-2 with varying weights of 10% palladium–charcoal as the catalyst.

x Acidic medium
○ Basic medium
● Neutral medium

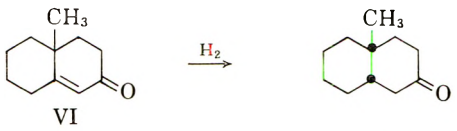
explain the increase in selectivity with decrease in amount of catalyst in the hydrogenation of substituted isopropylidenebicycloheptenes reported by DePuy and Story.[9]

IV V

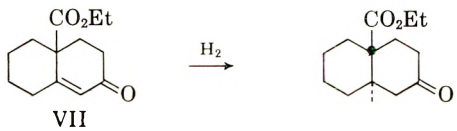
At very low catalyst ratios hydrogen diffusion is no longer the limiting factor, but, instead, the actual surface area of the catalyst. Thus, one may ascribe the effect observed to a lessening of the number of "active sites" available for reaction between the substrate and the hydrogen, both of which are in plentiful supply to the catalyst. It is possible then that the change in stereospecificity observed could be due to a crowding of substrate molecules on the catalyst surface combined with a rapid reaction which does not allow for any desorption of the substrate before hydrogenation takes place.

(4) G. W. Watt and M. T. Walling, Jr., *J. Phys. Chem.*, **59**, 7 (1955).
(5) Z. Csuros, *Chem. Abstr.*, **42**, 3726 (1948).
(6) T. Erdey-Grúz and J. Szabó, *ibid.*, **45**, 10009 (1951).
(7) H. O. House, R. G. Carlson, J. Muller, A. W. Noltes, and C. D. Slater, *J. Am. Chem. Soc.*, **84**, 2614 (1962).
(8) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961).
(9) C. H. DePuy and P. R. Story, *ibid.*, **82**, 627 (1960).

These results point out a discrepancy reported in the interpretation of the hydrogenation data given for the 10-substituted β-octalones. Hydrogenation of 10-methyl-$\Delta^{1,9}$-octalone-2 (VI) reportedly gives the *cis*-decalone,[10] whereas the 10-carbethoxy compound (VII) yields the *trans* compound.[11] McQuillan[12] has



VI

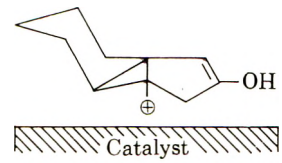


VII

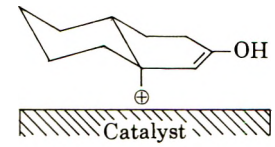
explained this by stating that the large size of the carbethoxy group hinders that adsorption on the catalyst surface which would lead to the formation of the *cis* isomer, but the smaller methyl group does not hinder this adsorption as much, thereby permitting the *cis* isomer to be formed. If this were the case, the even smaller 10-hydrogen of I would offer even less hindrance resulting in the formation of exclusively *cis*-β-decalone. The present data repudiates this as does the examination of molecular models mentioned earlier in which it appears that *trans* adsorption is somewhat more favored for I. The hydrogenations of the 10-substituted octalones is currently being re-examined in this laboratory.

It was considered possible that the change in the amount of the *cis* isomer formed using increasing quantities of catalyst could have been due to a preferential strong adsorption of the *trans*-β-decalone on the catalyst thereby removing some of this material from the reaction mixture when the catalyst was filtered. This consideration was dismissed by treating the catalysts from two duplicate runs in different ways. In one run, the catalyst was filtered, washed with a small amount of acetone, and the filtrate worked up as described in the Experimental. In the second run, the catalyst, after filtration, was refluxed with acetone, filtered, and the acetone added to the original filtrate which was then worked up as usual. The per cent of *cis*-β-decalone obtained in each run was the same.

In acid medium the situation is much the same as that in neutral medium providing one introduces the concept of hydride ion transfer from the catalyst surface to an initially formed carbonium ion adsorbed stereospecifically on the catalyst surface to account for the preponderance of *cis*-β-decalone formed.[13] At low catalyst quantities every adsorption of the carbonium ion on the "active sites" of the catalyst results in an immediate hydride ion transfer. This rapid reaction would not allow for any equilibration between the *cis* and *trans* adsorbed ions (VIII and IX) and would be, effectively, a kinetic controlled process. Above the inflection point, the quantity of hydrogen available has decreased sufficiently to permit equilibration between the two ions to occur before hydride ion transfer is accomplished.



VIII



IX

The data for hydrogenation in basic medium approximates that obtained in neutral medium except for the presence of a maximum as well as a minimum in the % *cis*-β-decalone curve but not in the rate curve. Two theories have been put forth concerning the effect of base on catalytic hydrogenation. It has been suggested, on one hand, that base modifies the adsorption characteristics of the catalyst.[14] On the other hand, the hydrogenation of α,β-unsaturated ketones in basic medium has been presumed to proceed through the initial formation of the enolate anion which is subsequently hydrogenated.[15] Since the quantity of base remained constant in the present instance, it could spread out more over the large quantities of catalyst affecting changes such as enolization in varying degrees.

The percentages of *cis*-β-decalone formed on the hydrogenation of I using various other catalysts and conditions are listed in Table I. The rates of hydrogenation of α,β-unsaturated ketones using a variety of catalysts and conditions have been published by Rylander,[16] but, while the stereochemistry of many products formed using platinum as the hydrogenation catalyst is known, similar data using rhodium has not been reported.

Examination of Table I shows that the use of platinum as catalyst has the same effects in acidic, basic, and neutral medium as does palladium but the differences are less pronounced. The use of acetic acid as the solvent gives less of the *cis* isomer than the use of ethanol, but the addition of hydrogen chloride to the acetic acid gives more of an increase in the formation of this compound. It can therefore be assumed that the same mechanism is operative with platinum as with palladium.

TABLE I

Catalyst	Solvent	*cis*-β-Decalone, %
PtO_2	Ethanol	62.7
PtO_2	Ethanol–acid	77.5
PtO_2	Ethanol–base	58.1
PtO_2	HOAc	55.8
PtO_2	HOAc–HCl	84.8
5% Rh/C	Ethanol	69.6
5% Rh/C	Ethanol–acid	86.9
5% Rh/C	Ethanol–base	82.5
2% $Pd/SrCO_3$	Ethanol	32.8

The gas–liquid chromatograph of the product mixture obtained in the hydrogenation of I in an acetic acid–hydrochloric acid solvent using a platinum catalyst shows the presence of small amounts of the *cis*- and *trans*-decalins and the *cis*- and *trans*-β-decalols in about the same ratio as the *cis*- and *trans*-β-decalones present. This indicates that the reaction occurs stepwise with saturation of the double bond occuring

(10) W. G. Dauben, J. B. Rogan, and E. J. Blanz, Jr., *J. Am. Chem. Soc.*, **76**, 6384 (1954).
(11) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *ibid.*, **77**, 48 (1955).
(12) F. J. McQuillan and W. O. Ord, *J. Chem. Soc.*, 2902 (1959).
(13) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).
(14) G. Stork, *J. Am. Chem. Soc.*, **69**, 576 (1947).
(15) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *ibid.*, **72**, 5524 (1950).
(16) E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.*, **24**, 1855 (1959).

first followed by the hydrogenation of the carbonyl group and hydrogenolysis of the resulting alcohol. This was shown to be the case in the hydrogenations reported by Rylander.[16] In all of the hydrogenations run here, this was the only instance of alcohol or hydrocarbon formation noted.

Use of rhodium on charcoal as the catalyst showed an increase in the % of the *cis* isomer formed on going from neutral to acidic medium but the effect is even less pronounced than that in the case of platinum. In basic medium, though, the effect is considerably different from that with palladium or platinum. Hernandez and Nord[17] have shown evidence, however, to the effect that rhodium hydrogenates by a different mechanism than does palladium. However, Yao and Emmett,[18] after reinvestigation of the work, state that the differences observed were better interpreted by difference in the activity of the palladium and rhodium catalysts used. This difference could also conceivably account for the change in stereospecificity observed here.

Apology should be made at this time for two typographical errors which appeared in the first paper of this series.[13] In Table I of that article the data for the % of *cis* and *trans* isomers formed using 2% palladium–strontium carbonate as the catalyst should be reversed and the solvent used with the 30% palladium–charcoal should have read ethanol–aqueous hydrochloric acid. Other differences between the data recorded in this table and Table I of the current article can be attributed to a difference in concentration of I, a different catalyst to substrate ratio, and a considerably more efficient separation of the isomers in the analysis procedure in the present instance.

Experimental

Apparatus.—The hydrogenations were carried out in an atmospheric pressure hydrogenator which was, effectively, a manifold to which wasat tached a gas buret filled with mercury connected to a leveling bulb, an 80-cm. mercury U-tube manometer, a small U-tube manometer filled with water and capable of being isolated from the rest of the system by means of a stopcock, a 100-ml. round-bottomed reaction flask stirred by means of a magnetic stirrer, and a three-way stopcock leading to an aspirator and a hydrogen cylinder.

The catalysts used were obtained from Engelhard Industries, Newark, New Jersey.

Rates of Hydrogenation.—The rates of hydrogenation were determined by measuring the amount of hydrogen taken up in the time interval between 5 and 15 min. after the reaction was started. The hydrogen pressure was kept constant at atmospheric pressure by raising the level of the mercury at a rate equal to that of hydrogen absorption by observing the relative heights of the water in the two arms of the water manometer during the operation. The rate of stirring the reaction mixture was kept constant throughout all of the runs. The temperature was 20° ± 2° for all determinations.

$\Delta^{1,9}$-Octalone-2.—A solution of 100 g. of cyclohexanone and 100 g. of morpholine in 1 l. of benzene was refluxed overnight with the water formed collected in a Dean–Stark water separator. After the water was entirely removed the solvent was evaporated and the residue distilled giving 198.5 g. (1.2 moles) of 1-morpholinocyclohexene, b.p. 123–127° (12 mm.). To a solution of this enamine in 1 l. of pure dioxane was added slowly 85.5 g. (1.2 moles) of freshly distilled methyl vinyl ketone and the resulting solution stirred at room temperature for 1 hr. and refluxed for 4 hr., after which time 1 l. of water was added and refluxing continued for an additional 10 hr. The solution was cooled, poured into an additional 1.5 l. of water and extracted with four 500-ml. portions of ether. The ether extracts were washed with 3 *N* hydrochloric acid, saturated aqueous sodium bicarbonate, water, and saturated sodium chloride solution and dried over magnesium sulfate. The solution was filtered, the ether removed, and the residue distilled giving 114.0 g. of $\Delta^{1,9}$-octalone-2 (I), b.p. 140–145° (1.2 mm.). This was shown by g.l.c. analysis to be an 85:15 α,β:β,γ unsaturation mixture[19]. After three recrystallizations at −80° from 700 ml. of petroleum ether (b.p. 60–110°) a mixture which contained about 3% of the β,γ unsaturated isomer, $\Delta^{9,10}$-octalone-2 could be obtained.[20]

Hydrogenation.—Into a 100-ml. round-bottomed flask was placed the catalyst, the solvent, a magnetic stirring bar, and 250 mg. of the 97:3% octalone mixture prepared above. The solvent was 20 ml. of 95% ethanol for neutral runs, 18 ml. of 95% ethanol, and 2 ml. of 3.0 *N* aqueous hydrochloric acid for acid runs, and 18 ml. of 95% ethanol and 2 ml. of 2.6 *N* aqueous sodium hydroxide for basic runs. The flask was attached to the hydrogenation apparatus and the apparatus evacuated and filled with hydrogen three times. The hydrogen pressure was equalized with the atmosphere and the magnetic stirrer turned on and kept at a constant setting for all runs to make constant any diffusion effect on the reaction. After hydrogen uptake had ceased, the flask was removed from the apparatus and the catalyst removed by filtration. In acidic and basic runs the filtrate was neutralized. Most of the ethanol was removed by distillation and the residue poured into water and extracted with ether. The ether extracts were evaporated and the residue subjected to gas–liquid chromatographic analysis as described below. In one instance a duplicate run using 1 g. of 10% palladium–charcoal the catalyst, after being removed from the reaction mixture, was refluxed with 25 ml. of acetone for 30 min. The catalyst was again removed by filtration and the acetone filtrate combined with the original filtrate and the total treated as described above. No difference in the per cent of the *cis*-β-decalone was detected using this modified procedure.

Gas–Liquid Chromatographic Analysis.—A 0.8-μl. sample was subjected to g.l.c. analysis by passing it through a 6-ft. 1/8-in. outside diameter stainless steel column containing 20% water soluble UCON on Chromosorb W. The temperature was programmed from 75° to 150° at 2.3°/min. Helium was the eluent gas at a flow rate of 30 cc./min. The retention times for *trans*-β-decalone and *cis*-β-decalone, were 17 and 19.5 min., respectively. Peak areas were measured using the peak height times peak width at half-height method. Over-all precision including duplicability of chromatograms and reproducibility of hydrogenation data was within ± 1%.

Acknowledgment.—The author is indebted to Dr. R. T. Conley for many stimulating discussions on this subject.

(17) L. Hernandez and F. F. Nord, *Experientia*, **3**, 489 (1947); *J. Colloid Sci.*, **3**, 363 (1948).

(18) Hsien-Cheng Yao and P. H. Emmet, *J. Am. Chem. Soc.*, **81**, 4125 (1959).

(19) D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961).

(20) P. Rosen, private communication (1960).

Amines Derived from Dihalopropenes. IV. The Absolute Configurations of the 1-(2-Methylene-1-aziridinyl)-3-buten-2-ols[1]

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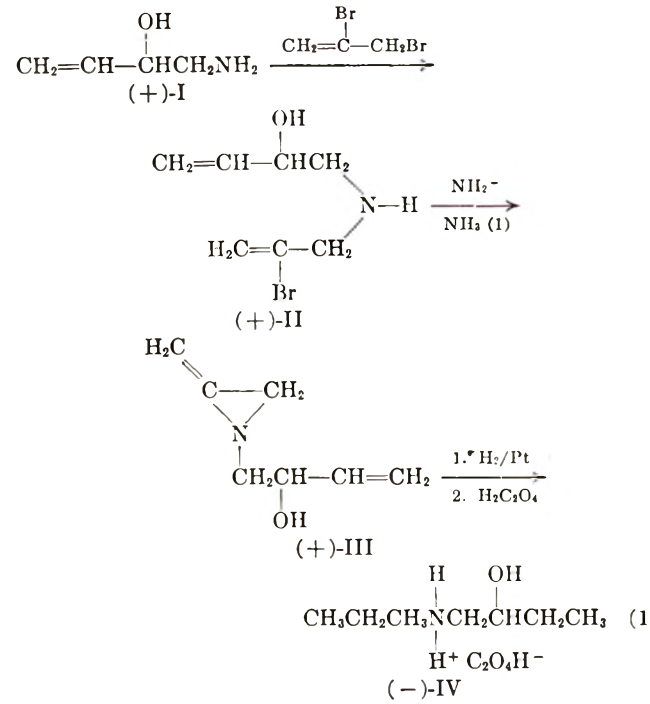
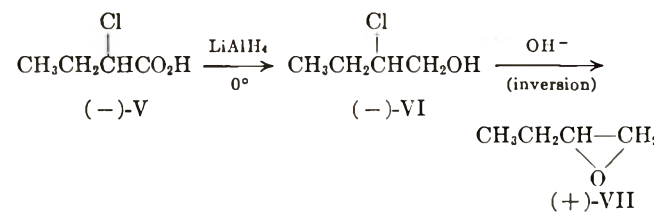
Hydrogenation of (+)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) yields the same enantiomer of 1-propylamino-2-butanol as is obtained from treatment of s-(+)-2-ethyloxirane with *n*-propylamine. Since neither of these reactions affects the asymmetric center, (+)-III must have the R-configuration.

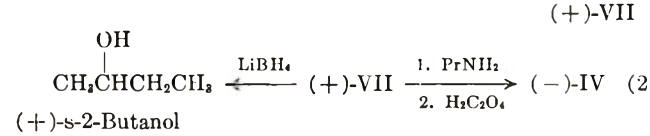
We reported recently that racemic 1-(2-methylene-1-aziridinyl)-3-buten-2-ol, the allenimine analog of the active component of Tetramin,[2] is more active against Adenocarcinoma 755 than (−)-III.[3] The absolute configurations of the 1-amino-3-buten-2-ols, which are used in the preparation of (+)- and (−)-III, were unknown. Therefore, to establish the absolute configurations of the enantiomers of III, it was necessary to relate the configuration of an optically active III to that of a compound whose absolute configuration was known.

Hydrogenation of (±)-III over Adams' catalyst, using the same conditions that convert N-alkylallenimines to the corresponding N-alkyl-*n*-propylamines,[4] was found to yield 1-propylamino-2-butanol, which could also be prepared in excellent yield from *n*-propylamine and 2-ethyloxirane (VII). As the absolute configurations of the 2-ethyloxiranes could be assigned with a high degree of certainty,[5] and as formation of 1-propylamino-2-butanol from either III or VII takes place without affecting the asymmetric center, it was decided to relate the configuration of an optically active III to that of an enantiomer of IV. The sequences of reactions used to establish the absolute configurations are shown as equations 1 and 2.

2-Chlorobutanoic acid (V), prepared by the action of sulfuryl chloride on butyric acid,[9] was fractionated, and the center cut was partially resolved by crystallization of its cinchonidine salt from methanol.[10] The levorotatory acid that was isolated was reduced with lithium aluminum hydride to (−)-2-chloro-1-butanol (VI),[10] and compound (−)-VI was treated with sodium hydroxide to give s-(+)-2-ethyloxirane (VII).[5]







One portion of compound s-(+)-VII, which had a specific rotation of $[\alpha]^{30}D$ +10.7° in benzene (*c* 6.5), was converted to 1-propylamino-2-butanol acid oxalate (IV) with a specific rotation of $[\alpha]^{26}D$ −9.6° in 50% ethanol (c 4.4), and another portion was converted with lithium borohydride to s-(+)-2-butanol,[7] which had a specific rotation of $[\alpha]^{26}D$ +6.3° (neat). As optically pure s-(+)-2-butanol has a specific rotation of $[\alpha]^{26}D$ +13.6° (neat),[11] and the preparations of IV and 2-butanol from 2-ethyloxirane take place without affecting the asymmetric center, specific rotations of $[\alpha]^{30}D$ ±23.1° and $[\alpha]^{26}D$ ±20.7° can be calculated, respectively, for the optically pure 2-ethyloxiranes in benzene and the optically pure 1-propylamino-2-butanol acid oxalates in 50% ethanol.

As both (+)-2-ethyloxirane and (+)-2-butanol are known to have the s-configuration, the (−)-1-propyl-

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This research was also supported by Grant CY-5528 from the National Cancer Institute of the Public Health Service. Part III: A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962).

(2) For a summary of early clinical data on Tetramin, compiled by F. R. White, see *Cancer Chemotherapy Rept.*, **4**, 52 (1959). Cancer Chemotherapy National Service Center, Bethesda, Md. See also, J. M. Venditti, A. Goldin, and J. Kline, *ibid.*, **11**, 73 (1961).

(3) A. T. Bottini and V. Dev, *J. Org. Chem.*, **27**, 968 (1962). The results of tests of (+)-III and (−)-III against Adenocarcinoma 755 using the same sets of controls should be received soon from the Cancer Chemotherapy National Service Center (CCNSC). Test data received from the CCNSC may be obtained from the authors on request.

(4) C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, **73**, 2925 (1951); A. T. Bottini and R. E. Olsen, *ibid.*, **84**, 195 (1962).

(5) (−)-3-Heptanol, which has been assigned the R-configuration,[6,7] is the product of the reaction of (+)-2-ethyloxirane and propylmagnesium bromide.[8] Thus, (+)-2-ethyloxirane can be assigned the s-configuration.[7]

(6) J. A. Mills and W. Klyne, "Progress in Stereochemistry," Vol. I, W. Klyne, ed., Academic Press, Inc., New York, N. Y., 1954, p. 205.

(7) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(8) P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931).

(9) G. Steinbrun, German Patent 1,014,092; *Chem. Abstr.*, **53**, 15981 (1959).

(10) K. Freudenberg and W. Lwowski, *Ann.*, **597**, 141 (1955).

(11) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

amino-2-butanol acid oxalate (IV) obtained from s-(+)-VII must have the R-configuration. Therefore, (+)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III), which also yielded (−)-IV, as well as the intermediates used in the preparation of (+)-III, (+)-1-amino-3-buten-2-ol (I)[12] and (+)-N-(2-bromoallyl)-2-hydroxy-3-butenylamine (II), must also possess the R-configuration. Further, the (+)-I used in the sequence of reactions leading to (+)-III was 87% resolved, and the observed specific rotation of $[\alpha]^{26}D$ −16.8° in 50% ethanol (c 4.2) for (−)-IV prepared from (+)-I was 81% of the specific rotation calculated for optically pure (−)-IV. This agreement indicates that less than 7% racemization accompanies the reactions used for the preparation of II, III, and IV.

It is of interest that the specific rotation of $[\alpha]^{26}D$ −25.0 ± 0.4° calculated by us for optically pure (−)-2-chloro-1-butanol (VI) is in fair agreement with the value of $[\alpha]^{25}D$ −23.9° calculated by Freudenberg and Lwowski.[10] For the purpose of these calculations, we assumed that conversion of VI to 2-butanol occurs without racemization, and Freudenberg and Lwowski assumed that the specific rotation of optically pure 2-chlorobutanoic acid (V) is $[\alpha]^{25}D$ −17.5° and that reduction of V with lithium aluminum hydride at 0° occurs without racemization. However, it must be noted that whereas the refractive indices observed by us for (−)-V and (−)-VI are in excellent agreement with values reported for (±)-V[13] and (±)-VI,[14] they are in only fair agreement with the values reported for (−)-V and (−)-VI.[10]

Experimental[15]

(+)-1-Amino-3-buten-2-ol (I).—The filtrates remaining[3] after the fractional crystallization of the (+)-camphor-10-sulfonate salt of (−)-I were concentrated to dryness with a rotary film evaporator. From the residue was obtained[3] 72.3 g. [68% based on the camphor-10-sulfonate salt] of (+)-enriched I, which had a boiling point of 78–79° (10 mm.); lit.,[12] b.p. 72° (8 mm.). A solution of 72.0 g. (0.827 mole) of (+)-enriched I was added to a cold solution of 192 g. (0.827 mole) of (−)-enriched camphor-10-sulfonic acid[16] dissolved in 300 ml. of absolute ethanol. To this solution was added 1.3 l. of anhydrous ethyl acetate, and the resulting solution was allowed to stand at room temperature for 24 hr. The white crystalline solid that separated was collected by suction filtration and washed with 100 ml. of ethyl acetate. It had a melting point of 141–143°. The salt was recrystallized four times from absolute ethyl acetate–absolute ethanol to yield 130.5 g. [49% based on (+)-enriched I] of (+)-1-amino-3-buten-2-ol-(−)-camphor-10-sulfonate, which had a melting point of 146.5–148.5°; lit.,[12] m.p. 148.5–150°.

(+)-Enriched I (27.6 g., 78%), with a boiling point of 84–85° (18 mm.), was regenerated from 130 g. of the sulfonate salt with potassium hydroxide. The material had a specific rotation of $[\alpha]^{30}D$ 25.3° (0.196 g./5 ml. of absolute ethanol). As optically pure (−)-I has a specific rotation of $[\alpha]^{30}D$ −29.0° (0.210 g./5 ml. of absolute ethanol),[3] the (+)-I obtained was 87% optically pure.

(+)-N-(2-Bromoallyl)-2-hydroxy-3-butenylamine (II).—A solution of 31.0 g. (0.155 mole) of 2,3-dibromopropene in 50 ml. of absolute ethanol was added dropwise to a cold (0°), mechanically stirred solution of 27 g. (0.31 mole) of (+)-I in 100 ml. of absolute ethanol. When the addition was complete, the reaction mixture was allowed to warm to room temperature and after 6 hr. was heated at reflux for 3 hr. The reaction mixture was worked up in essentially the same manner as described in the preparation of (−)-II.[3] (+)-II (23.1 g., 72%) was collected at 108–109° (1 mm.). The product had $n^{28}D$ 1.5130, $[\alpha]^{30}D$ 6.0° (0.368 g./5 ml. of absolute ethanol).

Anal. Calcd. for $C_7H_{12}NOBr$: C, 40.80; H, 5.87; N, 6.80; Br, 38.78. Found: C, 40.77; H, 5.81; N, 6.74; Br, 38.58.

Optically pure (−)-II has m.p. 34–36°, $[\alpha]^{23}D$ −6.2° (0.263 g./10 ml. of absolute ethanol), and not $[\alpha]^{23}D$ −3.5° as reported earlier.[3]

(+)-1-(2-Methylene-1-aziridinyl)-3-buten-2-ol (III).—Compound (+)-II (20.6 g., 0.10 mole)was treated with 9.75 g. (0.25 mole) of sodium amide in essentially the same manner as described in the preparation of (−)-III.[3] The product from the reaction was distilled under nitrogen through a semimicro Vigreux column, and four fractions were taken. The first three fractions (5.4 g., 43%) were collected at 68–71° (2 mm.). They possessed identical infrared spectra and refractive indices ($n^{25}D$ 1.4871), and the center fraction had $[\alpha]^{30}D$ 27.7° (0.247 g./5 ml. of absolute ethanol); lit.,[3] $[\alpha]^{20}D$ −30.5° (0.837 g./20 ml. of absolute ethanol) for optically pure (−)-III. The fourth fraction (4.7 g., 27%) was collected at 75–95° (2 mm.), with a sizeable fraction distilling at 94–95° (2 mm.), $n^{25}D$ 1.4873. Examination of the infrared spectrum of the fourth fraction indicated that it contained about two thirds of (+)-III and one third 1-(2-propynylamino)-3-buten-2-ol.[3]

(±)-2-Chlorobutanoic Acid (V).[9]—To a well stirred solution of 528 g. (6.0 moles) of butyric acid and 10 ml. of dimethylformamide at 80–85° was added dropwise 1215 g. (9.0 moles) of sulfuryl chloride in 6 hr. The resulting yellow solution was held at 90–95° for 2 hr. and distilled through a 600 × 8 mm. Poddielniak column fitted with a total reflux head. The weights, boiling points, and refractive indices of the fractions are given below. Only the third fraction was used in subsequent work. The reported refractive index for (±)-V is $n^{20}D$ 1.4411.[13]

Fraction	Weight, g.	B.p., °C.	(Mm.)	$n^{25}D$
1	117	107–111	(28)	1.4374
2	34	116–119	(32–35.5)	1.4389
3	153	122–123.5	(34)	1.4398
4	57	114.5–115	(18)	1.4438

(−)-2-Chlorobutanoic Acid (V).—The salt (m.p. 148.5–150°) obtained from evaporation of a solution prepared from 353 g. (1.2 moles) of cinchonidine (Fluka AG., Buchs, SG, Switzerland), 147 g. (1.2 moles) of (±)-V, and 300 ml. of methanol was suspended in 1500 ml. of boiling acetone and enough methanol (*ca.* 100 ml.) was added slowly to give complete solution. The solution was allowed to cool to room temperature and stand for 6 hr. The white crystals that separated were collected, and after four additional recrystallizations from acetone–methanol, they weighed 370 g. and had a melting point of 149.5–152°. This material was dissolved in 200 ml. of methanol, and the solution was allowed to stand at 0° for 2 weeks. The solid that separated weighed 107 g. (21%) and melted at 153.5–154.5°. To a mixture of 400 g. of crushed ice and 170 g. of 60% perchloric acid covered with 150 ml. of ether was added 107 g. (1.26 moles) of the above cinchonidine salt. The mixture was shaken vigorously, and after about 10 min., all of the cinchonidine salt had disappeared. The ether phase was separated, and the aqueous phase was extracted three times with 100-ml. portions of ether. The ether extracts were combined, washed twice with 20-ml. portions of water, and dried over magnesium sulfate. The ether was removed by distillation at atmospheric pressure, and distillation of the residual oil yielded 29.3 g. (93%) of (−)-2-chlorobutanoic acid, b.p. 93–94° (9 mm.), $n^{26}D$ 1.4377, $[\alpha]^{25}D$ −9.1° (0.374 g./5 ml. of chloroform); lit.,[10] b.p. 98.5° (14 mm.), $n^{25}D$ 1.4414, $[\alpha]^{25}D$ 17.2° (neat) for (+)-V.

(−)-2-Chloro-1-butanol (VI).—Following the procedure described by Freudenberg and Lwowski,[10] 29 g. (0.24 mole) of (−)-

(12) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950). Our results allow the assignment of the s-configuration to (−)-5-vinyl-2-thiooxazolidone, the antithyroid factor isolated from numerous plants of the *Brassicaceae* and synthesized by Ettlinger.

(13) E. Schjanberg, *Z. physik. Chem.* (Leipzig), [A] **172**, 197 (1935).

(14) H. M. Waddle and H. Adkins, *J. Am. Chem. Soc.*, **61**, 3361 (1939).

(15) All melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Rotations were taken with a Rudolph and Sons Model No. 251 polarimeter in 2-dm. tubes. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

(16) The (−)-camphor-10-sulfonic acid, which had a specific rotation of $[\alpha]^{31}D$ −24.6° (0.562 g./50 ml. of water), was obtained using the procedure of H. Burgess and C. S. Gibson, *J. Soc. Chem. Ind.*, **44**, 496T (1925). They reported a specific rotation of $[\alpha]^{20}D$ −28.15° in water for optically pure (−)-camphor-10-sulfonic acid, which indicates that our material was more than 87% optically pure.

V was reduced with 14.5 g. (0.38 mole) of lithium aluminum hydride to yield 20.5 g. (79%) of (−)-VI, which had b.p. 58–59° (22 mm.), $n^{25}D$ 1.4410, $[\alpha]^{26}D$ −12.0° (0.248 g./5 ml. of benzene), $[\alpha]^{26}D$ −11.6° (neat); lit.,[10] b.p. 53–54° (15 mm.), $n^{25}D$ 1.4442, $[\alpha]^{25}D$ +23.9° (neat), calculated for optically pure (+)-VI; lit.,[14] $n^{25}D$ 1.4410 for (±)-VI.

(+)-2-**Ethyloxirane** (**VII**).—To a vigorously stirred solution of 22.2 g. (0.56 mole) of sodium hydroxide and 40 ml. of water at 100° was added dropwise 20.0 g. (0.184 mole) of (−)-VI. The distillate that resulted was collected over a few pellets of sodium hydroxide and then distilled from fresh sodium hydroxide pellets. (+)-2-Ethyloxirane (10.1 g., 76%) was collected at 62–63°. It had $n^{25}D$ 1.3813, $[\alpha]^{30}D$ +10.7° (0.325 g./5 ml. of benzene) and an infrared spectrum superimposable on that of redistilled (±)-VII obtained from Farchan Laboratories.[17]

(+)-s-**Butanol**.[18]—2-Ethyloxirane (3.6 g., 0.05 mole) dissolved in 15 ml. of anhydrous ether was added dropwise to a well stirred mixture of 1.1 g. (0.05 mole) of lithium borohydride[19] in 30 ml. of ether. When the addition was complete, the mixture was heated at reflux for 2 hr. and allowed to stand overnight at room temperature. Water (10 ml.) was added slowly to the reaction mixture, and the phases were separated. The aqueous phase was saturated with sodium chloride and extracted twice with 15-ml. portions of ether. The ether extracts were combined and dried over potassium carbonate. Distillation yielded 2.70 g. (75%) of a fraction boiling at 88–91°. This fraction was dried over calcium oxide and then distilled to yield 1.6 g. of s-(+)-2-butanol, b.p. 97–99°, $n^{26}D$ 1.3922, d_4^{25} 0.8033, $[\alpha]^{26}D$ +6.3° (neat); lit.,[11] b.p. 99°, $n^{20}D$ 1.3954, d_4^{27} 0.8025, $[\alpha]^{27}D$ 13.52° (neat).

(±)-**1-Propylamino-2-butanol Acid Oxalate** (**IV**). A. **From 2-Ethyloxirane** (**VII**) **and** *n*-**Propylamine**.—(±)-2-Ethyloxirane (21.6 g., 0.30 mole) was added dropwise to a stirred, ice-cold solution of 35.4 g. (0.60 mole) of *n*-propylamine and 5.4 ml. of water. The solution was allowed to stand overnight at room temperature. The excess *n*-propylamine and water were removed by distillation, and the residual oil was distilled to yield 28.5 g. (73%) of 1-propylamino-2-butanol, b.p. 72–74° (7 mm.), $n^{25}D$ 1.4390.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.13; H, 13.12; N, 10.54.

The amino alcohol (1.3 g., 0.010 mole) was dissolved in 5 ml. of absolute ethanol, and the resulting solution was added to a solution of 1.26 g. (0.010 mole) of oxalic acid dihydrate in 10 ml. of absolute ethanol. The precipitate that formed was dissolved by warming the mixture. The white plates that separated when the solution was allowed to stand at room temperature for 3 hr. weighed 1.4 g. (64%) and melted at 159–160°. After one recrystallization from absolute ethanol, the acid oxalate melted at 159.5–160.0°.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 49.07; H, 8.49; N, 6.27.

B. **From III**.—A mixture of 2.5 g. (0.020 mole) of 93% (±)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) and 7% (±)-2-(2-methylene-1-aziridinyl)-3-buten-1-ol[3] in 100 ml. of absolute ethanol to which had been added 0.20 g. of platinic oxide was shaken under 30–35 p.s.i. of hydrogen for 5 hr. The reduction appeared to be complete within 1 hr. The catalyst was removed by filtration, and 2.5 g. (0.020 mole) of oxalic acid dihydrate was dissolved in the filtrate by warming. The solution was concentrated to a volume of 25 ml. and cooled. The first crop of crystals that separated (2.3. g., 52%) melted at 132–137°. After three recrystallizations from ethanol, the acid oxalate (1.7 g.) melted at 157–158°, and the melting point was not depressed by the addition of (±)-IV prepared from (±)-2-ethyloxirane (VII) and *n*-propylamine.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 48.58; H, 8.25; N, 6.10.

(−)-IV. A. **From** (+)-**VII and** *n*-**Propylamine**.—Using the same procedure described for the preparation of (±)-IV from (±)-VII, 3.6 g. (0.050 mole) of (+)-2-ethyloxirane and 5.9 g. (0.10 mole) of *n*-propylamine, in the presence of 1 ml. of water, were converted to 3.3 g. (50%) of (−)-1-propylamino-2-butanol, b.p. 74–76° (9 mm.), $n^{25}D$ 1.4388. The first crop of acid oxalate melted at 157.5–158.5°. After one recrystallization from absolute ethanol, the acid oxalate melted at 158.5–159.0° and had a specific rotation of $[\alpha]^{26}D$ −9.6° (0.220 g./5 ml. of 50% aqueous ethanol by weight).

B. **From** (+)-**III and** (+)-**1-(2-Propynylamino)-3-buten-2-ol**.—The fourth fraction (4.6 g. 0.037 mole) was hydrogenated as described for (±)-III. The first crop of acid oxalate (4.2 g., 51%) melted at 157–158°. After one recrystallization from absolute ethanol, the acid oxalate had a melting point of 158.5–159.0° and a specific rotation of $[\alpha]^{26}D$ −16.8° (0.211 g./5 ml. of 50% aqueous ethanol by weight). Admixture of the acid oxalate with (−)-IV obtained from (+)-VII did not depress its melting point.

(17) Levene and Walti[8] reported the preparation of (+)-VII, which had a specific rotation of $[\alpha]^{26}D$ +8.75° (neat), from (−)-1-bromo-2-butanol.

(18) Reduction of (±)-VII with lithium borohydride was reported by R. Fuchs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1631 (1954).

(19) The lithium borohydride was prepared as described by H. I. Schlesinger, H. C. Brown, and E. K. Hyde, *ibid.*, **75**, 209 (1953).

Preparation of a Glycoside of 2-Amino-2,3-dideoxy-3-mercaptoaltrose[1]

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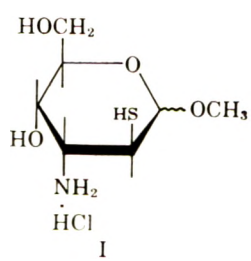
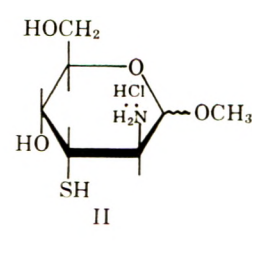
The synthesis of methyl 2-amino-2,3-dideoxy-3-mercapto-D-altropyranoside hydrochloride (II) is described.

An earlier paper in this series[2] described the synthesis of methyl 3-amino-2,3-dideoxy-2-mercapto-D-altropyranoside hydrochloride (I), prepared as a possible antiradiation drug. This synthesis utilized the conversion of a benzylthio group to the mercaptan function with sodium in liquid ammonia and required that the sugar blocking group be changed from the labile benzylidene to the stable (to sodium–liquid ammonia) ethylidene group prior to the debenzylation in order to permit



I



II

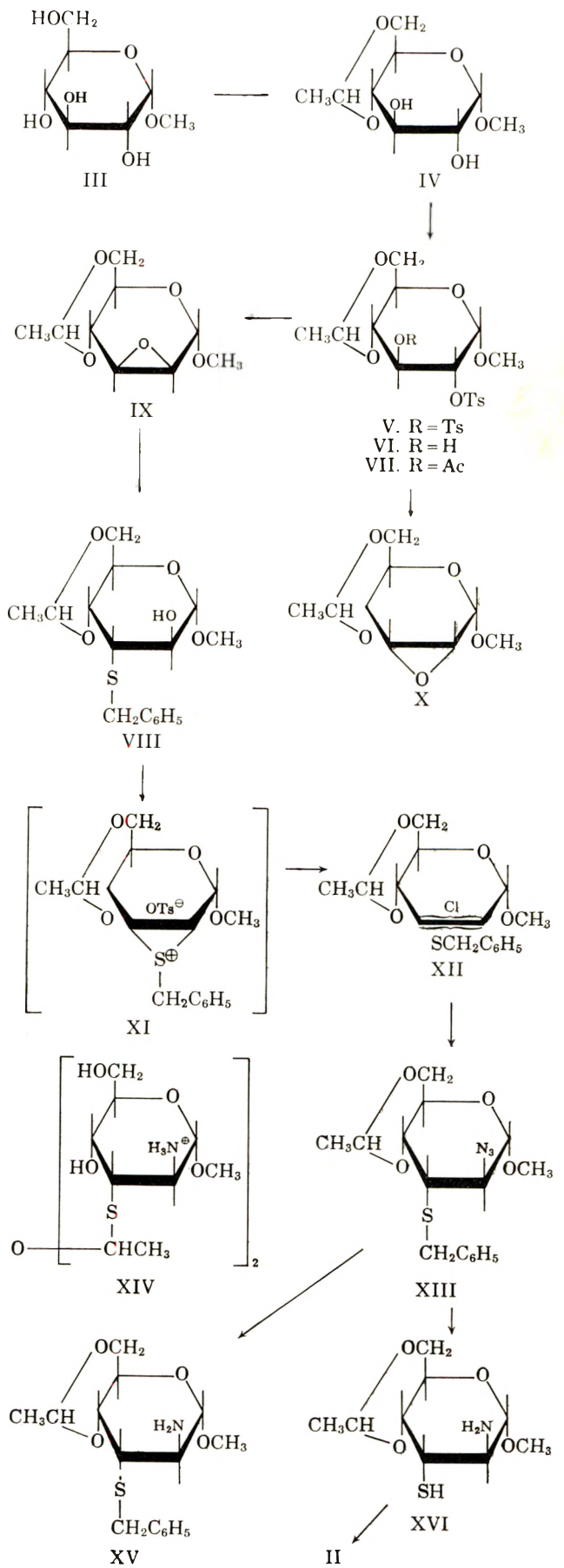
an easy isolation of the derived β-mercaptoamine. In order to circumvent this awkward deblocking-reblocking sequence, it was desirable to use an appropriate ethylidene-blocked sugar as the starting material. This manuscript describes the conversion of methyl 2,3-anhydro-4,6-O-ethylidene-α-D-mannopyranoside (IX) to the title compound (II).

(1) The work reported in this paper (no. 4 of the series) was carried out under the joint auspices of the Office of the Surgeon General, Medical Research and Development Command, under Contract no. DA-49-193-MD-2068 and of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, under Contract no. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of either sponsoring agency.

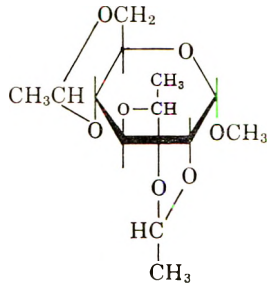
(2) J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3827 (1961).

Methyl α-D-glucopyranoside (III) was converted to the blocked glycoside (IV) with 1,1-dimethoxyethane and an acid catalyst, using the procedure of O'Meara and Shepherd[3] for the β-anomer of IV. Crude IV, with the appropriate proportions of *p*-toluenesulfonyl chloride, formed the crystalline ditosylate (V)[4] and the crystalline monotosylate (VI), the latter best isolated as the acetate (VII). Treatment of V with refluxing sodium methoxide gave a good yield of the anhydroalloside (X),[4] the reaction taking place in the same manner as with the 4,6-benzylidene analog of V[5] although requiring much more stringent conditions. Similarly, the monotosylate (VI) and the tosylate acetate (VII) with methanolic sodium methoxide at reflux furnished good yields of an isomeric epoxide that must be the anhydromannoside (IX), not previously described.

Ring-opening of IX with sodium benzyl mercaptide furnished an excellent yield of VIII, whose structure is assumed as resulting from transdiaxial ring opening according to the considerations elaborated in paper III of this series.[2] Treatment of VIII with tosyl chloride in pyridine afforded either a mixed chloride, tosylate (according to infrared evidence) or a pure, sirupy chloroglycoside, depending on the length of time the reaction was allowed to proceed. The formation of the chloride can be rationalized by assuming the episulfonium ion intermediate (XI). The reaction of XII with sodium azide afforded an excellent yield of a crystalline, sharply melting azide (XIII) whose structure is written on the assumption of *trans*-diaxial episulfonium ion opening at C-2.[2] The azide (XIII) was reduced to the crystalline amine (XV) with sodium borohydride in refluxing isopropyl alcohol,[6] although this was not a necessary step in the preparation of II. Treatment of XIII with sodium in liquid ammonia directly afforded the blocked aminomercaptan (XVI) as a nitroprusside-positive sirup. When XVI was treated with methanolic hydrogen chloride either at room temperature or at reflux, hygroscopic solids were obtained whose n.m.r. spectra in deuterium oxide showed varying amounts of a doublet centered at $\tau = 8.36$. Since the doublet attributable to the O-ethylidene methyl group in XIII was found at $\tau = 8.62$, it was apparent that the secondary methyl group of the supposedly deblocked product from XVI was in a different environment and, indeed, under the proper conditions it was possible to isolate from treatment of XVI with methanolic acid a material that gave excellent analytical agreement with structure XIV. It seems probably that the proximity of the C-4 hydroxyl and the C-3 thiol group is responsible for the formation of XIV, since such a difficulty was not noted in the deblocking step that gave compound I. Structure XIV bears a relationship to methyl 4,6-O-ethylidene-2,3-oxidodiethylidene-α-D-glucoside (XVII), which is formed when methyl α-D-glucoside (III) is treated with paraldehyde and acid.[7] Attempts to complete the conversion of XIV to II by more vigorous acid treatment or by reaction with mercuric chloride were fruitless. When the deblocking of XVI was conducted in the presence of excess ethanedithiol, however, the formation of XIV was prevented and compound II was isolated as a hygroscopic, amorphous solid that could be purified by precipitation from a methanol solution



(3) D. O'Meara and D. M. Shepherd, *J. Chem. Soc.*, 4232 (1955).
(4) E. G. Ansell and J. Honeyman, *ibid.*, 2778 (1952).
(5) F. H. Newth, *Quart. Rev.* (London) **13**, 30 (1959).
(6) P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Am. Chem. Soc.*, **84**, 485 (1962).
(7) H. Appel and W. N. Haworth, *J. Chem. Soc.*, 793 (1938).



XVII

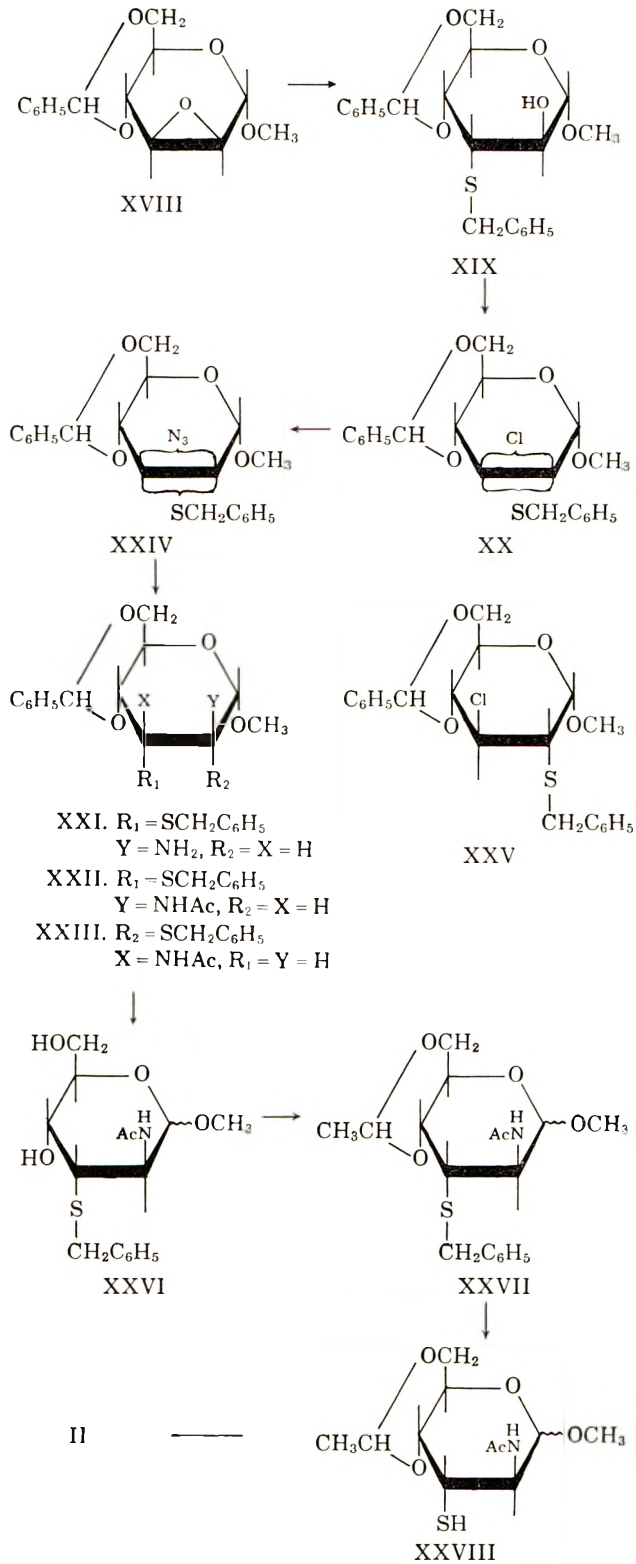
with ether. Similarly to I,[2] it tenaciously retained ether as evidenced both by analyses and by the ether C-methyl triplet n.m.r. resonance at $\tau = 8.78$. Attempts to hydrolyze II to the free sugar with aqueous hydrochloric acid were not encouraging; the reaction mixtures darkened rapidly. There is a strong probability of 1,6-anhydride formation from the hydrolysis of an altroside such as II,[8] a similar situation was noted with I.[2]

Prior to the preparation of IX, some attempts were made to prepare II from the 4,6-O-benzylidene-blocked epoxide (XVIII).[9] The reaction of XVIII with sodium benzyl mercaptide gave an excellent yield of XIX,[10] tosylation of which afforded a sirupy chloride (XX) whose formation can be rationalized in the same way as that of XII. Treatment of XX with sodium azide gave a widely melting solid which was predominantly the azide mixture (XXIV).

The reaction of XX with azide did not go to completion under the conditions used; lithium aluminum hydride reduction of the product permitted, after fractional crystallization of the reduction product, the separation of an amine (XXI) and a small amount of a chloride. The chloride must be compound XXV, whose C-2, C-3 diequatorial substituents would resist episulfonium ion formation. The 2-chloro-3-benzylthio isomer of XXV, where these substituents would occupy diaxial positions, would readily undergo azide displacement *via* the episulfonium ion intermediate, with the predominant cleavage of that ion occurring by *trans*-diaxial opening at C-2 to give XXI as the predominant amine after reduction of the azide mixture (XXIV).

When the reaction product from XX and sodium azide was reduced directly with hydride, then acetylated, two amides were isolated by recrystallization. The lower melting, very predominant compound gave the amine (XXI), on basic hydrolysis, and is assigned structure XXII; the higher melting amide than should be XXIII.

An attempt to provide a more definitive structure proof for XXII and XXIII was not successful. Both amides were desulfurized with Raney nickel, affording from the high melting amide a quantitative yield of XXXII as a crystalline solid, resulting from the concurrent hydrogenolysis of the benzylidene group. The lower melting amide gave a small amount of the crystalline, blocked amide (XXIX) along with the crude deblocked amide (XXX) which was not obtained analytically pure. Cleavage of the deblocked amides with methanolic hydrogen chloride afforded the hydrochlorides, XXXI as an impure, hygroscopic solid and XXXIII as an analytically pure solid. Periodate determinations on these two solids gave perplexing results; compound XXXI, which should not consume



XXI. $R_1 = SCH_2C_6H_5$, $Y = NH_2$, $R_2 = X = H$

XXII. $R_1 = SCH_2C_6H_5$, $Y = NHAc$, $R_2 = X = H$

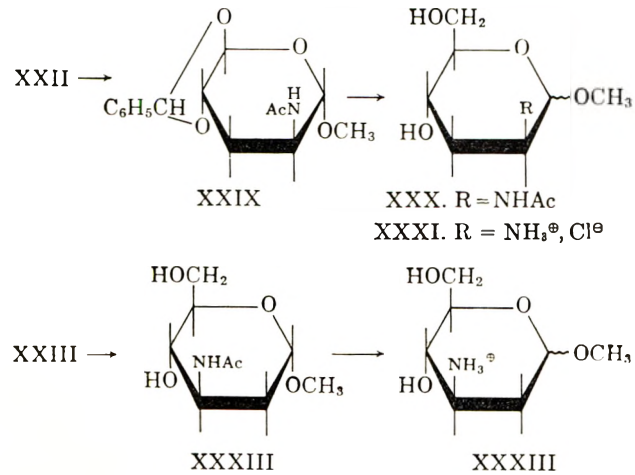
XXIII. $R_2 = SCH_2C_6H_5$, $X = NHAc$, $R_1 = Y = H$

periodate, took up approximately one mole of oxidant and XXXIII took up about two moles of periodate, with both compounds rapidly consuming most of the oxidant after one hour, then giving a slow but steady

(8) R. J. Ferrier and W. G. Overend, *Quart. Rev.* (London), **13**, 265 (1959).

(9) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(10) N. C. Jamieson and R. K. Brown, *Can. J. Chem.*, **39**, 1765 (1961), reported compound XIX while this work was in progress.



consumption of additional periodate.[11] In view of the ambiguous periodate results, structures XXII and XXIII are assigned on the basis of the episulfonium ion formation and opening discussed above.

The predominant amide (XXII) was deblocked with an acid ion–exchange resin to give XXVI as a sirup, which was reblocked with 1,1-dimethoxyethane and acid to afford XXVII as a widely melting, crystalline solid. Sodium and liquid ammonia treatment of XXVII yielded the crystalline thiol (XXVIII), which was converted to II, in low yield, by treatment with methanolic hydrogen chloride, separation of the insoluble mercuric mercaptide, and regeneration of II with hydrogen sulfide.

Experimental[12]

Methyl 4,6-O-Ethylidene-α-D-glucopyranoside (IV).—A suspension of 10.0 g. (51.4 mmoles) of methyl α-D-glucoside (III) in 40 ml. of 1,1-dimethoxyethane containing 0.40 ml. of concentrated sulfuric acid was stirred at room temperature for 18 hr., then adjusted to pH 7 with saturated aqueous sodium bicarbonate solution and evaporated *in vacuo*. The residue was extracted with three 40-ml. portions of boiling carbon tetrachloride, the combined extracts were filtered and dried over potassium carbonate, then evaporated *in vacuo*, leaving 12.46 g. of pale yellow, solid foam. The foam was triturated with two 50-ml. portions of petroleum ether (b.p. 30–60°), leaving 10.55 g. (98%) of a white solid, which was suitable for further conversion (lit.,[4] m.p. 76–77°).

Methyl 4,6-O-Ethylidene-2,3-di-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (V).—To a chilled (0°), stirred solution of 6.00 g. (27.2 mmoles) of the crude diol in 30 ml. of pyridine was added, dropwise, a solution of 30.0 g. (0.157 mole) of *p*-toluenesulfonyl chloride in 150 ml. of pyridine. The solution was stirred at room temperature for 4 days, then was poured into 500 ml. of ice–water. The brown solid, 15.74 g. (109%), was collected and recrystallized from 180 ml. of absolute ethanol to give 6.83 g. (47.4%) of tan plates, m.p. 155–156°. A previous preparation gave a 50% yield of V, m.p. 156–157° (lit.,[4] m.p. 154–155°); $\lambda_{max(\mu)}^{Nujol}$ 8.49 (OSO_2), 12.25 (phenyl); there was no —OH absorption near 3.0 μ; $[\alpha]^{24}D$ +59° [lit.,[4] $[\alpha]^{20}D$ +57.2° (0.6% in chloroform)].

Methyl 4,6-O-Ethylidene-2-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (VI) and Methyl 3-O-Acetyl-4,6-O-ethylidene-2-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (VII).—To a stirred solution of 5.73 g. (26.0 mmoles) of the crude diol (IV) in 30 ml. of pyridine was added 7.30 g. (38.3 mmoles) of *p*-toluenesulfonyl chloride, the temperature being maintained at 20–25°. The solution was stirred for 20 hr. at room temperature, then was poured, with stirring, into 200 ml. of ice–water. The mixture was extracted with four 25-ml. portions of chloroform and the combined extracts were washed with 50 ml. of saturated aqueous sodium bicarbonate solution and with two 50-ml. portions of water, then dried over magnesium sulfate, simultaneously decolorizing with Norit. The chloroform solution was evaporated *in vacuo*, the last traces of pyridine being removed by evaporation with toluene to afford 9.90 g. (102%) of a brown sirup. The sirup was crystallized from 50 ml. of absolute ethanol, affording 2.53 g. (26%) of leaflets, m.p. 147–155°, which were recrystallized from ethanol to give 2.18 g. of solid ditosylate (V) m.p. 154–156°. The mother liquors were evaporated to give 6.03 g. of sirup which, after two recrystallizations from isopropyl alcohol, afforded 1.26 g. (13%) of the analytical sample of monotosylate (VI), m.p. 150–151°; $\lambda_{max(\mu)}^{Nujol}$ 2.91 (OH), 8.52 (OSO_2), 12.36 (phenyl); $[\alpha]^{23}D$ +91° (1% in methanol).

Anal. Calcd. for $C_{16}H_{22}O_8S$: C, 51.3; H, 5.92; S, 8.56. Found: C, 51.4; H, 6.04; S, 8.53.

In another run, 7.06 g. (32.0 mmoles) of the crude diol (IV) was converted to 9.85 g. (82%) of the crude monotosylate (VI), using the above procedure with 7.60 g. (39.9 mmoles) of *p*-toluenesulfonyl chloride. A stirred solution of 9.66 g. of the sirup in 25 ml. of pyridine was treated with 25 ml. of acetic anhydride and stirred at room temperature for 18 hr. while protected from atmospheric moisture, then was poured into 500 ml. of ice–water. The aqueous mixture was stirred at room temperature for 30 min. and the brown solid, 9.12 g. (85% from IV), was collected by filtration. Recrystallization from 65 ml. of absolute ethanol gave 5.15 g. (48%) of crystals, m.p. 155–171°, and two more recrystallizations from absolute ethanol afforded 3.53 g. (33%) of the analytical product, m.p. 169–171°; $\lambda_{max(\mu)}^{Nujol}$ 5.86 (C=O), 8.09 (C—O—C), 12.19 (phenyl); there was no —OH absorption near 3.0 μ; $[\alpha]^{23}D$ +76°.

Anal. Calcd. for $C_{18}H_{24}O_8S$: C, 51.9; H, 5.81; S, 7.70. Found: C, 51.9; H, 5.49; S, 7.63.

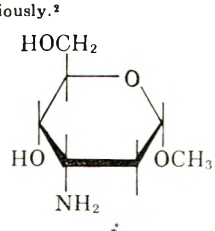
Methyl 2,3-Anhydro-4,6-O-ethylidene-α-D-allopyranoside (X).—A suspension of 20.0 g. (37.9 mmoles) of ditosylate (V), 6.00 g. (0.111 mmole) of sodium methoxide, and 300 ml. of methanol was heated at reflux for 18 hr. then cooled and filtered through Celite. The filtrate was diluted with 500 ml. of water, then extracted with two 300-ml. portions of chloroform. The combined extracts were washed with 300-ml. of water, dried over magnesium sulfate, and evaporated *in vacuo*. The white residue, 9.19 g., was sublimed at 80° and 0.7–0.9 mm., affording 5.01 g. (65.3%) of crystalline solid, m.p. 126–129° (lit.,[4] m.p. 125–126°); $\lambda_{max(\mu)}^{Nujol}$ 11.30 (epoxide). In a previous run, a melting point of 128–129° was obtained.

Methyl 2,3-Anhydro-4,6-O-ethylidene-α-D-mannopyranoside (IX).—A suspension of 1.29 g. (3.10 mmoles) of the acetate (VII), 0.34 g. (6.30 mmoles) of sodium methoxide, and 40 ml. of ethanol was heated at reflux for 18 hr. The cooled mixture was adjusted to pH 7 with glacial acetic acid, then evaporated *in vacuo* to give 1.48 g. of white solid. The solid was sublimed at 65° and 0.9 mm. to afford 0.54 g. (84%) of product, m.p. 98–100°. Recrystallization of the sublimate from 55 ml. of isopropyl alcohol gave a first crop of 0.41 g. (64%) of white needles, m.p. 100.0–100.5°, and a second crop of 0.05 g. (7.8%) of needles, m.p. 98.0–100.5°. The first crop was used as the analytical sample, and had $\lambda_{max(\mu)}^{Nujol}$ 11.16 (epoxide), $[\alpha]^{26}D$ + 108°.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.5; H, 6.98. Found: C, 53.4; H, 6.98.

On a large scale it was advantageous to partition the crude product between water and chloroform before the sublimation.

(11) M. J. Weiss, J. P. Joseph, H. M. Kissman, A. M. Small, R. E. Schaub, and F. J. McEvoy, *J. Am. Chem. Soc.*, **81**, 4050 (1959), reported on the anomalous overoxidation of aminofuranosides with periodate but found normal oxidant uptake with 2- and 3-aminopyranosides. However, J. B. Lee *J. Chem. Soc.*, 1474 (1960), reported on overoxidation with certain deoxyfuranosides and pyranosides and the combination of amino and deoxypyranosides in compounds XXXI and XXXIII may be responsible for the strange periodate results. However, compound *i*, which was reported in an earlier paper of this series[2] and which has the same general features as XXXI and XXXIII, was run as a control and took up precisely one mole of periodate as had been described previously.[2]



i

(12) Melting points are uncorrected and were obtained with the Fisher–Johns apparatus. The n.m.r. spectra were obtained using a Varian V-4311 spectrometer operated at 60 Mc. with samples dissolved in deuterium oxide and with tetramethylsilane as the reference standard. Optical rotations are for 1% solutions in chloroform unless otherwise noted.

Methyl 3-Benzylthio-3-deoxy-4,6-O-ethylidene-α-D-altropyranoside (VIII).—A solution of 8.00 g. (39.6 mmoles) of IX, 2.60 g. (48.2 mmoles) of sodium methoxide, 6.03 g. (48.5 mmoles) of benzyl mercaptan, and 200 ml. of methanol was stirred at reflux under nitrogen for 18 hr., cooled, and adjusted to pH 7 with glacial acetic acid, then poured into 400 ml. of ice–water. The product slowly solidified and was collected by filtration, washed with water and petroleum ether (b.p. 62–70°) and dried, affording 12.53 g. (97%) of solid. Recrystallization of the solid from 800 ml. of petroleum ether (b.p. 62–70°) gave 11.41 g. (89%) of product, m.p. 132–133°. From a previous run an analytical sample was obtained with m.p. 132.0–132.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.03 (OH), 14.00 (phenyl); $[\alpha]^{20}D$ −108°.

Anal. Calcd. for $C_{16}H_{22}O_5S$: C, 58.9; H, 6.80; S, 9.82. Found: C, 59.1; H, 6.51; S, 9.98.

Methyl 3(2)-Benzylthio-2(3)-chloro-2,3-dideoxy-4,6-O-ethylidene-α-D-altro(gluco)pyranoside (XII).—When 1.23 g. (3.77 mmoles) of VIII was treated with 2.8 g. (14.7 mmoles) of *p*-toluenesulfonyl chloride in 13 ml. of dry pyridine, initially at 0° for 1 hr., then at room temperature for 48 hr., 0.85 g. (*ca.* 65%) of sirupy product was isolated after a conventional work-up. The infrared spectrum showed no —OH absorption near 3.0 μ but did show some sulfonate ester absorption at 8.5 μ. Analysis verified the presence of some sulfonate ester.

Anal. Calcd. for $C_{16}H_{21}ClO_4S$ (XII): Cl, 10.28; S, 9.30. Found: Cl, 8.19; S, 9.98.

When the sulfonylation time was extended to 90 hr., an essentially quantitative yield of XII was isolated.

Anal. Calcd. for $C_{16}H_{21}ClO_4S$: C, 55.7; H, 6.14; Cl, 10.3; S, 9.30. Found: C, 56.8; H, 6.20; Cl, 10.6; S, 9.29.

Methyl 2-Azido-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-α-D-altropyranoside (XIII).—A stirred mixture of 11.9 g. (34.5 mmoles) of crude XII, 27 g. (0.42 mole) of sodium azide, and 300 ml. of 95:5 2-methoxyethanol–water was heated at 100–110° under nitrogen for 18 hr., then evaporated *in vacuo*. The residue was partitioned between dichloromethane and water to yield, after drying, decolorizing with Norit A, and evaporating, 12.1 g. of a partially crystalline sirup. Recrystallization of the crude product from 150 ml. of petroleum ether (b.p. 88–99°) gave 7.09 g. (58%) of crystalline solid, m.p. 137–138°. The analytical sample from another run had m.p. 137–138°; $\lambda_{max(\mu)}^{Nujol}$ 4.59, 4.70, and 4.78 (N_3); $[\alpha]^{28}D$ −99°.

Anal. Calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.7; H, 6.02; N, 12.9; S, 9.12. Found: C, 54.6; H, 6.09; N, 12.2; S, 9.30.

Methyl 2-Amino-3-mercapto-2,3-dideoxy-D-altropyranoside hydrochloride (II). Method A.—A solution of 2.00 g. (5.7 mmoles) of the azide (XIII) in 12 ml. of 1,2-dimethoxyethane was added dropwise, with stirring, to a solution of 0.80 g. (0.0348 g.-atom) of sodium in 35 ml. of liquid ammonia. The resulting mixture was stirred at reflux, with exclusion of moisture, for 30 min., then the blue color was discharged with excess solid ammonium chloride. The ammonia was evaporated under a nitrogen atmosphere, the residue was dissolved in 10 ml. of water, and the solution was adjusted to pH 7 with glacial acetic acid then extracted with two 20-ml. portions of dichloromethane while maintaining a nitrogen atmosphere. The combined extracts were washed with 17 ml. of water, decolorized with Norit A, and dried over magnesium sulfate. Evaporation of the dried extract afforded 0.68 g. of a yellow sirup whose infrared spectrum showed absorptions at 2.97 μ (NH_2) and 3.87 μ (SH). To the sirup was immediately added 3 ml. of ethanedithiol followed by 20 ml. of a 2% solution of hydrogen chloride in methanol, and the mixture was stirred at room temperature for 1 hr., then evaporated *in vacuo* to a semisolid residue which solidified when triturated with ether. The residue was reprecipitated from methanol–ether to yield 0.61 g. (44%) of cream-colored solid whose n.m.r. spectrum still showed some of the O-ethylidene methyl doublet centered at τ = 8.62. The solid was re-treated with methanolic hydrogen chloride and ethanedithiol at 50° for 5 hr., then worked up as before to give 0.49 g. (33% as the etherate) of solid, which had a wide decomposition range and showed essentially no ethylidene methyl resonance in the n.m.r. spectrum but which did show the ether C-methyl triplet centered at τ = 8.78. The analytical sample was dried *in vacuo* at 100°. On paper chromatography[13] in system A it gave a major spot with R_{Ad} 1.31 with some material staying at the origin.

Anal. Calcd. for $C_7H_{16}ClNO_4S \cdot 1/8(C_2H_5)_2O$: C, 35.3; H, 6.82; N, 5.49. Cl, 13.9; S, 12.6. Found: C, 35.6; H, 6.82; N, 5.53; Cl, 13.8; S, 12.8.

When deblocking of XVI was conducted in 2% methanolic hydrogen chloride at room temperature for 1 hr., the product (55% yield) was a hygroscopic solid, m.p. 124–146° dec.; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH weak), 4.92 and 6.25 ($NH_3^{\oplus}$); $[\alpha]^{27}D$ +27° (1% in methanol); it gave good elemental analyses for structure XIV and its n.m.r. spectrum showed the prominent S,O-ethylidene methyl doublet centered at τ = 8.36.

Anal. Calcd. for $C_{18}H_{38}Cl_2N_2O_9S_2$: C, 38.5; H, 6.82; N, 4.99; Cl, 12.6; S, 11.4. Found: C, 38.6; H, 6.71; N, 5.06; Cl, 12.5; S, 11.4.

Method B.—A solution of 0.44 g. (1.58 mmoles) of the blocked thiol (XXVIII) (see below) and 23 ml. of 5% methanolic hydrogen chloride was heated at reflux for 20 hr., then cooled and decolorized with Norit. The mixture was filtered and evaporated *in vacuo*, leaving a residue, which was washed with several portions of ether and evaporated again. The final residue, an orange foam, 0.46 g. (118%), was dissolved in 3 ml. of methanol and the solution treated with 5 ml. of a saturated solution of mercuric chloride in methanol. Water (about 15 ml.) was added to precipitate the mercaptide, which was collected by filtration. The gummy solid was suspended in methanol, and hydrogen sulfide was bubbled through the stirred mixture for 20 min. Filtration through Celite removed the mercuric sulfide, leaving a pale yellow filtrate, which was evaporated *in vacuo*. The resultant sirup was washed several times with ether and dried *in vacuo* to leave 0.10 g. (26% from XXVIII) of a hygroscopic, nitroprusside-positive, solid foam.

Anal. Calcd. for $C_7H_{16}ClNO_4S$: C, 34.2; H, 6.56; Cl, 14.4; N, 5.70. Found: C, 34.4; H, 6.84; Cl, 13.1; N, 5.32.

Methyl 2-Amino-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-α-D-altropyranoside (XV).—A mixture of 1.00 g. (2.84 mmoles) of XIII, 0.25 g. (6.6 mmoles) of sodium borohydride, and 10 ml. of isopropyl alochol was stirred at reflux for 16 hr., then evaporated *in vacuo*. The residue was partitioned between dichloromethane and water, and the organic phase, after washing with water and drying, was evaporated *in vacuo* to afford 0.89 g., (96%) of white solid. Recrystallization from petroleum ether (b.p. 88–99°) gave 0.67 g. (72%) of the analytical sample, m.p. 123–124°; $\lambda_{max(\mu)}^{Nujol}$ 3.00 and 3.05 (NH_2), weak; $[\alpha]^{25}D$ −106°.

Anal. Calcd. for $C_{16}H_{23}NO_4S$: C, 59.1; H, 7.12; N, 4.30; S, 9.85. Found: C, 59.1; H, 7.24; N, 4.31; S, 9.93.

Methyl 4,6-O-Benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside (XIX).—Compound XIX was prepared from XVIII,[8] using essentially the same conditions as in the preparation of VIII. The crude product (88%), m.p. 104–105°, was recrystallized from 60% aqueous ethanol to give the analytical sample, m.p. 105–106°; $\lambda_{max(\mu)}^{Nujol}$ 2.93 (OH); 13.28, 13.82, and 14.25 (phenyl); $[\alpha]^{31}D$ −108° [lit.,[10] m.p. 105–106°, $[\alpha]D$ −112°].

Anal. Calcd. for $C_{21}H_{24}O_5S$: C, 64.9; H, 6.23; S, 8.24. Found: C, 64.8; H, 6.10; S, 8.49.

Methyl 4,6-O-Benzylidene-3(2)-benzylthio-2(3)-chloro-2,3-dideoxy-α-D-altro(gluco)pyranoside (XX).—Compound XIX was converted to XX, using essentially the conditions described for the preparation of XII. The yield of orange sirup was slightly more than theoretical; the infrared spectrum showed no —OH absorption near 3.0 μ and essentially no sulfonate ester absorption at 8.5 μ.

Anal. Calcd. for $C_{21}H_{23}ClO_4S$: Cl, 8.72. Found: Cl, 9.15.

Reaction of XX with Sodium Azide.—A stirred mixture of 0.50 g. (1.23 mmoles) of the crude glycoside (XX), 0.85 g. (13.1 mmoles) of sodium azide, and 10 ml. of 2-methoxyethanol that contained 5% water was heated at reflux for 3 hr. in a nitrogen atmosphere, then evaporated *in vacuo*. The brown residue was partitioned between 40 ml. of water and 25 ml. of dichloromethane. The aqueous phase was extracted with two 10-ml. portions of dichloromethane and the combined dichloromethane solutions were washed with 15 ml. of saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Evaporation *in vacuo* left 0.53 g. (104%) of a tan solid, which was recrystallized once from 10 ml. of hexane and again from 5 ml. of hexane to yield 0.29 g. (57%) of pale yellow needles, m.p. 107–118°; $\lambda_{max(\mu)}^{Nujol}$ 4.73 (N_3), 13.19 and 14.31 (phenyl).

(13) Paper chromatography was run by the descending technique on Whatman no. 1 paper using the following solvent systems: A, isopropyl alcohol–2 *N* hydrochloric acid (65:35); B, *n*-butylalcohol–water; and C, *n*-butyl alcohol–acetic acid–water (4:1:5). Spots were detected with the sodium azide–iodine spray[14] and were located relative to adenine (R_f adenine = 1.00).

(14) E. Chargaff, C. Levine, and C. Green, *J. Biol. Chem.*, **175**, 67 (1948).

Anal. Calcd. for $C_{21}H_{23}N_3O_4S$: C, 61.0; H, 5.61; N, 10.2. Found: C, 61.4; H, 5.63; N, 9.22.

Subsequent work showed that the above sample contained an appreciable quantity (*ca.* 18%) of a chlorobenzylthio glycoside.

Methyl 2-Amino-4,6-O-benzylidene-3-benzylthio-2,3-dideoxy-α-D-altropyranoside (XXI) and Methyl 4,6-Benzylidene-2-benzylthio-3-chloro-2,3-dideoxy-α-D-glucopyranoside (XXV).—A stirred mixture of 5.00 g. (12.1 mmoles) of the crude azido glycoside (XXIV), 1.00 g. (26.3 mmoles) of lithium aluminum hydride, and 200 ml. of dry ether was heated at reflux for 17 hr. Absolute ethanol (4 ml.) was added dropwise to the cooled solution, followed by 100 ml. of 2 *M* aqueous sodium hydroxide. The mixture was stirred for 0.5 hr., then let stand until the inorganic salts had settled. The ether layer was decanted and the remaining mixture was filtered through Celite, the filter pad being washed well with ether. The layers of the filtrate were separated and the ether layer was combined with the ether reaction solution. The ethereal solution was washed with 50 ml. of water, then dried over magnesium sulfate. Evaporation *in vacuo* left 3.23 g. (69%) of a white solid, which was recrystallized from 150 ml. of heptane to yield 1.99 g. (42%) of white needles, m.p. 137–140°.

From a previous reaction an analytical sample was obtained that had m.p. 137–139°; $\lambda_{max(\mu)}^{Nujol}$ 3.01, 3.05, 3.09, 6.25 (NH_2); $[\alpha]^{24}D$ −86°.

Anal. Calcd. for $C_{21}H_{25}NO_4S$: C, 65.1; H, 6.50; S, 8.27. Found: C, 65.4; H, 6.66; S, 8.30.

The mother liquors from the separation of XXI were evaporated to dryness to yield 1.09 g. of solid, m.p. 95–115°. One recrystallization from 20 ml. of absolute ethanol yielded 0.40 g. (8.5%) of white solid, m.p. 135–150°. Three more recrystallizations from hexane afforded 0.18 g. (3.8%) of XXV as white needles, m.p. 154–156°; $\lambda_{max(\mu)}^{Nujol}$ 13.20, 14.08 and 14.35 (phenyl); there was no OH or NH_2 absorption at 3.0 μ; $[\alpha]^{24}D$ −106°.

Anal. Calcd. for $C_{21}H_{23}ClO_4S$: C, 62.0; H, 5.70; Cl, 8.72; S, 7.88. Found: C, 62.3; H, 5.86; Cl, 8.93; S, 7.90.

The amine (XXI) was also prepared by hydrolysis of the amide XXII (see below) with potassium hydroxide in aqueous 2-methoxyethanol; the product had m.p. 139–140° and an infrared spectrum identical to that of the amine from XXIV.

Methyl 3-Acetamido-4,6-O-benzylidene-2-benzylthio-2,3-dideoxy-α-D-glucopyranoside (XXIII) and Methyl 2-Acetamido-4,6-O-benzylidene-3-benzylthio-2,3-dideoxy-α-D-altropyranoside (XXII).—The crude mixed amine (XXI) 12.8 g., containing some XXV, was mixed with 80 ml. of acetic anhydride and 12 g. of anhydrous sodium acetate and stirred at 50° for 3 hr., then poured into 1 l. of ice water. The solid was collected and recrystallized from acetonitrile to afford 11.3 g. (80%) of material, m.p. 180–190°. The product was dissolved in 1500 ml. of 95% ethanol and chilled, yielding 2.7 g. (19%) of XXIII, m.p. 297–301° dec., $[\alpha]^{28}D$ −29° (1% in N,N-dimethylformamide). The infrared spectrum showed the same functional groups as that of XXII (see below), but the absorptions were somewhat displaced and of different intensities.

Anal. Calcd. for $C_{23}H_{27}NO_5S$: C, 64.3; H, 6.34; N, 3.26; S, 7.46. Found: C, 64.9; H, 6.51; N, 3.30; S, 7.66.

The filtrate from XXIII was evaporated *in vacuo* and the residue was recrystallized from 200 ml. of ethanol to give 5.7 g. (40%) of solid, m.p. 196–198°, and a second crop, 2.3 g. (16%), m.p. 185–195. The analytical sample, obtained in a previous run had m.p. 197–198°; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (NH), 5.94 (amide C=O), 13.10 and 14.25 (phenyl); $[\alpha]^{27}D$ −38° (1% in N,N-dimethylformamide) and $[\alpha]^{27}D$ −20°.

Anal. Found: C, 64.8; H, 6.08; N, 3.64; S, 7.45.

Methyl 2-Acetamido-3-benzylthio-2,3-dideoxy-D-altropyranoside (XXVI).—A suspension of 0.91 g. (2.12 mmoles) of the blocked glycoside (XXII), 5.1 g. of Amberlite IR-120(H) resin, and 35 ml. of 90% aqueous methanol was stirred at 50° for 18 hr., then filtered through Celite. The filtrate was evaporated *in vacuo* and the residue washed with several portions of hot petroleum ether (b.p. 62–70°) to leave 0.69 g. (95%) of tan foam; $\lambda_{max(\mu)}^{film}$ 2.90–3.08 (NH, OH), 6.02 (amide C=O), 13.0 and 14.2 (phenyl).

Methyl 2-Acetamido-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-D-altropyranoside (XXVII).—A mixture of 4.7 g. (13.8 mmoles) of the crude glycoside (XXVI), 20 ml. of 1,1-dimethoxyethane, and 0.10 ml. of concd. sulfuric acid was stirred at room temperature for 65 hr., while protected against atmospheric moisture. Dichloromethane (100 ml.) was added and the solution was washed with 40 ml. of saturated aqueous sodium bicarbonate solution, then with two 40-ml. portions of water. After being dried over magnesium sulfate and filtered, the solution was evaporated *in vacuo*, affording 4.81 g. (95%) of a pale yellow, viscous sirup; $\lambda_{max(\mu)}^{film}$ 3.05 (NH), 6.02 (amide C=O), 13.0 and 14.2 (phenyl); $[\alpha]^{25}D$ −81° (1% in methanol).

Anal. Calcd. for $C_{18}H_{25}NO_5S$: C, 58.8; H, 6.86; N, 3.81; S, 8.72. Found: C, 58.6; H, 6.90; N, 3.60; S, 8.40.

From another preparation, run only 21 hr., 1.02 g. (94%) of crude product was obtained as a yellow sirup. This material partially solidified on standing and was recrystallized from petroleum ether (b.p. 88–99°) to give 0.23 g. of solid, then recrystallized again from petroleum ether (b.p. 88–98°), yielding 0.10 g. of crystalline material, m.p. 110–121°. Two more recrystallizations from petroleum ether (b.p. 88–99°) gave 0.05 g. of probably quite pure α-anomer, m.p. 120–135°, $[\alpha]^{25}D$ +200° (0.7% in methanol).

Anal. Found: C, 58.6; H, 7.05; N, 3.58; S, 8.75.

Methyl 2-Acetamido-2,3-dideoxy-4,6-O-ethylidene-3-mercapto-D-altopyranoside (XXVIII).—To a solution of 0.61 g. (26.5 mg.-atoms) of clean, dry sodium in 20 ml. of dry liquid ammonia was added, dropwise and with stirring, 1.19 g. (3.23 mmoles) of the sirupy, but analytically pure, glycoside (XXVII) dissolved in 5 ml. of 1,2-dimethoxyethane. When the addition was complete, the mixture was stirred for 30 min., then the excess sodium was decomposed by the cautious addition of solid ammonium chloride. Ammonia was slowly evaporated from the white mixture, then the residue was dissolved in 20 ml. of water and the solution adjusted to pH 6–7 with glacial acetic acid. The aqueous solution was extracted with two 15-ml. portions of dichloromethane, the combined extracts were washed with 20 ml. of water, then dried over magnesium sulfate, and, after filtration, evaporated *in vacuo*, giving 0.72 g. (80%) of a pale yellow, crystalline, nitroprusside-positive solid. The solid was recrystallized from 6 ml. of isopropyl alcohol to give 0.09 g. of white crystals, m.p. 130–132°, and a second crop of 0.23 g. of product, m.p. 130–132°, but containing a small amount of material, probably disulfide, which remained unmelted at 200°. The first crop of solid was recrystallized from benzene, affording 0.05 g. of product, m.p. 129–132°; $\lambda_{max(\mu)}^{Nujol}$ 3.05 (NH), 3.85 (SH), 6.06 (amide C=O); there was essentially no phenyl absorption at 13.0 and 14.2 μ; $[\alpha]^{27}D$ +72° (1% in methanol).

Anal. Calcd. for $C_{11}H_{19}NO_5S$: C, 47.6; H, 6.91; N, 5.05; S, 11.6. Found: C, 47.9; H, 6.99; N, 5.01; S, 11.7.

From a similar reduction of 2.73 g. of XXVII was obtained 1.79 g. (87%) of crude thiol (XXVIII), m.p. 105–131°, $[\alpha]^{33}D$ +60° (1% in methanol). The material was homogeneous on paper chromatography[13] in solvent systems B and C, with R_{Ad} 3.55 and 1.79, respectively, the spots also being detectable with ultraviolet light.

Anal. Found: C, 47.4; H, 6.74; N, 4.81; S, 10.4, 11.0.

Metyl 3-Acetamido-2,3-dideoxy-α-D-glucopyranoside (XXXII).—A mixture of 1.50 g. of the amide (XXIII), *ca.* 20 g. of Raney nickel[15] (washed thoroughly with dioxane to replace the water), and 90 ml. of dioxane was stirred at reflux for 6 hr., then filtered through Celite and evaporated *in vacuo*. The residue was a viscous sirup, 0.85 g. (110%), which crystallized on standing. The material was recrystallized by dissolving it in a large volume of dichloromethane, filtering the solution, and concentrating the filtrate to a small volume. The chilled solution deposited material of analytical purity, m.p. 132–135°; $\lambda_{max(\mu)}^{Nujol}$ 3.00, 3.10 (NH, OH), 6.10 (amide C=O); no phenyl absorption in the 14–15-μ region.

Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.2; H, 8.01; N, 6.31.

Methyl 3-Amino-2,3-dideoxy-D-glucopyranoside hydrochloride (XXXIII).—A solution of 0.300 g. of XXXII in 40 ml. of saturated methanolic hydrogen chloride was heated at reflux with exclusion of moisture for 20 hr., then filtered and evaporated *in vacuo*, finally at 60° and 1 mm., leaving 0.20 g. (69%) of a yellow foam. The residue was dissolved in 20 ml. of methanol, the solution filtered, and the salt precipitated by the addition of excess ether. The very hygroscopic solid was collected by centrifugation and was washed with ether by centrifuging and decanting. It had $\lambda_{max(\mu)}^{Nujol}$ 3.0 (OH), 4.95, 6.23 ($NH_3^{\oplus}$).

Anal. Calcd. for $C_7H_{16}ClNO_4$: C, 39.4; H, 7.55; N, 6.56. Found: C, 39.4; H, 7.67; N, 6.61.

On titration with periodate, the product showed the consumption of 1.68 moles/mole after 1 hr., 1.81 moles/mole after

(15) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

3 hr., 1.94 moles/mole after 6 hr., and 2.33 moles/mole after 24 hr.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-α-D-mannopyranoside (XXIX).—The blocked amide (XXII), 2.54 g. (5.91 mmoles), was desulfurized with 25 g. of Raney nickel[15] according to the procedure described for the preparation of XXXII. The residue was extracted with hot petroleum ether (b.p. 88–91°) and the insoluble portion was partitioned between 15 ml. of benzene and 15 ml. of water. The aqueous extract was evaporated *in vacuo*, affording 0.96 g. of a colorless sirup (XXX) whose infrared spectrum showed the amide carbonyl at 6.02 μ and essentially no phenyl absorption in the 13–14.5-μ region.

The methanolysis of 0.74 g. of crude XXX, carried out as described for the preparation of XXXIII, gave 0.29 g. of the very hygroscopic salt (XXXI) which showed essentially no unfiltered amide absorption.

Anal. Calcd. for $C_7H_{16}ClNO_4$: C, 39.4; H, 7.55; N, 6.56; Cl, 16.6. Found: C, 39.2; H, 8.27; N, 5.66; Cl, 14.7.

On titration with periodate, the product showed the consumption of 0.74 mole/mole after 1 hr. and 3 hr., 0.81 mole/mole after 6 hr., and 1.12 moles/mole after 24 hr.

The benzene extract from the XXII desulfurization residue was evaporated *in vacuo* affording 0.63 g. of a white foam which was crystallized from isopropyl alcohol–petroleum ether (b.p. 30–60°) to give 0.24 g. of white needles, m.p. 162–173°. Two recrystallizations from ethyl acetate–petroleum ether (30–60°) yielded 0.15 g. of the analytical sample of XXIX, m.p. 169–171°; $\lambda_{max(\mu)}^{Nujol}$ 3.07 (NH), 6.10 (amide C=O).

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.5; H, 6.88; N, 4.56. Found: C, 63.1, H, 7.29; H, 4.47.

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The Reaction of 9-Chloro-*trans*-1-decalone with Methoxide Ion[1]

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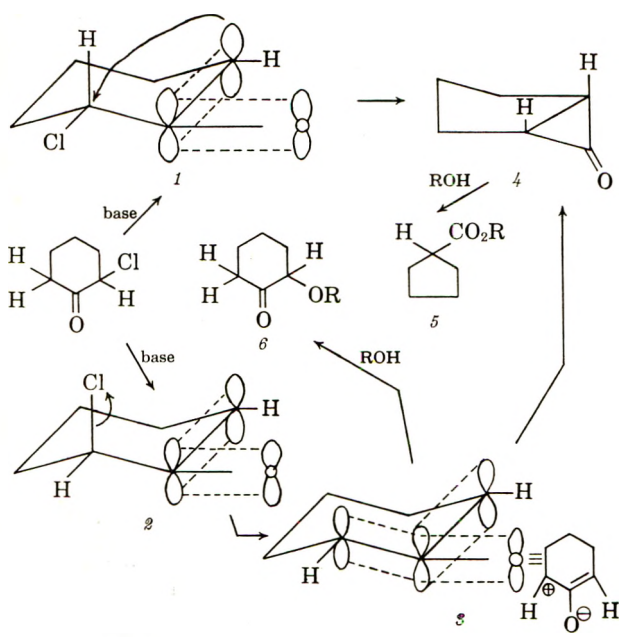
The reaction of 9-chloro-*trans*-1-decalone (**12**) with methanolic sodium methoxide yielded as the major products a mixture of 9-methoxy-*trans*-1-decalone (**14**), 9-methoxy-*cis*-1-decalone (**13**), and 2-methoxy-*trans*-1-decalone (**15**). The relationship of this reaction to the Favorskii rearrangement is discussed.

Previous studies of the Favorskii rearrangement[2] suggested that the reaction of α-halo ketones with bases to remove an α′-hydrogen atom could be followed either by an intramolecular S_N2 displacement (as in **1**) with inversion of configuration at the α-carbon atom[3] or by loss of halide ion (as in **2**) to form a zwitterionic intermediate **3** Although intervention of an intermediate such as **3** did not preclude a subsequent nonstereospecific Favorskii rearrangement—*e.g.*, the formation of **5**—in cases previously studied,[2a] it was clear that conditions favoring this intermediate **3** also favored the formation of solvolysis products such as **6**. In considering the applicability of these observations to the α-halocyclohexanone system, we have been led to the hypothesis that in order to maintain continuous *pi* orbital overlap the ionization **2** should be favored by an axial halogen atom and the displacement **1** should be favored by an equatorial halogen atom. Thus, the ionization process **2** should be enhanced not only by an increase in solvent polarity,[2a] but also by the presence of a halogen atom fixed in an axial conformation. Support for this idea is found in the reaction of several 9-α-halo-11-keto steroids (partial structure **7** necessarily containing an axial halogen atom) with alcoholic bases to yield 12-α-alkoxy ketones **8** rather than Favorskii rearrangement products.[4] The corresponding reaction with a 5-α-halo-6-keto steroid (partial structure **9**) was also reported to yield not a Favorskii product, but rather the 5-β-hydroxy ketone **10**.[5] The reported[3,6] failure of 2-chloro-2-methylcyclohexanone (**11**) to undergo a Favorskii rearrangement, only 2-hydroxy-2-methylcyclohexanone being isolated, may well be attributable to the same stereoelectronic effect since in this ketone both conformational factors[7] and dipole repulsion between the C=O bond and the C—Cl bond should favor the conformation **11** containing an axial chlorine atom.



(1) This research has been supported in part by a research grant from the Solvay Process Division of the Allied Chemical Corp. and in part by grant no. 594-A from the Petroleum Research Fund.

(2) (a) See H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961), and references cited therein, particularly (b) R. B. Loftfield, *ibid.*, **73**, 4707 (1951), and (c) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).

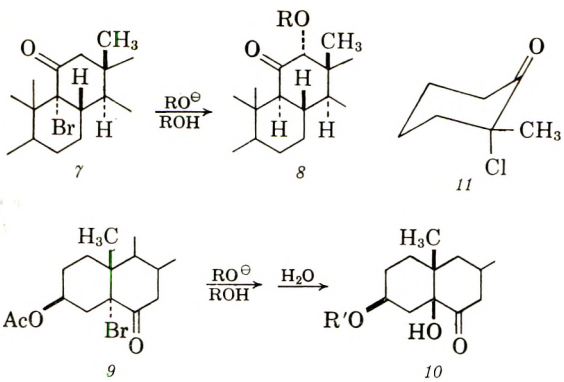
(3) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).

(4) (a) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960); (b) P. A. Diassi and R. M. Palmere, *J. Org. Chem.*, **26**, 5240 (1961).

(5) A. T. Rowland, *ibid.*, **27**, 1135 (1962). This product is suggested to arise from an intermediate epoxy ether (see ref. 6a).

(6) (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) M. Mousseron, F. Winternitz, and R. Jacquier, *Bull. soc. chim. France*, [5] **14**, 83 (1947).

(7) The free-energy differences between axial and equatorial conformations of a chlorine atom and a methyl group are 0.3 to 0.5 kcal./mole and 1.5 to 1.9 kcal./mole, respectively. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.



Although one might be tempted to conclude from these data that the energy barriers[2c] associated with the displacement process **1** or with the transformation **3** → **4** in a cyclohexanone system are so large that formation of the bicyclo[3.1.0] system **4** and, subsequently, the Favorskii product **5** is prohibited, this conclusion is clearly not valid since certain α-halocyclohexanones[2b] do yield Favorskii rearrangement products. Furthermore, the rearrangement of piperitone oxide[2a] to form Favorskii products in either a stereospecific or a nonstereospecific manner depending on reaction conditions indicates that the energy of neither transformation **1** → **4** nor **3** → **4** is prohibitively high. However, the aforementioned studies of the systems **7**, **9**, and **11** do suggest that reaction of the intermediate **3** with solvent (to form **6**) is more favorable than closure to the strained bicyclic system **4**. Since other structural features present in **7** and **9** might be imagined to hinder formation of a cyclopropanone and since the material balances reported from reactions of **7**, **9** and **11** certainly did not exclude the formation of substantial amounts of other products, it seemed advisable to investigate this question further. For this purpose we have studied the reaction of methanolic sodium methoxide with 9-chloro-*trans*-1-decalone (**12**),[8] a ketone possessing an unambiguously axial α-halogen atom with a minimum of structural complexity.

The results of this study (Chart I) indicate that primarily solvolysis products **13**, **14**, and **15** (the latter is not necessarily a kinetically controlled product) are formed from the chloro ketone **12** under conditions which afford good yields of Favorskii products from acyclic tertiary α-chloro ketones[2a] in a nonstereospecific rearrangement. These results are most readily explained by supposing that the zwittereonic intermediate (as in **3**) formed from ketone **12**, either because of the strain associated with closure to a bicyclo[3.1.0] system (as in **4**) or because of steric accessibility to attack by solvent, undergoes primarily reaction with solvent whereas the previously studied[2a] acyclic and conformationally mobile analog of **3** yields primarily a mixture of stereoisomeric cyclopropanones and, subsequently, Favorskii products.

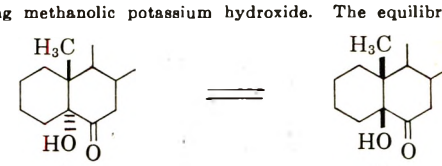
In order to learn whether formation of the enolate anion—*e.g.*, **2**—was much more rapid than loss of chloride ion—*e.g.*, **3**— the reaction was run to partial completion in methanol-d_1. Since the chloro ketone **12** recovered contained no appreciable enrichment in deuterium, we conclude that the formation of the enolate anion is either rate-determining or at least comparable in rate with the subsequent loss of chloride ion. In accord with our tentative conclusion[2] that chloride ion is lost from the enolate anion—*e.g.*, **2**—rather than from the free enol (the conjugate acid of **2**) is the fact that the chloro ketone **12** reacts more slowly in methanol solution in the absence of base; in the presence of added acid the reaction is also slower and product mixtures of different composition are formed. However, these observations by no means rigorously exclude the intermediacy of the enol. Since the 9-methoxy ketones **13** and **14** constitute the major fraction of the product mixture, the suggestion of Cox[4a] that an SN2 reaction—*i.e.*, **16**—may account for the reaction forming an alkoxy ketone is inappropriate for the chloro ketone **12**. As noted previously,[2] we see no compelling reason to invoke the explanation in other cases. The possible formation of the 9-methoxy ketone **13** (inversion at C-9) by an SN2 reaction between the chloro ketone **12** and methoxide ion appears most improbable in view of the tertiary nature of this alkyl chloride.

The stereochemical relationships between the various methoxy ketones were established by the reactions summarized in Chart I. The stereochemical assignments for the 9-substituted decalones **13**, **14**, **18**, and **19** follow both from the various spectra of these products (see Experimental) and from the equilibration of the two hydroxy ketones **18** and **19** (presumably *via* intermediate **20**) indicating that the *cis* isomer **18** and the *trans* isomer **19** are of comparable stability.[9] The structure of the epimeric 2-methoxy-1-decalones **15** and **17** follow from their spectral properties (see Experimental) and from a demonstration that only two hydrogen atoms are replaced by deuterium when the ketones **15** and **17** are treated with methanol-d_1 and base. The stereochemical assignments are based on the fact that base-catalyzed equilibration of either compound produces a mixture in which **15** (with a *trans*-decalin ring fusion and an equatorial substituent) and the ketone **17** (with a *trans*-decalin ring fusion and an axial substituent) are the predominate components with **15** being more stable than **17**.

In view of the fact that no appreciable quantity of either of the hydroxy ketones **18** and **19** was formed from the chloro ketone **12**, we were led to consider what factor might account for the apparently very different behavior[5] of the bromo ketone **9** (which gave the hydroxy ketone **10** as the only isolated product). Since our previous studies[2] indicated that the slight changes in reaction conditions (potassium hydroxide in methanol, sodium ethoxide in ethanol) almost certainly were not responsible for this differ-

(8) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).

(9) Y. Mazur and M. Nussim, *Tetrahedron Letters*, No. **22**, 817 (1961). In this study α- and β-5-hydroxy-6-keto steroids (**i** and **ii**) were equilibrated in refluxing methanolic potassium hydroxide. The equilibrium mixture



contained 92% of the *cis* isomer **ii**, the increased stability of the *cis* isomer being attributed to formation of a strong hydrogen bond. In our series **18** and **19**, the relative stability of the *cis* isomer (54–67% at equilibrium) is less overwhelming. This result is not unexpected, since the angular methyl group present in **i** and **ii** reduces the difference in energy between the *cis*- and *trans*-decalin systems present (see ref. 7).

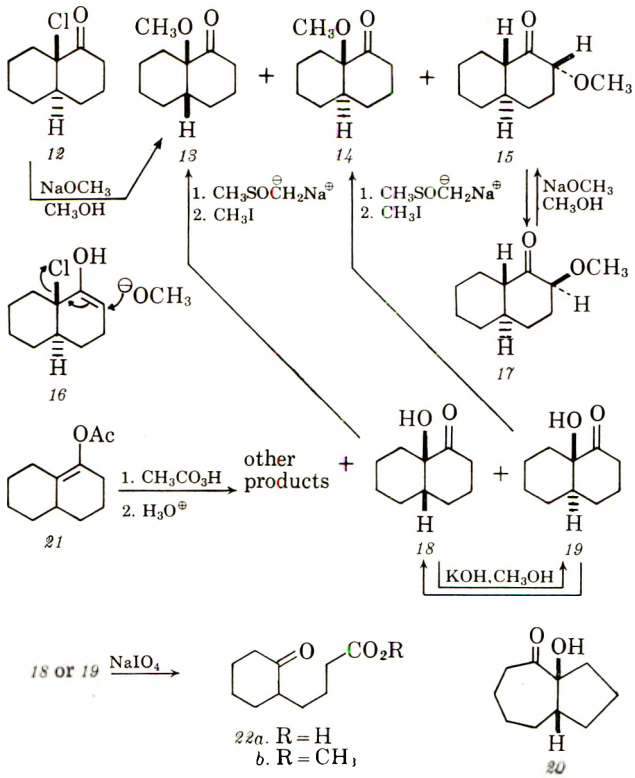
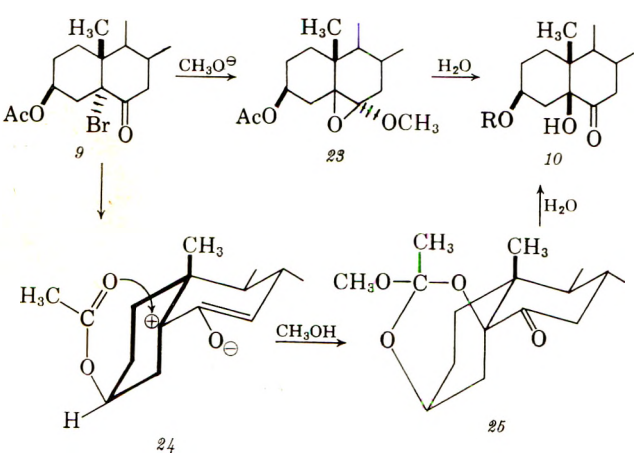


Chart I

ence, the most reasonable explanation appeared to lie in the presence of some structural feature present in **9** but not **12**. Rowland had argued[5] that the bromo ketone **9** was first coverted to the epoxy ether **23**[6a] and subsequently during the isolation process to the hydroxy ketone **10**. The fact that the 5β-hydroxy compound **10** was isolated was offered as stereochemical evidence for this reaction path. However, the finding[9] that the reaction conditions employed might suffice to interconvert the 5α- and 5β-hydroxy compounds renders this stereochemical evidence equivocal at best. Furthermore, we have been unable to discern any reason why the sequence **9** → **23** → **10** should be substantially more important with the ketone **9** than with the ketone **12**. We are, therefore, led to the conclusion that the differing behavior of the bromo ketone **9** is to be attributed to the presence of the 3β-acetoxyl function and suggest the reaction path **9** → **24** **25** → **10** in which the intermediate zwitterion **24** reacts intramolecularly with the acetoxy function more rapidly than it is attacked by solvent.



Experimental[10]

Reaction of 9-Chloro-*trans*-1-decalone (12) with Sodium Methoxide.—To a solution of sodium methoxide, prepared from 700 mg. (30.5 mg.-atoms) of sodium and 35 ml. of methanol, was added 999.5 mg. (5.38 mmoles) of 9-chloro-*trans*-1-decalone,[8] m.p. 39.5–41.5°. The solution, from which sodium chloride began to separate after a few seconds, was allowed to stand at room temperature for 12 hr. and then diluted with water and extracted with an ether–petroleum ether mixture. After concentration of the organic extract, the residual liquid (*ca.* 1 g.) was found to contain,[11] in order of elution, the *trans*-9-methoxy ketone **14** (30%), the *cis*-9-methoxy ketone **13** (27%), and the 2-methoxy ketone **15** (25%) as well as a number of minor components. Each of the three major components was collected[11] and redistilled in a short-path still. The *trans*-9-methoxy ketone **14**, b.p. 65–75° (0.65 mm.) $n^{25}D$ 1.4818, m.p. 23°, has infrared absorption[12] at 1713 cm.$^{-1}$ (C=O), an ultraviolet maximum[13] at 305.5 mμ (ε 40) and n.m.r. absorption[12] at 6.95 τ (singlet, 3H, O—CH_3) with complex absorption in the region 7.0–9.0 τ and no absorption at lower field than 6.8 τ.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt., 182. Found: C, 72.41; H, 10.01; mol. wt., 182 (mass spectrum).

The *cis*-9-methoxy ketone **13**, b.p. 65–75° (0.65 mm.), $n^{25}D$ 1.4851, m.p. 20°, has infrared absorption[12] at 1710 cm.$^{-1}$ (C=O), an ultraviolet maximum[13] at 301 mμ (ε 33) and n.m.r. absorption[12] at 6.91 τ (singlet, 3H, OCH_3) with complex absorption in the region 7.0 to 9.0 τ and no absorption at lower field than 6.8 τ.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt. 182. Found: C, 72.66; H, 9.98; mol. wt., 182 (mass spectrum).

Attempts to collect the 2-methoxy ketone **15** at relatively high column temperatures resulted in partial epimerization of ketone **15** to ketone **17**. Each of these two products was collected[11] at sufficiently low temperature to prevent epimerization and then distilled in a short-path still. The 2-methoxy ketone **15** (eluted second), b.p. 80–95° (0.55 mm.), m.p. 45–47°, has infrared absorption[12] at 1724 cm.$^{-1}$ (C=O). The ultraviolet absorption was obscured by the presence of traces of octalones (<2%) which we were unable to remove. The product has n.m.r. absorption[11] at 6.42 τ (1H, multiplet with splitting pattern not discernible but with a half-band width of approximately 20 c.p.s. as expected for an axial proton, $\diagdown$CH—O$\diagup$) and at 6.66 τ (3H, singlet, CH_3O) with complex absorption in the region 7.5 to 9.0 τ.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt., 182. Found: C, 72.50; H, 9.87; mol. wt., 182 (mass spectrum).

The 2-methoxy ketone **17** (first eluted), b.p. 70–85° (0.6 mm.), has infrared absorption[12] at 1715 cm.$^{-1}$ (C=O), an ultraviolet maximum[13] at 304.5 mμ (ε 50) and n.m.r. absorption[12] at 6.64 τ (1H, multiplet, splitting pattern not discernible but with a half-band width of approximately 5 c.p.s. as expected for an equatorial proton, $\diagdown$CH—O$\diagup$) and at 6.78 τ (3H, singlet, CH_3O) with complex absorption in the region 7.5 to 9.0 τ.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt., 182. Found: C, 72.41; H, 9.88; mol. wt., 182 (mass spectrum).

A solution of each of the pure 2-methoxy ketones **15** and **17** in methanolic sodium methoxide was refluxed for 10 hr. under nitrogen and then the neutral material was recovered in the usual way. Analysis[11] of each crude product indicated the

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) A gas chromatography column packed with Dow Corning silicone fluid, no. 710, suspended on ground firebrick was employed for this separation.

(12) Determined in carbon tetrachloride solution.

(13) Determined in 95% ethanol solution.

presence of 68% of the 2-methoxy ketone **15**, 11% of the 2-methoxy ketone **17** and 22% of a mixture of other components. A solution of 0.035 ml. of a mixture of the methoxy ketones **15** and **17** in methanolic sodium methoxide, prepared from 30 mg. (1.3 mg.-atoms) of sodium and 2.25 ml. of methanol-d_1, was refluxed under nitrogen for 10 hr. and then mixed with 15 ml. of deuterium oxide and 135 mg. (1.3 mmoles) of acetic anhydride (the pH of the final solution was 5–6). After the mixture had been extracted with an ether–petroleum ether mixture, the extract was concentrated. A sample of the 2-methoxy ketone **15**, collected,[11] and analyzed by mass spectrometry, was found to contain 8% d_0 species, 40% d_1 species, 52% d_2 species, and $<1\%$ d_3 species.

In subsequent reactions of the 9-chlorodecalone **12** with methanolic sodium methoxide run as previously described, the reaction was found to be complete in less than 1 min. at room temperature. A solution of 50.3 mg. (0.27 mmole) of the chloro ketone **12** in methanolic sodium methoxide, prepared from 20 mg. (0.87 mg.-atom) of sodium and 4.6 ml. of methanol-d_1, was swirled for 30 sec. and then quenched by the addition of a solution of 74 mg. (0.70 mmole) of acetic anhydride in 15 ml. of deuterium oxide. The crude organic product, recovered in the usual way, was found to contain 35% of the starting chloro ketone **12** as well as the methoxy decalones **13** (20%), **14** (21%), and **15** (7%). A sample of the chloro ketone **12** collected[11] from the mixture was found by mass spectrometric analysis to contain less than 5% of deuterium-containing species. After a solution of 100 mg. of the chloro ketone **12** and 10 mg. of *p*-toluenesulfonic acid in 3 ml. of methanol had been refluxed under nitrogen for 1 hr., the recovered product contained[11] a mixture of the unchanged chloro ketone (28%) and a component tentatively identified as $\Delta^{9,10}$-octal-1-one[8] (63%). After a mixture of 93.3 mg. (0.5 mmole) of the chloro ketone **12**, 240 mg. (2.86 mmoles) of sodium bicarbonate and 3.5 ml. of methanol had been stirred at room temperature for 96 hr., the recovered organic product contained[11] the unchanged chloro ketone **12** (66%) and the methoxy ketones **13** (10%), **14** (11%), and **15** (4%).

The 9-Hydroxy-1-decalones 18 and 19.—After a sample of 1-acetoxy-$\Delta^{1,9}$-octalin (**21**) had been converted to a mixture of octalones and accompanying by-products as previously described,[8] the $\Delta^{8,9}$-octal-1-one was separated from the mixture by extraction with pyrrolidine[14] and residual material was separated from lower boiling components and then chromatographed on Woelm, activity no. 3, alumina. The later fractions from the chromatograph, eluted with ether–hexane mixtures, contained[11] mixtures of the hydroxy ketones **18** and **19**. The minor component, *cis*-9-hydroxy-1-decalone (**18**, the first isomer eluted from the gas chromatograph), was collected and recrystallized from petroleum ether to separate the pure hydroxy ketone **18** as white prisms, m.p. 61–64°, identified with the previously described[8] sample, m.p. 62.5–63.5° by a mixed melting-point determination and comparison of infrared spectra. The product, which has an ultraviolet maximum[13] at 287.5 mμ (ϵ 34.5) and infrared absorption[12] at 3485 cm.$^{-1}$ (assoc. O—H) and 1708 cm.$^{-1}$ (C=O), shows evidence of intramolecular hydrogen bonding, consistent with the assigned stereochemistry,[9] since the band at 3485 cm.$^{-1}$, attributable to an associated hydroxyl function, is not replaced by a band at higher frequency as the solution is diluted.[15] The n.m.r. spectrum[16] of the material has a singlet at 6.09 τ (6.33 τ in carbon tetrachloride, 1H, O—H) and complex absorption in the region 7.2 to 9.0 τ.

The major component from the alumina chromatograph, *trans*-9-hydroxy-1-decalone (**19**, eluted second from the gas chromatograph) was isolated by fractional crystallization from pentane as white crystals, m.p. 38–44.5°. Sublimation (60–75° at 0.65 mm.) raised the melting point to 44–45°. The product has an ultraviolet maximum[13] at 300 mμ (ϵ 32.6) with infrared bands[12] at 3610 cm.$^{-1}$ (unassoc. O—H), at 3490 cm.$^{-1}$ (assoc. O—H), and at 1705 cm.$^{-1}$ (C=O). As the solution is diluted the relative intensity of the peak[15] at 3610 cm.$^{-1}$ increases indicating the lack of favorable geometry for intramolecular hydrogen bond formation.[9] The n.m.r. spectrum[16] has a singlet at 6.97 τ (O—H) superimposed on a multiplet in the region 6.9 to 7.2 τ (possibly the axial proton at C-2)[17] and complex absorption in the region 7.7 to 9.0 τ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; mol. wt., 168. Found: C, 71.21; H, 9.77; mol. wt., 168 (mass spectrum).

After a solution of 47.9 mg. of the *trans*-hydroxy ketone **19** in methanolic sodium methoxide, prepared from 208 mg. of sodium and 5 ml. of methanol, had been refluxed under nitrogen for 24.5 hr, the product was isolated in the usual way. The product mixture contained[11] 62% of the *trans* isomer **19** and 38% of the *cis* isomer **18**. A collected[11] sample of the *cis* isomer was identified both from its retention time and from its infrared spectrum. From a comparable reaction in which a solution of the *trans*-9-hydroxy ketone **19** in 17% methanolic potassium hydroxide was refluxed for 21.5 hr., the resulting mixture of 9-hydroxy ketones contained 46% of the *trans* isomer **19** and 54% of the *cis* isomer **18**. An equilibration starting with the pure *cis* isomer **18** afforded a mixture containing 33% of the *trans* isomer **19** and 67% of the *cis* isomer **18**. Because of competing side reactions more complete equilibrations of the hydroxy ketones **18** and **19** were not practical.

A solution of 100 mg. (0.595 mmole) of the *cis*-hydroxy ketone **18** and 160 mg. (0.75 mmole) of sodium periodate in 4 ml. of 50% aqueous methanol was allowed to stand at room temperature for 26 hr. and then diluted with water and extracted with ether. After the extract had been concentrated, crystallization of the residue from petroleum ether afforded 27.8 mg. (25.4%) of 4-(2-ketocyclohexyl)butyric acid (**22a**) as white plates, m.p. 55–58° (lit.,[18] 57.5–59.5°),[19] whose melting point was not depressed by mixing with the subsequently described authentic sample. A 36.9-mg. sample of the keto acid **22a** derived form the *cis*-hydroxy ketone **18** was esterified as subsequently described to yield 36.2 mg. (91%) of the crude methyl ester **22b**, b.p. 105–110° (0.8 mm.), from which a pure sample of the ester was collected[11] and identified with the subsequently described sample by comparison of retention times, infrared spectra, and mass spectra.

Similarly, reaction of 100 mg. (0.595 mmoles) of the *trans*-hydroxy ketone **19** with 161.5 mg. (0.75 mmole) of sodium periodiate in aqueous methanol for 18 hr. at room temperature yielded, after purification, 95.0 mg. (86.5%) of the keto acid **22a**, m.p. 60–62°. Esterification of a 78.2-mg. sample of this acid produced 65 mg. (77%) of the keto ester **22b**, b.p. 95–100° (0.27 mm.), which was identified as previously described.

An authentic sample of the keto acid **22a** was obtained as a by-product from the oxidation of a mixture of 1-decalols with chromic acid.[8] The keto acid, which crystallized from petroleum ether as white plates, m.p. 60.5–61.5°, has an ultraviolet maximum[13] at 287 mμ (ϵ 22.5) with broad infrared absorption[12] in the region 3400–2600 cm.$^{-1}$ (assoc. O—H) and a peak at 1705 cm.$^{-1}$, (C=O of ketone and carboxyl functions). A solution of 200.5 mg. (1.09 mmoles) of the keto acid **22a** and 3 drops of sulfuric acid in 3 ml. of methanol was refluxed for 1 hr. and then cooled and treated with excess aqueous sodium bicarbonate. The resulting mixture was extracted with ether and the extract was concentrated and distilled to separate 200 mg. (93%) of the crude methyl ester **22b** which contained[11] 10% of a minor component. The pure ester **22b**, b.p. 95° (0.2 mm.), n^{25}D 1.4635 (lit.,[20] n^{20}D 1.4762), was obtained by collection from the gas chromatograph and redistillation. The product has infrared absorption[12] at 1735 cm.$^{-1}$ (ester C=O) and at 1708 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; mol. wt., 198. Found: C, 66.69; H, 9.20; mol. wt., 198 (mass spectrum).

An authentic sample of pure[11] methyl 3-(2-ketocyclohexyl)-propionate, b.p. 114–115° (1.5 mm.), n^{25}D 1.4662 [lit.,[19] 135–137° (11 mm.), n^{20}D 1.4640], prepared by Dr. Harry Babad in our laboratories has infrared absorption[12] at 1735 cm.$^{-1}$ (ester C=O)

(14) H. O. House and H. W. Thompson, *J. Org. Chem.*, in press.

(15) A Baird infrared spectrophotometer equipped with a calcium fluoride prism was employed for this measurement.

(16) Determined as a solution in deuteriochloroform.

(17) See S. Brownstein, *J. Am. Chem. Soc.*, **81**, 1606 (1959). Similarly, the n.m.r. spectrum[12] of the chloro ketone **12** has a multiplet centered at 6.87 τ [1H, pattern consistent with coupling with the equatorial C-2 proton (J = 13 c.p.s.) and the two protons at C-3] as well as complex absorption in the region 7.5 to 9.0 τ.

(18) W. Herz, *J. Org. Chem.*, **22**, 630 (1957).

(19) Since the keto acid **22a** melts very close to its next lower homolog 3-(2-ketocyclohexyl) propionic acid [reported m.p. 64–66°, M. Häring and T. Wagner-Jauregg, *Helv. Chim. Acta*, **40**, 852 (1957)] and the infrared spectra of the two acids are not particularly distinctive, further characterization of the keto acid **22a** was considered appropriate.

(20) A. I. Kamneva and A. I. Efimenkova, *Trudy Moskv. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva*, No. **25**, 38 (1957); *Chem. Abstr.*, **52**, 14571 (1958). There is question as to the correctness of this assigned structure since the authors report the semicarbazone of the acid **22a** to melt at 252°, whereas others (ref. 17) report values in the range 185–189°.

