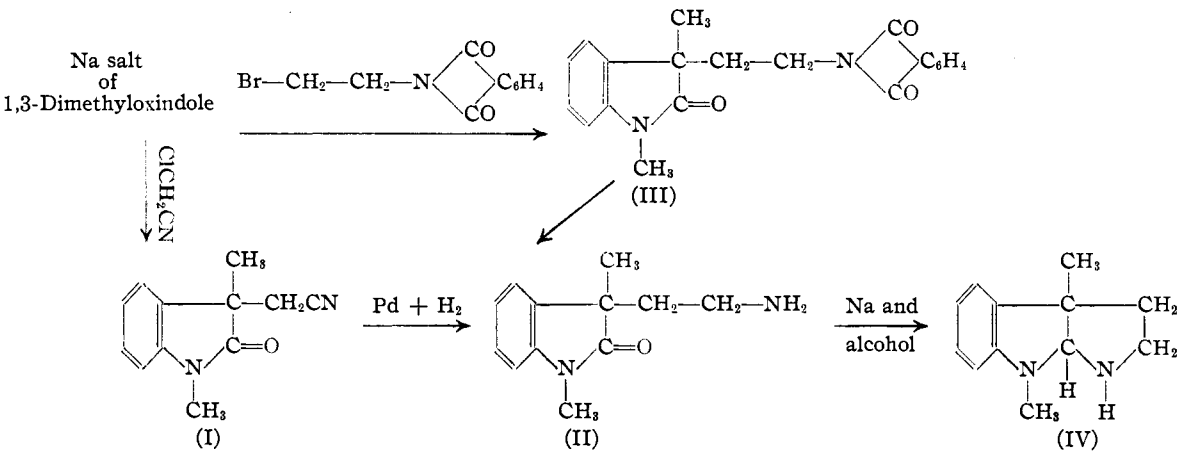
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

Studies in the Indole Series. III. On the Synthesis of Physostigmine

BY PERCY L. JULIAN AND JOSEF PIKL

In a previous communication[1] it was shown that the hydrogen attached to the carbon atom in the 3-position of 1,3-dialkyloxindoles is exceedingly active, enabling smooth alkylation of such oxindoles in the 3-position with alcoholate and the appropriate alkyl halide. Through employment of chloroacetonitrile, the grouping $-CH_2CN$ was introduced into 1,3-dimethyloxindole, and reduction of the nitrile (I) thus obtained with sodium and alcohol yielded a compound thought to be *d,l*-desoxynoreseroline (IV) and containing the basic ring structure assigned to the alkaloid physostigmine (eserine).

This paper records improvements in the earlier synthesis, together with strict proof that the final product is identical in structure with physostigmine, except for the group in the 5-position. Thus the ground work has been laid completely for a remarkably simple synthesis of the alkaloid in question, and new proof of its structure is herewith adduced.



Two phases of our earlier work left room for improvement. The reduction of a nitrile to an amine with sodium and alcohol does not result generally in good yields. Although our yields of the closed ring product were surprisingly good by this method, it was thought that they might be improved by beginning with the pure amine (II) instead of the nitrile (I). This is actually the case. Catalytic reduction of the nitrile yielded in excellent quantity the desired amine (II). The amine was also obtained from 1,3-dimethyloxindole by application of the Gabriel synthesis. For this purpose, the sodium salt of 1,3-dimethyloxindole was treated with β-bromo-ethylphthalimide[2] and the resulting 1,3-dimethyl-3-β-phthalimidoethyloxindole (III) suffered smooth cleavage to the amine (II). The amine on reduction with sodium and alcohol, even with sodium and boiling amyl alcohol, yielded 86% of the theoretical quantity of *d,l*-desoxynoreseroline (IV), and a product purer than that previously obtained.