TABLE I

CARBONYL ABSORPTION MAXIMA IN THE INFRARED AND ULTRAVIOLET

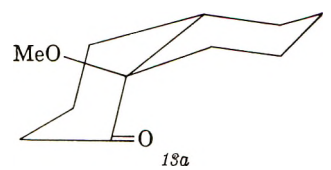
Compound	$\tilde{\nu}_{C=O}^{CCl_4}$, cm.$^{-1}$	λ_{max}^{EtOH}, mμ	Conformation of alpha electronegative substituent
trans-1-Decalone	1711	286.5 (ε 26.6)	
trans-9-Chloro-1-decalone (**12**), m.p. 40–41°	1723	300.5 (ε 45)	Axial
trans-9-Methoxy-1-decalone (**14**), m.p. 23°	1713	305.5 (ε 40)	Axial
cis-9-Methoxy-1-decalone (**13**), m.p. 20°	1710	301 (ε 33)	Axial
cis-2-Methoxy-*trans*-1-decalone (**15**), m.p. 45–47°	1724	...	Equatorial
trans-2-Methoxy-*trans*-1-decalone (**17**), liquid	1715	304.5 (ε 50)	Axial
cis-9-Hydroxy-1-decalone (**18**), m.p. 62.5–63.5	1708	287.5 (ε 34.5)	Presumably equatorial, intramolecular hydrogen bonding occurs
trans-9-Hydroxy-1-decalone (**19**), m.p. 44–45°	1705	300 (ε 32.6)	Axial, intermolecular hydrogen bonding occurs
cis-2-Hydroxy-*trans*-1-decalone (**12** in ref. 8), m.p. 76–76.7°	1712	275 (ε 38)	Presumably equatorial, hydrogen bonding occurs
cis-2-Acetoxy-*trans*-1-decalone (**9** in ref. 8), m.p. 72.5–73.5°	1730	284.5 (ε 29.3)	Equatorial

and at 1708 cm.$^{-1}$ (C=O) as well as many similarities to the methyl ester **22b** in the fingerprint region. However, the two homologous keto esters are readily distinguished by their mass spectra.

A solution containing 5.22 mmoles of the sodium derivative[21] of dimethyl sulfoxide was prepared from 179.6 mg. (7.5 mmoles) of sodium hydride, 18 ml. of dry (distilled from a mixture containing triphenylmethylsodium) dimethyl sulfoxide, and 2 mg. of triphenylmethane.[22] A solution of 84 mg. (0.5 mmole) of the *trans*-hydroxy ketone **19** in 0.85 ml. of ether was added to 2.0 ml. (0.58 mmole) of the dimethyl sulfoxide solution and then 2.75 g. (19.2 mmoles) of methyl iodide was added promptly. After the resulting mixture had been allowed to stand for 24 hr., it was diluted with water and extracted with petroleum ether. Concentration of the extract followed by distillation separated 71.4 mg. of colorless liquid, b.p. 70–85° (0.45 mm.), which contained[11] at least six components including the *trans*-methoxy ketone **14** (36%). A sample of the *trans*-methoxy ketone **14** was collected[11] and identified by comparison of its infrared spectrum with the spectrum of the previously described material.

The same alkylation precedure was applied to 168 mg. (1.0 mmole) of the *cis*-hydroxy ketone **18**, 1.0 mmole of the sodium derivative of dimethyl sulfoxide, 4.45 ml. of dimethyl sulfoxide, and 9.1 g. (64.2 mmoles) of methyl iodide being employed. From the crude reaction mixture which contained at least six components including the *cis*-methoxy ketone **13** (11%), a sample of the *cis*-methoxy ketone **13** was obtained by successive collection from two columns.[11,23] Although gas chromatography on two columns indicated that the collected sample was homogeneous and had the same retention time as the previously described methoxy ketone **13**, both the infrared and mass spectra of the collected sample indicated the presence of a minor component which we were unable to remove. Thus, the infrared spectra of the two samples were identical except for the presence of four additional weak bands (less than 15% of the intensity of the C=O stretching band or the C—H stretching band) at 1380, 1360, 975, and 910 cm.$^{-1}$ in the spectrum of the collected sample. The mass spectrum of the collected sample has peaks not present in the pure *cis*-methoxy ketone **13** at m/e 196 and 168; the relative intensities of the peaks at m/e 182 (molecular ion of **13**) and at m/e 196 (presumably the molecular ion of the contaminant) are in the ratio 100:32. Comparison of the thin layer chromatograms of the pure methoxy ketone **13** and the collected sample (employing both alumina and silica gel coatings) indicated that the collected sample contained primarily the methoxy ketone **13** accompanied by a contaminant. Thus, all of our data are in accord with the presence in the collected sample of the methoxy ketone **13** accompanied by small amounts of a second component, possibly the C-methyl derivative of the methoxy ketone **13**.

Spectroscopic Properties.—The positions of carbonyl absorption in the infrared and ultraviolet, summarized in Table I, indicate that the predominant conformations[7,24] of the compounds listed are in accord with the stereochemical assignments made. The data indicate that compound **13** exists predominately in the conformation shown in formula **13a**.



13a

(21) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(22) The triphenylmethane was added as an indicator. The solution was standardized by titrating a 2-ml. aliquot with diisopropyl ketone until the red color was discharged.

(23) A column packed with 20 M Carbowax suspended on ground firebrick was employed for this separation.

(24) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 175–176.

Partially Reduced Pyridines. I. The Properties of 3-Benzoyl-4-phenyl-1,4-dihydropyridine[1]

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The product of the reaction of phenylmagnesium bromide with 3-benzoylpyridine has been shown to have the structure 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) as suggested by Fuson and Miller.[3] A study of the physical and chemical properties of 3-benzoyl-4-phenyl-1,4-dihydropyridine has supported many of the postulated reactions and mechanisms of reactions of 1,4-dihydropyridines and reduced diphosphopyridine nucleotide (DPNH). Compound I has thus been shown to be a useful model for the coenzyme DPNH.

The discovery that the coenzymatic reaction of diphosphopyridine nucleotide involves the conversion of a pyridinium ring to a 1,4-dihydropyridine has led to an active interest in the mechanisms of reduction of pyridines and their salts, which includes, of course, the attack of nucleophiles on the pyridine derivatives.[4]

It is evident that these dihydropyridines contain enamine systems which should provide reactive sites at the 3- or 5-positions for the introduction of electrophilic substituents and at the 2-, 4-, or 6-positions for nucleophilic groups. During the course of such an investigation in this laboratory, Fuson and Miller[3] reported the synthesis of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) by the nucleophilic attack of the phenyl group of phenylmagnesium bromide on 3-benzoylpyridine. This 1,4-dihydropyridine system offered several structural features not available with the 1,4-dihydropyridine system which results from dithionite reduction of pyridinium salts or the Hansch synthesis. The nitrogen of I is secondary rather than tertiary, and there is a substituent on the 4-position of I but no substituent on the 5-position. I has a high molecular weight and an electron-withdrawing, unsaturated substituent which should increase the stability and crystallinity of the partially reduced pyridine rings. Thus compound I was attractive for studying the properties of 1,4-dihydropyridines.

The first problem was to ascertain unequivocally that the product of the Grignard reaction was indeed a 4-substituted 1,4-dihydropyridine.[5] The n.m.r. spectrum of the pyridine (IV) resulting from the chloranil oxidation of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was consistent only with the structure, 3-benzoyl-4-phenylpyridine (IV). A consideration of the n.m.r. spectrum of 3-benzoylpyridine (Fig. 1) shows that the bands due to the 4-hydrogen are the two triplets found at 1.95 and 1.84 τ. An examination of the n.m.r. spectrum of 3-benzoyl-4-phenylpyridine shows no bands between 2.05 and 1.27 τ. Thus it is evident that there is no 4-hydrogen in the latter compound proving the position of the phenyl substituent. That the nitrogen of I was secondary was evident from the infrared spectrum and the acylation of I to 1-acetyl-3-benzoyl-4-

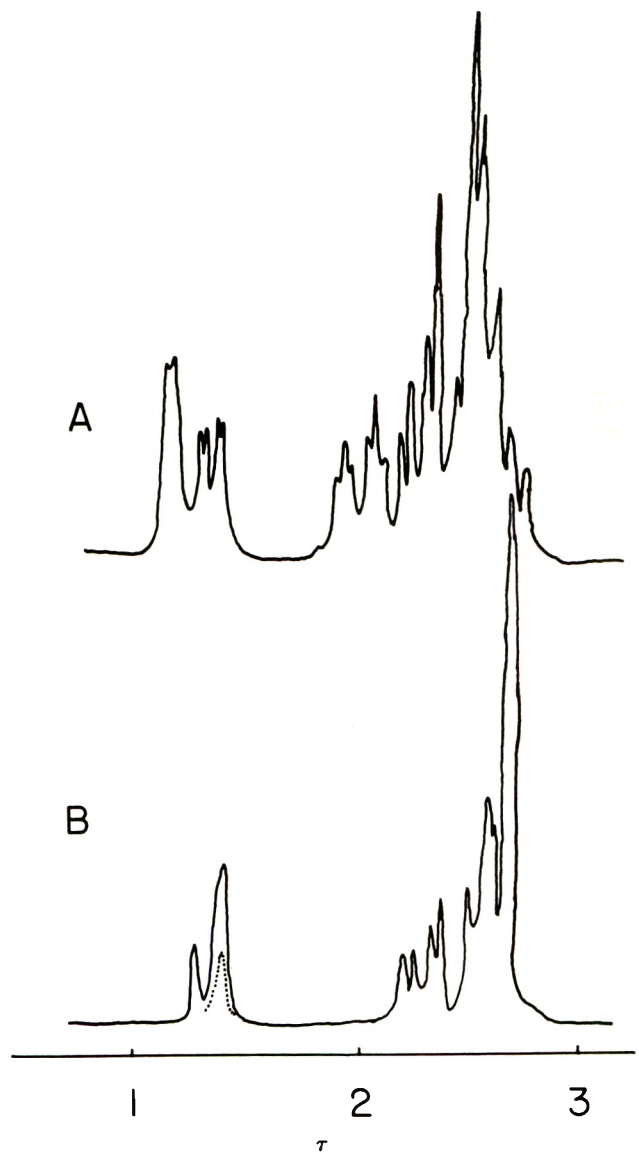


Fig. 1.—Nuclear magnetic resonance spectra of 3-benzoylpyridine (curve A) and 3-benzoyl-4-phenylpyridine (IV) (curve B).

(1) The research was presented in part as the University of New Hampshire Sigma Xi Lecture for 1959–1960, and before the Organic Division of the American Chemical Society at the 138th National Meeting in New York, N. Y., September 11–16, 1960.

(2) The material for this paper was taken from the thesis of David A. Nelson presented to the graduate faculty of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. Present address: Department of Chemistry, University of Wyoming, Laramie, Wyo.

(3) R. C. Fuson and F. A. Miller, *J. Am. Chem. Soc.*, **79**, 3478 (1957).

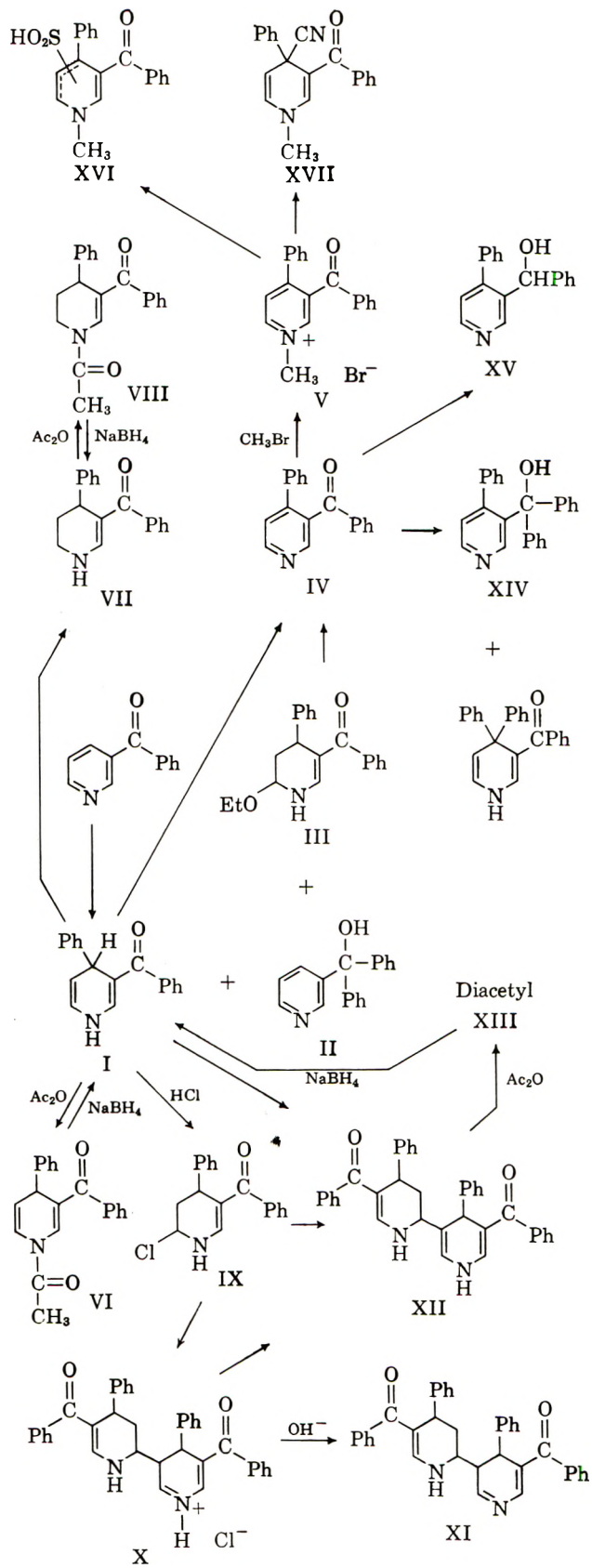
(4)(a) Series by F. H. Westheimer, see B. E. Norcross, P. E. Klinedinst, and F. H. Westheimer, *ibid.* **84**, 797 (1962), for leading references; (b) series by P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958), for leading references; (c) series by K. Schenker and J. Druey, *ibid.*, **42**, 1960 (1959), for leading references; (d) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958); *J. Am. Chem. Soc.*, **80**, 992 (1958); (e) series by E. M. Kosower, see E. M. Kosower, D. Hoffmann, and K. Wallenfels, *ibid.*, **84**, 2755 (1962); (f) K. Wallenfels and D. Hoffmann, *Tetrahedron Letters*, No. **4**, 154 (1962); (g) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3257 (1960); (h) D. C. Dittmer and J. M. Kolyer, *J. Org. Chem.*, **27**, 56 (1962); (i) N. Sugiyama, G. Inouye, and K. Ito, *Bull. Chem. Soc. Japan*, **35**, 927 (1962).

(5) The reactions of pyridines with organolithium and Grignard reagents are not consistent in giving either 1,2- or 1,4-dihydropyridines. Compare R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960) and R. A. Abramovitch and C. S. Giam, *ibid.*, **40**, 213 (1962), with R. Lukeš and J. Kuthan, *Collection Czech. Chem. Commun.*, **26**, 1422, 1845 (1961), and H. Gilman and H. A. McNinch, *J. Org. Chem.*, **27**, 1889 (1962).

phenyl-1,4-dihydropyridine (VI). A comparison of the ultraviolet absorption spectrum of I in methanol [λ_{max} 360 mμ (ϵ 1.08 × 10^4); λ_{max} 234 mμ (ϵ 1.14 × 10^4)] and acidic methanol [λ_{max} 305 mμ (ϵ 2.30 × 10^4); λ_{max} 236 mμ (ϵ 1.90 × 10^4)] with the behavior of other 3-benzoyl-1,4-dihydropyridines[6] further confirmed the 1,4-dihydro system of I. The catalytic hydrogenation of I in alcohol absorbed only one mole of hydrogen, and the product (VII) was resistent to further hydrogenation in neutral or acidic medium. The failure of VII to show absorption near 1675 cm.$^{-1}$ in the infrared spectrum was of some concern since Fuson and Miller[3] had assigned a band in this region in the spectrum of I to the carbon to oxygen double bond stretching frequency. A consideration of the infrared spectra of partially reduced 1-methyl-3-cyanopyridine[4c] and various β-amino-α,β-unsaturated ketones,[7] however, suggested that the carbon–oxygen stretching frequency of the carbonyl of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) should be at lower frequency than 1675 cm.$^{-1}$. Thus an absorption band which appears at 1618 cm.$^{-1}$ in the spectrum of I can be assigned to the carbonyl stretching vibration. A similar band appears at 1613 cm.$^{-1}$ in the spectrum of VII confirming the presence of the 2,3-double bond in VII. Thus the disappearance of the absorption band at 1675 cm.$^{-1}$ on hydrogenation of I leads to the assignment of this absorption to a stretching vibration of the 5,6-double bond of I and the assignment of the structure 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine to VII. The ultraviolet absorption spectrum of VII supports this assignment, for the spectrum of VII in methanol [λ_{max} 305 mμ (ϵ 2.40 × 10^4); λ_{max} 227 mμ (ϵ 1.04 × 10^4)] is similar to that observed on addition of acid to I, a reaction which supposedly attacks the 5,6-double bond of a 1,4-dihydropyridine.[4d] That VII retained the secondary nitrogen was confirmed by the infrared spectrum and acylation of VII to the 1-acetyl derivative VIII.

These spectral observations were useful in assigning the structure to an insoluble material which was obtained from a combination of the residues of many preparations of I. This material showed a very weak band at 1675 cm.$^{-1}$ and a medium band at 1620 cm.$^{-1}$ in the infrared spectrum, and absorption maxima at 302 mμ (1.50 × 10^4) and 230 mμ (9.0 × 10^3) in the ultraviolet spectrum. These properties suggest a 3-benzoyl-1,4,5,6-tetrahydropyridine system and, in combination with the elemental analyses, allow the assignment of structure as 3-benzoyl-6-ethoxy-4-phenyl-1,4,5,6-tetrahydropyridine (III) to the material formed by addition of the elements of ethanol to I during the recrystallization of I from ethanol. The structure was confirmed by the decomposition and dehydrogenation of III to 3-benzoyl-4-phenylpyridine (IV) on reaction with chloranil.

The nature of the reaction of acid with a 1,4-dihydropyridine has been shown to occur by an attack of a proton on the 5-position of the partially reduced ring. The resulting salt may then undergo attack by a nucleophile such as water, halide ion, etc., to give a 1,4,5,6-tetrahydropyridine. Few products have been isolated and characterized from such reactions, however.[4d] The reaction of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) with acid was investigated in an attempt further to elucidate this reaction. Possible structures for the products of these reactions and a possible mechanism for their formation can be derived by assuming a proton attack on the 5-position of I and a subsequent reaction of the resulting electrophile



(6) David A. Nelson, Ph.D. thesis, University of New Hampshire, June, 1960.

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

on a 5-position of a second molecule of I (see flow sheet).

The reaction of I with anhydrous hydrogen chloride in methanol, benzene, ether, or chloroform led to an unstable solid which on the basis of the ultraviolet absorption spectrum [λ_{max} 360 mμ (ϵ 3.6 × 10^3); λ_{max} 308 mμ (ϵ 1.14 × 10^4); λ_{inf} 234 mμ (ϵ 1.01 × 10^4)] in methanol and the infrared spectrum was assumed to be 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX). The reaction of IX with water, even treatment with 95% ethanol, gave a high melting material XII. The melting point and poor solubility of XII suggested a dimeric structure. Unlike dimers proposed by Anderson and Berkelhammer[4d] XII, on the basis of analyses, did not contain additional oxygen. The ultraviolet absorption spectrum of XII showed maxima at 360 mμ (ϵ 1.50 × 10^4) and 308 mμ (ϵ 2.40 × 10^4) suggesting that XII contained both a 1,4-dihydropyridine system such as I and a 1,4,5,6-tetrahydropyridine system such as VII. The infrared spectrum of XII also showed bands characteristic of both systems. XII was converted to an acetyl derivative (XIII), the analyses of which required a diacetyl derivative if XII were dimeric. These data all suggest the structure of XII to be 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine.

The recrystallization of the unstable compound IX from dry acetone led to a new material X which could be converted to the dimer XII on reaction with water. The infrared spectrum of X, however, clearly showed it to be an ammonium salt, for there was extensive absorption in the 2500-cm.$^{-1}$ region. More definitive, however, were two bands at 2080 and 1950 cm.$^{-1}$ which have been assigned by Witkop[8] to the H—$\overset{+}{N}$ of proton salts of pyridine or other H—$\overset{+}{N}$=C systems. Since aromatization of IX was unlikely under these conditions and since X gave an ultraviolet absorption spectrum characteristic of a 3-benzoyl-1,4,5,6-tetrahydropyridine system with reduced intensity, the compound was assigned a dimeric structure (X) with only one 1,4,5,6-tetrahydropyridine system but containing a C=$\overset{+}{N}$—H group.

The neutralization of a solution of X in nonaqueous solution gave a dimer (XI) isomeric with XII. This new dimer showed maximal ultraviolet absorption only at 306 mμ (ϵ 2.72 × 10^4) and 238 mμ (ϵ 2.08 × 10^4) indicative of a 3-benzoyl-1,4,5,6-tetrahydropyridine system. The infrared absorption spectrum showed a band at 1675 cm.$^{-1}$, but the absence of an absorption maximum at 360 mμ eliminated the possibility of a 1,4-dihydropyridine system. Thus it would appear that XI contains one benzoyl group not conjugated with the free pair of electrons on the nitrogen. These conditions are met by assigning the structure 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine to XI. A similar series of reactions was suggested by Schenker and Druey[4c] to explain the changes in the ultraviolet absorption spectrum of 1-methyl-3-cyano-1,4-dihydropyridine on addition of acid; however, they were unable to isolate or characterize any product from the reaction.[9]

The spectral properties of I described above as well as the failure of the carbonyl of I to undergo reaction with sodium borohydride, phenylmagnesium bromide, phenyllithium, and lithium aluminum hydride all suggest that the resonance form Ib contributes heavily to the structure of I. Similarly the properties of VII also suggest a high electron density on the carbonyl oxygen and nearly single bond character of the carbonyl C—O bond. The N-acetyl group of VI and VIII, the acetyl derivatives of I and VII, would be expected to interfere with the conjugation of the nitrogen free pair of electrons and the carbonyl group by forming a crossed conjugated system. Thus the sodium borohydride reduction of these compounds was investigated. A very remarkable reaction occurred. In each case the acetyl group was reductively removed to form the deacetyl or parent compound. For comparison the diacetyl (XIII) derivative of XII was treated with sodium borohydride, and 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was formed in 50% yield. These reactions appear to be the first examples of reductions of amides by sodium borohydride, and further confirm the unusual conjugation which exists between the nitrogen free pair of electrons and the carbonyl group, for instead of the acetyl group increasing the electrophilicity of the carbonyl carbon and allowing reduction of the ketone, the β-amino-α,β-unsaturated carbonyl system increased the electrophilicity of the amide carbonyl and thus allowed reduction to occur there. The nature of the amide grouping might be compared with that found with bridgehead lactams. Other properties which show these systems to be comparable are under investigation.

To eliminate the possibility that the 4-phenyl substituent was inducing an unusual reactivity on the 3-benzoyl function due to steric effects, the carbonyl properties of 3-benzoyl-4-phenylpyridine (IV) were investigated. Lithium aluminum hydride or sodium borohydride caused the reduction of the carbonyl group to produce 4-phenyl-3-pyridylphenylcarbinol (XV) with no apparent difficulty. The reaction of IV with phenylmagnesium bromide gave some material which appeared to result from an attack of the Grignard reagent on the pyridine nucleus; however, the only product characterized [4-phenyl-3-pyridyldiphenylcarbinol (XIV)] was formed by addition to the carbonyl. Thus the unusual properties of the carbonyl of I were caused by its conjugation with the dihydropyridine system and not some steric effect of the 4-phenyl substituent.

Attempts to cause the conversion of the quaternary salt of 3-benzoyl-4-phenylpyridine (V) to a dihydropyridine system by nucleophilic attack were largely unsuccessful. The reaction of V with sodium dithionite produced oils which could not be crystallized or purified, but the impure materials gave infrared and ultraviolet spectra characteristic of the 1,4-dihydropyridine system of I. From one reaction a crude solid was isolated. This material contained sulfur and appeared to be a derivative of the sulfinic acid XVI. An unstable solid was isolated from the reaction of V with an excess of sodium cyanide. The cyanide addition compound appeared to be a 1,4-

(8) B. Witkop, *J. Am. Chem. Soc.* **70**, 5597 (1954).

(9) The advantage of using a 1-unsubstituted 1,4-dihydropyridine, such as I, for the investigation of this reaction with acid is evident since isolable products were obtained by loss of a proton rather than requiring the addition of a nucleophile.

dihydropyridine, but its instability prevented the complete characterization. The elemental analyses of both of the latter compounds indicated an atom of oxygen in excess of the expected formulas XVI and XVII, respectively.

Experimental

3-Benzoyl-4-phenyl-1,4-dihydropyridine (I).—The title compound was prepared following the procedure of Fuson and Miller[3] with only slight modification. The hydrolysis of the Grignard reaction caused the precipitation of the product which was removed by filtration. Only a small amount of I mixed with most of the 3-pyridyldiphenylcarbinol (II) was obtained from the ether solution. Recrystallization of the dihydropyridine I from ethanol gave I, m.p. 148–152°, in yields comparable to those reported previously.

Anal. Calcd. for $C_{18}H_{14}NO$: C, 82.73; H, 5.79. Found: C, 82.94; H, 6.07.

A collection of the residues from a number of isolations of I and II was treated with ethanol, and a portion of the material was found to be insoluble. The material was recrystallized from dimethylformamide to give a small yield of 3-benzoyl-4-phenyl-6-ethoxy-1,4,5,6-tetrahydropyridine (III), m.p. 154–156°.

Anal. Calcd. for $C_{20}H_{22}NO_2$: C, 77.89; H, 7.15. Found: C, 77.91; H, 7.15.

The oxidation of 0.5 g. of III with 0.5 g. of chloranil in 50 ml. of benzene following the procedure of Fuson and Miller[3] gave a quantitative yield of 3-benzoyl-4-phenylpyridine (IV), m.p. 87–88°. The infrared spectrum of this material was identical with that of an authentic sample of IV prepared from I.

3-Benzoyl-4-phenylpyridine (IV).—The preparation of IV from I followed the method of Fuson and Miller[3] to give IV (64%), m.p. 87–88° (lit., m.p. 89.5–90.0°). The methobromide (V) of IV was prepared by allowing a solution of 7.5 g. of IV and 5.0 g. of methyl bromide in 50 ml. of methanol to stand for 24 hr. at room temperature. Removal of the solvent by distillation under reduced pressure gave a quantitative yield of V, m.p. 233–235°.

Anal. Calcd. for $C_{19}H_{16}BrNO$: Br, 22.56. Found: Br, 22.49.

1-Acetyl-3-benzoyl-4-phenyl-1,4-dihydropyridine (VI).—A solution of 1.0 g. of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) in 25 ml. of anhydrous pyridine was treated with 5.0 ml. of acetic anhydride. The mixture was heated on a steam bath for 4 hr. and poured into 200 ml. of water. The solid which separated was removed by filtration and recrystallized from ethanol–chloroform to give a quantitative yield of VI, m.p. 182–183°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65. Found: C, 79.37; H, 5.79.

3-Benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII).—A 5.0-g. sample of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was hydrogenated over 0.1 g. of platinum oxide in 100 ml. of ethanol. The catalyst was removed by filtration, and the filtrate deposited a quantitative yield of 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII), m.p. 180–181°.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.2; H, 6.52; N, 5.33. Found: C, 82.02; H, 6.74; N, 5.40.

1-Acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VIII).—Following the procedure for the preparation of VI, 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII) was converted in quantitative yield to the 1-acetyl derivative (VIII), m.p. 159–161°.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 79.20; H, 6.27; N, 4.59. Found: C, 79.28; H, 6.32; N, 4.59.

The Reactions of 3-Benzoyl-4-phenyl-1,4-dihydropyridine (I) with Hydrogen Chloride.—The reaction of 1.0 g. of I with hydrogen chloride in benzene led to the precipitation of an impure material which could not be purified without transformation. This impure material was assigned the structure 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX) although correct analytical data were not obtained. The recrystallization of IX from acetone caused the quantitative conversion to 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine hydrochloride (X), m.p. 168–172°.

Anal. Calcd. for $C_{36}H_{31}ClN_2O_2$: Cl, 6.36. Found: Cl, 6.36.

The reaction of IX or X with base in alcoholic solution and dilution of the resulting mixture with water led to the quantitative precipitation of 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine (XI). Recrystallization of the solid from ethanol gave XI, m.p. 220–225°.

Anal. Calcd. for $C_{36}H_{30}N_2O_2$: C, 82.70; H, 5.80; N, 5.37. Found: C, 82.51; H, 5 57; N, 5.38.

A mixture of 5.0 g. of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) with 10 ml. of 6 *N* hydrochloric acid in 50 ml. of ethanol was heated on a steam bath for several minutes and poured into 200 ml. of water to give a quantitative yield of 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (XII). Recrystallization of the solid from dimethyl formamide gave purified XII, m.p. 290–295°.

Anal. Calcd. for $C_{36}H_{30}N_2O_2$: C, 82.70; H, 5.80; N, 5.37. Found: C, 82.30; H, 5.59; N, 5.63.

XII was also formed in quantitative yield on diluting a methanolic solution of 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX) with water.

The diacetyl derivative (XIII) of XII was prepared by the procedure used for the syntheses of VI and VIII. Recrystallization of the solid from ethanol–chloroform gave purified XIII, m.p. 255–257°.

Anal. Calcd. for $C_{40}H_{34}N_2O_4$: C, 79.18; H, 5.66. Found: C, 79.71; H, 5.96.

The Reduction of the N-Acetyl Derivatives VI, VIII, and XIII.—A 0.5- to 1.0-g. sample of the acetyl derivative was dissolved in methanol, and 1–2 g. of sodium borohydride was added. When the reaction was complete, the solution was poured into water, and the solid which precipitated was collected by filtration. In each case the yield is indicated after the product. Each product was identified by melting point, mixture melting point, and infrared spectrum. 1-Acetyl-3-benzoyl-4-phenyl-1,4-dihydropyridine (VI) and 1-acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VIII) gave the parent pyridines I (80%) and VII (90%), respectively. 1-Acetyl-3-benzoyl-4-phenyl-5-[6-(1-acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (XIII), however, was converted to 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) (50%).

The Reactions of 3-Benzoyl-4-phenylpyridine (IV) and Its Methobromide (V). (a) **The Reaction of IV with Phenylmagnesium Bromide.**—Following the procedure for the preparation of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) from 3-benzoylpyridine,[3] 5.0 g. of 3-benzoyl-4-phenylpyridine (IV) was treated with an ethereal solution of 0.4 mole of phenylmagnesium bromide. The reaction mixture was hydrolyzed with ammonium chloride. A yellow precipitate formed during the hydrolysis; however, this material could not be purified. The infrared spectrum of this impure solid showed many bands charaacteristic of a 1,4-dihydropyridine.[5] The ethereal solution was concentrated and the residue was extracted with petroleum ether. The material which was insoluble was dissolved in ether, and a white solid precipitated from the ether solution. Recrystallization of the solid from ether gave a small yield of 3-(4-phenylpyridyl)diphenylcarbinol (XIV), m.p. 131–132°.

Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.43; H, 5.68. Found: C, 85.36; H, 5.72.

(b) **The Reaction of IV with Lithium Aluminum Hydride.**—The reaction of 1.0 g. of 3-benzoyl-4-phenylpyridine (IV) with an excess of lithium aluminum hydride in 50 ml. of anhydrous ether gave, after the usual work-up, a quantitative yield of 3-(4-phenylpyridyl)phenylcarbinol (XV), m.p. 148–149°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79. Found: C, 82.63; H, 5.99.

(c) **The Reaction of IV with Sodium Borohydride.**—The reduction of 1.0 g. of IV with 1.0 g. of sodium borohydride in 50 ml. of methanol gave a quantitative yield of XV, m.p. 147.5–148.0°. The infrared spectrum of this product was identical with that of the reduction product from lithium aluminum hydride.

(d) **The Reaction of the Methobromide V with Sodium Dithionite.**—A solution of 3.5 g. of 3-benzoyl-4-phenylpyridine methobromide (V) in 100 ml. of boiled water was treated with 4.6 g. of sodium bicarbonate and 7.0 g. of sodium dithionite under nitrogen. The red oil which precipitated during the reaction did not crystallize. Acidification of the reaction mixture and addition of a little ethanol caused the dissolution of the oil. The solution was neutralized with sodium bicarbonate, and the oil which separated was taken up in chloroform. The chloroform solution was divided into two parts. The solvent was removed from one portion and extraction of the residue with various organic solvents gave a small amount of the methobromide V as residue. The second portion of chloroform was saturated with hydrogen chlo-

ride, the solvent was removed by distillation under reduced pressure, and the residue was crystallized by trituration with petroleum ether. Recrystallization of the solid from isopropyl alcohol–ether gave a small yield of solid, m.p. 146–148°. The solid gave a negative Beilstein test for halogen and positive sodium fusion tests for nitrogen and sulfur. The compound appeared to be a 3-benzoyl-1-methyl-4-phenyldihydropyridinesulfinic acid (XVI), plus oxygen or water.

Anal. Calcd. for $C_{18}H_{16}NO_4S$: C, 64.00; H, 5.10. Found: C, 64.58; H, 5.21.

(e) **The Reaction of the Methobromide V with Sodium Cyanide.**—A 1.0-g. sample of V was dissolved in 50 ml. of water and 0.5 g. of sodium cyanide was added. A small amount of yellow precipitate formed. The addition of an additional 3.0 g. of sodium cyanide caused further precipitation. The solid was removed by filtration and washed with water. During this process the solid turned brown. Recrystallization of the solid was accompanied by a darkening in color. Thus analyses were determined on crude material, m.p. 75–80°. The analytical data suggest that this compound is a 3-benzoyl-1-methyl-4-phenyl-cyano-1,4-dihydropyridine (XVII), plus oxygen or water.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 76.00; H, 5.07. Found: C, 75.25; H, 5.10.

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The Synthesis of L-Valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline[1]

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The peptide sequence, L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline, which occurs in adrenocorticotropins, has been synthesized by the reaction of carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine azide with L-valyl-L-tyrosyl-L-proline benzyl ester, followed by hydrogenation and treatment with sodium in liquid ammonia. The protected pentapeptide was obtained in crystalline form. A side reaction was observed when carbobenzoxy-L-valine *p*-nitrophenyl ester was coupled with L-tyrosine methyl ester hydrochloride in the presence of *excess* triethylamine. The by-product was identified as O-(carbobenzoxy-L-valyl-)-L-tyrosine methyl ester. The di-substituted by-product, N,O-di(carbobenzoxy-L-valyl)-L-tyrosine methyl ester, was also isolated from this reaction.

The pentapeptide L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (VI) occurs at position 20–24 in the amino acid sequence[2–4] of adrenocorticotropins (ACTH) isolated from pituitary glands of various species. It is generally assumed[2,5] that the adrenocorticotropic activity resides in the sequence consisting of the first twenty-four or twenty-eight amino acid residues. Indeed, we have recently reported the synthesis[6] of a nonadecapeptide corresponding to the first nineteen amino acid residues of adrenocorticotropins and have shown that it possesses approximately 50% of the potency of the natural product. Subsequently, other investigators[7–9] have described briefly the synthesis of ACTH analogues consisting of 19, 20, 23, and 24 amino acid residues. In the course of the synthesis of the tetracosapeptide, we have obtained peptide VI and crystalline L-valyl-N$^{\epsilon}$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (V).

The scheme for the synthesis of VI is given in Fig. 1. The benzyl group was employed for the protection of the C-terminus in order to avoid saponification at the end of the synthesis. The protected dipeptide (I) carbobenzoxy-L-valyl-L-tyrosine methyl ester[10,11] was obtained in good yield by coupling carbobenzoxy-L-valine and tyrosine methyl ester *via* the dicyclohexylcarbodiimide (DCCI) procedure.[12] Carbobenzoxy-L-valyl-L-tyrosyl-L-proline benzyl ester (II)[14] was prepared in 75% yield by the reaction of carbobenzoxy-L-valyl-L-tyrosine azide with L-proline benzyl ester. The use of dicyclohexylcarbodiimide with carbobenzoxy-L-valyl-L-tyrosine was avoided because of the reported racemization with this combination in an analogous synthesis.[13] A sample of the protected tripeptide was hydrogenated exhaustively in the presence of palladium. The free tripeptide L-valyl-L-tyrosyl-L-proline was isolated and crystallized from methanol–water.

Carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine methyl ester[16] was prepared by the reaction of carbobenzoxy-L-

(1) Taken from a portion of the Ph.D. thesis of J. Ramachandran at the University of California, 1962.

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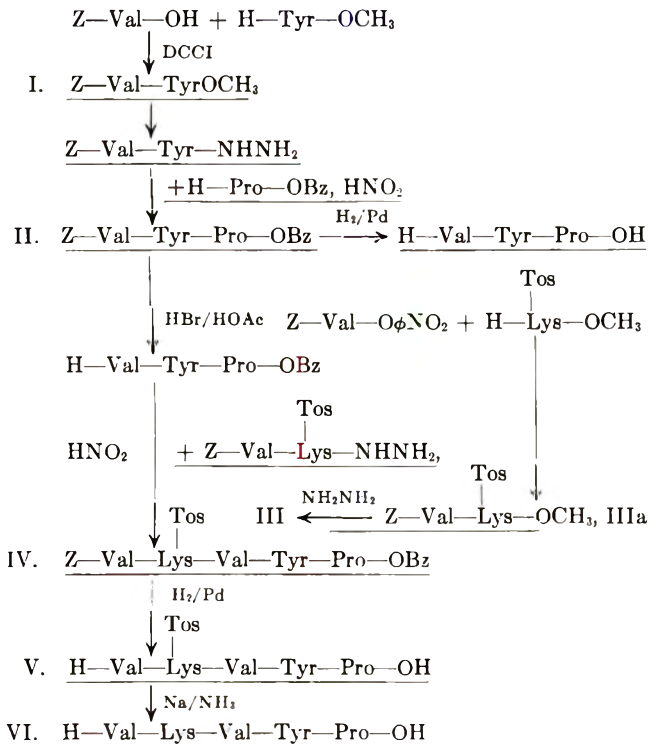

Fig. 1.—Outline of the synthesis of L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline; Z, carbobenzoxy; Bz, benzyl; Tos, *p*-toluenesulfonyl. Underlines indicate crystalline products.

valine *p*-nitrophenyl ester with N$^{\epsilon}$-tosyl-L-lysine methyl ester. The protected dipeptide was converted to the hydrazide (III). The azide of the protected dipeptide was prepared and allowed to react in ethyl acetate with L-valyl-L-tyrosyl-L-proline benzyl ester, which was prepared by treatment of II with hydrogen bromide in glacial acetic acid. It was advantageous to use the free tripeptide ester in this reaction instead of the hydrobromide,[17] since the free tripeptide ester was readily soluble in ethyl acetate whereas the hydrobromide could be dissolved in this solvent only by the addition of some dimethylformamide besides an equivalent of triethylamine. Thus, when the reaction in ethyl acetate was performed with the free tripeptide ester, the protected pentapeptide (IV) separated in crystalline form. IV was isolated in 75% yield and recrystallized from ethyl acetate.

Exhaustive hydrogenation of IV in the presence of palladium yielded the crystalline peptide V, L-valyl-N$^{\epsilon}$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline monohydrate. Removal of the tosyl group was accomplished by reduction with sodium in liquid ammonia. The free pentapeptide L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (VI) was isolated in 69% yield by desalting on an IRC-50 column.[18] VI was found to be homogeneous in paper chromatography in three different solvents and by paper electrophoresis in a buffer of pH 3.7. Amino acid analysis of an acid hydrolysate of the pentapeptide VI by the procedure of Spackman,[19] *et al.*, gave the following ratios of the amino acids: $Val_{2.0}Lys_{0.94}Tyr_{1.0}Pro_{1.0}$.

VI was digested with leucine aminopeptidase[20] (LAP), trypsin, and chymotrypsin. Paper chromatography of aliquots of these digests in the solvent system BPAW (*n*-butyl alcohol–pyridine–acetic acid–water) may be seen in Fig. 2. It was found that the LAP digest gave three spots which showed a positive reaction to ninhydrin: valine (R_f 0.42) and lysine (R_f 0.11) were identified by controls. The third ninhydrin-positive spot (R_f 0.55) also gave a positive reaction with the Pauly reagent.[21] No free tyrosine or free proline was detected. Quantitative amino acid analysis of an aliquot of the digest by the Spinco amino acid analyzer showed the molar ratio of valine to lysine to be exactly 2:1 and no tyrosine or proline were detected. Hence the third ninhydrin-positive spot (R_f 0.55) must represent L-tyrosyl-L-proline.

The tryptic digest revealed two ninhydrin-positive spots in chromatography on paper in the system BAW (*n*-butyl alcohol–acetic acid–water). As expected, one of these spots was also positive to the Pauly reagent and corresponded to L-valyl-L-tyrosyl-L-proline. The spot with the lower mobility corresponded to L-valyl-L-lysine. As may be seen in Fig. 2, chymotrypsin caused no splitting of the peptide bonds.

A Side Reaction in Peptide Synthesis with *p*-Nitrophenyl Esters.[22]—In an attempt to prepare I, carbobenzoxy-L-valine *p*-nitrophenyl ester was allowed to react with tyrosine methyl ester hydrochloride in the presence of two equivalents of triethylamine. The progress of the reaction was followed by paper chromatography in the solvent system BAW. The disappearance of ninhydrin positive material (tyrosine methyl ester) was followed. After eight hours' reaction, the chromatograms revealed the presence of unchanged tyrosine methyl ester, which gave a positive reaction with ninhydrin and the Pauly reagent; in addition, a second ninhydrin-positive spot with a high R_f was observed. This latter spot failed to give any reaction with the Pauly reagent (Fig. 3). The reaction mixture was worked up by removing the solvent *in vacuo*, redissolving the residue in ethyl acetate and removing the triethylamine hydrochloride crystals by filtration. When hydrogen chloride in ethyl acetate was added to the filtrate, a crystalline material separated. Paper chromatography in BAW showed that this crystalline product corresponded to the unknown spot which was positive to ninhydrin but negative to the Pauly reagent.[21] This compound could be recrystallized from methanol and microanalysis confirmed the structure of O-(carbobenzoxy-L-valyl)-L-tyrosine methyl ester hydrochloride (VII).

When VII was treated with 0.1 *N* sodium hydroxide for five minutes at room temperature, carbobenzoxy-L-valine and tyrosine methyl ester were formed, both of which were identified by paper chromatography. Further proof of the structure of the product was obtained

(17) When the hydrobromide of the tripeptide benzyl ester reacted with carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine azide in the presence of an equivalent of triethylamine, considerable amounts of unchanged tripeptide benzyl ester remained even after a week and could be removed from the product only by countercurrent distribution in the system consisting of chloroform–toluene–methanol–water (5:5:8:2, by volume). The protected pentapeptide IV was obtained from the peak with K = 0.21 in 38% yield and unchanged L-valyl-L-tyrosyl-L-proline benzyl ester was recovered from the peak with K = 9.

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(23) J. Ramachandran, abstract of paper presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

from an examination of the ultraviolet absorption spectrum. In Fig. 4 are shown the ultraviolet absorption spectra of an authentic sample of carbobenzoxy-L-valyl-L-tyrosine methyl ester, of O,N-dicarbobenzoxy-L-tyrosine, and of VII. It is evident that the characteristic absorption maximum of tyrosine at 275 mμ is absent from VII. The effect of alkali on the absorption spectra of these three compounds is shown in Fig. 5. With regeneration of the hydroxyl group in the presence of alkali, all three compounds exhibit the typical tyrosine absorption at 295 mμ. Now after acidification, the absorption maxima shift to shorter wave lengths (275 mμ) and all the compounds exhibit nearly identical spectra.

After the isolation of VII, the mother liquors yielded a small amount of another crystalline product that gave negative reactions with both ninhydrin and the Pauly reagent. Analysis established its structure as O,N-di(carbobenzoxy-L-valyl)-L-tyrosine methyl ester. This was further confirmed by its ultraviolet absorption spectra and by the results of mild alkali treatment. The latter gave rise to carbobenzoxyvalyltyrosine methyl ester and carbobenzoxyvaline, both of which were identified by paper chromatography.

VII was obtained in 40–50% yield. The reaction was then repeated under different conditions in order to establish the cause of the side reaction. No trace of VII was found when carbobenzoxy-L-valine *p*-nitrophenyl ester was allowed to react with tyrosine methyl ester in the absence of triethylamine; only traces of VII appeared on paper chromatograms when the reaction with tyrosine methyl ester hydrochloride was repeated with exactly one equivalent of triethylamine. Hence, it is apparent that the excess triethylamine removes the proton from the phenolic hydroxyl group, thus leaving a highly nucleophilic phenoxide ion which in preference to the amino group, is attacked by the *p*-nitrophenyl ester.

The incidence of the side reaction when other protected amino acid *p*-nitrophenyl esters are allowed to react with tyrosine methyl ester was then investigated. The appearance of a new ninhydrin-positive, Pauly-negative spot on the chromatograms in BAW was taken as an indication that the side reaction had occurred. The *p*-nitrophenyl esters of N^{α}-carbobenzoxy-N^{ϵ}-tosyl-L-lysine, N^{α}-carbobenzoxy-L-glutamine and N^{α}-carbobenzoxy-S-benzyl-DL-cysteine gave rise to O-substituted products when allowed to react with tyrosine methyl ester hydrochloride in the presence of more than one equivalent of triethylamine.

Experimental[24]

Carbobenzoxy-L-valyl-L-tyrosine Methyl Ester (I).—L-Tyrosine (45.3 g., 250 mmoles) was esterified with methanol (300 ml.) by the thionyl chloride method[25] to yield 46 g. (79%) of L-tyrosine methyl ester hydrochloride, m.p. 189–190°. L-Tyrosine methyl ester was prepared in 66% yield from the hydrochloride by treatment with alcoholic potassium hydroxide (m.p. 135°). L-Tyrosine methyl ester (3.9 g., 20 mmoles) was dissolved in 150 cc. of acetonitrile by warming. Carbobenzoxyl-L-valine (5.02 g., 20 mmoles) was added and the mixture cooled to 0°. Dicyclohexylcarbodiimide (4.12 g., 20 mmoles) was added and the reaction mixture was stirred for 4 hr. at 4° and for 15 hr. at room temperature. Dicyclohexylurea was filtered off and washed with 100 ml. of hot acetone. The filtrate and washings were concentrated *in vacuo* and the crystalline residue was recrystallized from 60

Fig. 2.—Enzymic digestion of the pentapeptide L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline.

I. L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline
II. I + leucine aminopeptidase
III. L-valyl-L-tyrosyl-L-proline
IV. I + trypsin
V. I + chymotrypsin

Fig. 3.—Reaction of carbobenzoxy-L-valine *p*-nitrophenyl ester with L-tyrosine methyl ester.

I. L-tyrosine methyl ester
II. I + carbobenzoxy-L-valine *p*-nitrophenyl ester + triethylamine

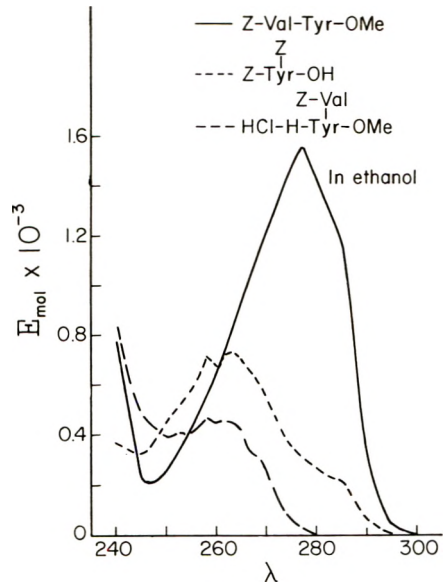

Fig. 4.—Ultraviolet absorption spectrum of O-(carbobenzoxy-L-valyl)-L-tyrosine methyl ester hydrochloride, and derivatives.

(24) All melting points were performed on a Fisher–Johns melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory of Department of Chemistry of this University. All samples for microanalyses were dried in an Abderhalden drying pistol with phosphorus pentoxide at 77° for 16 hr. at 0.3-mm. pressure. Paper chromatography was carried out on Whatman no. 1 filter paper at room temperature; the solvents used were *n*-butyl alcohol–acetic acid–water (BAW) in a ratio of 4:1:1 (by volume), *sec*-butyl alcohol–10% ammonia (SBA) in a ratio of 85:15 (by volume), *n*-butyl alcohol–pyridine–acetic acid–water (BPAW) in a ratio of 30:20:6:24 (by volume), and 3% ammonia–*sec*-butyl alcohol (ASB) in a ratio of 44:100 (by volume). Zone electrophoresis on paper (Whatman 3 MM) was performed at room temperature in a Spinco apparatus for 8 hr. at 400 volts with a pyridine–acetic acid buffer of pH 3.7.

(25) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1114 (1953).

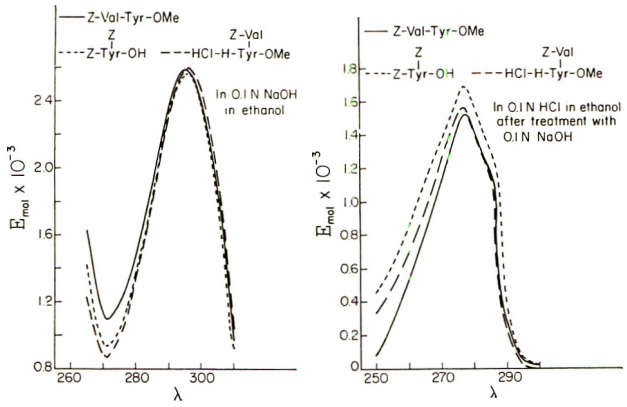

Fig. 5.—Effect of alkali on the ultraviolet absorption spectrum of O-(carbobenzoxy-L-valyl)-L-tyrosine methyl ester hydrochloride, and derivatives.

ml. of hot ethyl acetate to give 7 g. (81%) of the protected dipeptide ester, m.p. 150°; $[\alpha]^{25}D$ + 12.1° (*c* 1, pyridine); R_f BAW 0.83; R_f SBA 0.91. Lit.,[11] m.p. 155.5–156°; $[\alpha]^{25}D$ + 10.2° (*c* 4.8, pyridine).

Carbobenzoxy-L-valyl-L-tyrosine Hydrazide.—Carbobenzoxy-L-valyl-L-tyrosine methyl ester (2.91 g., 6.8 mmoles) was dissolved in 20 ml. of methanol, and 0.48 g. of hydrazine (15 mmoles) was added. Crystals appeared after an hour. The reaction mixture was left overnight, then stirred with methanol and water, filtered, and washed with water. Recrystallization from hot methanol (150 ml.) gave 2.6 g. (90%) of carbobenzoxy-L-valyl-L-tyrosine hydrazide, m.p. 247–248°. Lit.,[11] m.p. 239–241°.

L-Proline Benzyl Ester Hydrochloride.—L-Proline (22.8 g., 200 mmoles) was added to a mixture of 300 ml. of benzyl alcohol and 50 g. of thionyl chloride (prepared by adding the thionyl chloride to the alcohol at −5°). The mixture was stirred at room temperature for 48 hr., hydrochloric acid was removed *in vacuo*, and the residual solution was poured into 1 l. of anhydrous ether. The white crystalline material was filtered, washed with ether, and dried. Recrystallization from hot ethanol yielded 30 g. (64%) of L-proline benzyl ester hydrochloride, m.p. 148–149°. $[\alpha]^{25}D$ −43.3° (c 1, methanol). R_f BAW 0.62; R_f ASB 0.86. Lit.,[26] m.p. 148–148.5°; $[\alpha]^{28}D$ −41.6° (*c* 1.4, ethanol).

Carbobenzoxy-L-valyl-L-tyrosyl-L-proline Benzyl Ester (II).—Carbobenzoxy-L-valyl-L-tyrosine hydrazide (8.6 g., 20 mmoles) was dissolved in a mixture of 50 ml. of 2 *N* hydrochloric acid, 30 ml. of glacial acetic acid, and a few drops of ethyl acetate. This mixture was cooled to −2° and stirred vigorously with a vibromixer.[27] Sodium nitrite (1.4 g., 20 mmoles) was added in small portions over a period of 20 min. Stirring was continued for 30 min. Further operations were conducted in the cold room with reagents and glassware precooled to 0° for at least 2 hr. The azide was extracted into 60 ml. of ethyl acetate, and the solution was washed with water, 5% sodium bicarbonate, and then again with water. The organic layer was dried over anhydrous sodium sulfate. L-Proline benzyl ester hydrochloride (7.32 g., 30 mmoles) was suspended in 50 ml. of ethyl acetate, cooled to 0°, and stirred with 4.2 ml. of triethylamine (30 mmoles) for 60 min. The proline ester was filtered from triethylamine hydrochloride and washed with a few ml. of ethyl acetate. The azide solution was added and the volume of the mixture was reduced to half by evaporation *in vacuo* at 0°. Crystals appeared after 4 hr. The mixture was kept at 4° for 2 days and the protected tripeptide ester was filtered and washed with ethyl acetate to yield 9 g. (75%) of the product, m.p. 188–190°. Recrystallization from hot ethyl acetate gave a product that melted at 191–192°. $[\alpha]^{25}D$ −38.8° (*c* 1.2, pyridine). R_f BAW 0.83; R_f SBA 0.87. Lit.,[15] m.p. 186–188°; $[\alpha]^{21.5}D$ −40.6° (*c* 1, pyridine).

L-Valyl-L-tyrosyl-L-proline Benzyl Ester.—Peptide II (3.32 g., 5.5 mmoles) was finely ground in a glass mortar and stirred vigorously with 10 ml. of 4 *N* hydrobromic acid in glacial acetic acid for 15 min. at room temperature with the exclusion of moisture. The tripeptide ester hydrobromide was precipitated by the addition of 250 ml. of anhydrous ether. The precipitate was washed twice with ether by decantation. The residue was dissolved in 60 ml. of cold water that had been saturated with ethyl acetate and then was washed with ether (2 × 30 ml.). The aqueous phase was then brought to pH 8 with cold 5% sodium bicarbonate and the tripeptide base was extracted into ethyl acetate (2 × 50 ml.). The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was dried overnight over phosphorus pentoxide to yield 2 g. (77.8%) of L-valyl-L-tyrosyl-L-proline benzyl ester, m.p. 50–60°; $[\alpha]^{25}D$ −41.9° (*c* 0.6, methanol). R_f BAW 0.70; R_f SBA 0.83. Lit.,[15] $[\alpha]^{25}D$ −42.6° (*c* 1, methanol).

Anal. Calcd. for $C_{26}H_{33}N_3O_5$ (467.6): C, 66.8; H, 7.11; N, 8.98. Found: C, 66.5; H, 7.32; N, 8.77.

L-Valyl-L-tyrosyl-L-proline.—Carbobenzoxy-L-valyl-L-tyrosyl-L-proline benzyl ester (0.5 g., 0.83 mmole) was dissolved in a mixture of 20 ml. of glacial acid and 20 ml. of methanol, and hydrogenated for 6 hr. in the presence of freshly prepared palladium. The catalyst was filtered and washed and the filtrate and washings were evaporated *in vacuo*. The residue was crystallized from methanol-water to give 0.25 g. (75%) of L-valyl-L-tyrosyl-L-proline, m.p. 176–178°. The tripeptide was recrystallized from methanol-water, m.p. 177–178°; $[\alpha]^{25}D$ −27.4° (*c* 0.6, water). Lit.,[15] m.p. of the one-half hydrate, 206–208°, $[\alpha]^{22}D$ −29° (*c* 1, water). The difference in m.p. may be due to differences in water of crystallization. The tripeptide was found to be homogeneous in paper chromatography in three solvents and gave a positive reaction with ninhydrin and Pauly reagent; R_f BAW 0.53; R_f SBA 0.11; R_f BPAW 0.68. C, H, and N analyses indicated that the tripeptide crystallized with 1.25 moles of water.

Anal. Calcd. for $C_{19}H_{27}N_3O_5 \cdot 1.25\ H_2O$ (400): C, 57.1; H, 7.44; N, 10.5. Found: C, 57.0; H, 7.33; N, 10.8.

Paper electrophoresis revealed a single spot positive to ninhydrin and the Pauly reagent; mobility 0.23 with respect to lysine.

Carbobenzoxyl-L-valyl-N$^{\epsilon}$-tosyl-L-lysine Methyl Ester.—N$^{\epsilon}$-Tosyl-L-lysine methyl ester[16] hydrochloride (8.77 g, 25 mmoles) was suspended in 50 ml. of ethyl acetate, and the suspension was cooled in ice and stirred vigorously with 3.5 ml. of triethylamine (25 mmoles) for 30 min. The ethyl acetate solution was filtered into a flask containing 9.13 g. (25 mmoles) of carbobenzoxy-L-valine *p*-nitrophenyl ester,[28] and the precipitate of triethylamine hydrochloride was washed with 30 ml. of ethyl acetate. The reaction mixture was stirred at room temperature for 4 days. The protected dipeptide ester crystallized and was filtered and washed with ether. Yield 11.5 g. (83%), m.p. 131–132°; $[\alpha]^{25}D$ −18.8° (*c* 0.8, methanol); R_f BAW 0.91; R_f ASB 0.94. Lit.,[16] m.p. 130° $[\alpha]^{18}D$ −8° (*c* 1, acetic acid).

Carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine Hydrazide (III).—The protected dipeptide methyl ester described above (2.74 g., 5 mmoles) was dissolved in 30 ml. of methanol by warming and allowed to react with 0.5 ml. of hydrazine at room temperature. Crystals appeared after 3 hr. These were filtered after 12 hr. and washed with methanol to give 2.5 g. (91%) of III, m.p. 212°; $[\alpha]^{25}D$ −14.6° (*c* 4, acetic acid).

Anal. Calcd. for $C_{26}H_{37}N_5O_6S$ (547.7): C, 57.0; H, 6.81; N, 12.9; S, 5.85. Found: C, 57.3; H, 6.89; N, 12.8; S, 5.56.

Carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline Benzyl Ester (IV).—III (2 g., 3.66 mmoles) was dissolved in a mixture of 16 ml. of 1 *N* hydrochloric acid and 10 ml. of glacial acetic acid containing a few drops of ethyl acetate. The mixture was cooled to −2° and stirred vigorously with a Vibro-mixer,[27] and 0.276 g. of sodium nitrite was then added in small portions over a period of 20 min. Stirring was continued for another 30 min. Further operations were carried out in the cold room with equipment and reagents precooled to 0° for at least 2 hr. An equal volume of ice water was added and the azide was extracted into 40 ml. of ethyl acetate. The organic phase was washed with water, then with 5% sodium bicarbonate until neutral, and again with water. The ethyl acetate extract was dried over anhydrous sodium sulfate and filtered into a solution of 1.404 g. (3 mmoles) of L-valyl-L-tyrosyl-L-proline benzyl ester in 20 ml. of ethyl acetate at 0°. The total volume was reduced to about 50 ml. *in vacuo* at 0°, and the reaction mixture was kept at 4° for 3 days. A gelatinous precipitate was formed. After 3 days the solvent was removed *in vacuo*, the residue was again dissolved in fresh ethyl acetate, washed with 1 *N* hydrochloric acid, water, 5% sodium bicarbonate, and water, and, finally, the washed solution was dried over anhydrous sodium sulfate. The ethyl acetate

(26) R. E. Neuman and E. L. Smith, *J. Biol. Chem.*, **93**, 97 (1951).

(27) Vibro-mixer, A. G. Fuer Chemie-Apparatebau, Zurich, Model E1.

(28) B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 373 (1957).

solution was filtered and concentrated to a volume of 50 ml. The protected pentapeptide benzyl ester IV crystallized on standing; yield 2.2 g. (75%); m.p. 149–151°. Recrystallization from hot ethyl acetate improved the m.p. to 152.5–153.5°. $[\alpha]^{25}D$ −25.7° (c 1, dimethylformamide). R_f BAW 0.91; R_f ASB 0.94.

Anal. Calcd. for $C_{62}H_{86}N_6O_{11}S$ (983.2): C, 63.5; H, 6.77; N, 8.55; S, 3.26. Found: C, 63.4; H, 6.72; N, 8.80; S, 3.41.

L-Valyl-N$^\epsilon$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (V).—Carbobenzoxy-L-valyl-N$^\epsilon$-tosyl-L-valyl-L-tyrosyl-L-proline benzyl ester (0.5 g., 0.5 mmole) was dissolved in a mixture of 20 ml. of glacial acetic acid and 20 ml. of methanol, and the solution was hydrogenated for 8 hr. in the presence of freshly prepared palladium. The catalyst was filtered and washed with methanol. The filtrate and washings were evaporated to dryness to yield a crystalline residue, m.p. 215–218° dec. Recrystallization from hot methanol-water yielded 0.32 g. (84%) of V monohydrate, m.p. 240–241° dec.; $[\alpha]^{25}D$ −33.2° (c 1, acetic acid); R_f BAW 0.74; R_f ASB 0.67. C, H, and N analysis indicated that the pentapeptide crystallized with 1 mole of water.

Anal. Calcd. for $C_{37}H_{53}N_6O_8S \cdot H_2O$ (759.9) C, 58.5; H, 7.30; N, 11.1. Found: C, 58.6; H, 7.52; N, 11.1.

L-Valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline.—L-Valyl-N$^\epsilon$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline monohydrate (0.1 g.) was dissolved in 150 ml. of liquid ammonia freshly distilled from sodium, and small pieces of sodium were added with stirring until a blue color persisted for 30 min. Ammonia was allowed to evaporate and the residue was dried over phosphorus pentoxide and sulfuric acid. This material was dissolved in 10 ml. of 1 *M* acetic acid, applied onto an Amberlite ion-exchanger IRC-50 column (3 × 5 cm.) in the acid form, and the column was washed with 300 ml. of 0.1 *M* acetic acid and 300 ml. of water. The peptide was eluted with 60 ml. of pyridine–acetic acid–water (30:4:66). The eluate was evaporated to dryness at room temperature *in vacuo*, and the residue was dissolved in water and lyophilized to yield 62 mg. of the pentapeptide VI. Peptide acetate content was estimated on the basis of ultraviolet absorption at 275 mμ, to be 97.7%. Yield 69%. $[\alpha]^{\circ 25}D$ −67° (c 0.6, water) (calcd. for the free peptide). The peptide was found to be homogeneous in three solvent systems in paper chromatography and gave a positive reaction with ninhydrin and the Pauly reagent. R_f BAW 0.26; R_f BPAW 0.50; R_f ASB 0.37. Paper electrophoresis revealed a single spot positive to ninhydrin and the Pauly reagent; mobility 0.53 with respect to lysine.

Anal. Calcd. for $C_{30}H_{48}N_6O_7 \cdot CH_3COOH \cdot 1.5\ H_2O$ (691.9): C, 55.5; H, 8.02; N, 12.1. Found: C, 55.5; H, 7.7; N, 11.9.

One milligram of the peptide was hydrolyzed for 25 hr. at 110° in a sealed evacuated tube, with 0.5 ml. of constant boiling hydrochloric acid. Quantitative analysis in the Spinco amino acid analyzer[19] gave the following ratio for the amino acids: $Val_{2.0}$, $Lys_{0.94}$, $Tyr_{1.0}$, $Pro_{1.0}$.

Enzymic Digestion of VI.—The pentapeptide VI (1.0 mg.) was dissolved in 0.5 ml. of tris(hydroxymethyl)aminomethane (TRIS) buffer, pH 8, containing 0.002 *M* magnesium chloride. To this solution was added 0.1 ml. of LAP solution containing 0.5 mg. of the enzyme (Worthington Biochemical, lot no. 5917). The digestion mixture was kept at 37° for 24 hr.

Crystalline α-chymotrypsin and trypsin were commercial products (Armour); digestion of VI by these enzymes was carried out at 25° for 24 hr. in a solution of pH 8.5, with an enzyme–substrate ratio of 1/100 (w./w.).

Reaction of Carbobenzoxy-L-valine *p*-Nitrophenyl Ester with L-tyrosine Methyl Ester.—L-Tyrosine methyl ester hydrochloride (3.45 g., 15 mmoles) was suspended in 40 ml. of acetonitrile and 2.1 ml. of triethylamine was added. The solid dissolved readily. Carbobenzoxy-L-valine *p*-nitrophenyl ester (5.58 g., 15 mmoles) was added, followed by another 2.1 ml. of triethylamine (15 mmoles). The reaction mixture was stirred at room temperature. Paper chromatograms in BAW, after 8 hr. of reaction, showed the presence of unchanged tyrosine methyl ester (R_f BAW) 0.46, ninhydrin and Pauly positive), and a new ninhydrin positive Pauly negative spot, (R_f BAW 0.68). The solvent was removed *in vacuo* after 48 hr. and the residue was redissolved in 50 ml. of ethyl acetate. The crystalline material was filtered off (1.6 g., m.p. 252–254°), and was identified as triethylamine hydrochloride (mixed m.p. 252–254°). The filtrate was washed with water; the ethyl acetate layer was dried, and 7.5 ml. of 2 *N* hydrochloric acid in ethyl acetate was added. Crystals appeared in a few minutes. The mixture was kept at 4° for 6 hr. and filtered. The crystalline product was washed with ethyl acetate and dried over sodium hydroxide to yield 3 g. of a product which was identified as O-(carbobenzoxy-L-valyl)-L-tyrosine methyl ester hydrochloride (VII), m.p. 183–185°. A sample was recrystallized from methanol–ether, m.p. 186–187°. $[\alpha]^{25}D$ −26.7° (c 1, methanol).

Anal. Calcd. for $C_{23}H_{29}N_2O_6Cl$ (464.9): 59.4; H, 6.29; N, 6.03; Cl, 7.63. Found: C, 59.6; H, 6.43; N, 6.31; Cl, 7.90.

The filtrate from VII was washed with water, dried, and concentrated. A second crystalline material separated; it was recrystallized from methanol to yield 0.53 g. of a product which melted at 159–160, and which failed to give any reaction with ninhydrin or the Pauly reagent. The second crystalline product was identified as O,N-di(carbobenzoxy-L-valyl)-L-tyrosine methyl ester, m.p. 160°.

Anal. Calcd. for $C_{36}H_{43}N_3O_9$ (661.7): C, 65.3; H, 6.55; N, 6.35. Found: C, 65.8; H, 6.83; N, 6.55.

Determination of the ultraviolet absorption spectra of VII and other crystalline products in ethanol, alkali and acid was performed in a Beckman Model DU spectrophotometer.

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A New Synthesis of L-Glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine

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The hexapeptide, L-glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine, occurring in adrenocorticotropins and melanotropins, has been synthesized by a stepwise procedure beginning with the COOH-terminal glycine. Bioassay results showed that the hexapeptide is active as a melanocyte-stimulating and lipolytic agent. The following peptides were synthesized in crystalline form for the first time: L-tryptophylglycine *t*-butyl ester, N^G-tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester, carbobenzoxy-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester, N^α-carbobenzoxy-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester, N^α-carbobenzoxy-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine, *N*-*t*-butyloxycarbonyl-γ-benzyl-L-glutamyl-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester, and γ-benzyl-L-glutamyl-L-histidyl-L-phenylalanine-N^G-tosyl-L-arginyl-L-tryptophylglycine.

In connection with our previous synthesis[1,2] of the nonadecapeptide corresponding to the first nineteen amino acid residues of adrenocorticotropins (ACTH), we have reported a synthesis of the protected hexapeptide, N^α-carbobenzoxy-γ-benzyl-L-glutamyl-Im-benzyl-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine. Since this hexapeptide is a key peptide fragment for the synthesis of adrenocorticotropically and melanotropically (MSH) active products, it was deemed desirable to improve the synthesis by obtaining high yields and crystalline intermediates at each synthetic step. The present paper presents a new synthesis[3] of L-glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine (IX), by means of a stepwise procedure from the COOH-terminal residue.

Fig. 1 outlines the synthetic steps for each intermediate product, with its yield, obtained in the course of the synthesis of IX; the heavy underline indicates that the product had been obtained in crystalline form. Carbobenzoxyglycine *t*-butyl ester[6a] was hydrogenated and then crystallized as the hydrochloric acid salt.[6b] This salt was treated with triethylamine to liberate the free base and then condensed with carbobenzoxy-L-tryptophan by the dicyclohexylcarbodiimide (DCCI) procedure.[7] The protected dipeptide (I) failed to crystallize, but its free base (II) did crystallize on hydrogenation; II was then allowed to react, *via* DCCI, with crystalline N^α-carbobenzoxy-N^G-tosyl-L-arginine[8] to produce the amorphous protected tripeptide (III). The free base of the tripeptide ester (IV) crystallized on hydrogenation. This tripeptide ester was next condensed with carbobenzoxy-L-phenylalanine by the N-ethyl-5-phenylisoxazolium 3′ sulfonate procedure[9] to obtain the crystalline protected tetrapeptide (V). The tetrapeptide was hydrogenated and allowed to react with the azide of N^α-carbobenzoxy-L-histidine hydrazide[10] to produce the protected pentapeptide VI. After countercurrent distribution in the toluene system[2] to remove azide decomposition products, VI was crystallized from methanol solution; VI was further characterized by treatment with trifluroacetic acid to obtain the crystalline N^α-carbobenzoxy-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine. After hydrogenation, VI was then coupled with the crystalline *p*-nitrophenyl ester of N^α-*t*-butyloxycarbonyl-γ-benzyl-L-glutamic acid to produce the crystalline protected hexapeptide (VII).

The procedure outlined above for the synthesis of VII gave an over-all yield, based on the hydrochloride of glycine *t*-butyl ester, of approximately 30% of crystalline product. In the azide coupling step to obtain VI, an excess of the azide was used. In a normal azide coupling, an excess of peptide base is preferable in order to minimize the danger of Curtius rearrangement. However, an excess of azide was used to insure complete reaction of the tetrapeptide base; countercurrent distribution was shown to be an effective procedure in separating VI from contaminating decomposition products from excess N^α-carbobenzoxy-L-histidine azide. The protected hexapeptide VII was treated with trifluoroacetic acid to remove the *t*-butyloxycarbonyl and *t*-butyl ester groups, and then reduction in sodium in liquid ammonia[11] was performed to remove the γ-benzyl ester and tosyl groups. The resulting free peptide was purified by zone electrophoresis on starch. The purified product, IX, was submitted to paper chromatography in the solvent system consisting of *n*-butyl alcohol pyridine-acetic acid–water (15:10:3:12, v./v.), and to electrophoresis on paper in buffers of pH 3.6, 6.5, and 11.0; results of these experiments indicated that IX behaves as a homogeneous substance. Moreover, when IX was treated with leucine aminopeptidase[12] (LAP), it was digested completely to its constituent amino acids. Quantitative analyses of the digest by the procedure of Spackman, *et al.*,[13] in the Spinco amino acid analyzer gave a composition in molar ratios which is consistent

(1) C. H. Li, J. Meienhofer, E. Schnabel, D. Chung, T.-b. Lo, and J. Ramachandran, *J. Am. Chem. Soc.*, **82**, 5760 (1960).

(2) C. H. Li, J. Meienhofer, E. Schnabel, D. Chung, T.-b. Lo, and J. Ramachandran, *ibid.*, **83**, 4449 (1961).

(3) Kappeler[4] reported the synthesis of the glutaminyl analogue of this hexapeptide by a different route. Later, the same investigator in collaboration with Schwyzer[5] described the synthesis of IX by another scheme.

(4) H. Kappeler, *Helv. Chim. Acta*, **44**, 476 (1961).

(5) R. Schwyzer and H. Kappeler, *ibid.*, **44**, 1991 (1961).

(6) (a) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960); (b) While this manuscript was being prepared, it was noted that Taschner and co-workers [E. Taschner, C. Wasielewski, and J. F. Biernat, *Ann.*, **646**, 119 (1961)] have also prepared this compound by a different method.

(7) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(8) J. Ramachandran and C. H. Li, *J. Org. Chem.*, **27**, 4006 (1962).

(9) R. B. Woodward, R. A. Olafson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

(10) W. Holley and E. Sondheimer, *ibid.*, **76**, 1326 (1954).

(11) V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(12) R. L. Hill and E. L. Smith, *ibid.*, **228**, 577 (1957).

(13) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

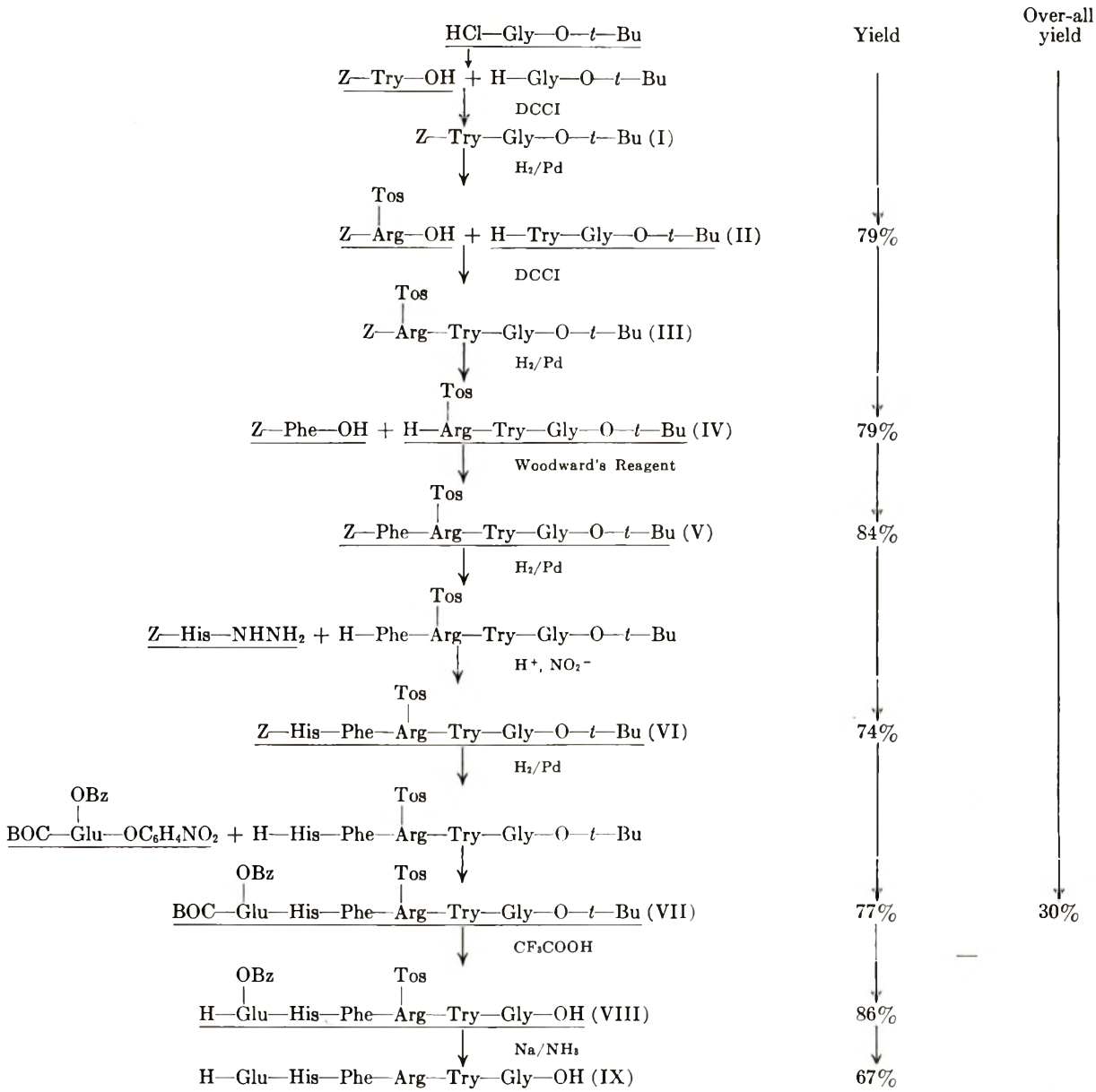

Fig. 1.—Outline of the synthesis of L-glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophyl glycine; Z, carbobenzoxy; Bz, benzyl; Tos, *p*-toluenesulfonyl; BOC, *t*-butyloxycarbonyl; *t*-Bu, *t*-butyl.

with the theoretical calculated values (molecular weight 830.9): $Glu_{1.06}$, $His_{0.97}$, $Phe_{1.02}$, $Arg_{1.08}$, $Try_{0.97}$, $Gly_{0.95}$.

Peptide IX was assayed for melanocyte-stimulating activity by the *in vitro* frog skin method,[14a] and on the basis of change in the melanophore index in hypophysectomized Rana pipiens.[14b] It was found that melanotrophic activities obtained by these two procedures (2×10^5 units per gram; a single dose of two micrograms caused a change in melanophore index from 1+ to 3+ within one hour in hypophysectomized frogs) were almost identical to values reported earlier[15] for the hexapeptide, glycine-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine. In agreement with previous conclusion,[15] it appears that glutamic acid can be replaced by glycine in IX without alteration of the melanocyte-stimulating potency.

By *in vitro* assay for lipolytic activity with perirenal fat pads of rabbits, IX was found to be active[16] in releasing non-esterified fatty acids with a calculated mean effective dose of twenty-three micrograms. Under the same conditions, the synthetic pentapeptide, L - histidyl - L - phenylalanyl - L - arginyl - L - tryptophylglycine, had only one-fiftieth of the lipolytic activity of IX.

Experimental[17]

Glycine *t*-Butyl Ester Hydrochloride.—Carbobenzoxyglycine *t*-butyl ester, 10.61 g., (40 mmoles) was prepared according to

(14) (a) K. Shizume, A. B. Lerner, and T. B. Fitzpatrick, *Endocrinology*, **54**, 533 (1954); (b) L. T. Hogben and D. Slome, *Proc. Roy. Soc.* (London), **B108**, 10 (1931).

(15) E. Schnabel and C. H. Li, *J. Biol. Chem.*, **235**, 2010 (1960).

(16) A. Tanaka, B. T. Pickering, and C. H. Li, *Arch. Biochem. Biophys.*, in press.

(17) All melting points were performed on a Fisher–Johns melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. All samples for microanalyses were dried in an Abderhalden drying pistol with phosphorus pentoxide at 77° for 16 hr. at 0.3-mm. pressure. Paper chromatography was carried out on Whatman no. 1 filter paper at room temperature; the solvents used were 1-butanol–acetic acid–water (BAW) in the ratio 4:1:1 and *sec*-butanol–10% ammonia (SBA) in the ratio of 85:15; the location of peptide spots was revealed by either the ninhydrin reagent, the Ehrlich reagent,[18] the Pauly reagent,[19] or the chlorine method.[20]

(18) J. Smith, *Nature*, **171**, 43 (1953).

(19) F. Sanger and H. Tuppy, *Biochem. J.*, **49**, 463 (1951).

(20) H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).

the procedure of Anderson and Callahan[6] and hydrogenated in 150 ml. of methanol with palladium (from 2 g. of palladium chloride) as catalyst for 2 hr. in a Vibro-mixer.[21] The catalyst was removed, and to the filtrate 36.5 ml. of 1.1 *N* hydrochloric acid was added. After evaporation to dryness *in vacuo* (20–25°), the flask containing the ester hydrochloride was kept in a desiccator *in vacuo* overnight over phosphorus pentoxide and sodium hydroxide pellets. The residue was dissolved in a small amount of methanol and crystallized by the addition of ether. After recrystallization from the same solvent system, 4.03 g. (60.5%), of glycine *t*-butyl ester hydrochloride were obtained[6b]; m.p. 137–140° $R_{f\ BAW} = 0.6$.

Anal. Calcd. for $C_6H_{14}N_1O_2Cl$ (167.7): C, 43.0; H, 8.41; N, 8.35. Found: C, 42.9; H, 8.22; N, 8.42.

N$^{\alpha}$-Carbobenzoxy-L-tryptophylglycine *t*-Butyl Ester (I).—Glycine *t*-butyl ester hydrochloride, 3.60 g. (21.4 mmoles), was suspended in 100 ml. of ethyl acetate and then cooled to 0° in an ice bath. A 3.0-ml. aliquot of triethylamine (21.4 mmoles) was added and the resulting suspension was stirred at 0°. Then 6.59 g. of carbobenzoxy-L-tryptophan (19.5 mmoles)[22] and 4.02 g. of N,N′-dicyclohexylcarbodiimide[7] (19.5 mmoles) were added and the mixture stirred for 1 hr. at 0° and then overnight at room temperature. The precipitate, dicyclohexylurea (DCU), was filtered off and the ethyl acetate solution was washed successively with 0.5% acetic acid, water, 1 *M* sodium carbonate, and water, and then dried over anhydrous sodium sulfate. The dried ethyl acetate solution was then evaporated to dryness *in vacuo* (20–25° bath). The residue was redissolved in acetone, more dicyclohexylurea was filtered off, and the acetone was evaporated *in vacuo* (20–25°). The original precipitate was washed with water to remove triethylamine hydrochloride and then filtered and dried. The total weight of dicyclohexylurea was 3.80 g. (87%); m.p. 235°. The N$^{\alpha}$-carbobenzoxy-L-tryptophylglycine *t*-butyl ester was isolated as a glassy material; wt., 8.24 g. (94%), m.p. 60–70°. It resisted all attempts at crystallization. $[\alpha]^{25}D$ −19.6° (*c* 1, methanol) $R_{f\ BAW} = 0.83$; $R_{f\ SBA} = 0.81$; Ehrlich, chlorine positive, single spot.

Anal. Calcd. for $C_{25}H_{29}O_5N_3$ (451.5): C, 66.5; H, 6.47; N, 9.31. Found. C, 66.2; H, 6.51; N, 9.60.

L-Tryptophylglycine *t*-Butyl Ester (II).—N$^{\alpha}$-Carbobenzoxy-L-tryptophylglycine *t*-butyl ester, 4.80 g. (10.6 mmoles), was dissolved in 100 ml. methanol. Palladium from 1 g. of palladium chloride was added and the peptide was decarbobenzoxylated by hydrogenation in a Vibro-mixer. When no more carbon dioxide could be detected, the catalyst was filtered and the methanol was evaporated *in vacuo* (20–25°). The peptide II was then crystallized from ethyl acetate-petroleum ether to give 2.84 g. (84%); m.p. 94–97°; $[\alpha]^{25}D$ + 2.3° (c 1, methanol).

Anal. Calcd. for $C_{17}H_{23}O_3N_3$ (317.4): C, 64.3; H, 7.30; N, 13.2. Found: C, 63.9; H, 7.51; N, 13.6.

N$^{\alpha}$-Carbobenzoxy-N^{G}-tosyl-L-arginyl-L-tryptophylglycine *t*-Butyl Ester(III).—N$^{\alpha}$-Carbobenzoxy-N^{G}-tosylarginine,[8] 4.62 g., (10.0 mmoles), was dissolved in 200 ml. of warm acetonitrile. The solution was cooled to room temperature, 3.59 g. of II (11.3 mmoles) were then added, and the solution then cooled to 0°. Dicyclohexylcarbodiimide in the amount of 2.06 g. (10. mmoles) was added with stirring at 0° for 1 hr., and the mixture was then placed overnight in the refrigerator at 4°. The dicyclohexylurea was filtered and the acetonitrile evaporated *in vacuo* (20–25°). The residue was redissolved in ethyl acetate and then washed with 0.5% acetic acid, water, 1 *M* sodium carbonate, water, and then the washed material was dried over anhydrous sodium sulfate. It was precipitated from ethyl acetate–petroleum ether to yield 6.40 g. (84%). The peptide resisted all attempts at crystallization. It was found to be homogeneous by paper chromatography. $R_{f\ BAW} = 0.82$, $R_{f\ SBA} = 0.75$, positive to Ehrlich regent and chlorine. $[\alpha]^{25}D$ −25.1° (c 1, methanol).

Anal. Calcd. for $C_{38}H_{47}O_8S\ N_7$ (761.9): C, 59.9; H, 6.22; N, 12.9. Found: C, 59.6; H, 6.01; N, 12.7.

N^{G}-Tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester (IV).—N$^{\alpha}$-Carbobenzoxy-N^{G}-tosyl-L-arginyl-L-tryptophylglycine *t*-butyl ester, 6.40 g., (8.4 mmoles) was dissolved in 150 ml. of methanol and then catalytically hydrogenated with palladium (from 1 g. of palladium chloride) as above. The catalyst was filtered off and the methanol evaporated *in vacuo* (20–25°). The peptide was crystallized from ethyl acetate; wt., 4.94 g. (79% over-all from the dicyclohexylcarbodiimide coupling step), m.p. 156–157°; $[\alpha]^{25}D$ +8.1° (*c* 1, methanol).

Anal. Calcd. for $C_{30}H_{41}O_6N_7S_1$ (627.8): C, 57.4; H, 6.58; N, 15.6. Found: C, 57.2; H, 6.71; N, 15.5.

Carbobenzoxy-L-phenylalanyl-N^{G}-tosyl-L-arginyl-L-tryptophylglycine *t*-Butyl Ester (V).—Carbobenzoxy-L-phenylalanine,[23] 5.23 g. (17.5 mmoles), was dissolved in 280 ml. of acetonitrile and then cooled to 0°. Triethylamine, 2.45 ml. (17.5 mmoles), and Woodward's reagent K,[9,24] 4.45 g. (17.5 mmoles), were added with stirring for 1 hr. at 0°. Then 10.24 g. of IV (16.0 mmoles) was added and the mixture stirred at room temperature overnight. The acetonitrile was evaporated *in vacuo* (20–25° bath) and the residue was dissolved in ethyl acetate–water (200:100 ml.). The ethyl acetate was then washed twice with water, twice with cold 1% citric acid, once with water, four times with 5% sodium bicarbonate, and then with water until the aqueous wash was neutral. The ethyl acetate layer was washed with saturated sodium chloride and then dried over anhydrous sodium sulfate. The ethyl acetate was evaporated *in vacuo* (20–25° bath), the dried residue was treated with fresh, dry ethyl acetate (150 ml.), and the peptide crystallized. Wt., 12.17 g. (84%); m.p., 160–162°; $[\alpha]^{25}D$ +18.8° (*c* 1, methanol).

Anal. Calcd. for $C_{47}H_{56}N_8O_9S$ (909.1): C, 62.1; H, 6.21; N, 12.3. Found: C, 62.1; H, 6.30; N, 12.6.

L-Phenylalanyl-N^{G}-tosyl-L-arginyl-L-tryptophylglycine *t*-Butyl Ester—Carbobenzoxy-L-phenylalanyl-N^{G}-tosyl-L-arginyl-L-tryptophyl glycine *t*-butyl ester, 3.85 g. (4.22 mmoles), was hydrogenated in 150 ml. of methanol with palladium (from 2 g. of palladium chloride). The catalyst was filtered off and the methanol evaporated *in vacuo* to give a glassy material, wt. 3.1 g. (95%). Single spot positive to ninhydrin and the Ehrlich reagent. $R_{f\ BAW} = 0.70$.

N$^{\alpha}$-Carbobenzoxy-L-histidyl-L-phenylalanyl-N^{G}-tosyl-L-arginyl L-tryptophylglycine *t*-Butyl Ester (VI).—An ice cold ethyl acetate solution of N$^{\alpha}$-carbobenzoxy-L-histidine azide prepared from 2.57 g. of the hydrazide (8.5 mmoles) as described by Holley and Sondheimer[10] was added to an ice cold solution of 3.1 g. of L-phenylalanyl - N^{G} - tosyl - L - arginyl - L - tryptophylglycine *t*-butyl ester (4.1 mmoles) in 20 ml. ethylacetate. In a few minutes the pentapeptide ester started to precipitate. The reaction mixture was stirred at 0°C. for 48 hr., and for 12 hr. at room temperature. The ethyl acetate was evaporated *in vacuo* at 0°, and the remaining amorphous material was dissolved in 20 ml. of methanol and added dropwise with stirring to 700 ml. of ether to precipitate the pentapeptide. After filtering and drying, 4.78 g. of crude material were obtained. Paper chromatography in the system BAW showed one Ehrlich positive spot with $R_f = 0.80$ and three Pauly positive spots with $R_f = 0.25$, 0.65, and 0.80. For further purification the material was subjected to countercurrent distribution in the system consisting of toluene–chloroform–methanol–water (5:5:8:2). After 100 transfers, the desired pentapeptide was identified by ultraviolet absorption at 280 mμ as the material in tubes 41–61 ($K = 0.96$). In paper chromatography, this material showed a single spot that was positive to the Pauly and Ehrlich reagents and migrated with $R_{f\ BAW} = 0.80$. Tubes 61–71 contained material that showed two Pauly-positive spots in paper chromatography: $R_f = 0.25$ and 0.65. The contents of tubes 41–61 were pooled and evaporated *in vacuo* (20–25°). The oily residue was dissolved in 30 ml. of methanol, and water was added until the beginning of a slight turbidity. After the solution had stood for 1 week at 0°, the pentapeptide ester crystallized, and was collected and dried. Yield: 3.74 g. (78%), m.p. 152–160°. The product was then recrystallized from the same solvent system, m.p. 158–160°; $[\alpha]^{25}D$ −32.6° (*c* 1, methanol)

Anal. Calcd. for $C_{53}H_{62}O_{10}N_{11}S_1 \cdot 1/2\ H_2O$ (1055.2): C, 60.3; H, 6.15; N, 14.6. Found: C, 60.3; H, 6.50; N, 14.3.

N$^{\alpha}$-Carbobenzoxy-L-histidyl-L-phenylalanyl-N^{G}-tosyl-L-arginyl L-tryptophylglycine.—The above protected pentapeptide ester VI (200 mg.) was dissolved in 2 ml. of trifluoroacetic acid in a nitrogen atmosphere. After being allowed to stand at room temperature for 15 min., ether was added to precipitate the product. The precipitate was washed well with ether to remove all excess trifluoroacetic acid, filtered, and then dried. The peptide acid was crystallized from dimethylformamide–ether to yield 154 mg. (73%), m.p. 162–164°, $R_{f\ SBA} = 0.16$; $[\alpha]^{25}D$ −20.7 (*c* 1, methanol).

Anal. Calcd. for $C_{49}H_{55}O_{10}N_{11}S_1 \cdot CF_3COOH$ (1104.1): C, 55.5; H, 5.11; N, 14.0. Found. C, 55.8; H, 5.51; N, 14.4.

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(24) *N*-Ethyl-5-phenylisoxazolium 3′-sulfonate, Pilot Chemicals, Inc. Watertown 72, Mass.

N-*t*-Butyloxycarbonyl-γ-benzyl-L-glutamic Acid *p*-Nitrophenyl Ester.—γ-Benzyl-L-glutamic acid,[25] 2.37 g. (10 mmoles), and MgO, 0.80 g. (20 mmoles), were suspended in 40 ml. of 50% dioxane and stirred for 1 hr. at room temperature. Then 3.0 g. of *t*-butyloxycarbonyl azide[26,27] (21 mmoles) was added and the mixture was stirred at 45–50° for 6 hr. The mixture was then poured into 250 ml. of ice cold water and some insoluble material (MgO) was filtered off. The aqueous solution was then extracted with 150 ml. of ethyl acetate (three times) to remove excess *t*-butyloxycarbonyl azide. The ethyl acetate washings were then washed twice with 20 ml. of 7.5% sodium bicarbonate and once with 50 ml. of water. The combined aqueous extracts were cooled at 0°, and the pH was adjusted to 3 with 10% citric acid (approximately 40 ml.). The acidified solution was then saturated with sodium chloride and extracted twice with 150 ml. of ethyl acetate. The ethyl acetate was washed with saturated sodium chloride, and then dried over anhydrous sodium sulfate. The ethyl acetate was evaporated *in vacuo* (20–25° bath) to leave the N-*t*-butyloxycarbonyl-γ-benzyl-L-glutamic acid as an oil, homogeneous in paper chromatography, $R_{f\ BAW} = 0.90$; $R_{f\ SBA} = 0.58$ (chlorine detection). Wt., 1.54 g. (46%), 4.5 mmole. The oil was dissolved in 20 ml. of ethyl acetate, cooled to 0°, and then 0.63 g. of *p*-nitrophenol (4.5 mmoles) and 0.9 g. of dicyclohexylcarbodiimide (4.5 mmoles) were added. The mixture was stirred at 0° for 2 hr. It was then placed in the refrigerator (4°) overnight. The dicyclohexylurea was filtered off, [wt. 0.77 g. (75%)] and the ethyl acetate was evaporated *in vacuo* (20–25° bath). The *p*-nitrophenyl ester was crystallized from ethyl acetate–petroleum ether (20–30 ml.) to yield 0.53 g. (52%), m.p. 120–121°; $[\alpha]^{25}D$ −32.7° (*c* 1, methanol).

Anal. Calcd. for $C_{23}H_{26}N_2O_8$ (458.3): C, 60.3; H, 5.68; N, 6.11. Found: C, 60.3; H, 5.90; N, 6.32.

N-*t*-Butyloxycarbonyl-γ-benzyl-L-glutamyl-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine *t*-Butyl Ester (VII). N$^\alpha$-carbobenzoxy - L - histidyl - L - phenylalanyl - N^G - tosyl-arginyl - L - tryptophylglycine *t*-butyl ester, 6.28 g. (6.0 mmoles), was dissolved in 150 ml. of methanol and catalytically hydrogenated with palladium from 2 g. of palladium chloride until no more carbon dioxide was detectable; $R_{f\ BAW} = 0.60$. The palladium was filtered off and the methanol was evaporated *in vacuo* (20–25° bath). The residue was dissolved in 50 ml. of acetonitrile and 3 ml. of dimethylformamide. A 3.04-g. sample of *N*-butyloxycarbonyl-γ-benzylglutamic acid *p*-nitrophenyl ester (6.6 mmoles) was added and the mixture was stirred for 2 days at room temperature. During the course of the reaction, the mixture became gelatinous, and more acetonitrile (approximately 50 ml.) was added to insure good stirring and mixing. After the 2 days of stirring, the solvents were evaporated *in vacuo* (20–25° bath) and the residue treated with a large volume of ether. The resulting precipitate was filtered, washed well with ether, and then dried. Weight of crude VII was 6.8 g. (93%). The product was then crystallized from warm methanol to yield 5.7 g. (77%), m.p. 162–164°. $[\alpha]^{25}D$ −22.5° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{62}H_{78}O_{13}N_{12}S_1$ (1231.4): C, 60.5; H, 6.38; N, 13.7. Found: C, 60.2; H, 6.43; N, 13.7.

γ-Benzyl-L-glutamyl-L-histidyl-L-phenylalanyl-N^G-tosyl-L-arginyl-L-tryptophylglycine (VIII).—The above protected hexapeptide, 0.62 g. (0.5 mmole), was dissolved in 2.0 ml. of trifluoroacetic acid in a nitrogen atmosphere. The solution was allowed to stand at room temperature for 15 min. and then added to 50 ml. of ether to precipitate the desired peptide. The precipitate was thoroughly washed with ether to remove excess trifluoroacetic acid, and then crystallized from the slow evaporation of a methanol solution to give 0.56 g. (86%), m.p. 165–168° (dec.); $[\alpha]^{25}D$ +12.0° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{53}H_{62}O_{11}N_{12}S_1 \cdot (CF_3COOH)_2 \cdot CH_3OH$ (1335.3): C, 52.2; H, 5.13, N. 12.6. Found: C, 52.1, H, 5.53; N, 13.0.

L-Glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine (IX).—The ditrifluoroacetate salt of VIII, 0.534 g., was dissolved in 100 ml. of liquid ammonia, and small pieces of sodium were added at the temperature of the boiling point of liquid ammonia (−33°) until the blue color persisted for 30 min.[11] The ammonia was then allowed to evaporate and the residue was dried completely in a vacuum desiccator over concentrated sulfuric acid. The residue was then desalted on an IRC-50 column, eluted with pyridine–acetic acid–water buffer (30:4:66), and then lyophylized to yield 0.300 g. (90%) of the crude free hexapeptide. A 50-mg. sample of this material was purified by zone electrophoresis on starch in 0.05 *M* sodium carbonate and run for 24 hr. at 200 volts to yield 37 mg. (74%) of a product that was homogeneous in paper chromatography in the BAW, SBA, and 1-butanol–pyridine–acetic acid–water (15:10:3:12) systems, and in paper electrophoresis in buffers of pH 3.6, 6.5, and 11.0. It appeared as a single spot, positive to ninhydrin, the Ehrlich, Pauly, and Sakaguchi reagents, and chlorine; $[\alpha]^{25}D$ −17.3° (*c* 1, in acetic acid).

Anal. Calcd. for $C_{39}H_{50}N_{12}O_9 \cdot CH_3COOH \cdot H_2O$ (909.0): C, 54.2; H, 6.21; N, 18.5. Found: C, 54.3; H, 6.78; N, 18.7.

LAP Digest of the Hexapeptide.—The above hexapeptide, 0.8 mg., was dissolved in 0.5 ml. of tri(hydroxymethyl)aminomethane (TRIS)buffer, (pH 8.5, 0.01 *M* Mg^+) and 0.008 ml. of a LAP solution (1 mg. of Worthington LAP, lot no. 5917 in 0.2 ml. of water) was added and the solution was incubated at 37° for 24 hr. Amino acid analysis by the Spinco amino acid analyzer[13] gave the following molar ratios: $Glu_{1.05}His_{0.97}Phe_{1.02}Arg_{1.08}Try_{0.97}Gly_{0.95}$.

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Preparation and Reactions of Triphenyltinlithium

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The preparation, properties, and reactions of triphenyltinlithium with water, triphenyltin fluoride, tri-*n*-butyl phosphate, ethyl iodide, benzyl chloride, bromobenzene, chlorotriphenylsilane, chlorotrimethylsilane, and carbon dioxide are described.

The preparation of triphenyltinlithium has been described in the literature by several investigators. In 1950, G. Wittig[2a] reported its preparation from phenyllithium and diphenyltin, as well as from triphenyltin bromide and metallic lithium in liquid ammonia. Gilman and Rosenberg[2b] later reported the preparation of triphenyltinlithium from stannous chloride and phenyllithium. In this manner the intermediate preparation of diphenyltin was eliminated. Blake, Coates, and

$$C_6H_5Li + (C_6H_5)_2Sn \longrightarrow (C_6H_5)_3SnLi \quad (1)$$

$$(C_6H_5)_3SnBr + 2Li \xrightarrow{NH_3} (C_6H_5)_3SnLi + LiBr \quad (2)$$

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(2a) G. Wittig, *Angew. Chem.*, **62**, 231 (1950); (b) H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **74**, 531 (1952).

$$3C_6H_5Li + SnCl_2 \longrightarrow (C_6H_5)_3SnLi + 2LiCl \quad (3)$$

Tate[3] recently reported on the preparation and reactions of tributyltin and triphenyltin derivatives of sodium and lithium. They prepared triphenyltinsodium by the reaction between sodium naphthalene and either hexaphenylditin, triphenyltin bromide, or tetraphenyltin in tetrahydrofuran (THF) or 1,2-dimethoxyethane as solvents. They prepared triphenyltinlithium, however, by the procedure of Gilman and Rosenberg[2b] (equation 3). Utilizing the organometallics so prepared, these investigators noted some differences in the reaction products and yields over those reported earlier in the literature[2b] for reactions between triphenyltinlithium and ethyl iodide or benzyl chloride. Since we have also observed differences in the reactions of triphenyltinlithium prepared by either equation 1 or 3 and by the method previously reported by us,[4] we now wish to report in more detail some properties and reactions of triphenyltinlithium.

It has been previously shown[4] that triphenyltinlithium can be prepared very easily from the reaction between triphenyltin chloride and metallic lithium in tetrahydrofuran or by the cleavage of hexaphenylditin with metallic lithium in tetrahydrofuran. It was suggested that the reactions occurring in the preparation of the organometallic are

$$(C_6H_5)_3SnCl + 2Li \xrightarrow{THF} (C_6H_5)_3SnLi + LiCl \quad (4)$$

$$(C_6H_5)_3SnLi + (C_6H_5)_3SnCl \xrightarrow{THF} (C_6H_5)_3SnSn(C_6H_5)_3 + LiCl \quad (5)$$

$$(C_6H_5)_3SnSn(C_6H_5)_3 + 2Li \xrightarrow{THF} 2(C_6H_5)_3SnLi \quad (6)$$

Gilman[5] has previously suggested the same sequence of reactions for the direct preparation of triphenylsilyllithium from chlorotriphenylsilane and metallic lithium in tetrahydrofuran.

The triphenyltinlithium reagent prepared as described above (equations 4–6) is dark olive-green and is stable when subjected to refluxing in a tetrahydrofuran solution for at least twenty-four hours. No evidence of solvent cleavage was observed.

Carbonation of the triphenyltinlithium immediately after its preparation or after 24 hours of refluxing in tetrahydrofuran produced no benzoic acid. This observation indicates that triphenyltinlithium as prepared above does not exist as a complex[6] in equilibrium with diphenyltin and phenyllithium.

$$(C_6H_5)_3SnLi \rightleftharpoons (C_6H_5)_2Sn + C_6H_5Li \quad (7)$$

A sample of triphenyltinlithium in tetrahydrofuran solution when stored in a refrigerator (0°) over a period of one month showed no sign of decomposition as measured by titration.[7] The triphenyltinlithium reagent does give a positive Color Test I[8] which is conveniently used to follow the reactions. Conversely triphenyltinlithium prepared *via* equation 3 has been reported[9] to give a negative Color Test I.

When triphenyltinlithium was allowed to react with chlorotriphenylsilane, a mixture of products was obtained. The main products were triphenylsilyltriphenyltin, hexaphenyldisilane, and hexaphenylditin. Three other products in lesser quantities were also identified as triphenylsilanol, triphenylsiloxytriphenyltin, and tetraphenyltin. The presence of the first three compounds indicates that a metal–halogen interchange occurred.

$$(C_6H_5)_3SnLi + (C_6H_5)_3SiCl \longrightarrow (C_6H_5)_3SnCl + (C_6H_5)_3SiLi \quad (8)$$

Various combinations of reactions between the organolithium intermediates with the metallic chlorides could account for the presence of the three major products. Separation of some of the products (triphenylsilyltriphenyltin and hexaphenyldisilane) by fractional crystallization was very difficult because of the similarity in solubilities. The desired product, triphenylsilyltriphenyltin, was finally separated from hexaphenyldisilane by repeated crystallizations from chloroform. Because of this separation difficulty, the exact yields of the products are unknown.

An attempt to prepare trimethylsilyltriphenyltin from triphenyltinlithium and chlorotrimethylsilane resulted again in a metal–halogen interchange yielding hexaphenylditin in 68.7% yield.

Several attempts to prepare triphenyltincarboxylic acid by carbonation of triphenyltinlithium have failed. Gilman and Rosenberg[9] and Blake, Coates, and Tate[3] also reported no triphenyltincarboxylic acid in carbonation reactions of triphenyltinlithium and triphenyltinsodium. Hexaphenylditin was isolated in our studies in an 85% yield.

The alkyl iodide, arylalkyl chloride, alkyl phosphate, aryl bromide, and triaryltin fluoride reacted in the normal metathetical manner to yield the desired products as shown in Table I.

TABLE I

REACTIONS OF TRIPHENYLTINLITHIUM

Reactants	Products	Yields, %
H_2O	$(C_6H_5)_3SnH$	69–74
$(C_6H_5)_3SnF$	$(C_6H_5)_3SnSn(C_6H_5)_3$	92
$(C_4H_9O)_3PO$	$(C_6H_5)_3SnC_4H_9$	70
C_2H_5I	$(C_6H_5)_3SnC_2H_5$	87
$C_6H_5CH_2Cl$	$(C_6H_5)_3SnCH_2C_6H_5$	78
C_6H_5Br	$(C_6H_5)_4Sn$	75
$(C_6H_5)_3SiCl$	$(C_6H_5)_3SiSn(C_6H_5)_3$, $(C_6H_5)_3SnSn(C_6H_5)_3$ $(C_6H_5)_3SiSi(C_6H_5)_3$, $(C_6H_5)_4Si$, $(C_6H_5)_3SiOSn(C_6H_5)_3$ $(C_6H_5)_3SiOH$	—
$(CH_3)_3SiCl$	$(C_6H_5)_3SnSn(C_6H_5)_3$	68.7
CO_2	$(C_6H_5)_3SnSn(C_6H_5)_3$	85

Essentially three different methods have been described in the literature for the preparation of organotin hydrides: (a) reduction of organotinsodium compounds[10] and organotinlithium compounds[11] with ammonium chloride or ammonium bromide in liquid am-

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(4) C. Tamborski, F. E. Ford, W. L. Lehn, G. Moore, and E. J. Soloski, *J. Org. Chem.*, **27**, 619 (1962).
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(9) H. Gilman and S. D. Rosenberg, *J. Org. Chem.*, **18**, 680 (1953).
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monia, (b) reduction of organotin halide[12] with lithium aluminum hydride, (c) reduction of organotin halides with amalgamated aluminum.[13] Triphenyltinlithium as prepared in this study is readily hydrolyzed with either saturated aqueous ammonium chloride solution or dilute hydrochloric acid to yield triphenyltin hydride in 70–75% yields.[14] Previously reported attempts[2a,11,15] to hydrolyze triphenyltinlithium prepared by equations 1 or 3 to the expected triphenyltin hydride were unsuccessful.

Experimental

Preparation of Triphenyltinlithium from Hexaphenylditin.—To a rapidly stirred mixture of 35.0 g. (0.05 mole) of hexaphenylditin and 3.5 g. (0.5 g.-atom) of lithium clippings was added enough tetrahydrofuran to form a thick paste. After about 3 min. the mixture started turning yellow-green. A total of 250 ml. of tetrahydrofuran was added dropwise during 8 min. The dark olive-green mixture gave a positive Color Test I within 5 min. After being stirred for 3 hr. the greenish black mixture was filtered through glass wool and a derivative was formed by one of the reactions below.

Preparation of Triphenyltinlithium from Triphenyltin Chloride.—A solution of 38.5 g. (0.1 mole) of triphenyltin chloride in 110 ml. of tetrahydrofuran was added during 3 min. to a stirred suspension of 6.9 g. (1.0 g.-atom) of lithium clippings in 100 ml. of tetrahydrofuran. The reaction was exothermic and the dark olive-brown solution gave a positive Color Test I within 7 min. After being stirred for 1 hr. the mixture was filtered through glass wool and a derivative was formed by one of the reactions below.

Preparation of Triphenyltin Hydride from Hexaphenylditin.—A solution of triphenyltinlithium prepared as described above from 0.05 mole of hexaphenylditin was hydrolyzed by pouring into 1 *M* hydrochloric acid. The mixture was extracted with ether and the organic layer was dried over sodium sulfate. Evaporation of the solvents left a semisolid residue from which was filtered 3.3 g. (9.6%) of hexaphenylditin, m.p. 226–234° (mixture melting point). The filtrate was distilled to give 25.8 g. (74%) of triphenyltin hydride, b.p. 142–143° (0.1 mm.) (lit.,[11] b.p. 155–157° at 0.1 mm.), $n^{25}D$ 1.6345. The infrared spectrum of this material was identical with that of an authentic sample.

Preparation of Triphenyltin Hydride from Triphenyltin Chloride.—A solution of triphenyltinlithium prepared as described above from 0.05 mole of triphenyltin chloride was hydrolyzed by pouring into 1 *M* hydrochloric acid. The mixture was extracted with ether and the organic layer was dried over sodium sulfate. Evaporation of the solvents left a semisolid residue from which was filtered 1.9 g. (10.9%) of hexaphenylditin, m.p. 230–235° (mixture melting point). The filtrate was distilled to give 12.1 g. (69%) of triphenyltin hydride, b.p. 145–149° (0.1 mm.) (lit.,[11] b.p. 155–157° at 0.1 mm.), $n^{26}D$ 1.6342, d^{25}_4 1.3771 This product was identified by comparison of the infrared spectrum with that of an authentic sample and by derivatization with bromine to yield triphenyltin bromide.

Preparation of *n*-Butyltriphenyltin.—A solution of triphenyltinlithium, prepared as described above from 0.05 mole of triphenyltin chloride, was added to a stirred solution of 13.3 g. (0.05 mole) of redistilled tri-*n*-butyl phosphate in 30 ml. of tetrahydrofuran during 5 min. The black mixture gave a negative Color Test I and was stirred for 30 min. The mixture was hydrolyzed with water, ether was added, and the mixture was acidified with hydrochloric acid. The organic layer was combined with ether extracts of the aqueous layer and dried over sodium sulfate. Evaporation of solvents left a tarry solid which was crystallized from 2-propanol to give 14.3 g. (70.3%) of *n*-butyltriphenyltin, m.p. 60–62.5° (lit.,[16] m.p. 61–62°).

Anal. Calcd. for $C_{22}H_{32}Sn$: C, 64.90; H, 5.94; Sn, 29.16. Found: C, 64.50, 64.76; H, 5.82, 5.83; Sn, 29.4.

Preparation of Ethyltriphenyltin.—A solution of triphenyltinlithium, prepared as described above from 38.6 g. (0.1 mole) of triphenyltin chloride, was added to a solution of 15.6 g. (0.1 mole) of ethyl iodide dissolved in 100 ml. of tetrahydrofuran over a period of 10 min. A slight heat of reaction was observed and after 5 min. Color Test I was negative. The reaction was stirred for an additional 90 min. and then hydrolyzed with ammonium chloride. The organic layer was separated and dried over sodium sulfate. Evaporation of solvents left 35.1 g. (93.1%) of crude product. Recrystallization from 95% ethanol yielded 32.7 g. (86.4%) of pure ethyltriphenyltin, m.p. 62–63° (lit.,[3] m.p. 57°).

Anal. Calcd. for $C_{20}H_{20}Sn$: C, 63.37; H, 5.32; Sn, 31.31. Found: C, 63.12, 63.27; H, 5.28, 5.19; Sn, 31.46, 31.20.

Preparation of Triphenylbenzyltin.—To a solution of triphenyltinlithium prepared as described above from 21.5 g. (0.055 mole) of triphenyltin chloride was added a solution of 6.96 g. (0.055 mole) of benzyl chloride in 55 ml. of tetrahydrofuran. The reaction mixture changed from dark green to dark brown and Color Test I was negative after 15 min. The mixture was hydrolyzed with saturated ammonium chloride, and the organic layer was separated and dried over sodium sulfate. Evaporation of solvents left 20.7 g. (85.5%) of crude product. Recrystallization from 95% ethanol yielded 18.1 g. (77.4%) of pure triphenylbenzyltin, melting point and mixture melting point 89.5–90.5° (lit.,[3] m.p. 90–91°).

This compound was also made (72% yield) from triphenyltinlithium prepared from hexaphenylditin.

Preparation of Tetraphenyltin from Bromobenzene.—A solution of triphenyltinlithium, prepared from 38.5 g. (0.1 mole) of triphenyltin chloride was added to 15.7 g. (0.1 mole) of bromobenzene dissolved in 100 ml. of tetrahydrofuran over a period of 8 min. The reaction was exothermic and a white precipitate formed immediately. After 20 min. of stirring Color Test I was negative. The reaction mixture was hydrolyzed with ammonium chloride followed by the addition of 200 ml. of ether. A white precipitate formed at the interface and was filtered. The ether layer was dried over sodium sulfate. The material at the interface melted between 220–225°, and a mixture melting point with an authentic sample of tetraphenyltin was not depressed. The infrared spectrum of this material was identical with that of tetraphenyltin. The yield of tetraphenyltin was 32.0 g. (75%).

The dried ether layer was evaporated to give 12.6 g. of material. Repeated crystallizations of this material gave 4.7 g. (13%) of hexaphenylditin, m.p. 223–227°. This product was identified by a mixture melting point with an authentic sample and by comparison of the infrared spectra. No other products were isolated.

Preparation of Hexaphenylditin from Triphenyltin Fluoride.—To a stirred solution of 3.70 g. (0.01 mole) of triphenyltin fluoride suspended in 100 ml. of tetrahydrofuran was added 0.01 mole triphenyltinlithium during 1 min. This medium brown suspension gave a negative Color Test I within 2 hr. After hydrolyzing with saturated ammonium chloride ether was added and the solution phase separated. Distillation of the organic layer left a white crystalline material with a melting point of 214–220°. Recrystallization from benzene yielded 6.41 g. (91.6%) of pure hexaphenylditin, m.p. 232–234°, which was identified by a mixture melting point with an authentic sample. No other products were identified.

Preparation of Triphenylsilyltriphenyltin.—To a stirred solution of triphenyltinlithium prepared as described above from 0.11 mole of triphenyltin chloride was added a solution of 29.5 g. (0.1 mole) of chlorotriphenylsilane in 100 ml. of tetrahydrofuran during 1 min. The black suspension gave a faintly positive Color Test I throughout 4 hr. of stirring. After hydrolysis with saturated ammonium chloride solution and addition of ether the resulting gray precipitate was filtered and recrystallized from chloroform; 18.1 g. (29.7%) of crude triphenylsilyltriphenyltin was obtained, m.p. 298–309° (cor.). Further recrystallization from chloroform gave 11.8 g. (19.4%) of white prisms, m.p. 299–303° (cor.) [lit.,[3] m.p. 289–291° (uncor.)]. This product was identified by a mixture melting point with an authentic sample and by comparison of the infrared spectra. Also obtained from the gray precipitate was 20.4 g. of crude hexaphenyldisilane, m.p. 313–335° (cor.). Work-up of the filtrate gave 8.3 g. of crude hexaphenylditin, m.p. 200–230° (cor.), 1.8 g. of crude tetraphenyltin which melted at 225.5–227° (cor.) after recrystalli-

(12) (a) A. E. Finholt, A. C. Bond, Jr., and H. Schlesinger, *J. Am. Chem. Soc.*, **69**, 1199 (1947); (b) A. E. Finholt, A. C. Bond, Jr., K. E. Wilzbach, and H. I. Schlesinger, *ibid.*, **69**, 2692 (1947).

(13) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luitjen, *Chem. Ind.* (London), 1290 (1958).

(14) Recently it has been shown that $[(C_6H_5)_3Sn]_2Mg$ can be hydrolyzed easily to yield triphenyltin hydride in 82% yield. C. Tamborski and E. J. Soloski, *J. Am. Chem. Soc.*, **83**, 3734 (1961).

(15) H. Gilman and S. D. Rosenberg, *J. Org. Chem.*, **18**, 1554 (1953).

(16) F. P. Kipping, *J. Chem. Soc.*, 2365 (1928).

zation from chloroform, 4.2 g. of crude triphenylsilanol which melted at 128–150° (cor.) after recrystallization from ligroin (b.p. 60–90°), and 5.9 g. of crude triphenylsiloxytriphenyltin which melted at 138–142° (cor.) after recrystallization from ligroin (b.p. 60–90°).

Attempted Preparation of Trimethylsilyltriphenyltin.—To a stirred solution of triphenyltinlithium, prepared as described above from 19.2 g (0.05 mole) of triphenyltin chloride, was added a solution of 8.2 g. (0.075 mole) of chlorotrimethylsilane in 50 ml. of tetrahydrofuran over a period of 4 min. The resulting black suspension gave a negative Color Test I and was stirred at room temperature for an additional 2 hr. After hydrolysis with 2 *M* hydrochloric acid and addition of ether the precipitate which formed was filtered. The ether layer was separated and dried over sodium sulfate. The precipitate which had formed at the interface was identified by infrared analysis and mixture melting point as hexaphenylditin. An additional small amount of hexaphenylditin was obtained from the ether layer. The total amount of hexaphenylditin obtained was 12.0 g. (68.7%), m.p. 233–236° (cor.). No attempt was made to isolate any other products resulting from the metal–halogen interchange.

Attempted Preparation of Triphenyltin Carboxylic Acid.—A solution of triphenyltinlithium prepared as described above from 0.05 mole of triphenyltin chloride was poured into a flask containing Dry Ice, forming a black mixture with a negative Color Test I. After the Dry Ice had disappeared, dry carbon dioxide was bubbled into the mixture intermittently for 20 hr. The mixture was hydrolyzed with cold 1 *M* hydrochloric acid and filtered to give 14.8 g. (85%) of hexaphenylditin, identified by a comparison of the infrared spectra and a mixture melting point with an authentic sample of hexaphenylditin. Work-up of the filtrate gave only a small amount of material which did not melt below 300°.

Secondary and Tertiary Perfluoroörganomercury Compounds

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Addition of mercuric fluoride to terminal fluoroölefins has been found to be a general method for the preparation of secondary and tertiary alkyl mercurials. Compounds we have prepared in this manner are bis(perfluoroisopropyl)mercury, bis(3H-1-trifluoromethylpentafluoropropyl)mercury, bis(3-chloro-1-trifluoromethylpentafluoropropyl)mercury, and bis(perfluoro-*t*-butyl)mercury. These organomercury compounds are unaffected by strong acids and bases at moderate temperatures. They are cleaved by halogens to secondary and tertiary perfluoroalkyl halides, which are useful for synthesis of other branched-chain fluorocarbon derivatives.

Several methods for preparing primary perfluoroalkyl mercurials have appeared in the literature. In one, fluoroalkyl iodides are heated with silver, copper, cadmium, zinc, or magnesium amalgam,[1] and in another mercuric fluoride is added to fluoroethylenes in arsenic trifluoride solution.[2] Branched fluoroalkyl mercurials are another matter, and until very recently no routes to such compounds were known. Because such branched mercurials should be starting materials for a great many secondary and tertiary fluoroalkyl derivatives, a largely unexplored area of chemistry, we have examined the addition of mercuric fluoride to terminally unsaturated fluoroölefins. This method has already been reported as a route to bis(perfluoroisopropyl)mercury,[3] a precursor of hexafluorothioacetone.

Preparation.—The synthesis described by Krespan, which utilizes arsenic trifluoride as a solvent, is not well suited for addition of mercuric fluoride to fluoroölefins containing more than two carbon atoms. However, the reaction proceeds readily with a large number of fluoroölefins when anhydrous hydrogen fluoride[4] is used as a solvent. Mercuric fluoride is soluble in hydrogen fluoride at 100° and autogenous pressure in an autoclave. Branched-chain mercurials synthesized by this method are given in Table I. The low yields for III and IV undoubtedly can be improved by more detailed examination of reaction conditions. The method can also be used to obtain the fluoroethyl mercurials, bis(pentafluoroethyl)mercury and bis(1-chloro-1,2,2,2-tetrafluoroethyl)mercury, described by Krespan.[2] In addition, we have made a new fluoroethyl derivative, bis(1,1-dichloro-2,2,2-trifluoroethyl)mercury, which was prepared in 69% yield from 1,1-dichloro-2,2-difluoroethylene.

TABLE I

FLUOROMERCURIALS FROM FLUOROÖLEFINS AND MERCURIC FLUORIDE

$$2R_1R_2C{=}CF_2 + HgF_2 \xrightarrow{HF} [R_1R_2CCF_3]_2Hg$$

Olefin	Product	Yield, %
$CF_3CF{=}CF_2$	$(CF_3)_2CF{-}Hg{-}CF(CF_3)_2$ (I)	60
$HCF_2CF_2CF{=}CF_2$	$HCF_2CF_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}F{-}Hg{-}\underset{\displaystyle CF_3}{\underset{\vert}{C}}FCF_2CF_2H$ (II)	73
$ClCF_2CF_2CF{=}CF_2$	$ClCF_2CF_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}F{-}Hg{-}\underset{\displaystyle CF_3}{\underset{\vert}{C}}FCF_2CF_2Cl$ (III)	*ca.* 5
$H(CF_2)_8CF{=}CF_2$	$H(CF_2)_8\underset{\displaystyle CF_3}{\underset{\vert}{C}}F{-}Hg{-}\underset{\displaystyle CF_3}{\underset{\vert}{C}}F(CF_2)_8H$ (IV)	Low
$(CF_3)_2CF{=}CF_2$	$CF_3{-}\underset{\displaystyle CF_3}{\underset{\vert}{C}}{-}Hg{-}\underset{\displaystyle CF_3}{\underset{\vert}{C}}{-}CF_3$ (V)	33

Usual conditions for these preparations are 100–150° and autogenous pressure. For bis(nonafluoro-*t*-butyl)mercury (V), temperatures of 180–200° were necessary. Addition of mercuric fluoride to the internal double bonds in such compounds as octafluoro-2-butene and

(1) (a) A. A. Banks, H. J. Emeleus, R. N. Haszeldine, and V. Kerrigan, *J. Chem. Soc.*, 2188 (1948); (b) H. J. Emeleus and R. N. Haszeldine, *ibid.*, 2948, 2953 (1949); (c) J. Banus, H. J. Emeleus, and R. N. Haszeldine, *ibid.*, 3041 (1950).

(2) C. G. Krespan, U. S. Patent 2,844,614 (July 29, 1958); *J. Org. Chem.*, **25**, 105 (1960).

(3) (a) E. G. Howard and W. J. Middleton, U. S. Patent 2,970,173 (January 31, 1961); (b) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Am. Chem. Soc.*, **83**, 2589 (1961); (c) W. T. Miller, Jr., M. B. Freedman, J. H. Fried, and H. F. Koch, *ibid.*, **83**, 4105 (1961).

(4) Use of hydrogen fluoride as a solvent was first suggested to us by Professor W. T. Miller, Jr.

hexafluorocyclobutene was not successful even at high temperatures. Efforts to prepare R_fHgF led only to bismercurials.

Structure.—The structures of the organomercury compounds were established by nuclear magnetic resonance studies. The α and β fluorine peaks of bis(perfluoroisopropyl)mercury (I) are widely separated, and the ratio of their areas is 1:6 (Fig. 1a). This is unlike the spectrum of diisopropylmercury,[5] in which the protons of the isopropyl group were not resolved because of overlapping of the peaks associated with the α and β protons. The α fluorine appears as a septet with relative intensities of 1:6:15:20:15:6:1 centered at 5109 c.p.s.[6] and a spin–spin coupling constant J of 12 c.p.s. (Fig. 1d). In addition, there are two, weak, symmetrical satellite bands at 4848 and 5370 c.p.s. due to the Hg^{199} isotope[5] (Fig. 1c). The six β fluorines appear as a doublet centered at 124 c.p.s. with a coupling constant of 12 c.p.s. in agreement with that found for the α fluorines (Fig. 1b). The doublet is also flanked symmetrically by two small satellite doublets at 60 and 72 and at 176 and 188 c.p.s. These results are in agreement with those expected for the iso rather than the normal perfluoropropyl group.

Bis(perfluoro-*t*-butyl)mercury (V) in confirmation of its structure shows a single fluorine n.m.r. peak at −447 c.p.s.[6] flanked by a pair of satellites at −372 and −522 c.p.s. The fluorine n.m.r. spectra of both bis(3H-1-trifluoromethylpentafluoropropyl)mercury (II) and bis(3-chloro-1-trifluoromethylpentafluoropropyl)mercury (III) have four resonance peaks with areas in the ratio of 2:2:1:3, which is in accord with a secondary alkyl structure rather than a primary one.

Reaction Mechanism.—Miller[3] has postulated an electrophilic mechanism for the addition of mercuric fluoride to fluoroölefins. The attack of mercuric ion upon terminal fluoroölefins and not upon internal fluoroölefins suggests that the difluorocarbonium ion $-\overset{\oplus}{C}F_2$ is more stable than the monofluorocarbonium ion $-\overset{\oplus}{C}F-$. The ability of halogens and especially fluorine to increase their covalency is well known.[7]

Properties.—The secondary perfluoroalkylmercury compounds are dense, colorless, distillable liquids. Bis(perfluoroisopropyl)mercury, which boils at 116–117° and melts at 20–21°, has a liquid range close to that of water. Its density is 2.53. Less symmetrical mercurials are slightly lower in density, although none in the series I through IV is below 2.4. The highly symmetrical tertiary alkyl mercurial V is a crystalline solid that sublimes so easily it has no appreciable liquid range at atmospheric pressure.

Secondary and tertiary perfluoroalkyl mercurials are more stable to heat and chemicals than corresponding primary compounds. They differ in this respect from nonfluorinated organomercurials in which case secondary and tertiary alkyl mercurials are less stable than

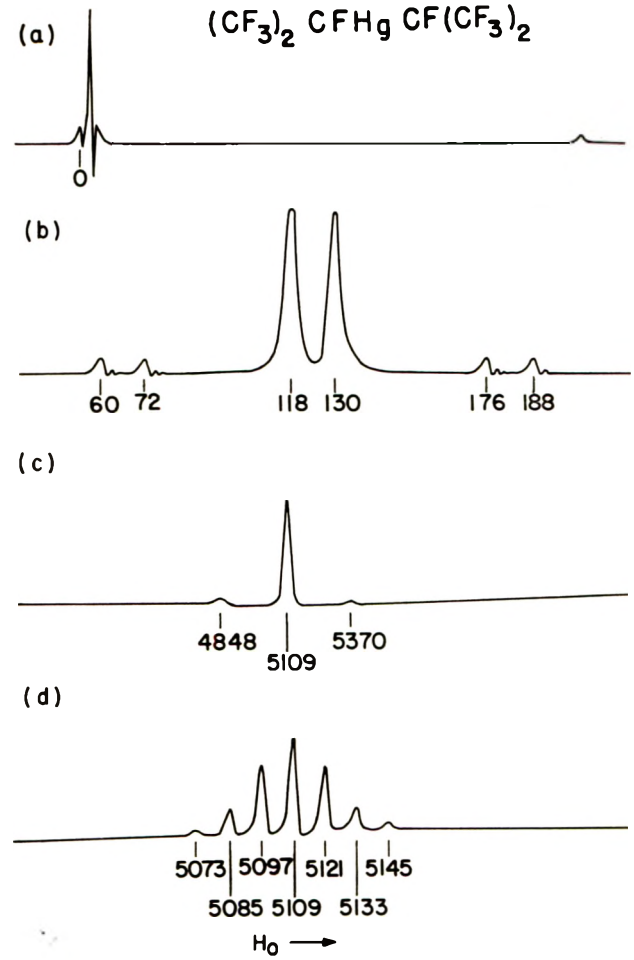


Fig. 1.—Fluorine magnetic resonance spectrum of bis(perfluoromethylethyl)mercury at (a) low resolution and (b), (c), and (d) high resolution (see ref. 6).

primary ones.[8] Anhydrous bis(perfluoroisopropyl)mercury does not change when heated several hours at 250°. At 350° or upon irradiation with strong ultraviolet light, it is decomposed to mercury and perfluoro-2,3-dimethylbutane.[9] Secondary and tertiary perfluoroalkyl mercurials are unaffected by aqueous alkali or boiling concentrated nitric acid and, when anhydrous, are stable to such metals as copper, iron, and aluminum at temperatures as high as 250°. However, in the presence of a trace of water they react vigorously with aluminum, even at room temperature.

Although bis(perfluoroisopropyl)mercury is not hydrolyzed by boiling water, it reacts with water at 200° in a sealed vessel to give 2H-heptafluoropropane and bis(perfluoroisopropylmercury)oxide. As shown in the following chart, the mercurial is also reduced by aqueous sodium sulfide, aqueous sodium stannite, and potassium iodide in boiling water. These reactions take a somewhat different course with certain fluoromercurials. For example, 1H-heptafluoro-2-butene and 1H-heptafluoro-3-butene are obtained by reactions of bis(1H - 1 - trifluoromethylpentafluoropropyl)mercury with aqueous sodium sulfide (see p. 186, col. 1).

Derivatives.—Secondary perfluoroalkyl mercurials react with halogens typically[1c] to form perfluoro-*sec*-alkyl iodides and bromides, the other product being a

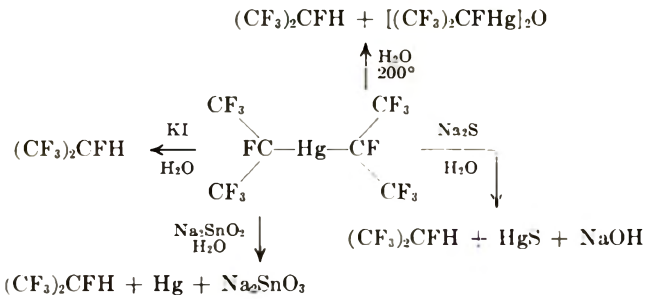
(5) R. E. Dessey, T. J. Flautt, H. H. Jaffe, and G. F. Reynolds, *J. Chem. Phys.*, **30**, 1422 (1959).

(6) 1,2-Difluorotetrachloroethane was used as a reference compound. The spectra were measured as a 40% solution in acetonitrile on a 40-Mc. Varian high resolution nuclear magnetic resonance spectrometer at 10,000 gauss.

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry, Henry Holt and Co., New York, N. Y., 1959, pp. 217–218; C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 70–90.

(8) C. S. Marvel and H. O. Calvery, *J. Am. Chem. Soc.*, **45**, 820 (1923).

(9) R. D. Chambers, W. K. R. Musgrave, and J. Savory, *J. Chem. Soc.* 3779 (1961); *ibid.*, 1993 (1962).



mercuric halide. Bis(perfluoro-*t*-butyl)mercury reacts with bromine to give perfluoro-*t*-butyl bromide, but its reaction with iodine is capricious. On one occasion, a product was obtained that almost certainly was perfluoro-*t*-butyl iodide. However, numerous attempts to repeat iodine cleavage of the tertiary mercurial failed.

The development of an easy method for obtaining secondary and tertiary perfluoroalkyl halides opens new possibilities for synthesis of many branched-chain derivatives. We have used the halides to prepare nitroso compounds. Ultraviolet irradiation of heptafluoro-2-iodopropane and nitric oxide[10] gave heptafluoro-2-nitrosopropane,[11] a blue gas boiling at −8 to −6°, in 53% yields. A tertiary nitroso compound, tris(trifluoromethyl)nitrosomethane,[11] has also been synthesized. This compound was obtained by irradiating perfluorobutyl bromide in the presence of nitric oxide. It is a blue liquid boiling at 23–24° and freezing at 0°.

Experimental

Bis(perfluoroisopropyl)mercury (I).[12]—Mercuric fluoride[13] (240 g., 1.01 moles), 70 g. of anhydrous hydrogen fluoride, and 300 g. (2 moles) of hexafluoropropylene were heated in a bomb[14] at 110° for 12 hr. The bomb was cooled and vented. The product was poured into a polyethylene bottle, which was loosely capped and set aside in a hood to allow excess hydrogen fluoride to evaporate. Traces of hydrogen fluoride were removed by stirring the product with sodium fluoride powder; alternatively the hydrogen fluoride was extracted with water and the product then dried with phosphorus pentoxide. Distillation of the product gave 323 g. (60%) of bis(perfluoroisopropyl)mercury, b.p. 115–116°, m.p. 20–21°, $n^{25}D$ 1.3244, d^{25}_4 2.5301. The mercury compound must be dry before distillation; otherwise an azeotrope, b.p. 90°, containing approximately 4.3% water results.

Anal. Calcd. for $C_6F_{14}Hg$: F, 49.38; Hg, 37.24. Found: F, 48.77; Hg, 37.13.

Perfluoroisopropylmercury Chloride.[12]—Bis(perfluoroisopropyl)-mercury (135 g., 0.25 mole) and 29 g. (0.25 mole) of thiophosgene were heated in a bomb at 200° for 5 hr. The bomb was cooled and vented, and the black, fuming liquid was distilled. In addition to recovered starting materials, there was obtained 32.9 g. (32%) of perfluoroisopropylmercury chloride, b.p. 173–178°. The mercury compound crystallized from cyclohexane as colorless needles, m.p. 77.0–78.3°.

This compound was also obtained as a by-product in the preparation of bis(perfluoroisopropyl)mercury. (The mercuric fluoride[13] used in this work contained chloride as an impurity.)

Anal. Calcd. for C_3ClF_7Hg: Cl, 8.75; F, 32.83; Hg, 49.52. Found: Cl, 9.09; F, 32.01; Hg, 48.96.

4H-Heptafluoro-1-butene.—Into a solution of 163 g. (4.06 moles) of sodium hydroxide (98%) in 800 ml. of methanol was dropped with stirring 1 kg. (4.06 moles) of 5H-octafluorovaleric acid. The solution was evaporated to dryness in evaporating dishes on a steam bath to give 1068 g. of salt. The salt was pyrolyzed in a flask in a Wood's metal bath at 250–280°; vapors were led into a solid carbon dioxide–acetone-cooled trap. Distillation gave 543 g. (73%) of 4H-heptafluoro-1-butene, b.p. 21°.

The assignment of the double bond to the 1-position was based on the infrared spectrum of the compound, which showed absorption at 5.58 μ, indicative of an olefinic bond substituted with three fluorine atoms.[15]

Bis(3H-1-trifluoromethylpentafluoropropyl)mercury (II).[12]—A mixture of 72 g. (0.3 mole) of mercuric fluoride,[13] 100 g. (0.55 mole) of 4H-heptafluoro-1-butene, and 100 g. of anhydrous hydrogen fluoride was placed in a bomb[14] and heated at 120° for 12 hr. After the hydrogen fluoride evaporated, the clear remaining liquid was washed with dilute aqueous sodium bicarbonate, dried under anhydrous calcium chloride, and distilled, b.p. 172.5–173°, weight 120 g. (73%). This material solidified at 0° and had a density of 2.44 g./ml.

Anal. Calcd. for $C_8H_2F_{16}Hg$: F, 50.3; Hg, 33.3. Found: F, 49.4; Hg, 32.5.

5-Chloroheptafluoro-1-butene.—The sodium salt of 5-chloroperfluorovaleric acid was pyrolyzed at 340°. 5-Chloroheptafluoro-1-butene, b.p. 34°, was obtained in 76% yield.

Anal. Calcd. for C_4ClF_7: Cl, 16.38; F, 61.4. Found: Cl, 16.77; F, 61.3.

Bis(3-chloro-1-trifluoromethylpentafluoropropyl)mercury (III.).[12]—A mixture of 36 g. (0.15 mole) of mercuric fluoride,[13] 56 g. (0.26 mole) of 4-chlorooctafluorobutene, and 100 g. of hydrogen fluoride was heated in a bomb[14] at 120° for 13 hr. The product was worked up as described for bis(3H-trifluoromethylpentafluoropropyl)mercury (II). In addition to 20 g. of mercury, there was obtained 8.6 g. (5%) of a liquid, b.p. 85–97° (20 mm.), m.p. −10°, density 2.42 g./ml.

Anal. Calcd. for $C_8F_{16}Cl_2Hg$: Cl, 10.5; Hg, 30.1. Found: Cl, 10.5; Hg, 30.4.

Bis(9H-1-trifluoromethylheptadecafluorononyl)mercury (IV).[16]—1H-Nonadecafluoro-9-decene, b.p. 73–74° (32 mm.), $n^{26}D$ 1.300, was prepared by pyrolysis of sodium 10H-perfluorodecanoate. Bis(9H-1-trifluoromethylheptadecafluorononyl)mercury, m.p. 100–101°, was prepared from the fluoroolefin as described in the previous examples.

Anal. Calcd. for $C_{20}H_2F_{40}Hg$: F, 63.2. Found: F, 62.9.

Bis(perfluoro-*t*-butyl)mercury (V).[12]—Mercuric fluoride,[13] (10 g.), 50 g. of anhydrous hydrogen fluoride, and 89 g. of a mixture of gases containing 17.3% perfluoroisobutylene,[17] 76.4% perfluorocyclobutane, and 6.0% perfluoromethylcyclobutane were heated in a bomb[14] at 200° for 12 hr. The bomb was allowed to cool to room temperature. The gases were removed and detoxified by bubbling them through 20% methanolic potassium hydroxide. The solid residue was triturated with dilute nitric acid to dissolve unchanged mercuric fluoride, washed with water, and dried over sulfuric acid. There was obtained 7.37 g. (33%) of white solid, which sublimed to give large crystals, m.p. 65–66°.

Anal. Calcd. for $C_8F_{18}Hg$: Hg, 31.42. Found: Hg, 31.20.

Bis(1,1-dichloro-2,2,2-trifluoroethyl)mercury.[12]—A mixture of 133 g. (1 mole) of 1,1-dichloro-2,2-difluoroethylene, 120 g. (0.5 mole) of mercuric fluoride, and 100 g. of anhydrous hydrogen fluoride was heated at 100° for 12 hr. in a bomb.[14] The product was a gray, granular solid that was recrystallized from chloroform to give 150 g. of bis(1,1-dichloro-2,2,2-trifluoroethyl)mercury as fine white needles, m.p. 180–185°. A second crop of crystals, 24 g., was obtained by evaporation of the filtrate of the first recrystallization. Total yield was 174 g. (69%). The fluorine n.m.r. spectrum of a chloroform solution contained a single unsplit absorption band flanked by two smaller satellite bands.

Anal. Calcd. for $C_4F_6Cl_4Hg$: Cl, 28.1. Found: Cl, 26.8.

Heptafluoro-2-iodopropane.—Bis(perfluoroisopropyl)mercury (540 g., 1 mole) and 510 g. (2 moles) of iodine were heated in a bomb at 200° for 8 hr. The bomb was chilled in an ice bath and vented. The chilled product was filtered; the use of a solid carbon dioxide trap in the suction system prevented large losses of

(10) Haszeldine has prepared CF_3NO from trifluoroiodomethane and nitric oxide. R. N. Haszeldine, *J. Chem. Soc.*, 2075 (1953); J. Banus, *ibid.* 3755 (1953); J. Jander and R. N. Haszeldine, *ibid.*, 912 (1954).

(11) I. L. Knunyants, E. G. Bykhovskaya, V. N. Frosin, and Ya. M. Kisel, *Dokl. Akad Nauk SSSR*, **132**, 123 (1960).

(12) The mercury compounds are volatile and their vapors are toxic.

(13) A technical grade supplied by the Harshaw Chemical Co. was used.

(14) "Hastelloy" (trademark of the Haynes Stellite Div. of Union Carbide Co., Kokomo, Ind.) was more satisfactory than stainless steel.

(15) D. G. Weiblen has briefly reviewed the infrared spectra of fluoroolefins in "Fluorine Chemistry," Vol. II, J. H. Simons, ed., Academic Press, Inc., New York, N. Y., 1954, pp. 453, 454. Terminal perfluoroolefins absorb at 5.56–5.58 μ.

(16) This compound was prepared by Dr. Donald Hummel of the Jackson Laboratory of the Du Pont Co.

(17) Perfluoroisobutylene is extremely toxic. It should be used only where ventilation is good enough to assure its concentration will not rise above 1–2 p.p.m. if the bomb is accidently discharged.

product. There was obtained 454 g. of the crude product, which on distillation yielded 439 g. (74%) of pale pink 2-iodoheptafluoropropane, b.p. 40°; reported, 40.0°.[18] It was protected from light and heat during storage.

The assignment of structure was supported by the n.m.r. spectrum. Two fluorine peaks were present in the ratio of 6:1. The larger peak was split into a doublet, and the smaller peak was split into seven peaks.

Anal. Calcd. for C_3F_7I: C, 12.18; F, 44.95; I, 42.89. Found: C, 12.63, 12.23; F, 44.60; I, 42.49.

2-Bromoheptafluoropropane.—Bis(perfluoroisopropyl)mercury (162 g., 0.30 mole) and 96 g. (0.60 mole) of bromine were heated in a bomb at 200° for 4 hr. The bomb was cooled to about 50°, and the gases were condensed into a solid carbon dioxide–acetone-cooled trap. Distillation gave 102 g. (68%) of heptafluoro-2-bromopropane,[9] b.p. 14–18°.

Anal. Calcd. for C_3F_7Br: F, 53.43; Br, 32.10. Found: F, 53.42, 53.27; Br, 31.83, 31.77.

Pyrolysis of Bis(perfluoroisopropyl)mercury. Tetradecafluoro-2,3-dimethylbutane.—Although the pyrolysis could be carried out in a bomb at 350°, better yields were obtained by passing the vapors through a hot tube. A Pyrex tube (25 mm. o.d.) was packed for 100 mm. of its length with quartz chips. The packed zone was maintained at 498°, and 50 g. of bis(perfluoroisopropyl)-mercury was dropped through at the rate of 9 ml. per hr. with a nitrogen flow of 9 l./hr. The products were collected in a trap cooled with ice followed by one cooled with solid carbon dioxide–acetone. There was obtained 13.5 g. (27%) of mercury and 17.7 g. (57%) of perfluoro-2,3-dimethylbutane, b.p. 60–61°; reported, 60.0°.[9] The n.m.r. spectrum supported the assigned structure.

Anal. Calcd. for C_6F_{14}: C, 21.32; F, 78.68. Found: C, 21.47; F, 78.23.

2H-Heptafluoropropane.—A. A three-necked flask was equipped with dropping funnel, stirrer, and reflux condenser connected to a solid carbon dioxide–acetone-cooled trap. The reducing agent, (a) 16.6 g. (0.1 mole) of potassium iodide dissolved in 100 ml. of boiling water or (b) 30 g. (0.12 mole) of sodium sulfide nonahydrate dissolved in 50 ml. of water, was placed in the flask and 27 g. (0.05 mole) of bis(perfluoroisopropyl)mercury was added dropwise with stirring. There were collected, respectively, (a) 12.1 g. (71%) and (b) 13.3 g. (78%) of crude product in the trap. Distillation of the latter product afforded 10.3 g. (60%) of 2H-heptafluoropropane, b.p. −8 to −7°. Gas chromatographic analysis (see below) of the distilled product indicated that it was 99% pure.

B. Bis(perfluoroisopropyl)mercury (13.5 g., 0.025 mole) was dissolved in 100 ml. of absolute ethanol. Then, 2.3 g. (0.1 mole) of sodium was added portionwise with ice-bath cooling over a period of about 4 hr. During addition, gases evolved were collected in a trap cooled with solid carbon dioxide and acetone. The reaction mixture was slowly diluted with water to a volume of about 300 ml. and warmed until gas evolution ceased. The 2H-heptafluoropropane in the trap weighed 5.1 g. (60% yield). Its infrared spectrum was identical with that published.[19] Mass spectral data established that the product was 93–96% 2H-heptafluoropropane. Vapor phase chromatography on a column of the ethyl ester[20] of "Kel F" acid 8114[21] supported on 40–60 mesh firebrick indicated the 2H-heptafluoropropane to be approximately 97% pure.

Perfluoro-*t*-butyl Bromide.—Four 50-ml. Carius tubes each were filled with 12.3 g. (0.0194 mole) of bis(nonafluoro-*t*-butyl)-mercury and 2 ml. (6.20 g., 0.0387 mole) of bromine. The tubes were sealed under a nitrogen atmosphere and heated at 300° for 8 hr. The contents of the tubes were sublimed into a cold trap. The trap was allowed to warm to room temperature, and the product was blown by a stream of nitrogen through a gas washing bottle containing 10% sodium carbonate solution, then through a calcium chloride tower, and finally into another cold trap. There was obtained a total of 27.6 g. (60%) of a volatile white solid. The product did not give a black mercuric sulfide precipitate with sodium sulfide solution and therefore was free of starting material. The sulfide solution did turn yellow, however, which suggested the possibility of oxidation of the sulfide to polysulfide by the nonafluoro-*t*-butyl bromide. The n.m.r. spectrum of the product in ether solution showed a single peak with no splitting. A sample in ether solution was analyzed *via* gas chromatography on the diglyceride of ω-trifluorohexanoic acid.[22] Only one peak besides the ether peak was found. A sample of the bromide in an evacuated sealed capillary (totally immersed in an oil bath) melted at 55.5–57.5°.

Anal. Calcd. for C_4F_9Br: F, 56.58; Br, 26.73. Found: F, 56.58, 56.82; Br, 26.54, 26.43.

Hydrolysis of Bis(perfluoroisopropyl)mercury. Bis(perfluoroisopropylmercury) Oxide.—Bis(perfluoroisopropyl)mercury (54 g.) and 10 ml. of water were heated in a bomb at 200° for 12 hr. The resulting crude solid (29 g.) was recrystallized from ether to give white crystals, m.p. 292–295°. The infrared spectrum (KBr) was blank from 2–7 μ; the n.m.r. spectrum in hexadeuteroacetone showed no proton resonance absorption, but the fluorine spectrum of the compound was characteristic of the $(CF_3)_2$-CFHg— group. These facts indicated the structure $[(CF_3)_2$-$CFHg]_2O$, which was confirmed by the analytical data.

Anal. Calcd. for $C_6F_{14}Hg_2O$: F, 35.22; Hg, 53.13. Found: F, 34.97; Hg, 53.36.

When this compound was dissolved in ethereal hydrogen chloride solution, a white solid was obtained. After crystallization from benzene and sublimation, the solid was identified as perfluoroisopropylmercury chloride by means of mixed melting point determination and comparison of its solution infrared spectrum with that of an authentic sample.

2H-Heptafluoropropane was expected as the by-product of the hydrolysis reaction and its formation was verified by collecting the off-gases from the bomb and examining them by gas chromatography. The retention time of the main component peak (90%) was the same as that of 2H-heptafluoropropane.

Heptafluoro-2-nitrosopropane.—A quartz, spiral mercury resonance lamp was placed inside a 22-l., two-necked glass flask fitted with a side-arm stopcock. The whole system was mounted on a mechanical shaker. Five kilograms of metallic mercury was poured into the flask. The flask was evacuated to less than 1-mm. pressure with an oil pump. Then, 134 g. (0.45 mole) of heptafluoro-2-iodopropane was allowed to vaporize into the flask (the pressure increased to 338 mm.), and 265 mm. of nitric oxide was admitted. Shaking was started, and the mixture was irradiated 3 hr. An additional 156 mm. of nitric oxide was admitted, and the system was irradiated 11 hr. At the end of this time, the pressure in the flask had decreased by a total of 367 mm. The gases were slightly green because of nitrogen dioxide, which was reduced to nitric oxide by shaking the system with the lamp extinguished. The blue gas was pumped from the reaction flask and was caught in a series of liquid nitrogen traps. The product was distilled to give 49.5 g. (55%) of heptafluoro-2-nitrosopropane, b.p. −8 to −6°. The n.m.r. spectrum was characteristic of the perfluoroisopropyl group.

Anal. Calcd. for C_3F_7NO: F, 66.83. Found: F, 66.78, 66.84.

Tris(trifluoromethyl)nitrosomethane.—The equipment described above was used. The flask was charged with 2.5 kg. of mercury. Into the evacuated flask was vaporized 21.5 g. (0.072 mole) of nonafluoro-*t*-butyl bromide. Then, 61 mm. (0.072 mole) of nitric oxide was admitted, and shaking was started. After 15 min. of shaking to scavenge nitrogen dioxide, the system was irradiated for 6 hr.

The gases were pumped into a series of three liquid nitrogen traps. The product in the traps was blown by a stream of nitrogen through a column of mercury to remove traces of NO_2 and caught again in a cold trap. The product was distilled through an ice–water-cooled condenser to give 8.4 g. (37%) of a deep blue liquid, b.p. 23–25°, f.p. *ca.* 0°. The n.m.r. spectrum of the product showed a single fluorine resonance peak with no splitting, as is expected for the perfluoro-*t*-butyl group. Gas chromatographic analysis using the ethyl ester[20] of "Kel-F" acid 8114[21] supported on firebrick showed that the product was 95% tris-(trifluoromethyl)nitrosomethane.

Anal. Calcd. for C_4F_9NO: F, 68.64. Found: F, 68.02.

Solubility of Mercuric Fluoride in Anhydrous Hydrogen Fluoride.—The solubility was demonstrated qualitatively. A sample

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of mercuric fluoride was sealed in a closely woven Teflon[23] cloth bag. After it was found that shaking the bag in a bottle did not allow the solid to pass through the interstices of the cloth, the bag was then shaken with anhydrous hydrogen fluoride in a sealed vessel at 100° for 2 hr. The vessel was cooled, the Teflon bag was removed, and the anhydrous hydrogen fluoride was allowed to evaporate to give almost a complete recovery of the mercuric fluoride.

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Friedelin and Related Compounds. VI.[1] Azahomofriedelanes

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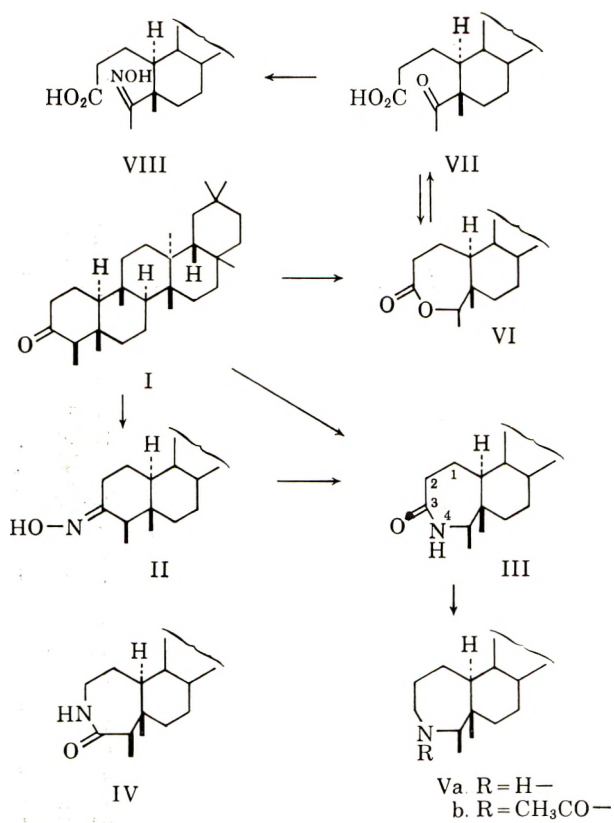
The structure of the product obtained by the Beckmann rearrangement of friedelin oxime (II) and Schmidt reaction of friedelin (I) has been established as 4-aza-A-homofriedelan-3-one (III) by its conversion to the friedelin lactone (VI) by the action of dinitrogen tetroxide.

Considerable work, much of which is reviewed in recent studies,[2-4] has been done on the preparation of azasteroids. The introduction of a nitrogen atom into the steroid ring A to yield the appropriate A-homolactam[3-5] is conveniently accomplished by the Beckmann rearrangement[6] of the easily available 3-ketoximes. Attention has also turned recently to the products obtained by Beckmann rearrangement of the 3-ketoximes[7,8] obtained from triterpenoids (β-amyrin, allobetulin) of the familiar dimethylcyclohexanol ring A structure.

The pentacyclic triterpenoid ketone, friedelin (I), provides a third type of ring A 3-ketone structure. The subjection of friedelin oxime to the action of phosphorus pentachloride in chloroform solution, typical conditions for rearrangement, was reported in 1935 by Drake and Shrader,[9] who established that the product was an "isomeric substance which is no longer an oxime." Their reluctance to formulate this product as a lactam can be attributed to their failure to hydrolyze it under a range of vigorous acid and base conditions or convert it to friedelin or a known derivative. The ready accessibility of friedelin oxime (II) as recently described,[10] has prompted the reinvestigation of this transformation.

Treatment of the oxime (II) with phosphorus pentachloride in chloroform solution gave a product with melting point in agreement with that previously reported,[9] although further purification was effected by chromatographic treatment. The same major product was isolated by the action of *p*-toluenesulfonyl chloride on the oxime in pyridine solution. The infrared spectrum of the product was consonant with an unstrained lactam structure, as expected from a normal Beckmann rearrangement, of which 4-aza-A-homofriedelan-3-one (III) and 3-aza-A-homofriedelan-4-one (IV) are the obvious possibilities. A distinction in favor of III is made on the evidence presented below. Chemical evidence for the presence of the lactam function in III was obtained by reduction with lithium aluminum hydride to give a secondary amine, $C_{30}H_{53}N$, formulated as Va. This yielded, on heating with acetic anhydride, an amide (Vb) whose infrared spectrum lacked an —NH— stretching signal.

Efforts to establish that the lactam had structure (III) by oxidation of the α-methylene group (absent in IV) to yield an α-ketolactam were unsuccessful, unchanged starting material being recovered in high yield after attempted oxidation with selenium dioxide under a variety of conditions[11] and with chromium trioxide in pyridine solution.[12]



The elegant method of conversion of N-alkylamides and lactams to esters and lactones by the action of

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heat on the corresponding N-nitroso derivatives has been reviewed and extended by White.[13] Treatment of the friedelin lactam with dinitrogen tetroxide in carbon tetrachloride at low temperature yielded a lactone, $C_{30}H_{50}O_2$, identified as 4-oxa-A-homofriedelan-3-one (friedelolactone) (VI), thus establishing formulation III for the rearrangement product from friedelin oxime. Initially, the crude nitrosation product was heated in *n*-heptane according to the conditions of White. Subsequently, infrared examination of the crude product showed the absence of lactam and nitroso group, the presence of the carbonyl group and established that the thermal treatment was superfluous. Another example of this lactam → lactone interconversion, where heat treatment is unnecessary, has recently been reported.[14]

The identification of the lactone was made by direct comparison with a product obtained by Baeyer–Villiger oxidation[15,16] of friedelin. Corey and Ursprung[15] treated friedelin with peracetic acid to obtain a lactone mixture which was not separated. In the present work, chromatographic purification of the crude oxidation mixture yielded the lactone identical with that obtained by nitrosation of the lactam. The structure (VI) for the lactone was confirmed by oxidation with chromic acid to yield friedonic acid (VII), further characterized as its methyl ester. The reconversion of friedonic acid to the lactone (VI) either by catalytic hydrogenation or reduction with sodium in *n*-propyl alcohol has been previously described.[17] The hindrance of the ketone group of friedonic acid and the methyl ester has been noted,[17] and no carbonyl derivatives have been previously reported. We find that friedonic acid readily forms an oxime (VIII) under those conditions, refluxing with hydroxylamine hydrochloride in aqueous pyridine, introduced for the characterization of the steroidal hindered 11-ketones.[18]

Friedelin reacted with hydrazoic acid under the usual Schmidt reaction conditions,[19] to give the same lactam (III). The migration of the 4-alkylmethylene group rather than the 2-methylene group is in agreement with the results found for the behavior of 2-alkylcyclohexanones under the same conditions.[20]

The assignment of structure (III) to the lactam indicates that the friedelin oxime described is that geometric isomer with the oxime hydroxyl group *anti* to the equatorial 4-β-methyl group where no pronounced steric effects exist.

Experimental[21]

Beckmann Rearrangement of Friedelin Oxime (II).—(a) Phosphorus pentachloride (1.75 g.) was added to a solution of friedelin oxime (1.74 g.) in chloroform (600 ml.), the mixture allowed to stand at room temperature for 16 hr., then concentrated to a volume of 50 ml. The solution was washed with water, dried (sodium sulfate), concentrated further to 5 ml., and diluted with methanol. The crystalline product (1.30 g., m.p. 312–318°) was collected. Purification by chromatography and elution with ether–methanol (19:1) gave 4-aza-A-homofriedelan-3-one (friedelolactam) (III) as platelets, m.p. 320–324°, $[\alpha]_D$ +11.5° (*c* 2.1), λ^{CHCl_3} 2.96, 3.47, 6.05, 6.89, 7.22, 7.25 (sh.), 7.35, 7.64, 8.56, 8.75, 8.87, 9.90, 10.31 μ (reported,[9] m.p. 316–318°).

Anal. Calcd. for $C_{30}H_{51}ON$: C, 81.57; H, 11.64; N, 3.17. Found: C, 81.32; H, 11.46; N, 3.27.

(b) *p*-Toluenesulfonyl chloride (0.8 g.) was added to a solution of friedelin oxime (630 mg.) in pyridine (40 ml.), the mixture heated on the steam bath for 3 hr., cooled, diluted with water, and extracted with chloroform. The extract was washed with water, concentrated, and diluted with methanol to give the product (310 mg.), m.p. 290–310°, which was chromatographed. Elution with benzene (480 ml.) gave a negligible residue, and with benzene–ether (3:1, 480 ml.) an unidentified solid (60 mg., m.p. 269–278°). Elution with benzene–ether (1:1) then yielded friedelolactam, m.p. 320–323°, $[\alpha]_D$ +11° (*c* 2.0).

The lactam was recovered unchanged after refluxing with selenium dioxide in acetic acid (18 hr.), aqueous acetic acid (2 days), aqueous dioxane (2 days), and benzyl acetate (3 hr.), and treatment with chromium trioxide in pyridine.

Action of Hydrazoic Acid on Friedelin.—Concentrated sulfuric acid (0.2 ml.) was added to a solution of friedelin (213 mg.) in chloroform (8 ml.) cooled in an ice bath. Hydrazoic acid (27 mg.) in chloroform (1.2 ml.) was then added over 15 min., followed by chloroform (3 ml.) containing sulfuric acid (2 drops). After the mixture had been stirred at 0° for 2 hr., it was poured into water, the chloroform layer washed and dried (sodium sulfate), methanol added, and the product recrystallized once to give friedelolactam (140 mg.), m.p. and mixed m.p. 318–319°, $[\alpha]_D$ +10° (*c* 1.5), with infrared spectrum identical with product from Beckmann rearrangement.

4-Aza-A-homofriedelane (Va.)—A solution of friedelolactam (230 mg.) in dry ether–benzene (1:1, 50 ml.) was added to lithium aluminum hydride (600 mg.) in ether (50 ml.), heated under reflux for 3 hr., worked up *via* water and ether extraction to yield a solid (221 mg.) which was recrystallized twice from chloroform–methanol to give 4-aza-A-homofriedelane as soft needles (60 mg.), m.p. 242–244°, $[\alpha]_D$ +8.5° (c 1.50), λ^{CHCl_3} 3.45, 6.87, 7.23, 7.35, 8.82, 9.91, 10.90 μ.

Anal. Calcd. for $C_{30}H_{53}N$: C, 84.24; H, 12.49; N, 3.27. Found: C, 84.75, H, 12.23; N, 3.80.

N-Acetyl-4-aza-A-homofriedelane (Vb).—The azahomofriedelane (60 mg.) in acetic anhydride (1 ml.) was heated on the steam bath overnight. On cooling, the mixture solidified, water was added, and the product (m.p. 215–217°) collected. One recrystallization from aqueous methanol gave the acetyl derivative as needles, m.p. 216–217°, $[\alpha]_D$ −30° (*c* 1.50), λ^{CHCl_3} 3.45, 6.19, 6.93, 7.25, 7.46, 7.70, 8.97, 9.35, 9.90, 10.09 μ.

Anal. Calcd. for $C_{32}H_{55}ON$; C, 81.81; H, 11.80; N, 2.98. Found: C, 81.91; H, 11.55; N, 3.31.

Nitrosation of Friedelolactam.—(a) Anhydrous sodium acetate (1.5 g.) was suspended in a saturated solution of dinitrogen tetroxide in carbon tetrachloride (15 ml.) at −60°. A solution of friedelolactam (240 mg.) in carbon tetrachloride (25 ml.) was added dropwise with swirling; the temperature was allowed to rise and was maintained at 0° for 20 min., then room temperature for 20 min. Ice was added to the mixture; the organic layer was separated, washed with water, sodium carbonate solution, and water, dried (sodium sulfate), and evaporated to give a solid which was dissolved in *n*-heptane (75 ml.) and heated under reflux for 16 hr. Removal of the hydrocarbon solvent gave a solid which was crystallized from ethyl acetate to give 4-oxa-A-homofriedelan-3-one (friedelolactone) (VI) as long soft needles (34 mg.), m.p. 306–308° (softens 298°),[22] $[\alpha]_D$ +38° (*c* 1.0), λ^{CHCl_3} 3.43, 5.79, 6.90, 7.22, 7.33, 7.48, 7.54, 7.79, 8.49, 8.78, 9.04, 9.31, 9.76, 10.23 μ.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found, C, 81.64; H, 11.31.

The crystallization residues (92 mg.) were dissolved in benzene and chromatographed to yield a further 50 mg. of the lactone.

(b) In a subsequent experiment, the infrared spectrum of the solid obtained after nitrosation showed absence of the lactam and presence of the lactone carbonyl band. Direct crystallization from ethyl acetate and chloroform–methanol (without heating in *n*-heptane) gave friedelolactone, m.p. 298–300° (softens 290°), $[\alpha]_D$ +40° (*c* 1.2).

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(21) Melting points were determined on a Gallenkamp melting point apparatus. All specific rotations were measured in chloroform solution, Merck acid-washed alumina was used for chromatography.
(22) Discrepancies in the reported melting point and the dependence on heating rate have been discussed by Takahashi and Ourisson (ref. 16).

4-Oxa-A-homofriedelan-3-one (Friedelolactone) (VI).—Peracetic acid (40%, 7.5 ml.) was added to a solution of friedelin (1.525 g.) in chloroform (70 ml.) and the mixture maintained at 58° for 17 hr. It was then concentrated until solid started to precipitate, methanol added, and the precipitate collected. This was dissolved in benzene, filtered to remove a little insoluble material, washed with water, and concentrated to yield well formed needles (1.34 g., m.p. 279–293°). Chromatography of this product (265 mg.) and elution with benzene (150 ml.) gave a solid (198 mg.) which was recrystallized once from ethyl acetate and once from chloroform–methanol to give friedelolactone as long felted needles, m.p. 303–306° (softens 294°), $[\alpha]_D$ +38° (*c* 1.9), undepressed by specimen obtained from friedelolactam.

Friedonic Acid (VII).—A solution of chromium trioxide (600 mg.) in water (10 ml.) and concentrated sulfuric acid (7.5 ml.) was added to a solution of friedelolactone (550 mg.) in acetic acid (300 ml., freshly distilled from potassium permanganate) and the mixture stirred at room temperature for 16 hr. Methanol was then added, the solution concentrated, diluted with water, and extracted with ether. Sodium hydroxide solution (15%, 200 ml.) was added to precipitate the salt at the interface. Much of the aqueous layer was run off and the ether removed by decantation. The precipitate was washed several times by decantation with water, then warmed on the steam bath to form a gel which gave a granular precipitate on acidification with hydrochloric acid. Two recrystallizations from aqueous ethanol gave friedonic acid (250 mg.) as fine felted needles, m.p. 205–207°, $[\alpha]_D$ −3° (*c* 1.6), λ^{CHCl_3} 2.85, 3.42, 5.88 (broad), 6.85, 7.20, 7.40, 7.79, 8.80 μ (reported,[23] m.p. 206–207°).

Methyl Friedonate.—Excess diazomethane in ether solution was added to friedonic acid (360 mg.) in ether (10 ml.), the solvent removed after 16 hr., and the residual solid crystallized from methanol to yield methyl friedonate as needles (300 mg.), m.p. 155–157°, $[\alpha]_D$ −2° (*c* 1.7), λ^{CHCl_3} 3.42, 5.79, 5.90, 6.88, 7.20, 7.40, 8.55, 8.95, 9.44, 10.10 μ (reported,[24] m.p. 153–154°, $[\alpha]_D$ +12°).

Friedonic Acid Oxime (VIII).—Friedonic acid (260 mg.) was added to a solution of hydroxylamine hydrochloride (355 mg.) in water (1 ml.) and pyridine (8 ml.). After the mixture had been heated under reflux for 20 hr., the solvents were removed under reduced pressure, the residue taken up in ether, washed with water, and dried (sodium sulfate). Removal of the ether gave a solid which crystallized from ethyl acetate to give friedonic acid oxime as stout needles (175 mg.), m.p. 238–240°.

Anal. Calcd. for $C_{30}H_{51}O_3N$: C, 76.06; H, 10.85; N, 2.96. Found: C, 75.43; H, 10.81; N, 2.87.

Acknowledgment.—The award of a research grant (A-3439) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service, is gratefully acknowledged.

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The Mutual Decomposition of Benzenesulfonyl Azide and *t*-Butyl Hydroperoxide[1]

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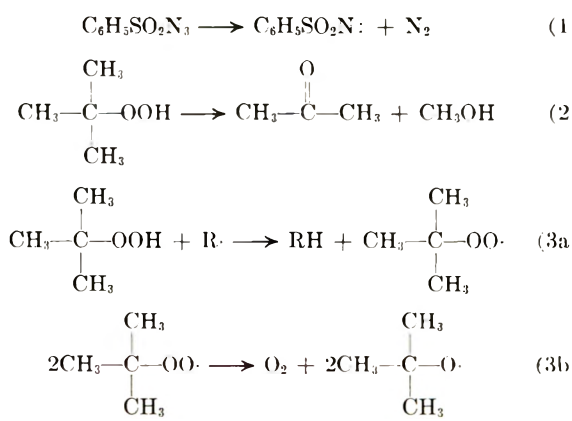
The system benzenesulfonyl azide–*t*-butyl hydroperoxide exhibits mutually induced decomposition of both reagents. The same system in the presence of iodine gives no induced decomposition of the azide, but shows two additional peroxide decomposition reactions, both of which involve both the azide and iodine.

On heating a chlorobenzene solution of benzenesulfonyl azide and *t*-butyl hydroperoxide, intermediates from the decomposing azide induce the decomposition of the peroxide, and intermediates from the peroxide induce the decomposition of the azide. Since a dozen or so different free radicals or diradicals and a correspondingly large number of chain-carrying and chain-breaking steps might plausibly be important in this system, readily interpretable kinetics are not to be expected. We undertook the investigation reported here as the result of a chance observation and were kept from discontinuing it immediately by certain interesting features which we now report.

The decomposition of benzenesulfonyl azide to the nitrene and nitrogen is a well known reaction.[2] It is known both to be accelerated by free radicals[2b] and to induce vinyl polymerization.[2c] The decomposition of *t*-butyl hydroperoxide[3] has two free radical paths, one leading to acetone and methanol, the other to oxygen and *t*-butyl alcohol.

Induced Decomposition of the Azide in the Presence of the Peroxide.—The decomposition of the azide in chlorobenzene at 126.7° can be followed by total gas evolution or by analysis for azide by means of the triphenylphosphine method described in the Experimental. Fig. 1 shows the results of some total gas evolution experiments. The gas evolution rate is equal to that expected from the uncatalyzed azide decomposition at the beginning of the reaction and at the end, but there is an intervening period of very fast nitrogen-plus-oxygen evolution lasting for about forty-five minutes. Extrapolation of the linear portion of the gas evolution curve back to zero time gives an azide concentration considerably less than the actual initial azide concentration. Fig. 2 shows the decrease in azide concentration as determined by the triphenylphosphine



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method. Superimposed on the same figure is the decrease in iodometric peroxide concentration for a similar run. Again we find a period of normal azide decomposition rate, a period of accelerated decomposition, and a return to the normal rate.

The induced decomposition of the azide can be prevented entirely either by adding iodine to the chlorobenzene solution or by using *p*-xylene as the solvent. Fig. 3 shows the evolution of nitrogen plus oxygen in the presence of iodine. The experimental points fall on a theoretical curve calculated from the usual first-order rate constant for the azide decomposing in chlorobenzene alone and a first-order rate constant for the peroxide determined iodometrically.

The products of the azide decomposition in chlorobenzene plus *t*-butyl hydroperoxide are the usual benzenesulfonanilides plus benzenesulfonamide and tar. In *p*-xylene plus *t*-butyl hydroperoxide, the product is benzenesulfonyl *p*-xylidide, almost quantitatively.

Induced Decomposition of the Peroxide in the Presence of the Azide.—The reaction induced by the simultaneous decomposition of benzenesulfonyl azide in chlorobenzene at 126.7° is reaction 3, nitrogen being evolved quantitatively and oxygen in 90% yield or better. Reaction 3 in the absence of azide proceeds at a negligible rate; the observed reaction under those conditions is (2). The rate of reaction 2, expressed as a first-order rate constant, is about 1.04×10^{-3} min.$^{-1}$ for an initial peroxide concentration of 0.065 *M*.

Iodometric titration of the peroxide in chlorobenzene in the presence of the azide shows peroxide decomposition occurring by a process of nearly zero order within the run, especially at low azide concentrations. A typical run is shown in Fig. 4.

At higher initial azide concentrations the behavior is more complicated, the zero-order rate constant k_{op} increasing during the run. The zero-order rate constants for runs of constant initial peroxide concentration (0.05 *M*) depend on the initial azide concentration as shown in Fig. 5. The upper branch at high azide concentration shows the rates late in the run, the lower branch the initial rates.

The effect of changing initial peroxide concentration at a constant initial azide concentration of 0.01 *M* is shown in Fig. 6.

The combined effect of changes in initial azide and peroxide concentration on k_{op} in chlorobenzene at 126.7° is given by equation 4, in which only runs of clearly zero order ($[A]_0 \leq 0.017$ *M*) were used to evaluate the parameters.

$$k_{op} = 3.1 \times 10^{-3}[A] + 26 \times 10^{-3}[P][A]^{1/2} + 0.45 \times 10^{-3}[P]\ M^{-1}\ \text{min.}^{-1} \quad (4)$$

The coefficient of the first term, 3.1×10^{-3}, is equal within experimental error to twice the normal first-order rate constant for the decomposition of the azide alone. That rate constant is 1.5×10^{-3} min.$^{-1}$ in chlorobenzene at 126.7°.

Equation 4 gives a clue to the general nature of the induced peroxide decomposition, but we have not been able to derive any entirely satisfactory mechanism. This may be partly the result of the purely mathematical difficulty of a system in which at least a dozen different radical intermediates are likely and partly the result of such complications as the partial sweeping

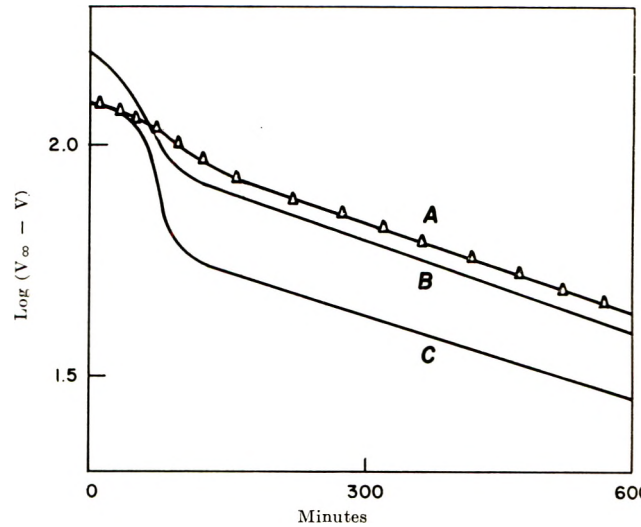

Fig. 1.—A. 0.05 *M* azide, 0.025 *M* peroxide; B. 0.05 *M* azide, 0.05 *M* peroxide; C. 0.033 *M* azide, 0.05 *M* peroxide.

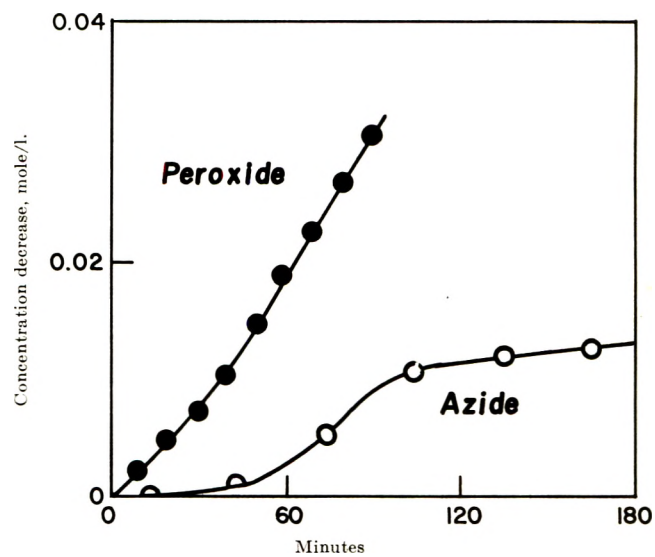

Fig. 2.—Two runs, both of initial azide concentration 0.033 *M* and initial peroxide concentration 0.05 *M*, chlorobenzene, 126.7°.

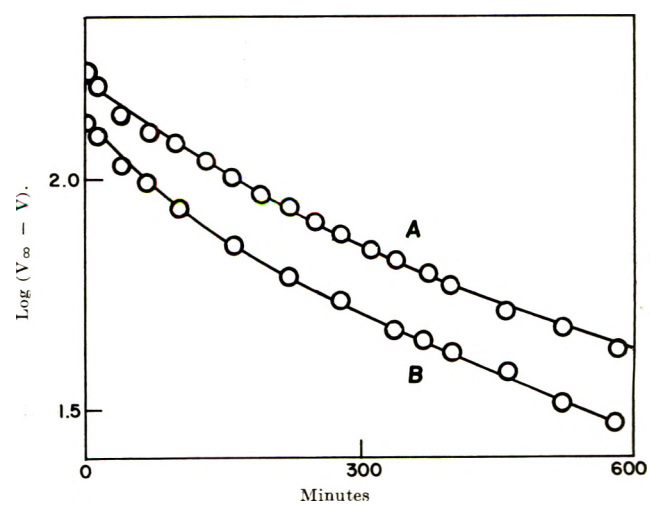

Fig. 3.—Gas Evolution with 0.01 *M* I_2 in C_6H_5Cl. *Experimental* points and *theoretical* curve: A. For 0.0497 *M* azide and 0.0499 *M* peroxide; B. For 0.0336 *M* azide and 0.0503 *M* peroxide.

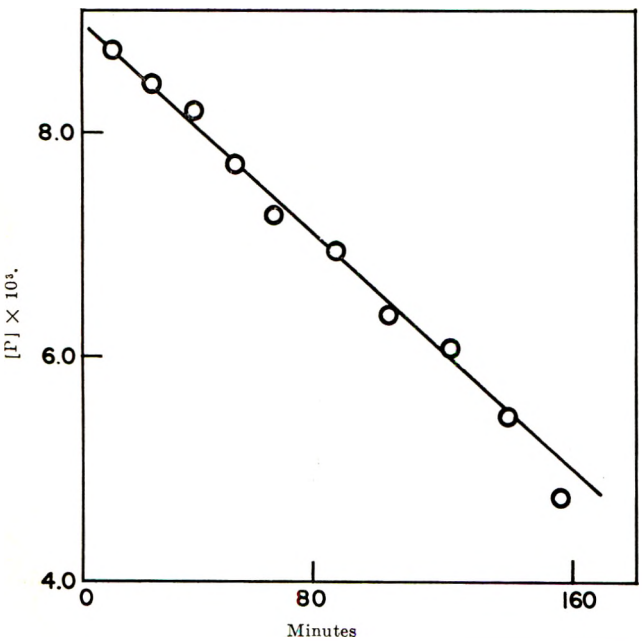

Fig. 4.—0.05 *M* peroxide and 0.006 *M* azide in C_6H_5Cl at 126.7°.

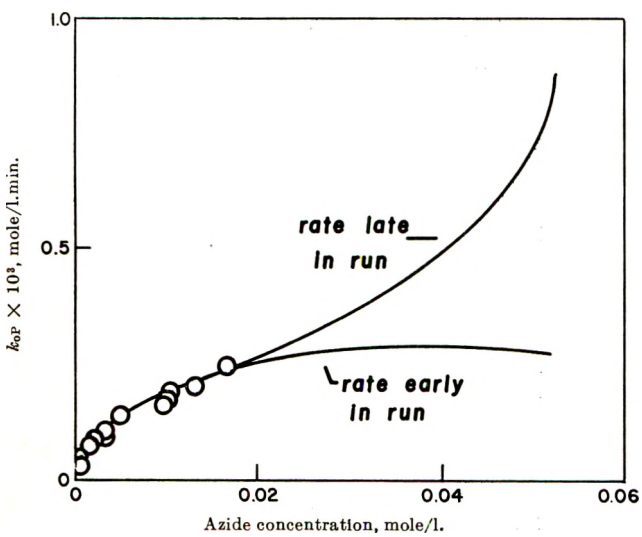

Fig. 5.—Dependence of peroxide decomposition rate on azide concentration for initial peroxide concentration 0.05 *M* in C_6H_5Cl at 126.7°.

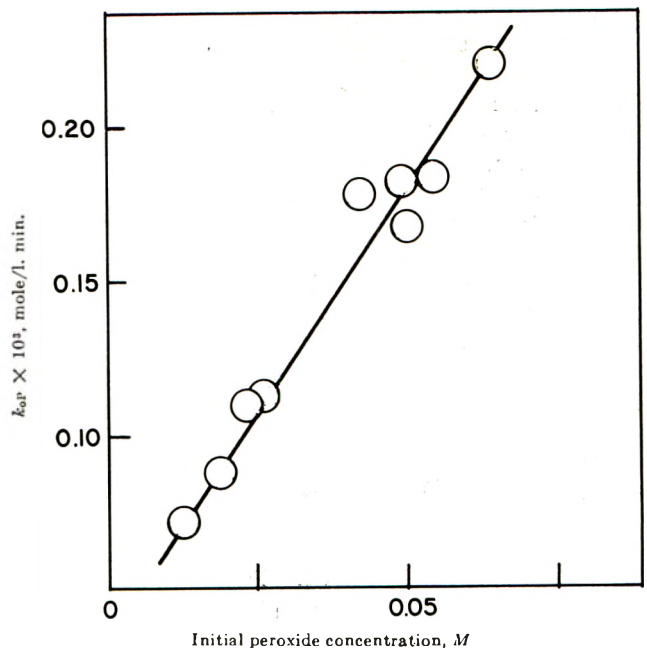

Fig. 6.—Dependence of peroxide decomposition rate on initial peroxide concentration in 0.01 *M* azide solutions in C_6H_5Cl at 126.7°.

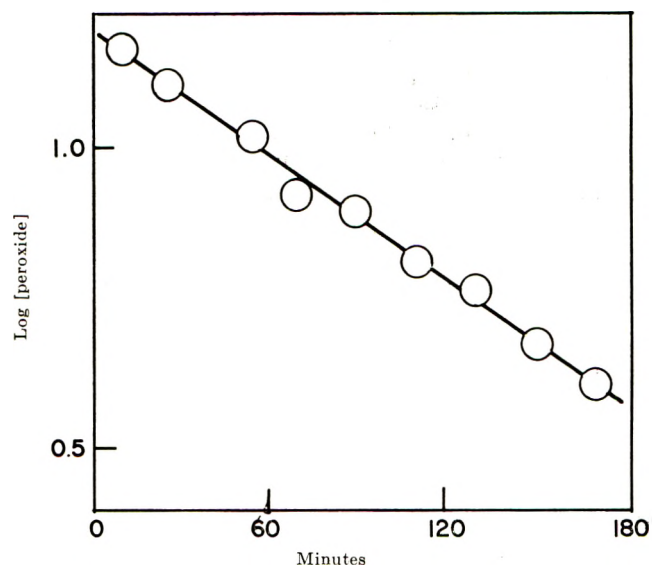

Fig. 7.—A first-order plot for a C_6H_5Cl, solution of iodine (0.01 *M*), azide (0.05 *M*), and peroxide (initially 0.05 *M*).

out of oxygen by the evolved nitrogen.[4] We note, however, that several mechanisms involving *t*-butoxy radicals, *t*-butylperoxy radicals, benzenesulfonyl nitrene, and substituted nitrogen-free radicals predict the $2k_1[A]$ term and terms in $[P]\ [A]^{1/2}$ and [P].

One such mechanism, involving chain transfer from 2he nitrene to a benzenesulfonanilide and chain-breaking ty bimolecular reaction of *t*-butoxy radicals, gives the $bk_1[A]$ and $[P]\ [A]^{1/2}$ terms but cannot account for the term in [P]. The latter is too large for an accompanying unimolecular decomposition of the peroxide.

The apparent zero-order rates within runs at low initial azide concentrations and the acceleration within runs at higher initial azide concentrations may be due to catalysis by some accumulating product of the azide decomposition reaction. A partly decomposed solution of the azide was found to give a faster peroxide decomposition than that for an otherwise comparable run in which both the azide and peroxide were added at the same time. Neither benzenesulfonamide nor benzenesulfonyl-*p*-chloroanilide is a catalyst, however.

Induced Decomposition of the Peroxide in the Presence of Iodine and the Azide.—In an attempt to divert some of the intermediates and simplify the kinetics we added iodine to the medium. The decomposition of the peroxide (without azide) in chlorobenzene in the presence of 0.01 *M* iodine is a reaction of apparently first order for which the rate constant k_{1P} is 3.4×10^{-3} min.$^{-1}$, about three times as great as that obtained without iodine. This reaction gives little or no gas. In the presence of iodine and the azide we observe two reactions, depending on the initial azide concentration.

At *high* initial azide concentrations (≥ 0.0124 *M*) the peroxide decomposition is clearly first order, as

(4) Vigorous sweeping with nitrogen during the reaction increases the rate by about a factor of two, much less than the effect reported in ref. 3a for the decomposition of the peroxide alone.

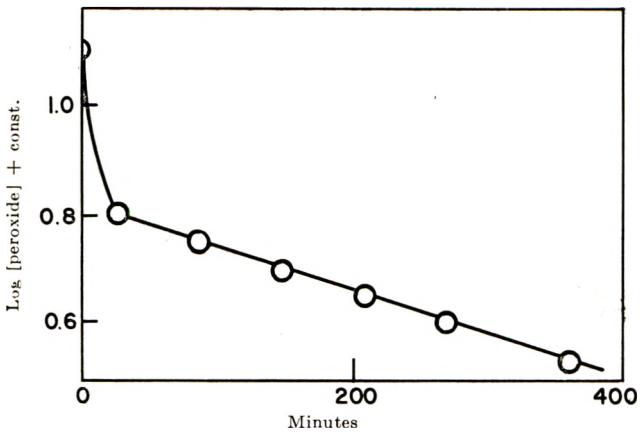

Fig. 8.—First order plot for peroxide decomposition in C_6H_5Cl at 126.7° with 0.01 *M* I_2 and 0.05 *M* initial peroxide concentration and a *low* (0.0016 *M*) azide concentration.

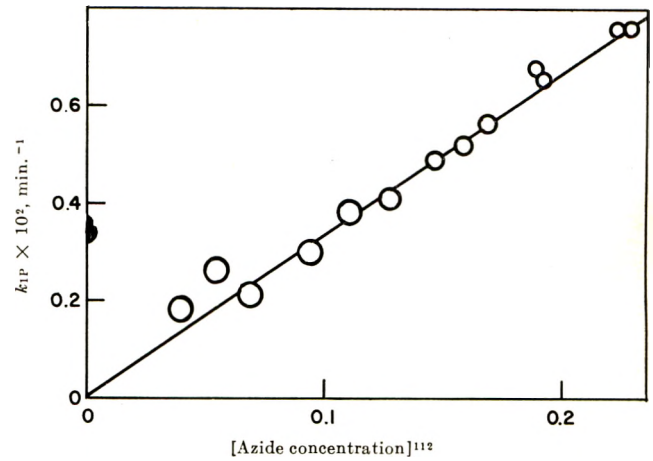

Fig. 9.—Dependence of k_{1P} on the square root of the azide concentration. The large circles are for runs having an initial fast part, like that of Fig. 8. The I_2 concentration is 0.01 *M* and the initial peroxide concentration is 0.05 *M*. The rate with *no azide* is shown by the filled circles.

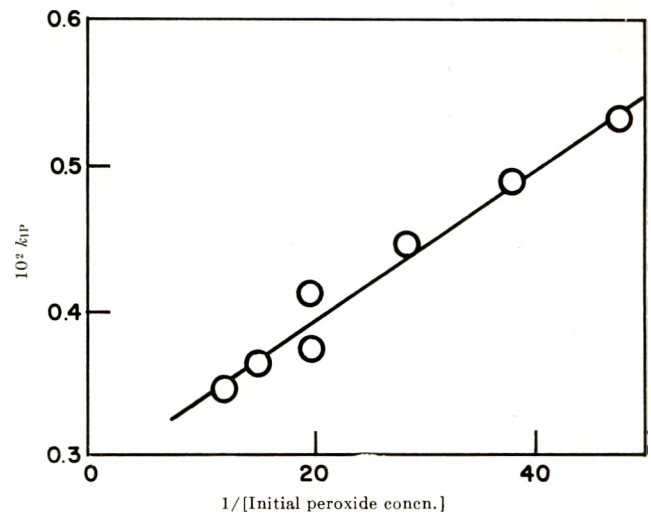

Fig. 10.—Dependence of k_{1P} for azide concentration 0.0164 *M* and I_2 concentration 0.01 *M* on 1/[P].

shown in Fig. 7. It is also clearly first order if benzenesulfonyl *p*-chloroanilide is added, even at lower azide concentrations.

At *low* initial azide concentrations ($\leq$0.0124 *M*) there is an extremely fast peroxide decomposition whose half-life is about five minutes or so. This reaction, like that of the peroxide plus iodine alone, gives no gas. It is much faster, however.

The initial fast peroxide decomposition soon stops, as shown in Fig. 8, and is succeeded by the first-order process leading to oxygen. Fig. 9 shows the linear relationship between k_{1P} for that process and the square root of the initial azide concentration. Initial iodine and peroxide concentrations were 0.01 and 0.05 *M*.

Fig. 10 shows a plot of k_{1P} against the reciprocal of the initial peroxide concentration for runs initially 0.01 *M* in iodine and 0.0164 *M* in azide.

The data of Fig. 9 and 10 are best fitted by equation 5 (in the presence of I_2, chlorobenzene, 126.7°).

$$k_{1P} = 0.4 \times 10^{-3} \frac{([A]_0)^{1/2}}{[P]} + 23 \times 10^{-3}([A]_0)^{1/2} \qquad (5)$$

It appears that the iodine–*t*-butyl hydroperoxide system is able to react in at least three ways. The first of these, in the absence of azide, is very likely a polar decomposition of the peroxide catalyzed by the iodine acting as a Lewis acid. The *fast initial peroxide decomposition* observed in the presence of low concentrations of *azide* might be a polar decomposition of the peroxide catalyzed by the positive halogen of N,N-diiodobenzenesulfonamide, *i.e.*, the nitrene diiodide. The inhibition of this initial fast reaction by benzenesulfonyl-*p*-chloroanilide might be explained by conversion of the nitrene and sulfonanilide to two nitrogen radicals by hydrogen transfer. The third reaction is the one whose rate constants are correlated by equation 5.

The form of equation 5 plus the effects of iodine and benzenesulfonyl-*p*-chloroanilide noted above suggest that the reaction consists of formation of the nitrene, chain transfer to form nitrogen-free radicals, some further chain transfer and chain-propagating steps, and one or more bimolecular termination steps. There are, unfortunately, a very large number of such mechanisms. Some of them lead to simple rate expressions incompatible with equation 5, others to rate expression of considerable mathematical complexity which might approximate (5) under special conditions. There is also at least one mechanism giving a *simple* rate expression compatible with (5). Although we do not wish to propose it as the mechanism of the reaction, we give it here as an example of the features which seem to be required. For convenience we let the azide be repre-

$$A \xrightarrow{1} N: + N_2$$

$$N: + NH \xrightarrow{2} 2N\cdot$$

$$N\cdot + I_2 \xrightarrow{3} (NI + I\cdot) \longrightarrow N\cdot + 2I.$$

$$I\cdot + P \xrightarrow{\text{fast}} HI + ROO\cdot$$

$$2ROO\cdot \xrightarrow{\text{fast}} 2RO\cdot + O_2$$

$$HI + P \xrightarrow{\text{fast}} H_2O + ROI$$

$$2N\cdot \xrightarrow{4} \text{chain breaking}$$

$$RO\cdot + P \xrightarrow{5} ROH + ROO\cdot$$

$$RO\cdot + I_2 \xrightarrow{6} ROI_2$$

$$2ROI_2\cdot \xrightarrow{\text{fast}} 2ROI + I_2$$

sented by A, the peroxide by P and by ROOH, the nitrene by N:, and the radicals $C_6H_5SO_2NH\cdot$ or $C_6H_5SO_2NAr\cdot$ indiscriminately by N·.

Assuming that ROI decomposes by an iodine-catalyzed polar mechanism and applying the steady-state approximation, the above mechanism gives an equation 6 of the required form.

$$k_{1P} = 4k_2[I_2]\left(\frac{k_1}{k_3}\right)^{1/2}\frac{[A]^{1/2}}{[P]} + \frac{2k_4k_2}{k_5}\left(\frac{k_1}{k_3}\right)^{1/2}[A]^{1/2} \qquad (6)$$

Experimental

Triphenylphosphine Method for the Azide.—A 5-ml. aliquot of the azide solution is added to 10 ml. of benzene in an azotometer equipped with a magnetic stirrer and a rotatable sidearm for adding a mixture of 5 ml. of triphenylphosphine reagent and 3 ml. of acetic acid. The triphenylphosphine reagent consists of 13.12 g. of triphenylphosphine in 50 ml. of chloroform. The gas buret is adjusted to zero, the sidearm is rotated so as to add the reagent, and the volume of nitrogen from the azide is read. Nitrogen is evolved quantitatively. A considerable excess of triphenylphosphine is used in order to destroy any unchanged peroxide.

$$(C_6H_5)_3P + C_6H_5SO_2N_3 \longrightarrow N_2 + (C_6H_5)_3\overset{+}{P}—\overset{-}{N}SO_2$$

$$(C_6H_5)_3P + (CH_3)_3COOH \longrightarrow (C_6H_5)_3PO + (CH_3)_3COH$$

Iodometry.—To a 10-ml. aliquot diluted with 25 ml. of isopropyl alcohol are added 5 ml. of acetic acid and 5 ml. of aqueous saturated potassium iodide solution, and the mixture is shaken and warmed for 20 min. at 60–70°. The solution is then diluted with water and titrated with 0.05 *N* thiosulfate.

For free iodine, the sample in isopropyl alcohol is titrated with thiosulfate without adding potassium iodide and acetic acid or warming.

Benzenesulfonylazide.—The method of preparation was essentially the same as that reported by Dermer and Edmison.[2a] Benzenesulfonyl chloride was allowed to react with sodium azide in an aqueous alcohol or aqueous acetone solution at about 0°. The product was taken up in ether, washed well with ice–water, and dried over sodium sulfate. If the solution was dried over calcium chloride, it became warm, bubbled, and turned pink or red. After the solvent was removed under reduced pressure at room temperature, the remaining oil was solidified by cooling in Dry Ice. It was then twice recrystallized from ether–petroleum ether (low boiling) and dried *in vacuo* at 30–40°. The azide melted at 13–14° and decomposed with bubbling at about 135°. The decomposition in chlorobenzene or xylene gave closely the theoretical amount of nitrogen.

***t*-Butyl Hydroperoxide.**—The commercial product was purified by fractional distillation through a short column, and the fraction, b.p. 38.5–39.5°/18 mm., was used for the rate measurements.

Chlorobenzene was dried over calcium chloride and distilled, b.p. 131–131.5°.

The Products of the Decomposition.—The product from the decomposition of 2.36 g. of the azide in chlorobenzene at 126° was chromatographed on alumina after evaporation of the solvent, giving 0.49 g. of oily crystals, 1.1 g. of needles, m.p. 123–128°, and 0.36 g. of plates, m.p. 114–120°. The first fraction melted at 116–120° after recrystallization from ether. The second melted at 127–129° after recrystallization from alcohol. The third fraction gave colorless plates, m.p. 119–121°. These products were identified by mixed melting points as the *m*-, *o*-, and *p*-chloroanilides of benzenesulfonic acid, respectively. The total yield was about 56% of the theoretical before purification.

In the presence of *t*-butyl hydroperoxide, the yield of these products was decreased. The low molecular weight material from 2.62 g. of azide and 1.16 g. of *t*-butyl hydroperoxide amounted to only 1.47 g. after chromatographic separation from tars, and the total yield of chloroanilides was less than 35%. *o*-Chloroanilide was the main product, and a small amount of unsubstituted benzenesulfonylamide was also obtained. There was a considerable amount of black material, insoluble in the usual organic solvents.

Reaction of Carbon Disulfide with Azide Ion[1]

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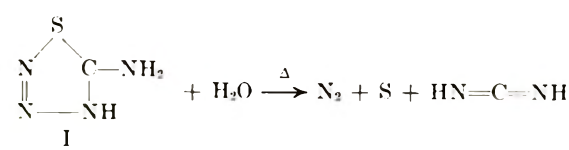
Departments of Chemistry, Roosevelt University, and DePaul University, Chicago, Illinois

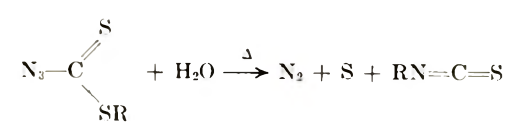
Received November 8, 1960

Carbon disulfide reacts with azide ion to form the 1,2,3,4-thiatriazolinethionate ion and not the acyclic azidodithiocarbonate ion as previously reported. A series of salts of thiatriazoline have been prepared and none shows evidence for the presence of the azido group. Esters of thiatriazolinethione prepared by the reaction of the sodium salt with alkyl or acyl halides have been found to be either 5-(substituted) mercapto-1,2,3,4-thiatriazoles or 4-substituted 1,2,3,4-thiatriazoline-5-thiones. These structures have been assigned on the basis of degradative and spectroscopic evidence. The chemistry of the so-called azidodithiocarbonates has been reinterpreted in terms of the thiatriazole structure.

During the course of the investigations[3] on the 1,2,3,4-thiatriazole ring system, Lieber and co-workers were struck by the similarity in their chemistry with that reported for substances described in the literature[4] as azidodithiocarbonates. For example, 5-amino-1,2,3,4-thiatriazole (I)[5] and azidodithiocarbonic acid (II. R = H), respectively, decompose on warming[6] in water.



I



II[7]

Other similarities in the chemistry of the so-called II led to a preliminary re-examination[5] of the structure of the products obtained by the condensation of azide ion with carbon disulfide. The absence of the characteristic azido group frequencies in the infrared spectra

(1) The authors gratefully acknowledge the support of this research by the U. S. Army Research Office.

(2) (a) To whom all correspondence should be addressed; (b) taken in part from M.S. thesis, DePaul University, 1960; (c) presently at the Indian Institute of Science, Bangalore, India.

(3) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959), which cites previous references in this series.

(4) L. F. Audrieth, *Chem. Rev.*, **15**, 169 (1934).

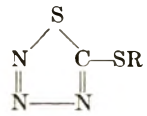
(5) E. Lieber, C. N. Pillai, J. Ramachandran, and R. D. Hites, *J. Org. Chem.*, **22**, 1750 (1957).

(6) Both structures I and II will slowly decompose in aqueous solution and room temperature.

(7) This is the structure corresponding to the descriptive name for this substance.

TABLE I

5-SUBSTITUTED MERCAPTO-1,2,3,4-THIATRIAZOLES

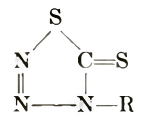


R	Organic halide	Yield, %	M.p., °C.[a] Found	Lit.	Formula	% S[b] Calcd.	Found
CH_3[c,d,e,b]	CH_3Br	40	34–35	34	$C_2H_3N_3S_2$	48.15	47.76
$C_6H_5CH_2$[f,g,e]	$C_6H_5CH_2Cl$	70	66–67	66	$C_8H_7N_3S_2$	30.58	30.45
4-$(O_2N)C_6H_4CH_2$[h,f,i]	4-$(O_2N)C_6H_4CH_2Cl$	99	100–102		$C_8H_6N_4O_2S_2$	25.22	25.10
$C_6H_5COCH_2$[h,f,i]	$C_6H_5COCH_2Cl$	98	89		$C_9H_7N_3OS_2$	27.02	27.10
4-$ClC_6H_4COCH_2$[h,f,i]	4-$ClC_6H_4COCH_2Cl$	95	106–108		$C_9H_6ClN_3OS_2$	23.60	23.48
4-$(C_6H_5)C_6H_4COCH_2$[h,f,i]	4-$(C_6H_5)C_6H_4COCH_2Br$	98	98		$C_{15}H_{11}N_3OS_2$	20.46	20.50
CN[i,j,k]	CNBr	83	84–85[l]	80.5–81[l]	$C_2N_4S_2$	44.47	44.41

[a] With decomposition. [b] All compounds evolved one mole of nitrogen per mole on thermal degradation. [c] Crystallized from methyl alcohol. [d] Reaction time was six hours. [e] See ref. 4. [f] Crystallized from acetone and water. [g] Reaction time was twenty-four hours. [h] New compound. [i] The reaction was found to occur instantaneously. [j] Washed with water. [k] See ref. 2. [l] Decomposition takes place without melting forming a solid containing sulfur.

TABLE II

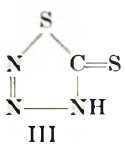
4-SUBSTITUTED THIATRIAZOLINETHIONES



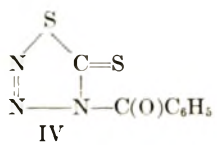
R	Organic halide	Yield, %	M.p., °C.[a] Found	Lit.	Formula	% S[b] Calcd.	Found
C_6H_5CO[c,d,e]	C_6H_5COCl	98	92–93	92–94	$C_7H_5N_3OS_2$	28.72	28.70
$(C_6H_5)_2CH$[c,f,g]	$(C_6H_5)_2CHBr$	63	62–64	67	$C_{14}H_{11}N_3S_2$	22.47	22.10
$(C_6H_5)_3C$[c,f,e]	$(C_6H_5)_3CCl$	88	91–92	102–104	$C_{20}H_{15}N_3S_2$	17.74	17.78

[a] With decomposition. All compounds evolved one mole of nitrogen per mole on thermal degradation. [c] See ref. 4. [d] An instantaneous reaction was observed. [e] Crystallized from chloroform. [f] The reaction time was three hours. [g] Crystallized from ether.

of azidodithiocarbonic acid[8] (II. R = H) and benzoylazidodithiocarbonate (II. R = C_6H_5CO), suggested that they were derivatives of the 1,2,3,4-thiatriazole ring system, the structures represented as III and IV,

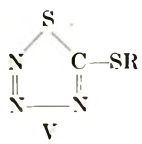


III

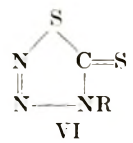


IV

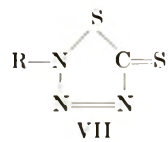
respectively. Structure III had been considered by Olivera-Mandala,[9,10] who rejected it in favor of II. On the basis of the older structure accepted for this reaction only one substitution product is possible[11] (II. R = alkyl or acyl). However, structure III can lead to three isomeric monosubstitution products[12] (V, VI, and VII). It was the objective of this investigation to prepare salts[13] and esters of the so-called azidodithiocarbonic acid and examine evidence for their structures in light of the fact that they are derivatives of the 1,2,3,4-thiatriazole ring system.



V



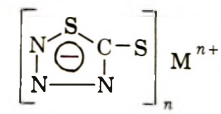
VI



VII

Results and Discussion

A series of ten esters (Tables I and II) as well as silver, lead, ammonium, guanidinium, anilinium, and benzylammonium salts of the so-called azidodithiocarbonic acid were prepared, all of which failed to show the characteristic asymmetric stretching frequency[14] of the azido group around 2140 cm.$^{-1}$, but showed characteristic frequencies of the 1,2,3,4-thiatriazole ring[3,15] in the regions 1610–1560 (w), 1320–1280 (v), 1240–1190 (v), and 1090–1000 (v) cm.$^{-1}$.[15b] The salts of thiatriazolinethione (III) are probable best represented by VIII, with the negative charge delocalized over the entire ring. These salts also show a band in the region

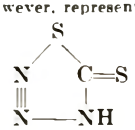


VIII (n = a small integer, M is a cation)

(8) G. B. L. Smith, F. Wilcoxon, and A. W. Browne, *J. Am. Chem. Soc.* **45**, 2604 (1923).

(9) E. Olivera-Mandala, *Gazz. chim. ital.*, **52**, II, 139 (1922).

(10) The structure was, however, represented by



with a triple bond between nitrogen atoms 2 and 3.

(11) L. F. Audrieth, J. R. Johnson, and A. W. Browne, *J. Am. Chem. Soc.*, **52**, 1928 (1930).

(12) The reaction involves the nucleophilic displacement of halogen from an alkyl or aryl halide by the anion of III.

(13) In a private communication Professor L. F. Audrieth expressed the opinion that the salts of II (R = H) in which the cations were heavy metals such as Ag^+ or Pb^{++} would exhibit the azido absorption frequencies in the infrared.

(14) E. Lieber, C. N. R. Rao, T. S. Chao, and C. W. W. Hoffman, *Anal. Chem.*, **29**, 916 (1957).

(15) (a) The discovery by infrared spectroscopy, that reactions which should theoretically lead to thiocarbamyl azides are, in reality, derivatives of the thiatriazole ring system, was made almost simultaneously by four investigators. See E. Lieber and F. Oftedahl, *J. Org. Chem.*, **24**, 1014 (1959). (b) See ref. 4a.

TABLE III

DEGRADATIVE STUDIES—IDENTIFICATION OF THIOCYANATES AND ISOTHIOCYANATES

Compound	M.p., °C.[a,b]	Synthetic m.p., °C. Found	Synthetic m.p., °C. Lit.	Infrared absorption assignments[c] —S—C≡N Degradative	—S—C≡N Synthetic	Frequency, cm.$^{-1}$ —N=C=S Degradative	—N=C=S Synthetic
NCSCN[d]	60	62	60/62	2174	2174		
$C_6H_5COCH_2SCN$[e]	73–74	74–75	74	2128	2146		
4-$ClC_6H_5COCH_2SCN$[f]	135–136	135–136	135.2	2169	2169		
4-$C_6H_5C_6H_4COCH_2SCN$[g]	138–140	138–141	...	2160	2164		
4-$NO_2C_6H_4CH_2SCN$[h]	85–86	85–86	85.5	2155	2155		
$(C_6H_5)_3CNCS$[i]	135–137	137–138	137			2083; 2020	2083; 2024
$(C_6H_5)_2CHNCS$[j]	Oil	Oil	61			2164; 2079	2183; 2150; 2088[k]
$(C_6H_5)_2CHSCN$[j]	...	Oil	59		2174; 2151; 2083[k]		

[a] This is the melting point of the product isolated from the thiatriazole degradation. [b] Mixture melting point with an authentic sample showed no depression. [c] In all cases the infrared absorption spectrum of the degradation product matched identically with that of the authentic sample. [d] See ref. 18. [e] See ref. 21. [f] See ref. 22. [g] New compound. *Anal.* Calcd. for $C_{15}H_{11}OSN$: S, 12.67. Found: S, 12.32. [h] See ref. 23. [i] See ref. 19. [j] See ref. 20. [k] This corresponds to a mixture of isothiocyanate and thiocyanate.

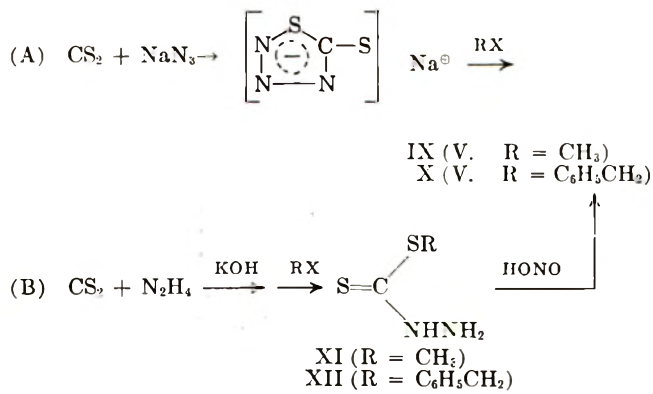


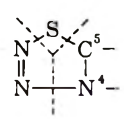
Chart I

Unequivocal Syntheses for Methyl and Benzyl Substitution Products of Thiatriazolinethione

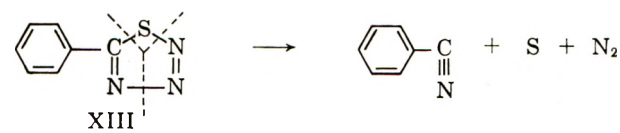
720–680 cm.$^{-1}$ probably due to the stretching of the exocyclic C—S band.

The question of deciding between the isomeric structures V, VI, or VII for the esters was established by unequivocal synthesis and by thermal degradation, using both methods wherever possible and making use of infrared spectroscopy. When the methyl (XI) and benzyl (XII) esters of dithiocarbazinic acid, respectively, were diazotized, the products isolated (IX and X) were shown to be identical to the carbon disulfide–sodium azide condensation (Chart I).

The structural interpretations based upon the degradation products obtained on pyrolyses of the substituted thiatriazolinethiones followed the assumption that the heterocyclic ring falls apart as follows:



the dotted lines representing heterolytic bond breaking. Abundant evidence for this mode of decomposition has been obtained. The mechanism for the thermal degradation of the thiatriazolinethiones is probably similar to that suggested for the 5-(substituted) aminothiatriazoles.[16] It may be noted that the degradation of the 5-(substituted) mercaptothiatriazoles (V) should yield organic thiocyanates while the 4-substituted derivatives (VI) should yield isothiocyanates. Thermal degradation of the 2-substituted derivatives (VIII) should yield isothiocyanates and azo compounds produced by the recombination of the radicals RN and CS. This assumption regarding the mode of thermal degradation of thiatriazoles (XIII) leads to benzonitrile, sulfur, and nitrogen:



Thermal degradation of the esters of thiatriazoles (Tables I and II) always gave rise to thiocyanates or isothiocyanates, thus indicating that these thiatriazole derivatives have structures V and VI with substituents in the 5- and 4-position. The isolation and identification of the organic thiocyanates or isothiocyanates produced in the degradation were based on the recognition of the *normal* or *isothiocyanate* group by infrared spectroscopy[17] and by comparison of the spectra and melting points with those of authentic specimens. Mixed melting points were also determined. The identifications of the degradative products were generally unequivocal (Table III). The structure assignments for the different thiatriazole derivatives are summarized in Tables I and II. It may be argued that the benzoyl, diphenylmethyl, and triphenylmethyl derivatives (Table II) may also be 5-(substituted) mercapto derivatives, since it is possible that the organic thiocyanates produced in the degradation might have isomerized into the corresponding isothiocyanates,[24–26] particularly in view of the fact that some of these thiocyanates have not been prepared.[27] It is felt that if such isomerization did occur, one would get mixtures of the thiocyanate and the isothiocyanate. Since only pure isothiocyanates were obtained as de-

(16) Lieber and co-workers: (a) *J. Org. Chem.*, **22**, 1054 (1957); (b) *Can. J. Chem.*, **35**, 832 (1957); (c) *ibid.*, **37**, 101 (1959).

(17) E. Lieber, C. N. R. Rao, and J. Ramachandran, *Spectrochim. Acta*, **13**, 296 (1959).

(18) E. Soderback, *Ann.*, **419**, 217 (1919).

(19) K. Elbs, *Ber.*, **17**, 700 (1884).

(20) H. L. Wheeler, *Am. Chem. J.*, **26**, 345 (1901).

(21) W. Borsche, *Ber.*, **75**, 1312 (1942).

(22) W. L. Judefind and E. E. Reid, *J. Am. Chem. Soc.*, **42**, 1043 (1920).

(23) J. A. Lyman and E. E. Reid, *ibid.*, **39**, 701 (1917).

(24) A. Iliceto, A. Fava, U. Mazzucato, and O. Rossetto, *ibid.*, **83**, 2729 (1961).

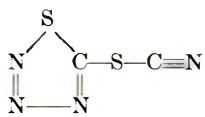
(25) C. N. R. Rao and S. N. Balasubrahmanyam, *Chem. Ind.* (London), 625 (1960).

(26) P. A. S. Smith and D. W. Emerson, *J. Am. Chem. Soc.*, **82**, 3076 (1960).

(27) E. Lieber and E. Oftedahl, *Chem. Ind.* (London), 1303 (1960).

gradation products, the thione structure VI for these thiatriazole derivatives seems correct. Further confirmation of the thione structure for the benzoyl, diphenylmethyl, and triphenylmethyl derivatives may be obtained by independent syntheses through the diazotization of the corresponding dithiocarbazinates (Chart I).[28] The thione structure (VI) for these derivatives was, however, substantiated by satisfactory assignments of group frequencies in the infrared spectra. Just like thiatriazolinethione (III), the three derivatives in Table II exhibited the "—N—C=S bands" in the regions 1490–1440, 1340–1320, and 1100–920 cm.$^{-1}$.[29] These derivatives showed only one band in the 700-cm.$^{-1}$ region which was clearly due to the C—H out-of-plane deformation of the monosubstituted benzene ring. The 5-mercapto derivatives (Table I), on the other hand, showed more than one band in the 720–680 cm.$^{-1}$ region, one of which is likely to be due to the exocyclic C—S stretching vibration.

Evidence for the structure of the cyano derivatives as 5-thiocyanothiatriazole, XIV, was unambiguous



XIV

both from degradative and spectroscopic data. The infrared spectrum of XIV showed a characteristic sharp nitrile frequency around 2185 cm.$^{-1}$. The absence of the N—C≡N unit was also confirmed by comparison with the spectrum of cyanamid. The degradation of XIV to N≡C—S—C≡N was easily established by isolation and comparison of spectra (Table III).

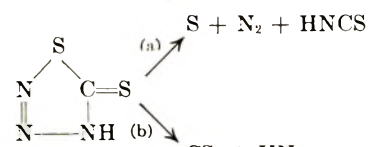
Thiatriazolinethione (III) is a strong acid. Its neutralization equivalent is readily determined by titration in aqueous solution. Smith, *et al.*,[30] studied the electrical conductivity of the so-called sodium and potassium azidodithiocarbonates, respectively, reported "azidodithiocarbonic acid" to be comparable to sulfuric acid in strength. The extensive delocalization offered by the thiatriazole anion (VIII) makes this observation understandable. Structure VIII also explains the proclivity of these salts to decompose into ionic thiocyanates.[31,32] In fact, the reaction between carbon disulfide and ionic azides can easily be pushed beyond the thiatriazoline stage so as to make it a preparative procedure for thiocyanate salts. Thus, Stolle[33] prepared sodium thiocyanate, in quantitative yield, by refluxing a mixture of sodium azide and carbon disulfide (in excess) in ethanol. Sulfur and nitrogen in quantities demanded by the equation

$$CS_2 + NaN_3 \longrightarrow NaSCN + N_2 + S$$

were also obtained. Audrieth, *et al.*,[34] prepared ammonium thiocyanate and tetramethylammonium thiocyanate by prolonged treatment (in refluxing ethanol) of ammonium azide and tetramethylammonium azide, respectively, with carbon disulfide. The ready formation of the thiocyanate ion can easily be interpreted as an internal oxidation–reduction of the thiatriazolinate ion.

The realization of the true structure of the carbon disulfide–azide ion condensation as VIII also reveals its possible mechanism of formation. Audrieth "assumed, on the basis that the condensation of covalently bonded azides fails, that the formation of the "azidodithiocarbonates" involved the transfer of an electron from the azide ion to "one of the sulfur atoms of the carbon disulfide." In view of the fact that the sulfur is in its lowest oxidation state this hypothesis appears untenable. It is suggested, in view of the isoelectronic relationship between carbon disulfide and azides, that the mechanism proposed by Lieber[35] for the condensation of azide ion with isothiocyanates is directly applicable to the condensation with carbon disulfide. There is reason to believe that, with suitable activation organic azides can be made to react with carbon disulfide. Thus, Borsche[21] isolated phenyl isothiocyanate from the reaction of carbon disulfide with phenylazide in the presence of aluminum chloride. Schonberg[36] obtained phenyliminodiphenylmethane by heating (110–140°) thiobenzophenone with phenyl azide. Both of these reactions are readily explicable on the basis that a thiatriazole is formed as an intermediate.

Previous work[8,37] on the properties of the carbon disulfide–azide ion condensation product has shown that III (azidodithiocarbonic acid) decomposes in aqueous solution by a monomolecular reaction but that the decomposition from the solid state is autocatalytic and is accelerated by one of its products of decomposition. The evidence indicates that the catalytic agent may be thiocyanic acid or one of its polymers. The present investigation would appear to favor the idea that the monomolecular reaction is simply the postulated internal oxidation–reduction leading to the formation of sulfur, nitrogen, and thiocyanic acid. In the solid state, however, two modes of decomposition can take place. It should be noted that route (b) (below)



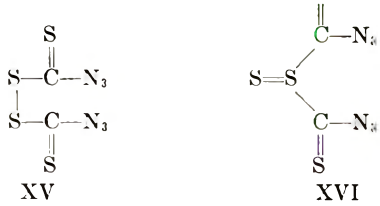
III

$$HSCN + 3HN_3 \longrightarrow NH_4SCN + 4N_2$$

for the decomposition of thiatriazolinethione III represents its simple dearrangement to carbon disulfide and hydrazoic acid. This has been demonstrated by the alkaline degradation of thiatriazolinethione conducted in the present investigation.

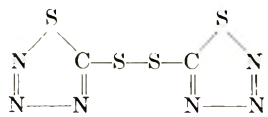
While the present investigation has not been concerned with the so-called azidocarbon disulfide,[4,37–39] it was considered relevant to interpret the structures and properties described in the literature. The structures previously given[4] for azidocarbon disulfide are

(28) Work along these lines is in progress at Roosevelt University.
(29) C. N. R. Rao and R. Venkataraghavan, *Spectrochim. Acta*, **18**, 541 (1962).
(30) G. B. L. Smith, F. P. Gross, G. H. Brandes, and A. W. Browne, *J. Am. Chem. Soc.*, **56**, 1116 (1934).
(31) A. W. Browne, L. F. Audrieth, and C. W. Mason, *ibid.*, **49**, 917 (1927).
(32) A. W. Browne and A. B. Hoel, *ibid.*, **44**, 2315 (1922).
(33) R. Stolle, *Ber.*, **55**, 1289 (1922).
(34) L. F. Audrieth, G. B. L. Smith, A. W. Browne, and C. W. Mason, *J. Am. Chem. Soc.*, **49**, 2129 (1927).
(35) E. Lieber and J. Ramachandran, *Can. J. Chem.*, **37**, 101 (1959).
(36) A. Schonberg, *J. Chem. Soc.*, 530 (1935).
(37) F. Wilcoxon, A. E. McKinney, and A. W. Browne, *J. Am. Chem. Soc.* **47**, 1916 (1925).
(38) L. F. Audrieth, *ibid.*, **52**, 2794 (1930).
(39) A. W. Browne, A. B. Hoel, G. B. L. Smith, and F. H. Swezey, *ibid.*, **45**, 2541 (1923).

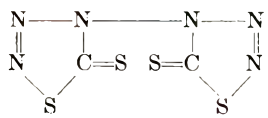


XV XVI

It is prepared[30] by the chemical or electrochemical oxidation of the free acid (*i.e.*, thiatriazolinethione, III). However, in terms of the thiatriazolinethione structure (V), the probable structures are XVII and XVIII. The substance is a white microcrystalline explosive solid[39] which decomposes fairly rapidly at room temper-

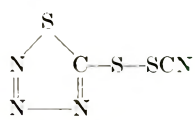


XVII



XVIII

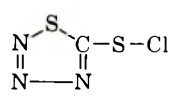
ature. At higher temperature the decomposition proceeds with explosive violence. On this basis structure XVIII is appealing since it contains a chain of six nitrogen atoms. However, structure XVII explains the formation of thiocyanogen, $(SCN)_2$, on degradation.[39] Structure XVII can also explain the formation of 5-(thiocyanato)mercaptothiatriazole (XIX) as a decom-



XIX

position product. The so-called azidocarbondisulfide is reported[39] to react with potassium hydroxide giving rise to the salts, $KSCSN_3$ and $KOSCSN_3$. In terms of the thiatriazole structure XVII these salts should be XX and XXI. Similarly, the structure of the so-called chlorine azidodithiocarbonate[40] should be XXII.

XX XXI



XXII

Experimental[41]

Thiatriazolinethione (III).—To a 125-ml. Erlenmeyer flask, containing 50 ml. of water, was added 12 g. (0.18 mole) of sodium azide and 20 ml. of carbon disulfide. The mixture was magnetically stirred for 6–8 hr. at room temperature. The resulting solution containing the sodium salt of thiatriazolinethione was filtered, chilled in an ice bath and treated with cold concentrated hydrochloric acid. The whitish yellow, crystalline precipitate was filtered and washed with 100 ml. of ice-cold water. The product was allowed to remain on the Büchner funnel for about 0.5 hr. to remove any hydrazoic acid present. The thiatriazolinethione, so prepared, was usually used immediately for further work, or preserved in a desiccator protected from light, and kept at a temperature below 10°. In this manner, it may be kept for 24–48 hr. without appreciable decomposition.

Anal. Calcd.: neut. equiv., 119. Found: neut. equiv., 120.

Ring Substitution Reactions through Sodium Thiatriazolinethionate.—The following general procedure was developed: The free acid, thiatriazolinethione, was converted to the sodium salt by neutralizing with a 30% solution of sodium hydroxide to the phenolphthalein end point. To this was added 200 ml. of acetone and the appropriate organic halide. This solution was allowed to stand for a sufficient length of time to ensure completion of the reaction, after which it was diluted with water. At this point the crude product either precipitated as a crystalline solid or as an oil. If the product was crystalline, it was collected on a Büchner funnel, washed with water, and recrystallized from an appropriate solvent. If the product was an oil, it was separated from the reaction solution by means of a separatory funnel, washed with water, and converted to the crystalline state by storage at low temperature. After the oily product had been converted to the crystalline state, it was recrystallized from an appropriate solvent. All of the compounds prepared were preserved at a temperature below −10° for the studies described below. Tables I and II summarize the esters of thiatriazolinethione prepared.

Potassium Dithiocarbazinate.—A solution of 66 g. (1.18 moles) of potassium hydroxide and 65 ml. of 85% hydrazine hydrate (1.1 moles) in 200 ml. of ethanol was stirred and cooled in an ice bath while 63 ml. (1.04 moles) of carbon disulfide was added dropwise. A heavy yellow oil, containing the potassium dithiocarbazinate, separated during the course of this addition. The resulting mixture was chilled and two volumes of ether were added in order to cause the separation of more of the desired product. The oily layer was separated from the ether–alcohol layer. This oily layer, containing the product, was used in the subsequent steps, for the preparation of the organic esters of dithiocarbazic acid. The solid, potassium dithiocarbazinate, was also prepared by removing the water from the oily layer. This was done *in vacuo* over phosphorus pentoxide in a desiccator placed in the refrigerator.

Methyl Dithiocarbazinate (XI).—The entire oily layer, from the above reaction containing the potassium dithiocarbazinate, was dissolved in 300 ml. of water. The resulting solution was cooled in an ice bath and 150 g. (1.05 moles) of methyl bromide was added, in approximately 20-g. portions, over a period of 3 hr. The reaction mixture was stirred and cooled during the addition of the methyl bromide. The product precipitated during the course of the reaction. The reaction mixture was allowed to stand for several hours (at ice-bath temperature) after the addition of the methyl bromide was complete. The product was collected and recrystallized from ether–ligroin. The purified product, 75.6 g. (62%), melted at 80.5–82°.[42]

Anal. Calcd. for $C_2H_6N_2S_2$: S, 52.07. Found: S, 52.46.

Benzylidene Methyl Dithiocarbazinate, M.p. 156–157°.[43] Benzyl Dithiocarbazinate (XII).—The preparation was similar to the methyl ester except that 64 g. (0.50 mole) of benzyl chloride was used to prevent disubstitution. The reaction mixture was stirred for 24 hr. at ice-bath temperature. The product was collected and recrystallized from benzene. The purified product, 36 g. (36%), melted at 124–125°.[43]

Anal. Calcd. for $C_8H_{10}N_2S_2$: S, 32.25. Found: S, 32.40.

Benzylidene Benzyl Dithiocarbazinate, M.p. 162–163°.[43] Diazotization of Dithiocarbazinates. 5-Methylmercapto-1,2,3,4-thiatriazole (V. R = CH_3).—To an ice-bath solution of 23.5 g. (0.21 mole) of methyl dithiocarbazinate in 95 ml. of 2.2 *N* hydrochloric acid (0.21 mole), three 50-ml. portions of a sodium nitrite solution containing a total of 14.7 g. (0.21 mole) of sodium nitrite were added under stirring. After the 50-ml. portions were added, the product was collected and washed with 10 ml. of ice–water and was recrystallized from methyl alcohol and was found to melt at 33–34°. The index of refraction was determined immediately after melting and was found to be 1.602 at 35°.

(40) W. H. Gardner and A. W. Browne, *J. Am. Chem. Soc.*, **49**, 2759 (1927).

(41) (a) Sulfur analysis were carried out by bomb peroxide fusion, followed by gravimetric barium sulfate. Nitrogen was determined by thermal decomposition collecting the gas in a Dumas azotometer. Metal analyses were standard procedures. Other analyses were carried out by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England. Melting points are uncorrected. (b) Infrared spectra were recorded using a Perkin–Elmer Model 21 spectrometer. Intensities are reported as w, weak and v, variable.

(42) L. F. Audrieth, E. S. Scott, and P. S. Kippur, *J. Org. Chem.*, **19**, 740 (1954).

(43) M. Busch, *J. prakt. Chem.*, **93**, 25 (1916).

Anal. Calcd. for $C_2H_3N_3S_2$: S, 48.15. Found: S, 47.80.

5-Benzylmercapto-1,2,3,4-triatriazole (V. R = $C_6H_5CH_2$).—The procedure was similar to that described above except that the sodium nitrite solution was added over a period of 1.5 hr. and the mixture stirred for an additional 4 hr. The product was recrystallized from acetone and water. The melting point of the purified product was found to be 65–67°.

Anal. Calcd. for $C_8H_7N_3S_2$: S, 30.58. Found: S, 30.10.

Salts of Thiatriazolinethione (VIII). (a) **Metallic Salts.**—The following general procedure was adopted. The heavy metal salts were prepared by the interaction of aqueous solutions containing freshly prepared thiatriazolinethione and aqueous solutions containing the appropriate metallic ion. After filtration and washing, a portion of the precipitate so obtained was set aside (in a vacuum desiccator over phosphorous pentoxide) for analysis and the remainder of the specimen preserved by suspending in white mineral oil and maintaining below −20°. These precautions were found to be essential due to the explosive instability of the heavy metallic salts. The mineral oil suspensions were utilized for the determination of the infrared absorption spectra at the earliest possible moment. In the same manner the analyses were carried out as early as possible after their preparation.

Silver thiatriazolinethionate (VIII. M = Ag^+; n = 1) was a white, slightly photosensitive solid. It was not recrystallized before analysis.

Anal. Calcd. for CN_3S_2Ag: Ag, 47.73. Found: Ag, 47.61.

Lead thiatriazolinethionate (VIII. M = Pb^{++}; n = 2) was obtained in the form of a light greenish yellow solid which was not purified further.

Anal. Calcd. for $C_2N_6S_4Pb$: 46.76. Found: Pb, 46.60.

(b) **Organic Nitrogen Salts. Ammonium Thiatriazolinethionate** (VIII. M = NH_4^+; n = 1). This compound was by prepared by neutralization of II[1] with ammonium hydroxide and isolated as a white crystalline solid by evaporation in a vacuum desiccator over phosphorus pentoxide at 5°, m.p. 110–115° dec.

Anal. Calcd. for $CH_4N_4S_2$: S, 47.09. Found: S, 46.78.

Guandininum Thiatriazolinethionate (VIII. M = $(NH_2)_3C^+$; n = 1).—This compound was prepared by adding thiatriazolinethione still moist, to an aqueous solution of guanidine carbonate until no further evolution gas was observed to take place. The turbid liquid was filtered, and the filtrate concentrated *in vacuo* over phosphorus pentoxide at 5°. After several days the crystalline material so obtained was recrystallized from water. The colorless crystals melted at 90–91° with decomposition.

Anal. Calcd. for $C_2H_6N_6S_2$: S, 35.99. Found: S, 36.05.

Anilinium Thiatriazolinethionate (VIII. M = $C_6H_5NH_3^+$; n = 1).—To a solution of benzene and aniline was added freshly prepared thiatriazolinethione, still moist. An oil separated, which was removed and shaken with dry benzene (to remove excess aniline). The oil so isolated was concentrated *in vacuo* over phosphorus pentoxide at 5°. After 2 hr. the solid yellow crystalline product was removed, washed with benzene, and allowed to dry, m.p. 70–72°.

Anal. Calcd. for $C_7H_8N_4S_2$: S, 30.21. Found: S, 30.27.

Benzylammonium Thiatriazolinethionate (VIII. M = $C_6H_5CH_2NH_3^+$; n = 1).—This compound was prepared by adding moist III to an ether solution of benzylamine. As aqueous lower layer appeared that was removed and washed several times with benzene. The aqueous layer so obtained was chilled and the product crystallized. This slightly yellow, crystalline product was removed from its aqueous suspension by filtration and washed several times with benzene. The decomposition point was found to be 99°.

Anal. Calcd. for $C_8H_{10}N_4S_2$: S, 28.34. Found: S, 28.18.

Degradative Studies. (a) **Reference Compounds.**—These were prepared by methods described in the literature and are summarized in Table III. The triphenylmethyl thiocyanate of Elbs[19] turned out to be triphenylmethyl isothiocyanate.[24,41,44] The procedure of Wheeler[42] for diphenylmethyl thiocyanate and diphenyl isothiocyanate gave mixtures[24] of these two compounds.