The amine (II) served not only the above-mentioned purpose, but enabled us to obviate another difficulty, namely, the methylation of *d,l*-desoxynoreseroline (IV) to *d,l*-desoxyeseroline (VII). This methylation is one of the most unpleasant features of any attempted synthesis of physostigmine which proceeds by way of the secondary bases like (IV) and its homolog with the nitrogen of the indole nucleus also secondary.[2,3] From the amine (II) it was easy to secure the benzylidene derivative (V) and this was almost quantitatively methylated by the elegant method of Decker[4] to the 1,3-dimethyl-3-β-methylaminoethyloxindole (VI), which solidified spontaneously on distillation. By a very complicated route, Boyd-Barrett and Robinson[5] arrived at this methylated amine (VI), which they describe as a colorless oil.

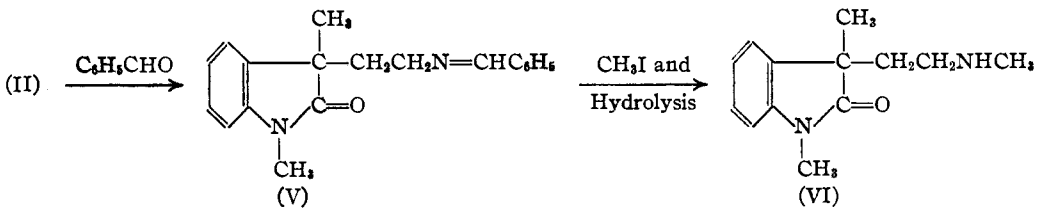
(1) Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).

(2) King, Liguori and Robinson, *J. Chem. Soc.*, 1416 (1934).

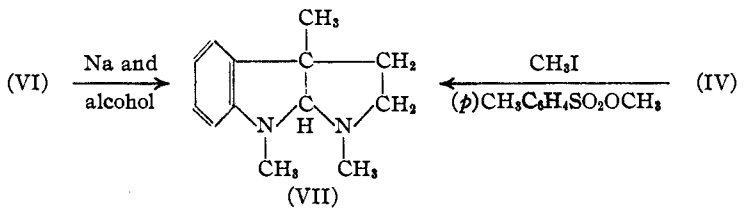
(3) *Cf.* Hoshino and Kobayashi, *Proc. Imp. Acad.* (Tokyo), **10**, 99–102 (1934).

(4) Decker, *Ann.*, **395**, 333 (1912).

(5) Boyd-Barrett and Robinson, *J. Chem. Soc.*, 318 (1932).

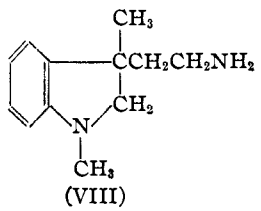


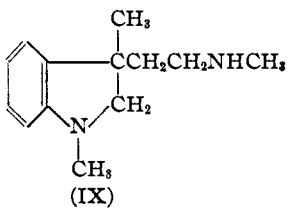
Our methylated amine (VI), like its parent (II), was smoothly reduced by sodium and alcohol in excellent yield to *d,l*-desoxyeseroline (VII), identical with the same product described by us in the earlier communication, and secured by methylation of *d,l*-desoxynoreseroline (IV) with methyl iodide. The compound (VII) prepared in this way was almost pure on first distillation. The little residue remaining proved to be nearly pure unchanged amine (VI) and was recovered as crystalline product. Methylation of desoxy-



noreseroline (IV) with methyl *p*-toluenesulfonate, a procedure employed by Robinson in the 5-ethoxylated series, yielded some of the same substance (VII) but in very unsatisfactory yield.

With the successful outcome of these experiments, and apparently parallel results in the 5-ethoxylated series, we were met by the necessity of proving conclusively the structures of our products (IV) and (VII). The alternative that they represented the dihydroindolyl amines (VIII) and (IX) could not be excluded satisfactorily solely on the basis of analytical figures,



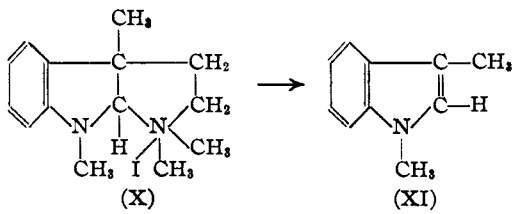


considering that (IV) and (VII) are both liquids, are sensitive compounds difficult to purify for analysis, and differ in their composition from the amines (VIII) and (IX) by a margin which might permit erroneous conclusions from analytical data alone. Moreover, it has been shown that catalytically, as well as with zinc and hydrochloric acid,[6] eserethole is reduced smoothly to the 5-ethoxy derivative of (IX). Whether nascent hydrogen in alkaline medium would effect the same conversion has not been investigated heretofore, and so in preparing *d,l*-eserethole by a method which involves reduction as its last step, this alternative had to be carefully reckoned with. Proof that sodium in alcohol did not reduce our amines (II) and (VI) to the dihydroindolyl derivatives (VIII) and (IX), respectively, is summarized in the paragraphs following.