(b) **Pyrolysis of 5-(Thiocyano)-1,2,3,4-thiatriazole** (V. R = CN).—Approximately 5 g. of the substance was refluxed in carbon disulfide for 3 hr. After the reflux period, the carbon disulfide was distilled and the distillate allowed to evaporate to dryness at room temperature. A white crystalline product was obtained having a melting point of 60°. This was identified as sulfur dicyanide by mixture melting point with an authentic specimen[18] and by comparative infrared absorption spectroscopy.

(c) **General Procedure for Thermal Degradation.**—About 0.04 mole of the thiatriazole was refluxed in benzene for 2 hr. at which time a sufficient quantity of ligroin was added to cause precipitation of the degradation product on cooling. The products so obtained, after recrystallization (see Table III for melting point data), were examined by infrared absorption spectroscopy to determine whether the degradative product, so obtained, was a normal thiocyanate or an isothiocyanate. The data obtained are summarized in Table III.

(d) **Degradation in Basic Solution.**—1:2 mole ratio of III and sodium hydroxide, in 200 ml. of water, was gently warmed on a hot plate until the evolution of nitrogen gas had ceased. During the process of heating the solution turned from yellow to a bright orange-red color. Carbon disulfide was identified by the detection of sodium thithiocarbonate. The other degradation products identified were thiocyanate ion, azide ion, and sulfide ion.

(44) A. Iliceto, A. Fava, and U. Mazzuccatv, *J. Org. Chem.*, **25**, 1445 (1960).

ortho Substitution–Rearrangement and Other Reactions of the Benzyldimethylanilinium Ion by Sodium Amide in Liquid Ammonia[1]

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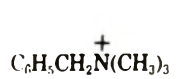
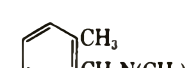
Whereas the benzyltrimethylammonium ion (I) undergoes exclusively the *ortho* substitution–rearrangement with sodium amide in liquid ammonia, the related benzyldimethylanilinium ion (III) exhibits, with this reagent, not only this type of rearrangement but also two other courses of reaction. One of the two latter courses of reaction involves a Stevens 1,2-shift, and the other self-condensation. The products formed from these two courses of reaction underwent β-elimination to give methylaniline and styrene, and dimethylaniline and stilbene, respectively. Also the self-condensation product underwent some rearrangement to produce apparently a dimeric amine. The *o*-xylyldimethylanilinium (XIV) ion exhibited similar reactions with sodium amide in liquid ammonia.

It has previously been shown[3] that the benzyltrimethylammonium ion I undergoes exclusively the *ortho* substitution–rearrangement with sodium amide in liquid ammonia to form tertiary amine II.



I



II

It has now been found that the related benzyldimethylanilinium ion (III) reacts with this reagent to give not only the *ortho* substitution–rearrangement

(1) Supported in part by the National Science Foundation.

(2) Tennessee Eastman Fellow, 1959–1960.

(3) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

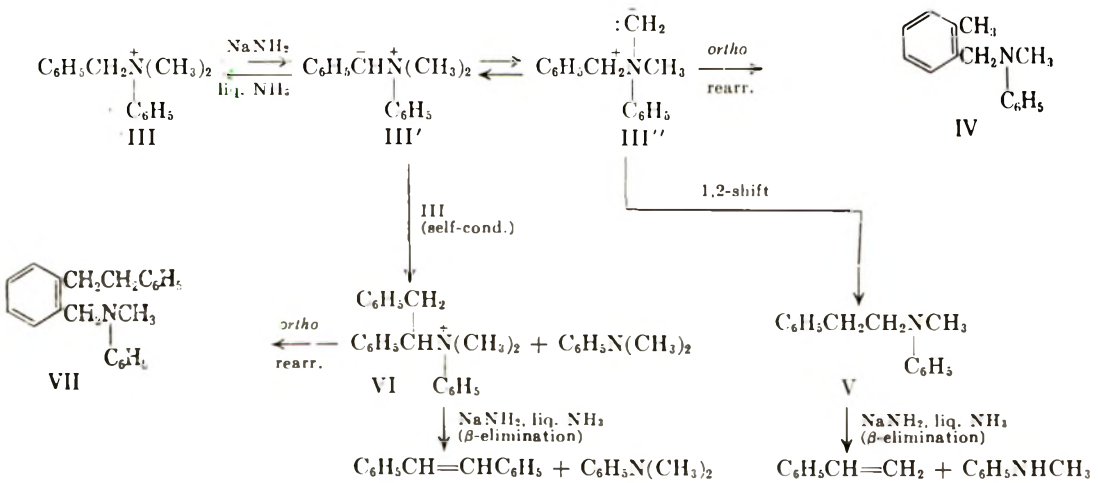
TABLE I

YIELDS OF PRODUCTS FROM 0.1 MOLE OF QUATERNARY ION III WITH 0.2 MOLE OF SODIUM AMIDE IN LIQUID AMMONIA UNDER VARIOUS CONDITIONS

Exp. no.	Liq. ammonia, total volume, ml.	Mode of addition	Addition time, min.	Total reaction time, min.	*ortho* product IV yield, %	*N*-Methylaniline yield, %	Styrene yield, %	*N*,*N*-Dimethylaniline yield, %	Stilbene yield, %	Dimeric product VII yield, %
1	1000	Direct	30	180	69	11	14	Trace		
2[a]	1000	Direct	30	150	69	6	10[d]	Trace		
3[b]	100	Direct	2	180	40	Trace		16	9	
4[c]	200	Direct	5	90	59			12[e]	2	
5	700	Inverse	7	180	50			6[e]	Trace	5
6	400	Inverse	25	210	27	Trace		30	3	31
7[c]	400	Inverse	30	300	50			22	8	14

[a] In this experiment 0.3 mole of reagent was used. [b] In this experiment 0.087 mole of III and 0.23 mole of reagent were employed. [c] Lithium amide (0.2 mole) was used instead of sodium amide. [d] Neutral material not identified but calculated as styrene. [e] Contains *N*-methylaniline.

Scheme A



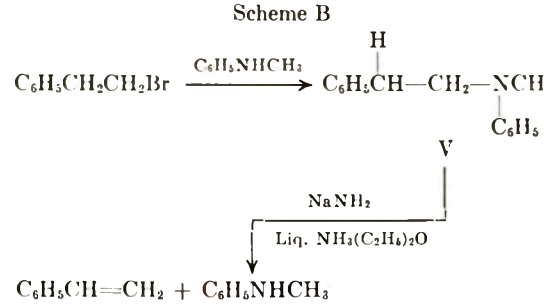
product IV[4] but also methylaniline, dimethylaniline, styrene, stilbene, and apparently dimeric amine VII. These products may be accounted for by Scheme A; their yields, obtained with two molecular equivalents of the reagent under various conditions, are summarized in Table I.

The structure of the *ortho* substitution–rearrangement product IV, which arose through the intermediate formation of the methyl carbanion III'', was established by independent synthesis from *o*-xylyl bromide and methylaniline (equation 1).

(1)

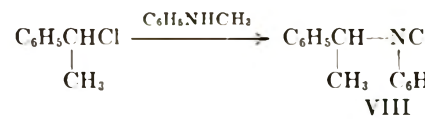
The methylaniline and styrene obtained from quaternary ion III (see Scheme A) evidently arose through a Stevens 1,2-shift of the benzyl group within the methyl carbanion III'' to form amine V, which then underwent β-elimination. That amine V can undergo such a β-elimination to form methylaniline and styrene under similar conditions was demonstrated employing an authentic sample of this amine (Scheme B). Liquid ammonia–ether was used as a solvent for this reaction since amine V appeared to be insoluble in liquid ammonia alone. When amine V was produced from III, it presumably underwent immediate β-elimination without precipitating.

Scheme B



Incidentally this appears to be one of the first demonstrated examples of β-elimination observed with an amine and an alkali amide in liquid ammonia, though this type of reaction is common with quaternary ammonium ions.

That methylaniline and styrene did not arise through amine VIII, which might have been formed by a Stevens 1,2-shift of a methyl group within the benzyl carbanion III', was indicated by the failure of an authentic sample of VIII (equation 2) to afford these products with sodium amide under similar conditions.



(2)

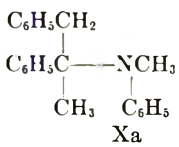
(4) After this manuscript on the bromide of III had been submitted for publication, our attention was called to a communication by L. P. A. Fery [*Bull. soc. chim. Belges*, **71**, 376 (1962)] who obtained amine IV, dimethylaniline, and methylaniline on treatment of the chloride of III with the reagent in yields of 85–90, 5, and 2%, respectively. Also E. J. Gaughan [Ph.D. thesis, Fordham University (1961) supervised by Dr. D. Hennessy] obtained amine IV in 82% yield from the chloride of III.

Although the Stevens 1,2-shift product V was not isolated from the reaction mixture of quaternary ion III with the alkali amide, evidence was obtained for its presence in the amine IV fraction of experiment 1 (see Table I and Experimental). Thus the vapor phase chromatogram[5] of this fraction showed not only a large peak for amine IV but also a small shoulder for a compound having the same retention time as the authentic sample of V and different from that found for the authentic sample of amine VIII. Moreover, a chromatogram[5] obtained on the amine fraction after further treatment (3 hr.) with sodium in liquid ammonia failed to show the shoulder; instead there appeared peaks for methylaniline and styrene, which are the β-elimination products of V.

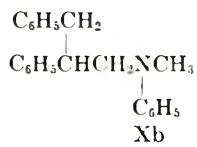
The dimethylaniline and stilbene obtained from quaternary ion III (see Scheme A) presumably arose by self-condensation of this quaternary ion through the benzyl carbanion III′ to form quaternary ion VI, which underwent β-elimination. That the self-condensation product VI can undergo such a β-elimination is indicated by an earlier observation[6] that the related quaternary ion IX exhibits mainly β-elimination under similar conditions to form stilbene (73%) and presumably trimethylamine (equation 3).

$$\underset{\text{IX}}{C_6H_5CH_2\text{—}C_6H_5CH\overset{+}{N}(CH_3)_3} \xrightarrow[\text{liq. } NH_3]{NaNH_2} C_6H_5CH{=}CHC_6H_5 \qquad (3)$$

The dimeric amine VII obtained from quaternary ion III apparently arose through self-condensation to form VI, which underwent an *ortho* substitution–rearrangement (see Scheme A). The analysis of this product fitted not only VII, but also the isomeric Stevens products Xa and Xb, which might have been formed from VI through 1,2-shifts of a methyl group and the 1,2-diphenylethyl group, respectively.



Xa



Xb

The nuclear magnetic resonance spectrum of the product supports structure VII, not Xa or Xb. Thus the spectrum showed, in addition to an aromatic background, three single peaks at τ values of 7.33, 7.23, and 5.85, which may be assigned to the groups in VII: methyl on nitrogen, methylene between phenyls, and methylene between nitrogen and phenyl, respectively. The relative areas of these peaks were approximately 3:4:2, respectively. Moreover the spectrum of the *ortho* substitution–rearrangement product IV, to which VII is related, showed peaks at 7.29 and 5.83 τ. The observed spectrum for the dimeric amine is not the spectrum that would be expected for amine Xb since the methylene and methinyl hydrogens of Xb should couple, thereby producing multiplets which were not observed. Neither should the observed spectrum fit a structure Xa since the peak for the methyl on carbon in the related compound VIII did not appear in the 7.2–7.4 region.

(5) A column packed with one part LAC-2R-446 on four parts Johns-Manville Chromasorb W (30–60 mesh) by weight was used.

(6) C. R. Hauser, W. Q. Beard, and D. N. van Eenam, *J. Org. Chem.*, **26**, 2062 (1961).

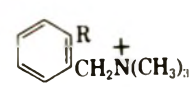
As might be expected the infrared spectrum of dimeric amine VII was similar to that of IV. However, the spectrum of VII showed bands at 690 and 700 cm.$^{-1}$, whereas, that of IV exhibited a single band at 690 cm.$^{-1}$. This is not surprising since these bands are probably due to five adjacent aromatic hydrogens[7] and VII has two such systems while IV has only one. Both spectra showed a broad band centering at 748 cm.$^{-1}$ due in part to five adjacent aromatic hydrogens and in part to four adjacent aromatic hydrogens.

Discussion

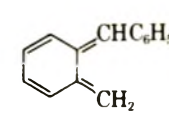
Although quaternary ion III underwent mainly the *ortho* substitution–rearrangement in most of the experiments listed in Table I, it also exhibited to an appreciable extent the Stevens 1,2-shift and self-condensation. The Stevens 1,2-shift was observed when the reaction was carried out in a relatively large amount of liquid ammonia (experiments 1 and 2), whereas, self-condensation occurred in a relatively small amount of liquid ammonia especially when the inverse addition procedure was employed (experiments 3–7). This favorable effect of the use of more concentrated solution[8] on the intermolecular self-condensation was anticipated since the *ortho* rearrangement and Stevens 1,2-shift are intramolecular.

The fact that quaternary ion III undergoes two courses of reaction besides the *ortho* substitution–rearrangement is interesting, since the related quaternary ion I exhibits only the last type of reaction to form II in 96% yield.[9] Evidently the phenyl group attached to nitrogen in III permits some Stevens 1,2-shift to occur by decreasing the rate of the *ortho* rearrangement, and allows some self-condensation to take place by furnishing a better leaving group (dimethylaniline compared to trimethylamine in I).

The self-condensation of III to form VI (see Scheme A) appears to be the first unambiguous example of such a self-alkylation of a quaternary ion by an alkali amide in liquid ammonia. Certain ring-substituted benzyltrimethylammonium ions, for example, the 2-methylbenzyltrimethylammonium ion XI, react with this reagent to form dimeric and higher polymeric amines and hydrocarbons besides the *ortho* substitution–rearrangement product.[3] However, these polymeric products might possibly arise not only through self-alkylation but also through an elimination reaction involving the 2-methyl group and the aromatic ring.[10] Indeed the 2-benzylbenzyltrimethylammonium ion (XII) undergoes exclusively the latter type of reaction to form poly-



XI. R = CH_3
XII. R = $CH_2C_6H_5$



XIII

(7) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 76.

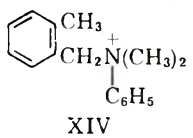
(8) Since the same amount of bromide III was used in most of the experiments, it presumably would be more concentrated in the smaller volumes of liquid ammonia than in the larger volumes, though its actual solubility was not ascertained (see Experimental).

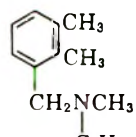
(9) F. N. Jones has observed that a v.p.c. of this product shows but a single peak indicating that it is uncontaminated with even a trace of the possible isomeric Stevens 1,2-shift product[5] or other by-products.

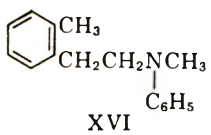
(10) See C. R. Hauser, W. Q. Beard, Jr., and F. N. Jones, *J. Org. Chem.* **26**, 4790 (1961).

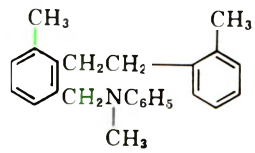
meric material, XIII presumably being an intermediate.[10]

Result with *o*-Xylyldimethylanilinium Bromide (XIV).—Similar to quaternary ion III, the related quaternary ion XIV reacted with sodium amide in liquid ammonia to form a mixture of five amines, which were shown by v.p.c. to be present in the relative proportions of about 13.8:1.0:7.0:10.0:trace. The last two of these amines were identified as dimethylaniline and methylaniline, respectively. Assuming the same courses of reaction to be operative for XIV that were indicated for III, the first three amine products would be the *ortho* substitution–rearrangement product XV, the Stevens 1,2-shift product XVI, and the higher boiling dimeric amine XVII, in that order. Some neutral material was also obtained.


XIV


XV


XVI


XVII

In view of the result with quaternary ion III under similar conditions (dilute solution) the relatively large amount of dimethylaniline and dimeric amine produced might seem surprising. In contrast to III, however, quaternary ion XIV might have afforded dimethylaniline not only through self-condensation but also by an elimination reaction as described above for XI, though the dimeric amine appears to have arisen only through self-condensation.

Experimental[11]

Benzyldimethylanilinium Bromide (III).—To a stirred solution of 51.3 g. (0.30 mole) of benzyl bromide in 200 ml. of acetonitrile was slowly added 36.3 g. (0.30 mole) of carefully purified *N*,*N*-dimethylaniline in 100 ml. of acetonitrile. After stirring for 5 hr., the reaction solution was allowed to stand overnight. Anhydrous ether (500 ml.) was slowly added with stirring to precipitate the quaternary salt, which was washed with dry ether, and dried in a vacuum desiccator to give 86.3 g. (98%) of bromide III, m.p. 153–155° on a Fisher–Johns block, 145–146° in sealed capillary on Mel-Temp (lit., m.p. 98°,[12] 129°,[13] 145°,[14] 203°[15]).

Anal. Calcd. for $C_{15}H_{18}NBr$: C, 61.65; H, 6.21; N, 4.79. Found: C, 61.51; H, 6.19; N, 4.88.

Because this quaternary salt appears to be unstable in certain solvents, for example, chloroform,[16] the following experiment was performed to ascertain its stability in liquid ammonia. A solution of 14.6 g. (0.05 mole) of the salt in 500 ml. of liquid ammonia was stirred for 3 hr., and 200 ml. of anhydrous ether was then added. The ammonia was evaporated, and the resulting ethereal suspension was filtered to recover 14.4 g. (99%) of unchanged bromide III, m.p. 145–146° (sealed tube). The ethereal filtrate was shown by v.p.c. to contain no organic solute.

Reactions of Bromide III with Sodium Amide.—These reactions were carried out several times employing direct and inverse addition procedures in relatively large and relatively small amounts of liquid ammonia. Generally 0.1 mole of the salt III and 0.2 mole of sodium amide were used. The conditions of reaction and yields of products are summarized in Table I. General directions for the two procedures are described below.

(A) **Direct Addition Procedure.**—To a stirred suspension of 0.2 mole of sodium amide in an appropriate amount of commercial, anhydrous liquid ammonia[17] (Dry Ice–acetone condenser) was added 0.1 mole of bromide III to produce immediately a bright yellow color that generally faded during the reaction period. The stirring was continued for an appropriate time, and 0.2 mole of solid ammonium chloride was then added. Anhydrous ether (200–300 ml.) was added and the liquid ammonia was evaporated overnight. The resulting ethereal suspension was filtered, and the ethereal filtrate extracted with excess 6 *N* hydrochloric acid. The remaining ethereal solution was dried over anhydrous magnesium sulfate and the solvent removed to give neutral products. The acid extract was made strongly basic with sodium hydroxide (cooling and stirring), and the liberated amines were extracted several times with ether. The combined ethereal extract was dried over anhydrous magnesium sulfate, and the solvent removed leaving a crude mixture of amines. After an indication of the composition of this crude mixture was obtained by v.p.c. on a small sample (*ca.* 0.05 g.), the mixture was fractionally distilled and each of the resulting fractions chromatographed. Identifications of the products are described below.

(B) **Inverse Addition Procedure.**—To a stirred suspension of 0.1 mole of the bromide of III in an appropriate amount of liquid ammonia (Dry Ice–acetone condenser) was added a suspension of 0.2 mole of sodium amide in an appropriate amount of liquid ammonia through a stopcock attached to the bottom of a flask. The resulting yellow mixture was stirred for an appropriate time (yellow color faded), and then worked up essentially as described above under (A). Identifications of the products are described below.

Identification of *N*,*o*-dimethyl-*N*-phenylbenzylamine (IV).—In all experiments there was obtained amine IV, b.p. 123–126° at 0.4 mm., at 130–131° at 0.6 mm., or at 162.5–164.5° at 5.4 mm., (lit.,[18] b.p. 200° at 35 mm.).

Anal. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.28; H, 7.99; N, 6.68.

The picrate of amine IV, after one recrystallization from ethanol, melted at 134–135° (lit.,[18] m.p. 110°).

Anal. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58; N, 12.72. Found: C, 57.23; H, 4.45; N, 12.71.

This picrate was also obtained with m.p. 112–113°. When a solution of this substance in ethanol was cooled and seeded with a sample, m.p. 134–135°, the picrate that crystallized had m.p. 134–135°.

Independent synthesis of amine IV was effected with 10.7 g. (0.10 mole) of *N*-methylaniline and 18.5 g. (0.10 mole) of *o*-xylyl bromide in 100 ml. of acetonitrile (refluxed overnight). After 95 ml. of acetonitrile was removed by distillation, 100 ml. of ether was added, and the mixture extracted with two 100-ml. portions of 3 *N* hydrochloric acid. The acid extracts were made strongly basic with concentrated sodium hydroxide solution (ice bath). The basic mixture was extracted with three 100-ml. portions of ether, the extracts dried over anhydrous magnesium sulfate, and the ether removed. The residue was distilled, giving 13.95 g. (66%) of amine IV, b.p. 130–134° at 0.5–0.6 mm. The picrate, after one recrystallization from ethanol, melted at 134–135°. On admixture with a sample of the picrate prepared from amine IV obtained from quaternary ammonium ion III, there was no depression of melting point. The infrared spectra of the two samples of amine IV were identical.

Identification of Other Products. (A) ***N*-Methylaniline and Styrene.**—The lower boiling amine fraction from experiments 1 and 2 (see Table I) was shown by v.p.c. to consist of *N*-methyl-

(11) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected. All vapor phase chromatography, unless otherwise indicated, was carried out on a column packed with one part polypropylene glycol on four parts Johns-Manville Chromasorb W (30–60 mesh) by weight. Infrared spectra were produced on either a Perkin–Elmer 21 spectrophotometer or a Perkin–Elmer Infracord; all solids were run in potassium bromide pellets, liquids on sodium chloride plates.

(12) M. S. Kharasch, G. H. Williams, and W. Nudenberg, *J. Org. Chem.*, **20**, 937 (1955).

(13) E. Wedekind, *Ber.*, **39**, 481 (1906).

(14) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, **82**, 5335 (1960).

(15) K. Nador and L. Gyermek, *Acta. Chim. Acad. Sci. Hung.*, **2**, 95 (1952).

(16) E. Wedekind and F. Paschke, *Ber.*, **43**, 1303 (1910).

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

(18) J. von Braun, *Ber.*, **43**, 1353 (1910).

aniline contaminated by a trace of *N,N*-dimethylaniline. The main peak was only enhanced by an authentic sample of *N*-methylaniline. The infrared spectrum of this fraction was essentially the same as that of *N*-methylaniline. The fraction from experiments 1 and 2 boiled at 39–40° at 0.55 mm. and 62–64° at 4–5 mm., respectively (lit.,[19] b.p. for *N*-methylaniline 46.8° at 1.0 mm. and 67.7° at 5 mm.). The picrate of the fraction had a m.p. and mixed m.p. 145–148° (not clear) (lit.,[20] m.p. 144.5°).

The neutral product from experiments 1 and 2 was evidently mainly styrene, which partly polymerized. Its infrared spectrum closely resembled that of styrene; and its dibromide, recrystallized from dilute ethanol, melted at 67–70° (lit.,[21] m.p. 74.0–74.5°). The dibromide when mixed with an authentic sample showed no depression of melting point.

(B) ***N,N*-Dimethylaniline and Stilbene.**—The lower boiling amine fraction from experiments 3–7 was shown by v.p.c. to consist of *N,N*-dimethylaniline contaminated, in certain cases (see Table I), with *N*-methylaniline. The main peak was only enhanced by an authentic sample of *N,N*-dimethylaniline. The infrared spectrum of the fraction was essentially the same as that of *N,N*-dimethylaniline. The fraction boiled at 66–67° at 7–8 mm., 64–65° at 6.0–6.5 mm., or 62.5° at 5.8 mm. (lit.,[19] b.p. 61.6° at 5 mm., 64.5° at 6 mm., and 67° at 7 mm.). The picrate of this fraction had a m.p. and mixed m.p. 157–160° (not clear) (lit.,[22] m.p. 163–164°).

From the neutral fraction from experiments 3–7 was isolated stilbene, m.p. 122–123° after recrystallization from methanol (lit.,[23] m.p. 124°). On admixture with an authentic sample of stilbene the melting point was not depressed. The infrared spectrum of the product was essentially the same as that of stilbene, and like authentic stilbene it fluoresced under ultraviolet light.

(C) **Amine VII.**—In experiments 5–7 there was obtained a dimeric (higher boiling) amine, b.p. 190–192° at 0.55 mm., 198–199° at 0.7 mm., and 199–203° at 1.10 mm.

Anal. Calcd. for $C_{22}H_{23}N$: C, 87.66; H, 7.69; N, 4.65. Found: C, 87.84; H, 7.73; N, 4.73.

The picrate of amine VII, after one recrystallization from ethanol, melted at 134–135°.

Anal. Calcd. for $C_{28}H_{26}N_4O_7$: C, 63.39; H, 4.94; N, 10.56. Found: C, 63.61; H, 4.96; N, 10.73.

The melting point of this picrate was depressed to 115–120° when mixed with the picrate of amine IV. However, the infrared spectrum of amine VII was quite similar to that of amine IV (see Discussion).

The n.m.r. spectrum of amine VII was obtained with a HR-60 Varian spectrometer at room temperature (30°) using a solution of approximately one part of amine VII to one part carbon tetrachloride by volume and tetramethylsilane as an internal standard (for details, see Discussion).

***N*-Methyl-*N*-phenylphenethylamine (V) and *N*,α-Dimethyl-*N*-phenylbenzylamine (VIII).**—A solution of 21.4 g. (0.20 mole) of *N*-methylaniline and 27.0 g. (0.15 mole) of β-phenylethyl bromide in 200 ml. of acetonitrile was refluxed for 20 hr. After the acetonitrile was removed, 200 ml. of ether was added, the mixture was extracted with 3 *N* hydrochloric acid. The combined acid extract was made basic with a concentrated solution of sodium hydroxide (cooled). The basic mixture was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, and the solvent removed. The residue was distilled, yielding 8.63 g. (40%) of *N*-methylaniline and 14.68 g. (48%) of *N*-methyl-*N*-phenylethylamine (V), b.p. 131–134° at 0.75 mm. (lit.,[24] b.p. 198–199° at 18 mm., m.p. 42–43° (lit.,[24] m.p. 44°).

Similarly a solution of 16.0 g. (0.15 mole) of *N*-methylaniliue and 21.5 g. (0.15 mole) of α-phenylethyl chloride in 150 ml. of acetonitrile was refluxed for 20 hr. There was isolated 7.14 g. (23%) of *N*,α-dimethyl-*N*-phenylbenzylamine (VIII), b.p. 121–124° at 0.6 mm. (lit.,[25] b.p. 158–165° at 7.0 mm.); 57% of the *N*-methylaniline was recovered.

Treatment of Amine V and VIII with Sodium Amide.—To a stirred suspension of 0.044 mole of sodium amide in 125 ml. of liquid ammonia (Dry Ice–acetone condenser) was added during 5 min., 4.2 g. (0.02 mole) of amine V in 125 ml. of anhydrous ether. The resulting green solution was stirred 3.25 hr. and 2.33 g. (0.044 mole) of solid ammonium chloride was added. The ammonia was allowed to evaporate and a dilute solution of sodium hydroxide was added to the resulting stirred ethereal suspension. The two layers were separated. The ethereal layer, combined with an ethereal extract of the aqueous layer, was dried over anhydrous magnesium sulfate and the solvent removed. The residue was distilled at 0.5–0.6 mm. giving 0.37 g. (17%) of *N*-methylaniline, b.p. 44–46°; 0.26 g. of mid-fraction, b.p. 46–134°; and 2.18 g. (52%) of unchanged amine V, b.p. 134–137°. The mid-fraction was shown by v.p.c. to consist mainly of *N*-methylaniline raising the total yield of this amine to approximately 29%. There was left 0.3–0.5 g. of residue, which presumably contained polystyrene.

When amine V was treated with sodium amide in liquid ammonia (without ether) for 3 hr., a trace of *N*-methylaniline and styrene were obtained as indicated by v.p.c. Most of amine V was recovered. The lack of appreciable reaction was presumably due to the insolubility of amine V in liquid ammonia in which it solidified.

When amine VIII was treated with sodium amide in either liquid ammonia, in which VIII was not soluble, or in liquid ammonia–ether, in which VIII was soluble, it gave only a trace of styrene and *N*-methylaniline as indicated by v.p.c. Most of VIII was recovered.

***o*-Xylyldimethylanilinium Bromide (XIV).**—Bromide XIV was prepared essentially as described by Wittig.[26,27] *o*-Xylyl bromide (3.7 g. 0.02 mole) and *N,N*-dimethylaniline (2.4 g., 0.02 mole) were mixed and allowed to stand overnight. The mixture was warmed slightly on a steam bath, and triturated with ethyl acetate. The white crystals thus produced were filtered, washed with anhydrous ether, and dried in a vacuum desiccator to constant weight, 6.0 g. (98%), m.p. 86–88° (lit.,[26] m.p. 87–88°).

Reactions of Bromide XIV with Sodium Amide.—To a stirred suspension of 0.033 mole of sodium amide in 500 ml. of liquid ammonia (Dry Ice–acetone condenser) was added during 5 min., 5.0 g. (0.016 mole) of bromide XIV. The initial green color of the reaction mixture was rapidly discharged. After 4 hr. the reaction mixture was neutrallized with 1.75 g. (0.033 mole) of solid ammonium chloride. Dry ether (400 ml.) was added and the liquid ammonia was evaporated overnight. After the salts were removed by filtration, the ethereal filtrate was extracted with two 50-ml. portions of 6 *N* hydrochloric acid and dried over anhydrous magnesium sulfate. On evaporation of the ether there remained 0.20 g. of unidentified neutral material. The combined acid extract was made strongly basic with sodium hydroxide pellets (cooling and stirring). The basic mixture was extracted with two 100-ml. portions of ether. The combined ether extract was dried over magnesium sulfate, and the ether evaporated leaving 0.9 g. of basic material which was subjected to vapor phase chromatography using a silicone rubber column (see Discussion). Of the five compounds indicated to be present only *N,N*-dimethylaniline and *N*-methylaniline were identified (enhancement technique). The infrared spectrum of the salt material (5.53 g.), which was removed by filtration, was practically identical with that of bromide XIV.

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(27) An attempt to prepare iodide XIV by treatment of amine IV with methyl iodide in acetonitrile afforded a mixture of salts containing the methiodide of dimethylaniline.

Comparison of the Initial and Final Stages of the Grignard Reduction Reaction[1]

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Methyl *t*-butyl ketone has been reduced with both the Grignard reagent and the dialkylmagnesium reagent from (+)-1-chloro-2-methylbutane in each case under two sets of conditions designed to isolate the initial and final stages of the reaction. The assumption was that the first alkyl group (in R_2Mg) would demonstrate different stereospecificity in the reduction than the second alkyl group (in RMgOR'). The per cents of asymmetric reduction from these four reactions were the same within experimental error. These results are interpreted as indicating that the same species is responsible for the reductions in each case and that indeed the first and second stages of the reaction have *not* been isolated due to a *relatively* rapid exchange reaction

$$2ROMgR \rightleftharpoons R_2Mg + (RO)_2Mg$$

Recent findings concerning the nature of the Grignard reagent[3] are best interpreted in terms of the formula $R_2Mg \cdot MgX_2$, in which the magnesium atoms retain their identity. If the Grignard reagent is indeed an etherate of $R_2Mg \cdot MgX_2$, then a difference might be expected in the reactivity of the first *vs.* the second R group attached to the magnesium atom. As the reaction proceeds, this predicted difference might be revealed in rates of reaction, relative proportions of products and/or in stereoselectivity. In the reaction of a Grignard reagent (I) with a carbonyl compound the initial product (II) should be that with both an akyl group (R) and an alkoxy group (OR') attached to magnesium. The OR' attached to the magnesium represents the alkoxy group resulting from either addition to (equation 1), or reduction of (equation 2),

$$\text{C=O} + R_2Mg \cdot MgX_2 \longrightarrow \text{R—C(OH)—O—MgR} \cdot MgX_2 \text{ (addition)} \quad (1)$$

$$\text{C=O} + R_2Mg \cdot MgX_2 \longrightarrow \text{H—C(OH)—O—Mg—R} \cdot MgX_2 + \text{olefin (reduction)} \quad (2)$$

the carbonyl compound. Enolization and condensation products could also be formed in the initial reaction and, to the extent that they occur, there will be alkoxy groups, OR', of still a different type. This "first stage" reaction can be abbreviated as in equation 3, where the OR' group represents this multiple character.

$$\underset{\text{I}}{\text{C=O}} + R_2Mg \cdot MgX_2 \longrightarrow \underset{\text{II}}{\text{R—Mg—OR'} \cdot MgX_2} \quad (3)$$

When the remaining alkylmagnesium group reacts with a second molecule of carbonyl compound, addition and/or reduction can again occur. But from the different steric requirements and electronic environment of the R group in $R_2Mg \cdot MgX_2$ (I) *vs.* $RMgOR' \cdot MgX_2$ (II), one would predict different rates, different ratios of products, and altered stereoselectivity in this "second stage" reaction (equation 4).

$$\underset{\text{II}}{\text{C=O}} + \text{R—MgOR'} \cdot MgX_2 \longrightarrow \underset{\text{III}}{\text{R''OMgOR'} \cdot MgX_2} \quad (4)$$

We have already postulated a difference[4] in the relative ratios of products resulting from the "first stage" reaction (equation 3) and the "second stage" reaction (equation 4) to explain the results obtained in the reaction of diisopropyl ketone with ethylmagnesium bromide in a flowing stream system. To compare further these consecutive stages of the Grignard reaction we have chosen to study the stereoselective reduction of methyl *t*-butyl ketone by the Grignard reagent from (+)-2-methyl-1-chlorobutane[5] and by the corresponding dialkylmagnesium compound[6] under conditions designed to isolate these stages. An amount of ketone equivalent to only one half of the R groups in the Grignard (or dialkylmagnesium) reagent was first added and after stirring six hours at room temperature the remainder of the reagent was consumed by the addition of acetaldehyde. This procedure was then reversed. The results are recorded in Table I.

It is apparent that within rather minor experimental limits it made *no difference in stereoselectivity* whether the methyl *t*-butyl ketone was added for the "first stage" of the Grignard reaction or for the "second stage" of the Grignard reaction, and furthermore the same was true for the (+)-di-2-methylbutylmagnesium reagent. However, differences in yields were observed, especially in the amount of condensation product formed when acetaldehyde was first added to the dialkylmagnesium reagent. It is difficult to evaluate the meaning of this latter observation since considerable condensation of the ketone could have occurred while stirring the reaction mixture in the presence of the basic magnesium alkoxides.

These results are in agreement with the interpretation that the Grignard structure is not RMgX, since the stereoselectivities observed in the reduction reaction were the same with either the Grignard or the dialkylmagnesium reagent. On the other hand, how can the previous discussion concerning the first and

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(2) National Science Foundation Cooperative Fellow 1959-1960; Dupont Teaching Fellow, 1960-1961.

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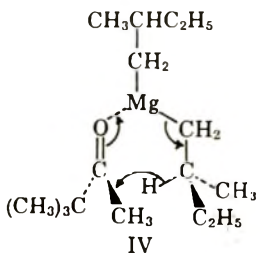
TABLE I

REACTION OF (+)-DI(2-METHYLBUTYL)MAGNESIUM OR CORRESPONDING GRIGNARD REAGENT WITH METHYL *t*-BUTYL KETONE

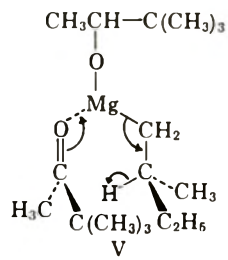
Organomagnesium		Pinacolone		Acetaldehyde		% yields pinacolone products[b]			Pinacolyl alcohol	Half phthalate	% excess dextro isomer	
Cpd.	Equiv.[a]	Order	Moles	Order	Moles	Enol.	Red.	Cond.	$[\alpha]^{24}D$	$[\alpha]D^{20}$	*c*	*d*
R_2Mg	0.205	First	0.10	Second	0.10	16	28	56	+0.93	+8.02	12.0	13.0
R_2Mg	.205	Second	.10	First	.10	63	26	11	+0.84	+7.98	10.9	12.9
"RMgX"	.17	First	.085	Second	.085	17	36	47	+0.88	+7.61	11.4	12.3
"RMgX"	.17	Second	.085	First	.085	12	39	49	+0.86	+7.84	11.1	12.7

[a] An equivalent of Grignard reagent is calculated as one formula weight of "RMgX" or one-half formula weight of $R_2Mg \cdot MgX_2$. [b] The distribution of products was determined by gas–liquid partition chromatography, the yield of pinacolone representing enolization, that of pinacolyl alcohol reduction, and that of the high boiling material condensation. [c] Corresponds to the per cent of asymmetric reduction based on the rotation of the gas chromatographically purified pinacolyl alcohol using the value of $[\alpha]^{20}D$ +7.71° of Pickard and Kenyon [*J. Chem. Soc.*, **105**, 1120 (1914)] for the pure carbinol. [d] Corresponds to the per cent of asymmetric reduction based on the rotation of the crystallized acid phthalate using the values $[\alpha]D$ 63.9° of the pure dextro isomer and takes into account the 97% optical purity of the (+)-1-chloro-2-methylbutane from which the optically active reducing agents were prepared.

second stages of the reaction of dialkylmagnesium compounds be reconciled with these results! Several possible explanations present themselves. It is barely possible that within experimental error the four reagents, R_2Mg, $RMgOR'$, $R_2Mg \cdot MgX_2$, and $RMgOR' \cdot MgX_2$, exert the same stereoselectivity in this reduction reaction. This can be stated in terms of the differences in energies of activities, $\Delta\Delta F^*$ for IV and its diastereomeric transition state and V and its diastereomeric



IV



V

transition state. Although these two transition states and their diastereomeric forms, where the methyl and *t*-butyl groups on the ketone are interchanged, seem very similar, they do in fact differ considerably. The Grignard asymmetric reduction reaction is very sensitive to small changes; for instance, the difference between 13% asymmetric reduction and 11% asymmetric reduction at room temperature represents a difference of only 0.030 kcal./mole in the energies of activations between the *d* and *l* transition states. Substitution of an ethyl group for the methyl group in the *t*-butyl ketone causes such a change in asymmetric reduction.[5] Certainly structures IV and V should reflect larger differences than this. This same line of reasoning can be used to dismiss the assumption that the reactive species in the Grignard reduction reaction is RMgX, since it seems quite unlikely that RMgX would have the same stereoselectivity as R_2Mg or $RMgOR'$.

It seems much more reasonable to assume that the great similarities in stereoselectivities, in spite of the apparent different reagents and differences in orders of addition, is a result of reduction by the same reducing species. Three mechanisms whereby this is possible suggest themselves. *First:* If we assume that the active reducing species in the Grignard reagent is R_2Mg and that the first stage of the reaction is slow compared to the second stage reaction, *i.e.*,

$$\text{C=O} + R_2Mg \xrightarrow{k_1} RMgOR' \qquad (5)$$

$$\text{C=O} + RMgOR' \xrightarrow{k_2} R'OMgOR' \qquad (6)$$

where $k_1 \ll k_2$

so that, regardless of the order of addition of reagents, each R_2Mg is completely consumed by conversion to $R'OMgOR'$ without the accumulation of $RMgOR'$ then the observed stereoselectivity would be the cumulative results of equations 5 and 6. However, the assumption that $R'OMgR$ reacts much faster than R_2Mg seems unlikely on the basis of the reaction of other known metalloörganic compounds. Thus Ziegler[7] reports that only one of the three alkyl groups in triethylaluminum will add to a carbonyl compound. The alkoxy group on magnesium would decrease the electrophilic character of the magnesium atom and thereby reduce its tendency to react with carbonyl compounds. This is shown in the much slower rate of the Meerwein–Ponndorf reaction *vs.* the Grignard reduction reaction.

Second: The same stereoselectivity would be observed if only one of the R groups in R_2Mg or only the R group in $RMgOR'$ *but not both* were responsible for the reduction. In the present experiments the yields of reduction products did not exceed 50% and so this would be theoretically possible. However, the yields of reduction products did not vary greatly from the "first stage" as compared to the "second stage" of the reaction, and furthermore, many Grignard reduction reactions exceed 50% yields; thus this simple alternative is inadmissable.

Third: The conditions for one reducing agent with constant stereoselectivity, but yields in excess of 50%, can be met by assuming that either R_2Mg or $RMgOR'$ (but not both) is the active reducing agent and that a rapid disproportionation reaction replenishes the active reducing species as the reaction progresses. This reducing species could be either R_2Mg or $RMgOR'$ produced by one of the other of the following disproportionation reactions.

$$2RMgOR' \xrightarrow{k_3} R_2Mg + Mg(OR')_2 \qquad (7)$$

$$R_2Mg + Mg(OR')_2 \longrightarrow 2RMgOR' \qquad (8)$$

where $k_1 \gg k_2$ and k_3 is the same order of magnitude or larger than k_2.

As discussed above, $RMgOR'$ should be less reactive than R_2Mg and thus equation 7 is favored as the key

(7) K. Ziegler, *Experientia*, Suppl. 2, **14**, 279 (1955).

disproportionation reaction and R_2Mg as the active reducing agent. Under these assumptions, reduction by RMgOR′ is minor under the usual preparative conditions for the Grignard reaction. If the rate of the "first stage" reaction (equation 5) is very rapid with respect to the "second stage" reaction (equation 6), then the speed of the disproportionation reaction needs to be fast only with respect to the over-all time of the reaction in order to explain the data in Table I.

The present conclusions apply only to the *reduction reaction* of the Grignard and dialkylmagnesium reagents and are in accord with our previous finding[8] that the nature of the halogen atom in the Grignard reagent has only a slight effect on the reduction reaction. The extent to which these ideas apply to the Grignard *addition reaction* is not known. Anteunis[9] has concluded that R_2Mg cannot be the active species in the addition reaction of the methyl Grignard reagent to benzophenone because of the observed kinetics and because only one of the two methyl groups in the dimethylmagnesium reacted. Because of the variations in the yields of addition products with different halogens of the Grignard reagent, we had previous postulated[8] that the Grignard addition reaction involved the halogen atom in the transition state. Addition takes place with pure dialkylmagnesium even more rapidly than with the Grignard reagent[9,10] and thus it would appear that there may be more than one mechanism for the addition reaction. In any event prior conclusions must be re-evaluated in the light of this postulated disproportionation reaction (equation 7).

This postulated disproportionation reaction (equation 7) adds another parameter to the variables in the Grignard reaction. It is possible that magnesium halide acts as a catalyst for this reaction which probably varies widely with the nature of the Grignard reagent. An application of this disproportionation concept may be able to rationalize the $R_2Mg \cdot MgX_2$ structure for the Grignard reaction with the many facts of the Grignard reaction now known.

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Experimental

Grignard from (+)-2-Methylbutyl Chloride.—The Grignard reagent from 123 g. (1.2 moles) of (+)-2-methyl-1-chlorobutane, $\alpha^{25}D$ +1.40° (1 dm., neat, 97% optically pure) and 31.6 g. (1.3 moles) of magnesium was prepared in 1 l. of anhydrous ether. The solution was allowed to settle and then decanted under nitrogen into a storage flask; titration indicated at 94% yield.

(+)-Di(2-methylbutyl)magnesium.—To 600 ml. (0.66 mole) of the Grignard reagent, prepared from the same (+)-2-methylbutyl chloride in ether, was added with stirring 76 g. (0.86 mole) of dioxane over a period of 4 hr. under a nitrogen atmosphere. After stirring for 24 hr. the mixture was transferred under nitrogen to centrifuge tubes which were capped and centrifuged. The supernatant solution was transferred to a graduated storage vessel; titration indicated an 80% yield of dialkylmagnesium compound.

Reaction of (+)-Di(2-methylbutyl)mgnesium with Methyl *t*-Butyl Ketone and Acetaldehyde.—To 275 ml. of an ether solution containing 0.205 equivalent (0.75 *N*) of (+)-di(2-methylbutyl)-magnesium was added over a 45-min. period 10 g. (0.1 mole) of methyl *t*-butyl ketone in 45 ml. of ether. After stirring for 6 hr. at room temperature 4.4 g. (0.1 mole) of freshly distilled acetaldehyde dissolved in 45 ml. of ether was added over a 45-min. period. After standing overnight the slightly turbid reaction mixture was hydrolyzed by the slow addition of a minimum amount of water. The ether solution was decanted from the crystalline precipitate of magnesium salts[11] and most of the ether removed by distillation through a 15-plate column. The residue was chromatographed using an Aerograph A-90-C gas chromatograph. The 150-cm. column was packed with Ucon Polar on firebrick. Each component was identified by comparison of retention times with authentic samples and by infrared spectrometric analysis of fractions trapped at the proper time from the effluent of the chromatograph. The percentage yields, 16% enolization, 28% reduction, and 56% condensation, were calculated from weight per cent as determined from the chromatogram.[12]

The reduction and condensation products were isolated using a Beckman Megachrome preparative gas chromatograph. The high boiling material proved to be the condensation product, 2,2,5,6,6-pentamethyl-4-hepten-3-one, $n^{20}D$ 1.4469, 2,4-dinitrophenylhydrazone; m.p. 147–148.5°. 2,2,5,6,6-Pentamethyl-4-hepten-3-one is reported to have the following properties, $n^{23}D$ 1.4500, 2,4-DNP, m.p. 147–148°.[13] The reduction product, methyl-*t*-butylcarbinol had the properties, $\alpha^{20}D$ +0.70 (1 dm., neat), acid phthalate $[\alpha]^{20}D$ 8.02° ($\alpha^{20}D$ +0.80°, *c* 9.97, $CHCl_3$, l = 1 dm.), m.p. 84.1–85.8°.

A second reaction, conducted exactly as the first except that the order of adding methyl *t*-butyl ketone and acetaldehyde was reversed, gave the results summarized in Table I. A third and fourth reaction using the Grignard reagent instead of the dialkylmagnesium compound, were carried out in the same manner with the results shown in Table I.

(13) P. D. Bartlett, *ibid.*, **76**, 2349 (1954).

Ambelline

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Degradative evidence is presented to show that ambelline possesses the stereo structure III (R = OH, R′ = H).

In one of our earliest isolation studies, we reported the occurrence of ambelline in *Amaryllis belladonna*.[2] Since that time, it has been detected in several other genera of the Amaryllidaceae, particularly in the *Nerine* spp.[3–5] Ambelline was characterized as a tertiary base, $C_{18}H_{21}NO_5$, with the oxygen atoms contained in two methoxyl groups, one methylenedioxy group, and one hydroxyl. Catalytic hydrogenation provided a single dihydro derivative.[2,6] One

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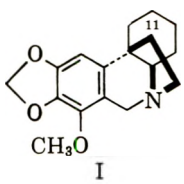
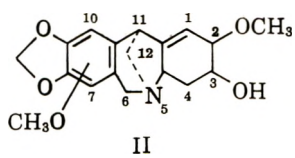
(5) R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 2620 (1959).
(6) An identical characterization was reported by J. Renz, D. Stauffacher, and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955), for traces of ambelline isolated from *Buphane fischeri* Baker.

methoxyl could be assigned to the aromatic ring because of strong infrared absorption at 1623 cm.$^{-1}$ and ultraviolet absorption of ambelline and its derivatives at 288 mμ.[7] This was confirmed by the chemical degradations discussed below.

Ambelline was recovered unchanged after treatment with 10% hydrochloric acid at room temperature for two hours. At elevated temperatures, this reaction mixture gave rise to a crude oil which was oxidized by manganese dioxide suspended in chloroform. The infrared absorption spectrum of the product showed a moderate band at 1675 cm.$^{-1}$. This provided the first clue that an allylic methyl ether might be present. Neither 90% formic acid nor 10% ethanolic potassium hydroxide at reflux temperature for two hours had any effect. Ambelline was stable to both ethanolic selenium dioxide and a suspension of manganexe dioxide in chloroform at room temperature for seventeen hours. Chemical reduction (lithium aluminum hydride in refluxing tetrahydrofuran) was unsuccessful and ambelline was recovered in 68% yield. Catalytic reduction with palladium on charcoal in either glacial acetic acid or ethanol, as well as platinum in glacial acetic acid, gave a single dihydro product. These chemical data permitted us to eliminate five of the seven basic ring systems known to occur in the Amaryllidaceae. Ambelline could be derived from the powellane (I)[8-10] or methoxymontanine (II)[11,12] or another, yet undiscovered, ring system.



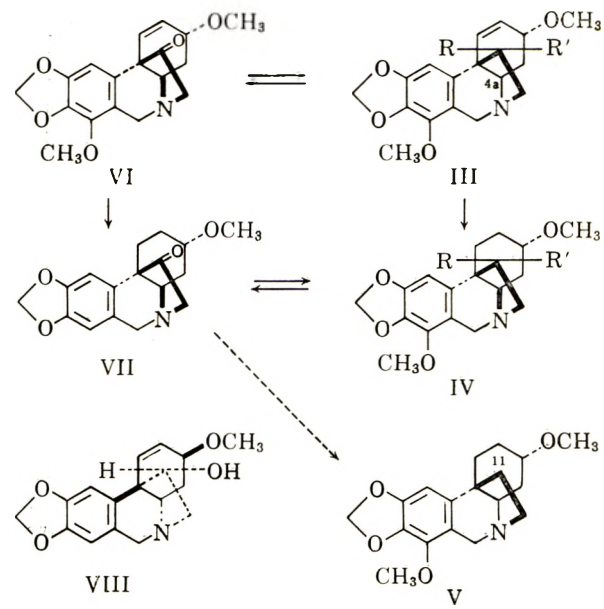
I



II

Several methods were found to convert the alcohol group of ambelline and its dihydro derivative to the corresponding ketone. Although an attempted oxidation of dihydroambelline utilizing fluorenone as an oxidant at room temperature was unsuccessful, the reaction was accomplished with cyclohexanone at reflux temperature. The product, oxodihydroambelline, also could be obtained by the prolonged oxidation of dihydroambelline with activated manganese dioxide. The preferred method used the pyridine-chromic oxide reagent.[13] Under these conditions, 76 and 78% yields of oxoambelline and oxodihydroambelline could be realized from ambelline and dihydroambelline, respectively. Oxoambelline and oxodihydroambelline showed carbonyl absorption at 1748 cm.$^{-1}$ and 1750 cm.$^{-1}$, respectively. Although neither ketone showed an ultraviolet absorption spectrum characteristic of a ketone conjugated with unsaturation, the multiple bands near 292 and 315 mμ suggested π-electron overlap between the carbonyl group and the aromatic ring. Such an effect had been noted earlier in the haemanthamine and crinamine series.[14] These data provided no preference between ring systems I and II because a C-11 ketone in I or a C-12 ketone in II would be compatible with our observations.

Because our earlier work had provided a large number of reference compounds in the powellane (I) series, it seemed advantageous to attempt to convert dihydroambelline to a deshydroxy compound which might be identical with dihydrobuphanidrine (V). As was found to be the case in the haemanthamine series,[14] Wolff-Kishner and Clemmensen conditions were not effective in converting the ketone to a methylene group. Reduction of ambelline tosylate with lithium aluminum hydride regenerated ambelline. Following the procedure which was successful for the conversion



of haemanthamine to (+)-dihydrobuphanisine,[14] dihydroambelline was treated with thionyl chloride and then lithium aluminum hydride. Only dihydroambelline was recovered. At this point we examined the hydroxyl stretching frequencies of ambelline and dihydroambelline at high dilution in carbon tetrachloride. Both compounds showed strongly bonded absorption (3564 and 3565 cm.$^{-1}$, respectively). The frequency of this absorption, when considered with our previous data on the anomalous ultraviolet absorption of the ketones, indicated that the hydroxyl group of ambelline and its dihydro derivative must be oriented in a direction toward the aromatic ring. The condition can be fulfilled either by a C-11 hydroxyl in I or a C-12 hydroxyl in II. This deduction would have the support of two negative results that were mentioned earlier. In dilute refluxing hydrochloric acid, haemanthamine (VIII) forms easily a cyclic ether between C-11 and C-3; epihaemanthamine (epimeric at C-11) affords the same ether in very poor yield. The observation that allylic methoxyl cleavage occurs in preference to ether formation when ambelline is heated with acid can be explained in terms of the epimeric hydroxyl configurations in the two alkaloids. Finally, it had been observed that epidihydrohaemanthamine could not be converted to dihydrobuphani-

(7) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 4807 (1955).

(8) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 3368 (1960).

(9) W. C. Wildman, *ibid.*, **80**, 2567 (1958).

(10) H. A. Lloyd, E. A. Kielar, R. J. Highet, S. Uyeo, H. M. Fales, and W. C. Wildman, *J. Org. Chem.*, **27**, 373 (1962).

(11) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *ibid.*, **25**, 2153 (1960).

(12) For reactions characteristic of each Amaryllidaceae ring system, see W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, ed., Academic Press, Inc., New York, N. Y., 1960, p. 289.

(13) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 427 (1953).

(14) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 197 (1960).

sine by successive treatment with thionyl chloride and lithium aluminum hydride.

To prepare the desired epidihydroambelline, we examined the sodium borohydride reduction of oxodihydroambelline. In methanolic solution, this reduction afforded a mixture of dihydroambelline (44%), an uninvestigated organoboron compound, and the desired epidihydroambelline (40%). Treatment of the latter compound, first with thionyl chloride and then lithium aluminum hydride, gave a homogeneous oily product possessing the same retention time by gas phase chromatography and infrared spectrum (liquid film) as dihydrobuphanidrine (V).[8-10] The picrate of deoxydihydroambelline had the same melting point and optical rotation as dihydrobuphanidrine picrate, and a mixture melting point determination showed no depression. The optical rotatory dispersion curves of the product and dihydrobuphanidrine were identical within experimental error. These reactions show that dihydroambelline is 11-hydroxydihydrobuphanidrine (IV. R = OH, R′ = H). In turn, oxodihydroambelline is VII.

To be consistent with the chemical reactivity of ambelline and oxoambelline, the isolated double bond can be only at C-1–C-2 or C-4–C-4a. A C-1–C-2 assignment could be anticipated by analogy with many other alkaloids of this ring system and was proven by several physical methods.

In contrast with the sodium borohydride reduction of VII, which provided nearly equal amounts of the two alcohols epimeric at C-11 (IV), oxoambelline afforded ambelline in over 90% yield. The filtrates from the ambelline recrystallization could be shown to contain traces of epiambelline (III. R = H, R′ = OH) by spectral methods. In dilute carbon tetrachloride solution these filtrates showed two peaks in the hydroxyl stretching region, 3603 and 3565 cm.$^{-1}$. Pure ambelline shows only one at 3565 cm.$^{-1}$. The 3603-cm.$^{-1}$ absorption is that predicted for epiambelline by analogy with haemanthamine (VIII) which shows absorption at 3598 cm.$^{-1}$. Hydrogenation of this mixture shifted the 3603 cm.$^{-1}$ band to 3630 cm.$^{-1}$, the frequency found for epidihydroambelline and other unbonded secondary alcohols. The 3565-cm.$^{-1}$ absorption, which is due to OH bonded to the π-electrons of the aromatic ring is unaffected by the reduction. If the double bond of ambelline were at C-4–C-4a, a far less favorable condition would exist for hydrogen bonding to the isolated double bond and the OH absorption would be higher than 3610 cm.$^{-1}$.

A close parallel exists between the pK_a values of ambelline and dihydroambelline (6.90 and 7.70, respectively) and haemanthamine and dihydrohaemanthamine (6.93 and 7.55, respectively). If the double bond of ambelline were C-4–C-4a, a much lower pK_a would be expected for it. The n.m.r. spectrum of oxoambelline shows two singlets for the lone aromatic proton at C-10 and the methylenedioxy protons (δ = 6.58 and 5.88, respectively). Between them, there is an AB pattern of *two* olefinic protons (δ = 6.52 and 6.18; J = 10). The proton at higher field is further split by coupling to a single proton (J = 5). These data give unequivocal evidence of C-1–C-2 saturation.

Our continuing interest in the biosynthesis of Amaryllidaceae alkaloids made it desirable to carry out one additional degradative sequence for future use. Oxohaemanthamine methiodide in refluxing alkali was converted to N-(6-phenylpiperonyl)sarcosine which could be hydrogenolyzed to sarcosine and 2-methyl-4,5-methylenedioxybiphenyl.[15] By identical reactions, oxoambelline methiodide gave 3-methoxy-2-methyl-4,5-methylenedioxybiphenyl and sarcosine.

Experimental[16]

Ambelline.—The principal sources of ambelline were *Nerine bowdenii* W. Wats.,[5] and an *Amaryllis belladonna* hybrid.[17] Preliminary characterization of the alkaloid was reported in an earlier paper.[2]

Dihydroambelline (IV. R = OH, R′ = H).—Prepared by the method described earlier,[2] the product was crystallized from ethyl acetate and sublimed at 170° (0.03 mm.), m.p. 195–197°; $[\alpha]_{589}^{25}$ −16°, $[\alpha]_{436}^{25}$ −42° (*c* 0.675); λ_{max} 287 mμ (log ϵ 3.19)[18]; OH band at 3565 cm.$^{-1}$. Catalytic reduction of ambelline in acetic acid at atmospheric pressure with either platinum or palladium also gave dihydroambelline.

Oxoambelline (VI).—To a solution of 2.5 g. of ambelline (m.p. 260°) in 100 ml. of dry pyridine was added a slurry of 4 g. of chromic acid anhydride in 50 ml. of pyridine. After stirring for 20 hr. at room temperature, the solution was poured on ice, and the excess of oxidizing agent was reduced by sodium sulfite. The solution was made basic with sodium carbonate and extracted four times with chloroform. The chloroform extracts were washed with water, dried with magnesium sulfate, and evaporated. The resulting viscous brown oil (2.2 g.) was chromatographed on 100 g. of Florisil. Benzene–ethyl acetate mixtures eluted 1.9 g. of colorless oil which crystallized from ether–hexane. Two further crystallizations from the same mixture gave a product melting at 118–119°; $[\alpha]_{589}^{26}$ −123°, $[\alpha]_{436}^{25}$ −442° (*c* 0.47); λ_{max} 292 mμ (log ϵ 3.31), 315 mμ (log ϵ 3.24). The optical rotatory dispersion curve shows a negative Cotton effect at 445 mμ (−2350°). The crystalline product was sublimed at 110° (0.03 mm.) and the resulting colorless glass was analyzed.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.41; H, 5.77; N, 4.39.

Oxoambelline also could be obtained by oxidation of ambelline with cyclohexanone and aluminum *t*-butoxide in toluene solution at 111°. The best yield by this method was 60%.

The hydrochloride was prepared in ether solution with gaseous hydrogen chloride. The precipitate was washed twice with ether, m.p. 222–224° (evac. cap.). Two recrystallizations from chloroform–ethyl acetate gave fine white crystals, m.p. 227–228° (evac. cap.); $[\alpha]_{589}^{22}$ −29° (*c* 0.70); λ_{max} 298 mμ (log ϵ 3.38), 308 mμ (log ϵ 3.41). The product is quite soluble in chloroform.

Anal. Calcd. for $C_{18}H_{20}NO_5Cl$: C, 59.10; H, 5.51; N, 3.83; $2OCH_3$, 16.96. Found: C, 59.33; H, 5.41; N, 3.95; OCH_3, 16.96.

The picrate was prepared in ethanol and recrystallized seven times from chloroform–ethanol, m.p. 225–228° dec. The analytical sample was dried overnight *in vacuo* at 75°.

(15) W. C. Wildman, H. M. Fales, and A. R. Battersby, *J. Am. Chem. Soc.*, **84**, 681 (1962); *ibid.*, **83**, 4098 (1961).

(16) Physical measurements of melting points, infrared and ultraviolet spectra, and optical rotations were performed on the instruments used in our previous papers. Hydroxyl stretching frequencies were determined at high dilution in carbon tetrachloride on a Beckman IR-7 infrared spectrophotometer. Unless noted to the contrary, all infrared spectra and optical rotations were determined in chloroform solution and all ultraviolet spectra in absolute ethanol. Gas phase chromatographs were obtained on a Barber–Colman Model 15 apparatus equipped with an argon ionization detector. The column was a 6 ft. × 4.3 mm. U-tube packed with 3/4% SE-30 on Chromosorb W, 80–100 mesh. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J. We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley of the National Institute of Arthritis and Metabolic Diseases, and Dr. Roy King, Iowa State University of Science and Technology, for the nuclear magnetic resonance spectra which were obtained on a Varian A-60 analytical nuclear magnetic resonance spectrometer operating at 60 Mc. Frequencies were obtained relative to tetramethylsilane as an internal standard by interpolation using the audio sideband technique.

(17) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(18) Contrary to our previous report,[2] no maximum is present at 245 mμ.

Anal. Calcd. for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.67; H, 4.12; N, 10.02.

The treatment of oxoambelline in acetone solution with methyl iodide at room temperature yielded a methiodide which was recrystallized from ethanol, m.p. 250–254° dec.; $[\alpha]_{589}^{24}$ −83°, $[\alpha]_{436}^{24}$ −284° (*c* 0.41; dimethylformamide–water, 1:1).

Anal. Calcd. for $C_{19}H_{22}NO_5I$: C, 48.42; H, 4.67; N, 2.97. Found: C, 48.41; H, 4.53; N, 3.19.

Oxodihydroambelline (VII).—Dihydroambelline (800 mg.) was oxidized and worked up by the method described for oxoambelline The resulting 750 mg. of brown oil was chromatographed on 40 g. of Florisil. Benzyl–ethyl acetate mixtures eluted 620 mg. of viscous, colorless oil which could be crystallized from methanol, m.p. 163–164°; $[\alpha]_{589}^{24}$ −247°, $[\alpha]_{436}^{24}$ −732° (c 0.30); λ_{max} 292 mμ (log ε 3.36), 313 mμ (log ε 3.24), λ_{inf} 250 mμ (log ε 3.70); in 1% hydrochloric acid–ethanol: λ_{max} 297 mμ (log ε 3.45), 305 mμ (log ε 3.46); λ_{inf} 253 mμ (log ε 3.58).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.05; H, 6.39; N, 4.34.

The picrate was prepared in ethanolic solution. Three recrystallizations from chloroform–ethanol gave the analytical sample, m.p. 249–250° dec.

Anal. Calcd. for $C_{24}H_{24}N_4O_{12}$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.55; H, 4.48; N, 9.95.

The methiodide was obtained by refluxing oxodihydroambelline with an excess of methyl iodide in acetone solution for 10 min. The crystals were filtered and recrystallized twice from water–ethanol to give the analytical sample, m.p. 275° dec.

Anal. Calcd. for $C_{19}H_{24}NO_5I$: C, 48.22; H, 5.07; N, 2.96. Found: C, 47.90; H, 5.23; N, 2.84.

Oxodihydroambelline also was prepared by oxidation of dihydroambelline with manganese dioxide in chloroform solution at room temperature or by catalytic hydrogenation of oxoambelline with palladium on charcoal in ethanolic solution.

Epidihydroambelline (IV. R = H, R′ = OH).—To a solution of 325 mg. of oxodihydroambelline in 10 ml. of methanol was added 750 mg. of sodium borohydride. An additional 10 ml. of methanol and two 500-mg. portions of hydride were added after 15 and 30 min., respectively. The mixture was allowed to stand for 2 hr. at room temperature and then was heated on the steam bath for 15 min. It was poured into a cold solution of 0.5 *N* sulfuric acid and made basic with sodium hydroxide. Extraction with chloroform yielded 350 mg. of oily product which was chromatographed on 30 g. of Florisil. Benzene–ethyl acetate (9:1) eluted 60 mg. of an organoboron compound (white crystals from ether–hexane, m.p. 156–158°). Ethyl acetate gave 130 mg. of crystals, m.p. 233–238°; after two recrystallizations from ethyl acetate, the product melted 238–240°. Sublimation at 190° (0.05 mm.) gave the analytical sample, m.p. 239.5°; $[\alpha]_{589}^{24}$ −67°, $[\alpha]_{436}^{24}$ −130° (*c* 0.135); λ_{max} 287 mμ (log ε 3.26); OH band at 3630 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20; 2OCH$_3$, 18.63. Found: C, 64.62; H, 6.88; N, 4.27; OCH$_3$, 19.11.

Further elution of the column with ethyl acetate–methanol mixtures afforded 142 mg. of crystalline dihydroambelline, m.p. 192°.

Refluxing the reaction mixture in acetic acid does not change the amount of boron-containing compound. Epidihydroambelline can be separated by gas chromatography from dihydroambelline. The latter has a considerably shorter retention time.

Epiambelline (III. R = H, R′ = OH).—A solution of 600 mg. of oxoambelline in 30 ml. of methanol containing a trace of boric acid was treated with 1 g. of sodium borohydride. The mixture was kept at room temperature for 2 hr. during which time two additional 500-mg. portions of hydride were added. The solution was heated on a steam bath for a few minutes. The reaction mixture was poured into cold 0.5 *N* sulfuric acid, made alkaline with 2 *N* sodium hydroxide, and extracted with chloroform. The resulting crude, crystalline product (580 mg.) was chromatographed on 20 g. of Florisil. Benzene–ethyl acetate mixtures eluted first a boron-containing compound which after recrystallization from methanol showed a melting range of 185–200°. Infrared analysis indicated that all subsequent fractions were ambelline, melting between 240 and 258°. One recrystallization of these combined fractions from chloroform–acetone gave 400 mg. of pure ambelline. The residue (110 mg.) in the mother liquors was rechromatographed on 5 g. of Florisil. All fractions were examined in the hydroxyl stretching region in dilute carbon tetrachloride. The first few fractions which were eluted with benzene–ethyl acetate (19:1) showed two bands at 3603 and 3565 cm.$^{-1}$. The band at 3565 cm.$^{-1}$ could be assigned to the hydroxyl group of ambelline, while the absorption at 3603 cm.$^{-1}$ is that predicted for epiambelline. After recrystallization of these fractions from chloroform–ethyl acetate, the product melted at 245–248° but had a much lower positive optical rotation than pure ambelline. Gas phase chromatography showed that the material was largely ambelline, but a second compound was eluted 0.5 min. later. The mixture could not be separated by chromatography on Florisil or recrystallization. It was hydrogenated catalytically with palladium on charcoal (10%) in ethanolic solution. The product showed the expected shift of one hydroxyl band to 3630 cm.$^{-1}$ (as in epidihydroambelline) with the other band remaining at 3565 cm.$^{-1}$ (as in pure ambelline and dihydroambelline). The yield of the epi compound in this reaction is estimated to be 3–5%.

Conversion of IV (R′ = OH) to Dihydrobuphaniedrine.—A solution of 75 mg. of epidihydroambelline in 10 ml. of freshly distilled thionyl chloride was refluxed for 2 hr. and then evaporated to dryness. Twenty-five milliliters of dry tetrahydrofuran was added and the solution was refluxed with 700 mg. of lithium aluminum hydride overnight. The cooled mixture was hydrolyzed with a saturated solution of sodium potassium tartrate and extracted thoroughly with chloroform. The resulting 65 mg. of crude, oily product was chromatographed on 3 g. of Florisil. A clear, liquid product (45 mg.) was eluted with ethyl acetate and ethyl acetate–ethanol mixtures.

The picrate was prepared in ethanol and recrystallized four times from chloroform–ethanol, m.p. 277–280° dec. It did not depress the melting point of pure dihydrobuphanidrine picrate, $[\alpha]_{589}^{25}$ +16°, $[\alpha]_{500}^{25}$ +37° (*c* 0.51); authentic dihydrobuphanidrine picrate, $[\alpha]_{589}^{24}$ +11°, $[\alpha]_{500}^{24}$ +27° (*c* 0.50).

Anal. Calcd. for $C_{24}H_{26}N_4O_{11}$: C, 52.74; H, 4.80; N, 10.02. Found: C, 52.41; H, 4.88; N, 10.46.

The picrate was dissolved in chloroform and passed through a column of Merck alumina. The eluted oil, b.p. 145° (0.01 mm.), was pure by gas phase chromatography and possessed the same retention time as dihydrobuphanidrine. Infrared spectra (liquid film) of the product and dihydrobuphanidrine were identical as were the optical rotatory dispersion curves, within experimental error.

N-(2-Methoxy-6-phenylpiperonyl)sarcosine Hydrochloride.—To a solution of 700 mg. of oxoambelline methiodide in 10 ml. of hot water was added 3 ml. of 50% sodium hydroxide. The solution was heated on the steam bath for 1 hr. The brown, gummy layer that formed was freed from excess alkali by decantation and dissolved in cold 6 *N* hydrochloric acid. The solution was saturated with sodium chloride and extracted five times with chloroform. The solvent was evaporated and the remaining oil was dissolved in a little hot acetone. A fine, crystalline precipitate formed, 450 mg., m.p. 182–185°. The product was recrystallized several times from methanol–acetone to give the analytical sample, m.p. 185.5–187°; λ_{max} 224 mμ (log ε 4.54); λ_{inf} 252 mμ (log ε 3.79), 288 mμ (log ε 3.35).

Anal. Calcd. for $C_{18}H_{20}NO_5Cl$: C, 59.10; H, 5.47; N, 3.83; Cl, 9.71. Found: C, 59.24; H, 5.50; N, 3.61; Cl, 9.55.

3-Methoxy-2-methyl-4,5-methylenedioxybiphenyl.—A solution of 200 mg. of N-(2-methoxy-6-phenylpiperonyl)sarcosine hydrochloride in 35 ml. of ethanol and 0.5 ml. of acetic acid was hydrogenated with 800 mg. of pre-equilibrated palladium on charcoal (10%). The reduction stopped after an uptake of 1.7 equivalents of hydrogen. The solution was filtered, diluted with water, and extracted with ether. The ether solution was washed three times with water, dried with magnesium sulfate, and evaporated to leave 90 mg. of a slightly yellow oil that was distilled at 120–130° (0.07 mm.); λ_{max} 258 mμ (log ε 3.25); λ_{max} 218 mμ (log ε 4.39), 287 mμ (log ε 2.90). The purity of the distillate was established by gas phase chromatography.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.51; H, 6.02.

The aqueous raffinate was concentrated to half volume and made basic with 2 *N* sodium hydroxide. A solution of 2 g. of *p*-toluenesulfonyl chloride in 60 ml. of benzene was added, and the emulsion was stirred for 24 hr. The layers were separated, and the alkaline aqueous layer was extracted with ether. The aqueous solution was acidified with 2 *N* hydrochloric acid and extracted four times with chloroform. Evaporation of the dried chloroform solution gave 80 mg. (60%) of crude N-tosylsarcosine,

m.p. 147–149°.[19] After recrystallization from acetone–hexane and ethyl acetate–hexane, the product was sublimed at 125° (0.07 mm.) to give the analytical sample, m.p. 151–152°.

(19) E. Fischer and M. Bergmann, *Ann.*, **398**, 118 (1913).

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.40; H, 5.36; N, 5.77; S, 13.21. Found: C, 49.33; H, 5.42; N, 5.79; S, 13.19.

Acknowledgment.—We are indebted to Messrs. D. L. Rogerson and J. D. Link for the processing of plant material and to Mrs. L. C. Warren for the instrumental aspects of the work.

Beckmann Rearrangements in Alicyclic Systems. V. Evidence for Carbonium Ion Intermediates in Acid-catalyzed Oxime Rearrangements[1,2]

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The Beckmann reactions of several 1,1-disubstituted 2-tetralone oximes in phosphorus pentachloride are shown to result in the formation in high yield of unsaturated nitriles from typical α-trisubstituted oxime fragmentation. Rearrangement of these oximes in polyphosphoric acid and the cyclization of the unsaturated nitriles in this medium are shown to proceed in such a fashion as to yield identical products, the expected lactam and α,β-unsaturated ketone. In each case studied, the ratio of lactam to unsaturated ketone was found to be identical to that obtained from the independent nitrile cyclizations under comparable conditions of temperature and time. It is concluded from these data that the lactam, although the expected product of Beckmann rearrangement, is produced *via* a Ritter cyclization of the nitrile intermediate from initial fragmentation of the oxime. These data support a mechanism for these reactions involving ionic intermediates in α-trisubstituted oxime rearrangements.

Recently,[3] the Beckmann rearrangements of 2,2-disubstituted 1-indanone oximes and related tetralone and benzosuberone oximes were reported to rearrange in the normal fashion to 3,3-disubstituted hydrocarbostyrils and homologous products. These reactions did not follow the same course of rearrangement as previously observed in other spiro-[4] and 2,2-disubstituted cycloalkanone oximes.[5] The literature indicates that the cleavage of an oxime which is completely substituted at the α-carbon is a rather general process.[6,7] Compounds of this class, together with certain bridged bicyclic ketoximes[8] and compounds bearing a β-hetero atom adjacent to the oximino group[9] follow the cleavage reaction rather than the normal course of rearrangement to an amide or a lactam. The structural features of these systems, in general, indicate that this process involves the ejection of a positive fragment from the β-position of an electron-deficient intermediate. Our interest in these processes has been centered about the examination of the rearrangement behavior of α-trisubstituted oximes, particularly, in cyclic systems. These studies have indicated that it may be possible to have more than one mechanistic route followed in the rearrangement of hindered ketoximes. In extending these studies, it was of interest to investigate model systems potentially capable of fragmentation but in which the previously reported α,β-unsaturated ketone formation from the unsaturated nitrile intermediate would compete with a second potential cyclization reaction through the Ritter reaction[10] involving the nitrile addition to the double bond to form an amide, identical in type to the expected product of Beckmann rearrangement. This second route would yield the normal Beckmann rearrangement product, but, *via* a reaction course which would be expected to proceed through such intermediate carbonium ion steps as to yield, in the case of an asymmetric α-carbon, a racemic product.[11] It is the purpose of this paper to show that this second mechanistic route is followed, at least, with a number of hindered ketoximes. This observation together with previous observations in rearrangements in cyclic systems adds additional information to the fundamental mechanistic processes involved in group migration from carbon to nitrogen and also indicates a similarity to analogous carbon–carbon rearrangement processes.

One of the most frequently quoted exceptions[12] to the generality of oxime fragmentation in the α-trisubstituted class of oximes is the polyphosphoric acid rearrangement of 1,1,4,4-tetramethyl-2-tetralone oxime. This oxime has been reported to rearrange normally to the expected lactam in 24% yield. The remaining products of the reaction were not characterized. Since the course of reaction in this case could follow either normal rearrangement or a fragmentation–recombination route, it was of interest to examine carefully the

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(2) This study was presented at the Metropolitan Regional Meeting, American Chemical Society, New York, N. Y., January 22, 1962.

(3) R. T. Conley and L. J. Frainier, paper IV of this series; *J. Org. Chem.*, **28**, 3844 (1963).

(4) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960); (b) R. T. Conley and M. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

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rearrangement of this system and related ketoximes for both lactam and α,β-unsaturated ketonic products. In addition, it was of further interest to contrast the independent cyclization of the unsaturated nitrile intermediates in polyphosphoric acid medium under the conditions used to effect oxime rearrangement.

The ketones used in this study were prepared using reported methods. 1,1,4,4-Tetramethyl-2-tetralone was prepared from 2,2,5,5-tetramethyltetrahydrofuranone by the procedure described by Bruson, Grant, and Bobko.[12] 1,1-Dimethyl- and 1,1-pentamethylene-2-tetralone were prepared by the alkylation of 2-tetralone with methyl iodide or pentamethylene dibromide, respectively, using potassium *t*-butoxide.[13] The oxime derivatives were prepared from the purified ketones using hydroxylamine hydrochloride and the pyridine–ethanol solvent system.[14]

Rearrangement Studies.—The rearrangement of 1,1-dimethyl-, 1,1,4,4-tetramethyl- and 1,1-pentamethylene-2-tetralone oximes using phosphorus pentachloride resulted in almost quantitative yields (93–96%) of the unsaturated nitriles (Figure 1) expected from oxime fragmentation. In the case of 1,1-dimethyl- and 1,1,4,4-tetramethyl-2-tetralone oxime cleavage, small amounts (3–4%) of the lactams, 2-aza-1,1-dimethyl-3-benzosuberone and 2-aza-1,1,5,5-tetramethyl-3-benzosuberone, respectively, were isolated during the chromatographic separation of the reaction products. The structure of the lactams was established unequivocally in further studies of the reactions of the unsaturated nitriles and their respective amides. Heating the unsaturated nitrile or amide in polyphosphoric acid resulted in the formation of identical lactams, characterized by their infrared spectrum and mixed melting point determinations. These cyclizations will be discussed later in this report in some detail.

Treatment of 1,1-dimethyl-2-tetralone oxime with hot polyphosphoric acid resulted in the formation of two major reaction products: the lactam, 2-aza-1,1-dimethyl-3-benzosuberone (24%) and an α,β-unsaturated ketone, 4,5-benzo-3-methylcyclohepta-2,4-dien-1-one (71%). The structure of this ketone was established by its characteristic substituted cinnamaldehyde ultraviolet spectrum with an intense maxima at 288 mμ and elemental analysis of the ketone and its 2,4-dinitrophenylhydrazone derivative. In addition, the structure could be readily deduced from previous studies[4,5] on α,β-unsaturated ketone formation under Beckman rearrangement conditions in polyphosphoric acid. The final confirmation of structure was obtained, again in light of previous work, by the polyphosphoric acid cyclization of the unsaturated nitrile, obtained in the phosphorus pentachloride oxime fragmentation reaction, to the lactam and the identical α,β-unsaturated ketone. In analogous fashion 1,1,4,4-tetramethyl-2-tetralone oxime gave 2-aza-1,1,5,5-tetramethyl-3-benzosuberone (24%) and 4,5-benzo-3,6,6-trimethylcyclohepta-2,4-dien-1-one (72%). Examination of the course of rearrangement of 1,1-pentamethylene-2-tetralone in polyphosphoric acid resulted in the isolation of 4,5-benzo-2,3-pentamethylenecyclohepta-2,4-dien-1-one also in 72% yield. In this latter case, the

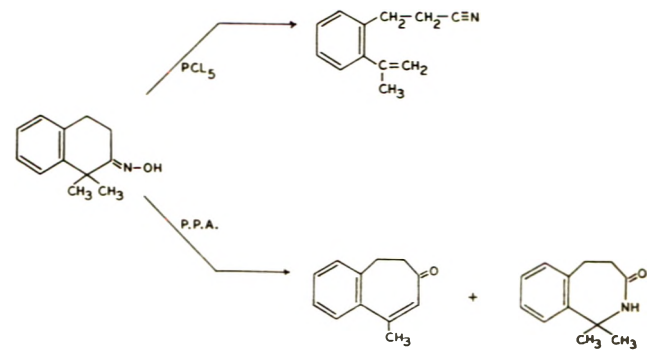

Figure 1

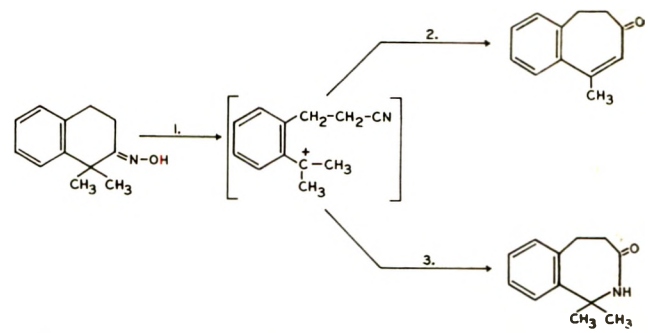

Fig. 2.—The fragmentation–recombination mechanism: step 1, fragmentation of the oxime to carbonium ion–nitrile intermediate; step 2, α,β-unsaturated ketone formation *via* the Hoesch reaction; step 3, lactam formation *via* the Ritter reaction.

lactam although identified in the crude reaction product mixture by infrared analysis was not isolated.

Noticeable in each of the above rearrangement cases in polyphosphoric acid was the remarkable consistency in yields and the ratio of unsaturated ketone to lactam, approximately 3:1 as determined by column chromatography. Further rearrangements were carried out at successively shorter time intervals of eight, five, and three minutes although the yields diminished as expected the ratio of ketone to lactam remained constant. The possibility occurred to us that the immediate precursor responsible for ketone formation might also be responsible for lactam formation *via* the Ritter cyclization of the unsaturated nitrile. In previous studies,[4b,5] we have shown that the nitrile intermediate must be essentially free after fragmentation, since the size of the new ring formed was consistent with existing thought on ring cyclization processes. In the cases studied here Hoesch cyclizations[15] to form the ketone and Ritter cyclization[10] to form the lactam result in seven-membered ring formation and therefore these processes would be expected to be competitive. It was felt that this postulate could readily be confirmed by studying the cyclization process of the unsaturated nitriles under conditions of time and temperature used in the oxime rearrangement studies. Typical results were obtained in the cyclization of 3-(2′-isopropenylphenyl)propionitrile. In runs of three, five, eight and ten minutes, the ratio of ketone to lactam was found to be identical to that observed in the oxime rearrangements. In the normal cyclization reaction of ten minutes at 125°, 4,5-benzo-3-methylcyclohepta-2,4-dien-4-one was isolated in 73% yield and the lactam, 2-aza-1,1-dimethyl-3-benzosuberone in 24% yield.

(13) M. Mousseron, R. Jacquier, and H. Christol, *Compt. rend.*, **239**, 1805 (1954).

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(15) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).

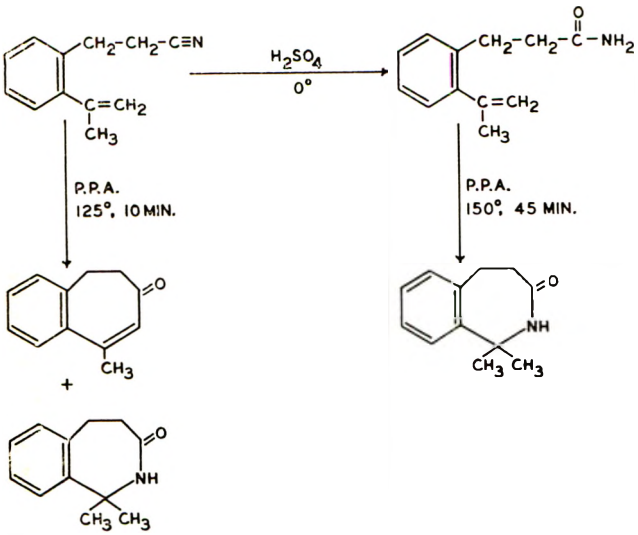

Figure 3

Similar results were obtained from the corresponding unsaturated nitriles obtained from phosphorus pentachloride fragmentation of 1,1,4,4-tetramethyl-2-tetralone oxime and 1,1-pentamethylene-2-tetralone oxime. The lactams and unsaturated ketones produced by nitrile cyclizations were identical in all respects to the Beckmann rearrangement products.

It was of further interest to attempt the cyclization of the unsaturated amide to the lactam under the rearrangement conditions since it remained a possibility that a portion of the nitrile was hydrated to amide prior to cyclization to the lactam. 3-(2′-Isopropenylphenyl)propionitrile was hydrated in cold concentrated sulfuric acid to 3-(2′-isopropenylphenyl)propionamide. Attempted cyclization of the unsaturated amide at 125° for ten minutes resulted in 96% recovery of starting amide. However, at 150° for forty-five minutes it was possible to isolate the lactam in good yield. This evidence, therefore, negates the possible formation of the lactam through an initial hydration to amide followed by cyclization route (Figure 3).

From these data it can be concluded that the lactam expected from the Beckmann rearrangement, although isolated, is not produced in the initial reaction step. Rather, the lactam and ketone are produced competitively by Ritter and Hoesch type cyclizations of the nitrile intermediate.

In contrast to existing thoughts on the Beckmann rearrangement involving concerted group migration, these studies support a two-step rearrangement mechanism,[11b] involving a oxime fragmentation followed by recombination of the fragments intramolecularly to produce the lactam product. These results point toward the necessity of modifying the present approach used in describing carbon–nitrogen rearrangement processes and interpreting data therefrom to include a more detailed analysis of the structural features of molecules thought to exhibit normal as well as anomalous behavior. Group migration of mono- and disubstituted α-carbon atoms with retention of configuration seems unquestionably the case. However, in trisubstituted α-carbon migration cases ionic intermediates may well be the most commonly found mode of group migration in oxime rearrangement in strong acid media.

Experimental

All melting points were taken using the capillary method and are uncorrected. The infrared spectra used for comparison were recorded using a Baird Model AB-2, Beckman IR-4 or IR-5 recording spectrophotometer with sodium chloride optics. The ultraviolet spectra were obtained using a Beckman DK-2A recording spectrophotometer. All ultraviolet spectra were determined on samples in ethanol solution.

Reactants.—2-Tetralone was prepared by the method of Soffer, Bellis, Gallerson, and Stewart.[16]

I. **Beckmann Rearrangements. 1,1-Dimethyl-2-tetralone Oxime. (A) With Phosphorus Pentachloride.**—To a cold solution of 1.00 g. (0.0053 mole) of 1,1-dimethyl-2-tetralone oxime in 40 ml. of anhydrous, thiophene-free benzene, 1.00 g. of phosphorus pentachloride was added slowly in small amounts. The mixture was allowed to warm slowly to room temperature. After 24 hr., the reaction mixture was cautiously hydrolyzed by the dropwise addition of 30 ml. of water. The benzene layer was decanted and washed successively with 20 ml. of water, 20 ml. of 10% sodium bicarbonate and 20 ml. of saturated sodium chloride solution. The benzene layer was separated and evaporated to yield 0.91 g. of a light tan oil. The oil was transferred to a micro distillation tube and the distillable portion removed as a light yellow oil, b.p. 87–91°/0.6 mm. After a single separation over alumina in ether solution, 0.84 g. (93%) of the unsaturated nitrile, 3-(2′-isopropenylphenyl)propionitrile was obtained. The nitrile group showed a characteristic infrared absorption for the nitrile group at 4.45 μ.

Anal. Calcd. for $C_{12}H_{13}N$: C, 81.17; H, 7.65; N, 8.18. Found: C, 81.31; H, 7.77; N, 8.03.

The residue from the microdistillation was transferred to a sublimation apparatus. After 2 hr. at 100° and 0.01 mm., 0.034 g. (3.4%) of 2-aza-1,1-dimethyl-3-benzosuberone was obtained, m.p. 113–114.5°. The infrared spectrum indicated a single N—H vibration at 2.95 μ and a 6.05 μ Amide I band (chloroform solution).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.20; H, 8.01; N, 7.32.

Hydration of 3-(2′-Isopropenylphenyl)propionitrile.—To 5 ml. of concentrated sulfuric acid cooled in an ice–salt bath, 0.15 g. (0.00088 mole) of 3-(2′-isopropenylphenyl)propionitrile was slowly added. The mixture was stirred until all of the nitrile had dissolved in the cold acid solution. After 2 hr. at 0.5°, the mixture was poured over crushed ice. The cold aqueous solution was extracted three times with 20-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo*. The solid residue was recrystallized five times from an ethyl acetate–petroleum ether mixture to yield 0.08 g. (50.5%) of the unsaturated amide, m.p. 131–132.5°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.92; H, 7.78; N, 7.51.

(B) Using Polyphosphoric Acid.—A mixture of 1.00 g. (0.0053 mole) of 1,1-dimethyl-2-tetralone oxime and 16.8 g. of polyphosphoric acid was heated at 125–130° for 10 min. On cooling, the mixture was hydrolyzed over crushed ice. The aqueous solution was treated with 10% sodium hydroxide solution until it was definitely alkaline. The alkaline solution was extracted four times with 60-ml. portions of chloroform. The chloroform extracts were combined dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue, a dark brown oil, was chromatographed over alumina in ether to yield two components.

Evaporation of the ether eluents yielded 0.65 g. (71%) of 4,5-benzo-3-methylcyclohepta-2,4-dien-1-one; λ_{max} 288 mμ, log ϵ 3.41.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.69, H, 7.02. Found: C, 83.72; H, 7.23.

The 2,4-dinitrophenylhydrazone was prepared by the method in the usual fashion.[5] After three recrystallizations from ethanol, scarlet plates of the 2,4-dinitrophenylhydrazone derivative were obtained, m.p. 156–156.5°.

Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.47; H, 4.67; N, 15.71.

Further elution of the alumina column with 1:1 ether–chloroform yielded, on evaporation of the solvents, 0.24 g. (24%) of 2-aza-1,1-dimethyl-3-benzosuberone, m.p. 113–114.5°.

(16) M. D. Soffer, M. P. Bellis, H. E. Gallerson, and R. A. Stewart, *Org. Syn.*, **32**, 97 (1952).

Similar runs of shorter durations (3, 5, and 8 min.) resulted in the isolation of unsaturated ketone and lactam in the ratio of yields of 3:1 on column chromatographic separation of the reaction mixtures.

Cyclization of 3-(2′-Isopropenylphenyl)propionitrile.—A mixture of 0.6 g. of 3-(2′-isopropenylphenyl)propionitrile and 12.9 g. of polyphosphoric acid was heated at 125–130° for 10 min. On cooling, the mixture was hydrolyzed over crushed ice. The aqueous mixture was made alkaline with 10% sodium hydroxide and the alkaline solution thoroughly extracted with chloroform. The extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a light brown oil.

Chromatographic separation of the oil in a manner identical with that described for the isolation of the polyphosphoric acid rearrangement products yielded 0.40 g. (73%) of 4,5-benzo-3-methylcyclohepta-2,4-dien-1-one which was characterized by mixed melting point determination of its 2,4-dinitrophenylhydrazone derivative with that obtained from oxime rearrangement, m.p. 156–156.5°. Further elution of the column yielded 0.14 g. (24%) of 2-aza-1,1-dimethyl-3-benzosuberone, m.p. 113–114.5°. Mixed melting point determination with the lactam obtained from oxime rearrangement showed no depression, m.p. 113–114.5°.

Cyclization of 3-(2′-Isopropenylphenyl)propionamide.—A mixture of 0.50 g. of the unsaturated amide and 2.4 g. of polyphosphoric acid was heated at 150–155° for 45 min. The reaction mixture was worked up in the usual manner. The infrared spectrum of the crude solid residue obtained on evaporation of the solvent was identical to that of the lactam isolated from phosphorus pentachloride oxime rearrangement. After a single sublimation, the colorless crystalline lactam, 2-aza-1,1-dimethyl-3-benzosuberone, melted at 113–114°. Mixed melting point with the Beckmann product did not depress, m.p. 113–114.5°.

A similar experiment carried out at 125° for 10 min. resulted in the recovery of 0.48 g. of the unsaturated amide.

II. 1,1-Pentamethylene-2-tetralone Oxime. (A) With Phosphorus Pentachloride.—To a cold solution of 0.23 g. (0.001 mole) of 1,1-pentamethylene-2-tetralone oxime in 10 ml. of anhydrous, thiophene-free benzene, 0.25 g. of phosphorus pentachloride was added slowly in small amounts. The mixture was allowed to slowly warm to room temperature. After 24 hr., the reaction mixture was hydrolyzed by the addition of 10 ml. of water. The benzene layer was separated and the aqueous portion extracted once with 10 ml. of benzene. The benzene layer and extract were combined and washed with 5 ml. of water, 5 ml. of 10% sodium carbonate and 5 ml. of saturated sodium chloride solution. The benzene solution was evaporated to yield a light yellow oil. The oil was chromatographed over alumina in ether solution to give on evaporation of the ether eluents 0.20 g. (96%) of an unsaturated nitrile, 3-(2′-cyclohexenylphenyl)propionitrile. The nitrile group showed a characteristic infrared absorption at 4.45 μ. A portion of the sample was rechromatographed in ether for elemental analysis.

Anal. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.39; H, 8.00; N, 6.50.

(B) Using Polyphosphoric Acid.—A mixture of 0.75 g. (0.003 mole) of 1,1-pentamethylene-2-tetralone oxime and 12.4 g. of polyphosphoric acid was heated at 125–130° for 10 min. On cooling the mixture was hydrolyzed over crushed ice. The aqueous solution was treated with 10% sodium hydroxide solution until definitely alkaline. The alkaline solution was extracted three times with 50-ml. portions of chloroform. The chloroform extracts were combined dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue, a light brown, viscous oil, was chromatographed over alumina in ether to yield in the ether eluents, 0.45 g. (72%) of 4,5-benzo-2,3-pentamethylene-2,4-dien-1-one; λ_{max} 287.5 mμ, log ϵ 3.48.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.89; H, 7.57.

The 2,4-dinitrophenylhydrazone was prepared by the method in the usual fashion.[5] After two recrystallizations from ethanol scarlet plates of the 2,4-dinitrophenylhydrazone derivative were obtained, m.p. 193–193.5°.

Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.23; H, 5.37; N, 14.54.

Cyclization of 3-(2′-cyclohexenylphenyl)propionitrile.—A mixture of 0.42 g. of 3-(2′-cyclohexenylphenyl)propionitrile and 11.6 g. of polyphosphoric acid was heated at 125–130° for 12 min. The reaction mixture was hydrolyzed, made alkaline, and extracted with chloroform in the usual manner. Conversion of the crude reaction product, from chloroform evaporation, to the 2,4-dinitrophenylhydrazone derivative yielded after two recrystallizations from ethanol, the 2,4-dinitrophenylhydrazone derivative of 4,5-benzo-2,3-pentamethylene-2,4-dien-1-one, m.p. 193–193.5°. No depression was observed on admixture of the sample from the ketone isolated in the Beckmann rearrangement in polyphosphoric acid.

III. 1,1,4,4-Tetramethyl-2-tetralone Oxime. (A) With Phosphorus Pentachloride.—To a cold solution of 1.50 g. (0.0069 mole) of 1,1,4,4-tetramethyl-2-tetralone in 60 ml. of anhydrous thiophene-free benzene, 1.50 g. of phosphorus pentachloride was added slowly in small amounts. After warming to room temperature, the mixture was allowed to stand for 24 hr. The mixture was hydrolyzed by the cautious addition of 50 ml. of water. The benzene layer was separated and washed successively with 25 ml. of water, 25 ml. of 10% sodium carbonate, and 25 ml. of saturated sodium chloride solution. The benzene was evaporated to yield 1.38 g. of a light tan oil. The oil was transferred to a micro distillation tube and the mixture distilled at reduced pressure. A light yellow liquid, b.p. 98–102°/0.6 mm., was obtained. The infrared spectrum indicated the characteristic infrared absorption at 4.45 μ for the nitrile group. The crude nitrile was purified over alumina in ether to yield 1.30 g. (94%) of 3-methyl-3-(2′-isopropenylphenyl)butyronitrile.

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.67; N, 7.10. Found: C, 85.20; H, 7.69; N, 6.85.

The solid, tar-like residue from the micro distillation was crushed and transferred to a sublimation apparatus. After two sublimations at 0.01 mm., 0.06 g. (4%) of 2-aza-1,1,5,5-tetramethyl-3-benzosuberone was obtained, m.p. 144–145° (lit.,[12] m.p. 144–145°).

Hydration of 3-Methyl-3-(2′-isopropenylphenyl)butyronitrile.—To 5 ml. of concentrated sulfuric acid cooled in an ice–salt bath, 0.20 g. of 3-methyl-3-(2′-isopropenylphenyl)butyronitrile was slowly added. The mixture was stirred until all the nitrile had dissolved in the cold acid solution. After 2 hr. at 0–5°, the mixture was poured over crushed ice. A semisolid mass separated which was isolated by decantation of the aqueous acid solution. The wet mass was dissolved in 20 ml. of chloroform. The chloroform solution was washed with 10 ml. of saturated sodium bicarbonate solution followed by 10 ml. of water. The chloroform was dried by passing the solution through a layer of anhydrous magnesium sulfate. After evaporation, the solid residue was recrystallized from ethyl acetate–petroleum ether mixture to yield 0.13 g. of the unsaturated amide, m.p. 158.5–160.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38, H, 8.81; N, 6.45. Found: C, 77.24, H, 8.71; N, 6.49.

(B) Using Polyphosphoric Acid.—A mixture of 1.50 g. (0.0069 mole) of 1,1,4,4-tetramethyl-2-tetralone oxime and 22.0 g. of polyphosphoric acid was heated at 125–130° for 10 min. On cooling, the mixture was hydrolyzed over crushed ice. The aqueous solution was extracted three times with 60-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a viscous oil which could be crystallized from petroleum ether to give 0.36 g. (24%) of 2-aza-1,1,5,5-tetramethyl-3-benzosuberone, m.p. 144–145°. No depression was observed on admixture with a sample of the lactam obtained in the phosphorus pentachloride rearrangement of the oxime.

The aqueous solution was made alkaline with 10% sodium hydroxide. The alkaline solution was extracted four times with 75-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 1.00 g. (72%) of 4,5-benzo-3,6,6-trimethyl-cyclohepta-2,4-dien-1-one, λ_{max} 288 mμ, log ϵ 3.70 (after purification over alumina in ether).

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.72; H, 7.87.

The 2,4-dinitrophenylhydrazone was prepared by the method in the usual fashion.[5] After three recrystallizations from ethanol scarlet crystals of the 2,4-dinitrophenylhydrazone were obtained, m.p. 226–227.5°.

Anal. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.10; H, 4.98; N, 14.70.

In similar runs for 3, 5, and 8 min. the ratio of ketone to lactam (3:1) was found to be constant in all experiments. Column chromatographic separation of the reaction mixture gave comparable results.

Cyclization of 3-Methyl-3-(2′-isopropenylphenyl)butyronitrile.—The cyclization of 3-methyl-3-(2′-isopropenylphenyl)butyronitrile in polyphosphoric acid was carried out as previously described. The yield of ketone and lactam were found to be identical to that obtained in the Beckmann rearrangement of the parent oxime.

Cyclization of 3-Methyl-3-(2′-isopropenylphenyl)butyramide.—The cyclization of 0.10 g. of 3-methyl-3-(2′-isopropenylphenyl)-butyramide using the procedure described previously for 3-(2′-isopropenylphenyl)propionamide at 150–155° for 45 min. resulted in the isolation of the lactam, 2-aza-1,1,5,5-tetramethyl-3-benzosuberone, m.p. 144–145°.

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Notes

A Rapid, Precise Procedure for the Quantitative Determination of Unsaturation in Organic Compounds *via* Hydrogenation

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We wish to report a simple procedure which permits the rapid, quantitative determination of unsaturation in representative organic compounds. The method utilizes the new active platinum metal catalysts prepared by the *in situ* treatment of platinum metal salts with sodium borohydride,[1] the *in situ* generation of hydrogen from sodium borohydride, and a modification of the valve[2] which automatically introduces sodium borohydride solution into the reaction mixture as the hydrogenation is proceeding. With these modifications, hydrogenation[3] becomes a rapid, precise tool for the determination of unsaturation.

The apparatus is shown in Fig. 1. In this device, the buret ends in a capillary tube which dips into a mercury well to a depth sufficient to support the column of solution (sodium borohydride in ethanol). As hydrogen is utilized in the hydrogenation flask, the pressure drops 5 to 10 mm. below atmospheric, drawing a small quantity of the borohydride solution through the mercury seal, where it rises to the top of the mercury and runs into the flask through the small vent holes located just above the mercury interface. The acidic solution in the flask converts the borohydride into hydrogen and the resulting increase in pressure seals the valve. The addition proceeds smoothly and automatically to the completion of the hydrogenation, with the amount of borohydride solution corresponding quantitatively to the amount of unsaturated compound contained in the flask.

The procedure was tested by hydrogenating 20.0, 10.0, and 5.00 mmoles of 1-octene, introduced as the pure liquid, and 5.00, 2.50, 2.00 and 1.00 mmoles of 1-octene, introduced as a standard solution in ethanol, using 1.00 *M*, 0.250 *M*, and 0.100 *M* sodium borohydride in ethanol. The procedure was extended to the hydrogenation of 4-methylcyclohexene, 1,5,9-cyclododecatriene, and ethyl oleate, as well as to a mixture of the above four unsaturated compounds. The results are summarized in Table I.

TABLE I

HYDROGENATION OF VARIOUS UNSATURATED COMPOUNDS

Compound	Amt., mmoles	$NaBH_4$ soln. *M*	Volume of $NaBH_4$ solution	Av.	F.S.E.[c]	Olefin found, mmoles
1-Octene	20.0[a]	1.00	4.95, 4.94, 4.90, 4.96, 4.95	4.94 ± 0.02	0.32	20.08 ± 0.020
	10.0[a]	1.00	2.46, 2.44, 2.48, 2.44, 2.42	2.45 ± 0.02	.16	9.96 ± 0.018
	5.00[a]	1.00	1.23, 1.22, 1.22, 1.24, 1.20	1.22 ± 0.02	.08	4.96 ± 0.016
	5.00[b]	0.250	4.57, 4.59, 4.62, 4.56 4.63	4.97 ± 0.03	.38	4.97 ± 0.030
	2.50[b]	.250	.27, 2.06, 2.24, 2.25, 2.25	2.26 ± 0.02	.19	2.45 ± 0.015
	1.00[b]	.250	0.92, 0.91, 0.90, 0.92, 0.91	0.91 ± 0.01	.08	0.99 ± 0.010
	2.00[b]	.100	4.31, 4.39, 4.30, 4.32, 4.30	4.32 ± 0.03	.25	1.98 ± 0.030
	1.00[b]	.100	2.18, 2.15, 2.20, 2.15, 2.20	2.18 ± 0.03	.13	1.00 ± 0.025
4-Methylcyclohexene	2.00[b]	.100	4.32, 4.35, 4.38, 4.36, 4.32	4.35 ± 0.03	.25	1.99 ± 0.025
1,5,9-Cyclododecatriene	0.67[b]	.100	4.32, 4.33, 4.37, 4.35, 4.35	4.34 ± 0.02	.25	1.99 ± 0.025
Ethyl oleate	2.00[b]	.100	4.35, 4.39, 4.32, 4.35, 4.37	4.36 ± 0.02	.25	2.00 ± 0.020
Mixture[d]	2.00[b]	.100	4.37, 4.39, 4.40, 4.37, 4.38	4.38 ± 0.10	.25	2.01 ± 0.012

[a] Introduced as the pure liquid. [b] Introduced as a 1.00 *M* solution in ethanol. [c] mmoles of hydrogen displaced by the volume of olefin or olefin solution introduced plus volume of sodium borohydride introduced (total volume in cc./25.0). [d] A mixture of 1-octene, 4-methylcyclohexene, 1,5,9-cyclododecatriene, and ethyl oleate, prepared by mixing aliquots of the 1 *N* ethanolic solutions.

(1) H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **84**, 1494, 2827 (1962).

(2) C. A. Brown and H. C. Brown, *ibid.*, **84**, 2829 (1962).

(3) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 37–40.

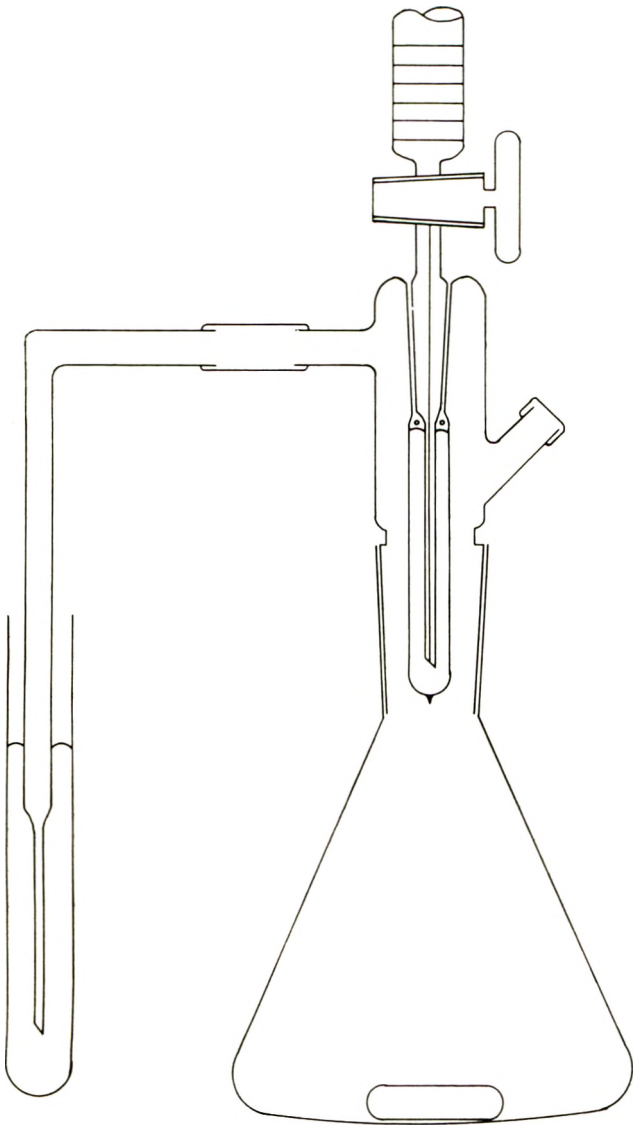

Fig. 1.—Apparatus for the quantitative hydrogenation of unsaturated compounds.

The precision and accuracy appear highly satisfactory It should also be pointed out that the five successive determinations were made consecutively with the same preparation of catalyst. Each determination required only 1–2 minutes for completion. Consequently, this apparatus and procedure appear to provide a highly convenient, precise analysis for unsaturation in organic compounds.

Experimental

Procedure.—A stock solution of sodium hydroxide in ethanol (0.100 *M*) was prepared by dissolving 4.00 g. of sodium hydroxide in 50.0 ml. of water and diluting to 1.0 l. with absolute ethanol. The standard sodium borohydride solution was prepared by adding 3.95 g. of sodium borohydride (Metal Hydrides Incorporated, 98%) to 100.0 ml. of this ethanolic solution and stirring magnetically until solution of the salt was complete. If the solution was not clear, it was filtered through a plug of glass wool. The solution was standardized by injecting 10.00 ml. with a hypodermic syringe into aqueous acetic acid and measuring the hydrogen evolved. The 0.250 *M* and 0.100 *M* sodium borohydride solutions were prepared by diluting aliquots of the 1.00 *M* solution with the sodium hydroxide–ethanol solution.

In the 125-ml. flask of the apparatus (Fig. 1) was placed 1.00 g. of Darco K-B carbon, 40.0 ml. of absolute ethanol, 1.00 ml. of 0.02 *M* chloroplatinic acid solution, and a Teflon-covered magnetic bar. The apparatus was assembled with a rubber stopple in the injection port. The flask was immersed in a beaker of water maintained at 25°. Injection of 5.00 ml. of 1.00 *M* sodium borohydride with a syringe into the vigorously stirred solution produced the catalyst. After about 1 min., 2.00 ml. of concentrated hydrochloric acid was injected, destroying the excess borohydride and providing a hydrogen atmosphere. A small quantity of 1-octene was injected to bring the apparatus to equilibrium.

The analysis was carried out by injecting either the pure liquid olefins or standard solutions of the olefin in ethanol with a syringe. Hydrogenation proceeded rapidly to completion. Generally, but 1 to 2 min. proved adequate for each individual determination. A total of 5 to 10 successive analyses could be carried out before the flask became inconveniently full.

In order to obtain the number of millimoles of double-bonds in the samples, it is necessary to add to the number of mmoles of "hydride" in the borohydride solution (1.00 *M* $NaBH_4$ = 4.00 *M* "hydride") the number of mmoles of hydrogen displaced by the volume of the sample introduced plus the volume of the borohydride solution used. Since 1 mmole of hydrogen at ordinary temperatures and pressures occupies a volume of very nearly 25 cc., this free space equivalent (F. S. E. of Table I) may be conveniently estimated by multiplying the sum of the added volumes by 0.04.

It should be pointed out that an alternative procedure in which hydrogen is generated in one flask and is utilized in a second provides a slightly modified method which may have advantages in some special cases.[2]

Presently we are exploring the applicability of this automatic hydrogenation procedure to the analysis of micro quantities of unsaturated compounds.

Acknowledgment.—We wish to acknowledge the financial support of the Esso Research and Engineering Co. which made this study possible.

Chelation as a Driving Force in Organic Reactions. V.[1] The Preparation of α-Nitro Esters through the Carboxylation of Nitroparaffins

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The synthetic utility of α-nitro esters dates almost from Steinkopf's[2] first synthesis of nitroacetic acid by the self-condensation of nitromethane. Reduction of the nitro group leads to α-amino esters,[3] reaction with Mannich bases provides a synthesis of δ-keto esters,[4] and treatment with sodium nitrite provides a synthesis of α-oximino esters.[5] However, the preparation of the nitro ester itself has not been simple, and, consequently, a number of techniques have been developed for their synthesis. Steinkopf used the nitration of diethyl methylmalonate in the preparation of α-nitropropionic acid.[6] Kornblum has developed a modification of the Victor Meyer reaction to convert α-halo esters to α-nitro esters.[7] The activity of the acidic α-hydrogen in ethyl nitroacetate has been utilized in a Michael addition to acrylonitrile and ethyl acrylate.[8]

(1) Previous paper in this series: H. L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, in press.
(2) W. Steinkopf, *Ber.*, **42**, 2026 (1909).
(3) D. A. Lyttle and D. I. Weisblatt, *J. Am. Chem. Soc.*, **69**, 2118 (1947).
(4) A. Dornow and A. Frese, *Ann.*, **581**, 211 (1953).
(5) N. Kornblum and J. H. Eicher, *J. Am. Chem. Soc.*, **78**, 1494 (1956).
(6) W. Steinkopf and A. Supan, *Ber.*, **43**, 3239 (1910).
(7) N. Kornblum, R. K. Blackwood, and J. Powers, *J. Am. Chem. Soc.* **79**, 2507 (1957).
(8) R. N. Boyd and R. Leshin, *ibid.*, **74**, 2675 (1952).

Aldehydes have been condensed with ethyl nitroacetate to synthesize diethyl 1,3-dinitro-2-alkylglutarates.[9]

In connection with our interest in chelation as a driving force in organic reactions, we have established that primary nitro compounds can be carboxylated with magnesium methyl carbonate to give α-nitro acids.[1,10] The purpose of this paper is to demonstrate that this carboxylation provides a facile preparative method for the synthesis of α-nitroesters.

The pale yellow magnesium methyl carbonate (MMC) solution which results from the saturation of a magnesium methoxide suspension in dimethylformamide with carbon dioxide is a reagent for the introduction of the carboxyl group into active hydrogen compounds such as primary nitro alkanes[10] and ketones,[11] as shown in equation 1. This product can then be esterified.

$$R{-}CH_2NO_2 \xrightarrow[2)\ HCl]{1)\ MMC} R{-}\underset{\displaystyle NO_2}{\overset{|}{C}}H{-}COOH \xrightarrow[CH_3OH]{HCl} RCHNO_2COOCH_3 \quad (1)$$

Previous work has shown that an excess of magnesium methyl carbonate is necessary to obtain a maximum conversion of the nitroalkane to the magnesium chelate of the nitro acid.[1] Therefore, a magnesium methyl carbonate nitroalkane ratio of 2 was used in carrying out the present preparative scale work. In general, when sufficient nitroalkane was available, one mole of the nitro compound was added to a liter of 2 *M* magnesium methyl carbonate at 60°. The product was then converted to the ester by either of two methods. The reaction mixture was hydrolyzed with cold aqueous hydrochloric acid, the nitro acid was extracted with ether, and after drying and removing the ether, the acid was esterified with cold methanolic hydrogen chloride. Alternatively, the magnesium chelate was precipitated from the dimethylformamide solution by pouring the reaction mixture into ether, and then esterifying the nitro acid by dissolving the chelate directly in methanolic hydrogen chloride. The yields and physical properties of a number of methyl esters of α-nitro acids prepared by carboxylation followed by esterification are given in Table I.

TABLE I

Nitro compound	Yield of $R{-}CHNO_2{-}COOCH_3$	$n^{\alpha}D$	B.p., °/mm.
CH_3NO_2	58	1.4253[a]	68/2
$CH_3CH_2NO_2$	47	1.4216	79/5
$CH_3CH_2CH_2NO_2$	44	1.4249	77/2.5
$CH_3(CH_2)_2CH_2NO_2$	43	1.4281	68/1
$CH_3(CH_2)_3CH_2NO_2$	45	1.4308	80/0.75
$(CH_3)_2CHCH_2NO_2$	40	1.4275	73/1
$CH_3(CH_2)_4CH_2NO_2$	47	1.4333	80/0.5
$C_6H_5CH_2CH_2NO_2$	40	1.5100	110/0.01

[a] Lit. $n^{20}D$ 1.4245; N. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, **71**, 3079 (1949).

To establish the identity of the esters, they were converted to the corresponding ammonium salts and analyzed for carbon, hydrogen and nitrogen. These analyses and melting points are given in Table II.

TABLE II

ANALYSES AND M.P. OF $[RCNO_2COOCH_3]^-NH^+$

R	M.p.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	138–140°	26.5	5.9	20.6	27.2	6.2	20.1
CH_3	126–127°	32.0	6.7	18.7	32.2	6.8	19.2
CH_3CH_2	109–110°	36.6	7.4	17.1	36.6	7.2	17.4
$CH_3CH_2CH_2$	116–118°	40.4	7.9	15.7	40.5	7.8	15.8
$CH_3(CH_2)_3$	105–106°	43.7	8.4	14.6	44.0	8.3	15.0
$CH_3(CH_2)_4$	104–105°	46.6	8.8	13.6	46.0	8.8	14.0
$C_6H_5CH_2$	122–123°	53.1	6.2	12.4	53.5	6.1	12.6

A few of the α-nitro esters were also converted to the α-amino ester hydrochloride by catalytic reduction with hydrogen in methanol. When reduction was complete, hydrogen chloride was added to the filtered solution to convert the aminoester to its salt. After evaporation of the methanol, the solid residue was recrystallized. In this fashion methyl α-nitrobutyrate and methyl α-nitrovalerate were converted to methyl α-aminobutyrate hydrochloride and methyl valinate hydrochloride, respectively. The Nef reaction was used to convert small samples of methyl nitropropionate and methyl nitrobutyrate to methyl pyruvate and methyl α-ketobutyrate. The α-ketoesters were isolated and identified as their 2,4-dinitrophenylhydrazones.

The carboxylation of primary nitro compounds offers a method of preparing nitro acids and esters on a synthetic scale, under mild conditions, through a method essentially free of side reactions. The high purity products can easily be reduced by catalytic methods at atmospheric pressure to give α-amino esters.

Experimental

Nitromethane, nitroethane, 1-nitropropane, 1-nitropentane, and 1-nitrohexane are commercially available materials which were redistilled before use. The remaining nitro compounds, except 2-phenylnitroethane, were prepared by the method developed by Kornblum[12] from the corresponding primary alkyl bromides. Phenylnitroethane was prepared by reducing ω-nitrostyrene with lithium aluminum hydride at −40° using the procedure developed by Schecter,[13] *et al.*

Magnesium Methyl Carbonate.—Eight liters of anhydrous methanol was placed in a 12-l. flask equipped with a reflux condenser, stirrer, and provisions for passing gas over the liquid. After the reaction of magnesium and methanol had been initiated using a few grams of magnesium, a total of 480 g. (20 moles) of magnesium turnings was added at a rate to maintain a constant, but controlled, reflux. After the magnesium had completely reacted, the excess methanol was stripped off at water pump vacuum. A 50° water bath was used to heat the mixture, and stirring was continued as long as possible to aid in removing the methanol. However, it is essential that some methanol remain in the solid mass or redissolution becomes extremely slow. When the pressure in the system dropped to the minimum that the water pump was capable of (approximately 20 mm.), enough dimethylformamide was added to the flask to give a total volume of 10 l. Then carbon dioxide was admitted to the stirred system as rapidly as it could be taken up. A bubble counter was used at the outlet of the system to maintain a positive pressure.

After all the magnesium methoxide had dissolved, a short bubble cap fractionating column was put on the flask and the temperature was raised to distill any remaining methanol. The reaction mixture was stirred under a slow stream of carbon dioxide during this distillation. The distillation was continued until the head temperature reached approximately 150°. Then the mixture was cooled to room temperature under carbon dioxide to assure saturation.

(9) A. Dornow and H. Menzel, *Ann.*, **588**, 40 (1954).
(10) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959).
(11) M. Stiles, *ibid.*, **81**, 2598 (1959).
(12) N. Kornblum, H. O. Larson, R. K. Blackwood, D. P. Mooberry, E. P. Oliveto, and G. E. Graham, *ibid.*, **78**, 1497 (1956).
(13) H. Schecter, D. E. Ley, and E. B. Roberson, Jr., *ibid.*, **78**, 4984 (1956).

The molarity of the solution with respect to magnesium was determined by adding a known volume to excess standard sulfuric acid, heating to dispel carbon dioxide, and back-titrating with sodium hydroxide. The carbon dioxide content of the reagent could be determined gasometrically; however, the interpretation of the result is not straightforward.[1] A magnesium methyl carbonate solution prepared in this fashion was used for seven months with no detectable change in its effectiveness. All the methyl esters were prepared in an identical fashion. The preparation of methyl α-nitrobutyrate is given as an illustration.

Methyl α-Nitrobutyrate. (a) **Carboxylation of Nitropropane.**—One liter of 2 *M* magnesium methyl carbonate was placed in a 2-l. flask equipped with a stirrer, a gas inlet tube, and a combination condenser and gas outlet. The reagent was heated, while stirring, to 60° under a carbon dioxide stream. When the temperature of the magnesium methyl carbonate solution had stabilized at approximately 60°, 89 g. of 1-nitropropane was added, and the carbon dioxide stream was replaced by a slow nitrogen stream.

After stirring for 6 hr. at 60°, the reaction mixture was cooled to 10° with an ice bath, and then either hydrolyzed or the magnesium chelate precipitated.

(b) **Hydrolysis and Esterification.**—The carboxylation mixture was poured with vigorous stirring into a mixture of 600 ml. of concentrated hydrochloric acid and 750 g. of ice that had been overlayed with 100 ml. of ether. The ether was separated and the aqueous layer extracted four times with 100-ml. portions of ether. The ether extracts were combined and given a preliminary drying for 15 min. with powdered anhydrous magnesium sulfate. After filtering off the magnesium sulfate, the drying was completed with phosphorus pentoxide. The essentially colorless ether solution was evaporated on a rotary film evaporator at room temperature or slightly below. While the ether was evaporating, 200 ml. of 2 *M* methanolic hydrogen chloride was cooled to −50°. This was poured into the flask containing the α-nitrobutyric acid and the mixture was allowed to warm spontaneously to room temperature and stand overnight. Approximately 100 ml. of the methanol was removed at room temperature, under vacuum, and the remaining reaction mixture was poured into 200 ml. of water. The aqueous solution was extracted five times with 50-ml. portions of ether, the ether dried over magnesium sulfate and distilled. The yield of methyl α-nitrobutyrate was 64.7 g. (44%), b.p. 77°/2.5, $n^{20}D$ 1.4249.

(c) **Precipitation and Esterification.**—The carboxylation mixture was poured with vigorous stirring into 2 l. of ether to precipitate the magnesium chelate of α-nitrobutyric acid and unchanged magnesium methyl carbonate. After decanting the supernatant liquid phase, 1 l. of methanol containing 200 g. of hydrogen chloride cooled to −50° was added to the solid precipitate. This mixture was allowed to warm spontaneously to room temperature and stand overnight. Approximately 600 ml. of methanol was distilled at room temperature under vacuum, and the remaining mixture was poured into 800 ml. of water. The aqueous system was extracted eight times with 50-ml. portions of ether. After drying the ether solution with magnesium sulfate, the product was distilled. The yield was 67 g. (45.5%) of methyl α-nitrobutyrate.

Preparation of Ammonium Salts.—Approximately 1.0 g. of the α-nitro ester was added to 25 ml. of 1 *M* ammoniacal methanol, and the reaction mixture was placed in the refrigerator overnight. The crystals were filtered off and recrystallized from 0.5 *M* ammoniacal methanol. The products were dried over potassium hydroxide in an ammonia atmosphere. All melting points were taken in sealed tubes. An analogous procedure gave the sodium salts of the methyl nitro esters when sodium methoxide was used in place of ammonia.

Preparation of Methyl α-Aminobutyrate Hydrochloride.—A solution of 1.47 g. (0.01 mole) of methyl α-nitrobutyrate in 40 ml. of methanol, in which was suspended 1.0 g. of 5% platinum on carbon (K&K Laboratories), was stirred, under hydrogen at 1 atm. until 670 ml. was consumed. The catalyst was filtered off, 10 ml. of 1.0 *M* methanolic hydrogen chloride was added to the filtrate, and the reaction mixture was evaporated to dryness in a film evaporator. The solid residue was recrystallized from ethanol–benzene, m.p. 136–138°, lit. 139°.[14]

Preparation of Methyl α-Ketobutyrate 2,4-Dinitrophenylhydrazone.—A sample of methyl α-nitrobutyrate (1.47 g.) was dissolved in 10 ml. of 2 *M* sodium methoxide. The mixture was poured into 20 cc. of ice cold concentrated hydrochloric acid. After filtering off the precipitated sodium chloride, the blue aqueous phase was extracted with ether and dried. After the blue color had faded, 2,4-dinitrophenylhydrazone reagent was added, the ether largely removed on the steam bath, and 10 ml. of methanol was added. The product crystallized after standing overnight in the refrigerator, m.p. 147–148°.

Anal. Calculated for $C_{11}H_{12}N_4O_6$: C, 44.90; H, 4.08; N, 19.05. Found: C, 44.9; H, 4.1; N, 19.2.

(14) T. Curtius and E. Müller, *Ber.*, **37**, 1274 (1904).

Dicyanoketenimine (Cyanoform)

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Contribution No. 807 from the Central Research Department Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

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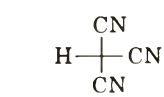
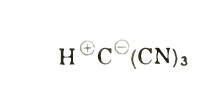
While salts and solutions of cyanoform have been known for a long time,[1] the nature of the free acid has not been established. Cox and Fontaine[2] reported the isolation of a material, m.p. 55–56°, "stable at room temperature for weeks, even when exposed to light and air," which they regarded as cyanoform. No such material could be isolated in our laboratories from aqueous or aquoethereal cyanoform solutions.

It was possible, however, to obtain by rapid evaporation of aquoethereal "cyanoform" a crystalline solid, obviously different from the material described by Cox and Fontaine. That it was indeed the anhydrous acid was established by analysis, by reaction with aqueous silver ion or *t*-butylamine to give, respectively, silver and *t*-butylammonium tricyanomethanide, and by reaction with ethanol to yield 1-amino-1-ethoxy-2,2-dicyanoethylene.

The free acid is unstable and forms an orange-red polymer on standing at room temperature, but can be purified by vacuum sublimation. The colorless, crystalline sublimate polymerizes slowly at room temperature, rapidly on heating above 70°, yet it has been stored unchanged for several days at −80°. The infrared spectra of the crude acid and of the sublimed material are essentially identical. The location of the nitrile band at 4.55 μ is sufficient to eliminate structures such as I and II and points to dicyanoketenimine, III, while the absence of ketenimine absorption[3] at 5.0–5.2 μ in conjunction with bands at 4.0, 4.4, and 5.6 μ, reminiscent of immonium bands,[4] is indicative of the



I



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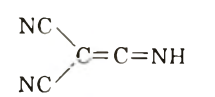
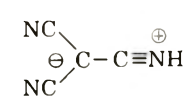


III



IV

(1) (a) H. Schmidtman, *Ber.*, **29**, 1172 (1896); (b) A. Hantzsch and G. Oswald, *ibid.*, **32**, 641 (1899); (c) L. Birkenbach and K. Huttner, *ibid.*, **62B**, 153 (1929).

(2) E. Cox and A. Fontaine, *Bull. soc. chim. France*, 948 (1954).

(3) C. L. Stevens and C. J. French, *J. Am. Chem. Soc.*, **75**, 657 (1953); on the other hand, R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 569 (1954), report the ketenimine band at 4.61 μ for N-methylbisdiethylsulfonylketenimine.

(4) B. Witkop, *Experientia*, **10**, 420 (1954); *J. Am. Chem. Soc.*, **76**, 5597 (1954).

zwitterionic form IV, known to contribute appreciably to the structure of negatively substituted ketenimines.[5a,b]

Dicyanoketenimine is completely ionized in aqueous[6] or aquoethereal solutions as judged by ultraviolet[6] and infrared spectra. In the form of hydronium tricyanomethanide it is reasonably stable, since the addition of water proceeds slowly.[7] On dehydration, however, dicyanoketenimine is obtained instead of tricyanomethane. This fact is not too surprising, as it is known that negatively substituted malononitriles exist as the 1,1-dicyanoethylene tautomers,[8] probably favored on account of their resonance stabilization through structures analogous to IV, impossible in substituted dicyanomethanes. By the analogy between the $(NC)_2C{=}C\langle$ and $O{=}C\langle$ groups,[9] tricyanomethane and dicyanoketenimine are cyanocarbon analogs of cyanic and isocyanic acid. In fact, addition reactions of "cyanoform" resemble closely those of isocyanic acid, as does its facile autoaddition–polymerization. The dicyanoketenimine structure accounts readily for all these properties.

Experimental

Aquoethereal "Cyanoform."—This solution was prepared from potassium tricyanomethanide[7] as previously described.[1a,b] According to Hantzsch and Oswald,[1b] the composition is cyanoform–water–ether in 1:10:10 ratio. A nuclear magnetic resonance spectrum of this solution had, apart from the ethyl peaks (triplet and quadruplet centered at $\tau = 9.04$ and $\tau = 6.70$, respectively), a single proton peak at $\tau = 4.00$. The relative intensities of these peaks supported the earlier analysis.[1b]

The infrared spectrum of the aqueoethereal solution was characterized by tricyanomethanide bands at 4.61, 7.97, and 8.03 μ.[10]

Dicyanoketenimine.[11]—Five milliliters of aquoethereal "cyanoform" was placed on a watch glass and evaporated rapidly by directing a stream of air over the surface until a thick slurry was obtained. It was filtered immediately and the yellowish crystals pressed dry; yield 150–160 mg. Sublimation of this material at 1 mm. starting at a bath temperature of 60° and slowly raising it to 90° gave about 70 mg. of white crystals. The sublimate has no melting point but starts turning orange at 70° and decomposes to a red tar around 140°.

Anal. Calcd. for C_4HN_3: C, 52.7; H, 1.11; N, 46.1. Found: C, 52.2; H, 1.45; N, 45.6.

The infrared spectrum (Nujol mull) is characterized by bands at 4.0, 4.4, 4.55, 5.6, 7.98, 9.76, and 12.16 μ and is not significantly different from that of the crude solid.

A sample of the sublimate was dissolved in water and a portion of the solution was treated with aqueous silver nitrate. Silver tricyanomethanide precipitated immediately and was identified by its infrared spectrum.

Another portion of the solution was treated with excess *t*-butylamine yielding, on concentration of the solution, *t*-butylammonium tricyanomethanide, identified by comparison with authentic material[7] (mixed melting point and superimposition of infrared spectra).

Treatment of sublimed dicyanoketenimine with excess ethanol afforded, on evaporation of the solution, a solid identified as 1-amino-1-ethoxy-2,2-dicyanoethylene by comparison with authentic material[9] (mixed melting point and superimposition of infrared spectra).

(5) (a) R. K. Bullough and P. J. Wheatley, *Acta Cryst.*, **10**, 233 (1957); (b) Dinitroacetonitrile [C. O. Parker, W. D. Emmons, H. A. Rolewicz, and K. S. McCallum, *Tetrahedron*, **17**, 79 (1962)], which may be regarded as dinitroketenimine exhibits properties that parallel those of cyanoform. It could not be isolated in anhydrous state and infrared data are, consequently, lacking.

(6) R. H. Boyd, *J. Am. Chem. Soc.*, **83**, 4288 (1961).

(7) S. Trofimenko, T. L. Little, and H. F. Mower, *J. Org. Chem.*, **27**, 433 (1962).

(8) F. Arndt, H. Scholz, and E. Frobel, *Ann.*, **521**, 95 (1935).

(9) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).

(10) F. A. Miller and W. K. Baer of Mellon Institute obtained values of 4.60 and 8.05 μ in aqueous solution and 4.60, 7.99, and 8.07 μ in the solid (private communication).

(11) Note: This procedure was found to be most convenient for preparing small samples of dicyanoketenimine. All of the operations must be conducted rapidly, as crude dicyanoketenimine and its concentrated solutions are unstable. Scaling up was not feasible as larger samples were much more prone to polymerize.

Nucleophilic Substitution at the Pyridazine Ring Carbons. I. Synthesis of Iodopyridazines

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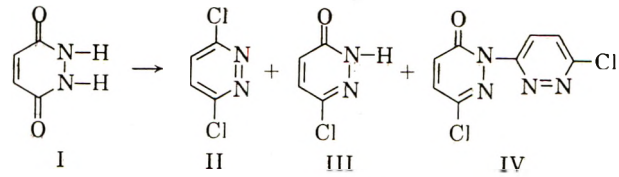
In recent years interest has grown in the chemistry of the substituted pyridazines because of the theoretical aspects of the pyridazine ring system[2,3] and because of biological activity shown by many of these compounds.[4,5] A study of structure-reactivity correlations of substituted pyridazines is being conducted in this laboratory. A general procedure was sought by which satisfactory yields of iodopyridazines could be obtained from readily available starting materials. Previously, Horning and Amstutz[6] reported that substituted iodopyridazines might be formed as by-products in the reduction of highly substituted chloropyridazines with red phosphorus and hydriodic acid.

The route which appeared attractive was the nucleophilic substitution at the ring carbons using chloro- or bromopyridazines as the substrate and iodide ion as the nucleophile since chloro- and bromopyridazines can be prepared by one- or two-step syntheses from commercially available starting materials. For example, maleic hydrazide (I) can be converted to chloro or bromo compounds.

In spite of the fact that the synthesis of 3,6-dichloropyridazine (II) using phosphorus oxychloride is described several times in the literature,[7,8] Feuer and Rubenstein[9] showed by meticulous work that the product from such reactions is contaminated with 3-chloro-6-hydroxypyridazine (III) and to a lesser extent with 1-(3′-chloro-6′-pyridazyl)-3-chloro-6-pyridazone (IV). The over-all yield of pure dichloropyridazine was of the order of 30%. Difficulties in obtaining dichloropyridazine of high purity were also encountered



I II III IV

(1) Participants in Undergraduate Research Training Grant NSFG11835 from the National Science Foundation.

(2) S. F. Mason, *J. Chem. Soc.*, 674 (1958).

(3) S. F. Mason, *ibid.*, 1240 (1959).

(4) J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(5) J. Druey, U.S. Patent 2,764,584 (1956).

(6) R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 707 (1955).

(7) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

(8) M. M. Rogers and J. P. English, U.S. Patent 2,671,086 (1954).

(9) H. Feuer and H. Rubenstein, *J. Org. Chem.*, **24**, 811 (1959).

in this laboratory and it was found that the recrystallization and sublimation process used by Feuer and Rubenstein was difficult and time-consuming since both dichloropyridazine and 3-chloro-6-hydroxypyridazine were recrystallized from the same solvent and both underwent sublimation. Separation of the compounds by vacuum distillation was also inconvenient because of the high melting points of the solids to be collected as distillates. (Dichloropyridazine melts at 66–68° and chlorohydroxypyridazine at 139–140°.) These two compounds have been found in this laboratory to interact under such conditions. Consequently, a method was sought to produce a maximum yield of dichloropyridazine which would be uncontaminated by the pyridazone. Actually, the problem became one of finding correct experimental conditions to minimize the hydrolysis of dichloropyridazine that normally occurs during the neutralization procedure required in the isolation of dichloropyridazine from the crude reaction mixture and to remove any small quantities of III and IV that might be formed. The specific experimental procedure is the result of over two hundred runs to find optimum conditions.[10]

It will be noted that the reaction mixture is triturated by adding small portions to dilute ammonium hydroxide at 0°. This prevents any local heating and consequent hydrolysis of dichloropyridazine. Any traces of III and IV are removed during the cold sodium hydroxide trituration step. Compound III is soluble in 1 *N* sodium hydroxide. Although 3,6-dichloropyridazine reacts rapidly with warm aqueous sodium hydroxide to produce III,[11] the rate of the reaction is very small at 0° or less.

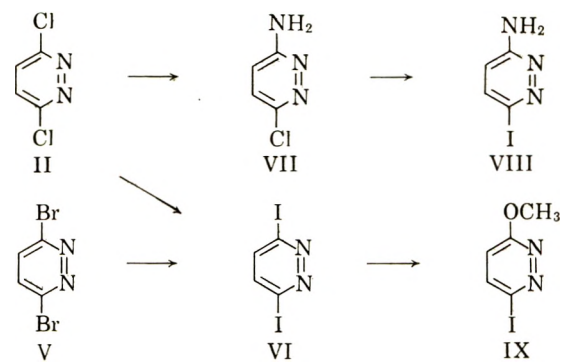
This same type of procedure using triturations in cold ammonium hydroxide and sodium hydroxide has also been used to prepare 3,6-dibromopyridazine, 4 - methyl - 3,6 - dichloropyridazine, 4 - methyl - 3,6-dibromopyridazine, 3,4,6 - trichloropyridazine, and 3,4,5,6 - tetrachloropyridazine in high purity. Therefore, a general procedure for preparation of pure chloro- and bromopyridazines, in which the formation of pyridazones by inadvertant hydrolysis is minimized, has been elucidated and should prove of value for synthetic and theoretical work for which pure compounds are required.

In the preparation of iodopyridazines three different reaction media were used. The first method utilized 50% hydriodic acid with heating under reflux. This took advantage of the solubility of the halopyridazines in acid and a large excess of iodide ion. Bruce and Perez-Medina[12] observed that 2-methyl-3-nitro-4,6-dichloro-5-cyanopyridine was converted to 2-methyl-3-nitro-4,6-diiodo-5-cyanopyridine during an attempted reduction of the nitro group with hydriodic acid and it was thus thought possible that chloro- or bromopyridazines might undergo halogen exchange with hydriodic acid under reflux. This method can, indeed, be used to synthesize iodopyridazines, but there was difficulty in isolation of the products and the yields were not high.

The second method involved the use of acetone with a stoichiometric amount of hydriodic acid. Investigation showed that the driving force behind this reaction was the formation of the insoluble hydroiodide salts of iodopyridazines in this media. The method proved useful for bromopyridazines, but not for chloropyridazines.

The third method, which proved to be superior in nearly all instances, consisted of combining anhydrous acetone solutions of the chloro- or bromopyridazine and sodium iodide with a catalytic amount of hydriodic acid present. This method utilizes the insolubility of sodium bromide and sodium chloride in anhydrous acetone to drive the reaction to completion. The reaction generally will begin without catalysis with bromopyridazines but yields are greatly improved by its use. The chloropyridazines generally fail to react without the addition of hydriodic acid as catalyst. The insoluble sodium halides formed during the course of the reaction provide a convenient method for following the progress of the reaction.

Thus, 3,6-dibromopyridazine (V) and 3,6-dichloropyridazine (II) were converted to 3,6-diiodopyridazine



(VI); 3,6-dichloropyridazine (II) was converted to the hydroiodide of 3-amino-6-iodopyridazine (VIII) by way of 3-amino-6-chloropyridazine (VII); and 3,6-diiodopyridazine was converted to 3-methoxy-6-iodopyridazine (IX).

Experimental

3,6-Dichloropyridazine.—A mixture of 61 g. (0.5 mole) of maleic hydrazide and 200 ml. of freshly distilled phosphorus oxychloride was placed in a 500-ml. three-necked flask equipped with a mechanical stirrer, thermometer, and reflux condenser connected to a sodium hydroxide trap. The mixture was heated on a water bath so that the internal temperature was held at about 70°. (Higher temperatures lead to formation of black viscous material.) The reaction was continued for 1 hr. after the rapid evolution of hydrogen chloride gas ceased, a total of about 3 hr. The excess phosphorus oxychloride was removed by vacuum distillation using a vacuum pump protected with an acetone–Dry Ice trap and a capillary bleed, pressure about 15 mm. The distillation temperature and pressure were adjusted as necessary so that the temperature of the heating bath was never higher than 80°. The sirupy residue was transferred to a beaker and cooled to − 10°.

A mixture of dilute ammonium hydroxide and chipped ice was prepared with a resulting concentration of about 2 *N*. A portion of this was placed in a cold mortar and to it were carefully added very small portions of the crude product for careful trituration. Two factors were frequently checked during this process, pH and temperature. The pH was kept at 8 or higher and the temperature was never allowed to rise above 0°. If the pH became too low, the contents of the mortar were decanted into a beaker and fresh ammonium hydroxide–ice mixture was added to the mortar. If the temperature started to rise, more ice was added.

(10) Trials performed by participants in Summer Science Training Program (1961) and Cooperative College–School Program (1962) sponsored by the National Science Foundation.

(11) S. Du Breuil, *J. Org. Chem.*, **26**, 3382 (1961).

(12) W. F. Bruce and L. A. Perez-Medina, *J. Am. Chem. Soc.*, **69**, 2571 (1947).

This process of triturating very small portions of the product, so small that local heating effects were eliminated, was continued until all of the material had been triturated at pH 8–11 at 0°. The solid was isolated by filtration and rapidly triturated with 100 ml. of cold (0° or less) 1 *N* sodium hydroxide followed by washing with distilled water to pH 7. The crude dichloropyridazine was air dried, 45 g. (60%) and then continuously extracted with petroleum ether (30–60°) to form pure dichloropyridazine, 28.6 g., white needles, m.p. 68–69° (lit.,[7] 68–69°).

3,6-Dibromopyridazine.—A mixture of 100 g. of maleic hydrazide (0.9 mole) and 431 g. (1 mole) of phosphorus pentabromide (prepared by very slow dropwise addition of bromine to phosphorus tribromide or to red phosphorus in a polyethylene flask or in a polyethylene beaker with an inverted glass funnel of appropriate size taped to the top of the beaker) was carefully triturated for 5 min. in a mortar and was quickly transferred to a polyethylene flask equipped with a reflux condenser. The flask was placed in a deep bath of boiling water and heated until evolution of white fumes of hydrogen bromide ceased, approximately 3 hr. The resulting orange solid was triturated as described for dichloropyridazine. The crude 3,6-dibromopyridazine was air dried, 104 g. (49%), and then continuously extracted with ligroin (60–70°) to form 71 g. of pure dibromopyridazine, silky white needles, m.p. 115–116° (lit.,[13] 115–116°).

4-Methyl-3,6-dichloropyridazine.—A mixture of 50 g. (0.4 mole) of citraconic hydrazide and 200 ml. (2.20 moles) of phosphorus oxychloride was stirred and heated as described for dichloropyridazine, triturated in the same manner to obtain 38.5 g. (60%), and then continuously extracted with ligroin (60–70°) to form 31 g. pure 4-methyl-3,6-dichloropyridazine, m.p. 83–84° (lit.,[14] 83.5–84°).

3,4,6-Trichloropyridazine.—Twenty grams (0.13 mole) of 4-chloro-3,6-dihydroxypyridazine prepared by the method of Mizzoni and Spoerri[14] and 75 ml. of phosphorus oxychloride were placed in a 250-ml. Erlenmeyer and heated under reflux in a boiling water bath for 1 hr. after complete solution occurred. The product was isolated in the new manner, dried in a vacuum dessicator, and extracted with petroleum ether to give 8.7 g. (30%) pure 3,4,6-trichloropyridazine, white needles, m.p. 57–58 (lit.,[14] 57–57.5°).

3,4,5,6-Tetrachloropyridazine.—Forty grams of 4,5-dichloro-3,6-dihydroxypyridazine prepared by the process of Pennino[15] was mixed with 150 ml. of phosphorus oxychloride and heated under reflux on a hot plate for 1 hr. after evolution of hydrogen chloride had ceased. Product was isolated as above to give 22 g. (46%) pure 3,4,5,6-tetrachloropyridazine, m.p. 85–86° (lit.[15] 85–86°).

4-Methyl-3,6-dibromopyridazine. Method A.—A mixture of 431 g. (0.1 mole) of phosphorus pentabromide and 84 g. (0.67 mole) of citraconic hydrazide was triturated in a mortar and transferred to a polyethylene flask equipped with a reflux condenser. The mixture was heated in a deep bath of boiling water for 8 hr., and it was then triturated and washed in the usual manner. The precipitate was thoroughly dried in air and in a vacuum oven to constant weight and extracted in a Soxhlet extractor with petroleum ether to give 68.6 g. (42%), white needles, m.p. 104–105°; λ_{max}^{EtOH} 276 mμ, ε 1240.

Anal. Calcd. for $C_5H_4Br_2N_2$: C, 23.81; H, 1.59; Br, 63.49; N, 11.11. Found: C, 24.44; H, 1.32; Br, 61.58; N, 10.89.

Method B.—A mixture of 8.3 g. (0.015 mole) of phosphorus pentabromide and 1.1 g. (0.008 mole) of 5-methyl-3-chloro-6-pyridazone prepared by the method of Linholter, *et al.*,[16] was thoroughly triturated and then heated under reflux on a boiling water bath for 0.5 hr. The mixture was cooled and 15 ml. of ice–water was added in small portions with stirring. The precipitate was collected and recrystallized from ethanol to give 0.4 g. (21%) white crystals, m.p. 104–105°.

Anal. Calcd. for $C_5H_4Br_2N_2$:C, 23.81; H, 1.59; Br, 63.49; N, 11.11. Found: C, 24.03; H, 1.62; Br, 63.68; N, 11.03.

3,6-Diiodopyridazine.—Three methods were developed using 3,6-dibromopyridazine as the starting material.

Method A.—A mixture of 1 g. (0.004 mole) of 3,6-dibromopyridazine and 8.5 ml. (excess) of 50% hydriodic acid was heated under reflux in an oil bath at 130° for 2 hr. The solid was removed by filtration, triturated with cold water, filtered, and dried. The crude solid was recrystallized using methanol–water, 0.4 g. (30%), white crystals, m.p. 157–158°; λ_{max}^{EtOH} 247 mμ, ε 14680.

Anal. Calcd. for $C_4H_2I_2N_2$: C, 14.76; H, 0.63; I, 76.19; N, 8.43. Found: C, 14.71; H, 0.67; I, 76.42; N, 8.29.

Method B.—To a solution of 10 ml. of 50% hydriodic acid dissolved in 25 ml. of acetone heated under reflux was added dropwise 8 g. of 3,6-dibromopyridazine dissolved in 25 ml. of acetone. The mixture was heated under reflux for 15 min. and the bright yellow solid was removed by filtration, 6.38 g., m.p. 171.5–172°. When this solid, the hydroiodide salt of 3,6-diiodopyridazine, was thoroughly triturated with 50 ml. of water, a pale yellow precipitate of 3,6-diiodopyridazine formed, 4.57 g. (41.3%), m.p. 162–163°, a portion of which was rewashed and crystallized from acetone–water, m.p. 157–158°.

Method C.—To a solution of 30 g. (0.2 mole) of sodium iodide dissolved in 150 ml. of dry acetone heated under reflux was added, dropwise with magnetic stirring over a 15-min. period, 23.8 g. (0.1 mole) of dibromopyridazine dissolved in 150 ml. of dry acetone. The reaction was heated and stirred under reflux for 0.5 hr. At the end of this period 2 drops of 50% hydriodic acid dissolved in 5 ml. of acetone were added. The same addition was repeated at half-hour intervals until three portions had been added. Heating was continued for 0.5 hr. after the last addition. The sodium bromide which formed was filtered from the solution and weighed (19.0 g.). An additional 5-ml. portion of the hydriodic acid–acetone solution was added to the filtrate and heated for another half-hour to confirm that the reaction was completed. By concentrating the acetone solution and crystallization there was obtained 25.2 g. (74%) of light tan flaky material, a portion of which was continuously extracted with petroleum ether to give white crystals, m.p. 157–158°.

Two methods were developed using **3,6-dichloropyridazine** as starting material.

Method A.—A mixture of 8.5 g. (0.057 mole) of 3,6-dichloropyridazine and 86 ml. of hydriodic acid was heated in an oil bath for 1 hr. at 150°. The solid was filtered from the solution and recrystallized three times from a mixed solvent of methanol–water to give white crystals, 10.7 g. (56%), m.p. 157–158°.

Method B.—To a solution of 30 g. (0.2 mole of sodium iodide) and 4 drops of 50% hydriodic acid dissolved in 150 ml. of acetone heated under reflux was added, dropwise with magnetic stirring over a period of 10 min., 14.9 g. (0.1 mole) of dichloropyridazine dissolved in 50 ml. of acetone. Two more portions of hydriodic acid–acetone solution were added at half-hour intervals as the mixture was heated under reflux for 2 hr. The precipitate of inorganic salt was removed by filtration, 4.58 g. A solution of 6 g. of sodium iodide, 4 drops of hydriodic acid, and 50 ml. of acetone was added and the solution was heated with stirring for 30 min. The inorganic salt (0.67 g.) was removed by filtration and the filtrate was concentrated to one-third volume by vacuum distillation and water (*ca.* 50 ml.) was added. Crude 3,6-diiodopyridazine, 25.9 g. (77.5%) of tan solid was obtained, a portion of which was extracted using a Soxhlet extractor and petroleum ether as solvent to give fine white needles, m.p. 157–158°.

3-Iodo-6-aminopyridazine Hydroiodide.—3-Amino-6-chloropyridazine was prepared by the procedure described by Steck, Brundage, and Fletcher.[13] One gram of 3-amino-6-chloropyridazine was heated for 1 hr. on a boiling water bath with an excess of 50% hydriodic acid (8 ml.). The crystals that formed were removed by filtration, washed with ethyl acetate, and dried, 0.18 g., m.p. 197–200° (dec.); λ_{max}^{EtOH} 222 mμ, ε 20750; 349 mμ, ε 19200.

Anal. Calcd. for $C_4H_5I_2N_3$: C, 13.75; H, 1.43; I, 72.78; N, 12.03. Found: C, 13.59; H, 1.45; I, 70.12; N, 11.89.

3-Iodo-6-methoxypyridazine.—To a solution of 0.9 g. (0.04 g.-atoms) of sodium in 50 ml. of dry methanol was added a solution of 11 g. (0.03 mole) of 3,6-diiodopyridazine in 200 ml. of methyl alcohol and allowed to stand overnight at room temperature. The solvent was removed at reduced pressure and the residue was dissolved in 50 ml. of ether, washed with two 10-ml. portions of water, and dried over anhydrous sodium sulfate. The ether was evaporated and the resulting solid was recrystallized from ligroin (66–75) to give 4.5 g. (58%) of flat white needles, m.p. 104–105°, λ_{max}^{EtOH} 226 mμ ε 13300; 290 mμ ε 1610.

Anal. Calcd. for $C_5H_5IN_2O$: I, 53.75; N, 11.87. Found: I, 52.47; N, 11.63.

(13) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, **76**, 3225 (1954).

(14) R. H. Mizzoni and P. E. Spoerri, *ibid.*, **76**, 2201 (1954).

(15) C. J. Pennino, U.S. Patent 2,846,433 (1958).

(16) S. Linholter, A. B. Kristensen, R. Rosenorn, S. E. Nielsen, and H. Kaaber, *Acta Chem. Scand.*, **15**, 1660 (1961).

Acknowledgment.—This work was supported in part by a grant from the Research Corporation. We wish to express our thanks to Dr. John E. Campion of Riker Laboratories, Inc., for his interest in this work and to the Analytical Division of Riker Laboratories for nitrogen and halogen analyses and spectra.

Organotin Chemistry. III.[1] Dibutyltin Diphenoxide

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Dialkyltin diphenoxides have been mentioned in the literature[2] but there are no details of the synthesis or characterization of a member of this class of materials. We prepared dibutyltin diphenoxide (I) by the action of sodium phenoxide on dibutyltin dichloride in heptane (1). The product is extremely sensitive to adventitious moisture and in order to prepare it, extreme care to exclude the atmosphere had to be exercised.

$$(n\text{-}C_4H_9)_2SnCl_2 + 2C_6H_5O^{\ominus}, Na^{\oplus} \longrightarrow (n\text{-}C_4H_9)_2Sn(OC_6H_5)_2 + 2NaCl \quad (1)$$

The diphenoxide I was hydrolyzed by water (2) to give tetrabutyl-1,3-diphenoxydistannoxane II in 95%

$$4Bu_2Sn(OC_6H_5)_2 \xrightarrow{H_2O} \underset{\text{II}}{\{[(n\text{-}C_4H_9)_2SnOC_6H_5]_2O\}_2} \quad (2)$$

$$2Bu_2Sn(OC_6H_5)_2 + 2Bu_2SnO \longrightarrow \text{II} \quad (3)$$

yield. II was also prepared by the reaction of dibutyltin oxide and I (3). The distannoxane II exist as a dimer.[1]

Experimental[3]

Dibutyltin Diphenoxide (I).—Sodium metal (46.0 g., 2 g.-atoms) was dissolved, during stirring, in 1 l. of absolute methanol contained in a three-necked flask provided with a nitrogen atmosphere, a drying tube, and a reflux condenser, with a Dean–Stark apparatus and mechanical stirring. To the freshly prepared solution of sodium methoxide, phenol (188.2 g., 2 moles) was added and the reaction mixture was refluxed for 2 hr. One liter of anhydrous heptane was then added and the methanol was removed by azeotropic distillation, and separation, in the Dean–Stark apparatus. Complete removal of methanol took some 18 hr. of reflux. Replenishment of the heptane lost by its solubility in methanol was made by periodic additions. As the stripping proceeded, a white solid, (sodium phenoxide) precipitated.

During stirring, a solution of dibutyltin dichloride (303.8 g., 1 mole) was added and the reaction mixture refluxed for 4 hr. The mass was then allowed to cool and the solids (NaCl) separated by vacuum filtration on a Büchner funnel, under a blanket of nitrogen; they were washed with 250 ml. of anhydrous heptane and air dried. These solids weighed 121.7 g. (104%, 2.08 moles).

The filtrate and heptane wash were combined and the heptane removed by vacuum distillation to give an orange oil which crystallized on cooling; yield 379.8 g. (90%; 0.90 mole). The crude yield was divided into two portions and characterized separately by both recrystallization and distillation.

Repeated recrystallizations from anhydrous pentane gave white crystals with a constant m.p. of 45–48° (sealed capillary).

Anal. Calcd. for $C_{20}H_{28}SnO_2$:Sn, 28.32; mol. wt., 419.12. Found: Sn, 28.47; mol. wt. (Thermistor Osmometer), 415.

Repeated vacuum distillations of a portion of the crude gave white crystalline material; b.p. 161°/0.35 mm.

Anal. Calcd. for $C_{20}H_{28}SnO_2$: Sn, 28.32. Found: Sn, 28.42.

The infrared spectra of the two materials were identical.

Carbon and hydrogen analyses gave erratic results which were ascribed to hydrolysis by adventitious moisture during shipping and handling. Attempts to titrate the material with alkali gave very poor end points. Therefore, a quantitative saponification was done in order to provide a second reliable analytical determination. The sample was saponified with alcoholic potassium hydroxide and the dibutyltin oxide isolated, washed with acetone, dried, and weighed. The results are expressed as % dibutyltin oxide (% Bu_2SnO). For the material purified by recrystallization:

Anal. Calcd. for $C_{20}H_{28}SnO_2$: % Bu_2SnO, 59.39. Found: % Bu_2SnO, 58.72.

For the material purified by distillation:

Anal. Calcd. for $C_{20}H_{28}SnO_2$: % Bu_2SnO, 59.39. Found: % Bu_2SnO, 58.28.

Hydrolysis of Dibutyltin Diphenoxide.—Dibutyltin diphenoxide (4.19 g., 10 mmoles) was stirred for 2 hr. with 100 ml. of water. The white solid was isolated by filtration, washed with water, pressed dry, and dried over phosphorus pentoxide *in vacuo;* yield 3.17 g. (2.4 mmoles, 95%). Recrystallization from hexane gave tetrabutyl-1,3-diphenoxydistannoxane; m.p. 137–139° (lit.[1] 137–139.5°), undepressed when mixed with authentic material. The infrared spectra and X-ray powder patterns were identical with those of an authentic sample.

Reaction of Dibutyltin Diphenoxide with Dibutyltin Oxide.—Dibutyltin oxide (6.23 g., 25 mmoles) was added to a solution of dibutyltin diphenoxide (10.48 g., 25 mmoles) in 125 ml. of anhydrous benzene. During stirring, the mixture was heated to boiling to achieve complete solution. The only slightly hazy solution was filtered while hot and the benzene removed by vacuum distillation.

A white crystalline solid was obtained in 99% yield (16.5 g., 12 mmoles). After one recrystallization from hexane, the melting point was 137–139.5° (lit.,[1] 137–139.5); it was undepressed when mixed with authentic material. The infrared spectra and X-ray powder patterns were identical with those of an authentic sample of tetrabutyl-1,3-diphenoxydistannoxane.

Acknowledgment.—The analyses were performed by Mr. H. Corbin and his associates with the exception of the C,H determinations which were done by Spang Microanalytical Laboratory, Ann Arbor, Michigan. The molecular weights and spectra were determined by Mr. I. Simmons and his associates.

(1) Paper II, Wm. J. Considine, J. J. Ventura, A. J. Gibbons, Jr., and A. Ross, *Can. J. Chem.*, in press.

(2) See R. Ingham, S. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

(3) All melting points are uncorrected.

Photodimerization of a Pseudoxazolone[1,2]

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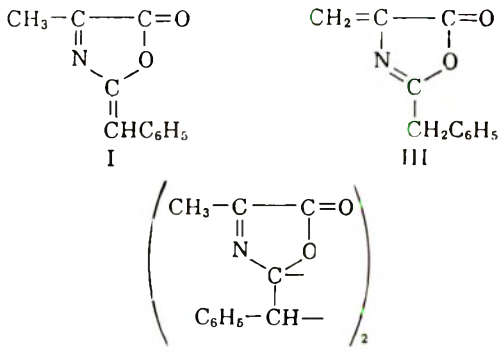
Pseudoxazolones[(5-[2H]oxazolones)] have been postulated by Bergmann[3] as intermediates in the formation of 5-[4H]oxazolones from N-(α-haloacyl)amino acids. A few pseudoxazolones have been isolated, of which only 2-benzylidene-4-methylpseudoxazolone (I) has received much attention. Ring closure of N-(α-chlorophenylacetyl)alanine (II) gives compound I, for which a

(1) This work was supported by a research grant from the National Science Foundation (G-9985).

(2) Abstracted, in part, from the Ph.D. thesis of E. J. Piasek, Illinois Institute of Technology, June, 1962.

(3) M. Bergmann and F. Stern, *Ann.*, **448**, 20 (1926).

variety of melting points (106–109°,[4] 122–123°,[5] and 155–170°[6]) have been reported. This variability might be due to the presence of the tautomeric 5-[4H]oxazolone (III), although geometric isomerism about the exocyclic double bond has been suggested.[7] Our research was, therefore, directed toward clarifying this point.



I III

IV

When compound II was treated with acetic anhydride in pyridine, a yellow solid, melting range 109–125°, was obtained. Compound I, m.p. 109–111°, was isolated from this material by sublimation. The intense infrared absorption at 1785 cm.$^{-1}$ is due to the lactone carbonyl group. The ultraviolet maxima at 240 mμ (ε 8640) and at 356 mμ (ε 33,200) are also consistent with the structure of I ($C_6H_5CH=C<$[8] and $C_6H_5CH=C-N=C-C=O$ chromophores, respectively).

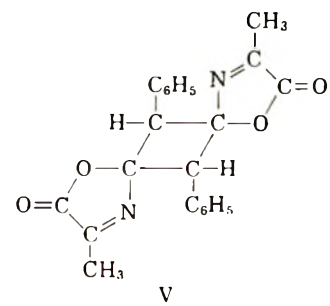
A white material (IV) remained after sublimation of I. Crystallization from a solution of methylcyclohexane and chloroform gave a substance, m.p. 209–210°, whose elemental analysis and molecular weight indicated that it was a dimer. On standing in ordinary light for several days, I developed a white crust, which was shown to be this dimer. Moreover, when I was irradiated with sunlight or ultraviolet light, the rate of dimer formation was markedly enhanced. That the dimerization is light-catalyzed was further substantiated by the absence of IV after a freshly prepared sample of I was placed in an opaque container.

In contrast to I, compound IV exhibited only end absorption in the ultraviolet, but possessed infrared bands at 1785 cm.$^{-1}$ and 1650 cm.$^{-1}$ (>C=N). The absence of ultraviolet absorption indicated that the chain of conjugation had been broken, presumably at the styryl moiety. The infrared spectrum suggested that the conjugation of the α,β-unsaturated carbonyl system remained intact, for the carbonyl group of the dimer absorbed at the same frequency as did the monomer.

Of several possibilities, only a cyclobutane structure for IV was in reasonable accord with the spectral data. The proton magnetic resonance spectrum of the dimer gave further support for this structure, since three kinds of hydrogen were found at τ = 2.6, 4.97, and 7.64. The broad band at 2.6 is attributed to the aromatic protons.[9] The bands at 4.97 and 7.64 appeared as sharp singlets in the intensity ratio of 1:3. The latter band may be assigned to the protons of a methyl group which is α to the double bond of an oxazole ring (τ = 7.60[10]), while the former is in agreement with values of 5–6 observed for highly deshielded protons of a substituted cyclobutane ring.[11,12]

The formation of cyclobutane compounds by photodimerization of conjugated carbonyl systems is well established.[11,13–15] Of special interest is the dimerization of benzylidene phthalide.[16] This dimer is so similar to IV that its formation provides supportive analogy for the proposed cyclobutane structure.

The n.m.r. spectrum does not supply sufficient evidence to allow a choice of stereoisomers of IV. However, the lack of line splitting militates against structures in which the cyclobutane ring protons are nonequivalent. One is tempted to favor a structure V, in which the monomers have added in a head to tail arrangement so as to place the phenyl groups *trans* to one another. However, it is recognized that in solid-state reactions, crystal geometry is an important consideration in determining the stereochemistry of the product.



V

Experimental[17]

2-Benzylidene-4-methylpseudoxazolone (I).—Twenty grams (0.083 mole) of N-(α-chlorophenylacetyl)alanine[5] was added to a solution of 60 ml. of pyridine (dried over potassium hydroxide) in 300 ml. of acetic anhydride. After 30 min., the contents were poured over 500 g. of ice, the mixture was stirred well, and the light yellow solid thus obtained was dried *in vacuo* for several days to give 13.8 g. (84.2%) of pseudoxazolone, m.p. 109–120° (reported m.p. 105–115[5]). This material was sublimed at 68° (1 mm.) to yield a yellow solid, m.p. 109–111°, λ_{max}^{EtOH} 240 (ε 8640) and 356 mμ (ε 33,200); $\nu_{max}^{CH_2Cl_2}$ 1785, 1680, and 1660 cm.$^{-1}$. Further sublimations failed to improve the melting point.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.84; N, 7.48; mol. wt., 187. Found: C, 70.58; H, 5.08; N, 7.68; mol. wt. (Rast), 187.

Photodimer (IV).—Dry, freshly prepared pseudoxazolone (1.48 g.) was placed in a vacuum desiccator and after 1 week a white solid had formed on its surface. The solid was sublimed at 80° (1 mm.) until only 37 mg. (2.5%) of white residue, m.p. 130–210°, remained. Crystallization of this solid was difficult to achieve, but the following procedure proved to be adequate: The crude product was dissolved in chloroform and methylcyclohexane was added so as to induce cloudiness. The satu-

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(6) M. Brenner and K. Rufenacht, *Helv. Chim. Acta*, **37**, 203 (1954).

(7) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 375.

(8) D. A. Bassi, V. Deulofeu, and A. F. Ortega, *J. Am. Chem. Soc.*, **75**, 171 1953).

(9) H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N.Y., 1960, p. 291.

(10) P. Yates and E. S. Hand, *Tetrahedron Letters*, No. **19**, 669 (1961).

(11) G. W. Griffin, A. F. Vellturo, and K. Furukawa, *J. Am. Chem. Soc.*, **83**, 2725 (1961).

(12) J. Corse, M. J. Finkle, and R. E. Lundin, *Tetrahedron Letters*, No. **1**, 1 (1961).

(13) A. Mustafa, *Chem. Revs.*, **51**, 1 (1952).

(14) E. C. Taylor and W. W. Paudler, *Tetrahedron Letters*, No. **25**, 1 (1960).

(15) R. Anet, *Chem. Ind.* (London), 897 (1960).

(16) A. Schönberg, N. Latif, R. Moubasher, and W. I. Awad, *J. Chem. Soc.*, 374 (1950).

(17) Melting points were determined on a Fisher–Johns block and are uncorrected.

rated solution was heated to boiling on a steam bath and clarified with charcoal. The volume of solution was reduced by air blowing while the sides of the flask were scratched vigorously. When a substantial amount of solid had separated, the contents were filtered under suction and the solid was dried under reduced pressure. Additional solid was obtained from the filtrate by repeating the above procedure. The photodimer was crystallized twice to yield a white solid, m.p. 209–210°, λ_{max}^{EtOH} only end absorption, $\nu_{max}^{CH_2Cl_2}$ 1785 and 1650 cm.$^{-1}$.

Anal. Calcd. for $(C_{11}H_9NO_2)_2$: C, 70.58; H, 4.84; mol. wt., 374.4. Found: C, 70.77; H, 5.18; mol. wt. (Rast), 386.

The rate of photodimerization was significantly increased by irradiation of the pseudoxazolone with visible or ultraviolet light. Two grams of I was placed on a sheet of aluminum foil and spread out to allow maximum surface exposure. The pseudoxazolone was irradiated with ultraviolet light (quartz lamp) for 2 days with frequent mixing of the solid in order to provide a fresh surface. Sublimation of the irradiated product gave 0.3 g. (15%) of dimer. The process was repeated to give additional product.

Infrared spectra were obtained on a Perkin–Elmer Model 21 double beam spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were measured with a Beckman DK-2 recording spectrophotometer. Proton magnetic resonance spectra were determined on a Varian Associates A-60 spectrometer.

Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Illinois.

Polymerization of Two Atom-bridged Bicyclic Amines

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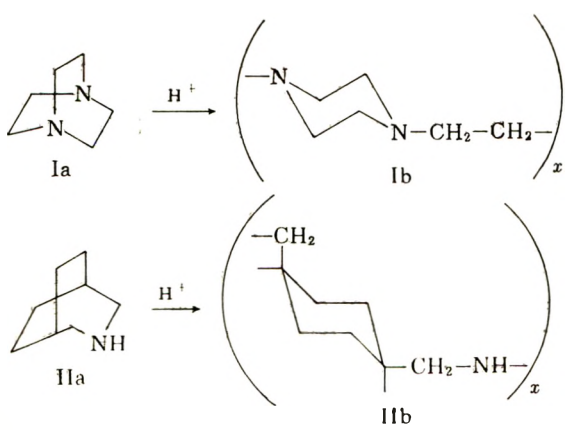
Relatively few ring-opening polymerizations of cyclic amines have been described. Ethylenimine polymerizes very readily[1] as would be expected for a highly strained ring. Pyrrolidine, piperidine, and hexamethylenimine were reported by Friederich[2] to give low polymers when heated with acid. Cope and Shen[3] polymerized 2,6-diazabicyclo[3.3.0]octanes to polybutyleneamines with boron trifluoride, while two groups[4,5] have reported the polymerization of the bond-bridged monomer 1-azabicyclo[4.2.0]octane.

On the basis of our earlier work[6] on ring-opening polymerization of atom-bridged bicyclic compounds, it was predicted that 1,4-diazabicyclo[2.2.2]octane Ia and 3-azabicyclo[3.2.2]nonane IIa should be polymerizable to ring-containing polyamines:

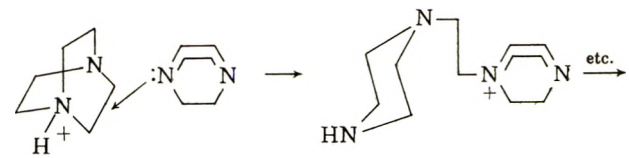


This proved to be the case.

Heating 1,4-diazabicyclo[2.2.2]octane for 10.7 hours at 200° with 0.073 mole % of benzenesulfonic acid converted the monomer to poly-1,4-ethylenepiperazine in 96% yield. The polymer Ib was a white, highly crystalline solid melting above 350° with decomposition.

3-Azabicyclo[3.2.2]nonane IIa polymerized less readily. Heating the monomer with 0.46 mole % of benzenesulfonic acid for 71 hours at 222° gave a 32% yield of polymer IIb, m.p. 115–130°.

The mechanism of the acid-catalyzed polymerization of amines probably involves nucleophilic attack by one amine molecule on the protonated or alkylated form of another:



Henecka and co-workers[7] have described analogous ring-openings of bicyclic ammonium ions by nucleophiles.

The strains which cause these bicyclic amines to polymerize are caused by repulsions between nonbonded hydrogens. The parent hydrocarbon bicyclo[2.2.2]-octane exists in a two-boat form.[8] The repulsions of the hydrogens in the bridges destabilize the molecule. Since 1,4-diazabicyclooctane exists in the same conformation and is similarly destabilized, its tendency to polymerize is expected. 3-Azabicyclo[3.2.2]nonane undergoes polymerization less readily because it thereby relieves only one strained boat cyclohexane ring by converting it to a chair form.

Experimental

Monomers.—1,4-Diazabicyclo[2.2.2]octane was obtained from the Houdry Process Corporation and 3-azabicyclo[3.2.2]nonane from the Tennessee Eastman Co. Both were sublimed at 100° (15 mm.) before use.

For convenience in manipulation the benzenesulfonic acid was supplied as the salt of the amine.

Catalysts.—The di(hydrobenzenesulfonate) of Ia was prepared by mixing 35.3 g. (0.20 mole) of redistilled benzenesulfonic acid and 11.22 g. (0.10 mole) of diazabicyclooctane in 350 ml. of ethyl acetate. The white precipitate was filtered and recrystallized from 800 ml. of ethanol to give 31.6 g. (73.7%) of white crystals of the di(hydrobenzenesulfonate), m.p. 297° on a heated bar.

Anal. Calcd. for $C_{18}H_{24}O_6N_2S_2$: C, 50.5; H, 5.64; N, 6.54. Found: C, 48.90, 49.02; H, 5.55, 5.59; N, 6.53, 6.64.

The hydrobenzenesulfonate of II was prepared by mixing 12.62 g. (0.1 mole) of amine and 15.82 g. (0.10 mole) of redistilled

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(6) H. K. Hall, Jr., *ibid.*, **80**, 6412 (1958).

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benzenesulfonic acid in 125 ml. of ethyl acetate. The precipitate was crystallized from ethyl acetate–ethanol (8:1) to give 19.9 g. (70.3%) of very slightly pink crystals, m.p. 123.5–124.5°.

Anal. Calcd. for $C_{14}H_{21}O_3NS$: C, 59.33; H, 7.47; N, 4.94. Found: C, 59.19, 59.07; H, 7.32, 7.30; N, 4.70, 4.69.

Polymerizations.—The amine and catalyst were weighed into a 23 × 196 mm. test tube under nitrogen. This was chilled to −80°, alternately evacuated and flushed with nitrogen, and was finally evacuated and sealed. The ampules were suspended in the vapor of boiling *m*-cresol or methyl salicylate to maintain them at 200° or 222°, respectively. They were shaken after a few minutes to ensure dissolution of the catalyst.

Under these conditions, a mixture of 10.0 g. of 1,4-diazabicyclooctane and 27.8 mg. of its di(hydrobenzenesulfonate) polymerized rather quickly at 200°. A solid white plug was noted after 1 hr., but heating was continued for an additional 9.7 hr. The tough white plug was broken up with a knife and hammer and extracted with ether to give 9.60 g. (96%) of white polymer, η_{inh} (*m*-cresol) 1.90. On a heated bar it blackened at 250° but did not melt below 390°.

Anal. Calcd. for $(C_6H_{12}N_2)_x$: C, 64.24; H, 10.79; N, 25.0. Found: C, 63.75, 63.76, 63.58, 63.48; H, 10.40, 10.47, 10.51, 10.41; N, 24.0, 24.3, 24.7.

A mixture of 10.0 g. of 3-azabicyclo[3.2.2]nonane and 105.1 mg. of its di(hydrobenzenesulfonate) became sirupy when heated for 71 hr. at 222°. Cooling, extraction of the product with ether, and drying gave 3.20 g. (32%) of white polymer, polymer melt temperature 115–130°.

Anal. Calcd. for $(C_8H_{16}N)_x$: C, 77.99; H, 10.63. Found: C, 75.95, 75.72; H, 11.79, 11.77.

The polymer appeared to be hygroscopic.

Polymer Properties.—Poly-1,4-ethylenepiperazine was obtained as an extremely crystalline white solid, insoluble in nonpolar organic solvents. A typical sample had an inherent viscosity of 1.06 in *m*-cresol and 2.11 in 99% formic acid. The end groups were determined by reaction with 2,4-dinitrofluorobenzene. A polymer of inherent viscosity 1.77 had a number average molecular weight of 8800, assuming reaction at only one end of the chain. The infrared spectrum was very similar to that of the model compound, N,N′-dimethylpiperazine. It showed small amounts of NH and NH^+ but no vinyl groups, so that no ring cleavage had occurred. Refluxing the polymer with aqueous alkali did not decrease its inherent viscosity, so that cross-links by quaternary ammonium linkage were not present.

The polyamine from 3-azabicyclo[3.2.2]nonane had inherent viscosities of 0.30 in *m*-cresol, 0.37 in tetrafluoropropanol, and 0.46 in 99% formic acid.

Acknowledgment.—The author is deeply indebted to Mrs. Nancy Abbadini and Mr. V. Good for excellent technical assistance and to Dr. S. A. Sundet for helpful encouragement.

2,2′-Diindoxyls

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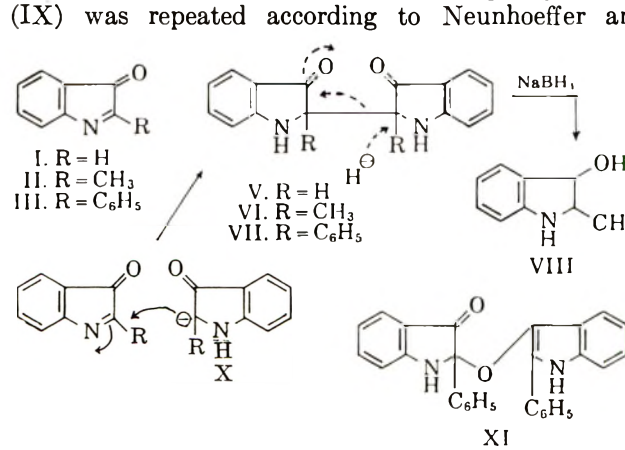
Received July 20, 1962

Indoxyl has long been known to be converted to indigo by air in the presence of sodium hydroxide,[2] but the presumed intermediate indoleninone (I) has never been isolated. Recently Neunhoeffer and Lehmann[3] reported the isolation of what they believed to be an indoleninone, namely 2-methylindoleninone (II), as a stable compound. The compound had a molecular weight of 280 in boiling dioxane (calcd. 147) and no spectroscopic data were reported to substantiate the assigned structure. The indoleninone was obtained from ethyl α-(2-carbethoxyanilino)propionate upon Dieckmann condensation, decarbethoxylation and air oxidation of the intermediate 2-methylindoxyl without isolation of intermediates.[2] Our experience with 2-substituted indoxyls[4] suggested that compounds of type II are very unstable and can not be isolated. Furthermore, in 1912, Kalb and Bayer[5] reported 2-phenylindoleninone as a red solid unstable to water or base, while Neunhoeffer[3] claimed the isolation from aqueous sodium hydroxide of both 2-phenyl- and 2-methylindoleninone as yellow stable materials.

The preparation of Neunhoeffer's "2-methylindoleninone," m.p. 174°, was repeated but the product, m.p. 174°, showed strong N–H absorption at 3400 cm.$^{-1}$ and carbonyl absorption at 1680 cm.$^{-1}$. The ultraviolet spectrum of the product displayed peaks at 395, 255, and 235 mμ characteristic of 2,2-disubstituted indoxyls.[6] The n.m.r. spectrum of the product in deuterated dimethylsulfoxide showed a singlet at 8.52 τ (isolated CH_3) and a weak singlet at 6.74 τ (NH) which shifted on addition of acetic acid. Molecular weight determination (289 ± 30; calcd. 292) confirmed a dimeric structure such as 2,2′-dimethyl-2,2′-diindoxyl (VI). Reduction of diindoxyl VI with sodium borohydride yielded 2-methyl-3-hydroxyindoline (VIII) which gave a positive ferric chloride test. Molecular weight determination showed VIII to be a monomer and this fact was confirmed by n.m.r. A possible path for cleavage of VI on hydride reduction is indicated by dotted arrows. Acidification of hydroxyindoline VIII yielded authentic 2-methylindole.

When the preparation of "2-phenylindoleninone" from ethyl α-(2-carbethoxyanilino)-α-phenylacetate (IX) was repeated according to Neunhoeffer and



Lehmann,[3] the product obtained was 2,2′-diphenyl-2,2′-diindoxyl (VII), m.p. 180–181°, rather than 2-phenylindoleninone, m.p. 102°. Kalb and Bayer[5] had observed that 2-phenylindoleninone (III) reacts readily with 2-phenylindoxyl (X) in basic solution to yield a dimer, m.p. 180°, for which they favored structure XI over VII. Both VI and VII were prepared by analogous methods and showed similar infrared and ultraviolet absorptions. This and the fact that diindoxyl VII lacked absorption characteristic of an indole chromophore at 280–290 mμ, render structure XI improbable.

The primary product expected from ring closure of diester IX followed by decarboxylation is 2-phenylin-

(1) Parke, Davis Research Fellow 1961–1962.

(2) *Cf.* P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. III, R. C. Elderfield, ed., J. Wiley and Sons, New York, N. Y., 1952.

(3) O. Neunhoeffer and G. Lehmann, *Ber.*, **94**, 2960 (1961).

(4) A. Hassner and M. J. Haddadin, *Tetrahedron Letters*, No. **21**, 975 (1962).

(5) L. Kalb and J. Bayer, *Ber.*, **45**, 2150 (1912).

(6) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2188 (1951).

doxyl (X. R = C_6H_5). Partial air oxidation of the latter to 2-phenylindoleninone (III) and immediate addition of the anion of X to indoleninone III in basic solution, as indicated above, can be postulated to explain the formation of 2,2′-diphenyl-2,2′-diindoxyl (VII). A similar path would explain the conversion of indoxyl (X. R=H) to indigo, via leucoindigo V.[7] While leucoindigo (V) is known[8] to air oxidize very readily to indigo, such a process is impossible for the substituted indoxyls VI and VII.

Experimental

All melting points are uncorrected. Analyses were performed by A. Bernhard, Muelheim, Germany. Infrared spectra were run in potassium bromide on a Beckman IR-5 instrument. Ultraviolet spectra were obtained in methanolic solutions. N.m.r. spectra were determined at 60 Mc. in deuteriochloroform, with tetramethylsilane as an internal standard, on a Varian A-60 spectrometer. Molecular weight determinations were obtained in benzene solution on a Mechrolab vapor pressure osmometer Model 301A.

2,2′-Dimethyl-2,2′-diindoxyl (VI).—Ethyl α-(2-carbethoxyanilino)propionate, b.p. 158–164°/3 mm. (lit.,[3] b.p. 196–202°/12 mm.) was prepared by anhydrous esterification of N-(2-carboxyphenyl)alanine (m.p. 209–211° dec.; ν_{max} 3350, 3300–2500, 1725, 1680, 1570 and 1520 cm.$^{-1}$; lit.,[3] m.p. 208–210°) or by esterification of ethyl α-(2-carboxyanilino)propionate, m.p. 95–102°, obtained in 85% yield from anthranilic acid and ethyl α-bromopropionate in neutral solution at 70°.

A solution of ethyl α-(2-carbethoxyanilino)propionate and sodium ethoxide in anhydrous ethanol was heated for 30 min. and poured into water. Aqueous hydrogen peroxide was added and VI was obtained as a yellow precipitate in 88% yield. It was crystallized from methanol–water and melted at 174–176°; reported[3] as II, m.p. 174°. If the reaction solution was poured into dilute hydrochloric acid or into water that was kept in an oxygen-free nitrogen atmosphere the same product (VI) slowly precipitated.

ν_{max} 3280 (NH, sharp and strong), 1675 and 1610 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3400 (NH), 1680, 1610, and 1580 cm.$^{-1}$. λ_{max} 395, 255 (shoulder), and 235 mμ (ε 6080, 17000 and 45300 respectively). Mol. wt.: 289 ± 30 (calcd. 292). N.m.r. singlet at 8.52 τ (CH_3) and weak singlet at 6.74 τ (NH) which shifts on addition of two drops of acetic acid.

Anal. Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.50; H, 5.63; N, 9.41.

2-Methyl-3-hydroxyindoline (VIII).—To a solution of 1.0 g. of diindoxyl (VI) in 200 ml. of methanol there was added 3 g. of sodium borohydride. The yellow color of the solution disappeared within 3 hr. The solution was evaporated under reduced pressure and the colorless residue was diluted with water and extracted thoroughly with ether. The dried ether extract upon evaporation yielded an oil that solidified on standing (0.92 g.).

Crystallization of the product from ether in the cold or from ether–petroleum ether (b.p. 30–60°) furnished fine white needles of 2-methyl-3-hydroxyindoline (VIII), m.p. 92–94°. The product gave a red coloration with ferric chloride in methanol within 30 min. at room temperature. Mol. wt.: 156 ± 4 (calcd. 147). The n.m.r. spectrum showed two doublets in the methyl region at 8.75 and 8.82 τ (J = 6.5 and 4 c.p.s., respectively) with approximate relative intensities of 1:4. The proton at C-3 was found at 5.35 and 5.46 τ (J = 6.5 and 4 c.p.s. respectively) and in approximate relative intensities of 1:4. This is in accord with a 1:4 ratio of *cis-trans* isomers in VIII.[9] The N—H and O—H absorption appeared as a single concentration-dependent peak in the 7–7.5 τ region. ν_{max} 3200–3000 (NH, OH, broad) and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{11}ON$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.23; H, 7.45; N, 9.30.

Conversion of 2-Methyl-3-hydroxyindoline (VIII) to 2-Methylindole.—Five drops of 1 *N* hydrochloric acid were added to a solution of 35 mg. of 2-methyl-3-hydroxyindoline (VIII) in 2 ml. of methanol. After 5 min. the solution was made basic with 5% sodium hydroxide and the turbid solution was extracted with ether. The dried ether solution was evaporated on a steambath to leave an oil that solidified on cooling (29 mg.). Crystallization from methanol–water gave needles of 2-methylindole, m.p. 59–59.5°. Admixture with authentic 2-methylindole showed no depression in melting point. The infrared spectrum of the product was superimposable with that of authentic 2-methylindole.

Ethyl α-Bromo-α-phenylacetate.—This ester, b.p. 115° at 3 mm. (lit.,[10] b.p. 150–151° at 10–15 mm.), was prepared by addition of bromine (30 g.) to a solution of 1 g. of phosphorus pentachloride in 20 g. of phenacetyl chloride on the steambath and pouring the reaction mixture after 48 hr. into absolute ethanol.

Ethyl α-(2-Carboxyanilino)-α-phenylacetate.—Anthranilic acid (15.4 g.) was dissolved in a solution containing 1 equivalent of sodium hydroxide and 27 g. of ethyl α-bromo-α-phenylacetate was added. The mixture was stirred and warmed to 45° for 5 min. and the precipitated white solid was collected by filtration (38 g., m.p. 174–176°). The product was soluble in 5% sodium hydroxide and in concd. hydrochloric acid. On recrystallization from methanol–water ethyl α-(2-carboxyanilino)-α-phenylacetate was obtained in shiny white needles that melted at 180–181°. The compounds exhibits blue fluorescence in methanol. ν_{max} 3400 (NH), 2700–2500 (carboxy OH), 1725 (ester C=O) and 1670 cm.$^{-1}$ (carboxy C=O).

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.29; H, 5.71; N, 4.58.

Ethyl α-(2-Carbethoxyanilino)-α-phenylacetate (IX).—Esterification of ethyl α-(2-carbethoxyanilino)-α-phenylacetate with ethanol in the presence of hydrogen chloride led to diester IX as white needles, m.p. 80–81° (lit.,[3] m.p. 72°). ν_{max} 3410, 1725, 1670 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.08; H, 6.40; N, 4.45.

2,2′-Diphenyl-2,2′-diindoxyl (VII).—To a solution of 1.5 g. of sodium in 30 ml. of absolute ethanol there was added 6 g. of ethyl α-(2-carbethoxyanilino)-α-phenylacetate (IX). The solution was heated under reflux for 40 min. At the beginning the solution developed a deep red color which later turned yellow. The cooled solution was poured into ice–water into which a stream of air was bubbled, and an immediate yellow precipitate appear. After 15 min. of stirring the yellow solid was collected by filtration, washed, and dried to give 2 g. (80%) of crude product m.p. 140–150°. After crystallization from methanol–water and then from benzene 2,2′-diphenyl-2,2′-diindoxyl (VII) melted at 180–182°, with reddening at 175° (lit.,[5] for VII or XI, m.p. 178–180°, with reddening at 178°). ν_{max} 3500 (NH), 1675 (conj. C=O) and 1620 cm.$^{-1}$. Mol. wt. 400 ± 12 (calcd. 406). λ_{max} 400, 260, and 233 mμ (ε 5600, 15000, and 61000, respectively).

Acknowledgement—Financial support of this work by the National Cancer Institute (Grant Cy-4474) is gratefully acknowledged.

(7) In this connection the isolation by E. Giovannini and Th. Lorenz, *Helv. Chim. Acta*, **40**, 1553 (1957), of indigo, presumably *via* leucoindigo, as a minor product in the reduction of isatin with lithium aluminum hydride should be mentioned.

(8) W. Manchet and J. Herzog, *Ann.*, **316**, 318 (1901).

(9) A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962), have shown that, in five-membered ring *N*-containing heterocycles, $J_{cis} > J_{trans}$ and the protons absorb at higher field in the *trans* isomer than in the *cis* isomer.

(10) N. Zelinsky and L. Buchstab, *Ber.*, **24**, 1877 (1891).

The Synthesis of Organolead–Sulfur Compounds

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Although compounds of the type $(Alk)_3PbSR$ have been described,[2] the corresponding $(C_6H_5)_3PbSR$ deriv-

(1) Research Fellow sponsored by The Lead Industries Association, 292 Madison Ave., New York, N. Y.

(2) (a) H. McCombie and B. C. Saunders, *Nature*, **159**, 491 (1947); (b) B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 919 (1949); (c) R. Heap and B. C. Saunders, *ibid.*, 2983 (1949); (d) R. Heap, B. C. Saunders, and G. J. Stacey, *ibid.*, 658 (1951).

TABLE I
SYNTHESIS OF $(C_6H_5)_3PbSR$ COMPOUNDS[a]

	M.p., °C.	Mol. wt. (calcd./found)	Yield, %	Analyses (calcd./found) C	H	S	Pb
$(C_6H_5)_3Pb—S—CH_3$	108–109°	486	100	46.99	3.74	6.60	42.67
		510		47.13	3.96	6.22	42.75
$(C_6H_5)_3Pb—S—C_2H_5$	67–68°	500	96	48.08	4.04	6.41	41.47
		518		48.22	4.08	6.20	41.50
$(C_6H_5)_3Pb—S—C_3H_7$	57–58°	514	95	49.10	4.32	6.24	40.34
		551		49.22	4.38	5.94	40.20
$(C_6H_5)_3Pb—S—C_4H_9$	Liquid $n^{20}D$ 1.6500	528	78	50.07	4.59	6.08	39.27
		534		50.35	4.52	5.68	38.86
$(C_6H_5)_3Pb—S—CH_2C_6H_5$	82–83°	562	95	53.45	3.95	5.71	36.89
		577		53.72	4.12	5.54	36.77
$(C_6H_5)_3Pb—S—C_6H_5$	106–107°	548	94	52.64	3.68	5.86	37.84
		556		52.67	3.78	5.89	37.42
$(C_6H_5)_3Pb—S—\overset{O}{\overset{\|\|}{C}}—CH_3$	92–93°	514	79	46.76	3.53	6.24	40.34
		511		46.85	3.63	6.11	40.17
$(C_6H_5)_3Pb—S—\overset{O}{\overset{\|\|}{C}}—C_6H_5$	93–94°	576	86	52.16	3.50	5.57	35.99
		578		52.31	3.62	5.51	36.37

[a] Melting points were determined using a Thomas-Hoover melting point apparatus and are corrected. Molecular weights were determined using a Mechrolab vapor pressure osmometer Model 301A (benzene solvent).

atives, with the exception of $[(C_6H_5)_3Pb]_2S$,[3] are not known. We have investigated synthetic methods for these compounds and have obtained alkylthio, arylthio, acetylthio, and aroylthio derivatives by interaction of triphenyllead chloride with lead(II) mercaptides or lead(II) salts of thio acids. Reactions of these compounds with acids and alkyl iodides were also investigated. Of four possible routes attempted,

(1) $2(C_6H_5)_3PbCl + Pb(SR)_2 \longrightarrow 2(C_6H_5)_3PbSR + PbCl_2$

(2) $(C_6H_5)_3PbSNa\ (I) + RX \longrightarrow (C_6H_5)_3PbSR + NaX$

(3) $(C_6H_5)_3PbOH + RSH \longrightarrow (C_6H_5)_3PbSR + H_2O$

(4) $(C_6H_5)_4Pb + RSH \longrightarrow (C_6H_5)_3PbSR + C_6H_6$

the reaction of triphenyllead chloride with lead mercaptides (route 1) gave the best results. Route 2, successful in the preparation of the corresponding germanium compounds,[4] was found not to be satisfactory for the case of lead. Sodium triphenyllead sulfide (I), prepared by the reaction of triphenyllead chloride and sodium sulfide, was not stable above 30° even when anhydrous conditions were maintained. In the presence of moisture, decomposition took place at even lower temperatures yielding bistriphenyllead sulfide and sodium sulfide[5]:

$$2(C_6H_5)_3PbSNa\ (I) \longrightarrow [(C_6H_5)_3Pb]_2S + Na_2S$$

The formation of I was proved by the reaction with methyl iodide at low temperatures to yield thiomethyl triphenyllead, $(C_6H_5)_3PbSCH_3$. This reaction was accompanied by the formation of bistriphenyllead sulfide resulting from the simultaneous decomposition of the sodium salt (I).

Route 3, previously used in the synthesis of trialkyl-substituted lead compounds,[2c] when applied to triphenyllead hydroxide and 1-butanethiol yielded thiobutyl triphenyllead, $(C_6H_5)_3PbSC_4H_9$, in 65% yield.

Route 4 has previously been attempted by Koton[6] in treating tetraphenyllead and thiophenol, but under the employed conditions only diphenyl disulfide, the lead salt of thiophenol and benzene, were obtained. Working at lower temperatures (refluxing chloroform) thiophenyl triphenyllead, $(C_6H_5)_3PbSC_6H_5$ was obtained in yields of 2%, the main product isolated being unchanged tetraphenyllead. Apparently the acidity of thiophenol is too weak to cleave the lead–carbon bond at temperatures below the decomposition point of the desired product.

The more acidic thiolacetic acid in excess, cleaved two phenyl groups from tetraphenyllead yielding diphenyllead bisthiolacetate in 60% yield.[2d] The same reaction, using molar equivalents of reactants yielded a mixture of triphenyllead thiolacetate and diphenyllead bisthiolacetate.

Route 1, which had been used in the synthesis of the corresponding silicon compounds,[7,8] was experimentally preferable to route 3 or 4 and, in addition, it could be applied more satisfactorily to the synthesis of diphenyllead bisthio substituted compounds as follows:

$$(C_6H_5)_2PbCl_2 + Pb(SR)_2 \longrightarrow (C_6H_5)_2Pb(SR)_2 + PbCl_2$$

Thus, prior synthesis of the lead salt of the mercaptan followed by reaction with triphenyllead chloride (method 1) resulted in a series of organolead–sulfur compounds as described in Table I.

They are white crystalline compounds, with the exception of the liquid butyl compound, and decompose above the melting point to a dark brown material. They are readily soluble in benzene, *n*-hexane, alcohol, chloroform, and most of the other common organic solvents. The infrared absorption spectra of all

(3) G. Grüttner, *Ber.*, **51**, 1303 (1918).

(4) M. C. Henry and W. E. Davidson, *J. Org. Chem.*, **27**, 2252 (1962).

(5) This reaction is analogous to the readily occurring dehydration of organolead hydroxides to the corresponding oxide as follows: $2(C_6H_5)_3PbOH \rightarrow (R_3Pb)_2O + H_2O$.

(6) M. M. Koton, E. P. Moskvina, and F. S. Florinskii, *Zh. Obshch. Khim.* (*J. Gen. Chem.*), **20**, 2096 (1950); *Chem. Abstr.*, **45**, 5644 (1951).

(7) M. Schmeisser and H. Müller, *Angew. Chem.*, **69**, 781 (1957).

(8) E. W. Abel, *J. Chem. Soc.*, 4406 (1960).

compounds show, besides the usual absorptions associated with aromatic compounds and the respective group attached to the sulfur, the band at 1052 cm.$^{-1}$, typical for organolead compounds.[9]

Methyl iodide reacted quantitatively at room temperature with thiomethyl triphenyllead to yield triphenyllead iodide and dimethyl sulfide, probably through an unstable sulfonium salt intermediate:

$$(C_6H_5)_3PbSCH_3 + CH_3I \longrightarrow [(C_6H_5)_3PbS(CH_3)CH_3]I^{\ominus} \longrightarrow (C_6H_5)_3PbI + (CH_3)_2S^{\oplus}$$

This reaction did not take place with triphenyllead thiolacetate; apparently the acetyl group decreases the electron density at the sulfur atom so that formation of a sulfonium intermediate becomes impossible.

Mineral acids cleaved the lead–sulfur bond preferentially; however, cleavage of lead–phenyl bonds was always detected. For example, mixtures of triphenyllead chloride, diphenyllead dichloride, and lead chloride were obtained from the reaction of thioalkyl triphenyllead compounds and hydrochloric acid.

Throughout the course of this work, thin-layer chromatography was found to be valuable for separation of the organolead compounds. Dithizone spray reagent reacted to form yellow spots with the monosubstituted lead compounds, red spots from the disubstituted products, and gave no reaction with tetraphenyllead.[10]

Experimental

A typical example for the preparation of the triphenyllead sulfur compounds described by route 1 is given.

The lead mercaptides[11] were prepared from the thiol and lead acetate in aqueous alcohol and after washing with water were dried in a vacuum desiccator.

Triphenyllead chloride, 4.86 g. (10 mmoles), and lead (II) *n*-propyl mercaptide, 1.79 g. (5 mmoles), in 100 ml. benzene were refluxed with stirring for 3 hr. During this time the yellow mercaptide was converted into white lead chloride which was filtered off at the end of the reaction period. The filtrate was evaporated and the residue recrystallized from ethanol, yield 4.84 g. (95%), m.p. 57–58°.

Preparation of Thiobutyl Triphenyllead from Triphenyllead Hydroxide and 1-Butanethiol (Route 2).—Triphenyllead hydroxide,[12] 0.91 g. (2 mmoles), and 1-butanethiol, 0.18 g. (12 mmoles), were mixed in 50 ml. of ethyl ether and shaken for 24 hr. Filtration and evaporation yielded a colorless oil. The oil was purified by chromatography on neutral alumina, eluting with benzene; yield: 0.68 g. (65%).

Synthesis of Thiomethyl Triphenyllead by Route 1.—Triphenyllead chloride, 4.86 g. (10 mmoles), was added to a stirred suspension of sodium sulfide pentahydrate, 8.40 g. (50 mmoles), in 100 ml. of ethyl alcohol during a period of 1 hr. while the reaction temperature was kept below 30°. The excess sodium sulfide and sodium chloride were filtered off and the alcohol removed from the filtrate under vacuum. The white residue was extracted with benzene and the benzene evaporated. To the remaining solid was added methyl iodide, 1.41 g. (10 mmoles), in 50 ml. of benzene. After filtering and evaporation of the benzene, recrystallization from ethanol and *n*-hexane gave bistriphenyllead sulfide, 1.14 g. (25%), m.p. 139–141° (identified by mixed melting point with an authentic sample[3]).

The combined mother liquor was concentrated and yielded thiomethyl triphenyllead, 3.47 g. (68%), m.p. 103–106°, recrystallized from *n*-hexane).

Reaction of Thiomethyl Triphenyllead with Methyl Iodide.—Thiomethyl triphenyllead, 1.12 g. (2.3 mmoles), was dissolved in excess methyl iodide (30 ml.). After a few minutes the solution became cloudy and a precipitation occurred slowly over a period of 6 hr. The excess methyl iodide was removed under vacuum and the residue shown to be 1.30 g. of pure triphenyllead iodide,[13] m.p. 140–141°. Mixed melting point with an authentic sample gave no depression.

Reactions of Tetraphenyllead with Thiolacetic Acid (Route 3). Diphenyllead Bisthiolacetate.—Tetraphenyllead, 2.58 g. (5 mmoles), dissolved in 20 ml. of thiolacetic acid was refluxed for 5 min. The excess of thiolacetic acid was removed under vacuum and the residue recrystallized from ethanol. The yield was 1.55 g. (60%) and the m.p. was 94–95°.

Anal. Calcd. for $C_{16}H_{16}O_2S_2Pb$: C, 37.56; H, 3.15; Pb, 40.50; S, 12.54. Found: C, 37.73; H, 3.36; Pb, 40.50; S, 12.46.

Diphenyllead bisthiolacetate was also prepared by the reaction of diphenyllead dichloride with lead thiolacetate—analogous to route 4—in boiling toluene; yield 81%.

The reaction of tetraphenyllead with 1 mole of thiolacetic acid in boiling benzene (2 hr.) yielded 70% tetraphenyllead, 12% triphenyllead thiolacetate, and 6% diphenyllead bisthiolacetate.

Thin-layer Chromatography.—Thin-layer chromatography of the organolead compounds was carried out on silica gel G (25 μ), using benzene as a solvent in most cases. Potassium permanganate solution or a solution of dithizone in chloroform[10] was used as a spray.

Acknowledgment.—The authors are grateful to C. DiPietro of these laboratories for the microanalyses.

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(10) S. R. Henderson and L. J. Snyder, *Anal. Chem.*, **33**, 1172 (1961).

(11) P. Borgstrom, L. M. Ellis, and E. Emmet Reid, *J. Am. Chem. Soc.*, **51**, 3649 (1929).

(12) R. West, R. H. Baney, and D. L. Powell, *ibid.*, **82**, 6269 (1960).

(13) L. S. Foster, W. M. Dix, and I. J. Gruntfest, *ibid.*, **61**, 1685 (1939).

The Stereochemistry of an Ivalin Degradation Product[1]

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The hydroxyketolactone II obtained by ozonolysis of dihydroivalin (I)[2] exhibited a positive Cotton effect (molecular amplitude about 1750°) which seemed surprising in view of the relatively strong negative Cotton effect displayed by 4-keto steroids (molecular amplitude −9400°) and *trans*-10-methyl-1-decalone.

The hydroxyl group, being equatorial and in the upper left quadrant, should, according to the octant rule,[3] make a positive contribution to the total dispersion picture. However, no reference compounds of incontrovertible stereochemistry had been scrutinized for the purpose of assessing the effect of hydroxyl groups in a situation of this type, and the observed inversion of the Cotton effect seemed, *a priori*, greater than might have been expected. It should also be noted that inspection of models failed to reveal any reasons for distortions due to steric or electrostatic interactions which might result in conformational changes.

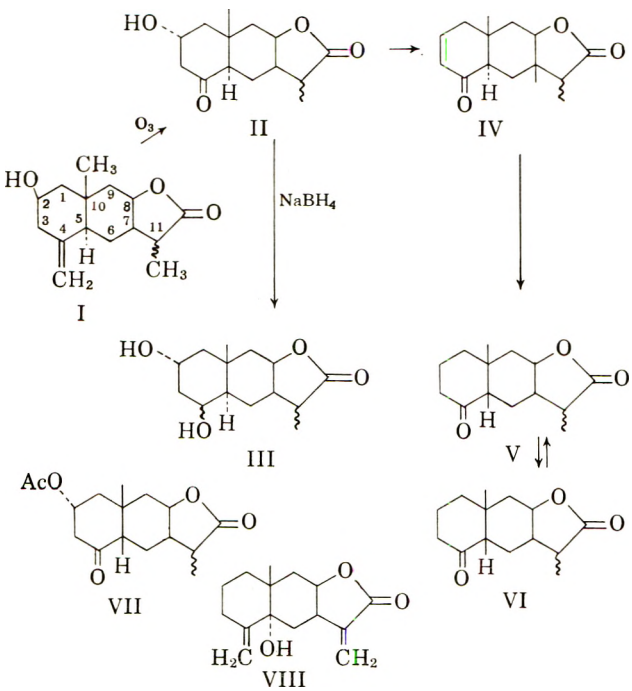
To explain the observed rotatory dispersion curve, we considered the possibility that epimerization at C-5 might have taken place during the work-up. This

(1) Supported in part by grants from the National Science Foundation (NSF-G-14396) and the Eli Lilly Company, Inc.

(2) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

(3) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and D. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1962).

would have resulted in a substance with a *cis* A-B-ring fusion, and, indeed, the curve of II was very similar to that of *cis*-10-methyl-1-decalone. We now report that this is not the case and that the hydroxyketolactone is accurately represented by II.



Sodium borohydride reduction of II gave a diol (III) which could be obtained more directly by sodium borohydride reduction of the ozonide derived from I. It is quite unlikely that the second route involves epimerization at C-5 since under similar circumstances the very labile 3-keto-A-nor-5-α-steroids are not converted to the more stable 5-β-isomers.[4] We conclude that the formation of II from I is not accompanied by inversion at C-5; and II must therefore have the same configuration at C-5 as I, *i.e.*, *trans*.

Since hydride reduction of 4-cholestanone is reported to give mainly 4-β-cholestanol,[5] the reduction of II might be expected to result in the formation of an axial C-4 hydroxyl group. However, the diol III was isolated in less than 50% yield so that no conclusion is possible about the stereochemistry of III at C-4.

Additional evidence for retention of configuration at C-5 was provided by the following reaction sequence. Dehydration of II, as described previously,[2] furnished the α,β-unsaturated ketone IV which was catalytically reduced to V, m.p. 201°. The optical rotatory dispersion curve of this substance was comparable to that of *trans*-10-methyl-1-decalone of appropriate absolute configuration (negative Cotton effect).[6] Hence, if II were a *cis* rather than a *trans* isomer, its conversion to V would have had to be attended by another epimerization at C-5, which again seemed extremely unlikely.

In the meantime, V has also been obtained[7] by degradation of telekin (VIII). The properties reported by Benešova, Herout, and Klyne[7] compared well with the properties of the material isolated by us. and a comparison of the rotatory dispersion curves kindly carried out by Professor Klyne established their identity.

Epimerization of V with potassium carbonate in tetralin yielded an equilibrium mixture containing 55% of V and 45% of a new substance,[8] which on the basis of the rotatory dispersion curve (positive Cotton effect) is the *cis* isomer VI.[9] Although the m.p. of VI was unsharp, it behaved as a pure substance on thin-layer chromatography and could be readily differentiated from V.

The composition of the equilibrium mixture did not differ significantly from the equilibrium mixture of the *cis*- and *trans*-10-methyl-1-decalones.[10] Hence substitution by a *cis*-lactone group at C-7 and C-8 appears to exert little effect on the relative stabilities of the 10-methyl-1-decalones.

The abnormally large effect of the 2-α-hydroxy group on the optical rotatory dispersion curve of II still remains to be explained. The acetate VII exhibits what appears to be a very weak positive Cotton effect of small amplitude (a about +7).[11] This could be due to the normal positive octant effect of acetate (Δa OAc = +32). The larger Δa for the hydroxyl group may perhaps arise through hydrogen bonding.

Experimental[12]

Ozonolysis of Dihydroivalin.—(a) A solution of 0.5 g. of I in 50 ml. of ethyl acetate was ozonized at −70°. Excess ozone was removed by a stream of oxygen. The solution was allowed to come to room temperature (separation of a solid) and transferred to a hydrogenating bottle. The solid was dissolved in methanol and added to the ethyl acetate solution which was reduced at 20 lb., catalyst 0.1 g. of 5% palladium–charcoal. After filtration and removal of solvent, there was obtained 0.3 g. of II, m.p. 178–180° on recrystallization from acetone–petroleum ether.

(b) A solution of 0.2 g. of I in 15 ml. of methylene chloride and 5 ml. of methanol was ozonized at −70°. The solution was allowed to come to room temperature and mixed with 0.2 g. of sodium borohydride in 10 ml. of methanol. After a half-hour, another 0.1 g. of sodium borohydride was added and left for 4 hr. Then 2 ml. of acetic acid was added, the solvent was evaporated *in vacuo*, the residue was mixed with water and thoroughly extracted with chloroform. The dried chloroform extracts were concentrated, and the residue recrystallized from benzene containing a small amount of ethanol; yield 0.05 g. of the diol III, m.p. 203–205°.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72; O, 25.17. Found: C, 65.69; H, 8.64; O, 25.39.

III was also obtained in 0.05 g. yield by sodium borohydride reduction of 0.15 g. of II in methanol, m.p. and m.m.p. 103–205°. The two samples had identical infrared spectra and mobility on a thin-layer chromatogram (acetone on silica gel).

Reduction of IV.—A solution of 0.35 g. of IV in 50 ml. of ethanol was reduced at atmospheric pressure with 50 mg. of 10% palladium–charcoal. Removal of solvent and recrystallization from alcohol furnished 0.26 g. of V, m.p. 201–202°, optical rotatory dispersion curve in methanol, $(\phi)_{305}$ −1180°, $(\phi)_{270}$ +1420°, a − 25, infrared bands at 1770 and 1715 cm.$^{-1}$, reported m.p. for the material from isotelekin[7] 202–203°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 71.16; H, 8.53; O, 20.31. Found: C, 70.98; H, 8.36; O, 20.52.

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(5) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. R. Summers, *J. Chem. Soc.*, 2876 (1955).

(6) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

(7) V. Benešova, V. Herout, and W. Klyne, *Collection Czech. Chem. Commun.*, **27**, 499 (1962).

(8) The percentage values are based on crystalline product isolated from the mixture, total recovery 70% of starting material.

(9) Compare with the curve of *cis*-10-methyl-1-decalone.[6]

(10) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958).

(11) For terminology, see W. Klyne, "Advances in Organic Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1960, p. 239.

(12) Melting points are uncorrected. Analyses are by Dr. F. Pascher, Bonn, Germany. Infrared spectra were run on a Perkin–Elmer Infracord spectrophometer in chloroform solution.

This substance was unaffected on refluxing with potassium carbonate in toluene. Sodium methoxide in refluxing methanol yielded starting material and three transformation products (thin-layer chromatogram); the mixture could not be separated by column chromatography.

A solution of 0.1 g. of V in 10 ml. of tetralin was refluxed with 100 mg. of freshly heated anhydrous potassium carbonate for 4 hr., allowed to stand at room temperature, and filtered. The potassium carbonate was washed with benzene, and the combined organic solvents evaporated *in vacuo*. The residue gave two spots on thin-layer chromatography (silica gel–anhydrous ether), one of which corresponded to starting material.

The crude product was dissolved in benzene and chromatographed over acid-washed alumina. Benzene eluted nothing. Benzene–anhydrous ether (2:1, 25-ml. fractions) eluted an oil in the first 50 ml. (fraction A) and a solid in the subsequent 75 ml. (fraction B). Fraction B on crystallization from ethyl acetate–petroleum ether yielded 0.04 g. of starting material, m.p. and m.m.p. 200°.

Fraction A on crystallization from ether–petroleum ether gave an epimer, wt. 0.03, which was homogeneous in thin-layer chromatography but had m.p. 97–107°. The m.p. did not improve even after four crystallizations. The infrared spectrum exhibited bands at 1770 and 1715 cm.$^{-1}$ and differed significantly from that of V in the fingerprint region. Optical rotatory dispersion curve in methanol, $(\phi)_{310}$ 2000°, $(\phi)_{270}$ −1100°, a + 31.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; O, 20.31. Found: C, 71.35; H, 8.58; O, 20.18.

The optical rotatory dispersion curve of VII[2] in methanol exhibited $(\phi)_{305}$ +800°, $(\phi)_{282.5}$ +110°, a + 7°. However, the weak intensities make it doubtful whether these values represent true peaks and troughs.

Acknowledgment.—We wish to express our thanks to Professor W. Klyne for the optical rotatory dispersion curves.

cis- and *trans*-Stilbene Sulfides

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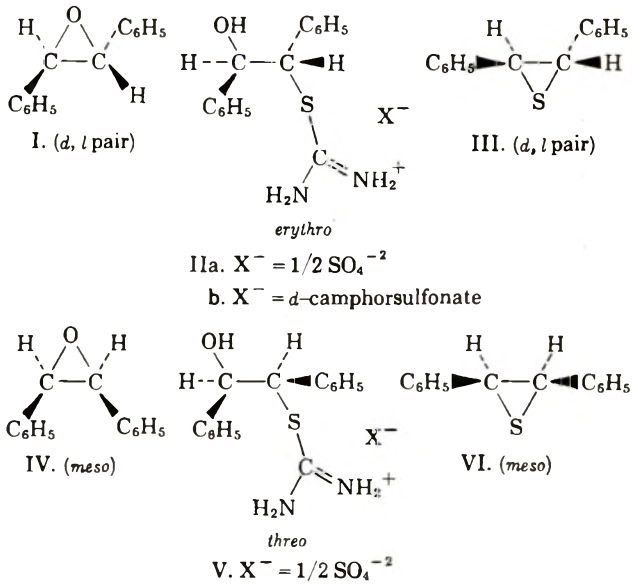
The preparation and reactions of a wide variety of stilbene oxides have been reported in the literature.[1] However, the sulfur analogues have not been previously described. Culvenor, Davies, and Health[2] attempted to convert stilbene oxide, presumably the *trans* isomer, to an episulfide by the use of thiourea. The only products isolated were stilbene, urea, and sulfur. This observation led them to conclude that stilbene episulfide was too unstable to exist. That both styrene sulfide[3] and tetraphenylethylene sulfide[4] have been reported suggested that the intermediate diphenyl and triphenylethylene sulfides should also be capable of existence.

Bordwell[5] reported the preparation of a variety of episulfides by treatment of epoxides with thiourea and acid to afford thiuronium salts, which when treated with alkali yielded episulfides. Application of Bordwell's procedure has afforded both *cis*- and *trans*-stilbene sulfides from the corresponding *cis*- and *trans*-stilbene oxides. The analytically pure thiuronium sulfates [*erythro*-*S*-(1,2-diphenyl-2-hydroxyethyl)thiuronium sulfate (IIa) from *trans*-stilbene oxide (I) and *threo*-*S*-(1,2-diphenyl-2-hydroxyethyl)thiuronium sulfate (V) from *cis*-stilbene oxide (IV)] were obtained in high yield without purification. When treated with base, the thiuronium salts afforded the expected sulfides (III from II and VI from V) in nearly quantitative yield. When stored at room temperature, unprotected from light, *cis*-stilbene sulfide (VI), m.p. 77–78°, is stable, but *trans*-stilbene sulfide (III), m.p. 53–54°, slowly deteriorates to what appears to be a polymer. When protected from light and stored at 5°, *trans*-stilbene sulfide is quite stable.



The fact that *trans*-stilbene oxide (I) afforded a lower melting sulfide than that derived from *cis*-stilbene oxide (IV) suggested that the reaction may not have proceeded through the generally accepted two-inversion path for conversion of simpler oxides to episulfides by thiourea[6] or thiocyanate,[7] but that perhaps the *trans* oxide had yielded the *cis* sulfide. The greater stability of the *cis* sulfide was also consistent with this possibility.

Evidence bearing on this question was obtained from ultraviolet and n.m.r. spectra, and stereochemical studies. The ultraviolet absorption maxima of *trans*-stilbene oxide (I) appear at longer wave lengths than those of *cis*-stilbene oxide (IV).[8] It has been shown that the red shifts in *trans*-stilbene oxide arise from conjugation of the three-membered ring with the two phenyl groups.[8] In the *trans* oxide the phenyl groups may assume that geometry which gives the most favorable orbital overlap. In the *cis* isomer, however, the steric hindrance of the two eclipsed phenyl groups is so great that its ultraviolet spectrum is almost identical to that of bibenzyl. The geometries of the sulfides cannot be much different from the oxides, so that, if the sulfur-containing three-membered ring is also

(1) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, chap. 1, pp. 1–60.

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(3) C. O. Guess and D. L. Chamberlain, *J. Am. Chem. Soc.*, **74**, 1342 (1952).

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(8) L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, Intern. Conf. Spect. 9, Lyons, France, 1961, Trans., Vol. 1–3, G.M.A.S., Paris-15e, France, 1962, in press. *Cf.* also M. Rogers, *J. Am. Chem. Soc.*, **69**, 2544 (1947) and N. H. Cromwell, F. H. Sumacher, and J. L. Adelfang, *ibid.*, **83**, 974 (1961).

capable of conjugation with the phenyl groups, similar red shifts should be observed for *trans*- relative to *cis*-stilbene sulfide. In the absence of such interaction the spectra of the *cis* and *trans* isomers should be identical. In any event the *cis* isomer should not absorb at longer wave lengths than the *trans*. The sulfide obtained from *trans*-stilbene oxide absorbs at a longer wave length than the isomeric sulfide thus indicating that configuration is retained. Davis has shown[9] that the sulfur analogue of ethylene oxide absorbs at a higher wave length than the oxide itself; the same relationship between oxides and sulfides is observed in this case. The data are given in Table I.

TABLE I

ULTRAVIOLET SPECTRAL DATA FOR *cis*- AND *trans*-STILBENE OXIDES AND *cis*- AND *trans*-STILBENE SULFIDES[a]

	$\lambda_{1\ max}$	ϵ	$\lambda_{2\ max}$	ϵ
		trans		
Oxide (I)[b]	228	(23,500)	267	(902)
Sulfide (III)	238	(17,300)	269.5	(1400)
		cis		
Oxide (IV)[b]	218	(12,250)	261	(470)
Sulfide (VI)	226	(10,600)	268	(800)

[a] Recorded on a Carey Model 11 spectrophotometer in 95% ethanol. [b] Ref. 8.

The n.m.r. spectra of *cis*- and *trans*-stilbene oxides are significantly different, and the spectrum of each sulfide is almost identical with that of the oxide from which it was derived. Although the lack of model compounds makes difficult a rigorous interpretation of these spectra in terms of structure, the downfield shift of the ethylenic CH resonance in *cis*-stilbene oxide relative to *trans*-stilbene oxide should be paralleled in the sulfur analogs. The demonstration of this relationship is taken as evidence for retention of configuration. The data are in Table II.

TABLE II

N.M.R. SPECTRAL DATA FOR *cis*- AND *trans*-STILBENE OXIDES AND *cis*- AND *trans*-STILBENE SULFIDES[a]

	trans		*cis*	
	(δ p.p.m.[b]) phenyl	(δ p.p.m.[b]) ethylene	(δ p.p.m.[b]) phenyl	(δ p.p.m.[b]) ethylene
Stilbene oxide	7.392	3.884	7.192	4.367
Stilbene sulfide	7.358	3.982	7.15	4.40

[a] Recorded on a Varian A-60 n.m.r. spectrophotometer at room temperature in deuteriochloroform. [b] Chemical shifts, in parts per million downfield from tetramethylsilane.

Absolute proof of the correctness of the stereochemical assignments was obtained by partial asymmetric synthesis of optically active *trans*-stilbene sulfide (III). *cis*-Stilbene sulfide (VI) has a plane of symmetry perpendicular to the central C—C bond and is therefore a *meso* compound. The *trans* isomer on the other hand does not have any of the elements of symmetry, and is therefore normally obtained as a racemate. The preparation of optically active *trans*-stilbene sulfide was achieved *via* the *erythro*-thiuronium *d*-camphorsulfonate (IIb) obtained from *trans*-stilbene oxide (I), thiourea and *d*-camphorsulfonic acid.

Repeated crystallization of the *d*-camphorsulfonate afforded a product (m.p. 209°, $[\alpha]^{20}D$ +29.7°) which when treated with sodium carbonate gave inactive *trans*-stilbene sulfide. The mother liquor from the first crystallization was evaporated and the residue treated with base to afford optically active *trans*-stilbene sulfide ($[\alpha]^{20}D$ +13.6° in hexane). At present we cannot estimate, but it is unlikely that a high degree of optical purity has been attained.

R. E. Davis, *J. Org. Chem.*, **23**, 216 (1958).

Experimental[10]

***erythro-S*-(1,2-Diphenyl-2-hydroxyethyl)thiuronium Sulfate (IIa).**—Following Bordwell's procedure[5] 5 g. (0.026 mole) of *trans*-stilbenze oxide (I)[11] was added gradually over 30 min. to a stirred solution of 15 ml. of water, 1.6 g. (0.85 ml., 0.032 equiv.) of concentrated sulfuric acid, and 2.5 g. (0.032 mole) of thiourea at room temperature. The resulting suspension was stirred for 20 hr. and the *erythro-S*-(1,2-diphenyl-2-hydroxyethyl)thiuronium sulfate was filtered and washed with ether. There was obtained 7.8 g. (95%) of analytically pure salt, m.p. 169–170°.

Anal. Calcd. for $C_{30}H_{34}N_4O_6S_3$: S, 14.95. Found: S, 14.72.

Attempts to recrystallize the salt from water, acetone, alcohol, or acetonitrile resulted in partial conversion to *trans*-stilbene sulfide (infrared spectrum and m.p.).

***trans*-Stilbene Sulfide (III).**—The intermediate thiuronium salt (IIa, 20 g.) was suspended in 40 ml. of water and made alkaline (pH 9) with 10% sodium carbonate. The mixture was stirred for 20 min. and the crude *trans*-stilbene sulfide (12 g., 90%, m.p. 49–50°) collected. Crystallization from methanol gave white, silky flakes, m.p. 53–54°.

Anal. Calcd. for $C_{14}H_{12}S$: C, 79.20; H, 5.70; S, 15.10. Found: C, 78.86; H, 5.70; S, 14.87.

***threo-S*-(1,2-Diphenyl-2-hydroxyethyl)thiuronium Sulfate (V).**—The above procedure was repeated with *cis*-stilbene oxide (IV).[11] The *cis*-stilbene thiuronium sulfate, m.p. 136–137°, was obtained in 73% yield.

Anal. Calcd. for $C_{30}N_{34}N_4O_6S_3$: S, 14.95. Found: S, 14.74.

***cis*-Stilbene Sulfide (VI).**—Neutralization of *threo-S*-(1,2-diphenyl-2-hydroxyethyl)thiuronium sulfate (V) afforded *cis*-stilbene sulfide in 90% yield, m.p. 71–72°. Crystallization from methanol gave white needles, m.p. 77–78°.

Anal. Calcd. for $C_{14}H_{12}S$: C, 79.20; H, 5.70; S, 15.10. Found: C, 79.00; H, 5.71; S, 14.90.

***erythro-S*-(1,2-Diphenyl-2-hydroxyethyl)thiuronium *d*-Camphorsulfonate (IIb) and Optically Active *trans*-Stilbene Sulfide.**—Treatment of *trans*-stilbene oxide (I) with thiourea, water, and *d*-camphorsulfonic acid afforded *erythro-S*-(1,2-diphenyl-2-hydroxyethyl)thiuronium *d*-camphorsulfonate, m.p. 176–180°, in 88% yield. The salt was repeatedly crystallized from absolute alcohol until the m.p. (209°) and rotation ($[\alpha]^{20}D$ = 29.7°) remained unchanged.

Anal. Calcd. for $C_{25}H_{32}O_5S_2N_2$: S, 12.70. Found: S, 12.56.

After each crystallization of the *d*-camphorsulfonate the mother liquor and a sample of the crystallized product were neutralized with sodium carbonate. The optical rotation of the *trans*-stilbene sulfide obtained in each case was measured in methanol. Only the sulfide obtained from the mother liquor of the first crystallization gave optically active sulfide (m.p. 49–51°). To avoid the possibility that some optically active starting material or intermediate salt might be present, the optical rotation was also measured in hexane. The optically active *trans*-stilbene sulfide in hexane had a specific rotation of 13.6° at 20°. *trans*-Stilbene sulfide recovered from the hexane had physical properties (ultraviolet and infrared spectra, and m.p.) identical with those of purified *trans*-stilbene sulfide. Optical rotations were measured on a Rudolph photoelectric polarimeter, Model 200As–8003.

Acknowledgment.—We are grateful to Mr. Norman Bhacca of Varian Associates for determining the n.m.r. spectra and to Mr. Michael Hrenoff for determination of the infrared and ultraviolet spectra. This work was supported (in part) by Cancer Research Funds of the University of California.

(10) Melting points are not corrected. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif.

(11) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Am. Chem. Soc.*, **80**, 2844 (1958).

The Reactivity of 1,2-Diaminosugars in the Osazone and Quinoxaline Formation in the Sugar Series

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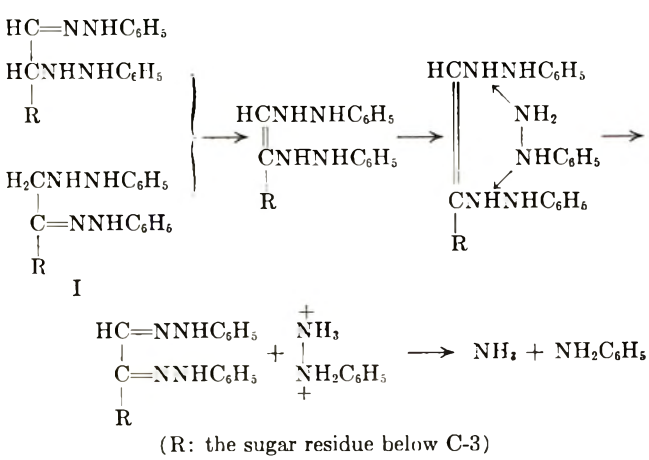
It has been reported elsewhere[1] that *N*-benzyl-(1-deoxy-1-*p*-toluidino)-D-fructosylamine is cleaved by molecular oxygen to give *N*-benzyl-D-arabinonamide while *N*-cyclohexyl-(2-cyclohexylamino-2-deoxy)-D-glucosylamine yields under similar mild conditions *N,N'*-bis(cyclohexyl)oxaldiamide, dicyclohexyliminoglyoxal, and cyclohexylammonium D-arabinonate as the cleavage products. It has been shown that the 1,2-diaminosugars are first rearranged into the enediamine structures which have powerful reducing abilities and that one of the primary oxidation products of the enediamine from the latter diaminosugar is 1,2-dicyclohexylimino-D-glucosone. Literature reporting the high reducing ability of enediamino compounds and their ready conversion into 1,2-diiminodiketo compounds by the action of atmospheric oxygen has also been reviewed.

Because the formation of osazones and quinoxalines in the sugar series involves the transformation of 1,2-diaminosugars into 1,2-diimino-osones, it appears that the above findings will help to elucidate the reaction mechanisms.

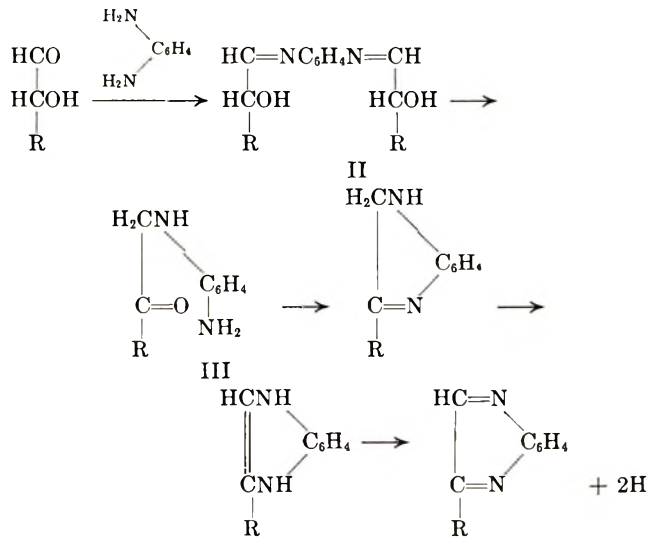
Among a number of the theories advanced for explaining the mechanism of the osazone formation,[2] the most widely accepted ones[3] are apparently the mechanisms by Weygand[4] and by Bloink and Pausacker.[5] In both mechanisms a 1,2-diaminosugar (I) is postulated as the key intermediate. The mechanism of the oxidation of this diaminosugar to diiminoosone differs between the two schemes and remains to be clarified.

Based upon the new evidence[1] concerning the 1,2-diamine-enediamine rearrangement and the powerful reducing ability of the rearrangement product, the following scheme could represent the last step in the formation of osazones.



(R: the sugar residue below C-3)

Formation of 2-substituted quinoxaline by the reaction of a reducing sugar and *o*-phenylenediamine has been shown to follow a mechanism similar to that of the osazone formation.[6] From the present knowledge on the reactivity of the 1,2-diaminosugars, the mechanism of the last step of the quinoxaline formation may be shown as follows:[7]



(R: the sugar residue below C-3)

The hydrogen acceptor in this reaction is atmospheric oxygen under ordinary reaction conditions, but hydrazine is a better acceptor since addition of hydrazine has been shown to improve the yield of the quinoxaline derivative.[6,8] To indicate the different ability as the hydrogen acceptor between molecular oxygen and hydrazine, a set of experiments was conducted with *N,N'*-di-D-glucosyl-3,4-diaminotoluene. In contrast to *o*-phenylenediamine, 3,4-diaminotoluene does not give the quinoxaline derivative in the reaction with D-glucose.[9] It was thought therefore that *N,N'*-di-D-glucosyl-3,4-diaminotoluene, the first intermediate (corresponding to II) in the reaction of the diaminotoluene and D-glucose, would be a good starting material to show the effect of hydrogen acceptors more distinctly in the quinoxaline formation. When *N,N'*-di-D-glucosyl-3,4-diaminotoluene was refluxed in 10% acetic acid for thirty minutes, the yield of the formed quinoxaline derivative was merely trace under an ordinary atmosphere, 7.8% under passing of oxygen through the solution and 18.2% when an equimolecular amount of hydrazine was added.

Experimental

***N,N'*-Di-D-glucosyl-3,4-diaminotoluene.**—A mixture of 36 g. of D-glucose, 12 g. of 3,4-diaminotoluene, 0.2 g. of ammonium chloride, and 300 ml. of methanol was refluxed for 30 min. Sepa-

(1) S. Kitaoka and K. Onodera, *Agr. Biol. Chem.*, **26**, 572 (1962).
(2) E. G. V. Percival, *Advan. Carbohydrate Chem.*, **3**, 23 (1948).
(3) W. Pigman, "The Carbohydrates," W. Pigman, ed., Academic Press Inc., New York, N. Y., 1957, p. 456.
(4) F. Weygand, *Ber.*, **73**, 1284 (1940); F. Weygand and M. Reckhaus, *ibid.*, **82**, 438 (1949); F. Weygand, H. Simon, and J. F. Klebe, *ibid.*, **91**, 1567 (1958); H. Simon, K.-D. Keil, and F. Weygand, *ibid.*, **95**, 17 (1962).
(5) G. J. Bloink and K. H. Pausacker, *J. Chem. Soc.*, 661 (1952).
(6) F. Weygand and A. Bergmann, *Ber.*, **80**, 255 (1947).
(7) Occurrence of the 1-amino-1-deoxyketose intermediate (III) in the quinoxaline formation has been postulated by Weygand and Bergmann (ref. 6). Since the only condensation product ever isolated of a reducing sugar and *o*-phenylenediamine is *N,N'*-diglycosyl-*o*-phenylenediamine (II), one glycosyl residue must be cleaved off at the formation of III. The reaction mechanism of this step is not clear.
(8) H. Ohle and J. J. Kruyff, *Ber.*, **77**, 507 (1944).
(9) P. Griess and G. Harrow, *ibid.*, **20**, 2205 (1887).

ration of the crystalline product was prompt, and, after cooling, the crude yield was 33.8 g. (70.4%). It was recrystallized from a large volume of aqueous methanol; m.p. 142–143°, $[\alpha]^{16}D$ −41° (c 0.5, pyridine, 24 hr.).

Anal. Calcd. for $C_{19}H_{30}N_2O_{10}\cdot 3H_2O$: C, 45.59; H, 7.25; N, 5.60. Found: C, 45.04; H, 7.16; N, 5.68.

2-D-*arabino*-Tetrahydroxybutyl-6-methylquinoxaline.—An amount of 4.5 g. of *N,N'*-di-D-glucosyl-3,4-diaminotoluene was heated to boiling in 50 ml. of 10% acetic acid for 30 min. Under an ordinary atmosphere no separable amount of the crystalline product was obtained, but, under vigorous passing of oxygen through the solution, this quinoxaline derivative was obtained in the yield of 0.35 g. (7.8%) after cooling. When the equimolecular amount of hydrazine was added to the reaction system under an ordinary atmosphere, the yield was 0.82 g. (18.2%). This compound had m.p. 177–178° and $[\alpha]^{16}D$ −200° (*c* 0.8, pyridine).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.87; H, 6.33; N, 10.61.