Our *d,l*-desoxynoreseroline (IV) is a secondary amine. It gives no carbylamine reaction. Repeated examination of it in the Grignard machine confirmed the fact that it gives only one mole of gas and consumes one mole of reagent. Its monobenzoyl derivative[1] in the Grignard machine gives no gas and consumes one mole of reagent. Treatment of (IV) with *p*-toluenesulfone chloride yields the expected sulfone ester, which in absolute ethereal solution gives no reaction with metallic sodium even after twenty-four hours of boiling. That the base does not have the structure, therefore, represented by (VIII) is conclusively demonstrated.

Our *d,l*-desoxyeseroline (VII) gives no gas in the Grignard machine and is therefore a tertiary base. It remains now only to prove that its reactions involving what we have called the basic ring structure of physostigmine, namely, the fused pyrrolidine-dihydroindole complex, run exactly parallel with those of natural eserethole. The methiodide of natural eseroline when heated in vacuum yields physostigmol,[7] the constitution of which was shown by Späth and Brunner[8] and by Stedman[9] to be that of 1,3-dimethyl-5-hydroxyindole. Our *d,l*-desoxyeseroline methiodide (X) behaves in parallel fashion, yielding smoothly desoxyphysostigmol (XI). This reaction seems

(6) Polonovski, *Bull. soc. chim.*, [iv] **23**, 357 (1918); Stedman and Barger, *J. Chem. Soc.*, **127**, 249 (1925).
(7) Straus, *Ann.*, **401**, 350 (1913); **406**, 332 (1914).
(8) Späth and Brunner, *Ber.*, **58**, 518 (1925).
(9) Stedman, *J. Chem. Soc.*, 1373 (1924).



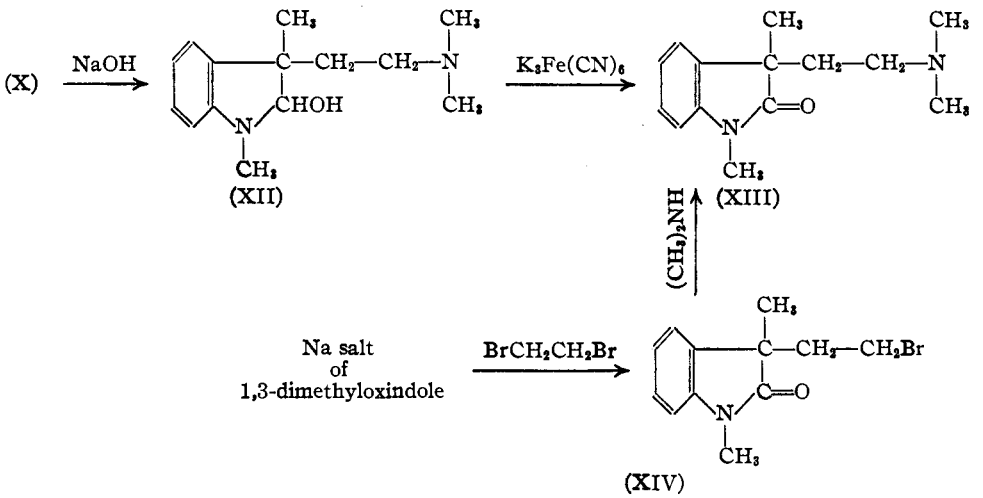
(X) (XI)

therefore to be a property of the basic ring structure of physostigmine. The constitution of (XI) was proved by comparison of its picrate with the picrate of a specimen synthesized from propionaldehyde and methyl phenyl hydrazine. A mixed melting point showed no depression.

When eserethole methiodide is treated with sodium hydroxide, eseretholemethine (5-ethoxylated derivative of (XII)) is obtained, a pseudo base which undergoes oxidation with potassium ferricyanide or with ammoniacal silver nitrate to 1,3-dimethyl - 3 - β - dimethylaminoethyl - 5 - ethoxy - oxindole.[10] Our methiodide (X), subjected to the same treatment, yielded in exactly similar fashion, 1,3-dimethyl-3-β-dimethylaminoethyl oxindole (XIII). To demonstrate its structure (XIII) was synthesized by an extension of our alkylation procedure in the oxindole series, demonstrating the great flexibility of this method. The sodium salt of 1,3-dimethyl oxindole was treated with a large excess of ethylene dibromide, reaction beginning at room temperature. The main product of this reaction, namely, 1,3-dimethyl-3-β-bromoethyl-oxindole (XIV), was converted on heating with dimethylamine into (XIII), identical with the product secured from our desoxyeseroline (VII).

Finally, both compounds (IV) and (VII) behave on catalytic reduction exactly as Barger[6] found natural eserethole to behave. Each takes up two atoms of hydrogen yielding the dihydrotryptamines (VIII) and (IX), respectively. These latter are characterized both by mono- and dipicrates. With one mole of picric acid, the monopicrate is formed, and on adding to the latter in alcoholic solution another mole of picric acid, the dipicrate crystallizes out. This represents a particularly beautiful observation in the case of (VIII), whose monopicrate is deep red, while the dipicrate is lemon yellow.

The series of reactions outlined above, made possible by the large quantities of material available from a method relatively simple and inexpensive, demonstrates conclusively that our products have the basic ring structure of physostigmine, and indeed offers further proof of the constitution of this alkaloid.



(X) (XII) (XIII) (XIV)

Experimental Part

1,3-Dimethyl-3-β-aminoethyloxindole (II)

(a) By Catalytic Method.—One gram of Adams palladium catalyst[11] was suspended in 50 cc. of glacial acetic acid in a hydrogenation duck similar to that suggested by Kindler[12] and 2 cc. of concentrated sulfuric acid added. After exhaustive hydrogenation of the catalyst, a solution of 10 g. of 1,3-dimethyloxindolyl-3-acetonitrile (I) in 50 cc. of glacial acetic acid was added dropwise. At a total pressure of about 1.5 atmospheres, slightly less than two moles of hydrogen were absorbed after several hours. The catalyst was filtered off, the acetic acid evaporated under diminished pressure, the residue taken up in water and shaken out with ether. The aqueous layer, made strongly alkaline, was extracted several times with ether. The amine distilled as colorless oil at 192–194°, 18 mm.; yield, 75% of the theoretical.

(10) Polonovski and Polonovski, *Compt. rend.*, **178**, 2078 (1924); Stedman and Barger, *J. Chem. Soc.*, 250 (1925).

(11) Adams, "Organic Syntheses," Coll. Vol. I, p. 458.

(12) Kindler and Peschke, *Arch. Pharm.*, **269**, 70 (1931).

Anal. Calcd. for $C_{12}H_{16}ON_2$: C, 70.55; H, 7.89. Found: C, 70.34; H, 8.20.

The yellow picrate of the amine crystallized from alcohol, in which it is difficultly soluble, m. p. 186°.

Anal. Calcd. for $C_{18}H_{19}O_8N_5$: C, 49.86; H, 4.43. Found: C, 49.94; H, 4.49.

The substance isolated in very small quantities in our earlier work as by-product in the reduction of the nitrile, and thought at that time to be the picrate of this amine, is another substance whose constitution is yet undetermined.

(b) By Gabriel Synthesis.—16.1 grams of 1,3-dimethyloxindole was readily converted by means of an equivalent quantity of sodium powder in 200 cc. of absolute ether into the sodium salt, under vigorous evolution of hydrogen. The salt at times remains in supersaturated solution in ether and on shaking crystallizes rapidly. To a suspension of it, thus formed in ether, 25.4 g. of solid β-bromoethyl phthalimide is added. The mixture exhibits a deep blue color, which gradually disappears as reaction proceeds in boiling ether. After refluxing overnight, water was added, and the solid which separated filtered off. It represented fairly pure 1,3-dimethyl-3-β-phthalimidoethyl oxindole (III) and melted at 141°; recrystallized from ether, m. p. 146°, yield 73% of the theoretical.