Acknowledgment.—The authors thank Mr. Hiroshi Doi for his assistance in the experimental work.

Dimethylamides from Alkali Carboxylates and Dimethylcarbamoyl Chloride

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Dimethylamides of carboxylic acids have become increasingly interesting in recent years because certain ones are good solvents for polymers composed mainly of acrylonitrile[1,2] and because they are excellent reaction solvents, particularly for nucleophilic displacements.[3] Ordinarily they may be prepared by almost any of the conventional means for synthesis of amides in general, including thermal reaction between the appropriate acid and dimethylamine, or reaction between dimethylamine and an acid chloride, anhydride, or ester.

Recently in our laboratories it became necessary to convert a small amount of the sodium salt of an acid into the corresponding dimethylamide as quantitatively as possible, yet with a high degree of product purity. While one of the preparative methods mentioned above might have been used, it appeared that each one offered some points of inconvenience and possible loss. A study of the literature did not suggest any more promising approaches until attention was drawn to the reaction between carboxylic acids and isocyanates to form monoalkylamides.[4] This reaction has been demonstrated[4b] to proceed through the intermediate formation of a relatively unstable mixed carboxylic–carbamic anhydride, RCOOCONHR'. Because a similar mixed anhydride should result from the action of a dialkylcarbamoyl chloride on a salt of a carboxylic acid, it seemed likely that such a reaction would be useful in preparing dialkylamides.

The mixed anhydrides from isocyanates and carboxylic acids are capable of decomposing by either of the routes shown below.[4c,d,e]

$$RCOOCONHR' \longrightarrow RCONHR' + CO_2 \quad (1)$$

$$2RCOOCONHR' \longrightarrow (RCO)_2O + (R'NH)_2CO + CO_2) \quad (2)$$

Fry[4c] demonstrated that all of the carbon dioxide formed in these reactions arose from the isocyanate used, and indicated further that the acid anhydride and dialkylurea formed in reaction 2 would interact at somewhat higher temperatures to form additional quantities of monoalkylamide as indicated in equation 3.

$$(RCO)_2O + (R'NH)_2CO \longrightarrow 2RCONHR' + CO_2 \quad (3)$$

These facts suggested that this reaction was potentially capable of giving high yields of monoalkylamides from carboxylic acids, and that dialkylamides might by synthesized equally well by the action of dialkylcarbamoyl chlorides on salts of carboxylic acids (equation 4).

$$RCOONa + R_2'NCOCl \longrightarrow NaCl + RCOOCONR_2'$$

$$RCOOCONR_2' \longrightarrow CO_2 + RCONR_2' \quad (4)$$

Support for this conclusion was obtained from the work of von Braun,[5] who obtained dimethylbenzamide almost quantitatively from the spontaneous decomposition of benzoyl dimethyldithiocarbamate. Somewhat

$$(CH_3)_2NCSSCOC_6H_5 \longrightarrow CS_2 + C_6H_5CON(CH_3)_2 \quad (5)$$

similarly, Herzog and Hancu[6] prepared the diphenylamides of benzoic and cinnamic acids by the action of diphenylcarbamoyl chloride on the appropriate acid in excess pyridine at 100°. Presumably this procedure involves a mixed anhydride as an intermediate.

$$C_6H_5COOH + (C_6H_5)_2NCOCl + C_5H_5N \longrightarrow C_6H_5COOCON(C_6H_5)_2 + C_5H_5N\cdot HCl$$

$$C_6H_5COOCON(C_6H_5)_2 \longrightarrow CO_2 + C_6H_5CON(C_6H_5)_2 \quad (6)$$

At the conclusion of the work described here, further search of the literature revealed that the reaction between salts of carboxylic acids and dialkylcarbamoyl chlorides is the subject of a patent.[7] Because the results reported here give some additional insight as to the general utility of the reaction, it is felt that they may be of value.

A synthesis of dimethylacetamide from potassium acetate and dimethylcarbamoyl chloride gave a 96.5% yield of product having the correct refractive index and containing less than 0.01% residual chlorine. Similarly, repetition of this experiment with labeled sodium acetate on two occasions gave yields of 94.2 and 95.8%, with isotopic conversions of 95.88 and 97.1%, respectively.

Other experiments were then performed to determine the generality of this reaction. Dimethylpropionamide with the correct refractive index was obtained in 97% yield. Sodium palmitate gave an 87% yield of dimethylpalmitamide. Sodium carbonate was converted to tetramethylurea in 96.5% yield; while the refractive index has not been previously reported, the product had the proper density and boiling point. The technique is not suitable for the preparation of dimethylformamide;

(1) G. H. Latham (to E. I. du Pont de Nemours & Co., Inc.), U.S. Patent 2,404,714 (July 23, 1946).

(2) G. F. D'Alelio (to Industrial Rayon Corp.), U.S. Patent 2,531,407 (November 28, 1950).

(3) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960).

(4) (a) C. Naegeli and A. Tyabji, *Helv. Chem. Acta*, **17**, 931 (1934); (b) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906); (c) A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953); (d) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 210 (1948); (e) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *ibid.*, **57**, 52 (1957).

(5) J. von Braun, *Ber.*, **36**, 3525 (1903).

(6) J. Herzog and V. Hancu, *ibid.*, **41**, 636 (1908).

(7) E. Stein and O. Bayer (to Farbenfabriken Bayer A.-G.), West German Patent 875,807 (May 7, 1953).

the intermediate mixed anhydride from sodium formate and dimethylcarbamoyl chloride decomposes in accordance with equation 2 to an appreciable extent. This mode of decomposition causes carbon monoxide to appear in the off-gases and tetramethylurea to be present in the liquid product. Fractional distillation of the liquid from two runs indicated that the ratio of dimethyl formamide to tetramethylurea was about 3.5 or 4 to 1. Application of the same reaction to a synthesis of N,N-dibutyldodecanamide from sodium laurate and N,N-dibutylcarbamoyl chloride gave a 78% yield of product.[8]

Extension of this reaction to the dibasic acid series was less successful. In spite of repeated efforts, no tetramethyloxamide could be obtained from sodium or potassium oxalate and dimethylcarbamoyl chloride. These salts appeared to be distinctly less reactive than those of the monobasic acids, and higher temperatures were required to cause reaction to occur. The only organic product isolated was tetramethylurea. A low yield (7.6%) of tetramethyloxamide was obtained by the technique of Herzog and Hancu,[6] but even in this case tetramethylurea was the major product isolated (44.4%). An authentic specimen of tetramethyloxamide was prepared by the action of dimethylamine on ethyl oxalate at 100°, and it was ascertained that this product would have been isolated if formed.

Very similar results were obtained from sodium malonate and dimethylcarbamoyl chloride; only small yields (*ca.* 10%) of tetramethylmalonamide were obtained. Again tetramethylurea was one of the products, but unexpectedly dimethylacetamide was also found present in large amounts. Sodium succinate gave tetramethylsuccinamide in yields of 53.5 and 49% in two experiments. Glutaric acid was not investigated, but it was found that sodium adipate gave an 86.5% crude yield of tetramethyladipamide (77% of recrystallized product suitable for analysis).

These results suggest that the reaction between sodium (or potassium) carboxylates and dialkylcarbamoyl chlorides is a fairly general means of preparing dialkylamides, provided that complications are not introduced by instability of an anhydride which may be formed through reaction 2 above.

Experimental[9,10]

Dimethylcarbamoyl chloride was Matheson, Coleman and Bell practical grade. It was fractionally distilled and a center cut (b.p. 61–64°/19 mm.) was taken for use in this work. Potassium acetate was Baker and Adamson reagent grade which had been recently fused. Sodium carbonate, sodium formate, and sodium oxalate were Baker and Adamson reagent grade. The other sodium salts were prepared by neutralization of the appropriate acid (Matheson, Coleman and Bell or Baker and Adamson, reagent grade) with sodium hydroxide to a phenolphthalein end point. They were isolated by evaporation of their solutions on a steam bath, and were dried in a vacuum oven at 100° for at least 24 hr.

Dimethylacetamide.—To a large heavy-wall test tube (4 cm. × 15 cm.) was charged 49 g. (0.5 mole) of fused potassium acetate. The salt was covered with 53.8 g. (0.5 mole) of dimethylcarbamoyl chloride and the vessel was attached to a condenser. This mixture was heated in a boiling water bath until no more gas was evolved (2–3 hr.) and was then heated briefly up to 150° in a glycerol bath. After cooling the tube was attached to a high vacuum assembly and all volatile matter was distilled into a similar vessel which was used as a vacuum trap. The contents of the trap were then warmed at 100° for 3 hr. with 15 g. of fresh potassium acetate, heated briefly at 150°, and distilled once more under high vacuum. The weight of dimethylacetamide so obtained was 42.0 g. (96.5%). A small sample was warmed with methanol to destroy any dimethylcarbamoyl chloride present, and the solution analyzed by high frequency titration. Found: Cl, approximately 0.001%. The refractive index was $n^{24}D$ 1.4366 (reported,[11,12] $n^{20}D$ 1.4384, $n^{25}D$ 1.4351).

Dimethylpropionamide.—Prepared on a 0.5-molar scale by the procedure described above, this compound was obtained in a yield of 49.0 g. (97.3%). The product contained 0.002% chlorine and had a refractive index of 1.4372 at 23.5° (reported,[12] $n^{25}D$ 1.4371).

Dimethylpalmitamide.—This dimethylamide was prepared in a generally similar fashion. Dimethylcarbamoyl chloride (0.18 mole) was heated to 105° with a slight excess of sodium palmitate until apparent reaction ceased, and the mixture was then heated briefly to 185°. Dimethylpalmitamide was extracted from the cooled reaction mixture by boiling with chloroform. After filtration and removal of the solvent, the residue was distilled under a pressure of 0.2–0.5 mm. in a modified Hickman still (bath temperature 150–160°). The yield of colorless distillate, crystallizing to a white solid, was 44.5 g. (86.8%). A sample twice recrystallized from ethanol for analysis had m.p. 43–45°. This compound apparently has not been previously reported.

Anal. Calcd. for $C_{18}H_{37}ON$: C, 76.32; H, 13.07. Found: C, 76.02, 76.42; H, 13.09, 13.22.

Tetramethylurea.—Dimethylcarbamoyl chloride (58.5 g., 0.5 mole) was heated with anhydrous sodium carbonate (25.5 g., 0.25 mole) under the same conditions used in making dimethylacetamide. Reaction occurred relatively slowly, and it was necessary to redistil the original product twice more from small amounts of sodium carbonate before the density agreed with the reported value and no further change occurred in the refractive index. Nevertheless, a high yield was obtained (28 g., 96.5%). The product had the following properties: d^{15} 0.9726 (reported,[13] d^{15} 0.972); b.p. 175° (reported,[13] 177.5°); $n^{25}D$ 1.4495 (not previously reported).

A sample prepared from dimethylamine and phosgene had b.p. 176° and $n^{25}D$ 1.4492.

Reaction between Sodium Formate and Dimethylcarbamoyl Chloride.—When half-molar quantities of sodium formate and dimethylcarbamoyl chloride were heated together at 100° a vigorous reaction ensued. After a reflux period of 1 hr. in a bath at 170° the reaction mixture was distilled under high vacuum as in the other runs. The yield of slightly yellow distillate was only 21.5 g. (theory, 36.5 g.). This material had $n^{25}D$ 1.4348 (reported,[12] $n^{25}D$ 1.4269).

This product was redistilled from 5 g. of sodium formate at atmospheric pressure and only the portion boiling between 150 and 160° was collected. The distillate was colorless, but had not changed appreciably in refractive index ($n^{24}D$ 1.4330). A second run was conducted at 80° (the lowest temperature at which gas evolution occurred) until reaction was essentially complete. A small portion of the evolved gas was passed through 50% potassium hydroxide solution in a crude pneumatic trough and it was found that not all of this gas was carbon dioxide, since a substantial portion was not absorbed. The unabsorbed gas was found to burn and was assumed to be carbon monoxide. The distilled product from this reaction had $n^{23.5}D$ 1.4318, and the yield was 28.7 g. of a theoretical 36.5 g. of dimethylformamide.

Two more similar batches of crude product were prepared by this second procedure. These were combined and fractionally distilled through a Nester and Faust spinning band column at atmospheric pressure. Results obtained are given in Table I.

The dimethylformamide obtained in this distillation still had the odor of an amine. It was warmed with a small amount of phosphorus pentoxide and was redistilled under reduced pressure. By this procedure 31.0 g. of dimethylformamide was recovered; $n^{22.5}D$ 1.4300. Bruhl[14] observed a refractive index of 1.4294 at this temperature.

Comparison of infrared spectra showed that the tetramethylurea isolated in this distillation was identical with the sample previously prepared. It was not entirely pure, since its refractive index was low, $n^{25}D$ 1.4438.

(8) This experiment performed by Dr. T. L. Tolbert.

(9) Melting points uncorrected.

(10) Analyses and infrared spectra by personnel of the Analytical Section, Chemstrand Research Center, Inc.

(11) B. V. Ioffe, *Zh. Obsch. Khim.*, **25**, 902 (1955).

(12) J. R. Ruhoff and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 4012 (1937).

(13) A. P. N. Franchimont, *Rec. trav. chim.*, **3**, 226 (1884).

(14) J. W. Bruhl, *Z. physik. chem.*, **22**, 389 (1897).

TABLE I

DISTILLATION OF REACTION PRODUCT FROM SODIUM FORMATE AND DIMETHYLCARBAMOYL CHLORIDE[a]

Cut no.	B.p. (atm.), °C.	Wt., g.	Identity	Per cent of charge	Per cent yield[d]
1	Up to 150	10.5	Forerun[b]	15.8	..
2	152–153	35.5	Dimethylformamide	53.4	73.1
3	153–172	2.5	Mixed, intermediate	3.8	..
4	173–175	10.0	Tetramethylurea	15.0	13.7
4	...	3.0	Residue[c]	4.5	..

[a] Original charge, 66.6 g. [b] The forerun had a strong amine-like odor and probably consisted of dimethylformamide heavily contaminated with dimethylamine. [c] The residue did not consist of nonvolatile matter, since it had already been distilled once in the high vacuum system. Presumably it was largely tetramethylurea. [d] Based on dimethylcarbamoyl chloride.

N,N-Dibutyldodecanamide.—A sample of dibutylcarbamoyl chloride was prepared by the action of excess phosgene on dibutylamine. Obtained in 80% yield, it had b.p. 100.5°/4 mm. Interaction of this product (76 g., 0.385 mole, 10% excess) with sodium laurate (77.5 g., 0.35 mole) under the conditions used in making dimethylpalmitamide gave 92.1 g. (78%) of the desired dibutylamide, b.p. 182°/1.8 mm., $n^{25}D$ 1.4543.

Anal. Calcd. for $C_{20}H_{41}NO$: C, 77.17; H, 13.18; N, 4.50. Found: C, 77.45, 77.54; H, 12.97, 13.27; N, 4.88, 4.70.

Reaction of Potassium Oxalate with Dimethylcarbamoyl Chloride.—Potassium oxalate monohydrate was converted to the anhydrous salt by heating in a vacuum oven to 100–120° for 24 hr., and was then ground to pass a 100-mesh sieve. The salt (51.5 g., 0.31 mole) was treated with 134 g. (1.24 moles, 100% excess) of dimethylcarbamoyl chloride and the mixture was heated at 100° for 40 hr. and at 150° for 4 hr. Gas evolution was slow; a part of the evolved gas was alkali-insoluble and was flammable. It was assumed to be carbon monoxide.

Distillation of the reaction mixture in the vacuum system gave 96 g. of distillate, which was dissolved in 500 ml. of methanol and allowed to stand several days, to destroy excess dimethylcarbamoyl chloride. At the end of this time, the solution was neutralized to phenolphthalein with methanolic potassium hydroxide, and the precipitated potassium chloride was filtered off. Methanol and water were removed from the filtrate by distillation through a 1-ft. Vigreux column. Distillation of the residue through a spinning band column gave methyl N,N-dimethylcarbamate (b.p. 131°), followed by tetramethylurea (b.p. 172–175°, 22 g., 61% based on potassium oxalate, $n^{25}D$ 1.4490). The residue in the distilling flask (4 g., $n^{26}D$ 1.4518) was liquid and could not be induced to crystallize. The melting point of tetramethyloxamide has been reported as 80° by Franchimont and Rouffaer,[15] who prepared it by the action of sodium on dimethylcarbamoyl chloride in dry ether.

An authentic sample of tetramethyloxamide was prepared by heating ethyl oxalate (292 g., 2.0 moles) with dimethylamine (295 g., approximately 6.5 moles) in a low pressure oxygen cylinder on a steam bath overnight. Distillation of the reaction mixture gave 261 g. (90.6%) of tetramethyloxamide, b.p. 158–160°/20 mm. The distillate crystallized very easily. Upon recrystallization from warm ether, in which it was difficultly soluble, it melted at 78–80°. The characteristics of the product gave assurance that it would not have been overlooked in the preceding experiment.

In contrast to the slow reaction above, oxalic acid reacted rapidly with dimethylcarbamoyl chloride in pyridine.[6] Anhydrous oxalic acid (90 g., 1.0 mole) was mixed with 325 ml. of dry pyridine, and dimethylcarbamoyl chloride (215 g., 2.0 moles) was added slowly from a dropping funnel. Reaction took place almost at once, with effervescence. When addition had been completed, the mixture was allowed to stand overnight, and was then treated with an excess of concentrated potassium carbonate solution to destroy pyridine hydrochloride. Fractional distillation of the separated and filtered pyridine layer gave 51.5 g. (44%) of tetramethylurea (impure, redistilled to give 36.5 g. of product boiling constantly at 175°, $n^{24.5}D$ 1.4490.) Distillation of the residue gave 11 g. (7.6%) of material which solidified on cooling and which yielded 9 g. of recrystallized tetramethyloxamide melting at 78–80°.

(15) A. P. N. Franchimont and H. A. Rouffaer, *Rec. trav. chim.*, **13**, 341 (1894).

Reaction of Sodium Malonate with Dimethylcarbamoyl Chloride.—Anhydrous sodium malonate (148 g., 1.0 mole) was stirred with dimethylcarbamoyl chloride (215 g., 2.0 moles) in a 1-l., three-neck flask for 8.5 hr. at an internal temperature of 110–120°. A slow stream of dry nitrogen was passed through the flask continuously during this period. Loss of any volatile liquid was prevented by passing exit gases through an efficient condenser, followed by a trap immersed in an ice–hydrochloric acid mixture. At the end of the heating period, when evolution of carbon dioxide had essentially ceased, the mixture was cooled, diluted with methylene chloride, and filtered. The weight of sodium chloride obtained was 115.5 g. (theory, 117 g.).

Methylene chloride was stripped from the filtrate by distillation from a steam bath, finally at slightly reduced pressure. The residue was distilled from a steam bath at 10 mm., and the distillate so obtained (113 g.) was dissolved in 500 ml. of methanol and allowed to stand at room temperature for several days to convert any unchanged dimethylcarbamoyl chloride to methyl N,N-dimethylcarbamate. The higher boiling residue was distilled at 1 to 2 mm. from an oil bath at 150–160° to give 20.5 g. of distillate and 23.0 g. of tar. This distillate was redistilled through a short Vigreux column to give 15 g. (9.5%) of tetramethylmalonamide, b.p. 138–140°/4 mm., $n^{24.5}D$ 1.4875. Corresponding values for an authentic sample (prepared by heating ethyl malonate (2.0 moles) with dimethylamine (10.0 moles) and a few milliliters of a strong aqueous solution of dimethylamine hydrochloride in a bomb at 150° for 8 hr.) were b.p. 135–138°/3.8–4.0 mm., $n^{24}D$ 1.4915. The yield of authentic sample was 251 g. (79.5%).

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.16; H, 8.86; N, 17.72. Found: C, 53.15, 52.93; H, 9.07, 9.17; N, 17.89, 17.94.

After standing 3 days, the methanolic solution was neutralized to phenolphthalein with a standard solution of sodium methoxide in methanol. Titration indicated that 0.0613 mole of dimethylcarbamoyl chloride had been present in the original distillate. After filtration, the neutralized solution was stripped of methanol at the steam bath and the residue was distilled through a 15″ column packed with glass helices. A forerun consisting mostly of methyl N,N-dimethylcarbamate and weighing 10 g. was collected at 130–132°. This was followed by 6 g. of an intermediate cut, boiling from 132–165°. Finally, 83 g. of a cut boiling at 165–177° was collected. Careful fractionation indicated that this liquid was composed of dimethylacetamide and tetramethylurea. Its percentage composition was determined by comparison of its refractive index with a plot of refractive index *vs.* composition for the system dimethylacetamide–tetramethylurea. The observed value ($n^{25}D$ 1.4444) corresponded to that of a mixture of 60% tetramethylurea and 40% dimethylacetamide. Thus the yield of dimethylacetamide based on dimethylcarbamoyl chloride was 19.1%, and the yield of tetramethylurea on the same basis was 43.0%.

Tetramethylsuccinamide.—Sodium succinate (81 g., 0.5 mole) was heated on a steam bath with dimethylcarbamoyl chloride (107.5 g., 1.0 mole) with magnetic stirring. Evolution of carbon dioxide was moderately vigorous. Heating was continued for about 12 hr. At the end of this period the mixture was cooled and filtered, the solid being washed with a little dimethylacetamide. Concentration of the filtrate was effected by distillation from a steam bath at 15–20 mm. The residue, containing possibly succinic anhydride and dimethylcarbamoyl chloride in addition to the desired product, was mixed with 200 ml. of concentrated ammonium hydroxide and stirred for 30 min. to ensure destruction of these substances. Product was then extracted from the dark solution by shaking three times with equal volumes of chloroform. After removal of chloroform from the combined extracts, the residue was distilled at a pressure of about 1 mm. Following a very small forerun, tetramethylsuccinamide was collected at 112–113° as a colorless liquid which rapidly set to a white solid. The yield of this product, m.p. 84.5–85.5°, was 42 g. (49%). Franchimont[16] reported a melting point of 81°.

Tetramethyladipamide.—Sodium adipate (100 g., 0.53 mole) was heated with dimethylcarbamoyl chloride (150 g., 1.4 moles, 40% excess) at 130° with stirring until evolution of carbon dioxide ceased. While the mixture darkened appreciably, it was noted that it never became so dark as the reaction mixtures from the lower dicarboxylic acids. Without cooling, the mixture was slowly diluted with chloroform and the solution was filtered through a mat of filter aid. The filtrate was stripped of chloro-

(16) A. P. N. Franchimont, *ibid.*, **4**, 202 (1885).

form at the steam bath and the residue distilled under reduced pressure (approx. 1 mm.). Crude product (91 g., 86.5%) was collected at 160–165°. On redistillation at 0.7 mm., this product was still yellowish in color and had a b.p. of 137–145°. This distillate was crystallized from 2.5 l. of isopropyl ether to give 80 g. (77%) of white needles, m.p. 82–83°.

Anal. Calcd. for $C_{10}H_{20}O_2N_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 60.11, 60.34; H, 10.16, 10.06; N, 14.02, 14.06.

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A Direct Synthesis of Sulfonium Perchlorates

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A few examples of the synthesis of trialkylsulfonium salts by direct alkylation of organic sulfides with perchloric acid–alcohol mixtures have appeared in the literature.[1,2] Recently the utility of this reaction has been demonstrated in the synthesis of 5-dimethylsulfonium-2-pentanone perchlorate from 5-methylmercapto-2-pentanone and perchloric acid in methanol.[3] The renewed interest in such reactions reported by Overberger, *et al.*,[4] prompt us to report our findings.

When equimolar quantities of dibenzyl sulfide and 70% aqueous perchloric acid were heated in benzyl alcohol solution for 2.5 hours at 65–70°, dilution with ether afforded an excellent yield of tribenzylsulfonium perchlorate. This reaction was extended to a number of aliphatic alcohol-sulfide systems, and gave surprisingly good yields of pure sulfonium salts if the time, temperature, and most important, the water content of the system were properly adjusted. The products were obtained as colorless crystals of high purity, and were dried for elemental analysis without recrystallization. The properties of the salts are recorded in Table I.

TABLE I

SULFONIUM PERCHLORATES—$R_3S^{(+)}ClO_4^{(-)}$

R	M.p.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzyl	171.5–174°[a]	62.29	62.58	5.23	5.27
n-Butyl	94–95°[b]	47.25	47.37	8.99	8.99
n-Propyl	155–157°	41.35	42.00	8.12	8.14
Ethyl	111.5–112.5°	32.95	32.74	6.91	6.73

[a] Reported 178°; J. de Pascual Teresa, *Anales real soc. españ. fis. quim.*, **45B**, 235 (1949). [b] reported 94°; ref. 5.

Discussion and Results

The initial attempts to prepare *n*-alkylsulfonium salts under the conditions used for the benzyl compound afforded only low yields. Even after heating the mixtures under reflux for 24 hours, the yields ranged from less than 1% (ethyl) through 24% (*n*-propyl) to 46% (*n*-butyl). A remarkable improvement was achieved when water was removed from the mixture by azeotropic distillation. Under these conditions tri-*n*-butylsulfonium perchlorate was obtained in a yield of 84%. The limited yield in the presence of water was in fact due to an equilibrium phenomenon. This was confirmed when the yields after 24 hours (46%) and 48 hours (45%) were shown to be the same. The equilibrium involved was not, however, reaction 1, since 92% of tri-*n*-butylsulfonium perchlorate was recovered unchanged after 24 hours of heating in butanol containing the same amount of water as was present under the conditions of synthesis.

$$Bu_3S^{(+)}ClO_4^{(-)} + H_2O \rightleftharpoons Bu_2S + BuOH_2^{(+)} + ClO_4^{(-)} \quad (1)$$

It was determined that one source of the variation in yields from the three aliphatic sulfides was the difference in boiling points of the alcohols used as solvents. A reaction carried out in a sealed vessel at 120° afforded 16% triethylsulfonium perchlorate without removal of water.

It is of interest to note the apparent total absence of carbon-skeleton rearrangement in the sulfonium salts. The tri-*n*-butylsulfonium perchlorate had a melting point identical with the previously reported value,[5] and the infrared spectra of all the compounds indicated them to be free of chain branching.

Several experiments were carried out without success in attempts to detect perchlorate ester formation by chemical means. A mixture of butanol and perchloric acid refluxed for 24 hours in the absence of dibutyl sulfide and titrated with potassium butoxide retained all of the original acid concentration. When water was azeotropically removed from such a mixture, only dark polymer was obtained. Another possible alkylating species is of course the alkyloxonium on $ROH_2^{(+)}$.[4]

If our conception of the reaction path is correct, it should be possible to accomplish direct synthesis of unsymmetrical sulfonium salts without the troublesome "alkyl scrambling" which frequently occurs in the synthesis of sulfonium salts from sulfides and alkyl halides.[6] Only the alkyl group corresponding to the alcohol should be introduced, and the non-nucleophilic nature of perchlorate ion as compared to halide ion should make the process irreversible. This possibility has been demonstrated in one case, the benzylation of dibutyl sulfide, which affords benzyldi-(*n*-butyl)-sulfonium perchlorate as a single product in 83.5% yield.

Experimental

Dialkyl sulfides were Eastman Kodak White Label materials. Perchloric acid was Baker Analyzed reagent grade. Melting points are uncorrected and were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were by Dr. S. M. Nagy of the Microchemical Laboratory, Massachusetts Institute of Technology. Infrared spectra were obtained in potassium bromide pellets on a Perkin–Elmer Model 21 spectrophotometer by Mr. Walter Legsdin and his associates of these laboratories.

Tribenzylsulfonium Perchlorate.—A solution of dibenzyl sulfide (0.77 g., 3.59 mmoles) in 5 ml. of benzyl alcohol was mixed with 0.512 g. (3.59 mmoles) of 70% perchloric acid. The resulting

(1) (a) O. Hinsberg, *Ber.*, **62**, 2167 (1929); (b) O. Hinsberg, *ibid.*, **69**, 492 (1936).

(2) J. de Pascual Teresa and H. Sanchez Bellido, *Anales real soc. españ. fis. quim.*, **50B**, 71 (1954).

(3) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).

(4) C. G. Overberger, P. Barkan, A. Lusi, and H. Ringsdorf, *ibid.*, **84**, 2814 (1962).

(5) E. R. Kline and C. A. Kraus, *ibid.*, **69**, 814 (1947). We did not find our sample of this compound to be unstable.

(6) W. Steinkopf, "Die Methoden der Organischen Chemie," 3rd ed., J. Houben, ed., Vol. 3, Verlag George Thieme, Leipzig, 1930, p. 1261.

mixture was heated for 2.5 hr. at 60–70°, cooled to room temperature, diluted with ether, and filtered. The product was washed with ether and dried, leaving 1.32 g. (91%) of colorless plates which were analyzed directly.

Trialkylsulfonium Perchlorates. (A) **Without Removing Water.**—A solution of 5 mmoles of dialkyl sulfide in 5 ml. of the corresponding alcohol was mixed with 0.72 g. (5 mmoles) of 70% perchloric acid and heated under reflux for 24 hr. The mixture was cooled to room temperature, diluted with 50 ml. of ether, and filtered to collect any sulfonium salt formed. Under these conditions the following yields were obtained: *n*-butyl, 46% (45% after 48 hr. reflux); *n*-propyl, 24%; ethyl, < 1%. The yield of triethylsulfonium perchlorate was raised to 15% if the reaction was carried out in ethanol solution in a sealed vessel at 120° for 24 hr.

(B) **With Removal of Water.**—A solution of 0.73 g. (5 mmoles) of di-*n*-butyl sulfide in 15 ml. of *n*-butyl alcohol was mixed with 0.72 g. (5 mmoles) of 70% perchloric acid and refluxed under a condenser with provision for periodic removal of solvent by distillation. A total of 6 ml. of distillate was collected over a 24-hr. period. Near the end of the reflux period an insoluble oil appeared in the reaction flask. The mixture was cooled and poured into 50 ml. of ether, precipitating 1.27 g. (84%) of tri-*n*-butylsulfonium perchlorate.

(C) **Benzyldi(*n*-butyl)sulfonium Perchlorate.**—A mixture of di-*n*-butyl sulfide (0.53 g., 3.59 mmoles), 70% perchloric acid (0.52 g., 3.59 mmoles) and 5 ml. of benzyl alcohol was heated at 70–80° for 4 hr., cooled and diluted with ether. The white solid product (1.02 g., 83.5%) had m.p. 70–72°. Recrystallization from acetone/ether in a Dry Ice–acetone bath left the melting point (71–73°) essentially unchanged.

Anal. Calcd. for $C_{15}H_{25}ClO_4S$: C, 53.48; H, 7.48. Found for crude product: C, 54.05; H, 7.48. Found after purification: C, 53.25; H, 7.21.

Our product was identical with a sample synthesized by the reaction of benzyl bromide and dibutyl sulfide in ether at 25° followed by conversion to the perchlorate with perchloric acid; m.p. 70–72°, mixture m.p. 72.5–73.5°; found on elemental analysis C, 53.44; H, 7.36. Our directly synthesized product thus is a single compound of unambiguous structure.

The formation of the sulfonium salts under the conditions of synthesis was shown not to be a reversible process by refluxing 3.02 g. (10 mmoles) of tri-*n*-butylsulfonium perchlorate, 10.0 ml. of dry butanol, and 0.43 g. of water for 24 hr. These conditions duplicate the solvent composition in the synthetic reaction (46% yield), but 2.78 g. (92%) of the sulfonium salt was recoverable unchanged by dilution with ether.

A 0.5 *N* solution of potassium *n*-butoxide was prepared by dissolving cautiously 9.775 g. (0.25 g.-atom) of potassium metal in 500 ml. of *n*-butyl alcohol, previously distilled from sodium. This reagent, prepared and stored under nitrogen, was used to titrate the perchloric acid content of butanol solutions[7] after refluxing for 24 hr. in the absence of dialkyl sulfide. The reagent was standardized by titration against benzoic acid in butanol. It was shown that a solution of 14.4 g. (0.1 mole) of 70% perchloric acid in 100 ml. of butanol retained 101% of the original acid concentration after 24 hr. reflux. Unfortunately, azeotropic removal of water led to formation of a black polymer in the butanol mixture.

Acknowledgment.—The authors wish to thank Professor D. H. R. Barton for a helpful discussion of this work.

(7) This is a modification of a standard method for the quantitative determination of potassium; see F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. II, 9th ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 272.

O-Acylation of Tyrosine during Peptide Synthesis

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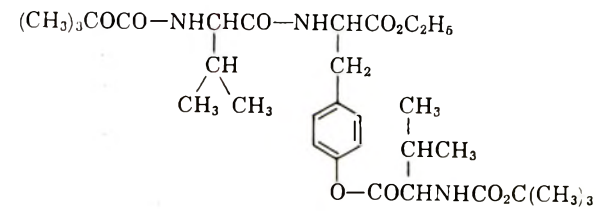
In the synthesis of angiotensin II amide-1 a great deal of difficulty was encountered in forming the valyl-tyrosine bond.[1,2] Only after many attempts were we able to obtain a 50% yield[2] (subsequently raised to 67%) of ethyl *t*-butyloxycarbonyl-L-valyl-L-tyrosinate (I) from N,N′-carbonyldiimidazole,[3,4] ethyl L-tyrosinate[5] and *t*-butyloxycarbonyl-L-valine.[6] The *N,N′*-dicyclohexylcarbodiimide,[7] tetraethylpyrophosphite,[8] and *p*-nitrophenyl ester[9] methods gave only intractable oils. The mixed anhydride method[10] gave a 65% yield of I as the two isomorphic forms (m.p. 139.5–141° and m.p. 151–152°) described earlier.[2] Dimorphism also occurred with N,N′-carbonyldiimidazole preparations but in an erratic fashion.

Since we were particularly interested in N,N′-carbonyldiimidazole, the formation of I was examined in more detail. A sample of a crude reaction mixture of I was separated on a silica gel column and ethyl N,O-bis(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate (II) was detected in a ratio of one part of II to eight parts of I. The structure of II was proved by synthesis



II

from I and *t*-butyloxycarbonyl L-valine using N,N′-carbonyldiimidazole as the condensing agent. It was further confirmed by ultraviolet spectra studies.

Of the methods studied the mixed anhydride method gave the most easily purified dipeptide I. Replacing the *t*-butyloxycarbonyl group by a carbobenzoxy group, as in ethyl carbobenzoxy-L-valyl-L-tyrosinate, gave similar findings. Table I shows that the purest product again resulted from mixed anhydride coupling. The melting point was used as the criterion of purity.

TABLE I

PREPARATION OF Z·Val-Tyr·OEt

Method	Yield, %	M.p. °C.
Mixed anhydride[a,b]	64	155–157°
p-Nitrophenyl ester[a,c]	67	145–147°
N,N′-Carbonyldiimidazole[d]	22	152–154°

[a] These literature results have been repeated and confirmed. [b] L. T. Skeggs, Jr., K. E. Lentz, J. R. Kahn, and N. P. Shumway, *J. Exptl. Med.*, 108, 283 (1958). [c] R. Schwyzer, B. Iselin, H. Kappeler, B. Riniker, W. Rittel, and H. Zuber, *Helv. Chim. Acta*, 41, 1273 (1958). [d] Worked up by the procedure cited in footnote *b*.

(1) Reported at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 21, 1962.

(2) R. Paul and G. W. Anderson, *J. Org. Chem.*, **27**, 2094 (1962).

(3) H. A. Staab, *Ann.*, **609**, 75 (1957).

(4) G. W. Anderson and R. Paul, *J. Am. Chem. Soc.*, **80**, 4423 (1958); R. Paul and G. W. Anderson, *ibid.*, **82**, 4596 (1960).

(5) E. Fischer, *Ber.*, **34**, 433 (1901).

(6) G. W. Anderson and A. C. McGregor, *J. Am. Chem. Soc.*, **79**, 6180 (1957); L. A. Carpino, C. A. Giza, and B. A. Carpino, *ibid.*, **81**, 955 (1959); R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959). Using Carpino's reagent we obtained a 50% yield of crystalline *t*-butyloxycarbonyl-L-valine, m.p. 78.5–82°; $[\alpha]^{25}D$ −5.7° (c 1.2, acetic acid).

(7) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(8) G. W. Anderson, J. Blodinger, and A. D. Welcher, *ibid.*, **74**, 5304 (1952).

(9) M. Bodanszky, *Nature*, **175**, 685 (1955).

(10) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

TABLE II

ULTRAVIOLET STUDIES[a]

Compound	Neutral media maxima		Basic media maxima[b]	
H·Tyr·OH[c] (L)	λ 223 (ε 8440)	λ 275 (ε 1410)	λ 240 (ε 11,600)	λ 294 (ε 2480)
H·Tyr·OEt (L)	λ 226 (ε 9180)	λ 278 (ε 1710)	λ 245 (ε 12,700)	λ 295 (ε 2550)
H·Tyr(OBz)·OH[d] (L)	λ 225 (ε 1210)	λ 275 (ε 107)	Obscured	λ 275 (ε 128)
B·Val-Tyr·OEt (2L)[e]	λ 225 (ε 9700)	λ 277 (ε 1640)	λ 245 (ε 13,450)	λ 295 (ε 2460)
N,O-(B·Val)$_2$-Tyr·OEt (3L)	λ 220 (ε 9010)	λ 265 (ε 322)	λ 245 (ε 13,150)	λ 295 (ε 2450)
N,O-(Ac)$_2$·Tyr·OH[c] (DL)		λ 264 (ε 321)		λ 295 (ε 2180)

[a] Read on a Beckman DU spectrophotometer or a Cary II recording spectrophotometer. [b] Two drops of 2 *N* sodium hydroxide were added to 3 ml. of neutral solution in a cuvette. The peaks were read 5 min. later. [c] Mann Research Laboratories. [d] Cyclo Chemical Corp. This compound is very insoluble in water and the extinction coefficient is probably low. The relative values from neutral to basic solution are accurate, however. [e] B = *t*-Butyloxycarbonyl.

Experimental

Isolation of By-products.—To a solution of 2.18 g. (10.0 mmoles) of *t*-butyloxycarbonyl-L-valine[6] in 10 ml. of tetrahydrofuran was added 1.95 g. (10.0 mmoles, 83% purity) of N,N′-carbonyldiimidazole.[3] After 30 min., 2.09 g. (10.0 mmoles) of ethyl L-tyrosinate[5] was added and the solution was left standing over the weekend. It was then concentrated under vacuum. The residue was taken up in 50 ml. of ether, washed with 40 ml. of *N* sulfuric acid, 20 ml. of saturated aqueous sodium bicarbonate and 40 ml. of water. The ethereal layer was dried over anhydrous sodium sulfate and evaporated to dryness. Scratching solidified the residue, giving 3.73 g. (91%), m.p. 127.5–150°. One gram of this solid was dissolved in chloroform and placed on 30 g. of silica gel in a column, 3.3 cm. × 8.5 cm. The column was eluted with seven 100-ml. portions of 20% ethyl acetate–80% chloroform, then six 100-ml. portions with progressively higher percentages of ethyl acetate. Each fraction was examined by thin layer chromatography on silica gel using 30% ethyl acetate in chloroform. On development with chlorine gas and *o*-tolidine–potassium iodide reagent,[11] fraction 3 gave one spot R_f 0.62 and fraction 4 showed two spots R_f 0.38 and 0.61. Fractions 5–9 gave only one spot at 0.38 as did a pure sample of I. The other fractions did not contain any material. Fraction 4 was rechromatographed and the new fractions combined with the corresponding old. Fractions 5–9 were recrystallized from ethyl acetate-petroleum ether to give 0.55 g. (50%) of I, m.p. 140–140.5°. Fraction 3 was recrystallized from 3 ml. of isopropyl alcohol to give 0.046 g. (4.2%) of a compound, m.p. 125–126.5°, presumed to be ethyl N,O-bis(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate (II). The ratio of II to I was 1 to 8. A mixed melting point of II with an authentic sample (see below) gave no depression. Both had identical R_f's on silica gel thin layer chromatography in 30% ethyl acetate in chloroform. The ultraviolet spectra was identical to that of an authentic sample of II.

The sulfuric acid wash of the crude product from above was examined for ethyl O-(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate, this type of compound having been described[12] recently. The acidic wash was neutralized with sodium bicarbonate and quickly extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and then evaporated to dryness. An ultraviolet spectrum was taken on this residue in neutral and in basic media. Normally, compounds with a free phenolic group such as tyrosine, ethyl tyrosinate and I experience a shift in from λ278 to λ295. This is accompanied by an increase in optical density of a factor of 1.5. O-Acylated compounds, as described below, have a shift from λ 264 to λ 295 with a 7.7-fold shift in optical density. The residue had a 2.3-fold shift from λ 277 to λ 295 indicating the presence of an O-acylated phenol. The λ 264 peak being small was obscured in neutral media. Thin layer chromatography of this residue on silica gel showed the presence of an unknown that was neither starting material nor product. No trace of II was detected.

Ethyl N,O-Bis(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate (II).—After 1.57 g. (7.23 mmoles) of *t*-butyloxycarbonyl-L-valine had been dissolved in 10 ml. of tetrahydrofuran, 1.41 g. (7.23 mmoles, 83% pure) of N,N′-carbonyldiimidazole was added. Thirty minutes later 2.95 g. (7.23 mmoles) of I was added. After 1 hr. the solution was concentrated under vacuum to a clear oil. The oil was worked up 16 hr. later by dilution with 10 ml. of water and 20 ml. ether. The ethereal layer was dried over anhydrous sodium sulfate, evaporated to dryness and the residue dissolved in chloroform. This was placed on a silica gel column and eluted with 20% ethyl acetate–80% chloroform. The ultraviolet absorption of each fraction was taken at λ 265 and λ 277. When a fraction came off whose absorption was greater at λ 277 than at λ 265, it was assumed the N,O-compound (II) was off the column. The purity of the various fractions was checked by thin layer chromatography. Those fractions with the correct ultraviolet absorption and with only one spot, R_f 0.62, were combined and recrystallized from 30 ml. of isopropyl alcohol. The product crystallized and was collected, 2.05 g. (34%), m.p. 124.5–126.5°, $[\alpha]^{25}D$ −35.4° ± 1.2° (*c* 4, ethanol).

Anal. Calcd. for $C_{31}H_{49}N_3O_9$: C, 61.26; H, 8.13; N, 6.91. Found: C, 61.48; H, 8.26; N, 7.09.

Proof of Structure.—A spot of I and one of II on paper were sprayed with ferric chloride in *n*-butyl alcohol and heated to 60° for 48 hr. The N,O-compound (II) gave a negative test indicating the phenolic hydroxyl was not free. The dipeptide (I) gave a positive test.

Ultraviolet spectra are described in Table II. Since phenolic esters are activated, one would expect base to convert II to I. The spectra bear this out. An ultraviolet spectrum of N,O-diacetyl-DL-tyrosine[13] gave detailed structure at the λ 264 peak (shoulder at λ 258, maximum at λ 264 and small peak at λ 272) corresponding exactly to the fine structure of the ethyl N,O bis(*t*-butyloxycarbonyl-L-valyl)-L-tyrosinate (II) peak at λ 265.

Acknowledgment.—We thank Mr. L. Brancone and staff for analysis and Mr. W. Fulmor and staff for optical rotations.

(13) Mann Research Laboratories.

(11) F. Reindel and W. Hoppe, *Ber.*, **87**, 1103 (1954).

(12) J. Ramachandran, Abstracts of Papers presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961, p. 49C.

Preparation and Reactions of Trialkyltinlithium

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Recent reports from this laboratory[1b] have shown a convenient preparation for triphenyltinlithium. This organometallic can be prepared through the reaction between metallic lithium and either triphenyltin chloride or hexaphenylditin in tetrahydrofuran (THF). This paper concerns the extension of the same general synthetic procedure to prepare trialkyltinlithium compounds.

Trialkyltinlithium compounds have been prepared

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previously by Gilman and Rosenberg[2] through the reaction between the alkyllithium compound and stannous chloride. Tributyltinlithium was treated with

$$2RLi + SnCl_2 \longrightarrow R_2Sn + 2LiCl \quad (1)$$

$$R_2Sn + RLi \longrightarrow R_3SnLi \quad (2)$$

$$R = C_2H_5 \text{ and } C_4H_9$$

butyl bromide to yield tetrabutyltin (52.5%) and with iodobenzene to yield a mixture of tetrabutyltin (27.8%) and tributylphenyltin (27.6%). Recently Blake, Coates, and Tate[3] utilizing the same procedure prepared tributyltinlithium and studied the reaction between it and chlorotrimethylsilane. The expected compound, trimethylsilyltributyltin $[(CH_3)_3SiSn(C_4H_9)_3]$, was not obtained. According to these investigators the reaction products obtained, butyltrimethylsilane and tetrabutyltin, indicated that the tributyltinlithium prepared according to equation 1 and 2 acted as though it were a mixture of butyllithium and dibutyltin.

In our studies on the preparation of trialkyltinlithium compounds we have found that the organometallic forms by the same mechanism suggested for the preparation of the triphenyltinlithium compound.[1b]

$$R_3SnCl + 2Li \longrightarrow R_3SnLi + LiCl \quad (3)$$

$$R_3SnLi + R_3SnCl \longrightarrow R_3SnSnR_3 + LiCl \quad (4)$$

$$R_3SnSnR_3 + 2Li \longrightarrow 2R_3SnLi \quad (5)$$

$$R = CH_3 \text{ and } C_4H_9$$

This is based on the following observations: (a) both the R_3SnCl and R_3SnSnR_3 will react with lithium in tetrahydrofuran to produce R_3SnLi, and (b) in the preparation of the organometallic from R_3SnCl, a by-product always found was the R_3SnSnR_3.

The trialkyltinlithium compounds gave a positive Color Test I[4] which is conveniently used to follow reactions of the organometallic with other reagents. Attempts to prepare the trialkyltinlithium from the trialkyltin chloride and metallic lithium in diethyl ether were unsuccessful. The trialkyltinlithium prepared in this study via equations 3, 4, and 5 undergoes some interesting reactions as seen in Table I. In no case was R_4Sn isolated, which is in contrast with the preparations mentioned above[2,3] which utilized equations 1 and 2.

TABLE I

R_3SnLi	Reactant	Product	% Yield
$(CH_3)_3SnLi^a$	C_2H_5Br	$(CH_3)_3SnC_2H_5$	59
$(CH_3)_3SnLi^a$	$(C_4H_9O)_3PO$	$(CH_3)_3SnC_4H_9$	31
$(CH_3)_3SnLi^a$	$(C_6H_5)_3SnCl$	$(C_6H_5)_3SnSn(CH_3)_3$ +	51
		$(C_6H_5)_3SnSn(C_6H_5)_3$	32
$(C_4H_9)_3SnLi^a$	H_2O	$(C_4H_9)_3SnH$ +	54
		$(C_4H_9)_3SnSn(C_4H_9)_3$	29
$(C_4H_9)_3SnLi^b$	H_2O	$(C_4H_9)_3SnH$ +	67
		$(C_4H_9)_3SnSn(C_4H_9)_3$	20
$(C_4H_9)_3SnLi^b$	$(CH_3)_3SiCl$	$(C_4H_9)_3SnSi(CH_3)_3$	78

[a] Prepared from R_3SnCl. [b] Prepared from R_3SnSnR_3.

In the reaction between trimethyltinlithium and triphenyltin chloride a metal–halogen interchange must have occurred; this would account for obtaining hexaphenylditin as one of the products. No attempt was made to isolate hexamethylditin, the other product of the metal–halogen interchange. In contrast with the previously reported work[3] (equations 1 and 2), tri-*n*-butyltinlithium (prepared *via* equations 3, 4, and 5) does react with chlorotrimethylsilane to give the desired product, trimethylsilyltributyltin, in 78% yield.

The results of this investigation and those reported earlier for triphenyltinlithium[1b] provide a convenient general method for the preparation of either trialkyltinlithium or triphenyltinlithium from the reaction of lithium in tetrahydrofuran with either R_3SnCl or R_3SnSnR_3.

Experimental

Preparation of Trimethyltinlithium.—A solution of 39.8 g. (0.2 mole) of trimethyltin chloride in 150 ml. of tetrahydrofuran was added to a stirred, cooled suspension of 13.9 g. (2 g.-atoms) of lithium clippings in 150 ml. of tetrahydrofuran slowly enough to enable maintaining the mixture below 5°. After only one-third of the solution had been added the light green mixture gave an intense positive Color Test I.[4] The reaction was exothermic and between 1 and 2 hr. after the addition had been completed the mixture turned dark green. After being stirred for 3 hr. the mixture was filtered through glass wool and derivatives were prepared as described below.

Preparation of Ethyltrimethyltin.—To a stirred solution of trimethyltinlithium prepared as described above from 0.2 mole of trimethyltin chloride was added a solution of 21.8 g. (0.2 mole) of ethyl bromide in 160 ml. of tetrahydrofuran slowly enough to enable maintaining the mixture below 0°. The light brown mixture gave a negative Color Test I and was hydrolyzed with saturated ammonium chloride. The organic layer was combined with ether extracts of the aqueous layer and dried over magnesium sulfate. Evaporation of solvents left a liquid residue which was distilled to give 22.6 g. (58.7%) of ethyltrimethyltin, b.p. 104–105.5° (lit.,[5] b.p. 106° at 746 mm.), $n^{20}D$ 1.4527.

Anal. Calcd. for $C_5H_{14}Sn$: C, 31.14; H, 7.32. Found: C, 31.10, 30.88; H, 7.02, 7.08.

Preparation of *n*-Butyltrimethyltin.—To a stirred solution of trimethyltinlithium prepared as described above from 0.05 mole of trimethyltin chloride was added a solution of 13.3 g. (0.05 mole) of tri-*n*-butyl phosphate in 30 ml. of tetrahydrofuran during 25 min. The black mixture gave a negative Color Test I and was stirred for 80 min., then was hydrolyzed with water. The organic layer was combined with ether extracts of the aqueous layer and dried over sodium sulfate. Evaporation of solvents left a liquid residue which was distilled to give 3.4 g. (31%) of *n*-butyltrimethyltin, b.p. 46–46.5° (14 mm.) (lit.,[5] b.p. 149–150° at 724 mm.), $n^{20}D$ 1.4567.

Anal. Calcd. for $C_7H_{18}Sn$: C, 38.06; H, 8.21. Found: C, 38.38, 37.83; H, 8.11, 8.21.

Preparation of 1,1,1-Trimethyl-2,2,2-triphenylditin.—To a stirred solution of trimethyltinlithium prepared as described above from 0.1 mole of trimethyltin chloride was added a solution of 38.5 g. (0.1 mole) of triphenyltin chloride in 75 ml. of tetrahydrofuran slowly enough to enable maintaining the mixture below 0°. The dark brownish black mixture gave a negative Color Test I and was hydrolyzed with saturated ammonium chloride. The organic layer was combined with ether extracts of the aqueous layer and dried over magnesium sulfate. Evaporation of solvents left a white solid which was swirled with boiling ethanol leaving undissolved 11.3 g. (32.3%) of hexaphenylditin, m.p. 230–234° cor., identified by a mixture melting point with an authentic sample. From the filtrate was obtained 26.2 g. (50.9%) of 1,1,1-trimethyl-2,2,2-triphenylditin, m.p. 103–106° cor. Recrystallization from ethanol gave white crystals, m.p. 107–108.5° cor. (lit.,[6] m.p. 106°).

Anal. Calcd. for $C_{21}H_{24}Sn_2$: C, 49.09; H, 4.71; Sn, 46.20; mol. wt., 513.8. Found: C, 49.10, 49.22; H, 4.67, 4.74; Sn, 45.61, 46.04; mol. wt., 525, 507.

Preparation of Tri-*n*-butyltinlithium from Hexa-*n*-butylditin.—A stirred mixture of 58.0 g. (0.1 mole) of hexa-*n*-butylditin, 6.9 g.

(2) H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **75**, 2507 (1953).
(3) D. Blake, G. E. Coates, and J. M. Tate, *J. Chem. Soc.*, 618 (1961).
(4) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).
(5) Z. M. Manulkin, *J. Gen. Chem. USSR*, **13**, 42 (1943); *Chem. Abstr.*, **38**, 331 (1944).
(6) C. A. Kraus and R. M. Bullard, *J. Am. Chem. Soc.*, **48**, 2131 (1926).

(1.0 g.-atom) of lithium clippings, and 200 ml. of tetrahydrofuran, after not reacting for 30 min. at room temperature, was heated to 53°. Within 4 min. the mixture turned olive-green, evolved a small amount of heat, and gave a strong positive Color Test I. After being stirred for 4 hr. the black mixture gave a very intense positive Color Test I. The mixture was filtered through glass wool and derivatives were prepared as described below.

Preparation of Trimethylsilyltri-*n*-butyltin.—To a stirred solution of tri-*n*-butyltinlithium prepared as described above from 0.1 mole of hexa-*n*-butylditin, was added a solution of 23.9 g. (0.22 mole) of chlorotrimethylsilane in 100 ml. of tetrahydrofuran slowly enough to enable maintaining the mixture below 0°. The black mixture gave a negative Color Test I and was filtered. After distilling the tetrahydrofuran and filtering the lithium chloride, the residue was vacuum distilled to give 56.6 g. (77.8%) of trimethylsilyltri-*n*-butyltin, b.p. 88° (0.2 mm.), $n^{20}D$ 1.4873. The infrared spectrum shows peaks at 1250 cm.$^{-1}$ and 840 cm.$^{-1}$ characteristic of the trimethylsilyl group.

Anal. Calcd. for $C_{15}H_{36}SiSn$: C, 49.60; H, 9.99. Found: C, 49.40; 49.46; H, 9.73, 9.70.

Preparation of Tri-*n*-butyltin Hydride from Hexa-*n*-butylditin.—A solution of tri-*n*-butyltinlithium prepared as described above from 0.1 mole of hexa-*n*-butylditin was hydrolyzed with water. The organic layer was combined with ether extracts of the aqueous layer and dried over magnesium sulfate. Evaporation of solvents left a liquid residue which was distilled to give 39.1 g. (67%) of tri-*n*-butyltin hydride, b.p. 63–64° (0.41–0.48 mm.) (lit.,[7] b.p. 76–81° at 0.7–0.9 mm.), $n^{22}D$ 1.4721.

Anal. Calcd. for $C_{12}H_{28}Sn$: C, 49.52; H, 9.69. Found: C, 49.56, 49.26; H, 9.35, 9.40.

Hexa-*n*-butylditin was also obtained (11.8 g., 20%); this was identified by comparison of its infrared spectrum with that of an authentic sample.[8]

Preparation of Tri-*n*-butyltinlithium from Tri-*n*-butyltin Chloride.—A mixture of 65.1 g. (0.2 mole) of tri-*n*-butyltin chloride and 15.0 g. (2.0 g.-atoms) of lithium clippings was stirred for 1 hr. Although the mixture turned dark, Color Test I was negative. When tetrahydrofuran (100 ml.) was slowly added the reaction became exothermic, the mixture turned dark green, and Color Test I became positive. After being stirred for 2 hr. the mixture was filtered through glass wool and a derivative was prepared as described below.

Preparation of Tri-*n*-butyltin Hydride from Tri-*n*-butyltin Chloride.—A solution of tri-*n*-butyltinlithium prepared as described above from 0.2 mole of tri-*n*-butyltin chloride was hydrolyzed with water. The mixture was treated in the same way as described above in the preparation of tri-*n*-butyltin hydride from hexa-*n*-butylditin. The yield of tri-*n*-butyltin hydride was 31.6 g. (54%), b.p. 46–49° (0.18 mm.), $n^{22}D$ 1.4720. Hexa-*n*-butylditin was also obtained (16.5 g., 28%), $n^{22}D$ 1.5089. The infrared spectrum of this material was identical with that of an authentic sample.[8]

(7) J. G. Noltes and G. J. M. van der Kerk, "Functionally Substituted Organotin Compounds," Tin Research Institute, Greenford, Middlesex, England, 1958, p. 94.

(8) The hexa-*n*-butylditin was obtained from Metal and Thermit Corp., Rahway, N. J. The sample, $n^{25}D$ 1.5090, was analytically pure.

The Polarographic Reduction of *p*-Fluoroiodobenzene

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The polarographic reduction of *p*-fluoroiodobenzene was found to proceed normally to fluorobenzene contrary to the report of Colichman and Liu.[1] The early wave at −0.72 volt ascribed by these investigators to the reduction of the fluorine atom, is probably caused by the presence of *p*-nitrofluorobenzene as an impurity.

(1) E. L. Colichman and S. K. Liu, *J. Am. Chem. Soc.*, **76**, 913 (1954).

TABLE I

POLAROGRAPHIC BEHAVIOR OF SUBSTITUTED BENZENES

Benzenes	$E_{1/2}$ (S.C.E.)	I_d
Iodobenzene	−1.73	2.86
p-Fluoroiodobenzene	−1.69	3.15
p-Nitrofluorobenzene	−0.74	5.40
p-Diiodobenzene	−1.61	2.96
	−1.79	2.96

The purified sample used in this study from vapor-phase chromatographic analysis still contained about 1% of this compound. *p*-Diiodobenzene which could arise in the preparation of *p*-fluoroiodobenzene from *p*-fluoroaniline was eliminated as another possible contributor to this early wave by its polarographic behavior.

The polarographic data for the various compounds and iodobenzene are reported in Table I. *p*-Diiodobenzene gave two waves of equal height close together. The half-wave potentials were calculated by using one-fourth and three-fourths of the total diffusion current.

The half-wave potentials for the first three compounds are slightly more negative than the values reported by Colichman.[1] The value for iodobenzene is, however, in good agreement with the data reported by others.[2]

Experimental

The current–voltage curves were obtained with a Sargent Model XXI Polarograph.

All measurements were made in a water thermostat at 25° ± 0.1° using an H cell fitted with a calomel electrode. The buffer solution used had a pH of 7 and contained 0.060 *M* lithium chloride, 0.024 *M* potassium acetate, and 0.013 *M* acetic acid in 90% alcohol. The composition was the same as that used by Colichman.[1]

The dropping mercury electrode at a pressure of 72 cm. had a drop time of 3.00 seconds (open circuit) in distilled water. The value of m was 1.97 mg. sec.$^{-1}$ with a calculated value of $m^{2/3}t^{1/6}$ of 1.90 mg.$^{2/3}$sec.$^{-1/2}$.

The iodobenzene was obtained from stock. *p*-Fluoronitrobenzene and *p*-diiodobenzene were obtained from the Eastman Kodak Co. *p*-Fluoroiodobenzene was obtained from the Pierce Chemical Co., Rockford, Ill. All samples were checked for purity by vapor-phase chromatography.

Gas chromatograms were obtained using a didecyl phthalate column at 171° with helium as the carrier gas at 20 p.s.i. The retention times of *p*-fluoroiodobenzene and *p*-nitrofluorobenzene were 12 min., and 16 min. and 45 sec., respectively, at a flow rate of 1 ml./sec.

(2) C. S. Ramanathan and R. S. Subrahmanya, *Proc. Indian Acad. Sci.*, **47A**, 379 (1958).

The Reductive Cleavage of 2,5-Dimethyltetrahydrofuran Hydroperoxide in the Presence of Carbon Tetrachloride[1]

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The reductive cleavage of certain hydroperoxides has been reported in the literature.[3–5] The reaction in-

(1) Taken from the Master's thesis of Donald F. Anderson.

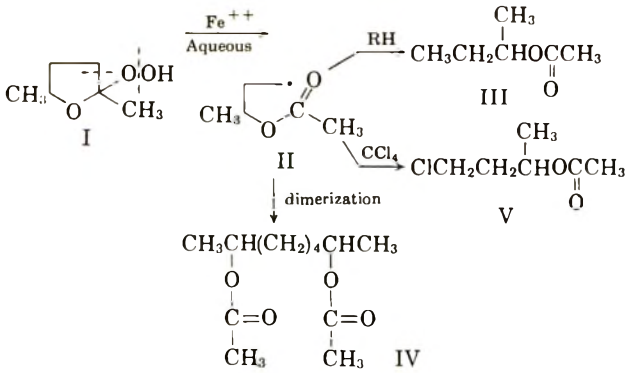
(2) To whom inquiries should be sent.

(3) Jennings H. Jones and Merrell R. Fenske (to Esso Research and Engineering Co.), U. S. Patent 2,989,563 (June 20, 1961).

(4) J. Braunworth and G. W. Crosby, Abstracts of Papers presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, 13-O.

(5) W. Cooper and W. H. T. Davidson, *J. Chem. Soc.*, 1180 (1952).

volving 2,5-dimethyltetrahydrofuran hydroperoxide[3] (I) apparently proceeds through free radical II, when aqueous ferrous ion is the reducing agent, to give *sec*-butyl acetate (III) by hydrogen abstraction from the solvent molecules, or 2,7-octanediol diacetate (IV) by dimerization of II as the principal products.



We have checked the work done by previous investigators on 2,5-dimethyltetrahydrofuran hydroperoxide with aqueous ferrous ion[3] and have extended this work by accomplishing the decomposition of I in the presence of carbon tetrachloride to produce 4-chloro-2-butyl acetate (V) along with IV. The production of V apparently proceeds by a reaction sequence similar to that for the formation of III except that in the presence of carbon tetrachloride the radical II reacts by extracting a chlorine atom to form V rather than by extracting a hydrogen atom from a solvent molecule as is the case with aqueous ferrous ion alone.

The extent of dimerization of II to produce IV when the reaction was done with aqueous ferrous ion along with carbon tetrachloride was comparable to that observed when the decomposition was done with aqueous ferrous ion alone (46 and 36%, respectively). In the experiment with carbon tetrachloride no III resulted but the yield of V with carbon tetrachloride approaches the yield of III in the absence of carbon tetrachloride (see Table I).

TABLE I

YIELD[a] OF VARIOUS ESTERS FROM DECOMPOSITION OF 2,5-DIMETHYLTETRAHYDROFURAN HYDROPEROXIDE

Compounds	Aqueous Fe^{++} only	Aqueous Fe^{++} with CCl_4
4-Chloro-2-butyl acetate	..	19
sec-Butyl acetate	32	..
2,7-Octanediol diacetate	46	36

[a] The yields given are in mole per cent in terms of the moles of hydroperoxide appearing as a particular product.

In addition to the ester-like material characterized in the reaction with carbon tetrachloride, a dark, viscous residue was recovered which amounted to 32 weight % of the starting hydroperoxide. This residue was not characterized.

Experimenta

Production of Hydroperoxide.—A sample of 2,5-dimethyltetrahydrofuran was allowed to stand in a glass reaction flask in contact with oxygen for a period of 6 weeks. Intermittent stirring was used to assure saturation with oxygen at all times. At the end of the 6-week period, analysis by the method of Wagner, Smith, and Peters[6] for hydroperoxide content indicated that the sample consisted of 38.6 g. of 2,5-dimethyltetrahydrofuran hydroperoxide and 139.4 g. of 2,5-dimethyltetrahydrofuran.

Decomposition of Hydroperoxide in the Presence of Carbon Tetrachloride.—The mixture described above was added, dropwise, to a mixture consisting of a saturated solution of ferrous sulfate heptahydrate, 1 l. of methanol, and 500 ml. of carbon tetrachloride. The methanol was added in an attempt to produce a homogeneous reaction medium but did not accomplish this end as two phases were present all during the reaction. The reaction mixture was contained in a 3-l., three-neck, round-bottom flask, equipped with an efficient stirrer, a condenser, and a dropping funnel from which the hydroperoxide was added. The reaction mixture was maintained at 30° by use of an ice bath as the reaction was quite exothermic. After the reaction was complete the resulting organic and water layers were separated and investigated individually.

The water layer contained no organic material boiling above 100°.

The organic layer was washed with three 100-ml. portions of potassium carbonate solution, then dried overnight with anhydrous magnesium sulfate. The dry organic layer was subjected to a simple distillation and separated into three large fractions. The first fraction boiled 59–78° and contained chloroform, methyl alcohol, carbon tetrachloride, 2,5-dimethyltetrahydrofuran, and water. The second fraction was collected at 78–81° was mainly carbon tetrachloride. The remaining material was charged to a fractionation column (about 30 theoretical plates, glass-packed) and fractionally distilled. Additional chloroform, methanol, carbon tetrachloride, 2,5-dimethyltetrahydrofuran, and water were obtained. After the material boiling below 100° was removed, the pressure was reduced and distillation was continued. Two significant fractions were subsequently distilled. One fraction, which was eventually found to be 4-chloro-2-butyl acetate, possessed the following properties: b.p. 59–64°/13 mm. (lit.,[7] 71–72°/16 mm.), $n^{20}D$ 1.4280 (lit.,[7] 1.4273), m.p. of 3,5-dinitrobenzoate 113–114° (lit.,[7] 113–114°), sapon. equiv. 80.7 (corresponding to elimination of hydrogen chloride).

Anal. Calcd. for $C_6H_{11}ClO_2$: C, 48.6; H, 7.97; Cl, 23.5; O, 20.6. Found: C, 48.6; H, 7.55; Cl, 22.2; O, 21.7.

Qualitative infrared analysis indicated carbon–chlorine bonding in the material.

The other fraction, b.p. 71–115°/10 mm., $n^{20}D$ 1.4285, sapon. equiv. 115, was water-white and did not contain chlorine. This fraction was not rigorously characterized but on the basis of work by previous investigators[3] plus the information cited above was assumed to be a diol diacetate, possibly 2,7-octanediol diacetate.

Decomposition of Hydroperoxide with Ferrous Ion Alone.—The decomposition and work-up of the hydroperoxide accomplished in the presence of aqueous ferrous ion alone was similar to that described for the carbon tetrachloride experiment. The principal products were *sec*-butyl acetate and 2,7-octanediol diacetate (see Table I) as had been established previously.[3]

Acknowledgment.—The authors are indebted to Dr. J. H. Jones of the Petroleum Refining Laboratory at The Pennsylvania State University for supplying the 2,5-dimethyltetrahydrofuran used in this investigation.

(6) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

(7) S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, **79**, 952 (1957).

The Synthesis of the β-D-Glucoside of Medicagenic Acid, an Alfalfa Root Saponin[1]

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The β-D-glucoside of medicagenic acid has been synthesized by a four-step procedure. Crystalline

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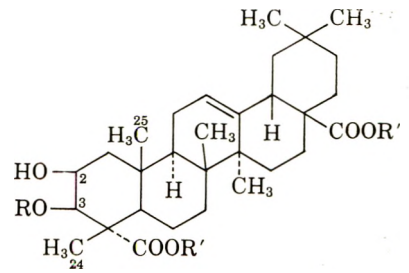
medicagenic acid, obtained by hydrolysis of an alfalfa root saponin concentrate, was transformed into the dibenzohydryl ester by reaction with diphenyldiazomethane. This derivative was condensed with acetobromoglucose by the Koenigs–Knorr reaction. Deacetylation of the reaction product produced the β-D-glucoside of dibenzohydryl medicagenate. Hydrogenolysis of this compound afforded the β-D-glucoside of medicagenic acid. The principal intermediates in the synthesis were carefully purified and identified from chemical constants and elemental analysis. The glucoside prepared by this procedure was identical in all respects to a naturally occurring root saponin reported earlier from this laboratory[2] which was characterized as 2β-hydroxy-3β-(β-D-glucopyranosyl)-Δ^{12}-oleanene-23, 28-dioic acid. The equivalence of the two compounds was established by melting point determinations, optical rotation, elemental analyses, and infrared spectra.

During the last decade a number of investigators have made valuable contributions leading to a better understanding of the molecular structure of aglycones occurring in water soluble saponins found in alfalfa.[3–8] Of particular interest to this research has been the establishment of the structure of medicagenic acid, since a saponin containing this aglycone has been found to be quite abundant in the roots of the alfalfa plant. In an earlier communication the isolation and characterization of this saponin was reported. Because this compound presented a simple glucose side chain, it appeared ideal as a compound for synthetic duplication.

The method of synthesis was similar to that previously found successful for the preparation of the β-D-glucoside[9] and the β-D-quinovoside[10] of oleanolic acid. The acid functions were protected by esterification with diphenyldiazomethane, since the benzohydryl groups may be conveniently removed later by catalytic hydrogenolysis without reduction of the carboxylic acid.[11] The glucoside of the diester was produced by the method of Koenigs and Knorr[12] as modified by Miescher and Mystre,[13] using silver carbonate as the catalyst. Following deacetylation of the glucoside, the diester was subjected to hydrogenolysis using a palladium catalyst, resulting in the formation of the β-D-glucoside of medicagenic acid.

No attempt was made to block the axial 2β-hydroxy group as the greater reactivity toward substitution at an equatorial position (3β) has been well substantiated by a number of investigators.[14] Further, a scale model of ring A of medicagenic acid indicated that considerable steric interference to 2β substitution would arise from the axial C-24 and C-25 methyls. These considerations, coupled with the bulky nature of the attacking species (tetra-O-acetyl-β-D-glucopyranosyl), would make substitution at the axial position virtually impossible and thus the 3β-glucoside was the expected product. Since the saponin thus obtained is identical to the natural alfalfa root saponin, it appears that the enzymatic synthesis conducted in the plant also favors the 3β-glycosidic position.

A repetition of this synthesis using C^{14}-labeled glucose is being considered in this laboratory. The saponin so prepared could be of value for determining the role of such compounds in plant and animal physiology.



I. R, R′ = H
II. R = H, R′ = $(C_6H_5)_2CH$
III. R = Tetra-O-acetyl-β-D-glucopyranosyl, R′ = $(C_6H_5)_2CH$
IV. R = β-D-glucopyranosyl, R′ = $(C_6H_5)_2CH$
V. R = β-D-glucopyranosyl, R′ = H

Experimental[15]

Isolation and Purification of Medicagenic Acid (I).—The isolation of the alfalfa root saponin followed the procedure previously described in the literature.[2] Nine kilograms of the dried root powder yielded approximately 120 g. of crude light brown saponin. This was not purified further but was hydrolyzed directly by refluxing with 8 l. of 1 *N* ethanolic-hydrochloric acid (1:1) for a period of 72 hr.[5] The crude acid was precipitated by addition of an equal volume of water and then dissolved in a minimum of hot dioxane, the solution decolorized with activated carbon and allowed to cool. The medicagenic acid crystallized from the solution in the form of needles, two recrystallizations from dioxane affording a pure product with the same constants as published earlier.[3] The needles exhibit parallel extinction between crossed nicols and have a negative sign of elongation.

Dibenzohydryl Medicagenate (II).—Dry medicagenic acid (15.06 g., 0.03 mole) was dissolved in 500 ml. of dioxane contained in a 1-l. three-necked flask equipped with a stirrer, thermometer, and gas delivery tube. The flask was placed in a water bath maintained at 60°,[16] a solution of 19.4 g. (0.10 mole) of diphenyldiazomethane in 100 ml. dioxane added, and the stirrer started. The nitrogen evolved was measured by displacement of water and in this manner the course of the reaction could be followed. At the end of 60 hr. the theoretical amount of nitrogen had been evolved and the color of the reaction mixture had changed from deep red to straw yellow. The solution was removed from the flask and evaporated to dryness in a rotary film evaporator. The resulting gummy yellow residue was kneaded with small quantities of hot ethanol until no more color could be removed. A white solid remained which crystallized without difficulty from acetone-water, a single recrystallization resulting in 15.3 g. (61.2%) of the dibenzohydryl ester. The product crystallized as broad needles melting sharply at 235° which exhibited a positive sign of elongation; $[\alpha]^{25}D$ +46.7° in chloroform (*c*, 0.0190 g./ml.).

Anal. Calcd. for $C_{56}H_{66}O_6$: C, 80.54; H, 7.97. Found: C, 80.38; H, 8.03.

Tetra-O-acetyl-β-D-Glucopyranoside of Dibenzohydryl Medicagenate (III).—In a 500-ml. three-necked flask fitted with a stirrer, addition funnel, and distilling head was placed a solution of 8.35

(2) R. J. Morris, W. B. Dye, and P. S. Gisler, *J. Org. Chem.*, **26**, 1241 (1961).
(3) E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, *J. Am. Chem. Soc.*, **76**, 2271 (1954).
(4) A. L. Livingston, *J. Org. Chem.*, **24**, 1567 (1959).
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(7) C. B. Coulson and T. Davies, *ibid.*, **13**, 53 (1962).
(8) W. A. Lourens and M. B. O'Donovan, *S. Afr. J. Agr. Sci.*, **4**, 151 (1961).
(9) E. Hardegger, H. J. Leeman, and F. G. Robinet, *Helv. Chim. Acta*, **35**, 824 (1952).
(10) E. Hardegger and F. G. Robinet, *ibid.*, **33**, 1871 (1950).
(11) E. Hardegger, Z. El Hewaili, and F. G. Robinet, *ibid.*, **31**, 439 (1948).
(12) W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).
(13) K. Miescher and C. Mystre, *Helv. Chim. Acta*, **27**, 231 (1944).
(14) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 222.

(15) All melting points are corrected. Analyses were performed by C. F. Geiger, Ontario, Calif.
(16) At significantly higher temperatures considerable amounts of bis(diphenylmethyl)ketazine were formed, while lower temperatures resulted in a prohibitively long reaction time.

g. (0.01 mole) of dibenzohydryl medicagenate in 200 ml. of dry benzene. Previously dried silver carbonate (10 g.) was added, the stirrer started, and a small fraction of benzene distilled to remove traces of water. A solution of 8.2 g. (0.02 mole) of acetobromoglucose in 100 ml. of benzene was then added slowly over a period of 2 hr., during which time the benzene–water azeotrope was continually removed by distillation. The reaction mixture was then filtered and the filtrate returned to the flask. Fresh silver carbonate (5 g.) was added and once more 4.1 g. (0.01 mole) of acetobromoglucose in 100 ml. benzene was added over a 2-hr. period, with continuous distillation. After addition was completed the mixture was warmed an hour on the water bath, cooled, filtered, and the filtrate evaporated to dryness. Attempts to crystallize the amorphous product were unsuccessful and it was considered expedient to attempt purification at a later stage of the synthesis.

β-D-Glucopyranoside of Dibenzohydryl Medicagenate (IV).—The dried residue (16.3 g.) from the Koenigs–Knorr reaction was deacetylated by solution in 100 ml. of absolute ethanol to which 1 g. of sodium had been added. This solution was boiled under reflux for 1 hr. and then poured into 100 ml. of cold water. The glucoside precipitated as a white amorphous solid which was filtered and washed with water on the filter. The product, which could not be crystallized, was chromatographed on 150 g. of activated alumina, elution being effected with methanol. Evaporation of the eluant yielded 4.10 g. (41%) of the amorphous β-D-glucopyranoside of dibenzohydryl medicagenate, m.p. 136–140° dec.

Anal. Calcd. for $C_{62}H_{76}O_{11}$: C, 74.67; H, 7.68. Found: C, 74.24; H, 7.64.

β-D-Glucopyranoside of Medicagenic Acid (V).—The glucoside of dibenzohydryl medicagenate (2.0 g., 0.002 mole) was dissolved in 60 ml. of absolute ethanol and 2.0 g. of 5% palladium on charcoal added. The mixture was shaken with hydrogen at room temperature and a pressure of 60 p.s.i. for 72 hr. At the end of this time the catalyst was removed and the filtrate evaporated to a white residue. The diphenylmethane formed by the reduction was removed by suspending this residue in water and steam distilling until no more of the hydrocarbon could be detected in the distillate. The glucoside was filtered and dissolved in ethanolic sodium hydroxide, diluted with water, and shaken with ether. Careful neutralization of the aqueous layer with hydrochloric acid resulted in the precipitation of the glucoside of medicagenic acid which was filtered and dried *in vacuo* for 4 hr. at 60°. The white amorphous product (0.75 g., 57%) melted at 253–255° and gave an $[\alpha]^{23}D$ of +71.4 in ethanol (*c*, 0.01793 g./ml.). Identity of this product with the naturally occurring alfalfa root saponin was demonstrated by infrared comparison and an undepressed mixture melting point.

Anal. Calcd. for $C_{36}H_{56}O_{11}$: C, 65.04; H, 8.49. Found: C, 65.55; H, 8.60.

Transacetalation. The Reaction Pathway[1]

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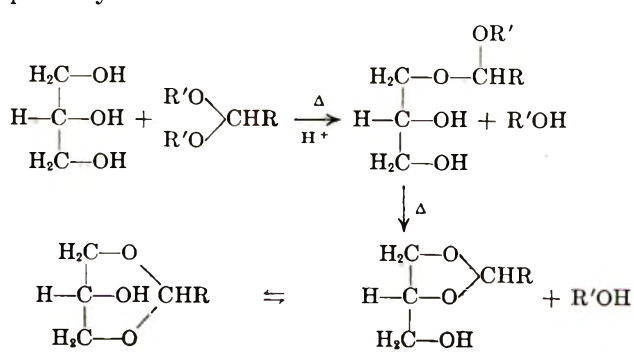
A previous report[3] showed that primary alcohols in acetal linkage may be exchanged with glycerol leading to the formation of 1,2-cyclic glycerol acetals. During the synthesis of the 1,2-benzylidene glycerol acetal (2-phenyl-4-hydroxymethyl-1,3-dioxolane) by transacetalation from the diethylacetal of benzaldehyde a stepwise evolution of alcohol was noted. The same phenomenon was noted in the synthesis of other low molecular weight glycerol acetals. This stepwise evolution of alcohol suggested the occurrence of an intermediate in the synthesis of 1,2-glycerol acetals by this reaction. Such an intermediate could be either the mixed ethyl–glycerol acetal or possibly a hemiacetal. Of these two possibilities the mixed acetal would appear to be the more likely, particularly in view of the demonstrated success in the syntheses of open structure type mixed acetals.[3–5]

With the above possibilities in mind, the synthesis of the ethylidene glycerol acetal (2-methyl-4-hydroxymethyl-1,3-dioxolane) by transacetalation from diethyl acetal was stopped after the evolution of one-half the theoretical quantity of alcohol and the products in the reaction mixture were isolated. Two fractions were obtained. One fraction, isolated in a very low yield, had physical constants identical with the 1,2-ethylidene glycerol acetal reported earlier.[3] The other fraction in much higher yield had entirely different physical constants. Acylation of this latter fraction with tetradecanoyl chloride followed by subsequent cleavage of the acetal linkage led to the isolation of 1,2-dimyristin whose melting point agreed with that reported by Daubert and King.[6] These data show that the transacetalation reaction progressed *via* the mixed acetal stage.

The fraction, subsequently shown to be 1,2-ethylideneglycerol, could have arisen during the initial reaction or during the distillation procedure. The latter possibility would suggest that ring closure took place under the influence of heat alone and did not require an acid catalyst. This was subsequently shown to be the case by stopping the synthesis of benzylideneglycerol acetal by the transacetalation reaction after evolution of one-half the theoretical amount of alcohol, neutralizing the catalyst, and again heating the reaction mixture. The 1,2-benzylideneglycerol acetal was obtained in good yield. Subsequently the synthesis of the 1,2-ethylideneglycerol acetal was achieved by heating the isolated mixed ethyl–glycerol acetal to a temperature of 115–120°. Attempts at the isolation of the mixed acetal where palmital dimethyl acetal was used in the transacetalation reaction were unsuccessful. This finding may be explained by the high temperature (130°) needed in this case for initiating the first step in the reaction. This temperature was apparently high enough to cause immediate ring closure.

The findings reported in this investigation and those reported earlier on the interconversion of benzylidene glycerols[3] show that the transacetalation reaction for the preparation of cyclic glycerol acetals follows the pathway:



(1) This work was supported by a grant from the Life Insurance Medical Research Fund, N. Y., and by research grants G-9744 and G-21305 from the National Science Foundation.

(2) Biology Branch, Research and Development Division, U. S. Atomic Energy Commission, Oak Ridge, Tenn.

(3) C. Piantadosi, Carl E. Anderson, E. A. Brecht, and C. L. Yarbro, *J. Am. Chem. Soc.*, **80**, 6613 (1958).

Experimental

Synthesis of the Mixed Ethyl–Glycerol Acetal.—In a three-necked flask equipped with a stirrer, a thermometer, and a condenser for the collection of alcohol were placed 55 g. of glycerol, 35 g. of diethyl acetal, and 50 mg. of sulfosalicylic acid. The reaction mixture was heated on an oil bath and ethanol began to evolve at 94°. The first step in the evolution of ethanol was complete at 104°; yield of ethanol was 102% as calculated for the mixed acetal. The reaction was stopped at this point by chilling in an ice bath. After chilling, the reaction mixture was extracted three times with 125-ml. portions of ether. The combined extracts were washed with 50 ml. of a 0.1 *N* sodium hydroxide and then with distilled water and dried over anhydrous potassium carbonate. The ether was removed under reduced pressure leaving a yellowish oil which had an odor distinctly different from that of diethyl acetal, acetaldehyde or 1,2-ethylideneglycerol. This oil was further purified by fractional distillation at 3 mm. Two fractions were obtained: Fraction I, b.p. 53–55° (3 mm.); $n^{25}D$ 1.4395; yield was 21% as calculated for the mixed ethyl–glycerol acetal. Fraction II, b.p. 65–66° (3 mm.); $n^{25}D$ 1.4405 (These constants are identical with those reported earlier for 1,2-ethylideneglycerol acetal.[3]); yield was 3.1% as calculated for 1,2-ethylideneglycerol acetal.

Preparation of 1-2-Dimyristin from the Mixed Ethyl–Glycerol Acetal.—In a glass-stoppered Erlenmeyer flask were placed 9.6 g. of the product from fraction I, 12 ml. of pyridine, and 10 ml. of purified chloroform. This mixture was chilled thoroughly in an ice bath. To the chilled mixture were added in a dropwise manner 29 g. of myristoyl chloride. A crop of white crystals appeared and the solution became yellow in color. After the reaction was completed, 150 ml. of ether was added and a voluminous precipitate appeared which went back into solution upon addition of 150 ml. of ice–water. The ether layer was removed, washed with 10% sodium bicarbonate, then with ice–water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure leaving a waxy solid. Yield of crude material was 99% as calculated for the dimyristoyl derivative of the mixed acetal.

The acetal group was removed by acid hydrolysis. The crude material was dissolved in 40 ml. of ether and 40 ml. of concentrated hydrochloric acid was added in a dropwise manner to the constantly shaken ether solution cooled in an ice–salt mixture. After the addition of acid was complete, the ether layer was separated and washed repeatedly with 100-ml. portions of ice–water. After each wash a troublesome emulsion occurred. Each water wash was extracted with three 100-ml. portions of ether, these extracts being added to the original ether solution. The combined ether fractions were dried over anhydrous sodium sulfate and placed in the cold room at 5° overnight, where a small amount of white precipitate formed. The ether solution was concentrated to a volume of 50–75 ml. by evaporation and the precipitate filtered on a Büchner funnel. The precipitate was shown to be mostly the soap of myristic acid, although repeated crystallization from ethanol at 5° produced a few milligrams of a white crystalline material melting at 71–72°. This melting point compared favorably with that reported for β-monomyristin.[7]

The ether filtrate from the above procedure was evaporated to dryness under reduced pressure. The residue obtained was dissolved in 50 ml. of acetone, and 50 ml. of water was added. This mixture was placed in the cold room overnight at 5° where a light yellow precipitate formed. This precipitate was recrystallized repeatedly from acetone until a white crystalline material melting sharply at 59° was obtained and which showed no change in melting point upon subsequent recrystallizations. This melting point corresponded exactly with that reported for 1,2-dimyristin.[7]

Investigation of Conditions for Ring Closure in the Synthesis of 1,2-Glycerol Acetals.—The synthesis of 1,2-benzylideneglycerol acetal from 0.1 *M* diethyl acetal of benzaldehyde and 0.1 *M* glycerol was carried out by the procedure previously described[3] with the following modification. After evolution of one-half of the theoretical quantity of alcohol, the reaction was stopped and the product extracted with ether and base in the usual manner. The ether was removed under reduced pressure and the oil which remained was heated to temperatures of 110–135° where evolution of the second half of the alcohol occurred. Distillation of the reaction mixture gave an 80% yield, b.p. 130–131° (3 mm.); $n^{30}D$ 1.5350. These constants compare with those reported earlier for 1,2-benzylideneglycerol acetal.

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(5) M. M. Delepine, *Bull. soc. chim. Paris*, (3) **25**, 574 (1901); *Chem. Zentr.*, **72**, II, 185 (1901).
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Reaction of Chloral Hydrate with Aliphatic Amines in Water

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It has been shown by Blicke and Lu that chloral hydrate reacted with N-methyl-α-methylhomopiperonylamine or piperidine to form the N-formyl derivative in almost quantitative yield.[1] More detailed investigation with a number of amines showed that formylation with the aid of chloral in chloroform under anhydrous conditions is an excellent general procedure for the acylation of a strong organic base.

The purpose of this work was to establish whether the formylation could be performed in water (equation 1) at the same time differentiating between formamide synthesis through chloral hydrolysis followed by ammonium formate dehydration (equation 2).

$$RNH_2 + CCl_3CH(OH)_2 \xrightarrow{H_2O} RNHCHO + CHCl_3 \quad (1)$$

$$[R\overset{+}{N}H_3\ HCOO^-] + CHCl_3 \longrightarrow RNHCHO + H_2O \quad (2)$$

Four aliphatic amines representing various degrees of steric hindrance and one aliphatic diamine were studied (Table I).

TABLE I

REACTION OF AMINES WITH CHLORAL HYDRATE

$$RNHR' + CCl_3CH(OH)_2 \longrightarrow RNR'CHO + [RNH_2R'\ HCOO^-]$$

R	R′	Yield, % RNR′CHO	Yield, % [RNH₂R′HCOO⁻]
n-C_4H_9—	H	78.5	...
t-C_4H_9—	H	6.0	92.0
Cyclohexyl—	H	72.5	2.1
$(CH_3)_2N(CH_2)_3$—	H	73.5	8.3[a]
C_2H_5—	C_2H_5	41.5	19.7[b]

[a] Isolated as an N,N-Dimethylpropanediammonium formate–formic acid (3:1) azeotrope. [b] Isolated as a diethylammonium-formate–formic acid (3:2) azeotrope.

Hydrolysis to an ammonium formate was evident with *t*-butylamine and to a much lesser extent with all the other amines except the *n*-butyl analog. Ammonium formate dehydration was eliminated as a major route to formamides in this investigation on the basis of a comparison of conditions employed and those required for dehydration. The conditions for dehydration were determined previously in the course of distilling mixtures containing excess amine and 89% formic acid. The appropriate ammonium formates were isolated as solids, binary azeotropes with formic

(1) F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

acid, or ternary azeotropes with formic acid and formamides depending on the particular amine.[2] Appreciable dehydration to formamide required atmospheric distillation over 100°. In contrast, the chloral hydrate reactions were performed at room temperature and the formamides were isolated by extraction with chloroform followed by vacuum distillation.

The hydrolysis of chloral occurs presumably by a mechanism such as that given by Gustafson and Johanson[3]; either hydroxide ion or amine could serve as the base. There is no obvious relationship between amine basicity and degree of either formylation or hydrolysis. However, steric hindrance appears to play an important role. Appreciable hydrolysis only with *t*-butylamine implies that approach of the amine nitrogen to the carbonyl carbon is hindered to such an extent that no formylation was detected. Except for such hindered compounds the reaction of chloral hydrate with amines in water is an acceptable procedure for the preparation of formamides.

Experimental

General Procedure for the Reaction of Chloral Hydrate with Aliphatic Amines in Water.—To a magnetically stirred solution (200 ml.) of the appropriate amine (0.5 mole) in water was added an aqueous solution (150 ml.) of chloral hydrate (82.5 g., 0.5 mole). A liquid or solid separated and the temperature rose to not higher than 45°. The mixture was allowed to stir overnight at room temperature. In all cases two liquid layers remained. The aqueous layer was extracted with chloroform. The chloroform extracts were combined with the organic layer and vacuum distillation gave the appropriate formamide. The aqueous portion was evaporated on a rotating evaporator at 50° under water-aspirator vacuum to give either a solid ammonium formate or a liquid residue. The liquid was distilled to give an ammonium formate azeotrope with formic acid. The various formamides, ammonium formates, and ammonium formate azeotropes were characterized by comparison with authentic samples. Elemental analyses, indices of refraction, infrared absorption curves, boiling points, and melting points were used for this purpose.

Acknowledgment.—The author wishes to acknowledge the technical assistance of Mary D. Pankau. Elemental analyses were performed by the Analytical Research Branch, U. S. Army Chemical Research and Development Laboratories.

(2) E. J. Poziomek and Mary D. Pankau, unpublished results.
(3) C. Gustafson and M. Johanson, *Acta Chem. Scand.*, **2**, 42 (1948).

Complexes of Sugars with Molybdate

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In the course of an investigation of the biological function of molybdenum, complexes of sugars with this metal in aqueous solution have been studied.

Bourne, Hutson, and Weigl have reported the results of paper ionophoresis studies of sugars in acidified molybdate solution.[2] These authors concluded from their results that pyranose sugars possessing three hydroxyl groups in a *cis-cis*-1 (ax), 2 (eq), 3 (ax), arrangement (chair form) complex with molybdate.

(1) Abstracted from the M.S. thesis of S. Kiang, Utah State University, 1962.
(2) E. J. Bourne, D. H. Hutson, and H. Weigl, *J. Chem. Soc.*, 4252 (1960).

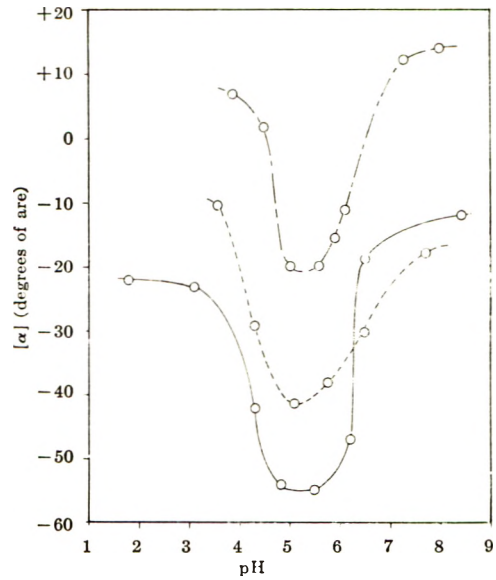

Fig. 1.—Effect of pH on specific rotation ([α]) of sugar–molybdate complexes.
Ratio of sugar to molybdate, 1:1; temp., 25.0 ± 0.5° C.
— — — — D-mannose
———— D-ribose
— · — D-lyxose

Polarimetric studies of these complexes have verified these conclusions. It was found that when molybdate was added to a solution of a sugar with the correct structure at a pH near 5 a large change in optical rotation due to complex formation occurred, while little or no change occurred with sugars not having this structure. Table I gives the results with various sugars. It can be seen that only those having the necessary 1 (ax), 2 (eq), 3 (ax) arrangement complex. The absence of one of the necessary hydroxyls prevents complexing, as with 2-deoxy-D-ribose and α-methyl-D-mannopyranoside.

TABLE I

Sugars that complex	Sugars that do not complex
D-Mannose	D-Glucose
D-Lyxose	D-Galactose
D-Ribose	D-Arabinose
	D-Xylose
	2-Deoxy-D-ribose
	α-Methyl-D-mannopyranoside

Fig. 1 indicates that the optimum pH for complex formation is about 5.5 and most studies were done in this region.

Continuous variations plots (Fig. 2) show that the ratio of molybdenum:sugar in the complexes is 1:1 in all cases. The plots also show that the complexes are relatively weak. This was confirmed by measuring the optical rotation of a solution of D-mannose in the presence of increasing molybdate concentration. It was found that the optical rotation of the solution did not become constant until a tenfold excess of molybdate had been added.

It is interesting to note that the sign of the rotation for mannose changes upon complex formation. This is undoubtedly due to the fact that the equilibrium mixture of D-mannose consists predominantly of the α-iso-

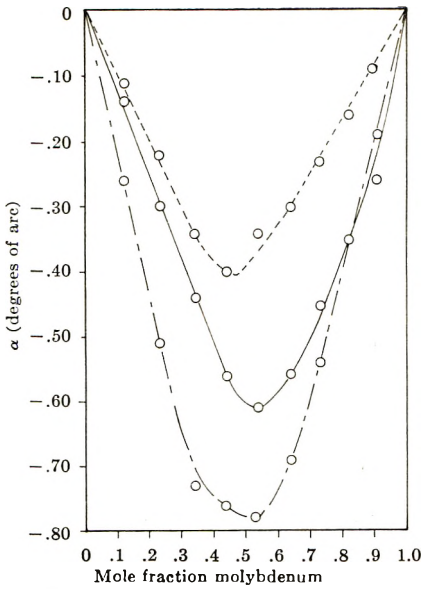

Fig. 2.—Continuous variations plots for sugar–molybdate complexes. The difference in optical rotation (α) between solutions of sugar plus molybdate and solutions containing the same concentration of sugar is plotted *vs.* mole fraction molybdenum.
pH 5.0 in 1.5 *M* acetate buffer; temp., 25.0 ± 0.5 °C.
Sum of sugar plus molybdate concentration, 0.1000 *M*
— — — — D-mannose
———— D-ribose
— · — · D-lyxose

mer[3] and has a positive rotation. However, only the β-isomer can complex and the inversion of the rotation is due to the transformation to this form upon complex formation. D-Lyxose is similar to D-mannose, except that the equilibrium mixture has a negative rotation and complex formation with the β-isomer makes the rotation more negative. D-Ribose is a somewhat different case. There are two possibilities for the ax-eq-ax hydroxyl arrangement. The first involves hydroxyls 1, 2, and 3 and the second, hydroxyls 2, 3, and 4. In the first case, only the α-isomer can complex. Therefore, since the α-isomer is more dextrorotatory, the addition of molybdate should cause the rotation of the solution to become more positive. However, the rotation becomes more negative. This indicates that the complexing must occur with hydroxyls 2, 3, and 4, and does not involve hydroxyl 1.

It is clear that complexing with molybdate provides a simple method to detect the presence of a *cis-cis*-1 (ax), 2 (eq), 3 (ax) triol system in a pyranose. A large change in the optical rotation upon addition of molybdate at a pH near 5 indicates this arrangement. Furthermore, complexing with molybdate suggests a method for determining the configuration of the anomeric carbon for sugars having the necessary 2 (eq), 3 (ax) structure, similar to the use of borate, which would not suffer from the ambiguities of the borate method.[4]

Experimental

Sodium molybdate (Baker certified reagent) was dried at 105° for 24 hr. Its purity was determined to be 99.7% by the α-benzoinoxime method.[5] D-Mannose, D-ribose, D-lyxose, D-xylose, D-arabinose, α-methyl-D-mannopyanoside, and 2-deoxy-D-ribose were purchased from Nutritional Biochemicals Corp. D-Glucose and D-galactose were Eastman Kodak Co. products. These compounds were used without further purification since their melting points checked the literature values.

Polarimetric measurements were made with a Schmidt and Haensch polarimeter, reading to ± 0.01° of arc. Temperature was controlled to 25.0 ± .2° by use of a jacketed polarimetric tube. All measurements were made at the sodium D line (5890 Å.). Sufficient time was allowed for each solution to reach a constant rotation before measurements were made.

Acknowledgment.—This work was supported by grants from Research Corporation and the Public Health Service (Grant GM-08347-02, Division of General Medical Sciences).

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(4) J. Boeseken, *Advan. Carbohydrate Chem.*, **4**, 189 (1949).
(5) H. B. Knowles, *J. Res. Natl. Bur. Stand.*, **9**, 1 (1932).

The Effect of Ether Oxygen on the Methylene Stretching Absorptions

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In all types of aliphatic hydrocarbons the methylene group, —CH_2—, gives rise to an asymmetrical stretching vibration near 2926 cm.$^{-1}$ and a symmetrical stretching vibration near 2853 cm.$^{-1}$.[1] The positions of the absorption bands are fairly constant. Ordinarily the intensity of the band at 2926 cm.$^{-1}$ is stronger than the one at 2853 cm.$^{-1}$, but when carbonyl or ester groups are attached to the methylene group the intensity of both bands is diminished.[2] It has also been reported that in oxygen-containing materials, generally, the extinction coefficient of the methylene group is affected.[3]

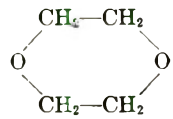
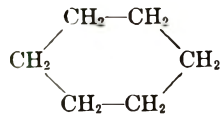
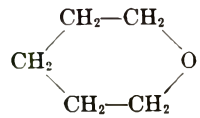
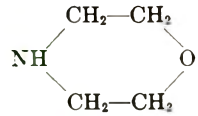
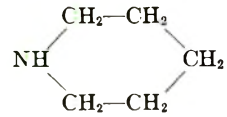
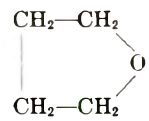
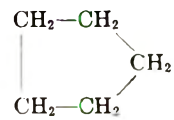
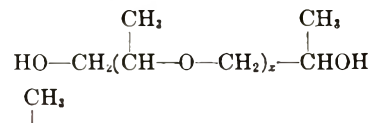
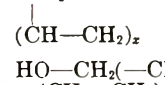
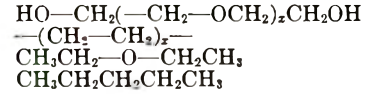
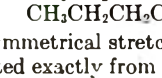
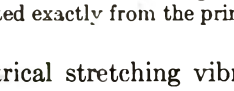
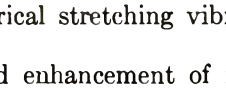
We have accumulated some data which show that the oxygen of an ether linkage can affect the methylene group in two ways, by shifting the asymmetrical stretching absorption to a higher frequency, and sometimes by enhancing the intensity of the symmetrical stretching absorption.

In the course of examining some rather complex compounds containing ether oxygen adjacent to methylene groups, a very sharp, intense absorption band was always found near 2856 cm.$^{-1}$. Because of the complexity of some of the materials, simpler and better known compounds were selected for investigation. These are listed in Table I.

The first example in the table is 1,4-dioxane, in which each methylene group is attached to oxygen without intervening functional groups. Four absorption bands are found in this region of the spectrum of 1,4-dioxane. The high frequency band is near 2967 cm.$^{-1}$, the low frequency band near 2858 cm.$^{-1}$, 109 cm.$^{-1}$ apart. The origin of the bands between the two has not been assigned and will not be discussed here. The work of Pozefsky and Coggeshall[3] in a study of sulfurized and oxygenated compounds, lends considerable weight to the assignment of the other two bands to the asymmetrical CH_2 stretching vibration at

(1) R. N. Jones and C. Sandorfy, "Technique of Organic Chemistry, Vol. IX, Chemical Applications of Spectroscopy," Interscience Publishing Co., New York, N. Y., 1956, p. 338.
(2) S. A. Francis, *J. Chem. Phys.*, **19**, 942 (1951).
(3) A. Pozefsky and N. D. Coggeshall, *Anal. Chem.*, **23**, 1611 (1951).

TABLE I

Compound	Formula	—CH_2— stretching frequency, cm.$^{-1}$ Asymmetric frequency	Intensity[a]	Symmetric frequency
1,4-Dioxane		2967	w	2858
Cyclohexane		2941	s	2858
Tetrahydropyran		2946	s	2856
Morpholine		2959	w	2841
Piperidine		2926	s	2857
Tetrahydrofuran		2976	s	2857
Cyclopentane[b]		2959 (?)	s	2874 (?)
Polypropylene glycol		2976	s	2874
Polypropylene		2958	s	2841
Polyethylene glycol		2941	w	2856
Polyethylene		2907	s	2849
Ether		2985	Equal	2865
Pentane		2958	s	2874

[a] Intensity relative to that of the symmetrical stretching band. w = weaker; s = stronger. [b] From Sadtler standard spectra no. 680. The frequencies cannot be located exactly from the printed spectra.

2967 cm.$^{-1}$ and to the symmetrical stretching vibration at 2858 cm.$^{-1}$.

The shifting of frequency and enhancement of intensity of the bands under discussion can best be illustrated by comparing the spectrum of 1,4-dioxane with that of cyclohexane. In both compounds the symmetrical stretching frequency of the methylene group occurs near 2858 cm.$^{-1}$, but the asymmetrical stretching frequency occurs 26 cm.$^{-1}$ higher in the spectrum of 1,4-dioxane than it does in that of cyclohexane. Thus it is evident that this shift to higher frequency is caused by the presence of oxygen in the molecule.

In the straight chain compounds, polyethylene and polyethylene glycol, listed in Table I, the symmetrical methylene absorption shift from polyethylene to polyethylene glycol is only 7 cm.$^{-1}$ higher while the asymmetrical methylene absorption shift is 34 cm.$^{-1}$ higher.

In a slightly more complicated situation, in which a methyl group enters the picture, a comparison of the spectra of ethyl ether and pentane may be made. In this situation it is difficult to assign bands to individual methyl or methylene groups. However, the absorption band of highest frequency occurs in ethyl ether at 2985 cm.$^{-1}$ as compared to 2958 cm.$^{-1}$ in pentane. Because in ethyl ether the methyl group is not attached directly to oxygen, the effect of oxygen on this group would be limited and it seems more likely that the band at 2985 cm.$^{-1}$ is attributable to the asymmetrical stretching vibration of the methylene group. Therefore, a shift of 27 cm.$^{-1}$ higher from pentane to ether is observed. The —CH_2— symmetrical stretching vibration of ether shifts only 9 cm.$^{-1}$ higher when compared with that of pentane.

Other materials in the table show the same stability of position for the symmetrical stretching absorption and the shift to higher frequency for the asymmetrical stretching absorption. In general, when ethers are compared with corresponding hydrocarbons, the preceding behavior is noted.

Another feature noted is the enhancement of the intensity of the symmetrical methylene stretching vibration when ether oxygen is present. In the spectra of 1,4-dioxane, polyethylene glycol, and ethyl ether, the

intensity of the symmetrical absorption is equal to or stronger than the asymmetrical, while in the spectra of cyclohexane, polyethylene, and pentane the situation is reversed. The intensity of the symmetrical methylene stretching absorption seems to be related to the number of $-CH_2O$ groups present in the molecule, as can be seen by comparing the spectra of tetrahydropyran, tetrahydrofuran, and 1,4-dioxane. However, in the more complex molecule, polypropylene glycol, this correlation cannot be applied.

The effect of ether oxygen on the methyl stretching vibration has been reported.[4,5] A similar effect appears to apply to the methylene group. It is believed that the C—H force constants are greater in the presence of the more electronegative oxygen, which causes the asymmetrical methylene stretching vibration to shift to higher frequencies. It may be concluded that a greater net dipole moment change occurs with the symmetrical methylene vibration than with the asymmetrical when oxygen of ether type is present and that, therefore, the intensity of the asymmetrical absorption band is enhanced.

All the samples were examined by Perkin–Elmer, Model 21 spectrophotometer with a calcium fluoride prism. Most of the samples were obtained from Eastman Kodak Co. and were used without further purification. Carbon tetrachloride was used as a solvent. The thickness of the cell was 0.2 mm.

(4) H. B. Henbest, G. D. Meakins, B. Nicholls, and A. A. Wagland, *J. Chem. Soc.*, 1462 (1957).

(5) F. Dalton, R. D. Mill, and G. D. Meakins, *ibid.*, 2927 (1960).

Quantitative Study of the Interconversion of Hydrindane Isomers by Aluminum Bromide

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In connection with investigations of aluminum halide isomerization of polycyclic hydrocarbons,[3] the development of quantitative techniques for studying the relative stabilities of isomers was desired.[4] The interconversion of *cis*- and *trans*- hydrindane was chosen as a model system, since the present study should complement nicely two recent investigations which employed different methods to obtain the same thermodynamic information. Allinger and Coke[5] equilibrated the two isomers at high temperatures by means of the hydrogenation–dehydrogenation action of a palladium-on-charcoal catalyst and studied the variation of the relative equilibrium concentrations with temperature. Browne and Rossini[6] determined the heats of combustion, isomerization, and formation of the pure isomers in both the liquid and gaseous states.

In the present investigation equilibration was carried out by aluminum bromide, which offers the advantage over aluminum chloride of being somewhat soluble in organic liquids. The catalyst, a powerful Lewis acid, effects equilibration by an ionic chain process[4]; abstraction of a hydride ion produces a carbonium ion which can react further by several paths, *e.g.*, fragmentation and rearrangement, in addition to reverting to one of the hydrindane isomers.[7] It was found that these undesired side reactions could be suppressed by the addition of small amounts of indane, which was more effective than benzene for this purpose.[4]

The relative equilibrium concentrations were determined at four different temperatures ranging from 251–320.3° K.[8] By gas chromatographic analysis identical compositions wereo btained approaching equilibrium from both the *cis* and *trans* sides. The results are shown in Table I.

TABLE I

EQUILIBRIUM COMPOSITION OF HYDRINDANE ISOMERS

T, °K.	K[a]	% *trans*
251	1.926	65.8
277	1.728	63.3
300.0	1.586	61.3
320.3	1.482	59.7

[a] See ref. 8.

From these data a plot of ln K *vs.* $1/T$ was made and a straight line of best fit was calculated by the method of least squares; the slope of this line gave $-\Delta H/R$. The value of ln K at 298° from the graph was used to calculate $-\Delta F^{298}$ and $-\Delta S^{298}$ was estimated from the equation, $\Delta F = \Delta H - T\Delta S$. The thermodynamic values obtained are summarized in Table II, along with literature values.

TABLE II

THERMODYNAMIC VALUES FOR HYDRINDANE ISOMERIZATION

State	T, °K.	$-\Delta H$, kcal./mole	$-\Delta S$, e.u.	$-\Delta F$, kcal./mole	Ref.
Liquid	298	0.74 ± 0.52	1.68 ± 0.10	0.24 ± 0.52	6
Gas	298	1.04 ± 0.53			6
Liquid (?)	552	1.07 ± 0.09	2.30 ± 0.10	[a]	5
Liquid	298	0.58 ± 0.05	1.00 ± 0.06	0.28 ± 0.06	This work

[a] Extrapolation of Allinger and Coke's data[5] to 298° gives ln K = 0.642; $-\Delta F$ (298°) = 0.38 kcal./mole.

Agreement between our results and those of Browne and Rossini[6] is very good; however, if the relative heat capacities of the hydrindane isomers can be considered nearly constant over the range from 552–298° K., there is a small but significant difference between our values and those of Allinger and Coke.[5] The data of the latter authors correspond closely to that

(1) National Science Foundation Predoctoral Fellow, 1962–1963.

(2) Alfred P. Sloan Research Fellow.

(3) P. von R. Schleyer and M. M. Donaldson, *J. Am. Chem. Soc.*, **82**, 4645 (1960); P. von R. Schleyer and R. D. Nicholas, *Tetrahedron Letters*, No. **9**, 305 (1961).

(4) For a review, see H. Pines and J. M. Mavity, "The Chemistry of Petroleum Hydrocarbons," Vol. 3, B. T. Brooks, *et al.*, eds., Reinhold Publishing Corp., New York, N. Y., 1955, chap. 39, pp. 9–58.

(5) N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, **82**, 2553 (1960).

(6) C. C. Browne and F. D. Rossini, *J. Phys. Chem.*, **64**, 927 (1960).

(7) N. D. Zelinsky and M. B. Turowa-Pollak, *Ber.*, **62**, 1658 (1929), reported the treatment of hydrindane (mostly *cis* isomer from hydrogenation) with aluminum bromide at steam-bath temperature. They claimed that the product was *trans*-hydrindane, but it is clear from the properties of the material they reported and from our experience with this reaction that fragmentation, disproportionation, etc., are the main reactions under these conditions, rather than isomerization.

(8) In keeping with the convention used previously[5,6] the isomerization is regarded to proceed from *cis*- to *trans*-hydrindane; K (equil.) = (*trans*/*cis*).

reported for the *gaseous* state at 298° K.[6] The large experimental error precludes any definite conclusion, but the data do suggest that despite a concerted and seemingly effective effort to maintain their samples in the liquid state, Allinger and Coke may have had an appreciable fraction of their samples in the gaseous state at the temperatures used. Perhaps the high pressures developed during the equilibrations, when the samples were heated well above their boiling points, can account for some of the difference.

As predicted in the literature,[5,6] *trans*-hydrindane is the more stable isomer at room temperature, due to a more favorable enthalpy. At higher temperatures (above 466° K.[5]) the *cis* form is more stable because of a more favorable entropy. The conformational implications of these facts have been considered in detail.[5,6,9]

Experimental

Preparation of the Hydrindanes.—One liter of commercial indene and 40 g. of 5% palladium on charcoal were placed in a 4-l. bomb. Hydrogen pressure of 1000–2000 p.s.i. and a temperature of 160° were maintained for 24 hr. Distillation of the crude product through a 100-cm. column filled with Podbielniak "Heli-Pak" packing gave 600 g. of material boiling at 159–166°. The remainder of the product was primarily indane (b.p. 177°).

The hydrindane mixture obtained from the hydrogenation product, containing approximately 70% *cis* isomer, was used for approaching the equilibria from the *cis*-rich side. *trans*-Rich material was made by equilibrating a 100-g. portion of the hydrogenation product mixture with 10 g. of aluminum bromide at room temperature overnight. Distillation of this product through the 100-cm. packed column gave 75 g. of material containing more than 80% *trans* isomer.

The pure isomers were prepared only in small quantities. Two careful distillations of 50 g. of the hydrogenation mixture through the 100-cm. packed column gave 3 g. of material boiling at 166° (755 mm.), which was shown by gas chromatographic analysis to be greater than 99.5% pure *cis* isomer. Two similar distillations of 50 g. of the mixture containing 70% *trans*-hydrindane gave 2 g. of material boiling at 159° (760 mm.). Gas chromatographic analysis showed that this material was better than 98% pure *trans*-hydrindane.

Equilibration.—Sample mixtures were prepared by stirring 15 ml. of either *cis*- or *trans*-rich hydrindane with freshly powdered aluminum bromide at room temperature for 5 min. Aliquots (2–3 ml.) of this aluminum bromide-saturated hydrindane solution were then pipetted into 5-ml. Pyrex ampoules and sealed. The samples were then placed in the desired temperature-controlled environment for the equilibration period, which ranged from 1 day at the higher temperatures to several weeks at the lower temperatures. The concentration of indane necessary to retard fragmentation and yet allow equilibration at a reasonable rate was a very critical factor in carrying out these equilibrations. This had to be determined by trial and error for each temperature, which ultimately required the preparation and analysis of approximately 200 samples. The concentrations of indane required varied from zero for the 251° K. sample to 6–7% for the 320° K. sample. Equilibrations at 251 and 277° K. were carried out in rooms closely regulated at those temperatures. Although fluctuations of 2° occurred, the equilibrations were so slow that the average temperatures can be used. At 300.0 and 320.3° K., the samples were immersed in oil baths regulated to ±0.05°. Individual samples were removed and analyzed regularly to follow the progress of each group of *cis*- or *trans*-rich samples toward equilibrium. This assured that the equilibrium was approached from both sides at each temperature. When an ampoule was opened, the sample was pipetted immediately into a test tube containing 10 ml. of cold water and mixed thoroughly to destroy the catalyst. The hydrindane layer was then pipetted off, dried with 0.5 g. of anhydrous potassium carbonate, and centrifuged.

Analysis.—The gas chromatographic analyses were carried out on a Perkin–Elmer Vapor Fractometer using a 300-ft. Golay "R" column at a temperature of 100° and helium pressure of 20 p.s.i. The separation was complete, and the retention times were 8.4 min. (*trans*) and 9.3 min. (*cis*). The product of the retention time and the peak height was taken as the measure of each peak. The number thus obtained for the *trans* peak was then divided by the corresponding number for the *cis* peak to get the ratio of *trans*- to *cis*-hydrindane. Two standard samples were carefully prepared and analyzed ten times each. These data showed that a correction factor of 0.942 for the *trans*- to *cis*-hydrindane ratio was required. This factor was applied to the results of all analyses.

(9) *Cf.* also W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

Acknowledgment.—We wish to thank Dr. B. Franko and Mr. W. McCarthy of the Food Machinery and Chemical Corporation for carrying out the hydrogenation of indene. The gas chromatographic apparatus was purchased with a Grant-In-Aid from the Food Machinery and Chemical Corporation.