Anal. Calcd. for $C_{20}H_{18}O_3N_2$: C, 71.83; H, 5.42. Found: C, 71.66; H, 5.65.

Cleavage of the phthalimido derivative was best effected by the beautiful method of Robinson[13] with hydrazine hydrate, yielding about 80% of the theoretical quantity of highly pure amine (II), b. p. 185–186°, 16 mm.

As by-product of the alkylation reactions with the sodium salt of 1,3-dimethyloxindole, small quantities of a compound of m. p. 152° were often isolated. It proved to be 1,3-dimethyldioxindole and was secured quantitatively when moist air was passed into an ethereal suspension of the sodium salt of 1,3-dimethyloxindole.

Anal. Calcd. for $C_{10}H_{11}O_2N$: C, 67.79; H, 6.21. Found: C, 67.74; H, 6.40.

The methyl ether, prepared by methylation with dimethyl sulfate, was identical with that described by Kohn and Ostersetzer.[14]

Reduction of Amine (II) to *d,l*-Desoxynoreseroline (IV).—To a solution of 5 g. of amine (II) in 500 cc. of absolute alcohol, 20 g. of sodium was added in the course of about two hours. After cooling 200 cc. of water was added and the alcohol removed under diminished pressure. The residue in the flask was extracted with ether and the ethereal solution distilled; 4 g. of desoxynoreseroline, distilling over at 156–165°, was collected. The picrate obtained from this distillate was very pure before recrystallization, m. p. 158–159°, and identical with that obtained in the earlier work from reduction of the nitrile (I) with sodium and alcohol.

A similar experiment carried out in boiling isoamyl alcohol yielded about the same quantity of desoxynoreseroline, equally as pure as that described in the foregoing paragraph.

Three grams of the desoxynoreseroline in ether–petroleum ether was treated with an equivalent quantity of methyl *p*-toluenesulfonate and let stand for two days in the ice chest. From the oil which separated, a very small amount of the picrate of desoxyeseroline, m. p. after several recrystallizations, 179–180°, could be obtained. A more insoluble and higher melting picrate could also be isolated. The material on such methylation was, therefore, as difficult to purify as that obtained with methyl iodide and further experiments in this direction were abandoned.

1,3-Dimethyl-3-β-benzalaminoethyloxindole, (V).—20.4 grams of amine (II) was mixed with 10.6 g. of freshly distilled benzaldehyde. The mixture became turbid and warm almost immediately. After standing for about one hour, the water was removed in vacuum and the residue was recrystallized from ether–petroleum ether, m. p. 102°, yield almost quantitative.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.03; H, 6.91. Found: C, 78.02; H, 7.18.

1,3-Dimethyl-3-β-methylaminoethyloxindole (VI).—A mixture of 12.8 g. of the Schiff base (V) and 7 g. of methyl iodide in a sealed tube was heated for two hours at 100°. The tube was opened, 40 cc. of 90% alcohol was added and the mixture heated in a water-bath until most of the alcohol had boiled away. The contents of the tube were transferred to a separatory funnel with the aid of hydrochloric acid and ether, and extracted with ether. The aqueous layer, made alkaline, was extracted with ether and the ethereal extract, after drying over potassium hydroxide, distilled. The amine came over at 182–184°, 17 mm., and crystallized immediately; yield, 8.1 g.; recrystallized from ether–petroleum ether, m. p. 87°.

Anal. Calcd. for $C_{13}H_{18}ON_2$: C, 71.52; H, 8.30. Found: C, 71.40; H, 8.44.

The picrate of this amine, difficultly soluble in alcohol, melted at 227°.

Reduction of the Amine (VI) to *d,l*-Desoxyeseroline (VII).—This reduction was carried out in essentially the same manner as with the unmethylated amine, somewhat more sodium being used. The yield was 85% of the theoretical. In each of two reductions a small amount of unchanged amine could be recovered. This constituted about the only impurity in the final product. In the Grignard machine, a slight turbidity was noticed on addition of the reagent to the tertiary base, but less than 0.10 mole of gas was liberated. The base was purified by addition of a small amount of Grignard reagent from the machine, the solution heated on a water-bath for some minutes to induce coagulation of magnesium compound, and filtered rapidly through finely spun glass wool. The base on recovery was analyzed.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.19; H, 8.96. Found: C, 76.75; H, 9.03.

The picrate of the base (VII) obtained from the product of this experiment was almost pure before recrystallization. No difficulty was experienced in purifying it, and the melting point was slightly higher than formerly observed, 179–180°, although intimate mixture gave no depression of the melting point.

N-*p*-Toluenesulfonyl-*d,l*-desoxynoreseroline.—Desoxynoreseroline was treated according to the method of Hinsberg and Kessler[15] for separation and recognition of

(13) Robinson, *J. Chem. Soc.*, 1433 (1932).

(14) Kohn and Ostersetzer, *Monats.*, **32**, 905 (1911).

(15) Hinsberg and Kessler, *Ber.*, **38**, 908 (1905).

primary and secondary amines. The sulfonyl compound melted at 114° and was recovered unchanged from ether solution, after twenty-four hours of boiling with metallic sodium. No trace of sodium salt due to presence of primary amine could be detected. For analysis the sulfonyl compound was recrystallized from ether–petroleum ether.

Anal. Calcd. for $C_{19}H_{22}O_2N_2S$: C, 66.63; H, 6.49. Found: C, 66.48; H, 6.41.

Pyrolytic Decomposition of *d,l*-Desoxyeseroline Methiodide into Desoxyphysostigmol (XI).—0.8 grams of *d,l*-desoxyeseroline was dissolved in 5 cc. of methyl alcohol and treated with 1 cc. of methyl iodide. After standing overnight, the methyl alcohol and excess iodide were removed in vacuum and the residue distilled in high vacuum. At about 180–200° (temperature of air bath) 0.25 g. of desoxyphysostigmol or 1,3-dimethylindole (XI) distilled over. The deep red picrate, crystallizing in long needles from methyl alcohol, melted at 144° and gave no depression with a sample made from 1,3-dimethylindole synthesized by the well-known method of Fischer.

Conversion of Desoxyeseroline Methiodide (X) into 1,3-Dimethyl-3-β-dimethylaminoethyloxindole (XIII).—3.3 grams of *d,l*-desoxyeseroline was dissolved in 20 cc. of absolute ether and 5 cc. of methyl iodide added. After a few seconds the mixture becomes turbid and reaction is over after about an hour. The ether is then decanted from the sirup, which is taken up in water. The aqueous solution after basifying is extracted with ether. The oil which remains on evaporation of the ether, and which represents crude *d,l*-desethoxyeseretholemethine (XII), did not crystallize. It was dissolved in a small quantity of alcohol, treated with a strongly alkaline solution of 11 g. of potassium ferricyanide and boiled for five minutes. The cooled mixture was extracted with ether and the ethereal extract yielded 2.2 g. of an oil distilling at 167–173°, 14 mm. It gave a picrate of m. p. 132° after recrystallization from methyl alcohol.

Anal. Calcd. for $C_{20}H_{23}O_8N_5$: C, 52.04; H, 5.03. Found: C, 52.29; H, 5.14.

The picrolonate, recrystallized from alcohol, melted at 192°.

Anal. Calcd. for $C_{24}H_{28}O_6N_6$: C, 58.04; H, 5.68. Found: C, 58.00; H, 5.91.

Synthesis of 1,3-Dimethyl-3-β-dimethylaminoethyloxindole (XIII).—To the sodium salt from 32.2 g. of 1,3-dimethyloxindole suspended in ether, 300 g. of ethylene dibromide was added. The temperature rises on the addition to about 32°. The mixture was maintained overnight at the boiling point of ether. The ether was distilled off, water was added, the heavier layer separated and the ethylene dibromide distilled therefrom under diminished pressure. The water layer was neutral. The residue, on removal of excess ethylene bromide, distilled mainly at 150–160°, 1 mm.; yield 61%.