Azasteroids. III.[1] 3-Aza-A-homo Androgens

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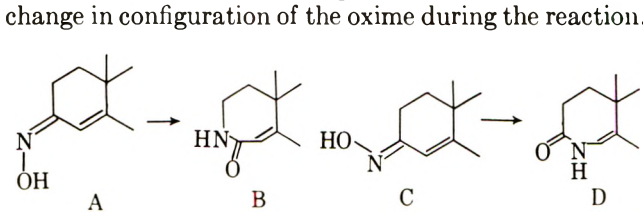
The continuing search for modified steroids with hormonal or antihormonal activity is currently emphasizing structures with hetero atoms incorporated in the polycyclic nucleus.[2–4] Our own interest has been in azasteroids[1,5] which are particularly attractive since they are potentially available from any ketosteroid *via* oxime and Beckmann rearrangement. The present report concerns work leading to A-homo derivatives of testosterone and 17α-methyltestosterone.

Beckmann rearrangement of an α,β-unsaturated ketoxime may give either an α,β-unsaturated lactam or an enamine lactam depending on the stereochemistry of the starting oxime. Thus, *syn*-oxime A leads to lactam B while *anti*-oxime C should give lactam D assuming no change in configuration of the oxime during the reaction.

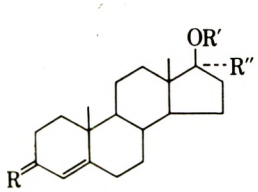


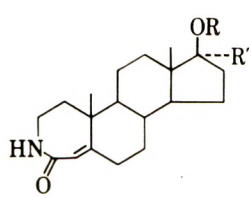
The structure of the lactam may be determined by the position of the ultraviolet maximum,[6] lactams of type B showing a maximum around 220 mμ while those of type D absorb maximally around 240 mμ. Some steroid A-homolactams derived from Δ⁴-3-ketones have been described[7–9] and all seem to be of type B. It would also be useful to have a simple method for distinguishing between *syn*- and *anti*-α,β-unsaturated oximes both for purposes of structure assignment and for determination of homogeneity. We felt that nu-

(1) Part II. R. H. Mazur, *J. Am. Chem. Soc.*, **82**, 3992 (1960).
(2) T. L. Jacobs and R. B. Brownfield, *ibid.*, **82**, 4033 (1960).
(3) M. Gut and M. Uskokovic, *J. Org. Chem.*, **26**, 1943 (1961).
(4) N. J. Doorenbos and C. L. Huang, *ibid.*, **26**, 4106 (1961).
(5) R. H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1959).
(6) R. H. Mazur, *J. Org. Chem.*, **26**, 1289 (1961).
(7) C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 3641 (1961).
(8) C. W. Shoppee, G. Krueger, and R. N. Mirrington, *ibid.*, 1050 (1962).
(9) N. J. Doorenbos and H. Singh, *J. Pharm. Sci.*, **51**, 418 (1962).

clear magnetic resonance spectroscopy might serve this purpose due to the expected shift in the vinyl proton position caused by the proximity of the hydroxyl group in the *syn*-oxime A. Some precedent was found in the observation of Phillips[10] that *syn*- and *anti*-aldoximes showed different chemical shifts of the aldehyde proton. We confirmed this premise very simply as we had at hand the isomers of isophorone oxime of known configuration.[6] Thus, the n.m.r. spectrum[11] of *syn*-isophorone oxime showed a downfield shift of the vinyl proton of 42 c.p.s. relative to the *anti*-oxime. The same effect was observed with our steroid Δ^4-3-ketoximes (43 c.p.s. downfield shift for *syn*-I, 42 c.p.s. for *syn*-II) and, in addition, the 19-methyl peak was shifted downfield 2–3 c.p.s. in the *syn* isomer relative to the *anti* isomer. Subsequent to our findings, the same results were reported by Slomp.[12] Thus, combination of n.m.r. and ultraviolet spectra permit assignment of configurations to unsaturated ketoximes and their Beckmann rearrangement products and, within limits, allow percentage composition of mixtures to be determined.

We have made the surprising observation that in the present work, the Beckmann product is not necessarily related configurationally to the starting oxime according to the accepted mechanism of the rearrangement. The conditions we employed (thionyl chloride in dioxane) apparently led to a thermodynamically controlled product for the α,β-unsaturated oximes. In both cases, only one lactam (the 3-aza-Δ^{4a}-4-ketone) could be isolated which would be the isomer expected from the *syn*-oxime. However, n.m.r. showed testosterone propionate oxime (I) to be a mixture of *syn* and *anti* isomers containing only about 10% *syn*. 17α-Methyltestosterone acetate oxime (IV) was the pure *anti* compound with no detectable amount of *syn*-oxime present. Unexpectedly, 17α-methyltestosterone oxime (II) was a 1:1 mixture of *syn* and *anti* forms, presumably a molecular complex. It is not possible to say whether the conditions of the rearrangement caused isomerization of the starting oximes or whether the reaction proceeded through an intermediate having little or no configurational stability. In any case, our results suggest the need for caution in relating the stereochemistry of oximes with the structure of derived lactams.





I. R = NOH, R' = C_2H_5CO, R'' = H
II. R = NOH, R' = H, R'' = CH_3
III. R = O, R' = CH_3CO, R'' = CH_3
IV. R = NOH, R' = CH_3CO, R'' = CH_3
V. R = C_2H_5CO, R' = H
VI. R = R' = H
VII. R = CH_3CO, R' = CH_3
VIII. R = H, R' = CH_3

The general synthetic scheme involved protection of the 17-hydroxyl group as an ester, formation of the oxime, Beckmann rearrangement to a seven-membered lactam and saponification of the 17-ester. Testosterone propionate gave the oxime I which was rearranged to the lactam V and hydrolyzed to 3-aza-17β-hydroxy-A-homo-4a-androsten-4-one (VI). 17α-Methyltestosterone acetate (III) *via* oxime IV yielded lactam VII and, after saponification, 3-aza-17β-hydroxy-17-methyl-A-homo-4a-androsten-4-one (VIII).

(10) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

(11) N.m.r. spectra were determined on a Varian A-60 spectrometer in deuteriochloroform at 10% concentration using tetramethylsilane as an internal standard. The positions of the peaks are reported in cycles per second downfield from the standard.

(12) G. Slomp and W. J. Wechter, *Chem. Ind.*, (London), 41 (1962).

Experimental[13]

Testosterone Propionate Oxime (I).—Commercial testosterone propionate U.S.P. (6.88 g., 0.02 mole) and 2.08 g. (0.03 mole) of hydroxylamine hydrochloride were dissolved in 50 ml. of pyridine. Two milliliters of water was added to give a clear solution which was heated 1 hr. on the steam bath. The solution was poured into 500 ml. of water, the crude oxime filtered, washed with water, and dried to yield 7.03 g. (98%) of compound I, m.p. 165–175°. Crystallization from 95% ethanol gave long needles, m.p. 170–176°. Recrystallization from methanol raised the m.p. to 177–183° (lit.,[14] m.p. 167–170°); n.m.r.[11,15] 348 c.p.s. (*anti*), 391 c.p.s. (*syn*), area ratio about 9:1.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.41; H, 9.04; N, 4.15.

17α-Methyltestosterone Oxime (II).—The above procedure was followed using 27.42 g. (0.09 mole) of 17α-methyltestosterone and 8.35 g. (0.12 mole) of hydroxylamine hydrochloride in 250 ml. of pyridine; yield of crude II, 28.39 g. (100%), sinter 208°, m.p. 212–215°. Crystallization from methanol gave thick prisms, m.p. 224–228° (lit.,[16] m.p. 198–202°); n.m.r. 348 c.p.s. (*anti*), 390 c.p.s. (*syn*), area ratio about 1:1.

Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75.68; H, 9.84; N, 4.41. Found: C, 75.51; H, 9.81; N, 4.48.

17α-Methyltestosterone Acetate (III).—17α-Methyltestosterone (50.0 g.) and 4.0 g. of *p*-toluenesulfonic acid monohydrate were dissolved in 800 ml. of isopropenyl acetate and about 300 ml. distilled over a period of 5 hr. During the last 0.75 hr. the head temperature was constant at 96°. The cooled solution was washed twice with 2 *N* potassium bicarbonate, dried over sodium sulfate, and the solvent removed under vacuum.

A portion of the viscous residue (8.55 g., 0.022 mole) in 180 ml. of methanol was treated with 8.80 ml. (0.044 mole) of 5 *M* potassium carbonate and water added until the solution became homogeneous (40 ml. required). The solution was heated 5 min. under reflux, concentrated under vacuum to about 100 ml. and 200 ml. of water added to give the desired 17α-methyltestosterone acetate as needles, 6.62 g. (87%), m.p. 164–167°. Two crystallizations from ethanol raised the melting point to 174.5–176°; $[\alpha]^{23.5}D$ +85° (c 1, chloroform); λ_{max}^{MeOH} 240 mμ, ϵ 16,800 [lit.,[17] m.p. 172–173°; $[\alpha]^{20}D$ +88° (chloroform)].

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.93; H, 9.21.

17α Methyltestosterone Acetate Oxime (IV).—Crude III (29.74 g., 0.086 mole) was converted to the oxime by the procedure of the first example using 12.0 g. (0.172 mole) of hydroxylamine hydrochloride in 300 ml. of pyridine. The oxime was purified by chromatography on silica gel and the desired product eluted with 20% ethyl acetate in benzene. Crystallization from ethyl acetate–cyclohexane gave the oxime IV as feathery needles, 17.43 g. (56%), m.p. 157–159°; $[\alpha]^{24}D$ +100° (c 1, methanol); λ_{max}^{MeOH} 240 mμ, ϵ 20,800; n.m.r. 348 c.p.s. (*anti*).

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.46; H, 9.35; N, 3.75.

3-Aza-17β-propionoxy-A-homo-4a-androsten-4-one (V).—Compound I (14.40 g.) in 350 ml. of purified dioxane was cooled to 10° and 15 ml. of thionyl chloride added with stirring at such a rate that the temperature remained below 15°. After 1 hr. at room temperature, the solution was stirred vigorously and 350 ml. of 2 *N* potassium bicarbonate added. The mixture was extracted with ethyl acetate, the organic layer washed twice with 5%

(13) We would like to thank R. T. Dillon and associates for analyses and spectra. Analytical samples were dried overnight at room temperature under high vacuum. Melting points were not corrected. Column chromatography was carried out by M. Winkler, R. Furkert, N. Bilek, and C. Nuernberg (direction E. G. Daskalakis).

(14) Merck Index, 7th ed., Merck and Co., Inc., 1960, p. 1019.

(15) Under the same conditions, *anti*-isophorone oxime[6] had a vinyl proton peak at 356 c.p.s., *syn*-isophorone oxime[6] at 398 c.p.s.

(16) Merck Index, 7th ed., Merck and Co., Inc., 1960, p. 684.

(17) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 309 (1960).

sodium sulfate, dried over sodium sulfate, and the solvent distilled. The residue was chromatographed on silica gel. Elution with ethyl acetate and subsequent crystallization from aqueous methanol yielded the lactam V as plates, 7.14 g. (50%), m.p. 238–239°; $[\alpha]^{27}D$ +14° (*c* 1, methanol); λ_{max}^{MeOH} 220 mμ, ε 16,500.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.17; H, 9.04; N, 4.02.

3-Aza-17β-hydroxy-A-homo-4a-androsten-4-one (VI).—Compound V (1.08 g., 0.003 mole) in 50 ml. of methanol was treated with 3.0 ml. of 4 *N* lithium hydroxide and the solution allowed to stand 4 hr. at room temperature. Neutralization with acetic acid, dilution with 50 ml. of water, and concentration under vacuum to approximately 50 ml. gave the desired lactam VI as needles, 0.91 g. (100%), m.p. 278–281°. Crystallization from ethanol raised the m.p. to 288–291°; $[\alpha]^{24}D$ +23° (*c* 0.5, chloroform); λ_{max}^{MeOH} 221 mμ, ε 17,700.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 74.95; H, 9.65; N, 4.73.

17β-Acetoxy-3-aza-17-methyl-A-homo-4a-androsten-4-one (VII).—Oxime IV (3.59 g., 0.01 mole) in 80 ml. of purified dioxane was stirred with 1.44 ml. (0.02 mole) of thionyl chloride for 1 hr. at room temperature. The work-up was essentially as described for compound V. Chromatography of the crude product on silica gel and elution with 50% ethyl acetate in benzene yielded lactam VII, 2.13 g. (59%), m.p. 250–252°. Crystallization from 50% ethanol gave needles, m.p. 253–254°; $[\alpha]^{25}D$ +2° (*c* 1, methanol); λ_{max}^{MeOH} 220 mμ, ε 17,200.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.66; H, 9.26; N, 3.93.

3-Aza-17β-hydroxy-17-methyl-A-homo-4a-androsten-4-one (VIII).—Acetate VII (3.59 g., 0.01 mole) in 225 ml. of methanol containing 22.4 g. (0.40 mole) of potassium hydroxide was allowed to stand 48 hr. at room temperature. The solution was neutralized with acetic acid, diluted with 400 ml. of water, and concentrated under vacuum to approximately 400 ml. to give the hydroxylactam VIII, 3.08 g. (97%), m.p. 287–290°. Crystallization from 50% methanol yielded needles, m.p. 291–293°; $[\alpha]^{25}D$ −3° (*c* 1, methanol); λ_{max}^{MeOH} 221 mμ, ε 17,100.

Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.76; H, 9.88; N, 4.52.

The Epoxidation of Certain α,β-Unsaturated Ketones with Sodium Hypochlorite

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The epoxidation of α,β-unsaturated carbonyl compounds[1] and of 1,4-naphthoquinones[2] may be effected by means of hydrogen peroxide in alkaline medium. In most such cases the reactions are run under homogeneous conditions, whereby an organic solvent such as methanol, ethanol, or dioxane is employed if the unsaturated compound is not soluble in water. The anion of *t*-butyl hydroperoxide has also been found to convert α,β-unsaturated ketones to the corresponding epoxides.[3] The hypochlorite ion has also been used as an epoxidizing agent, wherein it presumably behaves analogously to the hydroperoxide and alkylhydroperoxide ions. Thus, 1,4-naphthoquinone has been converted to 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone by reaction with aqueous calcium hypochlorite under heterogeneous conditions.[4] The epoxides of some α,β-unsaturated aldehydes were isolated, in low yield, from the products of the reactions of the carbonyl compounds with sodium hypochlorite.[5] *trans*-Dibenzoylethylene oxide has been prepared by the hypochlorite oxidation of the unsaturated diketone in dioxane,[6] although no report of the yield was included.

While alkaline hydrogen peroxide is an excellent reagent for the epoxidation of most α,β-unsaturated carbonyl compounds, there are certain advantages to be realized in the use of sodium hypochlorite or calcium hypochlorite solutions for the same purpose. It was ascertained in this work that an ordinary commercial hypochlorite bleach solution is quite satisfactory and, consequently, provides a much less expensive and less hazardous reagent than concentrated hydrogen peroxide. In the course of an investigation, now in progress, dealing with the reactions of unsaturated carbonyl compounds with hypochlorites and related substances, it was found that the epoxidation is particularly effective when conducted in pyridine solution. The basicity of the solvent precludes the necessity of using another base, such as sodium hydroxide, in conjunction with a water-miscible organic solvent, such as dioxane.[6] Both benzalacetophenone and *trans*-dibenzoylethylene have been epoxidized with the sodium hypochlorite–pyridine reagent. The reactions are rapid and the yields almost quantitative.

The heterogeneous reaction of 1,4-naphthoquinone with aqueous calcium hypochlorite[4] results in a high yield of the corresponding epoxide. However, the reaction requires about twenty-four hours at room temperature for completion. In an effort to reduce the reaction time epoxidation under homogeneous conditions was indicated. The reaction of 1,4-naphthoquinone with aqueous sodium hypochlorite in dioxane led to the formation of the epoxide in 71% yield, after a reaction time of only a few minutes. When pyridine was used in place of dioxane the oxidation apparently proceeded beyond the epoxide stage, since no epoxide could be isolated. Instead, a brown solid, of as yet undetermined structure, was produced. In dioxane, to which dilute sodium hydroxide had been added, the reaction of 1,4-naphthoquinone with aqueous sodium hypochlorite resulted in the formation of about a 50% yield of the epoxide and other colored products. 2-Methyl-1,4-naphthoquinone behaves similarly to 1,4-naphthoquinone. In dioxane, the epoxide is produced in good yield, whereas in the more basic solvents (pyridine, or dioxane plus sodium hydroxide) red-brown solid products are formed.

It is of interest to note that in at least three instances claims to have epoxidized 1,4-naphthoquinone or 2-methyl-1,4-naphthoquinone with hypochlorous acid, according to Zincke's procedure, have been made.[7] As was pointed out previously, the reagent actually employed by Zincke was calcium hypochlorite. In order to verify these assertions, the reactions of 1,4-naphthoquinone and of 2-methyl-1,4-naphthoquinone with hypochlorous acid were investigated. In the case

(1) E. Weitz and A. Scheffer, *Ber.* **54**, 2327 (1921).

(2) (a) E. Weitz, H. Schobbert, and H. Seibert, *ibid.*, **68B**, 1163 (1935); (b) L. F. Fieser, W. P. Campbell, E. M. Fry, and M. D. Gates, *J. Am. Chem. Soc.*, **61**, 3216 (1939).

(3) N. C. Yang and R. A. Finnegan, *ibid.*, **80**, 5845 (1958).

(4) (a) Th. Zincke, *Chem. Ber.*, **25**, 3599 (1892); (b) J. Madinaveitia, *Rev. acad. cienc. Madrid*, **31**, 617 (1934).

(5) C. Schaer, *Helv. Chim. Acta*, **41**, 560 (1958); C. Schaer, *ibid.*, **41**, 614 (1958).

(6) R. C. Fuson and R. Johnson, *J. Am. Chem. Soc.*, **68**, 1668 (1946).

(7) (a) A. Madinaveitia and J. Saenz de Buruaga, *Anales soc. espan. fis. quim.*, **27**, 647 (1929); (b) J. Madinaveitia, *ibid.*, **31**, 750 (1933); and (c) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3170 (1948).

of 1,4-naphthoquinone some epoxide was, indeed, produced, but in very low yield and only after reaction times of the order of several days at room temperature. Most of the starting material was recovered unchanged. No detectable amount of epoxide was formed in the reaction of the 2-methyl-1,4-naphthoquinone with hypochlorous acid. It appears that the formation of epoxide from naphthoquinone in contact with aqueous hypochlorous acid was due to the reaction with the hypochlorite ion, which is present in very low concentration.

Experimental[8]

Epoxidation of Benzalacetophenone.—To a solution of 1.0 g. (0.048 mole) of benzalacetophenone in 7.5 ml. of pyridine was added 11 ml. of fresh 5.25% sodium hypochlorite solution (Clorox). The yellow color of the solution faded almost immediately and heat was evolved.[9] When the mixture became colorless, or nearly so, 25 ml. of water was added, causing the precipitation of the white crystals of the epoxide. The product was filtered, washed thoroughly with water and then recrystallized from ethanol. There was obtained 1.0 g. (94%) of the epoxide, m.p. 89–90°. The identity of the compound was verified by a mixed melting point determination with an authentic sample of 1,3-diphenyl-2,3-epoxy-1-propanone, prepared by the method of Weitz and Scheffer.[1] The infrared spectra of the prepared compound and the authentic sample were identical.

trans-Dibenzoylethylene oxide was prepared in the manner described above from *trans*-dibenzoylethylene. A 93% yield of the epoxide, m.p. 131.5–132.0°, was obtained. The identity was verified by a mixed melting point determination and comparison of infrared spectra with an authentic sample.

Epoxidation of 1,4-Naphthoquinone.—Ten milliliters of 5.25% sodium hypochlorite was added to a solution of 1.0 g. of 1,4-naphthoquinone in 20 ml. of dioxane. Heat was evolved and the mixture was cooled by an external water bath. After 2 min., the mixture was pale yellow and remained the same color for an additional minute. Thirty-five milliliters of water was added and the light yellow precipitate was recovered by filtration. After washing thoroughly with water, the crude product was recrystallized from ethanol. A yield of 0.8 g. (71.5%) was realized. The melting point of the product and that of a mixture of the product with 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone was 134–136°.

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(8) All melting points are uncorrected.

(9) It would be advisable to provide external cooling if the reaction is run on a larger scale.

The Stereochemical Configuration of 5-Hydroxylysine and Synthesis of (+)-1,5-Diamino-2-hydroxypentane (Hydroxycadaverine)[1]

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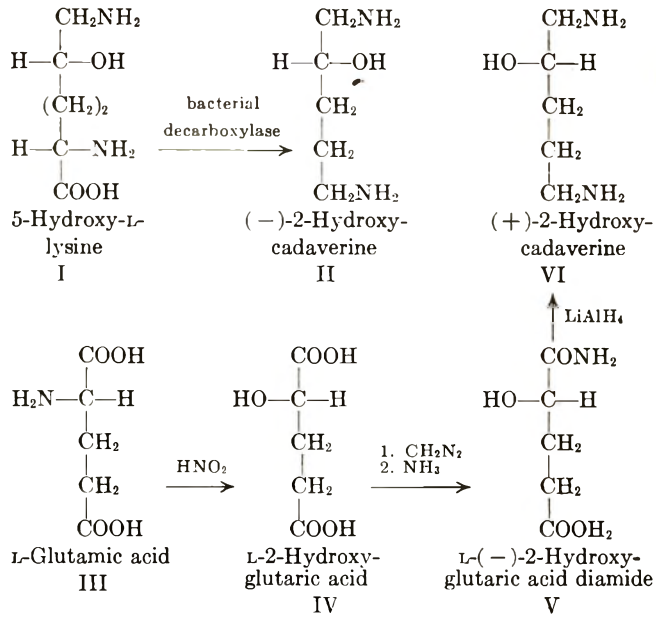
5-Hydroxylysine remains as the last of the protein-bound amino acids for which the stereochemical configuration has not been definitely established by chemical means.



Witkop has applied Hudson's lactone rule to *N*-acylated derivatives of hydroxyamino acids. From the results obtained with natural 5-hydroxylysine[2] he concluded that this amino acid should have the *erythro* configuration.

We have recently studied the decarboxylation of 5-hydroxylysine by bacterial L-lysine decarboxylase.[3] The natural isomer I gave the levorotatory dihydrochloride of 1,5-diamino-2-hydroxypentane [(−)-2-hydroxycadaverine] II, ($[\alpha]_{589}^{25}$ −14.8°]) from which a levorotatory dibenzoate was prepared.

This communication describes the synthesis of the dextro isomer of 2-hydroxycadaverine VI by a route which establishes its absolute configuration and consequently that of the second asymmetric center in 5-hydroxy-L-lysine. The steric correlation is shown in the Fischer projection formulas of the compounds involved. Deamination of L-glutamic acid III is known to proceed with retention of configuration[4] to yield L-2-hydroxyglutaric acid IV. This hydroxy acid was converted to the levorotatory diamine V which on reduction with lithium aluminum hydride in boiling diglyme[5] gave the dextrorotatory diamine dihydrochloride VI ($[\alpha]_{589}^{28}$ +11.1°).

On benzoylation in sodium hydroxide a dextrorotatory dibenzoate ($[\alpha]_{589}^{21}$ +23.6°) was obtained which was identical in melting point and infrared spectrum with the levo-compound, ($[\alpha]_{589}^{25}$ −21.6°), obtained after benzoylation of the amine II formed in decarboxylation of natural 5-hydroxy-L-lysine. These results confirm the *erythro* configuration deduced by Witkop[2] from rotational measurements.

Experimental

L-2-Hydroxyglutaric Acid.—L-Glutamic acid (Merck Co.) was deaminated with nitrous acid[6] and the hydroxyglutaric acid isolated as a crude barium salt.

(1) Supported by a grant from Riksföreningen mot Reumatism.

(2) B. Witkop, *Experientia*, **XII**, 372 (1956).

(3) S. Lindstedt and G. Lindstedt, *Arkiv Kemi*, **19**, 447 (1962).

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, New York, N. Y., 1953.

(5) Diglyme = dimethyl ether of diethylene glycol.

(6) E. Fischer and A Moreschi, *Ber. Deut. Chem. Ges.*, **45**, 2447 (1912).

2-Hydroxyglutaric Acid Diamide.—A solution of 7 g. of the barium salt of L-2-hydroxyglutaric acid in 40 ml. of water was passed through a short column of the cation exchanger Dowex-50 × 4 (50–100 mesh, H^+-form). The column was washed with water and the combined effluents evaporated to dryness *in vacuo* at 30°. The residual oil, 3.5 g., was kept in the desiccator overnight, dissolved in 20 ml. of ice-cold methanol and esterified with diazomethane to yield 4.1 g. of crude dimethyl 2-hydroxyglutarate. This material, 3.5 g., was dissolved in 20 ml. of dry methanol and the solution saturated with ammonia at 0°. After keeping for 24 hr. at room temperature 2.7 g. of the diamide was filtered off, m.p. 181–182° (lit.,[7] 182°) $[\alpha]_{589}^{22}$ −33°, (*l* 2; *c* 1.48 in water).

Anal. Calcd. for $C_5H_{10}O_3N_2$ (146.15): C, 41.09; H, 6.90; N, 19.17. Found: C, 41.03; H, 6.79; N, 18.79.

(+)-1,5-Diamino-2-hydroxypentane Dihydrochloride.—The L-2-hydroxyglutaric acid diamide, 0.5 g., was placed in a small filter paper thimble in the neck of a flask fitted with a reflux condenser. The flask contained a suspension of 1.0 g. of lithium aluminum hydride in 50 ml. of refluxing diglyme.[8] After 20 hr. the amide had been extracted into the boiling solution. After cooling excess lithium aluminum hydride was decomposed with 3 ml. of water followed by 3 ml. of 1 *N* sodium hydroxide. The precipitate was filtered off and washed with hot ethanol. After adjusting to pH 3 the solution was evaporated and the residue put onto a column of Dowex-50 × 4 (200–400 mesh; 54 × 1.2 cm. in 1 *N* hydrochloric acid). The column was eluted with 1 *N* hydrochloric acid (200 ml.) followed by 3 *N* hydrochloric acid which eluted the hydroxyamine after further 70–80 ml. effluent. The amine hydrochloride crystallized on evaporation of the hydrochloric acid *in vacuo* and was recrystallized twice from ethanol to give 0.08 g. of m.p. 166–167°, $[\alpha]_{589}^{28}$ +11.1°, (*l* 1; *c* 2 in water).

Anal. Calcd. for $C_5H_{16}ON_2Cl_2$ (191.1): C, 31.42; H, 8.44; N, 14.66. Found: C, 31.52; H, 8.47; N, 14.11.

(+)-1,5-Dibenzamido-2-hydroxypentane.—(+)-1,5-Diamino-2-hydroxypentane dihydrochloride, 0.09 g., were dissolved in 5 ml. of 1 *N* sodium hydroxide and 0.4 ml. of benzoyl chloride added in portions with stirring. After standing overnight in the refrigerator 0.08 g. of crystals were filtered off and recrystallized from ethyl acetate, m.p. 130–32°, $[\alpha]_{589}^{21}$ +23.6° (*l* 1; *c* 0.84 in pyridine).

Anal. Calcd. for $C_{12}H_{22}O_3N_2$ (326.4): C, 69.92; H, 6.77; N, 8.59. Found: C, 70.08; H, 6.96; N, 8.61.

(7) C. Ravenna and R. Nuccorini, *Gazz. chim. ital.*, **58**, 861 (1928).

(8) Dried over calcium hydride and redistilled from lithium aluminum hydride.

The Chemistry of Ylids. VIII. Synthesis of Nitrones *via* Sulfur Ylids[1]

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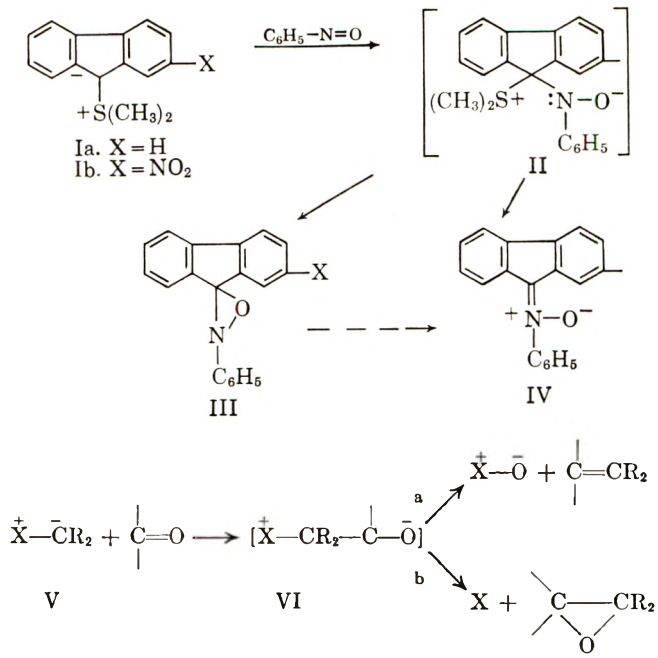
In our original report on the preparation and reactions of sulfur ylids[2] we noted briefly that 9-dimethylsulfoniumfluorenylide (Ia) reacted with nitrosobenzene to form what appeared to be N-phenylfluorenone ketoxime (IVa) rather than the expected oxazirane (IIIa). We wish to report further studies on this reaction.

It has been well established[3] that phosphorus- and arsenic-containing ylids (V. X = PR'_3, AsR'_3) react with carbonyl compounds by initial attack of the ylid carbanion on the carbonyl carbon to form an intermediate betaine (VI). The reaction goes to completion *via* a four-membered transition state resulting in the ultimate formation of an olefin and the appropriate phosphine oxide or arsine oxide (path a). It has been shown[4] that these same ylids will react with nitrosobenzene in an analogous fashion to form the expected N-phenylimines. For example, triphenylphosphoniumfluorenylide and nitrosobenzene afforded fluorenone anil in 84% yield.[4a]



Johnson and LaCount[2] have recently shown that sulfur ylids (V. X = SR'_2) also react with carbonyl compounds by attack of the ylid carbanion on the carbonyl carbon to form a similar betaine intermediate. However, the oxyanion portion of this betaine (VI. X = SR'_2) displaced the sulfide group forming an epoxide as the major product (path b). By analogy it was expected that sulfur ylids would react with nitrosobenzene to form oxaziranes (III), thereby providing another synthetic route to these unique compounds. Oxaziranes have been intensely studied since their original synthesis by Emmons.[5]

An exothermic reaction took place upon mixing the ylid (Ia) and nitrosobenzene, ultimately affording a quantitative yield of the *nitrone* (IVa). Microanalytical data and hydrolysis of the product to fluorenone were both consistent with either structure IIIa or IVa. That the product was, in fact, the nitrone (IVa) and not isomeric oxazirane (IIIa) was demonstrated by infrared absorption at 6.06 μ (C=N), 6.51 and 7.48 μ (N=O) and by the ultraviolet spectrum which showed the long wave length absorption (351 mμ) expected of a fluorenylidene system and not the simple fluorenyl spectrum expected for IIIa. The substance was also shown to react in a 1,3-addition reaction with diethyl fumarate to form an isoxazolidine.[6]

The generality of this reaction was demonstrated using 9-dimethylsulfonium-2-nitrofluorenylide (Ib) and dimethylsulfonium(diphenyl)methylide, both of which afforded the corresponding nitrones in good yield when

(1) (a) We gratefully acknowledge the financial support of the National Science Foundation through Grant No. G-17345; (b) for the previous paper in this series see A. W. Johnson and V. J. Hruby, *J. Am. Chem. Soc.*, **84**, 3586 (1962).

(2) A. W. Johnson and R. B. LaCount, paper VI, *ibid.*, **83**, 417 (1961).

(3) G. Wittig, H. D. Weigmann, and M. Schlosser, *Chem. Ber.*, **94**, 676 (1961); A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

(4) (a) A. W. Johnson, unpublished observations; (b) A. Schonberg and K. H. Brosowski, *Chem. Ber.*, **92**, 2602 (1959).

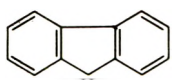
(5) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).

(6) G. R. Delpierre and M. Lamchen, *Proc. Chem. Soc.*, 386 (1960).

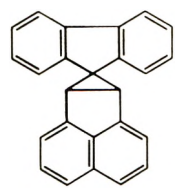
reacted with nitrosobenzene. Krohnke[7] had previously shown 9-(1-pyridinium)fluorenylide to react with *p*-nitroso-N,N-dimethylaniline to afford the corresponding nitrone and we have recently shown[2] that the same ylid will react with the unsubstituted nitrosobenzene to afford the nitrone (IVa).

Our curiosity as to the mechanism of the formation of nitrones from these sulfur ylids was aroused since, as mentioned above, we had expected to obtain the oxaziranes. Three explanations for this turn of events seemed feasible and were subsequently tested.

It was conceivable that the sulfur (and nitrogen) ylids were first decomposing to carbenes which then reacted with nitrosobenzene to form nitrones rather than oxaziranes. Franzen[8] has shown that nitrogen ylids can be decomposed to carbenes and several of the by-products from the reaction of the sulfur ylid (Ia) with carbonyl compounds were best accounted for by decomposition of Ia to the fluorenyl carbene (VII).[2] More recent work[1b] has demonstrated that other sulfur ylids can be decomposed under mild conditions to carbenes which can in turn be trapped with acenaphthylene. However, an attempt to trap the carbene by heating the sulfur ylid (Ia) with acenaphthylene gave none of the expected adduct (VIII). It was apparent, therefore, that under the conditions for nitrone formation, the ylid (Ia) was reacting as an ylid and not as a carbene.



VII



VIII

In an effort to determine how a carbene might react with nitrosobenzene we studied the reaction of 9-diazofluorene with the latter. An exothermic reaction took place resulting in the rapid evolution of nitrogen and the precipitation of a high yield of the nitrone (IVa). A similar reaction took place between diphenyldiazomethane and nitrosobenzene, again affording a nitrone. Schonberg and coworkers[9] have shown that diazofluorene will react with acenaphthylene under gentle heating to form the adduct (VIII), thereby demonstrating the facility with which diazofluorene is converted to a carbene. Thus, it initially appeared that the nitrone (IVa) was the product of a carbene reaction with nitrosobenzene. However, it is somewhat problematical whether it was a carbene (VII) or diazofluorene itself that was reacting with nitrosobenzene. Diazofluorene could well be reacting as an ylid, the nucleophilic C-9 of the fluorenyl portion attacking the nitrogen end of the nitroso group. The nitrone would then be the expected product by analogy with the sulfur ylid reactions. The spontaneity with which the reaction took place leads us to prefer the latter explanation and to conclude the nitrone (IVa) not to be the product of a carbene reaction with nitrosobenzene.

As an alternate explanation it appeared possible that the desired oxazirane (IIIa) was in fact the initial product of the ylid reaction but that it had isomerized to the nitrone (IVa) under the reaction conditions. Emmons[5] has shown that oxaziranes can be thermally isomerized to nitrones and Splitter and Calvin[10] noted that N-phenyloxaziranes were particularly labile, rearranging to anilides. As a result, several attempts were made to prepare the oxazirane (IIIa) and determine its stability.

The oxidation of fluorenone anil, a method for oxazirane synthesis developed by Emmons,[5] afforded not the expected IIIa but the isomeric nitrone (IVa). The fact that an oxidation did occur leads us to suspect that the oxazirane was initially formed but rapidly rearranged to the nitrone (IVa) under these conditions. Photolysis of the nitrone (IVa), a procedure by which Splitter and Calvin[10] isomerized nitrones to oxaziranes, gave only unchanged starting material. 9-Diazofluorene and nitrosobenzene would not react below 0°, both substances being recovered unchanged. Between 0 and 5° a red ethereal solution of the two reactants or a solid mixture in a capillary could be observed rapidly changing to yellow with simultaneous evolution of nitrogen and gradual precipitation of the nitrone. No intermediate product or color change could be observed in either case. Thus we were unable to prepare the oxazirane (IIIa). If the latter was an intermediate in the reaction between sulfur ylids and nitrosobenzene, it was obviously very short-lived.

As a third and rather remote explanation for the formation of IVa from the reaction of Ia with nitrosobenzene it was conceivable that in the intermediate betaine (II) the lone electron pair on nitrogen, rather than those on the oxyanion, actually displaced methyl sulfide. This was considered unlikely due to the relative nucleophilicity of the two groups. In addition, if such were the case one might expect to have obtained some nitrone from the reaction of a phosphorus ylid with nitrosobenzene since an analogous betaine intermediate was involved. Such was not the case.

We conclude that the reaction of sulfur and nitrogen ylids and of diazo compounds with nitrosobenzene is best explained by the initial formation of an unisolable oxazirane as a very short-lived intermediate which rapidly isomerized to a nitrone.

Experimental[11]

N-Phenylfluorenone Ketoxime (IVa). A. From the Ylid (Ia).—To a solution of 0.95 g. (8.9 mmoles) of nitrosobenzene in 40 ml. of dry ether was added 2.0 g. (8.9 mmoles) of 9-dimethylsulfoniumfluorenylide (Ia).[2] Nitrogen and heat were evolved and a yellow precipitate formed. After stirring for 3 hr. the yellow precipitate (2.3 g., 96%) was filtered and dried, m.p. 189–191°. Recrystallization from 95% ethanol gave fine yellow needles of IVa, m.p. 194.5–196.5°, λ_{max}^{Nujol} 6.06, 6.22, 6.51, 7.48, 13.00, 13.75 and 14.75 μ; λ_{max}^{EtOH} 236 mμ (log ϵ 4.5), 260 (4.4), and 351 (4.3).

Anal. Calcd. for $C_{19}H_{13}NO$: C, 84.10; H, 4.83; N, 5.16. Found: C, 84.40; H, 5.25; N, 5.01.

B. From 9-Diazofluorene[12]—A slurry of 1.92 g. (0.01 mole) of 9-diazofluorene and 1.07 g. (0.01 mole) of nitrosobenzene in 40 ml. of dry ether was stirred for 1 hr. During that time the red color vanished, nitrogen was evolved, and a yellow precipitate

(7) F. Krohnke, *Chem. Ber.*, **83**, 253 (1950).

(8) V. Franzen, *ibid.*, **93**, 557 (1960); V. Franzen and G. Wittig, *Angew. Chem.*, **72**, 417 (1960).

(9) A. Schonberg, A. Mustafa, and N. Latif, *J. Am. Chem. Soc.*, **75**, 2267 (1953).

(10) J. S. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958).

(11) All melting points are uncorrected. Microanalyses were by A. Bernhardt, Mülheim, Germany. Infrared spectra were recorded as Nujol mulls on a Perkin–Elmer Infracord. Ultraviolet spectra were recorded on a B and L 505 Spectronic in 95% ethanol solutions.

(12) This reaction was originally reported by Staudinger and Miescher, *Helv. Chim. Acta*, **2**, 578 (1919).

formed. The latter was filtered and dried (2.38 g., 88%) then recrystallized from 95% ethanol as yellow needles, m.p. 194–196° (lit.,[12] m.p. 192–193°). It was shown to be identical to that prepared from A above by admixture melting point and comparison of infrared spectra.

C. From 9-(1-Pyridinium)fluorenylide.—Treatment of 1-(9-fluorenyl)pyridinium bromide with nitrosobenzene as described previously[2] gave yellow needles, m.p. 192–193°, identical to that prepared from A and B above.

Warming the nitrone (IVa) in ethanolic sulfuric acid for 1 hr. led to a disappearance of the yellow color. Quenching with water followed by extraction of the neutral and basic fragments with ether led to the recovery of the oily β-phenylhydroxylamine, λ_{max} 2.91 and 3.05 μ, and fluorenone, which crystallized from hexane as yellow needles, m.p. 81–83°, identical to an authentic sample.

A solution of 0.54 g. of the nitrone (IVa) and 0.34 g. of diethyl fumarate in 15 ml. of benzene was heated under reflux for 24 hr. Removal of the solvent followed by trituration with 95% ethanol gave 0.10 g. of unchanged nitrone, m.p. 194–196°. Dilution of the filtrate with water afforded 0.42 g. (58%) of crude 2-phenyl-3,3-diphenylene-4,5-dicarbethoxyisoxazolidine, m.p. 74–80°. Recrystallization from 80% ethanol gave colorless microcrystals, m.p. 76–78°, λ_{max} 5.65, 5.75, 13.25, 13.64, and 14.55μ.

Photolysis of the Nitrone (IVa).—A solution of 0.27 g. of the nitrone in 25 ml. of acetonitrile was irradiated in a quartz tube for 3 hr. using a Hanovia quartz lamp. No color change could be observed. Evaporation of the solvent and crystallization of the tan residue from 95% ethanol afforded unchanged nitrone, m.p. 193–194.5°.

Oxidation of Fluorenone Anil.—Ten milliliters of a solution of peracetic acid in methylene chloride prepared according to Emmons[5] directions, was added to a cold stirred solution of 1.25 g. of fluorenone anil[4,13] in 10 ml. of methylene chloride. After standing overnight at room temperature the solution was washed with water and dilute ammonia then dried. Removal of the solvent *in vacuo* left a brown solid which, upon trituration, afforded yellow crystals (0.90 g., 68%), m.p. 182–187°, which crystallized from 95% ethanol as fine yellow needles, m.p. 191–193°, identical to an authentic sample of the nitrone (IVa).

N-Phenylbenzophenone Ketoxime. A. From Diphenyldiazomethane.—To a red solution of 1.0 g. of diphenyldiazomethane[14] in 25 ml. of dry ether was added 0.55 g. of nitrosobenzene. Heat and nitrogen were evolved immediately and the nitrosobenzene slowly dissolved as a colorless precipitate began to form. After 15 min. the precipitate (0.96 g., 68%) was removed by filtration and dried. It crystallized from 60% ethanol as colorless fine plates, m.p. 223–225°, λ_{max} 6.10, 6.27, 6.65, 7.45, 12.79, and 14.50 μ; λ_{max}^{EtOH} 230 mμ (log ε 4.2) and 310 mμ (4.0)).

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.56; H, 5.49; N, 5.35.

B. From Dimethylsulfonium(diphenyl)methylide.—Treating a slurry of dimethylbenzhydrylsulfonium bromide in tetrahydrofuran with butyllithium resulted in a deep red solution of the sulfur ylid. Reaction of this solution with nitrosobenzene followed by quenching with water and extracting with ether gave the crude nitrone, m.p. 210–220°. Crystallization from 60% ethanol afforded colorless plates, m.p. 223–226°, identical to that prepared in A above.

Warming a solution of the nitrone (0.54 g.) in 20 ml. of 95% ethanol containing 6 ml. of 50% sulfuric acid for 1 hr. led to dissolution of the solid. The colorless solution was quenched with water then the neutral and basic components were separated and removed by ether extraction. The basic fraction (an oil) was identified as β-phenylhydroxylamine by its infrared spectrum. The neutral fraction was identified as benzophenone by its infrared spectrum and by conversion to its hydrazone, m.p. 97–100°, identical to an authentic sample.

N-Phenyl(2-nitro)fluorenone Ketoxime (IVb).—To a purple solution of 0.96 g. of dimethylsulfonium(2-nitro)fluorenylide (Ib) in 30 ml. of methylene chloride was added 0.30 g. of nitrosobenzene. The solution was heated under reflux for 1 hr. during which time the color changed to yellow. Evaporation of the solvent and trituration of the residue afforded 0.60 g. (76%) of crude nitrone (IVb), m.p. 217–220°. Crystallization from benzene afforded fine light orange needles, m.p. 224–225°, λ_{max} 6.60, 7.50, 13.00, 13.20, 13.75, and 14.43 μ.

(13) G. Reddelien, *Chem. Ber.*, **43**, 2479 (1910).

(14) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

Some New Reactions of Methylsulfinyl and Methylsulfonyl Carbanion[1]

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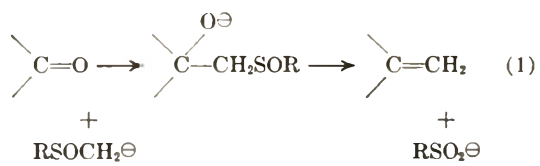
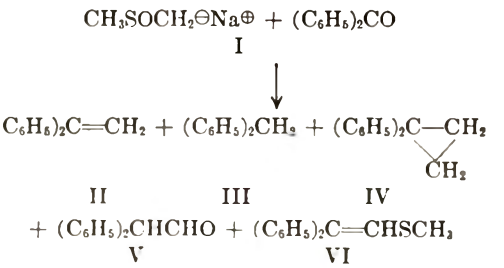
Recently we have described the generation and properties of the methylsulfinyl carbanion (I) and some applications of this extremely useful reagent in synthesis. In this and subsequent work, for example, solutions of the anion in dimethyl sulfoxide have been employed as the key feature of a very convenient and effective modification of the Wittig olefin synthesis.[2,3] It occurred to us that the reactivity of the methylsulfinyl carbanion and the extraordinary properties of dimethyl sulfoxide as a solvent might allow a Wittig type of olefin synthesis directly from the sulfinyl carbanion and certain carbonyl compounds:



(1)

Consequently an investigation was initiated of the reaction of such carbanions with benzophenone under conditions which are more drastic than those required to form the simple carbonyl addition product. The case of benzophenone seemed especially favorable since the carbonyl addition reaction is known to proceed in good yield[2] and is obviously not complicated by competing reactions such as enolate formation.[4]

In fact, the reaction of methylsulfinyl carbanion with benzophenone at 75–100° did afford distillable hydrocarbon products; a satisfactory conversion was obtained by rapid heating of the reactants from room temperature to 100° and maintenance at the higher temperature for several hours. Under these conditions a volatile product was obtained containing the hydro-



(1) This work was supported by a grant (RG-6966) from the National Institutes of Health.

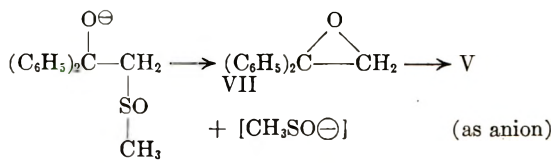
(2) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(3) A solution of the methylsulfinyl carbanion in dimethyl sulfoxide is prepared by heating sodium hydride with excess dry sulfoxide under nitrogen at 75° and then standardized by aqueous titration of an aliquot with standard acid. An equivalent amount of this anion is then added to a solution of the phosphonium salt in dry dimethyl sulfoxide (under nitrogen). After a few minutes the carbonyl compound is added with stirring and the reaction is allowed to proceed at room temperature for thirty minutes (or longer with hindered carbonyl compounds). Dilution with water, extraction, and appropriate isolation procedures then afford the Wittig product in very satisfactory yields (often much superior to those obtained under the customary conditions in ether or tetrahydrofuran).

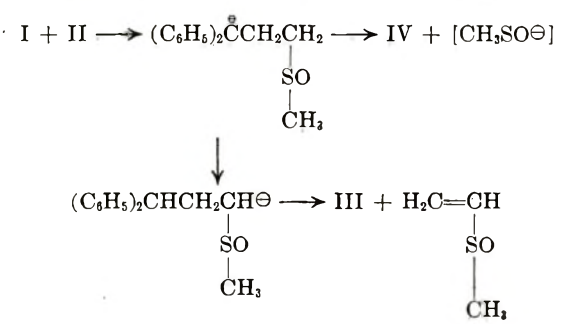
(4) During this investigation we learned of similar studies in the laboratory of Prof. C. Walling, Columbia University. Our results are published simultaneously through mutual agreement.

carbons 1,1-diphenylethylene, diphenylmethane, and 1,1-diphenylcyclopropane and, in addition, diphenylacetaldehyde and 1,1-diphenyl-2-methylthioethylene (VI). The nondistillable products were not investigated. The reaction of the carbanion I with 1,1-diphenylethylene under the same conditions was studied next and it was found that both diphenylmethane and 1,1-diphenylcyclopropane resulted.

It is evident that the process of olefin formation described by equation 1 does occur and also that other reaction pathways are available to the intermediate β-oxysulfoxide anion and to the olefinic product as well. The formation of diphenylacetaldehyde (V) probably occurs by base-catalyzed rearrangement of 1,1-diphenylethylene oxide (VII):



The epoxide V may also be a precursor of the olefin II although this seems less likely than the pathway given by equation 1. It is possible that the cyclopropane IV and diphenylmethane result from the sequence:



Finally we have observed that the reaction of methylsulfonyl carbanion ($CH_3SO_2CH_2^-$) with benzophenone in dimethyl sulfoxide under similar conditions also gave the hydrocarbons II, III, and IV and diphenylacetaldehyde.

These new reactions, though not of obvious synthetic utility at the moment, raise a number of questions which warrant additional attention and which might lead to serviceable preparative procedures.

Experimental

Reaction of Methylsulfinyl Carbanion with Benzophenone.—A solution of methylsulfinyl carbanion was prepared by heating with stirring a mixture of 0.055 mole of powdered sodium hydride and 50 ml. of dry dimethyl sulfoxide (distilled from calcium hydride, b.p. 64°/4 mm.) under nitrogen at 75°, until the evolution of hydrogen ceased (about 40 min.). The pale yellow solution was cooled to about 15° in a water bath and a solution of 9.1 g. (0.05 mole) of benzophenone in 20 ml. of dimethyl sulfoxide was added by hypodermic syringe over a 3-min. period. After stirring for 5 min., the reaction mixture was placed in an oil bath, the temperature was rapidly raised to 100°, and stirring was continued at this temperature for 2 hr., during which time a deep red color developed. The cooled mixture was poured into 200 ml. of cold water, extracted with ether, and the extracts washed three times with water, dried over anhydrous sodium sulfate, and evaporated to yield 7.9 g. of an orange oil. Distillation of the oil under reduced pressure through a short-path Vigreux column yielded a first fraction of 4.5 g. of colorless liquid, b.p. 75–115°/0.2 mm., and a second fraction of 0.5 g. of pale yellow oil, b.p. 115–140°/0.2 mm. A dark red resinous material remained in the distilling flask.

Vapor phase chromatographic (v.p.c.) analysis of the first fraction on an F and M Model 300 gas chromatograph, using a 6-ft. column of 20% silicone rubber on Chromosorb, temperature 225°, input pressure 20 p.s.i., flow rate 34 ml. helium/min., showed the presence of four components, which were identified as being diphenylmethane, 1,1-diphenylethylene, 1,1-diphenylcyclopropane, and diphenylacetaldehyde. Retention times were 9 min. 10 sec., 11 min. 31 sec., 14 min. 30 sec., and 17 min. 46 sec., respectively, and the percentages were 30, 47, 3, and 20%, respectively. Identification was accomplished by collecting a sample of each compound from the v.p.c. column and comparing the infrared spectrum with that of an authentic sample. The infrared spectrum of authentic 1,1-diphenylcyclopropane was kindly provided by Dr. H. Simmons, Du Pont Co. The v.p.c. retention time of each authentic sample was also matched with the corresponding one in the mixture. The 2,4-dinitrophenylhydrazone (m.p. 152–153°) of the diphenylacetaldehyde from the mixture had an undepressed melting point when mixed with the same derivative from authentic diphenylacetaldehyde.

The following n.m.r. data (Varian A-60) were obtained for these products (τ values at 60 mc.). Diphenylacetaldehyde: (carbon tetrachloride) doublet centered at 0.02 τ (J 2.7 c.p.s.), 1 proton; singlet at 2.65 τ, 10 protons; doublet centered at 5.33 τ (J 2.7 c.p.s.), 1 proton. Diphenylethylene: (neat) multiplet at 2.75 τ center, 10 protons; singlet at 4.57 τ, 2 protons. Diphenylmethane: (neat) singlet at 2.86 τ, 10 protons; singlet at 6.22 τ, 2 protons. 1,1-Diphenylcyclopropane: (carbon tetrachloride) singlet at 2.87 τ, 10 protons; singlet at 8.78 τ, 2 protons.

The second distillate fraction was filtered through 20 g. of Merck alumina, using pentane as eluent, in order to remove the coloring matter and a trace of diphenylacetaldehyde. V.p.c. analysis of the colorless oil thus obtained, under the above conditions, showed a single component with retention time 37 min. 46 sec. A sample collected from the v.p.c. column crystallized when scratched with a glass rod. Recrystallization from 95% ethanol gave colorless needles, m.p. 72.5–73.5°. The structure assigned to the solid was 1,1-diphenyl-2-methylthioethylene on the basis of its n.m.r. spectrum and analysis. The n.m.r. spectrum had a methyl singlet at 7.7 τ, an olefinic proton singlet at 3.5 τ and sharp phenyl peaks at 2.63 and 2.75 τ. The proton integral ratio was 3:1:10, respectively.

Anal. Calcd. for $C_{15}H_{14}S$[5]: C, 79.61; H, 6.23; S, 14.17. Found: C, 79.46; H, 6.23; S, 14.22.

Reaction of Methylsulfonyl Carbanion with Benzophenone.—A solution of methylsulfonyl carbanion was prepared by heating with stirring a mixture of 0.055 mole of sodium hydride, 5.64 g. (0.06 mole) of dimethyl sulfone and 50 ml. of dry dimethyl sulfoxide under nitrogen, at 75°, until hydrogen evolution ceased (30 min.). The same procedure as described above was repeated, using 9.1 g. (0.05 mole) of benzophenone, etc. Evaporation of the ether gave 8.1 g. of orange oil. Upon distillation, distillate boiling over the range 70–112°/0.15 mm. was collected to yield 4.4 g. of colorless liquid. V.p.c. analysis under the same conditions as above showed that the liquid consisted of three major components which were identified as diphenylmethane (38%), 1,1-diphenylethylene (46%), and diphenylacetaldehyde (15%). A small amount of 1,1-diphenylcyclopropane (less than 1%) was also present.

Reaction of Methylsulfinyl Carbanion with 1,1-Diphenylethylene.—A solution of methylsulfinyl carbanion was prepared under nitrogen as described from 0.044 mole of sodium hydride and 50 ml. of dry dimethyl sulfoxide. Diphenylethylene (7.2 g., 0.04 mole) was added neat to the stirred solution at room temperature to produce a deep red color. The procedure described above was again repeated to yield, after evaporation of the ether, 9.4 g. of red oil. Upon distillation, distillate boiling over the range 60–95°/0.15 mm. was collected to yield 2.8 g. of pale yellow liquid. A dark red resinous material remained in the distilling flask. The distillate was filtered through 20 g. of Merck alumina, using pentane as eluent, to remove the small amount of coloring matter. The recovery of colorless liquid was almost quantitative. V.p.c. analysis of the liquid under the same conditions as above showed the presence of two components, identified as diphenylmethane (64%) and 1,1-diphenylcyclopropane (36%). Samples of each were collected and their infrared and n.m.r. spectra were found to be identical to those of authentic samples.

(5) By C. Daessle, Montreal.

Products of the Base-catalyzed Reaction of Benzophenone with Dimethyl Sulfoxide[1]

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Several recent studies have demonstrated that the basic properties of alkoxide ions are greatly enhanced in strongly polar nonhydroxylic solvents such as dimethyl sulfoxide.[2] Accordingly, it seemed plausible to investigate the base-catalyzed homogeneous hydrogenation of benzophenone[3] in this medium, to see if the reaction could be realized under milder conditions than are required in *t*-butyl alcohol (180°, 2000 lbs./in.^{2} hydrogen pressure). Initial experiments showed a fairly rapid disappearance of benzophenone, even at 80°, but with no consumption of hydrogen or production of benzhydrol. Further study showed that hydrogen was indeed not involved in the process, and heating benzophenone in dimethyl sulfoxide under nitrogen in the presence of either potassium *t*-butoxide or dimethyl sulfoxide anion (from dimethyl sulfoxide and sodium hydride) led to a variety of hydrocarbon products including 1,1-diphenylethylene, diphenylmethane, and 1,1-diphenylcyclopropane.[4] Yields of some typical experiments, determined by gas–liquid chromatographic analysis (g.l.c.) are shown in Table I. Several nonhydrocarbon products were also detected and are discussed below.

TABLE I

BASE-CATALYZED REACTIONS OF BENZOPHENONE AND DIMETHYL SULFOXIDE

(Equimolecular quantities of base and ketone at 70–80°)

		Yield (%)		
Time	Base	Ph_2CH_2	$Ph_2CH{=}CH_2$	Ph_2
10 min.	BuOK	1.5	6.8	trace
12 hr.[a]	BuOK	10	3.6	trace
2 min.	NaH	...	32.5	8.8
4.5 hr.	NaH	1.4	10.1	trace
14 hr.	NaH	4.8	17.3	...

[a] Base added slowly over first 10 hr.

Our results reflect the striking complexity of base-catalyzed reactions in dimethyl sulfoxide, and we proposed that our products can be rationalized by the following reaction scheme:

$$CH_3SOCH_3 + C_4H_9O^- \rightleftharpoons C_4H_9OH + CH_3SOCH_2^- \quad (1)$$

$$CH_3SOCH_2^- + Ph_2CO \rightleftharpoons CH_3SOCH_2CPh_2O^- \quad (2)$$

$$CH_3SOCH_2CPh_2O^- \longrightarrow CH_3SO_2^- + CH_2{=}CPh_2 \quad (3)$$

$$CH_3SOCH_2^- + CH_2{=}CPh_2 \rightleftharpoons CH_3SOCH_2CH_2\bar{C}Ph_2^- \quad (4)$$

$$CH_3SOCH_2CH_2\bar{C}Ph_2 \longrightarrow CH_3SO\bar{C}HCH_2CHPh_2 \quad (5)$$

$$CH_3SO\bar{C}HCH_2CHPh_2 \longrightarrow CH_3SOCH{=}CH_2 + \bar{C}HPh_2 \longrightarrow CH_2PH_2 \quad (6)$$

$$CH_3SOCH_2CH_2\bar{C}CPh_2 \longrightarrow CH_3SO^- + \text{(cyclopropane)} \quad (7)$$

(cyclopropane: CH_2 bridging CH_2–CPh_2)

Reaction 1 is expected, since the sulfoxide is a weak base, and 2 has recently been reported by Corey and Chaykovsky[5] and also by Russell.[6] However, we find that the equilibrium indicated is measurable and strongly temperature dependent. Thus, while quenching a reaction mixture of benzophenone and the dimethyl sulfoxide anion at 25° gives an 80% yield of 2-methylsulfinyl-1,1-diphenylethanol, CH_3SOCH_2-Ph_2OH, quenching at 65° (or treating the alcohol with a mole of NaH at that temperature and quenching) gives 80% benzophenone.

Step 3 appears analogous to the Wittig reaction, and should probably be formulated as occurring *via* a cyclic transition state

$$CH_3{-}SO{-}CH_2CPh_2O^- \longrightarrow CH_3{-}\underset{\displaystyle O}{\overset{\displaystyle {}^-O{-}CPh_2}{S}}{-}CH_2 \longrightarrow CH_3SO_2^- + CH_2{=}CPh_2 \quad (8)$$

Sequence (4,5,6) amounts to carbanion addition to diphenylethylene, a prototropic shift, and a reverse Michael addition. Reaction 7 is essentially an internal S_N2 displacement analogous to those involved in several other cyclopropane ring syntheses. It requires the expulsion of a rather unusual anion, which presumably disproportionates or is otherwise consumed.

In addition to hydrocarbon products, the reaction scheme proposed also predicts the formation of several less volatile sulfur containing molecules. We have recovered a mixture of water soluble sulfur containing salts from our reaction mixtures, and g.l.c. analysis shows additional peaks of longer retention time from which sulfur containing products have been isolated, but have not been definitely identified.

Since 1,1-diphenylethylene is postulated as an intermediate in the formation of diphenylmethane and 1,1-diphenylcyclopropane, we have also examined its reaction with dimethyl sulfoxide anion. On heating the two together for fifteen hours in dimethyl sulfoxide at 80° the diphenylethylene is entirely consumed and diphenylmethane (17%) and 1,1-diphenylcyclopropane (6%) are both produced, consistent with our scheme. However, the major reaction product isolated on quenching and distillation is another hydrocarbon, 3,3-diphenylpropene. This interesting reaction, which appears to be general for a number of olefins, will be the subject of a subsequent communication.

Experimental

Equilibrium Addition of Dimethyl Sulfoxide to Benzophenone.—One mole of sodium hydride was dissolved in 400 ml. of freshly distilled dry dimethyl sulfoxide with warming. The mixture was cooled to 25°, an equivalent of benzophenone added in small portions, and the mixture allowed to stand for 30 min. On quenching with ice–water an 80% yield of 1,1-diphenyl-2-methylsulfinylethanol was isolated, m.p. after recrystallization from benzene, 150–150.5°.[5] When a similar experiment was carried out at 65°, 80% benzophenone was recovered and identified by mixed melting point and infrared spectra. Addition of the addi-

(1) Support of this work by a grant from the National Science Foundation and a fellowship to L.B. by American Cyanamid Co. is gratefully appreciated.

(2) *Cf.* for example A. Schriesheim, J. E. Hofmann, and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **83**, 3731 (1961).

(3) C. Walling and L. Bollyky, *ibid.*, **83**, 2968 (1961).

(4) While this work was in progress we learned of a similar finding by Professor E. J. Corey. Our studies are published simultaneously by mutual agreement.

(5) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(6) G. A. Russell, E. G. Janzen, H. Becker, and F. J. Smentowski, *ibid.*, **84**, 2652 (1962).

tion product to dimethyl sulfoxide to which an equivalent of sodium hydride had been added, followed by heating at 65° for 24 hr. and quenching with water at that temperature also gave benzophenone, 80%.

Reaction of Benzophenone and Dimethyl Sulfoxide.—Equivalent quantities of potassium *t*-butoxide (or sodium hydride) and benzophenone were added to dimethyl sulfoxide in a dry box to give an approximately 0.5 *M* solution which was stirred under nitrogen at 70–80°. The reaction mixture (or an aliquot) was cooled and poured into water, and the resulting mixture extracted with carbon disulfide or methylene chloride, the extract dried, and solvent removed. The residue was examined by g.l.c., either directly or after a preliminary vacuum distillation, using an Aerograph Model A 350 instrument and silicone column programmed at 160–240°, 6°/min. with biphenyl as an internal standard. Products were identified as follows.

Diphenylmethane, 1,1-Diphenylethylene.—Products obtained by collection of g.l.c. peaks had retention times, infrared spectra and n.m.r. spectra identical with authentic samples.

1,1-Diphenylcyclopropane.—The product obtained by collection of the appropriate g.l.c. peak showed an infrared spectrum consistent with the indicated structure, and a two-peak n.m.r. spectra, $\tau = 2.95$ (aromatic) and $\tau = 8.76$ (methylene) relative areas 5:2.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.73%; H, 7.36%. Found: C, 92.46%; H, 7.36%.

Reaction of 1,1-Diphenylethylene with Dimethyl Sulfoxide.—The reaction was carried out in the same manner as those involving benzophenone. After heating for 18 hr. at 80°, the mixture was quenched with water, extracted, the solvent removed, and the residue vacuum distilled. G.l.c. analysis showed diphenylmethane (17%) and 1,1-diphenylcyclopropane (6%), identified as above, together with another major peak (77%) of longer retention time. This was collected and identified as 3,3-diphenylpropene, on the basis of infrared, ultraviolet, and n.m.r. spectra and analysis. Infrared and ultraviolet spectra were those expected for two phenyl groups and an unconjugated $-CH=CH_2$. The n.m.r. spectra showed three peaks (relative areas 10:1:3, respectively), 3.06, (singlet, aromatic H); 3.9 (broad multiplet $-CH=$); and 5.26 (unsymetric multiplet Ph_2CH- plus $=CH_2$).

Anal. Calcd. for $C_{15}H_{14}$: C, 92.73%, H, 7.36%. Found: C, 92.97%, H, 7.31%.

Synthesis and Absorption Spectra of 5-(Substituted) Amino-1,2,3-thiadiazoles[1]

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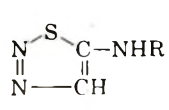
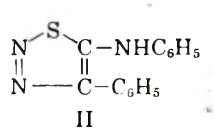
A series of 5-(substituted) amino-1,2,3-thiadiazoles (I) have been prepared by the reaction of diazomethane with organic isothiocyanates, first discovered by Pechmann[4,5] and later examined by Sheehan.[6] Its extension



I



II

to diazo derivatives other than diazomethane has not been studied. A further limitation of the reaction is the inertness of diazomethane to methyl isothiocyanate.

This paper reports on the synthesis of eight new compounds of type I (Table I) as well as the successful condensation of phenyldiazomethane with phenyl isothiocyanate to form 4-phenyl-5-anilino-1,2,3-thiadiazole (II). The infrared and ultraviolet absorption spectral data for these compounds have also been studied. (See p. 258 for Tables I, II, and III.)

The ultraviolet absorption data (Table II) in I clearly show that the thiadiazole ring is aromatic in nature. Comparison of the spectra of I with those of 5-(substituted phenyl)amino-1,2,3,4-thiatriazoles[7] indicates that the thiadiazole ring is less electronegative than the thiatriazole ring. This is understandable since in the later heterocycle a nitrogen atom replaces a carbon of the thiadiazole system. It has been similarly found that the tetrazole ring is more electronegative than the triazole ring.[8]

The major characteristic infrared frequencies of the 5-(substituted phenyl)amino-1,2,3-thiadiazoles are listed in Table III with the appropriate assignments. The assignments were made following the recent review on the infrared spectra of heterocyclic systems by Katritsky.[9] It is not possible to assign frequencies to the N=N and C=C of the thiadiazole ring since it is a conjugate system.

Experimental[10]

The mode of synthesis is essentially that described by Sheehan.[5] The results are summarized in Table I. With two exceptions, noted in Table I, the product precipitates on refrigeration over periods from 1 to 3 days. Where precipitation of product did not occur the ether was removed and the residue recrystallized or precipitated by means of another solvent. The typical procedure is illustrated for one of the new compounds and for II.

5-Benzylamino-1,2,3-thiadiazole (I. R = $C_6H_5CH_2$).—To a solution of 15 g. (0.10 mole) of benzyl isothiocyanate was added 0.2 mole of a cold etheral solution of diazomethane.[11] The solution was refrigerated overnight and the ether evaporated to dryness. Yellow needles weighing 1.4 g. (7.3%) were obtained. The analytical sample was recrystallized from absolute ethanol yielding white needles, m.p. 93–95°.

5-(*p*-Nitrophenylamino)-1,2,3-thiadizole (I. R = 4-$O_2NC_6H_5$).—A tan powder results on the reaction of *p*-nitrophenyl isothiocyanate and diazomethane in cold ether. Many attempts were made in numerous solvents to obtain an analytically pure specimen. The evidence shows it to be the least stable type I and that it is obtained in its highest state of purity on initial precipitation from the reaction mixture.

4-Phenyl-5-anilino-1,2,3-thiadiazole (II).—To a solution of phenyl isothiocyanate (0.008 mole, 1.1 g.) in 10 ml. of dry ether was added 40 ml. (0.008 mole) of phenyldiazomethane in ether[12] and the mixture allowed to refrigerate overnight. The ether was removed by evaporation and the liquid residue was boiled in 50 ml. of dry ethanol. On cooling a yellow powder is precipitated (in some trials a portion of the ethanol must be removed before precipitation can be induced), yielding 1.1 g. (53%) which melted to a viscous liquid at 80–83°.

Anal. Calcd. for $C_{14}H_{11}N_3S$: N, 16.72; S, 12.67. Found N, 16.48; S, 13.18.

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(1) The authors gratefully acknowledge the support of these studies by the U. S. Army Research Office.

(2) To whom all correspondence should be addressed.

(3) Present address, Indian Institute of Science, Bangalore, India.

(4) H. V. Pechmann and A. Nold, *Ber.*, **29**, 2588 (1896).

(5) H. V. Pechmann, *ibid.*, **28**, 861 (1895).

(6) J. C. Sheehan and R. T. Izzo, *J. Am. Chem. Soc.*, **71**, 4059 (1949).

(7) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).

(8) E. Lieber, C. N. R. Rao, T. S. Chao, and J. Ramachandran, *J. Org. Chem.*, **23**, 1916 (1959).

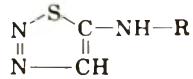
(9) A. R. Katritzky, *Quart. Rev.*, **4**, 353 (1959).

(10) Analyses were done by Drs. G. W. Weiler and F. B. Strauss, Oxford, England. Melting points (Fisher block) are uncorrected. The infrared spectra were obtained with the Perkin–Elmer 21-C infrared spectrophotometer with sodium chloride optics. The ultraviolet spectra were obtained in purified dioxane (0.05 mg./ml.) on a Beckman DU spectrophotometer. The wave lengths throughout are expressed in millimicrons and the intensities of absorption in terms of the logarithm of the molar extinction coefficients.

(11) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1951.

(12) P. Yates and B. L. Shapiro, *J. Org. Chem.*, **23**, 759 (1958).

TABLE I. 5-(Substituted) Amino-1,2,3-thiadiazoles

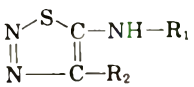


R[a]	Yield, %[d]	Crystalline[e] form	M.p., °C.[g]	Formula	N Calcd.	N Found	S Calcd.	S Found
C_6H_5	42.0	Grey needles	180	$C_8H_7N_3S$	23.71	23.80	18.09	17.80
$C_6H_5CH_2$[b]	7.3	White needles	93–95	$C_9H_9N_3S$	22.19	22.21	16.75	16.52
4-$O_2NC_6H_4$	20.0	Tan powder	206–209	$C_8H_6N_4SO_2$	25.18	23.80	14.42	13.80
4-$CH_3OC_6H_4$	10.0	Colorless flakes[f]	155–157	$C_9H_9N_3SO$	20.30	20.40	15.48	15.10
4-ClC_6H_4	10.0	Tan powder	173–175	$C_8H_6N_3SCl$[h]	19.85	19.60	15.17	15.71
4-BrC_6H_4	13.0	Brown flakes	187–189	$C_8H_6N_3SBr$[i]	16.40	16.15	12.50	12.77
4-$CH_3C_6H_4$	35.5	Yellow needles	172–174	$C_9H_9N_3S$	22.19	22.40	16.75	16.38
4-$(CH_3)_2NC_6H_4$[c]	23.0	Green powder	168–170	$C_{10}H_{12}N_4S$	25.42	24.60	14.53	14.00
$C_{10}H_7$[k]	20.0	Yellow needles	161–162	$C_{12}H_9N_3S$	18.50	18.35	13.55	14.26
3-BrC_6H_4	37.0	Tan scales	165–166	$C_8H_6N_3SBr$[j]	16.40	16.80	12.50	12.85

[a] All are new compounds with exception of R = C_6H_5 (lit.,[5] m.p. 179–180°). [b] Product did not precipitate; ether was removed and residue recrystallized. [c] Product did not precipitate; ether was removed and product precipitated by benzene. [d] Represent first crop of crystals. [e] From ethanol. [f] From chloroform. [g] With decomposition except R = $C_6H_5CH_2$. [h] Cl: calcd., 16.78; found, 16.90. [i] Br: calcd., 31.17; found, 31.15. [j] Br: calcd., 31.17; found, 31.40. [k] α-Naphthyl.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 5-(SUBSTITUTED) AMINO-1,2,3-THIADIAZOLES



R_1	R_2	λ_{max}	Log ϵ_{max}	λ_{max}	Log ϵ_{max}	λ_{max}	Log ϵ_{max}
$C_6H_5CH_2$	H	240	4.54	266	4.48	296	4.53
3-Br—C_6H_4	H	246	4.21			314	4.34
						324	4.36
4-Cl—C_6H_4	H	258	3.94			310	4.26
						330	3.97
4-CH_3—C_6H_4	H	246	3.90			324	4.21
α-Naphthyl	H	232	4.47	236	4.27	334	4.21
				240	4.28		
C_6H_5-	C_6H_5	236	4.05	242	3.89	316	3.49
				254	3.84		
				274	3.71		
C_6H_5-	H	240	3.96	280	3.66	318	4.05
4-$CH_3OC_6H_4$	H	230	4.06			320	3.77
		240	4.03				
4-BrC_6H_4	H	252	3.93			320	4.24
4-$(CH_3)_2NC_6H_4$	H	260	4.34			324	4.17

TABLE III

MAJOR CHARACTERISTIC INFRARED FREQUENCIES OF 5-(SUBSTITUTED) AMINO-1,2,3-THIADIAZOLES

Cm.$^{-1}$[a]	Assignment
3220 m	Bonded N—H stretching
1650–1590 v	N—H deformation
1560–1475 v[b]	Ring stretching
1350–1280 v[d]	C—N stretching
1265–1200 v	C—H in-plane deformation
1190–1175 v[d]	C—H in-plane deformation
1150–950 v[d]	Ring breathing
910–890 w	Ring breathing
705–670 w	C—H out-of-plane deformation

[a] Intensity: m, medium; w, weak; v, variable. [b] One or more bands. [c] Two bands. [d] At least one band.

Some Reactions of Fluorinated Cyclobutenes with Grignard Reagents

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In an attempt to find a simple method for introducing alkyl and aryl substituents into fluorocyclobutenes, our attention was turned to the reaction of Grignard reagents with these compounds. This had not been carried out previously.

The reaction of Grignard reagents with fluoroölefins, such as $CF_2{=}CCl_2$, $CF_2{=}CFCl$, and $CF_2Cl{-}CF{=}CF_2$, has already been described by Tarrant, *et al.*[2] These workers found that apparently addition first occurs across the double bond and the resulting adduct loses MgX_2 to give a new, longer chain fluoroölefin. The reaction goes with poor yield (10–20%) using aliphatic Grignard reagents and with better yields (30–70%) using aromatic Grignard reagents.

The preparation of some alkyl derivatives (mono- and dimethyl, mono- and dibutyl, and diphenyl) of perfluorocyclobutene, has been previously described by Dixon,[3] using the reaction with alkyllithium. This reaction, however, gives in poor yields (20–40%) only the diphenyl derivative with phenyllithium and a mixture of mono- and dialkyl derivatives (the latter predominating) with alkyllithium.

In this study, when the perfluorocyclobutene was treated with excess alkylmagnesium bromide under mild conditions, the monoalkyl derivatives in high yields (75–85%) (methyl excepted) had been obtained. Under stronger conditions, the monoalkyl derivatives with excess Grignard reagent gave comparable yields of the dialkyl derivatives. However, the reaction with phenylmagnesium bromide gave both the mono- and diphenyl derivatives (ratio 1:1) in a total yield of 80%.

Some reactions with vinyl- and perfluoroalkylmagnesium bromide have been attempted, but only high boiling polymeric materials were isolated.

When 1,2-dichloro-3,3,4,4-tetrafluorocyclobutene was treated with alkyl Grignards, the substitution of one vinylic chlorine took place quite readily. The substitution of the second vinylic chlorine, on the contrary, does not easily take place, even after refluxing the monoalkyl derivative for twenty-four hours in ether. This reaction has been carried out in a sealed Pyrex tube in ether under autogenous pressure, and only above 100° a reaction took place. The reaction products isolated were: starting material (25%), 1,2-diethyl-3,3,4,4-tetrafluorocyclobutene (16%) (this product was identical

(1) Montecatini Industrial Research Fellow (1961–1962). Work done at the University of Colorado.

(2) P. Tarrant and D. A. Warner, *J. Am. Chem. Soc.*, **76**, 1624 (1954).

(3) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).

TABLE I
PHYSICAL PROPERTIES OF THE CYCLIC ETHERS

Compounds	Yield, %	B.p., °C./mm.	d^{25}_4	$n^{25}D$	Calcd. C	Calcd. H	Calcd. F	Calcd. Cl	Found C	Found H	Found F	Found Cl
CF_2—C—Et | || CF_2—C—F	75	66–68/630	1.2421	1.3303	41.87	2.93	55.20		41.52	2.78	55.12	
CF_2—C—Et | || CF_2—C—Et	75	134–136/630 69–70/60	1.110	1.3735	52.74	5.53	41.72		53.03	5.78	41.62	
CF_2—C—n-C_3H_7 | || CF_2—C—F	83	86–88/630	1.199	1.3421	45.17	3.79	51.04		44.95	4.00	51.28	
CF_2—C—n-C_3H_7 | || CF_2—C—n-C_3H_7	76	77/25	1.060	1.3908	57.13	6.71	36.15		57.28	6.59	36.01	
CF_2—C—C_6H_5 | || CF_2—C—F	80	67–68/15	1.354	1.4606	54.56	2.27	43.15		54.85	2.47	43.24	
CF_2—C—CH_3 | || CF_2—C—Cl	80	77–78/630	1.337	1.3602	36.03	1.73	43.54	20.32	36.00	1.92	43.39	20.61
CF_2—C—C_2H_5 | || CF_2—C—Cl	75	98/630	1.292	1.3723	38.21	2.67	40.30	18.81	38.46	2.65	40.21	19.02
CF_2—C—n-C_3H_7 | || CF_2—C—Cl	78	118/630	1.236	1.3795	41.50	3.49	37.51	17.50	41.53	3.70	37.71	17.41
CF_2—C—C_6H_5 | || CF_2—C—Cl	65	78–80/5	1.371	1.5012	50.77	2.13	32.12	14.99	51.00	2.50	32.31	14.49

to that already obtained from the reaction of 1-ethyl-2,3,3,4,4-pentafluorocyclobutene with ethylmagnesium bromide) and a difficultly separable mixture of five high boiling products that were partially resolved by vapor phase chromatography, but not identified. These may be a mixture of the triethyl derivatives formed from the substitution of the allylic fluorines.

What has been found in this study is in agreement with the base-catalyzed reactions of alcohols with perfluorocyclobutene and 1,2-dichloro-3,3,4,4-tetrafluorocyclobutene.[4,5]

Proof of Structure.—In the infrared spectra of the mono- and dialkyl derivatives of perfluorocyclobutene, there is evidence that the substitution of the vinylic fluorines took place. Thus, the double bond of perfluorocyclobutene absorbs at 1790 cm.$^{-1}$ and the monoalkyl derivatives exhibit a shift of the double bond absorption band to 1720–1730 cm.$^{-1}$. The dialkyl derivatives do not exhibit any absorption (or very weak at 1705 cm.$^{-1}$) as the tetrasubstituted double bond is perfectly symmetrical.

The reaction probably goes through the addition of the reagent (RMgX) to the double bond, and the intermediate product thus formed loses the magnesium halide giving the substituted olefin.

$$\begin{array}{l} CF_2\text{—}CF \\ \quad\|\quad\| \\ CF_2\text{—}CF \end{array} + RMgX \longrightarrow \begin{array}{l} CF_2\text{—}CF(R) \\ \quad\|\quad\| \\ CF_2\text{—}CF(MgX) \end{array} \longrightarrow \begin{array}{l} CF_2\text{—}C\text{—}R \\ \quad\|\quad\| \\ CF_2\text{—}C\text{—}F \end{array} + MgXF$$

However, in the reaction of 1,2-dichloro-3,3,4,4-tetrafluorocyclobutene with Grignard reagents, the first step goes in the same way, but the displacement of the second chlorine is much more difficult because of the lesser tendency of chlorine to undergo mesomeric shift. In such a case, the vinylic chlorine atom shows the usual inertness toward displacement.

(4) J. D. Park, M. L. Sharrah, and J. R. Lacher, *J. Am. Chem. Soc.*, **71**, 2337 (1949).

(5) J. D. Park, C. M. Snow, and J. R. Lacher, *ibid.*, **73**, 2342 (1951).

Experimental

1-Methyl-2,3,3,4,4-pentafluorocyclobutene (I).—In a 500-ml. three-neck flask fitted with a gas inlet tube, a stirrer, and a Dry Ice condenser connected to a bubbler, 250 ml. of 3 *M* ethereal solution of methylmagnesium bromide (0.75 mole) was introduced and cooled to 0°. A 50-g. sample (0.30 mole) of perfluorocyclobutene was bubbled into the ethereal solution in a period of 1 hr. and further maintained for 2 hr. at 0° and for another 20 hr. at room temperature. The reaction mixture was then warmed to gentle reflux of the ether for 4 hr. After cooling again to 0°, 150 ml. of 20% hydrochloric acid was dropped in very slowly to decompose the Grignard reagent. The decomposition is very exothermic and a strong evolution of methane occurred. The ethereal solution was separated and the aqueous layer extracted three times with ether. The combined extracts were washed with bicarbonate solution and dried over anhydrous sodium sulfate. Distillation yielded 11 g. (22%) of I; b.p. 44–45°/630 mm.; $n^{4}D$ 1.3225; d^{4}_4 1.377; molecular refraction: calcd. for $C_5H_3F_5$, 23.44; found, 22.92. Dixon[3] reports a boiling point of 50°/730 mm. for this compound.

The preparation of the other derivatives in general followed along similar lines. These reaction products and their properties are tabulated in Table I.

Reaction of 1-Ethyl-2-chloro-3,3,4,4-tetrafluorocyclobutene with Ethylmagnesium Bromide.—In a high pressure Pyrex tube fitted with a valve and a pressure gage, 100 ml. of a 3 *M* ethereal solution of ethylmagnesium bromide (0.3 mole) and 18.5 g. (0.1 mole) were introduced. The tube was then warmed to 100–110° for 30 hr. The formation of a grayish precipitate was noticed after a few hours and the pressure had increased to about 120 p.s.i.g. After cooling, the residual pressure was discharged and the content treated with 100 ml. of 20% hydrochloric acid. The ethereal layer was separated and the water layer extracted three times with ether. The combined extracts, washed with bicarbonate solution and dried over sodium sulfate, were distilled. After removal of the ether, 18 g. of a high boiling residue was obtained. Fractionation of the residue under reduced pressure yielded 6 g. of starting material, 4 g. of III (b.p. 68–75°/60 mm.) and 7 g. of a fraction distilling at 70–80°/0.5 mm. which upon vapor phase chromatography was resolved into five products which as yet have not been identified (column: silicon D/C/710, temp. = 200°).

Acknowledgment.—The authors are indebted to Montecatini Industries of Milan, Italy, for making it possible for one of us (L.F.) to have a leave of absence and support to carry out this work at the University of Colorado.

A Direct Synthesis of 4-Azanaphthoquinones-1,2[1]

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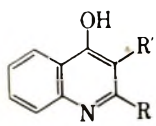
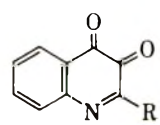
The difficulty encountered in the attempt to prepare azabenzoquinones[2] by the oxidation of hydroxy- and aminopyridones[3] suggested that fusion of a benzene ring to either an *o*- or *p*-azabenzoquinone might increase their stability. The reported synthesis and stability of 4-azanaphthoquinone-1,2 (IVa)[4] prompted an investigation of the chemistry of azanaphthoquinones. The present paper describes the preparation of two 4-azanaphthoquinones-1,2, IVa and IVb.



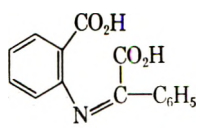


IVa. R = H
b. R = CH_3

Ia. R = R′ = H
b. R = CH_3, R′ = H
c. R = C_6H_5, R′ = H

IIa. R = H, R′ = CHO
b. R = CH_3, R′ = CHO
c. R = C_6H_5, R′ = CHO

IIIa. R = H, R′ = OH
b. R = CH_3, R′ = OH
c. R = C_6H_5, R′ = OH



V

The synthesis of IVa and IVb now reported utilizes the extension of the Reimer–Tiemann reaction to hydroxyquinolines. This approach finds analogy in the observation of Bobranski[5] that 4-hydroxyquinoline and 4-hydroxyquinaldine are formylated with sodium hydroxide and chloroform. Unfortunately a rigid structure proof of the products was not provided in either case.

Formylation of Ia, b, c under Bobranski's conditions proceeded as desired with formation of 3-formyl-4-hydroxyquinolines, IIa,b,c, in good yields. 3,4-Dihydroxyquinoline (IIIa) and 3,4-dihydroxyquinaldine (IIIb) were obtained from Dakin oxidations of IIa and IIb with sodium hydroxide and hydrogen peroxide in satisfactory yields. Oxidation of IIIa and IIIb was accomplished with silver oxide and/or chromium trioxide. The products have been assigned the structure of 4-azanaphthoquinone-1,2 (IVa) and 3-methyl-4-azanaphthoquinone-1,2 (IVb), respectively. Condensation of the azaquinones with *o*-phenylenediamine gave the corresponding phenazines supporting the initial assignments of the formyl group in IIa and IIb.

In sharp contrast to the foregoing results, the Dakin oxidation of 2-phenyl-3-formyl-4-hydroxyquinoline (IIc) with sodium hydroxide and hydrogen peroxide to 2-phenyl-3,4-dihydroxyquinoline (IIIc) was unsuccessful. The major product was the anthranil of phenylglyoxylic acid (V) whose structure was confirmed by hydrolysis to phenylglyoxylic acid. Apparently in addition to the Dakin oxidation of the formyl group in IIc a Baeyer–Villiger transformation occurs with oxidation of an intermediate peroxide and ring fission. All attempts to stop the reaction at the dihydroxy stage were unsuccessful.

Experimental[6]

Preparation of the 4-Hydroxyquinolines (Ia–c).—4-Hydroxyquinaldine,[7] 2-phenyl-4-hydroxyquinoline,[8] and 4-hydroxyquinoline[9] were prepared according to the literature cited.

Preparation of the 3-Formyl-4-hydroxyquinolines (IIa–c).—3-Formyl-4-hydroxyquinoline[5] and 3-formyl-4-hydroxyquinaldine[10] were previously prepared.

A mixture of 2-phenyl-4-hydroxyquinoline (2.87 g., 0.013 mole), 2 g. of powdered sodium hydroxide, and 2 ml. of chloroform was heated at 50° for a few minutes and 3 ml. of water added. The slurry was gently refluxed for 6 hr. with 2 ml. of chloroform being added at 2-hr. intervals. The excess chloroform was removed *in vacuo* and the resulting slurry filtered. The dried solid was extracted twice with 20–30 ml. of hot water and the washings combined with the original filtrate. Acidification with glacial acetic acid afforded a yellow suspension which precipitated as a yellow sirup that solidified upon standing. Several recrystallizations from ethanol afforded yellow needles of 2-phenyl-3-formyl-4-hydroxyquinoline, m.p. 250–252°, 1.2 g. (37%).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.63. Found: C, 77.27; H, 4.52; N, 5.57.

The aldehyde formed a 2,4-dinitrophenylhydrazone which recrystallized from ethyl acetate and ethanol as red needles, m.p. 275–277.5° dec.

Anal. Calcd. for $C_{22}H_{15}N_5O_5$: C, 61.54; H, 3.52; N, 16.31. Found: C, 61.27; H, 3.45; N, 16.41.

General Procedure for the Dakin Oxidation of 3-Formyl-4-hydroxyquinolines (IIa–b).—To a solution of 0.007 mole of the 3-formyl-4-hydroxyquinolines in 7 ml. of 1 *N* sodium hydroxide, 9.5 g. of 3% hydrogen peroxide was added in one portion and allowed to stand overnight at room temperature. A color change from deep orange to yellow was accompanied by an exothermic reaction. Upon cooling to room temperature the dihydroxyquinolines could be isolated.

3,4-Dihydroxyquinoline recrystallized from 95% ethanol as yellow microcrystals, m.p. 222–227° dec., 18% yield.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.13; H, 4.21; N, 8.75.

3,4-Dihydroxyquinaldine recrystallized from 95% ethanol as a pale yellow powder, m.p. 275–281° dec., 49% yield.

(1) Part of this work was carried out in the Department of Chemistry, Tulane University, New Orleans, La.

(2) In the present study, azaquinones designates nitrogen as a member of the quinone ring.

(3) J. H. Boyer and S. Kruger, *J. Am. Chem. Soc.*, **79**, 3552 (1957).

(4) M. Passerini, T. Bonciani, and N. Di Gioia, *Gazz. chim. ital.*, **61**, 959 (1931).

(5) B. Bobranski, *Chem. Ber.*, **69**, 1113 (1888).

(6) Semimicro analyses by Alfred Bernhardt Microanalytisches Laboratorium, Max Planck Institute, Mülheim (Ruhr), Germany. Melting points are uncorrected.

(7) G. A. Reynolds and C. R. Hauser, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 593.

(8) R. C. Fuson and D. M. Burness, *J. Am. Chem. Soc.*, **61**, 2890 (1939).

(9) R. G. Gould, Jr., and W. A. Jacobs, *ibid.*, **61**, 2890 (1939).

(10) M. Conrad and L. Limpach, *Chem. Ber.*, **21**, 1965 (1888).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.66; H, 4.99; N, 7.85.

4-Azanaphthoquinone-1,2 (IVa).—To a solution of 0.10 g. (0.62 mmole) of 3,4-dihydroxyquinoline in 10 ml. of glacial acetic acid at 20°, a suspension of 0.5 g. of chromium trioxide in 10 ml. of glacial acetic acid was added slowly. The mixture was warmed on a steam bath to 40° and allowed to stand at room temperature overnight. The dark green mixture was diluted with 50 ml. of water and the pale yellow microcrystals of 4-azanaphthoquinone-1,2 that separated were collected and recrystallized from methanol or dioxane, 45 mg. (45%), dec. > 285°.[4]

Anal. Calcd. for $C_9H_5NO_2$: C, 67.92; H, 3.17; N, 8.80. Found: C, 67.98; H, 3.25; N, 8.62.

A phenazine derivative of IVa was prepared from *o*-phenylenediamine dihydrochloride and sodium acetate in glacial acetic acid and recrystallized from xylene as a red powder, dec. > 300°.

Anal. Calcd. for $C_{16}H_9N_3$: C, 77.90; H, 3.92; N, 18.17. Found: C, 77.98; H, 4.17; N, 17.90.

3-Methyl-4-azanaphthoquinone-1,2 (IVb).—A solution of 0.11 g. (0.0062 mole) of 3,4-dihydroxyquinaldine in 50 ml. of anhydrous methanol was shaken with 4 g. of dry silver oxide and 15 g. of anhydrous sodium sulfate for 10 min. and filtered. The yellow filtrate was evaporated to dryness under reduced pressure at room temperature and the yellow residue collected. Four recrystallizations from 95% ethanol afforded yellow plates of 3-methyl-4-azanaphthoquinone-1,2, 46 mg. (42%), m.p. 261–265° dec. Elemental analysis was not obtained due to unstability.

3-Methyl-4-azanaphthoquinone-1,2 upon treatment with *o*-phenylenediamine dihydrochloride and sodium acetate in glacial acetic acid afforded the corresponding phenazine, which recrystallized from benzene as red plates, m.p. 321–322.5° dec.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.42; H, 4.39; N, 17.41.

Dakin Oxidation of 2-Phenyl-3-formyl-4-hydroxyquinoline (IIIc).—To a solution of 0.42 g. (0.0017 mole) of 2-phenyl-3-formyl-4-hydroxyquinoline in 1.7 ml. of 1 *N* sodium hydroxide, 2.31 g. of 3% hydrogen peroxide was added in one portion. A color change from deep orange to pale yellow was accompanied by an exothermic reaction. Upon cooling to room temperature the disodium salt of the anthranil of phenylglyoxylic acid (V) precipitated which recrystallized from 95% ethanol as yellow microcrystals, dec. > 350°, 380 mg. (72%).

Anal. Calcd. for $C_{15}H_9NO_4Na_2$: C, 57.51; H, 2.90; N, 4.47. Found: C, 57.28; H, 3.11; N, 4.77.

Refluxing V with an excess of 2,4-dinitrophenylhydrazine in ethanol (10% hydrochloric acid) afforded the 2,4-dinitrophenylhydrazone of phenylglyoxylic acid, m.p. and mixture m.p. 196–197°.

Acknowledgment.—We are indebted to the National Institutes of Health, U. S. Public Health Service (Grant CA-06566), for partial financial support of this work.

Hydroboration of Diphenylacetylene

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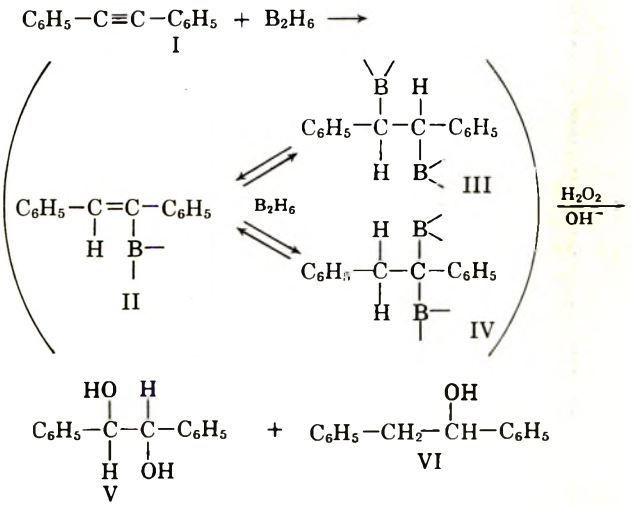
Received August 6, 1962

Addition of diborane to olefins (hydroboration) followed by oxidative workup has been shown to be a reaction of general utility in the synthesis of alcohols.[1] The reaction is stereospecific—*i.e.*, *cis* addition of the elements of water, and the least substituted alcohol is generally formed.[1a,b]

(1)(a) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957); H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959) and subsequent papers; for a review see H. C. Brown, *Tetrahedron*, **12**, 117 (1961). (b) A. Hassner and C. Pillar, *J. Org. Chem.*, **27**, 2914 (1962).

We were interested in applying this hydration scheme to the formation of *d,l* or *erythro* diols from acetylenes. Terminal acetylenes have been reported to yield aldehydes on hydroboration.[2,3] When we applied the reaction to diphenylacetylene (I) we found that in addition to the expected *d,l*-dihydrobenzoin (V) (37%), a large amount (40%) of 1,2-diphenylethanol (VI) was also formed. Small amounts of *trans*-stilbene and of desoxybenzoin were also found. No *meso*-dihydrobenzoin nor any rearranged 1,1-diphenyl-1,2-ethanediol was detected. The starting diphenylacetylene was virtually free of any stilbene as shown by infrared studies.

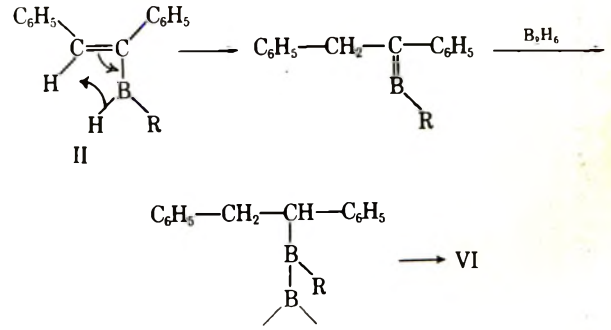


It is apparent that 1,2-diphenylethanol (VI) cannot result by a normal path from either of the expected intermediates II, III, or IV. Desoxybenzoin could be formed in the reaction on oxidation of intermediate II or IV and hydrolysis. To ensure that, at the time of formation of desoxybenzoin, diborane or any B—H compound needed to effect reduction to VI will have been destroyed, acetone was added prior to oxidative work-up; this did not affect the product distribution. Brown and Zweifel[3] also observed predominant formation of monoalcohols in the hydroboration of acetylenes and attributed these results to hydrolytic cleavage of an intermediate of type IV.[4] Alternatively, borane-induced elimination of the elements of >B—B< from intermediate III, followed by hydroboration of the resulting stilbene, could lead to alcohol VI and at the same time explain the isolation of a small amount of *trans*-stilbene. Abnormal products of a different nature were reported in the hydroboration of di-*tert*.-butyl-

(2) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 1512 (1959).

(3) H. C. Brown and G. Zweifel, *ibid.*, **83**, 3834 (1961).

(4) One also could envisage a process of internal hydride transfer in intermediate II, as pictured:



acetylene.[5] It appears that hydroboration of acetylenes is not a cleanly predictable reaction but leads to a mixture of products

Experimental

All melting points are uncorrected. Infrared spectra were run in potassium bromide on a Beckman I R 5 instrument.

Reaction of Diphenylacetylene (I) with Diborane.—Diphenylacetylene (I), m.p. 60–61°, was prepared from stilbene *via* the dibromide.[6] Its infrared spectrum, by comparison with spectra of mixtures of diphenylacetylene and stilbene, indicated the presence of less than 2% of stilbene if any. Into a solution of 1.0 g. of diphenylacetylene (I) in dry tetrahydrofuran at 0° was passed diborane, generated from 3 g. of sodium borohydride and excess boron trifluoride etherate in diglyme. The solution was kept at 4° for 14 hr. Excess diborane was destroyed by addition of ice and the mixture was stirred with 25 ml. of 3 *N* sodium hydroxide and 15 ml. of 25% hydrogen peroxide for 40 min. The mixture was extracted with ether. The organic layer was washed with ferrous sulfate solution, then five times with water, dried, and evaporated. The residue (1.05 g.) was taken up in benzene and chromatographed over 30 g. of Merck aluminum oxide. The eluted fractions were evaporated and the residues identified by infrared, melting point, and mixed melting point comparison with authentic samples. The following results were obtained: Fraction 1 (35 mg.) melted at 125°. Upon crystallization from aqueous alcohol and then from petroleum ether (b.p. 40–60°) it gave material melting at 124–126°; mixed with *trans*-stilbene, m.p. 127°, it melted at 124–126°.

Fractions 2–4 (34 mg. of an oil that slowly crystallized) were identified by infrared and through its 2,4-dinitrophenylhydrazone, m.p. 203–205°, as desoxybenzoin.

Fraction 5 (453 mg.) melted at 46–56° and upon crystallization from petroleum ether (b.p. 60–90°) at 59–62°. Mixed melting point and infrared comparison with authentic material, m.p. 65°, prepared by hydroboration of *trans*-stilbene, identified it as 1,2-diphenylethanol (VI).

Fraction 6 (78 mg.) was a mixture difficult to separate.

Fractions 7–9 (372 mg.) were essentially *d,l*-dihydrobenzoin (V). Crystallization from water followed by drying and recrystallization from petroleum ether (b.p. 60–90°) gave material m.p. 120–120.5°, identical in all respects with authentic *d,l*-dihydrobenzoin, prepared from benzil.

Fractions 10–11 (17 mg.) were likewise slightly impure *d,l*-dihydrobenzoin.

Acknowledgment.—We gratefully acknowledge financial support (Grant CY-4474) by the National Institutes of Health.

(5) T. J. Logan and T. J. Flautt, *J. Am. Chem. Soc.*, **82**, 3446 (1960).

(6) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1957, p. 181.

Some Studies on Tropenylazulenes[1,2]

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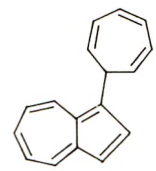
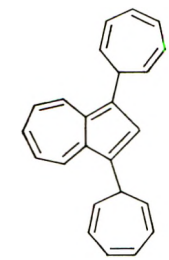
The recent publication of the reaction of azulene with tropenium perchlorate and of an attempt to obtain the interesting (1-azulyl)tropenium ion[5] prompt us to report the results of similar, independent studies. Our objectives were, first, the preparation of tropenylazulenes[6] and, second, the removal of a hyride ion to form a (1-azulyl)tropenium ion structure.

Treatment of azulene with tropenium fluoroborate afforded two crystalline products, 1-tropenylazulene (I) and 1,3-dinitropenylazulene (II). The latter was the principal product even when an excess of azulene was used.[7] With a 50% excess of azulene, for example, 19% of I and 51% of II were obtained, and if one equivalent of pyridine was present the yield of II was 62%.

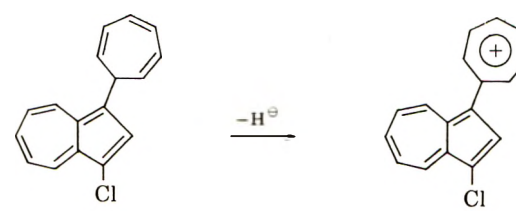


I



II

As the formation of a (1-azulyl)tropenium ion would involve reaction with a positive species, a 1-tropenylazulene having a simple, inert substituent in the nucleophilic 3-position was desired and 1-tropenyl-3-chloroazulene (III) was chosen. The reaction of 1-chloroazulene with tropenium fluoroborate gave a blue oil which exhibited an absorption maximum in the visible spectrum corresponding to that expected for III,[8] but was unaccountably difficult to purify and gave only fair analytical values. The n.m.r. spectrum was consistent with the assigned structure. There were three sets of multiplets centered at *ca.* 3.3, 3.8, and 4.57 p.p.m., each of relative intensity two, for the three types of vinyl protons, and a triplet at 6.67 p.p.m. of intensity one for the saturated hydrogen. The remainder of the spectrum corresponded to that of a 1,3-disubstituted azulene.[9] The further fact that this same substance was formed by the reaction of I with N-chlorosuccinimide established its identity sufficiently to permit its use in the hydride exchange experiments.



III IV

The addition of a slight excess of triphenylmethyl fluoroborate to a solution of III in dry acetonitrile caused a rapid color change from blue to green. From the reaction mixture were isolated a small amount of a colorless solid identified as tropenium fluoroborate by its ultraviolet spectrum, a low yield of triphenylmeth-

(1) From the Ph.D. thesis of Lanny L. Replogle, University of Washington, July, 1960.

(2) Supported in part by a grant (G 7397) from the National Science Foundation.

(3) National Science Foundation Senior Postdoctoral Fellow, 1960–1961.

(4) National Science Foundation Cooperative Fellow, 1959–1960. Present address: Department of Chemistry, San Jose State College, San Jose, Calif.

(5) K. Hafner, A. Stephan, and C. Bernhard, *Ann.*, **650**, 42 (1961).

(6) Tropenyl will be used as the name for the 7-cycloheptatrienyl group.

(7) K. Hafner, *et al.* (ref. 5), reported II to be the sole product of their analogous reaction.

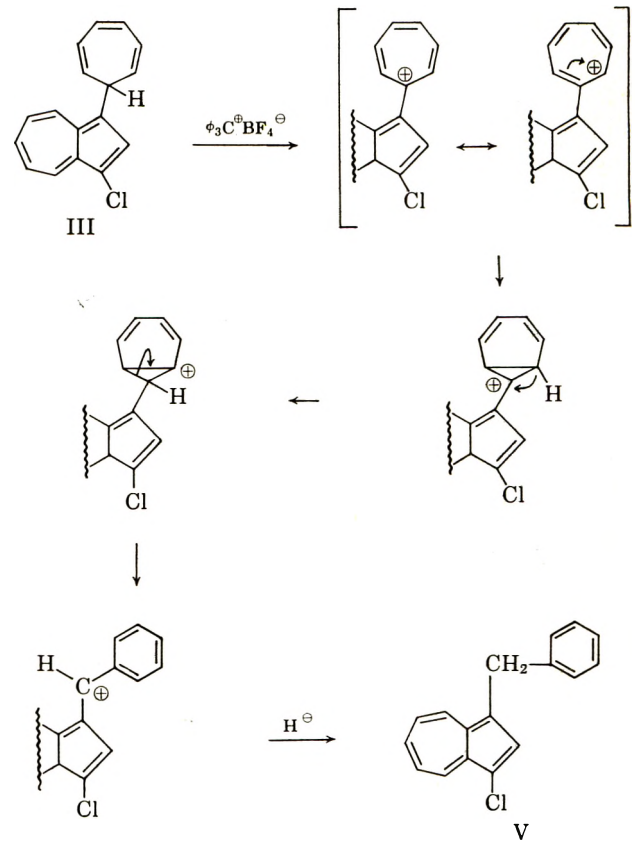
(8) λ_{max} (obsd.) 628 mμ, λ_{max} (calcd.) 630 mμ based on $\Delta\lambda_{max}$ for the chloro group as +30 mμ [*cf.* E. J. Cowles, *J. Am. Chem. Soc.*, **79**, 1093 (1957)], and $\Delta\lambda_{max}$ for the tropenyl group as +20 mμ (see Experimental).

(9) A. G. Anderson and L. L. Replogle, unpublished results.

ane, some 1-triphenylmethyl-3-chloroazulene, and a brown, gummy material. The formation of triphenylmethane showed that some hydride exchange had occurred. The identity of the 1-triphenylmethyl-3-chloroazulene was established by the formation of an identical product from the triphenylmethylation of 1-chloroazulene. These findings are most plausibly explained in terms of the formation of an azulyltropenium ion (IV) and subsequent electrophilic displacement of the tropenium moiety by the triphenylcarbonium ion. The latter step finds analogy in the elimination of the tropenium ion from β-tropenylalkyl halides[10] and identical behavior was observed by Hafner, *et al.*[5] The facility with which groups which can form stable positive ions undergo this type of displacement has been noted with a number of 1,3-disubstituted azulenes.[11]

Further evidence for the existence of IV was sought in the brown, gummy material. The infrared spectrum of this had a large, broad peak in the 9–10-μ region which is characteristic of the fluoroborate ion.[12] The dark green solution formed with methylene chloride[5] showed a strong peak at 485 mμ and azulene-like absorption in the ultraviolet. Reid, *et al.*,[13] have found strong absorption in the region 450–500 mμ for most 1-substituted azulenium salts. As was the case in the study by Hafner and co-workers,[5] all efforts to isolate a pure substance were unsuccessful. The addition of a hydride ion to IV would be expected to occur on the tropenyl ring to regenerate III and/or tautomeric isomers. As tropenium salts are reduced by sodium borohydride in good yield,[14] the brown, gummy product from one run was treated with this reagent. There were obtained triphenylmethane and two oils which appeared to be isomeric with III. One of these and an oil obtained from the mixture prior to the addition of sodium borohydride, both green in color, showed essentially identical absorptions in the ultraviolet and visible regions which were also very similar to those of III, but differed slightly in their infrared spectra from each other and from III, and are postulated to be tautomeric isomers of III. To see if such a product might have been formed *via* III by the presence of excess sodium borohydride, III was treated with this reagent under the same reaction conditions. Only unchanged III was recovered. The other oil, blue-green in color, likewise had a visible spectrum almost identical to that of III but differed in absorption in both the ultraviolet and infrared regions. The n.m.r. spectrum of this material showed a split peak (τ = 2.87 and 2.90) of relative intensity very close to five[15] and an unsplit saturated hydrogen peak at τ = 5.7 of intensity two, but no indication of vinyl hydrogens. A structure consistent with these data is 1-benzyl-3-chloroazulene (V) and this suggestion was confirmed by comparison of the ultraviolet, visible, infrared, and n.m.r. spectra of material prepared by the chlorination of 1-benzylazulene with those of the reduction product.

The formation of V can be explained as shown. In view of the fact that III was shown to be unaffected by the sodium borohydride, and therefore a base-catalyzed rearrangement such as occurs with certain tropolones[16] is excluded, it is difficult to envision any reasonable alternative route. If V did arise from IV this represents the first example of the rearrangement of a tropenium ion to a benzyl cation.[17] In the present system



the benzylazulyl cation could well be the more stable structure as it would appear to have appreciably less steric hindrance to complete conjugation than the azulyltropenium ion.

The failure to isolate a pure azulyltropenium salt was not unexpected in that Kirby and Reid[18] found that only aromatic aldehydes with electron-releasing groups gave isolable salts upon condensation with azulene, and even these decomposed upon attempted recrystallization.

(10) K. Conrow, *J. Am. Chem. Soc.*, **79**, 1093 (1957).

(11) A. G. Anderson and R. N. MacDonald, *ibid.*, **81**, 5669 (1959); A. G. Anderson, R. Scotoni, E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957); A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

(12) C. L. Coté and W. W. Thompson, *Proc. Roy. Soc.* (London), [A], **210**, 217 (1951); B. P. Susz and J.-J. Wuhrmann, *Helv. Chim. Acta*, **40**, 722 (1957).

(13) D. H. Reid, W. H. Stafford, W. L. Stafford, G. MacLennan, and A. Voight, *J. Chem. Soc.*, 1110 (1958).

(14) H. J. Dauben and L. McDonough, private communication.

(15) The occurrence of the bands from the 5- and 7-hydrogens in the same region precluded an exact measurement of the intensity. The split maximum was attributed to the presence of a small amount of 1-triphenylmethyl-3-chloroazulene as the triphenylmethyl group was shown to give two aromatic hydrogen peaks at τ = 2.88 and 2.93, and the sample of pure 1-benzyl-3-chloroazulene gave a single peak at τ = 2.89.

(16) *Cf.* T. Nozoe, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, ed., Interscience Publishers, Inc., New York, N. Y., 1959, chap. 7.

(17) Subsequently H. J. Dauben and D. Bertelli (private communication) obtained 7-benzylcycloheptatriene from the reaction of ditropenyl with triphenylcarbonium hexachloroantimonate. In this case the intermediate tropenyltropenium salt could be isolated and solutions of this were observed to undergo the rearrangement. The conversion of tropenium ion to benzaldehyde by the action of bromine probably proceeds through a cycloheptatriene intermediate.[15]

(18) E. C. Kirby and D. H. Reid, *J. Chem. Soc.*, 494 (1960).

Experimental[19]

1-Tropenylazulene (I) and 1,3-Ditropenylazulene (II).—To a solution of 192 mg. (1.5 mmoles) of azulene and 0.08 ml. (1 mmole) of pyridine in 20 ml. of reagent grade anhydrous methanol was added 178 mg. (1 mmole) of tropenium fluoroborate, and the mixture was allowed to stand at room temperature for 2 hr. and 50 min. It was then warmed on a steam bath for 10 min., poured into water, and extracted with ether. The residue from the ether extract was carefully chromatographed over basic alumina. Continued washing with petroleum ether developed a blue-purple band and two blue bands and from the first, which was eluted with this solvent, was obtained 113 mg. of azulene. The remaining two bands were eluted with a 50:1 petroleum ether–methylene chloride mixture. Rechromatography of the residue from the first blue fraction afforded 42 mg. (19%) of crystalline 1-tropenylazulene, m.p. 55–58°. The analytical sample prepared by sublimation under reduced pressure consisted of blue needles, m.p. 59–60.5°. A cyclohexane solution showed λ_{max} in mμ (ε) in the ultraviolet at 241 (19,000), 279 (48,000), 331 (3200), 337 (3400), 345 (5200), 362 (3000) and shoulders at 283 (44,000), 323 (2300), 334 (3300), and 359 (2500), and in the visible at 601 (320), 625 (280), 656 (280), and 724 (110) with shoulders at 561 (230), 580 (270), and 687 (140).

Anal. Calcd. for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.12; H, 6.51.

Removal of the solvent from the second blue fraction gave 96 mg. (62%) of 1,3-ditropenylazulene as dark blue blades, m.p. 133–135°. A sample recrystallized from methylcyclohexane melted at 135–136°.[5] A cyclohexane solution exhibited λ_{max} in mμ (ε) in the ultraviolet at 243 (29,000), 282 (48,000), 347 (7000) and 364 (5500), and in the visible at 619 (370), 674 (320), and 753 (120) with shoulders at 574 (260) and 645 (320).[5] The n.m.r. spectrum showed resonance peaks centered at 6.65 p.p.m. (saturated hydrogens), 4.45, 3.77, and 3.26 p.p.m. (three types of vinyl hydrogens), and for the azulene ring hydrogens at *ca.* 3.11 p.p.m. (5- and 7-positions), 2.57 p.p.m. (6-position), 1.88 p.p.m. (4- and 8-positions), and 1.87 p.p.m. (2-position) of the expected intensity and multiplicity.

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.73; H, 6.48.

1-Tropenyl-3-chloroazulene (III). A. From 1-Chloroazulene.—To 51.5 mg. (0.317 mmole) of 1-chloroazulene dissolved in 10 ml. of ethanol was added 53 mg. (0.298 mmole) of tropenium fluoroborate. The mixture was allowed to stand at room temperature for 2 hr. and 15 min. and was then poured into a dilute sodium bicarbonate solution. The whole was extracted with methylene chloride, and the solvent was removed from the organic extracts. The residual blue oil was chromatographed over activated basic alumina. Petroleum ether developed two blue bands and the first, which was small, was eluted with this solvent. A 25:1 petroleum ether–methylene chloride mixture eluted the main band and removal of the solvent from this gave 63 mg. (83%) of 1-chloro-3-tropenylazulene as a blue oil. A cyclohexane solution showed peaks in mμ (ε) in the ultraviolet at 242 (24,000), 286 (49,000), 352 (5700), 366 (4700), and 371 (5100) with shoulders at 328 (2500) and 341 (3800), and in the visible at 628 (420), 687 (350), and 765 (130) with shoulders at 583 (300), 606 (360), 656 (360), and 730 (160). The infrared spectrum was recorded. The n.m.r. spectrum showed resonance peaks centered at 6.77 p.p.m. (saturated hydrogen), 4.57, 3.8, and 3.27 p.p.m. (three types of vinyl hydrogens), and for the azulene ring hydrogens at *ca.* 3.0 p.p.m. (5- and 7-positions), 2.54 p.p.m. (6-position), 2.10 p.p.m. (2-position), and 1.98 and 1.75 p.p.m. for the 4- and 8- (or 8- and 4-) positions of the expected intensity and multiplicity.

Anal. Calcd. for $C_{17}H_{13}Cl$: C, 80.79; H, 5.18. Found: C, 81.28; H, 5.31.

B. From 1-Tropenylazulene.—A mixture of 19 mg. (0.087 mmole) of 1-tropenylazulene, 13 mg. (0.097 mmole) of N-chlorosuccinimide, and 5 ml. of dimethylformamide was allowed to stand at room temperature for 12 hr. and was then poured into water. The whole was extracted with ether and the separated ethereal solution washed throughly with water. Removal of the solvent from the organic layer left a blue oil which was chromatographed over basic alumina. Petroleum ether developed two blue bands; the first of these was removed with 25:1 petroleum ether–methylene chloride and the second with a 10:1 mixture of the same solvents. The second fraction yielded 11 mg. (50%) of a blue oil which was identical (ultraviolet, visible, and infrared spectra) to the material obtained in method A.

1-Triphenylmethyl-3-chloroazulene.—To 119 mg. (0.735 mmole) of 1-chloroazulene in 20 ml. of acetonitrile was added 240 mg. (0.728 mmole) of triphenylmethyl fluoroborate. The mixture was allowed to stand at room temperature for about 30 min., was then poured into water and the whole was extracted with methylene chloride. The organic extracts were washed with water, the solvent then removed, and the blue crystalline residue was chromatographed over basic alumina. Petroleum ether developed a small and a large blue band. The former was eluted with 10:1 petroleum ether–methylene chloride and from this fraction were obtained 13 mg. of 1,3-dichloroazulene.[20] Continued elution removed the larger band and the residue from this eluate amounted to 223 mg. (76%) of 1-triphenylmethyl-3-chloroazulene, m.p. 199–203°, after recrystallization from ligroin. The analytical sample recrystallized from methanol as large blue plates, m.p. 204–206°. A cyclohexane solution exhibited λ_{max} in mμ (ε) in the ultraviolet at 243 (33,000), 292 (62,000), 349 (3900), 359 (5700), 368 (3800), and 377 (6900) with shoulders at 287 (56,000), 302 (52,000), 334 (2300), and 344 (3400), and in the visible at 630 (440), 687 (360), and 767 (120) with shoulders at 585 (120) and 662 (360).

Anal. Calcd. for $C_{29}H_{21}Cl$: C, 86.01; H, 5.23. Found: C, 86.35; H, 5.31.

Reaction of 1-Tropenyl-3-chloroazulene with Triphenylmethyl Fluoroborate.—About 20 ml. of dry acetonitrile was distilled from a flask containing phosphorus pentoxide into a 100-ml. round-bottomed flask which contained 78 mg. (0.308 mmole) of 1-tropenyl-3-chloroazulene. Triphenylmethyl fluoroborate (103 mg., 0.312 mmole) was then added quickly, the flask was stoppered, and the mixture, which quickly turned green, was allowed to stand for 20 hr. Removal of the solvent with a rotary evaporator left a dark brown solid. This was triturated with two 100-ml. portions of dry petroleum ether. The extracts, which were blue, were set aside. The gummy residue was treated with about 15 ml. of methylene chloride and the dark green solution which resulted decanted from some colorless crystals. A solution of the latter in sulfuric acid gave an ultraviolet spectrum identical with that with an authentic sample of tropenium fluoroborate. The green methylene chloride solution exhibited λ_{max} in mμ (D_{max}) in the ultraviolet at 287 (2.90), 296 (2.7), 324 (0.8), 373 (0.7), and 392 (0.7), and in the visible at 485 (1.2), 620 (0.3), and 675 (0.4). Removal of the solvent and trituration of the residue with two 50-ml. portions of dry ether gave a gummy brown residue and a blue ether solution. The latter was combined with the petroleum ether extracts of the same color. Chromatography of the residue from this solution over basic alumina with prolonged elution with petroleum ether separated 28 mg. (37%) of triphenylmethane, m.p. 84–89°. A sample crystallized from ethanol melted at 90–92° alone and at 91–93° when mixed with an authentic sample. The ultraviolet spectra of the product and sample were identical. The first of two blue bands which had developed was eluted with a 25:1 petroleum ether–methylene chloride mixture, and the second (smaller) band with a 1:1 mixture of the same solvents. The first fraction contained 31 mg. (25%) of 1-triphenylmethyl-3-chloroazulene, identical (m.p., m.m.p., ultraviolet and visible spectra) with an authentic sample.[21] The solid material from the second fraction (*ca.* 7 mg.) contained triphenylcarbinol but was not investigated further. The gummy brown residue [presumed to be mostly [1-(3-chloroazulyl)]tropenium fluoroborate (IV)] showed a large, broad peak at 9–10 μ[12] and slowly turned purplish blue on standing. The shaking of a green methylene chloride solution (λ_{max} at 485 mμ[13]) of it with water caused the color of both phases to become blue

(19) Melting points are uncorrected and were taken on a Fisher–John apparatus. Ultraviolet and visible absorption spectra were recorded with a Model 11S or 14 Cary recording spectrophotometer. Infrared spectra were obtained with a Perkin–Elmer Model 21 recording spectrophotometer. The n.m.r. spectra were recorded by Mr. B. J. Nist with a 60-Mc. Varian Associates high resolution spectrometer with carbon tetrachloride as the solvent and with tetramethylsilane or hexamethyldisilane as an internal standard. Elementary analyses were performed by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England, and by Dr. Alfred Bernhardt, Microanalytical Laboratory, Max-Planck Institute, Mülheim (Ruhr), Germany.

(20) This materially was presumably present as an impurity in the 1-chloroazulene used.

(21) In qualitative experiments tropenium fluoroborate was also obtained from reactions of III with excess triphenylmethyl fluoroborate in methylene chloride or chloroform, and 1-triphenylmethyl-3-chloroazulene was isolated from a reaction of III and *ca.* an equivalent amount of triphenylmethyl fluoroborate.

and then all of the colored material went into the organic layer; the blue solid recovered could not be crystallized. Efforts to obtain material of analytical purity corresponding to IV were unsuccessful.

1-Benzyl-3-chloroazulene (V).—To a solution of 35.5 mg. (0.163 mmole) of 1-benzylazulene in 10 ml. of dimethylformamide was added 22 mg. (0.165 mmole) of N-chlorosuccinimide. The reaction mixture slowly turned green and after a few hours it was allowed to stand in a refrigerator (at *ca.* 10°) overnight. The mixture was poured into water, the whole extracted with ether, and the green ether layer was then washed several times with water. Removal of the solvent left a green oil which was chromatographed on basic alumina. Elution with petroleum ether developed a blue band and a green band. The blue band was eluted with a 25:1 petroleum ether–methylene chloride solvent and afforded 30 mg. (73%) of 1-benzyl-3-chloroazulene as a blue-green oil. A cyclohexane solution showed λ_{max} in mμ (D_{max}) in the ultraviolet at 238 (0.43), 287 (1.04), 328 (0.04), 336 (0.07), 343 (0.09), 351 (0.13), 368 (0.12) with a shoulder at 293 (0.85), and in the visible at 629 (1.31), 660 (1.12), 689 (1.10), and 772 (0.39) with shoulders at 584 (0.91), 609 (1.16), and 730 (0.49). The infrared spectrum was essentially identical to that of the product obtained from the sodium borohydride reduction of the presumed [1-(3-chloroazulyl)]tropenium fluoroborate (below). The n.m.r. spectrum showed resonance peaks centered at 5.65 p.p.m. (saturated hydrogens), 2.89 p.p.m. (phenyl hydrogens), and for the azulene ring hydrogens at 2.52 p.p.m. (2-position), 2.54 p.p.m. (6-position), 1.89 and 1.78 p.p.m. (4- and 8-positions). The peaks for the 5- and 7-hydrogens were partially covered by the large phenyl hydrogen peak and the centers for these could not be determined.

Reaction of Presumed [1-(3-Chloroazulyl)]tropenium Fluoroborate (IV) with Sodium Borohydride.—Freshly chromatographed 1-tropenyl-3-chloroazulene (117 mg., 0.463 mmole) and triphenylmethyl fluoroborate (149 mg., 0.452 mmole) were allowed to react in the same manner as described above. The acetonitrile was removed (rotary evaporator) and the residue was subjected to a pressure of *ca.* 0.3 mm. (vacuum pump) for several minutes. The almost black crystalline material was then triturated with two 50-ml. portions of dry petroleum ether, a 50-ml. portion of dry ether, and a further 50-ml. portion of petroleum ether. The last two extracts were almost colorless. Removal of the solvent from the combined triturates and chromatography of the residue gave 22.5 mg. (21%) of triphenylmethane, 61 mg. of 1-triphenylmethyl-3-chloroazulene (isolated and characterized as described above), and 7 mg. of a green oil.

The brown, semicrystalline residue was triturated with methylene chloride and the green solution decanted from undissolved tropenium fluoroborate (identified as previously described). The methylene chloride was removed *in vacuo* and about 20 ml. of dry acetonitrile distilled onto the residue. To the dark green solution which formed was added 15 mg. (0.396 mmole) of sodium borohydride. The color of the solution immediately turned to a dark blue, then to a lighter blue and finally to a blue-green, all within a few minutes. The reaction mixture was poured into water and the whole extracted with petroleum ether. Removal of the solvent from the extract left a blue-green oil which was chromatographed on basic alumina. Petroleum ether eluted 11.5 mg. of triphenylmethane and then two blue-green fractions. From the second fraction was obtained 11 mg. of a green oil. The first fraction was rechromatographed. Petroleum ether eluted an additional 3.5 mg. of triphenylmethane, and a blue band having a blue-green tail developed. The main portion of this band was removed with 20:1 petroleum ether–methylene chloride and afforded 36 mg. of a blue-green oil. Continued elution removed the trailing portion which gave an additional 11 mg. of the green oil obtained from the second blue-green fraction. This green oil and the one obtained from the petroleum ether trituration prior to reduction had essentially identical ultraviolet and visible spectra. A cyclohexane solution of each showed λ_{max} in mμ (D_{max}) in the ultraviolet at 240 (0.76), 283 (1.26), 288 (1.30), 295 (1.24), 300 (1.23), 354 (0.18), and 370 (0.18) with a shoulder at 347 (0.14), and in the visible at 630 (1.27), 660 (1.10), 690 (1.09), and 774 (0.39) with shoulders at 585 (0.93), 610 (1.14), and 735 (0.49). The infrared spectra of the two oils were slightly different. The ultraviolet, visible, and infrared spectra of both oils were very similar to those of 1-tropenyl-3-chloroazulene (III) and on this basis the oils are postulated to be tautomeric isomers of III. The elementary analysis was performed on the product isolated after reduction.

Anal. Calcd. for $C_{17}H_{13}Cl$: C, 80.79, H, 5.18. Found: C, 81.30; H, 5.55.

A cyclohexane solution of the blue-green oil (which was not analytically pure) exhibited λ_{max} in mμ in the ultraviolet at 239, 287, 328, 336, 343, 352, and 368 with a shoulder at 293 and in the visible at 630, 660, 690, and 773 with shoulders at 586, 610, and 732. A sample for analysis was obtained by taking a center cut of the band upon rechromatography and heating the recovered oil at 65° *in vacuo* (0.2 mm.) for 2 days. The infrared and n.m.r. spectra of this material were essentially identical to those of the product from the chlorination of 1-benzylazulene (above) and both are therefore indicated to be 1-benzyl-3-chloroazulene.

Anal. Calcd. for $C_{17}H_{13}Cl$: C, 80.79, H, 5.18. Found: C, 80.90; H, 5.48.

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Selective Catalytic Hydrogenation of Nitroölefins

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The objective of this study was the catalytic hydrogenation of a straight-chain and a cyclic conjugated 1-nitroölefin to the corresponding oximes. The formation of nitroalkane was also investigated. 1-Nitro-1-octadecene and 1-nitrocycloöctene were chosen as model compounds. Their convenient synthesis was reported recently.[1]

The examples of catalytic hydrogenation of nitroolefins to oximes reviewed in the literature[2,3] are limited to compounds of the nitrostyrene type. Hydrogenation of substituted nitrostyrenes[4] with palladium on carbon in pyridine gives the corresponding oximes. Phenylacetaldoxime[5] was obtained from 1-phenyl-2-nitroethylene if the hydrogenation was carried out with platinum catalyst in alcohol containing a small amount of acid; the use of alcohol without the acid[5,6] leads to 1,4-dinitro-2,3-diarylbutane. The conversion of conjugated nitroölefins to nitroöalkanes by catalytic methods using neutral media has been studied[7] for various types of nitroölefins.

Table I summarizes our data on selective hydrogenation of 1-nitrocycloöctene I to cycloöctanoneoxime II and nitrocycloöctane III and of 1-nitro-1-octadecene IV to stearaldoxime V and 1-nitroöctadecane VI.

All reactions were carried out with palladium-on-carbon catalyst using 1.3–4 wt. % palladium metal based on nitroölefin. 1-Nitrocycloöctene I was quantitatively converted into a 5:1 mixture of cycloöctanoneoxime II and cycloöctanone VII. Whether 1.0 or 0.5 mole of hydrogen chloride was used per mole of I

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TABLE I

THE SELECTIVE HYDROGENATION OF 1-NITROCYCLOÖCTENE AND 1-NITRO-1-OCTADECENE[a]

Run	Nitro-olefin	Solvent	HCl/nitro-olefin (moles)	Wt. % pyridine in methanol	Mole % composition of crude products: Oxime II	Oxime V	Nitroalkane III	Nitroalkane VI	Carbonyl compound VII[d]	Carbonyl compound (VIII)[e]	H_2/nitro-olefin (moles)
1	I	Methanol	1	..	83[b]	..	0	..	17[b]	..	2.1
2	IV	Methanol	0.5	..	..	73	..	2	..	13[c]	1.8
3	I	Pyridine	..	..	60[b]	..	3	..	Trace	..	2.5[f]
4	IV	Pyridine	..	..	..	60	..	..	..	..	1.9[f]
5	I	Methanol	..	1.3	Trace	..	83	..	10	..	1.0
6	IV	Methanol	..	2.0	..	Trace	..	50[c]	..	10[c]	1.1

[a] See Experimental for conditions and analytical procedures. [b] The analytical values were confirmed by isolation of the pure compounds by distillation. [c] Isolated by chromatography. [d] VII = cycloöctanone. [e] The values are estimated and based on the assumption that the carbonyl compound is stearaldehyde VIII. [f] The amounts of consumed hydrogen given are corrected for hydrogenation of pyridine which was determined separately.

had no effect on the product composition. If, however, only 0.05 mole of hydrogen chloride was employed, the initial rate of hydrogenation was faster than in the experiments with the higher acidity at constant catalyst concentration and the yield of oxime II decreased, while the amount of ketone VII stayed constant. The infrared spectrum of the crude product of run 2 showed a carbonyl absorption: if the latter is assigned to stearaldehyde VIII (its formation would be analogous to the formation of ketone VII from nitro-olefin I), the amount of VIII is estimated at about 13%.

With pyridine as solvent, the rate of hydrogenation of both nitroölefins (runs 3 and 4) was significantly slower than with acidic methanol. Pyridine itself was hydrogenated slowly under the conditions of the reaction. Piperidine can add[8] to nitroölefins. Reactant stability tests in pyridine without hydrogen and with amounts of added piperidine corresponding to that assumed to be formed by hydrogenation of pyridine showed that the straight-chain nitroölefin IV was much less stable than the cyclic nitroölefin I. The latter had been found to be perfectly stable in acidic methanol. Thus, the lower yields of oximes in pyridine are explained.

The selective hydrogenation of the double bond succeeded to a different extent with both nitroölefins (runs 5 and 6). The rate of hydrogenation of the cyclic nitroölefin I decreased sharply after one mole of hydrogen had been consumed per mole of nitroölefin. In the reduction of 1-phenyl-2-nitroethylene in neutral alcohol[5] or acetic acid[6] solvent with platinum catalyst, 1,4-dinitro-2,3-diarylbutane had been obtained. A molecular weight determination of the isolated product of run 6 showed that it was monomeric VI. Other workers[7a] had reported a good yield of 1-nitroöctane by hydrogenation of 1-nitro-1-octene with a small amount of platinum in acetone. With 1-nitro-1-octadecene IV and amounts of platinum from 1–10%, our analyses indicated the presence of 34–43% of 1-nitro-1-octadecane VI in the crude product.

The origin of cycloöctanone VII in run 1 is of interest. Theoretically, it might arise (1) from hydrolysis of oxime II since water is formed in the reaction, (2) from hydrogenation of some oxime II to the imine and subsequent hydrolysis, or (3) from 1,4-addition of hydrogen to I and subsequent Nef[9] decomposition of the resulting *aci*-form of III to nitrous oxide and VII. The first possibility was excluded since it was shown that pure oxime II was not hydrolyzed under the conditions of run 1 with added water and without hydrogen; oxime V was stable to hydrolysis under the work-up conditions of run 2. While the Nef reaction of III was not investigated, further hydrogenation of oxime II was found to occur to some extent since one mole of cycloöctanone-oxime hydrochloride consumed two moles of hydrogen during thirty hours under conditions of run 1.

Although cycloöctanone VII can be separated by distillation from its oxime II, the ketone VII was converted quantitatively to oxime II by treatment of the crude reduction product of run 1 with hydroxylamine and a sodium acetate–acetic acid buffer in methanol solvent, thus giving II in >90% yield of theory. The hydrogenation of crude 1-nitrocycloöctene I, as prepared by addition of dinitrogen tetroxide to cycloöctene and elimination with triethylamine,[1] has provided cycloöctanoneoxime in an over-all yield of at least 83% (based on olefin).

Experimental

Melting points are uncorrected.

Analytical Technique.—The data of Table I were determined by quantitative infrared analysis. They represent mole per cent composition of the crude yields which were 94–97% for runs 1–5 and 90% for run 6. In several cases (footnotes *b* and *c*, Table I), the pure compounds were isolated from the crude products; the isolated yields were 1–5% lower than the analytical values. The methods applied are described in a previous paper.[1]

All spectra were measured in carbon tetrachloride. The amounts of compounds III, VI, and VII were determined by the ratio method.[1] Oxime V was analyzed by measuring the intensity of the free OH absorption. Oxime II was analyzed by both methods, and the two types of analyses agreed within 5% in all cases. The free OH absorptions of the oximes were determined at concentrations of $<0.4 \times 10^{-3}$ mole/l., using *dry* carbon tetrachloride solvent and 9-cm. quartz cells. In concentrations $> 0.4 \times 10^{-3}$ mole/l., hydrogen bonding disturbed the measurements. The oximes were analyzed with a Beckman IR 4 infrared spectrophotometer. A Perkin–Elmer Infracord spectrophotometer served for the determination of the other compounds.

Hydrogenation.—The reactions were carried out on a 2–50 mmole scale at room temperature and 10–60 p.s.i. hydrogen pressure using a Parr hydrogenator with 80–500 ml. reaction vessels. In runs 1, 2, 5, and 6, catalyst and solvent were prehydrogenated. The catalyst was 5% palladium on carbon; its percentage, as given below, is wt. % palladium metal based on nitroölefin.

Cycloöctanoneoxime (II) (Run 1).—A solution of 5.43 g. (35 mmoles) of 1-nitrocycloöctene[1] in 175 ml. methanol containing 35 mmoles of dry hydrochloric acid was hydrogenated with 3.25 g. of catalyst (3% palladium). During 6 min., the reaction temperature increased from 26 to 32° and 2 moles of hydrogen was consumed per mole of nitroölefin. The reaction was continued

(8) D. E. Worrall, *J. Am. Chem. Soc.*, **49**, 1598 (1927).

(9) (a) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955); (b) H. Feuer and A. T. Nielsen, *J. Am. Chem. Soc.*, **84**, 688 (1962).

for 10 min. longer with very small consumption of hydrogen. After addition of 35 mmoles of sodium acetate, the catalyst was filtered and extracted with methanol. The combined methanolic solutions were vacuum-concentrated to about 20 ml. After addition of 200 ml. of water, the mixture was extracted with ether and the combined ethereal solutions were washed with sodium bicarbonate solution and water. After vacuum evaporation of the ether and water, 4.61 g. (96% yield) of crude product was obtained which analyzed (infrared) for 83% cyclooctanoneoxime and 17% cyclooctanone. The vapor phase chromatogram of this crude product showed that the two major compounds were nearly uncontaminated with other by-products. An aliquot of the mixture was separated by microdistillation to give 78% oxime II and 16% ketone VII. The infrared spectrum of cyclooctanone VII, which was isolated by preparative vapor phase chromatography also, was identical with that of authentic material ($\epsilon_{5.88\mu}/\epsilon_{3.40\ \mu} = 1.44$). The infrared spectrum of the oxime II was identical with that of authentic cyclooctanoneoxime obtained by a 16-hr. reaction of equimolar amounts of cyclooctanone, hydroxylamine hydrochloride, and sodium acetate in water–methanol solvent at room temperature and subsequent work-up as described above; b.p. 63° (0.08 mm.), m.p. 41.7–42.7° (reported[10] m.p. 26–28°), $\epsilon_{2.74\ \mu} = 1.19 \times 10^2$ l. cm.$^{-1}$ mole^{-1}, $\epsilon_{2.74\ \mu}/\epsilon_{3.40\ \mu} = 0.52$.

Anal. Calcd. for $C_8H_{15}NO$: C, 67.99; H, 10.71; N, 9.92. Found: C, 67.66; H, 10.42; N, 9.69.

In another run, 4.05 g. of a crude hydrogenation product containing 70% of oxime II, 23% of cyclooctanone VII, and 7% of impurity was converted to cyclooctanoneoxime by treatment with a mixture of 2.8 g. (40 mmoles) of hydroxylamine hydrochloride, 10.8 g. (80 mmoles) of sodium acetate trihydrate, 40 ml. of methanol, and 15 ml. of water for 40 min. at 50°. After work-up as described above and drying of the product for 24 hr. at 5 mm., 3.76 g. (91%) of material was obtained, which analyzed for 93% oxime II and 0% ketone VII.

Cyclooctanoneoxime was also prepared by hydrogenating 5.5 wt. % 1-nitrocyclooctene in pyridine (run 3) with 1.3% palladium for 16 hr. The product was worked up as described above with the difference that the pyridine was removed by azeotropic distillation with heptane after the catalyst had been filtered and extracted with ether.

Stearaldoxime (V) (Run 2).—A solution of 594 mg. (2 mmoles) of 1-nitro-1-octadecene[1] in 10 ml. of methanol containing 1 mmole of dry hydrochloric acid was hydrogenated with 183 mg. of catalyst (1.3% palladium). During 20 min., 1.8 moles of hydrogen was consumed per mole of nitroolefin and the rate of hydrogenation decreased sharply. After addition of 2 mmoles of sodium acetate, the mixture was worked up as described for cyclooctanoneoxime. The isolated crude product (528 mg., 94% yield) analyzed for 73% stearaldoxime content. If the carbonyl absorption, present at 5.75 μ in the crude product, is assigned to stearaldehyde, the amount of the latter is estimated at 13%. Pure stearaldoxime, m.p. 88.0–89.8° (reported[11] m.p. 89°), $\epsilon_{2.74\mu} = 1.30 \times 10^2$ l. cm.$^{-1}$ mole^{-1}, was obtained by recrystallization from methanol and hexane.

Hydrogenation of 3.7 wt. % 1-nitro-1-octadecene in pyridine (run 4) for 9 hr. using 4% palladium and subsequent work-up as described for II gave a crude product (96% crude yield) which contained 60% stearaldoxime.

Nitrocyclooctane (III) (Run 5).—A solution of 2.15 g. (13.8 mmoles) of 1-nitrocyclooctene in 100 ml. of methanol and 1 g. of pyridine was hydrogenated with 0.94 g. of catalyst (2.2% palladium). The rate of hydrogenation dropped when slightly less than 1 mole of hydrogen had been consumed (10 min.) per mole of nitroolefin. After filtration, methanolic extraction of the catalyst, and vacuum evaporation of the solvents with added heptane, 2.05 g. (96% crude yield) of crude product was obtained which analyzed for 83% nitrocyclooctane and 10% cyclooctanone. Pure nitrocyclooctane, n^{20}D 1.4819 (reported[12] n^{20}D 1.4812), $\epsilon_{6.45\mu}/\epsilon_{3.40\mu} = 3.29$, was obtained by preparative vapor phase chromatography (6 ft. × 3/4 in. o.d. column packed with 25% GE-30 silicone gum rubber on Chromosorb W; helium flow rate, 200 ml./min.; temperature, 165°; retention time, 12 min. for VII, 37 min. for III). The isolated cyclooctanone was spectrally identified (100% pure).

(10) N. A. Rosanow and M. Belikow, *J. Russ. Phys. Chem. Soc.*, **61**, 2303 (1929); *Chem. Abstr.*, **24**, 3765 (1930).

(11) H. Stephen, *J. Chem. Soc.*, 1876 (1925).

(12) Badische Anilin-u.-Soda-Fabrik, British Patent 720,646 (December 22, 1954).

1-Nitrooctadecane (VI) (Run 6).—A solution of 672 mg. (2.26 mmoles) of 1-nitro-1-octadecene in 10 ml. of methanol and 0.17 g. of pyridine was hydrogenated with 1.3% palladium. Since there was no break in the hydrogen uptake/time curve, the reaction was terminated after 1.1 moles of hydrogen had been consumed per mole of nitroolefin (11 min.). After work-up, as described for III, 612 mg. of crude product (90% crude yield) was isolated. When 489 mg. of this material was chromatographed on silicic acid, using *n*-hexane containing 10% benzene as eluent, 255 mg. (yield about 50%) of pure 1-nitrooctadecane VI, m.p. 39.5–41°, $\epsilon_{6.44\ \mu}/\epsilon_{3.40\mu} = 0.91$, was isolated.

Anal. Calcd. for $C_{18}H_{37}NO_2$: C, 72.18; H, 12.45; N, 4.67; mol. wt. (in benzene), 299.5. Found: C, 72.16; H, 12.41; N, 4.56; mol. wt. (in benzene), 308.

N-Methyl-1,2,3,4,4a,9a-hexahydrocarbazoles by Catalytic Hydrogenation

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For forty years N-methyl-1,2,3,4,4a,9a-hexahydrocarbazole,[3] prepared by tin–hydrochloric acid reduction of N-methyl-1,2,3,4-tetrahydrocarbazole,[4] has been the only known N-methylated 1,2,3,4,4a,9a-hexahydrocarbazole, although a respectable number of 1,2,3,4-tetrahydrocarbazoles, with or without methyl groups in 9-position, have been obtained by Fischer indole synthesis and its improved versions.[5] When metal–acid, including sodium and ethanol, was applied to N-methyl-1,2,3,4-tetrahydrocarbazoles, the benzene ring of which had been substituted by one or more methyl groups, the corresponding hexahydrocarbazoles were actually found, but the yields failed to exceed 13%. An estimation of the equilibria involved in the catalytic hydrogenation of tetrahydrocarbazoles suggested the application of low hydrogen pressure together with an acidic solvent, which would both favor the formation of hexahydrocarbazoles and inhibit their overreduction to 1,2,3,4,5,6,7,8-octahydrocarbazoles.

With Adams' platinum oxide,[6] 9-methyl- and the (5–8),9-dimethyl-1,2,3,4-tetrahydrocarbazoles gave the corresponding 1,2,3,4,4a,9a-hexahydrocarbazoles in yields of 85% and better. Glacial acetic acid served as the solvent; occasionally a small amount of hydrochloric acid had to be added. Prolonged hydrogenation under these conditions led to other acid-soluble oils, presumably dodecahydrocarbazoles, which were not investigated. The formation of acid-insoluble by-products was negligible. The hydrogenation rates were nearly identical for all reactions.

The N-methyl-1,2,3,4,4a,9a-hexahydrocarbazoles are basic liquids,[7] virtually insoluble in water or aqueous

(1) A portion of this work was submitted to Tuskegee Institute as a M.S. thesis.

(2) Presented at the Southeastern Regional Meeting of the American Chemical Society in Birmingham, Ala., November 4, 1960.

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(6) R. Adams, V. Vorhees, and R. L. Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 463.

(7) Exception: 6,8,9-trimethyl-1,2,3,4,4a,9a-hexahydrocarbazole, m.p. 59–60°, glassy prisms; J. C. Kelley, in progress.

alkali, but reversibly soluble in 2 *N* mineral acids. In the absence of rough surfaces they may be distilled in an aspirator vacuum without decomposition. Their odor resembles that of N,N-dimethylaniline. Despite their reducing nature they are quite stable on the shelf, although they gradually darken. They undercool easily and, as a rule, congeal glassy rather than crystallize.

As tertiary anilines the N-methyl-1,2,3,4,4a,9a-hexahydrocarbazoles add methyl iodide with great ease to give the water-soluble, benzene-insoluble N,N-dimethyl-1,2,3,4,4a,9a-hexahydrocarbazolium iodides. These salts crystallize slowly from water, alcohol, or acetone as white needles or glass-clear prisms of remarkable mechanical strength, which tend to stick tightly to glass. When forced out of solution rapidly, the salts may appear as milky emulsions, settle soon as oils, but within an hour they are usually crystallized. They are completely stable on the shelf. At-random tests on gradient agar plates[8] revealed some activity against *Escherichia coli* and *Staphylococcus aureus*.

The hydrogenation of tetrahydrocarboline derivatives to hexahydrocarbolines by the same technique has been accomplished,[9] which fact may be of interest in the Rauwolfia alkaloid chemistry.

Experimental

6,9-Dimethyl-1,2,3,4-tetrahydrocarbazole.—To a mixture of 50 ml. of acetic acid and 23.6 g. of cyclohexanone 18.3 g. of α-methyl-α-(*p*-tolyl)hydrazine was added during 0.5 hr. while stirring and refluxing. After another hour's refluxing and stirring the cooled solution deposited 17 g. of pink needles, m.p. 87°. A second crop of 3 g. was obtained by diluting the mother liquor with its volume of water. Distillation and recrystallization from methanol gave 16.2 g. of pure 6,9-dimethyl-1,2,3,4-tetrahydrocarbazole, m.p. 89–90°, b.p. 213–214°; (25 mm.); yield 59%. No peroxide formation was observed.[10]

6,9-Dimethyl-1,2,3,4,4a,9a-hexahydrocarbazole.—A 3.0-g. sample of 6,9-dimethyltetrahydrocarbazole in 35 ml. of glacial acetic acid containing 2 ml. of hydrogen chloride-saturated glacial acetic acid was hydrogenated on 100 mg. of platinum oxide (Adams')[6] with 400 ml. of hydrogen at room temperature and atmospheric pressure (2.5 hr.) in a modified Parr apparatus.[11] The solution was suction-filtered and rendered alkaline with 30% sodium hydroxide; the oily base and three subsequent ether extracts, 50 ml. each, were combined and extracted three times with 30 ml. of 2 *N* hydrochloric acid. The ether extract of the alkalinified aqueous extract was dried with potassium carbonate, evaporated, and the residue (1.4 g.) distilled at 122° (0.8 mm.) to give 1.2 g. of an almost colorless oil, which began to darken when exposed to air for several days.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51: N, 6.96. Found: C, 83.50; H, 9.56; N, 7.14.

6,9,9-Trimethyl-1,2,3,4,4a,9a,-hexahydrocarbazolium Iodide.—A solution of 0.5 g. of 6,9-dimethylhexahydrocarbazole and 0.5 ml. of methyl iodide in 5 ml. of benzene was allowed to stand at room temperature. After 2 days the hard yellowish crystals were collected and repeatedly recrystallized from alcohol to give white crystals, m.p. 168–70° dec.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46; I, 36.98; N, 4.08. Found: C, 52.69; H, 6.63; I, 37.09; N, 3.98.

8,9-Dimethyl-1,2,3,4-tetrahydrocarbazole.—This compound was first obtained by a method analogous to the 6,9-dimethyltetrahydrocarbazole synthesis from α-methyl-α-(*o*-tolyl)hydrazine. Since the reaction of methyl-*o*-tolylnitrosamine by Fischer–Arbuzov[12] method gave only low yields, *o*-tolylhydrazine [m.p. 53–56°, b.p. 145–150° (15 mm.)] was prepared in 66.5% yield by sulfite reduction of *o*-toluenediazonium chloride at −10 to −5° with subsequent heating to 60°, and 8-methyl-1,2,3,4-tetrahydrocarbazole[10] was obtained in 51% yield by Borsche[13] condensation in glacial acetic acid; m.p. 91–95° after distillation at 206° (14 mm.). To avoid the formation of peroxide,[10] the substance was not recrystallized.

Dimethyl sulfate (30 ml.) was added during 1 hr. to a stirred, refluxing mixture of 150 g. of sodium hydroxide, 46.5 g. of 8-methyltetrahydrocarbazole, 100 ml. of water, and 40 ml. of acetone. After stirring for 15 additional minutes and refluxing, the mixture was diluted with an equal volume of water and acidified with a mixture of 100 ml. of concentrated sulfuric acid and 100 ml. of water. The 8,9-dimethyltetrahydrocarbazole was washed with water, air-dried, stirred with a little cold methanol to remove unchanged 8-methyltetrahydrocarbazole, recrystallized from ethyl acetate and from acetone or ligroin (b.p. 100–105°) to give colorless needles, m.p. 151–152°. The substance did not form peroxides.[10]

8,9-Dimethyl-1,2,3,4,4a,9a-hexahydrocarbazole.—The procedure was analogous to the preparation of the 6,9-isomer; however, the low solubility of the 8,9-dimethyltetrahydrocarbazole in glacial acetic acid (0.4%) at room temperature required a different solvent. A mixture of 75 ml. of benzene, 75 ml. of glacial acetic acid, and 2 ml. of hydrogen chloride-saturated glacial acetic acid was used for 3 g. of 8,9-dimethyltetrahydrocarbazole, from which were obtained 1.55 g. of crude 8,9-dimethyl-1,2,3,4,4a,9a-hexahydrocarbazole and 1.3 g. of starting material. The 8,9-dimethyl-1,2,3,4,4a,9a-hexahydrocarbazole, distilled at 172° (15 mm.), turned green after short standing in the air and deposited a dark amorphous material in the course of 2 weeks. The remaining yellow liquid was distilled to give an almost colorless oil which became brown after 3 months.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.22; H, 9.88; N, 7.14.

Although the freshly prepared compound did not crystallize under any circumstances and stayed liquid for months at −27°, repeated cooling of the 1-year-old sample with liquid nitrogen and allowing it to reach −5° caused crystallization. The 1-year-old material liquefied at −4 to −2°.

8,9,9-Trimethyl-1,2,3,4,4a,9a-hexahydrocarbazolium Iodide.—The preparation was analogous to that of the 6,9,9-isomer; m.p. 188–189° dec.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46; I, 36.98; N, 4.08. Found: C, 52.43; H, 6.74; I, 36.72; N, 3.79.

(5,7),9-Dimethyl-1,2,3,4-tetrahydrocarbazole.—To a stirred, refluxing solution of 6 g. of cyclohexanone in 50 ml. of glacial acetic acid, 7.8 g. of α-methyl-α-(*m*-tolyl)hydrazine [b.p. 90–92° (1.9 mm.); by Fischer–Arbuzov[12] reduction] was added dropwise. After refluxing for a total of 1.25 hr. the mixture deposited 7.6 g. of the two isomers at room temperature, and an additional 0.8 g. in the refrigerator. The product was washed, air-dried, distilled at 158–160° (1.8 mm.), and recrystallized from methanol to give white needles, m.p. 66–80°. The isomers could partly be separated by fractional high-vacuum sublimation at 50° (0.03 mm.) in an Emich flask packed with Podbielniak Heli-Pak. The sublimate reached a m.p. of 85–94°, the residue 98–106°.[14] No peroxides were noticed.

(5,7),9-Dimethyl-1,2,3,4,4a,9a-hexahydrocarbazole.—The mixture of isomers, 3.0 g., was hydrogenated as described for 6,9-dimethyl-1,2,3,4-tetrahydrocarbazole to give 0.5 g. of the (5,7),9-dimethylhexahydrocarbazoles, b.p. 136° (0.4 mm.), and 2.5 g. of starting material.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.31; H, 9.91; N, 7.19.

(8) W. Szybalski and V. Bryson, *J. Bacteriol.*, **64**, 489 (1952); the microbiological tests were carried out by Lieselotte K. Bloss.

(9) J. C. Kelley, work in progress.

(10) G. Anderson and N. Campbell, *J. Chem. Soc.*, 2855 (1950).

(11) The Parr catalytic apparatus (Parr no. 3911) was modified as follows. The pressure tank and gage was replaced by a set of three inverted graduated cylinders serving as gas burets of 1000, 500, and 100 ml. They were connected by a manifold with each other, the reaction vessel and a three-way stopcock leading to the vacuum line and to the hydrogen tank (Matheson lecture bottle with prepurified-grade hydrogen). The commercial reaction vessel was replaced by a 100- or 250-ml. round-bottom flask with a standard-taper 29/42 connected with the gas inlet by a glass tubing with a 29/42 male ground joint and a short piece of vacuum rubber tubing. A rubber stopper, size 12, with a depression accommodated the round-bottom flask in the shaker. The hydrogen uptake was read on the gas burets with leveled bulbs.

(12) E. Fischer, *Ann.*, **190**, 175 (1878); A. E. Arbuzov and F. G. Valitova, *Zh. Obshch. Khim.*, **27** (89), 2354 (1957); compare R. H. Poirier and F. Benington, *J. Am. Chem. Soc.*, **74**, 3192 (1952).

(13) W. Borsche, A. Witte, and W. Bothe, *Ann.*, **359**, 49 (1908).

(14) C. v. Williams, Undergraduate Research Program Participant, sponsored by the National Science Foundation.

Acknowledgment.–The authors wish to express their gratitude to the George Washington Carver Foundation and the Research Corporation (Research-Cottrell, Inc.) who jointly supported this work.

Ring Nonplanarity and Aromaticity in Porphyrins. Nuclear Magnetic Resonance Spectra of Etioporphyrin II and Its N-Alkyl Compounds

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To account for the known existence of N-alkylporphyrins it has been proposed from considerations of steric factors and visible spectra[1,2] and, more recently, analog computations[3] that at least one pyrrole ring must be out of the over-all plane of the porphyrin ring. However, no detailed experimental investigations of the manner in which the porphyrin ring accommodates the alkyl group substituted on nitrogen at the center of the ring and of the effect such an accommodation has on the aromaticity of the macrocycle have been reported. Here we report the n.m.r. spectra of etioporphyrin II (Fig. 1, R = H),[4] N-methyletioporphyrin II (Fig. 1, R = CH_3), and N-ethyletioporphyrin II (Fig. 1, R = CH_2CH_3) in deuteriochloroform. These spectra are interpreted as indicating that the porphyrin ring in etioporphyrin II is planar, whereas in each of the N-alkyl compounds there are definite deviations from planarity. N-Alkylation results in only a small change in ring current field strength and, consequently, the aromaticity may also be considered to be altered only slightly.

With the presumably planar[5] etioporphyrin II the ring positions for each type of substituent appear equivalent (Fig. 2, I) and the assignments are clear (Table I).[4] The spectra of the N-alkyl etioporphyrins are characterized by non-equivalence in ring positions. The N-alkyl protons appear at extremely high field consistent with the findings for porphyrin nitrogen bound protons[4,6] and their being within a strong ring current field. The fact that both N—CH_3[7] and N—Et—CH_2 are at significantly higher fields than N—Et—CH_3 provides evidence for the ring current effect being stronger near the center of the macrocycle.

The nature of the non-equivalence of ring positions in the N-alkyl compounds proves to be consistent with a definite nonplanar conformation of the molecules. Upon examination of models, a most reasonable manner for the N-alkyl group to be accommodated involves: (1) pyrrole ring I (Fig. 1) being somewhat out of the over-all plane of the ring with its nitrogen above the plane and its β-carbons below; (2) rings II and IV being out of the plane, to a lesser extent, with their nitrogen atoms below and their β-carbons above; and (3) ring III remaining essentially in the plane. The n.m.r. spectra suggest this is indeed the case. Thus the R—CH_3 of ring I is considerably out of the over-all plane, those of rings II and IV somewhat out of the plane, and that of ring III in the plane. If it is assumed that the further the protons of a given R—CH_3 are out-of-plane the lesser will be the ring current field effect, then the R—CH_3 protons of types A, B, and C may be assigned to ring I, rings II and IV, and ring

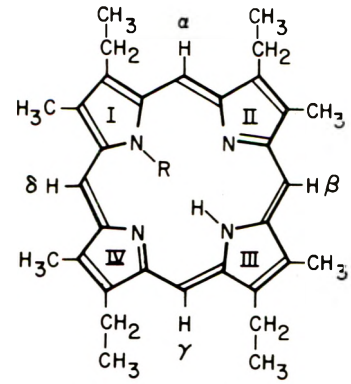

Figure 1

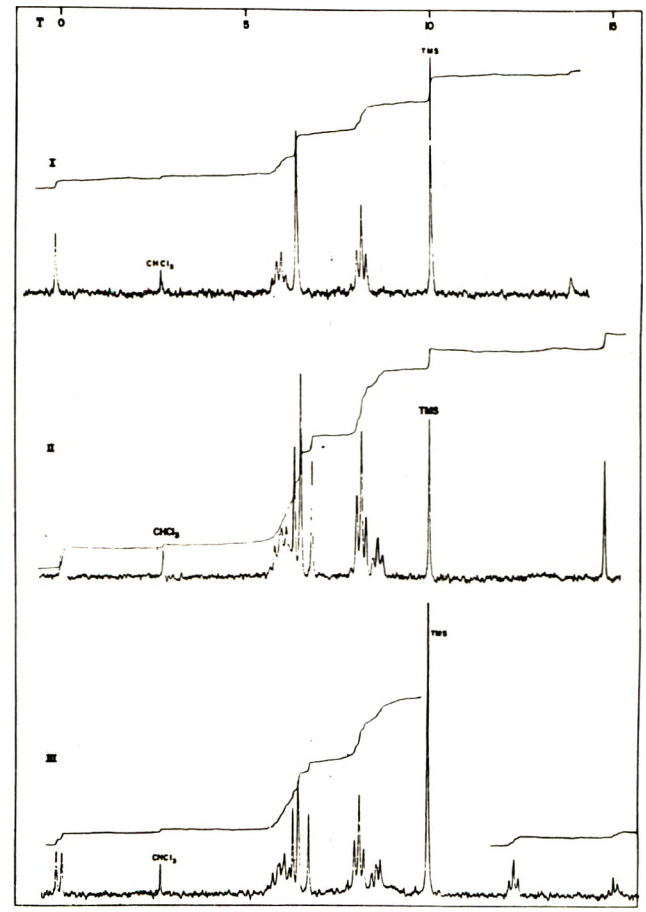

Fig. 2.—N.m.r. spectra in deuteriochloroform. I, etioporphyrin II; II, N-methyletioporphyrin II; III, N-ethyletioporphyrin II.

(1) W. K. McEwen, *J. Am. Chem. Soc.*, **68**, 711 (1946).
(2) R. C. Ellingson and A. H. Corwin, *ibid.*, **68**, 1112 (1946).
(3) A. H. Corwin, J. Walter, and R. Singh, *J. Org. Chem.*, in press.
(4) W. S. Caughey and W. S. Koski, *Biochem.*, **1**, 923 (1962).
(5) M. B. Crute, *Acta Cryst.*, **12**, 24 (1959).
(6) E. D. Becker and R. B. Bradley, *J. Chem. Phys.*, **31**, 1431 (1959); J. Ellis, A. H. Jackson, G. W. Kenner, and J. Lee, *Tetrahedron Letters*, **2**, 23 (1960).
(7) For convenience the following abbreviations are used in this paper: R—CH_3 for ring methyl, R—Et—CH_3 for methyl of ring ethyl, N—CH_3 for nitrogen bound methyl, N—Et—CH_3 for methyl of nitrogen bound ethyl, R—Et—CH_2 for methylene of ring ethyl, N—Et—CH_2 for methylene of nitrogen bound ethyl.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA

Protons[a]	Type	Etioporphyrin II	N-Methyletioporphyrin II	N-Ethyletioporphyrin II
N—Et—CH_3				12.37
N—Et—CH_2				15.16
N—CH_3			14.89	
N—H		13.79	13.12 (broad)	Not observed
R—Et—CH_3	A		8.58	8.61[b]
	B	8.13	8.15	8.14
R—CH_3	A		6.80	6.78
	B		6.50	6.48
	C	6.38	6.34	6.35
R—Et—CH_2	A		6.04	6.06
	B	5.89	5.86	5.88
Methine—H	A		0.03	0.04
	B	−.11	−.01	−.08

[a] See footnote 7. [b] This triplet is distorted somewhat by a weak broad band on the high field side. Although the origin of this band is uncertain, it is probably due, at least in part, to water which has often been observed in this region. This is an extremely low field position for N–H which, to be sure, was not observed elsewhere in the spectrum.

III, respectively. Integration data show a proton ratio of 3:6:3 for types A, B, and C, respectively. In the R—Et—CH_3 spectra integration shows three protons for type A and nine protons for type B. Here the type A triplet can be assigned to ring I and the R—Et—CH_3 groups of the other rings, being essentially equivalent, appear as type B. Assignments of the number of protons to each type of R—Et—CH_2 are not completely clear but the overlapping quartets are roughly equivalent in area. Slight non-equivalence is also found in the methine proton spectra. The α and δ protons can be expected to be essentially equivalent and different from the β and γ protons, which are also equivalent; a pair of peaks, each representing two protons, is indeed observed. These spectra might be compared with those of etioporphyrin II and thereby assign type A to the α and δ protons and type B to the β and γ protons. More likely, however, the nonplanar substituents in ring I result in less effective shielding of the α and δ protons than is the case with the β and γ protons and thereby make an opposite assignment the correct one. Thus for each of the N-alkyl compounds the n.m.r. data are consistent with and provide experimental evidence for a conformation with reasonable deviations from planarity. It should be added, however, that an evaluation of the effect of N-alkylation in the absence of conformational changes has not been attempted.

The ring current field strength appears to be only slightly less in the N-alkyl compounds than in etioporphyrin II. This can be concluded from the similarity in the spectra for protons remaining inplane (the methine protons and R—CH_3 and R—Et protons assigned to ring III) in the N-alkyl compounds compared with etioporphyrin II spectra.[4] If a single large ring current field is considered to be present and the strength of this field to be a measure of the degree of π-electron delocalization and consequently a measure of aromaticity, as has been done with six π-electron systems,[8] annulenes,[9] and porphyrins,[4] it is apparent that the deviations from planarity encountered here do not markedly affect the aromaticity of these compounds. (Metal ions complexed with the central nitrogen atoms and electron-withdrawing peripheral substituents do affect ring current field strengths.[4]) Furthermore these data suggest that appreciable deviations from over-all ring planarity can occur at the expense of little energy. Therefore the possibility of such nonplanarity must be given careful consideration in porphyrins and metalloporphyrins. The possibility of nonplanarity in palladium (II) complexes was suggested previously.[4]

(8) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(9) R. A. Raphael, *Proc. Chem. Soc.*, 97 (1962).

Experimental

The n.m.r. spectra were obtained with a Varian A-60 spectrometer in $\sim 0.09\ M$ deuteriochloroform solutions with tetramethylsilane as an internal standard. Concentrations were varied without significant effect on the spectra. The data are reported as τ values.

Materials.—Etioporphyrin II was prepared as described previously.[4] N-methyletioporphyrin II and N-ethyletioporphyrin II were kindly supplied by Professor A. H. Corwin.

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Synthesis of 2β-Hydroxy Steroids. II[1,2]

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We have previously described a method for the synthesis of 2β-hydroxylated steroids which resulted in the synthesis of 2β-hydroxytestosterone.[1] The chemistry of the 2β-hydroxyl group is interesting since, from a thermodynamic standpoint, the 2β-configuration (axial) would be expected to be less stable when compared with the 2α-configuration (equatorial) and thus would tend to isomerize to the more stable 2α-form. In agreement with this, synthetic studies have shown that prolonged treatment of 2β-hydroxylated-Δ^4-3-keto steroids with potassium acetate in acetic acid does isomerize the 2β-function to the stable 2α-form.[4] However, since our communication[1] still other 2β-hydroxylated steroids have been obtained from microbiological incubations.[5] In view of this increased interest in

(1) P. N. Rao and L. R. Axelrod, *J. Am. Chem. Soc.*, **82**, 2830 (1960), should be considered as Part I of the series.

(2) This work was supported by a grant (A-3270) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

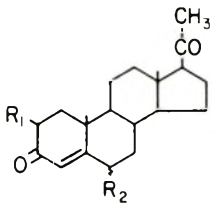
(3) This paper represents part of a thesis submitted by H. R. Gollberg to the Graduate School of St. Mary's University, San Antonio, Tex., in partial fulfillment of the requirements for the degree of Master of Science.

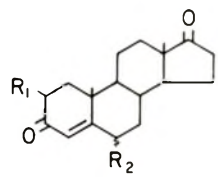
(4) (a) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953); (b) R. L. Clark, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955).

(5) (a) M. Shirasaka, M. Tsuruta, and M. Nakamura, *Bull. Agr. Chem. Soc. Japan*, **22**, 273 (1958); (b) M. Shirasaka, R. Takasaki, R. Hayashi, and M. Tsuruta, *ibid.*, **23**, 245 (1959); (c) K. Tanabe, R. Takasaki, R. Hayashi, and M. Shirasaka, *Chem. Pharm. Bull.* (Tokyo), **1**, 804 (1959); (d) M. Shirasaka and M. Tsuruta, *Arch. Biochem. Biophys.*, **87**, 338 (1960); (e) L. L. Smith, H. Mendelsohn, T. Foell, and J. J. Goodman, *J. Org. Chem.*, **26**, 2859 (1961).

2β-hydroxy steroids we have now extended our earlier method to synthesize 2β-hydroxyprogesterone (IV) and 2β-hydroxy-4-androstene-3,17-dione (IX). This appears to be a general synthetic route to the preparation of 2β-hydroxy steroids.

Progesterone and 4-androstene-3,17-dione were brominated with N-bromosuccinamide in carbon tetrachloride essentially as described in the literature to give respectively 6-bromoprogesterone (I)[4a] and 6-bromo-4-androstene-3,17-dione (VI).[6] Rearrangement of the 6-bromo-Δ⁴-3-ketones by refluxing with potassium acetate in glacial acetic acid for twelve minutes gave a mixture of 2α- and 2β-acetates. These conditions have been shown to produce optimum yields of the 2β-isomer.[1]





I R_1 = H; R_2 = Br
II R_1 = α-OAc; R_2 = H
III R_1 = β-OAc; R_2 = H
IV R_1 = β-OH; R_2 = H
V R_1 = α-OH; R_2 = H

VI R_1 = H; R_2 = Br
VII R_1 = α-OAc; R_2 = H
VIII R_1 = β-OAc; R_2 = H
IX R_1 = β-OH; R_2 = H
X R_1 = α-OH; R_2 = H

In the progesterone series, the mixture of 2-acetates was fractionally crystallized to yield the known 2α-acetoxyprogesterone (II)[4a] and 2β-acetoxyprogesterone (III), both in 20–25% yield. Similar fractionation of the 2-acetates of 4-androstene-3,17-dione gave the known 2α-acetoxy-4-androstene-3,17-dione (VII)[7] in 15–20% yield and 2β-acetoxy-4-androstene-3,17-dione (VII) in 25–30% yield.

The 2β-acetates II and VIII were separately hydrolyzed under controlled conditions with one equivalent of 1 *N* methanolic potassium hydroxide at room temperature to give respectively 2β-hydroxyprogesterone (IV) and 2β-hydroxy-4-androstene-3,17-dione (IX) *without isomerization to the 2α-form*. Similar hydrolysis of the 2α-acetates II and VII afforded the known 2α-hydroxyprogesterone (V)[4a] and 2α-hydroxy-4-androstene-3,17-dione (X). The structures of the 2β-esters III and VIII as well as the 2β-hydroxy compounds IV and IX are based on their elemental analyses, infrared and ultraviolet spectral data, and the following evidences. It has been shown that 2β-hydroxy-Δ⁴-3-keto steroids exhibit strong negative molecular rotatory differences (ΔMD), with the values varying from −519 to −768.[1,5e] In keeping with this, the ΔMD values observed for IV and IX are −748 and −648, respectively. Refluxing either the 2β-acetate (III) or the 2β-hydroxy compound (IV) for four hours with potassium acetate in glacial acetic acid resulted exclusively in the corresponding 2α-compounds. Their identities were established by mixture melting point determinations and by a comparison of their infrared spectra with authentic samples. Further, acetylation of IV with pyridine–acetic anhydride gave the back the 2β-acetate (III) thus proving that no inversion of the 2β-configuration occurred during the hydrolysis.

It has been noted that in mild alkaline solutions 2β- and 2α-hydroxyls attain equilibrium with one another; therefore, the same alkaline ultraviolet spectrum must result for both configurations of a given pair of 2-hydroxy-Δ⁴-3-keto steroids.[8] Accordingly, treatment of IV, V, IX, and X with alkaline ethanol solution resulted in ultraviolet curves identical to those obtained by Meyer.[9] Consequently, IV and IX must contain the 2β-configuration. We have also observed that 2β-hydroxy steroids absorb at slightly higher wave lengths (bathochromic shift) in the ultraviolet region when compared with the 2α-hydroxy compound. Thus the ultraviolet absorption for the 2β-hydroxy compounds IV and SX is 242 mμ whereas for the 2α-hydroxy compounds V and X it is 240 mμ. Ultraviolet curves were also taken of the 2-hydroxy compounds in concentrated sulfuric acid according to Zaffaroni.[10] The 2α-hydroxy compounds V and X[11] had absorptions at 298 and 346 mμ, of which the peak at 298 mμ was stronger. Similar curves taken of the 2β-hydroxy compounds IV and IX also showed absorptions at 298 and 347 mμ. However, in this case, the absorption intensities were reversed with the 347-mμ peak having the stronger absorption.

Experimental[12]

6-Bromoprogesterone (I).—Progesterone (10 g.) reacted as described in the literature[4a] to yield 6-bromoprogesterone (I, 6.85 g., 48%), m.p. 137–138° dec. One further crystallization raised the melting point to 138.5–141° dec. (lit.,[4a] anal. sample m.p. 143–145° dec.). This product was used without further purification for the next reaction.

6-Bromo-4-androstene-3,17-dione (VI).—4-Androstene-3,17-dione (4.072 g.) was brominated also as described in the literature[6] to give 6-bromo-4-androstene-3,17-dione (VI, 3.694 g., 58%), m.p. 170° dec. which was used without further purification for the next reaction (lit.,[6] analytical sample m.p. 175–177° dec.).

2α-Acetoxyprogesterone (II).—A mixture of 6-bromoprogesterone (I, 8.38 g.), anhydrous potassium acetate (21 g.), and glacial acetic acid (110 ml.) was stirred and boiled under reflux for 12 min., cooled, and poured into ice–water. The precipitated material was filtered, washed thoroughly with cold water, collected, and crystallized from ethyl acetate–petroleum ether to give 2α-acetoxyprogesterone (II, 1.24 g., 22%) which melted at 182–190°. Further crystallization from the same solvent afforded the analytical product, m.p. 196.5–197.5°, $[\alpha]_D$ +165° (*c* 1.03), λ_{max} 240 mμ (ε 17,383), ν_{max} 1737 cm.⁻¹ (acetate carbonyl), 1682 cm.⁻¹ (20-ketone), 1673 cm.⁻¹ (conjugated carbonyl), 1605 cm.⁻¹ (C=C of the conjugated ketone), 1213 and 1232 cm.⁻¹ (acetoxy) (lit.,[4a] m.p. 197–198°, $[\alpha]_D$ +164°).

Anal. Calcd. for $C_{23}H_{32}O_4$ (372.5): C, 74.16; H, 8.66. Found: C, 73.87; H, 8.65.

2β-Acetoxyprogesterone (III).—The first two mother liquors from the above crystallization were combined and further fractionated from acetone–petroleum ether to give 2β-acetoxyprogesterone (III, 1.21 g., 22%), m.p. 120–125°. Three additional crystallizations from ethyl acetate–petroleum ether gave the

(6) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(7) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **77**, 145 (1955).

(8) H. L. Herzog, M. J. Gentles, E. B. Hershberg, F. Carvajal, D. Sutter, W. Charney, and C. P. Schaffner, *ibid.*, **79**, 3921 (1957).

(9) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1955).

(10) A. Zaffaroni, *J. Am. Chem. Soc.*, **72**, 3828 (1950).

(11) J. S. Baran, *ibid.*, **80**, 1687 (1958).

(12) All melting points were determined on samples dried under high vacuum at 60° for 24 hr. and are uncorrected. The ultraviolet absorption spectra were determined in methanol with a Cary recording spectrophotometer (Model 11 MS). The infrared absorption spectra were determined in a KBr disk on a Perkin–Elmer (Model 21) spectrophotometer. All optical rotations were measured in chloroform solution at 25 ± 3° on a Zeiss–Winkel polarimeter. All microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

analytical sample, m.p. 126–127°, $[\alpha]_D$ 32° (*c* 0.86), λ_{max} 242 mμ (ε 16,092), ν_{max} 1740 cm.$^{-1}$ (acetate carbonyl), 1693 cm.$^{-1}$ (20-ketone), 1673 cm.$^{-1}$ (conjugated carbonyl), 1615 cm.$^{-1}$ (C=C of the conjugated carbonyl), and 1210 cm.$^{-1}$ (acetoxy).

Anal. Calcd. for $C_{23}H_{32}O_4$ (372.5): C, 74.16; H, 8.66. Found; C, 73.68; H, 8.83.

2α-Acetoxy-4-androstene-3,17-dione (VII).—The mixed acetates obtained by similar acetolysis of 6-bromo-4-androstene-3,17-dione (IV, 4.652 g.) were fractionally crystallized from methanol to yield 2α-acetoxy-4-androstene-3,17-dione (VII, 450 mg., 15%), m.p. 210–211.5°, $(\alpha)_D$ +138° (*c* 0.66), λ_{max} 240 mμ (ε 15,262), ν_{max} 1733 cm.$^{-1}$ (fused five-membered ring ketone and acetate carbonyl), 1680 cm.$^{-1}$ (conjugated carbonyl), 1605 cm.$^{-1}$ (C=C of the conjugated carbonyl), 1217 and 1233 cm.$^{-1}$ (acetoxy) (lit.,[8] m.p. 209–210°, $[\alpha]_D$ +146).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.4): C, 73.23; H, 8.19. Found: C, 73.20; H, 8.19.

2β-Acetoxy-4-androstene-3,17-dione (VIII).—Further fractionation of the above mother liquors from dilute methanol gave 2β-acetoxy-4-androstene-3,17-dione (VIII, 865 mg., 25%), m.p. 156–158°, $[\alpha]_D$ −8.9° (c 1.03), λ_{max} 242 mμ (ε 14,472), ν_{max} 1736 and 1745 cm.$^{-1}$ (acetate carbonyl and 17-ketone), 1688 cm.$^{-1}$ (conjugated carbonyl), 1620 cm.$^{-1}$. (C=C of the conjugated carbonyl), and 1225 cm.$^{-1}$ (acetoxy) (lit.,[13] m.p. 157–158°, $[\alpha]_D$ −5.9°).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.4): C, 73.23; H, 8.19. Found: C, 73.12; H, 8.11.

Saponification of 2-Acetoxy Compounds. 2α-Hydroxyprogesterone (V).—2α-Acetoxyprogesterone (II, 600 mg.) was dissolved in methanol (18.3 ml.) and dry nitrogen was bubbled through the solution. Then exactly one equivalent of methanolic potassium hydroxide (1.4 ml. of a 1 *N* solution) was added and the solution was stirred at 30° for *4 min.* Then methanol (10 ml.) containing 2 drops of water was added and stirring continued for an additional *4 min.* (total time 8 min. at 30°). The solution was then acidified with 1 *N* acetic acid (2 ml.), concentrated to one-third volume, diluted with water, chilled in an icebox, and filtered to give 2α-hydroxyprogesterone (V) which was crystallized from acetone–petroleum ether, m p. 184–187°, $[\alpha]_D$ +188° *c* 1.09), λ_{max} 240 mμ (ε 15,474), ν_{max} 3560 cm.$^{-1}$ (hydroxyl), 1695 and 1675 cm.$^{-1}$ (20- and 3-ketones), and 1615 cm.$^{-1}$ (C=C of the conjugated carbonyl) (lit.,[4a] m.p. 182–183° $[\alpha]_D$ +199°).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.5): C, 76.32; H, 9.15. Found: C, 76.16; H, 9.52.

2β-Hydroxyprogesterone (IV).—Saponification of the 2β-acetate (III, 607 mg.) exactly as described above furnished 2α-hydroxyprogesterone (IV) in quantitative yield, m.p. 191–193°, $(\alpha]_D$ −51° (*c* 1.02), λ_{max} 242 mμ (ε 15,728), ν_{max} 3565 cm.$^{-1}$ (hydroxyl), 1695 and 1675 cm.$^{-1}$ (20- and 3-ketones), and 1625 cm.$^{-1}$ (C=C of the conjugated carbonyl).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.5): C, 76.32; H, 9.15. Found: C, 76.46; H, 9.25.

2α-Hydroxy-4-androstene-3,17-dione (X).—Controlled hydrolysis of the 2α-acetate (VII, 285 mg.) by the above-described procedure gave 2α-hydroxy-4-androstene-3,17-dione (X), crystallized from acetone–petroleum ether, m.p. 160–161°, $[\alpha]_D$ +204° (*c* 1.01), λ_{max} 240 mμ (ε 15,266), ν_{max} 3430 cm.$^{-1}$ (hydroxyl), 1738 cm.$^{-1}$ (five-membered ring ketone), 1665 cm.$^{-1}$ (conjugated carbonyl), and 1600 cm.$^{-1}$ (C=C of the conjugated carbonyl).[14]

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.4): C, 75.46; H, 8.67. Found: C, 74.77; H, 8.33

2β-Hydroxy-4-androstene-3,17-dione (IX).—Similar hydrolysis of the 2β-acetate (VIII, 533 mg.) afforded 2β-hydroxy-4-androstene-3,17-dione (IX), which crystallized from acetone–petroleum ether, m.p. 144–147°, $[\alpha]_D$ −32° (*c* 0.99), λ_{max} 242 mμ (ε 14,830), ν_{max} 3480 cm.$^{-1}$ (hydroxyl), 1735 cm.$^{-1}$ (five-membered ring ketone), 1675 cm.$^{-1}$ (conjugated carbonyl), and 1610 cm.$^{-1}$ (C=C of the conjugated carbonyl) (lit.,[13] m.p. 143–145°, $[\alpha]_D$ −36.8°).

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.4): C, 75.46; H, 8.67. Found: C, 74.75; H, 8.60.

(13) R. M. Dodson, A. H. Goldkamp, and R. O. Muir, *J. Am. Chem. Soc.*, **79**, 3921 (1957); **82**, 4026 (1960).

(14) Compound X has been described as "known" by several authors.[8,11] However, a thorough search of the literature indicated that the physical constants of this compound have never been described. Therefore, this note appears to be the first to list the physical constants for 2α-hydroxy-4-androstene-3,17-dione (X).

The Synthesis of Some Quaternary Aminophosphonium Salts Containing Siloxyl, Alkenyl, and Arylalkyl Groups

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We have previously reported that *t*-butylaminodiphenylphosphine reacts with benzyl chloride and with bis(chloroethyl) ether to produce quaternary aminophosphonium chlorides.[1] We now have extended this procedure to include the reactions of 1,4-dibromobutene-2, bis(bromomethyl)tetramethyldisiloxane, *p*-fluorobenzyl chloride, and 9,10-bis(chloromethyl)anthracene with *t*-butylaminodiphenylphosphine to produce the corresponding *t*-butylaminophosphonium salts. Further, we have converted *P*-(9,10-anthracenedimethyl)-bis[*t*-butylaminodiphenylphosphonium chloride] to the corresponding hexafluorophosphate and picrate. *t*-Butylaminobenzyldiphenylphosphonium chloride was converted to the hexafluorophosphate, picrate, and borohydride. *P*-(Hexamethyldisiloxane)bis[(*t*-butylamino)diphenylphosphonium bromide], which was isolated only in the crude state, was characterized by conversion to the picrate. During the course of these experiments it was found that *t*-butylaminodiphenylphosphine reacts with ethanolic solutions of mercuric chloride and silver nitrate, respectively, to give the compounds $t\text{-}C_4H_9NHP(C_6H_5)_2 \cdot HgCl_2$ and $t\text{-}C_4H_9NHP(C_6H_5)_2 \cdot AgNO_3$.

Experimental[2]

Materials.—*t*-Butylaminodiphenylphosphine was prepared by the previously reported procedure.[3] The previously reported procedure[1] for the synthesis of *t*-butylaminobenzyldiphenylphosphonium chloride was modified by using toluene instead of benzene as solvent and by reducing the reflux time to 10 hr. By this means the yield was improved to 97%. 9,10-Chloromethylanthracene was prepared by the method of Miller, Amidon, and Tawney.[4] *p*-Fluorobenzyl chloride was obtained from Beacon Chemical Industries, Inc. Potassium borohydride was obtained from Callery Chemical Company. Bis(bromomethyl)tetramethyldisiloxane and 1,4-dibromobutene-2 were purchased from Peninsular ChemResearch, Inc. All compounds obtained from commercial sources were used as received.

Reaction of *t*-Butylaminodiphenylphosphine with RCH_2X Compounds.—The reaction of *t*-butylaminodiphenylphosphine with 9,10-chloromethylanthracene is described to illustrate the procedure used. A mixture of 5.2 g. (0.02 mole) of *t*-butylaminodiphenylphosphine and 2.8 g. (0.01 mole) of 9,10-bis(chloromethyl)anthracene in 35 ml. of dimethylformamide was stirred at reflux for 5 hr. The reaction mixture was cooled and then filtered. The yellow micro-crystalline solid was thoroughly washed with benzene and ethyl ether, and dried. The product weighed 6.5 g. (82% yield) and melted with decomposition at 279°.

This general procedure also was used for the preparation of *P*-(*p*-fluorobenzyl)(*t*-butylamino)diphenylphosphonium chloride, *P*-(1,4-butene-2)bis[(*t*-butylamino)diphenylphosphonium bromide], and *P*-(hexamethyldisiloxane)bis[(*t*-butylamino)di-

(1) H. H. Sisler and N. L. Smith, *J. Org. Chem.*, **26**, 4733 (1961).

(2) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points and boiling points were uncorrected.

(3) H. H. Sisler and N. L. Smith, *J. Org. Chem.*, **26**, 611 (1961).

(4) M. W. Miller, R. W. Amidon, and P. O. Tawney, *J. Am. Chem. Soc.*, **77**, 2845 (1955). See also A. E. Kretov and M. R. Rovenskii, *J. Gen. Chem. USSR*, (Eng. Transl.), **30**, 667 (1960), for modifications.

TABLE I

PRODUCTS OF *t*-BUTYLAMINODIPHENYLPHOSPHINE REACTIONS AND THEIR DERIVATIVES

Compound	Yield, %	M.p., °C	C% Calcd. Found	H% Calcd. Found	N% Calcd. Found	P% Calcd. Found	X% Calcd. Found
(I) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_6H_5]^+[BH_4]^-$	97	167° dec.)	76.04 76.06	8.60 8.43	3.86 3.85	8.53 8.38	B% 2.98 3.18
(II) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_6H_5]^+[PF_6]^-$		139–140°	55.98 55.93	5.52 5.56	2.84 2.83		
(III) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_6H_5]^+[OC_6H_2(NO_2)_3]^-$		104° (dec.)	60.52 59.93	4.90 5.06	9.74 9.51		
(IV) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_6H_4F]^+[Cl]^-$	41	225° (dec.)	68.73 68.41	6.52 6.76	3.49 3.69	7.71 7.67	
(V) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2CH{=}CHCH_2P(C_6H_5)_2\text{-}t\text{-}C_4H_9]^{++}2Br^-$	54	129° (dec.)	59.35 59.05	6.36 6.55			Br% 21.94 21.50
(VI) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_{14}H_8CH_2P(C_6H_5)_2\text{-}t\text{-}C_4H_9]^{++}2Cl^-$	82	279° (dec.)	72.99 72.75	6.64 6.53	3.40 3.57		
(VII) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_{14}H_8CH_2P(C_6H_5)_2\text{-}t\text{-}C_4H_9]^{++}2PF_6^-$		259° (dec.)	57.14 57.37	5.20 5.34	2.78 2.62		
(VIII) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2C_{14}H_8CH_2P(C_6H_5)_2\text{-}t\text{-}C_4H_9]^{++}2OC_6H_2(NO_2)_3^-$		240° (dec.)	61.03 60.90	4.69 4.84	9.65 9.35		
(IX) $[t\text{-}C_4H_9NHP(C_6H_5)_2CH_2Si(CH_3)_2OSi(CH_3)_2CH_2P(C_6H_5)_2\text{-}t\text{-}C_4H_9]^{++}2OC_6H_2(NO_2)_3^-$		164° (dec.)	53.09 53.56	5.35 5.27	9.91 10.40	5.48 5.96	
(X) $t\text{-}C_4H_9NHP(C_6H_5)_2\cdot HgCl_2$	98	216° (dec.)					Cl% 13.41 13.28
(XI) $t\text{-}C_4H_9NHP(C_6H_5)_2\cdot AgNO_3$	97	161° (dec.)			6.55 6.26		

phenylphosphonium bromide] except that toluene was used as solvent in the first case and benzene in the others. Also, the reflux period was extended to 14 hr. for the preparation of *P*-(*p*-fluorobenzyl)(*t*-butylamino)diphenylphosphonium chloride.

Preparation of Derivatives. Picrates.—The reaction of *P*-benzyl(*t*-butylamino)diphenylphosphonium chloride with picric acid is described to illustrate the procedure used in the preparation of the aminophosphonium picrates.

An aqueous solution of *P*-benzyl(*t*-butylamino)diphenylphosphonium chloride was added dropwise with stirring to an ethanolic solution of picric acid. A yellow precipitate formed. Ethanol was added with gentle warming until the product dissolved. On standing, yellow needles of the desired picrate separated.

Hexafluorophosphates.—The reaction of *P*-benzyl(*t*-butylamino)diphenylphosphonium chloride with potassium hexa-

fluorophosphate is described to illustrate the procedure used in the preparation of the aminophosphonium hexafluorophosphates.

An aqueous solution of *P*-benzyl(*t*-butylamino)diphenylphosphonium chloride was added with stirring to an aqueous solution of potassium hexafluorophosphate. A granular precipitate of the aminophosphonium hexafluorophosphate forms immediately. The precipitate was washed with water and dried in air.

Borohydrides.—The preparation of *P*-benzyl(*t*-butylamino)-diphenylphosphonium borohydride is described.

A cold solution of 2.0 g. (5 mmoles) of *P*-benzyl(*t*-butylamino)-diphenylphosphonium chloride was added with stirring to a cold solution of 0.3 g. (5 mmoles) of potassium borohydride in 25 ml. of distilled water. The product crystallized immediately. Stirring was continued for 0.5 hr. after the addition of the aminophosphonium chloride. The resultant product was filtered, and the solids were washed twice with distilled water and dried *in vacuo*. The white powder thus obtained melted with decomposition at 167° and weighed 2.0 g. (quantitative yield).

The product hydrolyzed to benzyldiphenylphosphine oxide (m.p. 191–192°) in 95% ethanol.

Physical and Analytical Data.—The physical properties, analytical data, and yields for the various syntheses are summarized in Table I.

Characteristic infrared bands, other than those already reported,[1] which were useful in identifying the various aminophosphonium salts are listed in Table II.

TABLE II. INFRARED DATA

I	2210 (w)	BH_4^-
II[5]	840 (s)	PF_6^-
V	1630 (m)	—C=C—
VI	850 (s)	$—C_6H_4—$
VII	840 (s)	PF_6^-
IX	1070 (w)	—Si—O—Si—

Discussion

These results suggest that the method for producing various substituted aminophosphonium salts by the *P*-alkylation of the appropriate substituted aminophosphine has a wide range of application. Furthermore, the ready conversion of various substituted aminophosphonium halides to the corresponding salts with other amines has been demonstrated. Finally, in view of the established fact that substituted aminophosphonium halides undergo hydrolysis to the corresponding substituted phosphine oxides,[6] the ready synthesis of a variety of substituted aminophosphonium halides suggests an interesting new path to complex tertiary phosphine oxides.

Acknowledgment.—It is a pleasure to express our thanks to Dr. Darel Straub for his interest and helpful suggestions. The work reported by this communication was supported in large part by W. R. Grace and Company through a contract with the University of Florida.

(5) K. Bubler and W. Bues, *Z. anorg allgem. Chem.*, **308**, 62 (1961).
(6) H. H. Sisler, H. Ahuja, R. Drago, and N. L. Smith, *J. Am. Chem. Soc.*, **81**, 2982 (1959).

The Stereochemistry of the Pulegenic Acids

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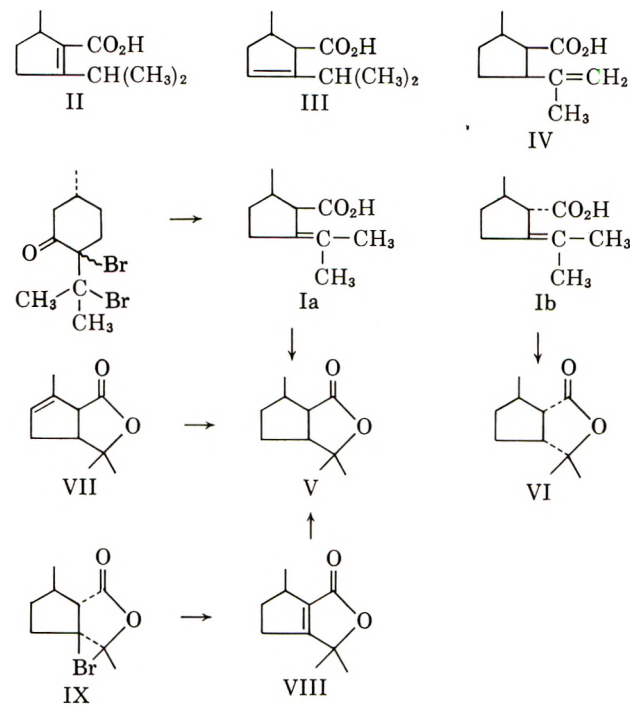
The action of alkali on pulegone dibromide is known to afford pulegenic acid, 5-isopropylidene-2-methyl-1-cyclopentanecarboxylic acid (I).[1–5] The close structural relationship between pulegenic acid and various naturally occurring alkaloids and terpene lactones suggest its use as an intermediate in the elaboration of these natural products. Consequently, we have reexamined the formation of pulegenic acid from pulegone dibromide and have found that a mixture of *cis*-Ia and *trans*-Ib is produced with aqueous potassium hydroxide, where *trans*-Ib is the predominant product when sodium methoxide is employed.

The formulation of the pulegenic acids as Ia and Ib was supported by their spectral properties. The acids showed end adsorption only in the ultraviolet and did not exhibit n.m.r. signals characteristics of vinyl protons. These observations rule out the presence of compounds II, III, and IV.



Attempts to separate acids Ia and Ib met with no success. However, the action of dilute hydrochloric acid on the acids afforded the lactones V, m.p. 48–49°, and VI, m.p. 19°, which were readily separated by vapor phase chromatography. The pulegenic acid prepared by the use of aqueous potassium hydroxide gave a lactone mixture comprised of 60% V and 40% VI, whereas the acid obtained with sodium methoxide afforded 8% V and 92% VI. The formation of identical ratios (60/40 and 8/92) of *cis*- and *trans*-2-hydroxymethyl - 3 - isopropylidene - 1 - methylcyclopentane[6] by lithium aluminum hydride reduction of the acids ensured that epimerization had not occurred during their lactonization.

(1) (a) O. Wallach, *Ann.* **289**, 349 (1895); (b) **300**, 259 (1898); (c) **327**, 125 (1903); (d) **392**, 49 (1912).
(2) O. Wallach, *ibid.*, **414**, 233 (1918).
(3) L. Bouveault and L. Tetry, *Bull. soc. chim. France*, [3] **27**, 307 (1902).
(4) H. Rupe and J. Burgin, *Ber.*, **43**, 1228 (1910).
(5) H. Rupe and K. Schafer, *Helv. Chim. Acta*, **11**, 463 (1928).
(6) J. Wolinsky, B. Chollar, and M. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962).

The stereochemistry assigned to the lactones V and VI and their parent pulegenic acids was suggested by the formation of lactone V, m.p. 48–49°, on catalytic hydrogenation of carvenolide (VII)[7] and lactone VIII, obtained by dehydrobromination of the bromolactone IX. Hydrogen addition should occur stereospecifically from the least hindered side of VII and VIII; this leads to the conclusion that the lactone m.p. 48–49° has a *cis–cis* configuration as depicted by V. The lactone m.p. 19°, on the assumption it possesses a thermodynamically stable *cis* ring-fusion, is formulated as *cis–trans* VI.

The course of the Favorskiĭ rearrangement reflects the likelihood that pulegone dibromide is a mixture of *cis* and *trans* isomers. Stereospecific rearrangement[8] with aqueous potassium hydroxide affords a kinetically controlled mixture of *cis*-Ia and *trans*-Ib. With sodium methoxide, on the other hand, methyl esters are produced initially and are subject to epimerization; the more thermodynamically stable *trans* ester results and is converted to *trans*-Ib during the reaction work-up.

Experimental[9]

***trans*-Pulegenic Acid-Ib.**—To a stirred and cooled solution of 102 g. (0.67 mole) of (+)-pulegone (n^{26}D 1.4821, 95% by v.p.c.) in glacial acetic acid was added dropwise 100 g. (0.626 mole) of bromine. After stirring for 30 min. the solution was poured onto crushed ice and the resulting oily dibromide was washed with water. The combined water washings were extracted with 35–37° petroleum ether. The petroleum ether was added to the dibromide and the resulting solution was washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Attempts to purify the dibromide led to rapid darkening and decomposition.

The dried petroleum ether solution obtained above was added dropwise to a heated and stirred solution of 105 g. of sodium methoxide in 500 ml. of methanol. The petroleum ether was distilled from the reaction as the addition proceeded. After the addition was completed and all the hydrocarbon had been distilled, the solution was kept at reflux for 2 hr. Water, 300 ml., containing 20 g. of potassium hydroxide was added and the solution was heated to reflux for 3 hr. and then steam distilled to remove neutral by-products. The cooled distilland was extracted with ether to remove polymeric products and then acidified with dilute sulfuric acid. The resulting mixture was extracted with ether. The ether solution was dried and distilled to give 66.0 g. (63%) of Ib, b.p. 105–109° (1 mm.) [lit.[5] b.p. 144–150° (11 mm.)], n^{25}D 1.4797, ϵ_{220} 1,566; n.m.r. 60, 66 (CH_3—CH—), 98 [$(CH_3)_2$C=C)], 130, 140 (—CH_2—), 170, 175 (—CH—), and 696 c.p.s. (CO_2H).

***cis*- and *trans*-Pulegenic Acids, Ia and Ib.**—Pulegone dibromide was prepared as described above except care was not taken to dry the product. The crude dibromide, from 70 g. of (+)-pulegone, was added to a heated and stirred solution of 130 g. of potassium hydroxide in 2 l. of water. The undissolved organic material floated to the top of the solution after 5 hr. After cooling and extracting with ether, the alkaline solution was acidified and worked up as described above to give 32.7 g. of Ia and Ib, b.p. 97–108° (0.5–0.7 mm.), n^{25}D 1.4767, ϵ_{220} 1,740; n.m.r. identical with that of Ib except for additional signals at 204 c.p.s. (—CH—) and a shift of the carboxyl proton to 624 c.p.s.

***cis–trans*-Lactone VI.**—*trans*-Pulegenic acid, 27 g., was heated at reflux for 2 hr. with 200 ml. of 4:1 aqueous hydrochloric acid. The mixture was extracted with ether and the ether solution was washed free of unchanged acid with sodium bicarbonate solution. The ether solution was dried and distilled to give 19.4 g. (71%) of lactone, b.p., 74–76° (0.5 mm.). Vapor phase chromatography of this product indicated the presence of 8% of the *cis–cis*-lactone V. A sample of VI isolated by v.p.c. showed m.p. 15–19°, ν_{max} 5.70 μ, $[\alpha]^{31}$D = 0, and n.m.r. 65, 71 (CH_3—CH—), 81 (CH_3—C—CH_3); and 98.4, 104.6, 145.7 and 153.4 c.p.s.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.71; H, 10.02.

***cis–cis*-Lactone V. A. From *cis*- and *trans*-Pulegenic Acids.**—The pulegenic acids obtained by rearrangement of pulegone dibromide with aqueous alkali were heated with 4:1 hydrochloric acid as described above to give a liquid b.p. 82–84° (2 mm.). Repeated recrystallization from petroleum ether at −78° gave a solid m.p. 30–32° which was shown to be a mixture of V and VI. Analysis of the original product by v.p.c. indicated the presence of 60% V and 40% VI. *cis–cis*-V isolated by v.p.c. showed m.p. 47–48° $[\alpha]$D −75.8°, ν_{max} 5.72 μ (lit.,[1d] m.p. 50–51°, $[\alpha]$D −56.85°).

B. From the Unsaturated Lactone VIII.—To a solution of 0.99 g. of *cis*-Ia and *trans*-Ib in carbon tetrachloride was added 1.28 g. of bromine. The resulting solution was washed with water and sodium carbonate solution and the carbon tetrachloride was removed. The residue was crystallized repeatedly from petroleum ether at −78° and distilled evaporatively to give an oil, ν_{max} 5.65 μ, whose n.m.r. spectrum indicated the presence of a mixture of stereoisomers.

Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.59; H, 6.12. Found: C, 48.75; H, 5.87.

Addition of bromine to *trans*-Ib afforded a crystalline bromolactone, m.p. 30–31°; n.m.r., 77, 83 (CH_3—CH—), 87.5, 97.5 ($(CH_3)_2$C), 123, 169, and 171 c.p.s.

The mixture of stereoisomeric bromolactones obtained above was heated for 4 hr. with triethylamine in benzene. The triethylamine hydrobromide was removed and the solution was washed with water and dilute hydrochloric acid. The solvent was removed and the residue recrystallized from petroleum ether at −78° to yield a white solid, m.p. 39–39.5°. Sublimation *in vacuo* raised the melting point of VIII to 40.5–41.5° (lit.,[1b] m.p. 44–45°). The lactone VIII displayed λ_{max} 222 mμ, ϵ 9,170, ν_{max} 5.72 μ, and n.m.r. signals at 68, 74 (CH_3—CH—), 86.6 ($(CH_3)_2$C), 149.6, 152.2, and 170.6 c.p.s.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.45.

A solution of the lactone VIII in ethyl acetate was hydrogenated using platinum oxide as a catalyst. After removing the catalyst and solvent, the residue was recrystallized from petroleum ether to give a white solid, m.p. 48.5°, $[\alpha]$D −77.8°, whose infrared spectrum was identical with that of the lactone V.

C. From Carvenolide VII.—Carvenolide (VII) was prepared from *d*-carvone according to the procedure described by Wallach[7] and showed m.p. 41°, $[\alpha]$D −183°, end absorption only in the ultraviolet, ϵ_{220} 1,000, ν_{max} 5.66 μ, and a n.m.r. spectrum, 78.8, 85.4 ($(CH_3)_2$C), 105 (CH_3—C=C—), 142 (—CH_2—), an octet centered at 187 (R_2CH—), 196.9, 207 (CO—CH—C=C), and 302 c.p.s. (CH=C—), consistent with the assigned structure VII. Hydrogenation of carvenolide in ethyl acetate using platinum oxide as a catalyst afforded a white solid, m.p. 48–49°, undepressed when mixed with lactone V, $[\alpha]$D −48.1° (*c* 3.12, EtOH), whose infrared spectrum was identical with that of lactone V.

(7) O. Wallach, *Ann.*, **305**, 245 (1899).

(8) For a recent comprehensive review of the Favorskiĭ rearrangement see A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

(9) All boiling and melting points are uncorrected. Nuclear magnetic resonance spectra were measured at 60 Mc. by W. E. Baitinger with the Varian Associates V-4300-B and A-60 spectrophotometers. Chemical shifts are given with reference to tetramethylsilane. Vapor phase chromatographic separations and analyses were conducted at 185° with a 20% Carbowax 20M on firebrick column, with helium as the carrier gas. The compositions of the mixtures were determined by measuring the ratios of the individual peak areas, *cf.* M. Dimbat, P. E. Porter, and F. H. Stross, *Anal. Chem.*, **28**, 290 (1956). The microanalyses were performed by Dr. C. S. Yeh and associates.

The Lead Tetraacetate Oxidation of Isoborneol

RICHARD E. PARTCH[1]

Department of Chemistry, University of Rochester, Rochester, New York

Received July 9, 1962

A requirement for large quantities of π-camphether (III)[2-4] prompted a study of the oxidation of isoborneol (I) utilizing a method recently investigated by Jeger.[5]

Isoborneol (I), on treatment with lead tetraacetate under vigorous reaction conditions (80°), affords the cleavage products α-campholenicaldehyde (IV) and iso-α-campholenic aldehyde (V) in good yield (Table I). Mild conditions (25°) lead only to camphor (VI) and camphene (VII) (Table II).

TABLE I

GAS–LIQUID PARTITION CHROMATOGRAPHY DATA[a]—SOME PRODUCTS OF VIGOROUS OXIDATION

Compound	Retention time, min.	Relative amount
VII	6.4	1
Acetic acid	11.7	3
π-Camphether (III)[b]	13.6	..?
IV	20.0	12
V	22.1	8
VI	24.5	1

[a] See ref. 9. [b] See ref. 4.

TABLE II

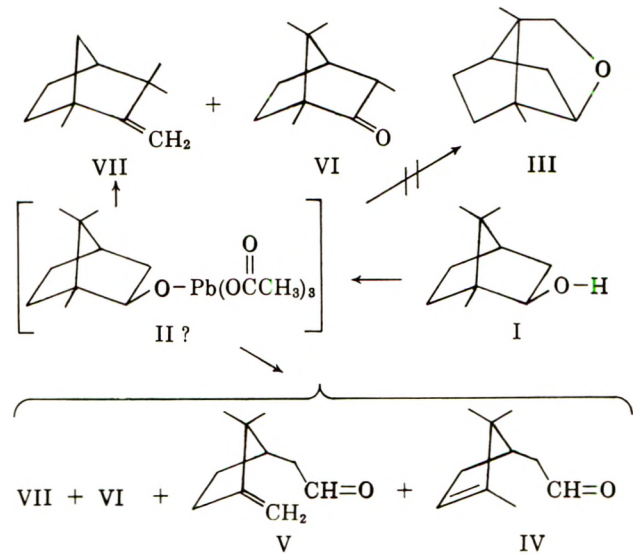
GAS–LIQUID PARTITION CHROMATOGRAPHY DATA[a]—SOME PRODUCTS OF MILD OXIDATION

Compound	Retention time, min.	Relative amount
VII	6.5	1
Acetic acid	11.7	2
VI	25.2	4
I	35.0	8

[a] See ref. 9.

α-Campholenicaldehyde (IV), the major product of the vigorous reaction, was identified by n.m.r. and infrared spectroscopy and by elemental analysis as well as by comparison of derivatives. Srinivasan[6,7] obtained this substance by photolyzing camphor in a variety of solvents. Mosher[8] reported that isoborneol, on treatment with chromic acid, yields only 4% of the related compounds 3-hydroxy-2,2,3-trimethylcyclopentaneacetic acid and α-campholenic acid.

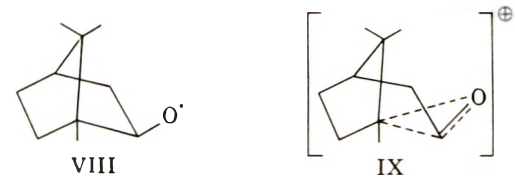
The previously unreported iso-α-campholenicaldehyde (V) was isolated by gas chromatography. Its structure was assigned on the basis of its n.m.r. and infrared spectra and its elemental analysis.



When chromatographed at 145°, iso-α-campholenicaldehyde (V) undergoes some isomerization to α-campholenicaldehyde (IV).[9] The per cent conversion is low (5% increases in IV), however, and little change in concentration appears to occur during isolation. Similar isomerizations are numerous.[10-12]

Small amounts of camphor and camphene from both the vigorous and mild oxidations of isoborneol were identified by comparison of retention times with authentic samples, and, in the case of camphor, by formation of the 2,4-dinitrophenylhydrazone derivative. Camphene (VII) presumably arises from the facile Wagner-Meerwein rearrangement of isoborneol. Camphor and camphene are unaffected by oxidation; isoborneol, under the conditions of vigorous oxidation but without lead tetraacetate, affords only minute amounts of camphene.

On the basis of previous studies of lead tetraacetate oxidations,[13,14] the assumed lead ester intermediate (II) may decompose through structures VIII and/or IX.



(1) DuPont Teaching Fellow, University of Rochester, 1961–1962. Present address, Department of Chemistry, New Mexico Highlands University, Las Vegas, N. M.

(2) 1,7-Dimethyl-9-oxatricyclo[2.2.1.2^{2,7}]nonane.

(3) Previously prepared by F. Semmler and K. Bartelt, *Chem. Ber.*, 4165 (1907).

(4) Recently prepared by Mr. Roger Napier, Department of Chemistry, University of Rochester, Rochester, N. Y.

(5) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959); B. Kamber, G. Cainelli, D. Arigoni, and O. Jeger, *ibid.*, **43**, 347 (1960).

(6) R. Srinivasan, *J. Am. Chem. Soc.*, **81**, 2604 (1959).

(7) Photolysis experiments by the author have shown that irradiation of isoborneol in cyclohexane (under nitrogen) affords low yields of camphor. The experiments were conducted in a quartz cell at 50° with both a Hanovia lamp (mercury, medium pressure, 100 w.) and a hydrogen lamp. The hydrogen lamp experiment gave rise to several other unidentified products.

(8) W. A. Mosher and E. O. Langerak, *J. Am. Chem. Soc.*, **73**, 1302 (1951).

(9) Use was made of a 15-ft. reoplex on Chromosorb column at 145° and a helium flow rate of 110 cc. per minute. A Wilkens "Aerograph" gas chromatograph with a Brown recorder was the instrument employed for separations.

(10) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 520 (1950).

(11) A. C. Cope and E. E. Schweizer, *J. Am. Chem. Soc.*, **81**, 4577 (1959).

(12) A. C. Cope, P. T. Moore, and W. R. Moore, *ibid.*, **81**, 3153 (1959).

(13) G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961).

(14) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 536.

It is not possible to decide unequivocally whether homolytic or heterolytic processes are involved.[15] Camphor is *not* an intermediate as it was unchanged in a control experiment.

Finally, camphor (VI) and iso-α-campholenicaldehyde (V), but not α-campholenicaldehyde (VI) may be formed by an intramolecular concerted decomposition of the lead ester II. Peterson models (using tetrahedral carbon for the lead atom) indicate that little strain is present in transition states leading to such products.

Experimental

Oxidation under Vigorous Conditions.—A mixture of 9.0 g. (0.09 mole) anhydrous calcium carbonate in 200 ml. of dry benzene was placed in a three-necked flask equipped with a condenser, stirrer, and drying tube. After heating the stirred mixture to 40°, 20.0 g. (0.045 mole) of freshly prepared, dry lead tetraacetate was added. The heterogeneous mixture was brought to reflux and a solution of 4.31 g. (0.028 mole) isoborneol in 50 ml. of benzene was added in one batch. Stirring and refluxing was continued for 2 hr. After cooling, filtration gave a pale yellow solution which was washed with 15% potassium iodide, 10% sodium thiosulfate, and water. Excess lead tetraacetate was detected. The organic layer was dried over anhydrous magnesium sulfate and reduced in volume under vacuum to yield 4.2 g. of a pale yellow oil.

Chromatography on neutral alumina (Woelm, activity I) achieved only partial separation of the products.

An attempt to distil part of the crude oil through a 3- in. Vigreux column under nitrogen ended in considerable polymer formation. Only one fraction was obtained; a pale yellow liquid b.p. 80–83° at 14 mm. Infrared analysis of the distillate indicated the presence of aldehyde–olefin functional groups. Gas chromatography showed this fraction to be composed of more than one component.

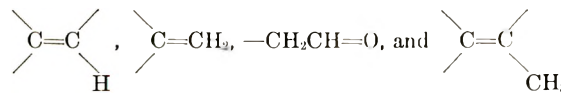
Gas chromatography[9] on the crude oil indicated the presence of not less than ten components. Only five appeared to be in high enough concentration to allow immediate identification.

The high concentrations of α-campholenicaldehyde (IV), iso-α-campholenicaldehyde (V) and acetic acid allowed collection and identification. Component IV (50% yield based on relative gas chromatographic peak areas) showed distinct aldehyde (2670 and 1718 cm.$^{-1}$) and trisubstituted alkene (1649 and 795 cm.$^{-1}$) functional group absorptions in the infrared. The semicarbazone of IV, m.p. 141–142.5° (CH_3OH), was comparable with an authentic sample (m.p. 142–142.5°)[6]; m.m.p. 141–143°.

Component V (30% yield) showed the same aldehyde absorption as IV, however, the alkene absorption had shifted to 875 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O$ (V): C, 78.89; H, 10.59. Found: C, 78.91; H, 10.67.

Further proof of the structures IV and V was obtained by n.m.r. analysis. The spectrum was taken on a mixture of IV and V in carbon tetrachloride. The proton magnetic resonance signals at 0.35, 4.85, 5.31, 7.66, and 8.40 τ indicate the presence of the functional groups —CH=O,



respectively.

Oxidation under Mild Conditions.—The procedure in this experiment was identical to that described for the vigorous oxidation except the mixture was stirred at room temperature (instead of reflux) for 20 hr. Work-up of the product gave a yellow oil which showed signs of partial crystallization. Benzene was added until the solid dissolved (1 ml.) and the resulting solution was submitted to gas chromatographic analysis. Camphor (VI), camphene (VII), and isoborneol were the only products. The amount of camphene formed was about the same as in the vigorous oxidation. Camphor, however, had become a major product (Table II).

Acknowledgment.—The author is grateful to Drs. R. L. Autrey and M. Gates for helpful comments. Acknowledgment is also given to Mr. Roger Napier for his assistance.

(15) Compare, P. T. Lansbury, V. A. Pattison, and J. W. Diehl, *Chem. Ind.* (London), **14**, 653 (1962).

Communications TO THE EDITOR

Intermolecular Group Transfer During Beckmann Rearrangement. VI

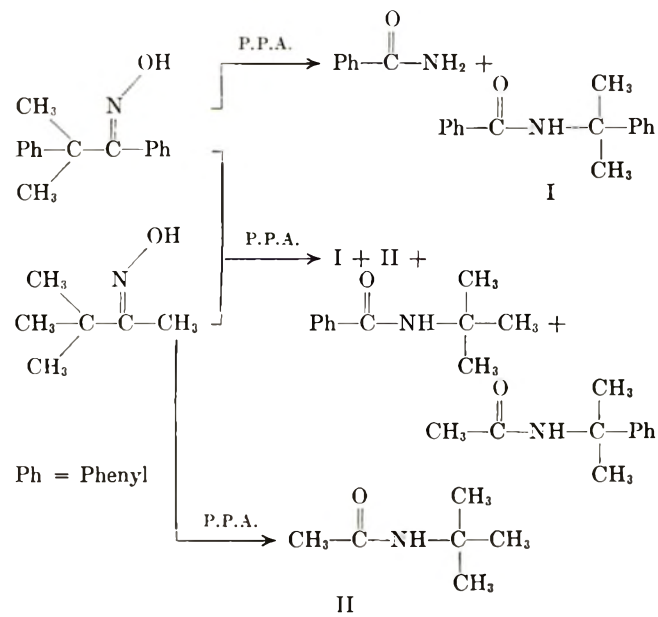
Sir:

It is a basic postulate of carbon–nitrogen rearrangement theory that group migration is an intramolecular transfer process in which the configuration of the migrating α-carbon remains unchanged. Previous work[1] has established the validity of this conclusion for a variety of rearrangements to electron-deficient nitrogen.[2] Recently, we reported the fact that certain oximes of the α-trisubstituted type[3,4] do not follow this rearrangement route, but apparently undergo an initial fragmentation to an intermediate nitrile and a carbonium ion. These two fragments then recombine in a Ritter reaction[5] to form an amide (in the case of a cyclic ketoxime, fragmentation would yield an unsaturated nitrile[6] which on recombination would yield a lactam).

We wish to report the first observed intermolecular transfer of groups during a molecular rearrangement of the carbon–nitrogen type. This observation clearly demonstrates that an alternate mechanism of fragmentation–recombination plays an important role in hindered ketoxime rearrangements.

On heating a mixture of 2-phenylisopropylphenyl ketoxime and pinacolone oxime at 130° for 10 minutes in polyphosphoric acid, a mixture of amides was obtained. From the amide mixture, four secondary amides could be characterized after separation on an alumina column: N-*t*-butylacetamide (24.6%), m.p. 97–98°; N-*t*-butylbenzamide (9.2%), m.p. 134.5–135°; N-(2-phenylisopropyl) acetamide (6.3%), m.p. 50–52° and N-(2-phenylisopropyl) benzamide (21.0%), m.p. 161–162°. All samples were unequivocally identified by mixed melting point determination and comparison of their infrared spectra with those of authentic samples (prepared from the appropriate amine and acid chloride). Each of the respective oximes on rearrangement at conditions identical to those used in the crossover experiment yielded a single secondary amide product.[7] In the case of 2-phenylisopropylphenyl ketoxime, benzamide (63%) was the primary rearrangement product in polyphosphoric acid due to fragmentation. We have observed in analogous cases that the recombination step (the Ritter reaction) is quite poor in disubstituted benzyl ketoxime rearrangements.

The possibility remained that amide exchange during this process was responsible for the observed mixed amides. Heating N-*t*-butylacetamide and N-(2-phenylisopropyl) benzamide under the conditions of the rearrangement studies resulted, after chromatographic isolation, in almost quantitative recovery of each amide. No other contaminating amides possible from an exchange reaction could be detected.



These data clearly demonstrate the existence of a fragmentation–recombination mechanism for the Beckmann rearrangement of α-trisubstituted ketoximes and for other oximino compounds in which a particularly stable carbonium ion is possible in the intermediate stage of the rearrangement process. This study raises the interesting possibility of partial or complete group racemization during Beckmann[8] and possibly Schmidt reactions. We hope to report this and the full details of our present report in the near future.

Acknowledgment.—This investigation was supported by grant #B-3628 from the Department of Health, Education, and Welfare, Public Health Service.

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RECEIVED SEPTEMBER 25, 1962

(1) (a) For summary see: G. W. Wheland in "Advanced Organic Chemistry," 3rd ed., John Wiley and Sons, Inc., New York, N.Y., 1960, pp. 597–610; (b) For review of the Beckmann rearrangement see: L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(2) (a) J. Kenyon and D. P. Young, *J. Chem. Soc.*, **263** (1941); (b) A. Campbell and J. Kenyon, *ibid.*, 25 (1946).

(3) Abstracts of Papers, Metropolitan Regional Meeting, American Chemical Society, New York, N. Y., January 22, 1962.

(4) It should be noted that an almost simultaneous disclosure was made shortly thereafter by R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).

(5) J. J. Ritter and P. P. Minieri, *ibid.*, **70**, 4045 (1948).

(6) For typical examples see: R. T. Conley and R. J. Lange, *J. Org. Chem.*, **28**, 210 (1963), paper V of this series.

(7) This is consistent with the observation of N. H. P. Smith, *J. Chem. Soc.*, 4209 (1961), in which oxime isomerization was not observed in polyphosphoric acid.

(8) R. K. Hill and O. T. Chortyk, ref. 4, have shown inversion of configuration is possible in the Beckmann rearrangement. However, the possibility remains in this study that the process could have been a cage reaction.

The Linkage in a Disaccharide from Carboxyl-reduced Heparin

Sir:

The position of the linkage in the disaccharide,[1] tentatively identified as *O*-α-D-glucopyranosyl-(1→4)-

(1) M. L. Wolfrom, J. R. Vercellotti, and D. Horton, *J. Org. Chem.*, **27**, 705 (1962).

2-amino-2-deoxy-α-D-glucopyranose (I) hydrochloride, from a hydrolyzate of partially desulfated, carboxyl-reduced, partially acetylated heparin,[2] has been firmly established. Methylation[3] of *N*-acetylated I (II)[1] (25 mg.) followed by hydrolysis with 2 *N* hydrochloric acid for 3 hr. at 100° and separation of the neutralized hydrolyzate on an Amberlite IR-120 (H^+) ion-exchange column gave a component (3 mg.) by water elution; crystallized from ethanol–ether it had m.p. 83–85° and gave an X-ray powder diffraction pattern identical to that of 2,3,4,6-tetra-*O*-methyl-α-D-glucose. Concentration of a *N* hydrochloric acid eluate of the column gave crystalline 2-amino-2-deoxy-D-glucose HCl (5 mg.) and a sirup which, after *N*-acetylation,[4] crystallized from ethanol–ether to give 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-glucose (III), yield 6 mg., m.p. 232–233°, $[\alpha]^{19}D$ +72 (5 min.) → +37 ± 5° (6 hr., final, H_2O) in agreement with reported constants,[3,5] X-ray powder diffraction data[6]: 10.92 s (2), 8.45 w, 5.58 m (3), 4.38 vs (1), 4.15 w, 3.78 vw, 3.47 vw, 3.07 vw, 2.73 m (3), 2.22 m. A product identical to III was isolated from the *N*-acetylated hydrolyzate of a sample of 92% methylated chitin.[7] Both samples of III were identical by X-ray powder diffraction pattern, and by paper and thin-layer chromatography, with an authentic sample[3] kindly furnished by Professor R. Kuhn. The alditol produced on reduction of II[1] had an $M_{glucitol}$ value of 0.38 on electrophoresis in molybdate buffer,[8] further indicative of a (1→4)-linked disaccharide structure.

Enzymic synthesis of I-HCl ($[\alpha]D$ +147°) and II ($[\alpha]D$ +110°) has been reported,[9] but without elemental analytical data, proof of crystallinity, or rigorous proof of structure.

Acknowledgment.—Support of the National Science Foundation (Grant G13967) is gratefully acknowledged. The heparin used was kindly furnished by the Upjohn Co., Kalamazoo, Michigan.

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RECEIVED SEPTEMBER 20, 1962

(2) M. L. Wolfrom, J. R. Vercellotti, and G. H. S. Thomas, *J. Org. Chem.*, **26**, 2160 (1961).
(3) R. Kuhn and A. Gauhe, *Chem. Ber.*, **95**, 518 (1962).
(4) S. Roseman and J. Ludowieg, *J. Am. Chem. Soc.*, **76**, 301 (1954).
(5) R. W. Jeanloz, *J. Org. Chem.*, **26**, 905 (1961).
(6) Interplanar spacing, Å, CuK_2 radiation. Relative intensities, estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.
(7) M. L. Wolfrom, J. R. Vercellotti, and D. Horton, to be published.
(8) E. J. Bourne, D. H. Hutson, and H. Weigel, *Chem. Ind.* (London), 1047 (1959).
(9) Z. Selinger and M. Schramm, *J. Biol. Chem.*, **236**, 2183 (1961); *cf.* P. Hoffman and K. Meyer, *Federation Proc.*, **21**, 1064 (1062).

A Second Disaccharide from Carboxyl-reduced Heparin

Sir:

The isolation and characterization of three components from the hydrolyzate of partially desulfurated, carboxyl-reduced, partially acetylated heparin[1] has already been described.[1,2] A fourth, minor, component (I–HCl), $R_{glucose}$ 0.27 (solvent A)[3] is the subject of this Communication. It was isolated, in 5% yield, by preparative paper chromatography, from the same hydrolyzate mixture from which the disaccharide *O*-α-D-glucopyranosyl-(1→4)-2-amino-2-deoxy-α-D-glucose (II) hydrochloride ($R_{glucose}$ 0.32, solvent A[3]) had been isolated.[2] The yield of I-HCl could be considerably improved, at the expense of the yield of II, if the heparin derivative was treated with hydrazine for 10 hr. at 90° before hydrolysis.[4] Crystallized from ethanol–water–ether, I-HCl had m.p. 175–181° dec., $[\alpha]^{19}D$ +97 (3 min.) → +54° (1.5 hr., final, *c* 0.55, water), X-ray powder diffraction data[5]: 9.32 w, 7.64 w, 6.05 w, 5.05 vw, 4.82 vw, 4.28 m, 3.89 s (2), 3.46 w, 3.03 m (3,3), 2.79 vs (1), 2.66 m (3,3), 1.96 w, 1.86 w, 1.74 vw, 1.71 vw. The substance gave positive Benedict, ninhydrin, and chloride reactions, was chromatographically homogeneous in solvents A, B, and C,[3] and gave 8% of the color produced by an equimolar amount of 2-amino-2-deoxy-D-glucose in the Elson–Morgan determination.[6]

Anal. Calcd. for $C_{12}H_{24}ClNO_{10}$: N, 3.72. Found: N, 4.09.

N-Acetylation[7] of I-HCl (50 mg.) gave *N*-acetylated I (III), crystallized frm ethanol–ether, yield 35 mg. (70%), m.p. 124–125°, $[\alpha]^{20}D$ +125 (5 min.) → +75 ± 10° (2.5 hr., final, *c* 0.2, H_2O), X-ray powder diffraction data[5]: 8.67 s (2), 4.23 m, 5.99 m, 2.86 vs (1), 2.58 s (3), 2.18 w, 2.06 w. III was Benedict positive, ninhydrin negative, chromatographically homogeneous in solvents A ($R_{glucose}$ 0.47), B, and C,[3] and gave 19% of the color given by an equimolar amount of 2-acetamido-2-deoxy-D-glucose in the Morgan–Elson determination.[8]

Anal. Calcd. for $C_{14}H_{25}O_{11}N \cdot 3H_2O$: C, 38.97; H, 7.19; N, 3.24; H_2O, 12.53; mol. wt., 431. Found: C, 39.16; H, 6.89; N, 3.11; H_2O, 12.98; mol. wt.,[9] 394.

Borohydride reduction of III by the procedure described[2] for *N*-acetylated II gave the alditol (IV) corresponding to III, yield 63%, as a chromatographically homogeneous, non-reducing sirup, $R_{glucose}$ 0.49 (solvent B),[3] $[\alpha]^{19}D$ +55° (*c* 0.42, aq. ethanol), $M_{glucitol}$ 0.33 (molybdate buffer).[10] Hydrolysis of IV with 2 *N* hydrochloric acid for 2 hr. at 100° gave 2-amino-2-deoxy-D-glucose hydrochloride, identified by its X-ray powder diffraction pattern, and a component with the same paper chromatographic properties as D-glucitol. These observations indicate that I is a disaccharide with the unit sequence *O*-(2-amino-2-deoxy-D-glucosyl)→D-glucose. Indications from color re-

(1) M. L. Wolfrom, J. R. Vercellotti, and G. H. S. Thomas, *J. Org. Chem.*, **26**, 2160 (1961).
(2) M. L. Wolfrom, J. R. Vercellotti, and D. Horton, *ibid.*, **27**, 705, (1962); **28**, 278 (1963).
(3) Paper chromatographic data refer to 4:1:5-butanol–ethanol–water (solvent A), 5:5:1:3 pyridine–ethyl acetate–acetic acid–water (solvent B), or 9:2:2 ethyl acetate–acetic acid–water (solvent C).
(4) To be published.
(5) Interplanar spacing, Å, CuK_α radiation. Relative intensities, estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.
(6) L. A. Elson and W. T. J. Morgan, *Biochem. J.*, **27**, 1824 (1933); R. Belcher, A. J. Nutten, and C. M. Sambrook, *Analyst*, **79**, 201 (1954).
(7) S. Roseman and J. Ludowieg, *J. Am. Chem. Soc.*, **76**, 301 (1954).
(8) D. Aminoff, W. T. J. Morgan, and W. M. Watkins, *Biochem. J.*, **51**, 379 (1952).
(9) C. E. Childs, *Anal. Chem.*, **26**, 1963 (1954).
(10) E. J. Bourne, D. H. Hutson, and H. Weigel, *Chem. Ind.* (London) 1047 (1959).

action data,[11] specific rotation of IV, and electrophoretic data[10] would suggest an α-D-(1→4) interglycosidic linkage as the strongest possibility; further studies for unequivocal identification of this linkage are in progress.

Acknowledgment.—Support of the National Science Foundation (Grant G13967) is gratefully acknowledged. The Upjohn Co., Kalamazoo, Michigan, kindly furnished the heparin used.

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RECEIVED SEPTEMBER 20, 1962

(11) A. B. Foster and D. Horton, *Advan. Carbohydrate Chem.*, **34**, 264 (1959).

Solvent Effects in Organometallic Reactions. I

Sir:

While the simple system of reactants metal alkyl–alkyl halide has been most commonly compounded, the variety of reaction paths available to this system has never been fully elucidated. In a study we have initiated to find the effect of conditions (particularly solvent effects) on the course of reactions of alkyllithiums with primary and secondary alkyl chlorides and bromides, interactions recognized include: coupling of the two reagents, β-elimination of the halide to an alkene, and α-elimination to a carbene, which may rearrange to an alkene or react further with the organometallic. We wish to report here still another reaction course, *direct reduction of alkyl halides by lithium alkyls*, a course which is facilitated by non-polar solvents.

A solution of 1-bromoöctane (0.01 mole) and butyllithium (0.015 mole) in hexane was refluxed overnight and washed with aqueous ammonium chloride. Gas chromatographic analysis showed that the products from the alkyl halide consisted of 66% octane, 32% dodecane, and small amounts of two less volatile materials. In a similar manner, butyllithium in refluxing hexane converted bromocyclohexane into cyclohexane (56%), cyclohexene (5%), and coupled product (33%). Other alkyl halides reduced to alkanes by butyllithium include 1- and 2-chloroöctane, 2-bromoöctane, 1-chloroisopentane, 4-chloroheptane, and fluoro- and chlorocyclohexane.

A logical route to this type of result might be through a halogen–metal interchange (1) that would, for example, convert bromoöctane to octyllithium which in work-up would be hydrolyzed (2) to octane.

$$CH_3(CH_2)_6CH_2Br + C_4H_9Li \longrightarrow CH_3(CH_2)_6CH_2Li + C_4H_9Br \quad (1)$$

$$CH_3(CH_2)_6CH_2Li + H_2O \longrightarrow CH_3(CH_2)_6CH_3 + LiOH \quad (2)$$

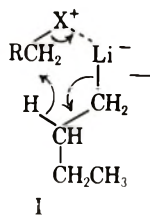
However, this route would require formation of butyl bromide, which is not found. Butene is formed and escapes as a gas during the reaction. From this, one could conceive that during this reaction possibly the butyllithium cracks to lithium hydride (3), which reduces the alkyl halide (4). However, we find that butyllithium alone (or with added lithium chloride) is stable in refluxing hexane, and further, that lithium

$$C_4H_9Li \xrightarrow{\Delta} CH_3CH_2CH{=}CH + LiH \quad (3)$$

$$RX + LiH \longrightarrow RH + LiX \quad (4)$$

hydride in refluxing hexane does not reduce chlorocyclohexane but slowly dehydrohalogenates it.

We conclude that the route of this reaction is direct reduction of the alkyl halide by the lithium alkyl, perhaps through a quasi ring complex (I) like that depicted in (5). The intermediacy of I requires that



$$\longrightarrow RCH_3 + LiX + CH_3CH_2CH{=}CH_2 \quad (5)$$

I

β-hydrogen of the lithium reagent appear in the alkane. We have prepared 2-tritiobutyllithium and reduced chlorocyclohexane with it. Radioactivity from the lithium reagent does appear in the cyclohexane proced.[1]

It is felt that the use of a hydrocarbon solvent, *e.g.*, the absence of polar solvents (such as the commonly used ethers), facilitates complexation of the organometallic by the alkyl halide allowing reduction reaction 5. Our findings on the course of reactions of lithium alkyls with alkyl halides to produce alkenes and carbenes and solvent effects on these reactions will be reported subsequently.

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(1) While our present data are insufficient to calculate satisfactorily the isotope effect in this reaction, our finding that the cyclohexane produced has about the same molar radioactivity as the starting 2-tritiobutyl bromide suggests the possibility of an inverse isotope effect; because of the statistical factor, the cyclohexane should gain only half the organometallic's activity. More data of greater precision are being gathered to measure this isotope effect precisely.