Without further purification, the crude 1,3-dimethyl-3-β-bromoethyloxindole (XIV) was heated at 100° for five hours in a sealed tube with slightly more than twice the molecular quantity of pure dimethylamine. The semi-solid mass was taken up in water and ether, and a little non-basic material was removed from the acidified mixture by shaking out with ether. The base, recovered in the usual manner, distilled at 168–169°, 14 mm., and was obtained in good yield. The picrate was pure without further crystallization, m. p. 132°, and was identical with that obtained from *d,l*-desoxyeseroline (VII). Likewise were the picrolonates identical.

Catalytic Hydrogenation of Desoxyeseroline and Desoxynoreseroline.—*d,l*-Desoxyeseroline (VII) was reduced catalytically according to the method outlined by Stedman and Barger. Two atoms of hydrogen were taken up, and the resulting dihydro product (IX) isolated in the usual manner. It yielded a monopicrate, when equivalent quantities of the base and picric acid were brought together in alcohol, m. p. 129°. Another equimolecular quantity of picric acid added to the alcoholic solution of the monopicrate, precipitated the dipicrate, m. p. 153°. The latter was analyzed.

Anal. Calcd. for $C_{25}H_{26}O_{14}N_8$: C, 45.31; H, 3.96. Found: C, 45.17; H, 4.15.

d,l-Desoxynoreseroline (IV) behaves in similar fashion, yielding the dihydro derivative (VIII). The deep red monopicrate melted at 136° and was fairly readily soluble in most organic solvents; recrystallized from benzene.

Anal. Calcd. for $C_{18}H_{21}O_7N_5$: C, 51.53; H, 5.06. Found: C, 51.69; H, 5.16.

The dipicrate, difficultly soluble in most solvents, melted at 179° with decomposition; recrystallized from alcohol.

Anal. Calcd. for $C_{24}H_{24}O_{14}N_8$: C, 44.43; H, 3.73. Found: C, 44.60; H, 3.96.

The authors gratefully acknowledge a grant to one of them from the Rosenwald Fund, which is defraying some of the expenses of this investigation. They wish also to renew their expressions of appreciation to Dean W. M. Blanchard, Senior Professor of Chemistry, without whose enthusiastic support the work could not have progressed to its present stage.

Summary

1. Oxindole and its monoalkyl derivatives substituted in the 3-position readily yield sodium salts with metallic sodium, which salts can be made to react with various types of halogen compounds.

2. In this way, 1,3-dialkyl-oxytryptamines, which are intermediates in a synthesis of the basic ring structure of physostigmine, have been prepared.

3. Reduction of the suitable oxytryptamines to the physostigmine ring structure, offers an improvement over our earlier method of reducing oxindolylacetonitriles, particularly because it obviates the difficulty of methylating *nor* products in the final stage.

4. Reactions of synthetic desoxyeseroline have been shown to proceed in exactly parallel

fashion with those of natural eseroline, thus demonstrating the identity of the ring structure found in physostigmine with that of the synthetic products described in this and an earlier communication.

GREENCASTLE, INDIANA RECEIVED DECEMBER 17, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

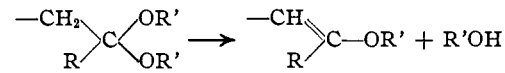
The Preparation of Some α-Unsaturated Ethers from 2,2-Dimethoxyalkanes[1]

BY D. B. KILLIAN, G. F. HENNION AND J. A. NIEUWLAND

Introduction

In the condensation of alcohols with various acetylenes, catalyzed by a mercury salt and a suitable acid, to form acetals or ketals, it has been quite generally believed that vinyl ethers are intermediates in the reaction.[2,3,4] Such vinyl ethers, however, have never been isolated from these reactions, although they have been synthesized by other methods. It is known that such ethers are extremely reactive to alcohols in the presence of traces of acid, being converted to acetals.[5]

Faworski[6] prepared isopropenyl ethyl ether from methylacetylene and alcoholic potash at 170–180°. Alkylacetylenes other than methylacetylene rearrange to disubstituted acetylenes.[6,7,8] Phenylacetylene similarly adds one molecule of alcohol, but the addition is reversed and compounds of the type $C_6H_5CH{=}CH(OR)$ are formed.[8] Moureu[9] prepared 2-methoxy-, ethoxy- and propoxyheptene-1 by heating the alkoxyamylacrylic acid at 150–175°. Claisen[10] succeeded in splitting diethyl acetal to ethyl vinyl ether by heating with phosphorus pentoxide and quinoline. Ethyl isopropenyl ether was obtained similarly from 2,2-diethoxypropane. The thermal decomposition of acetals and ketals to α-unsaturated ethers was studied by Sigmund and Uchann.[11] Johannissian and Akunian[12] split cyclohexanone diethyl acetal to 1-ethoxycyclohexene by heating with traces of *p*-toluenesulfonic acid. These reactions may be expressed by the equation



These interesting desaturation reactions have not been studied extensively nor has their generality been established.

Hill and Pidgeon[2] prepared the monovinyl ethers of glycol and trimethylene glycol and showed that ring closure to the ethylidene compound proceeded with explosive violence when a trace of acid was added. We have observed that ketals of the type $R(CH_3)C(OCH_3)_2$ are readily split, by merely heating with a small amount of *p*-toluenesulfonic acid, to yield substituted vinyl ethers of the type $RC(OCH_3){=}CH_2$. Readdition of methyl alcohol to the double bond is quantitative when the ether and alcohol are mixed and a trace of acid added. The ketal may be isolated readily if the acid is neutralized prior to distillation. Addition of a foreign alcohol is likewise quantitative but in this case a mixture of three ketals is obtained, *viz.*, the dimethyl ketal, the ketal of the foreign alcohol and a mixed ketal. However, by using an excess of the foreign alcohol the methyl ether or the 2,2-dimethoxyalkane may be directly converted to the ether of the foreign alcohol by distilling the mixture from a trace of acid through a suitable fractionating column so as to remove all methyl alcohol and excess foreign

TABLE I

α-UNSATURATED ETHERS, R—C(OR′)=CH₂

(Asterisk denotes new compound)

No.	R	R′	Compound
1	C_4H_9—	CH_3—	*2-Methoxyhexene-1
2	C_4H_9—	C_2H_5—	*2-Ethoxyhexene-1
3	C_4H_9—	*n*-C_3H_7—	*2-Propoxyhexene-1
4	C_4H_9—	*n*-C_4H_9—	*2-*n*-Butoxyhexene-1
5	C_4H_9—	iso-C_4H_9—	*2-Isobutoxyhexene-1
6	C_5H_{11}—	CH_3—	2-Methoxyheptene-1
7	C_5H_{11}—	*n*-C_3H_7—	2-Propoxyheptene-1
8	C_6H_5—	CH_3—	α-Methoxystyrene

(1) Fifth paper on the chemistry of alkylacetylenes and their addition compounds; previous paper, THIS JOURNAL, **56**, 1802 (1934).

(2) Hill and Pidgeon, *ibid.*, **50**, 2718 (1928).

(3) Nieuwland, Vogt and Foohey, *ibid.*, **52**, 1018 (1930).

(4) Hennion, Killian, *et al.*, *ibid.*, **56**, 1130 (1934).

(5) Ellis, "The Chemistry of Petroleum Derivatives," The Chemical Catalog Co., Inc., New York, 1934, p. 679.

(6) Faworski, *J. prakt. Chem.*, [2] **37**, 531 (1888).

(7) Faworski, *ibid.*, [2] **44**, 208 (1891).

(8) Moureu, *Compt. rend.*, **138**, 288 (1904).

(9) Moureu, *Bull. soc. chim.*, [3] **31**, 522 (1904).

(10) Claisen, *Ber.*, **31**, 1021 (1898).

(11) Sigmund and Uchann, *Monatsh.*, **51**, 234 (1929).

(12) Johannissian and Akunian, *C. A.*, **25**, 921 (1931).