the constants: m. p. 133–134°; $[\alpha]_D$ 0° ⟶ +14°, MeOH.

Aldehydo-galactose pentaacetate ethyl hemiacetal was also prepared from its oxime monohydrate by the Claisen[4] procedure, using glacial acetic acid and sodium nitrite, in approximately the same yield as in the above deoximation procedure. The oxime acetate (2 g.) was dissolved in 30 cc. of glacial acetic acid and a solution of 2 g. of sodium nitrite in 10 cc. of water added over a period of ten minutes. The solution was stirred for forty minutes at room temperature and then for ten minutes at 40°. It was then poured into 150 cc. of water, chloroform added and also 40 g. of sodium bicarbonate. The product was then worked up as above; yield, 1.6 g. of crude material; m. p. 134–135°, after recrystallization from absolute ethanol.

Preparation of *Aldehydo*-*d*-galactose Ethyl Hemiacetal from *d*-Galactose Semicarbazone.—Galactose semicarbazone proved to be very insoluble in the acetylating reagents and rather vigorous conditions were required to effect its acetylation. As Wolfrom[11] recorded only the melting point for *aldehydo*-galactose semicarbazone pentaacetate, this substance was prepared again and recrystallized from hot water to constant rotation. The melting point, around 200° (dec.), was unreliable but the rotation, unchanged on recrystallization, was $[\alpha]_D^{25}$ +89° (*c*, 2.2; $CHCl_3$).

Galactose semicarbazone[9b] (4 g.) was added to a mixture of 32 cc. of pyridine and 16 cc. of acetic anhydride, stirred for forty hours in a 55° bath, and poured into 500 cc. of ice and water containing 32 cc. of glacial acetic acid. The crystalline product was removed by filtration; yield, 3.2 g.; m. p. 185–190°; $[\alpha]_D$ + 63°, $CHCl_3$. This product was a mixture, but it was found that it was unnecessary to separate it into its components for use in the next step.

The acetylated galactose semicarbazone (1.6 g.) was dissolved in 25 cc. of warm ethanol and treated with sodium nitrite and hydrochloric acid as described under the deoximation of *aldehydo*-glucose oxime pentaacetate, except that the reaction was carried out at 70°. Absolute ethanol (20 cc.) was added to the chloroform extract and this yielded 1 g. of crystalline product on evaporation at room temperature. The products from several such runs were combined and twice recrystallized from absolute ethanol; m. p. 134–135°; $[\alpha]_D^{22}$ +1.2° ⟶ +13.7° (*c*, 1.0; MeOH; 45 hours). The product was thus identified as very pure *aldehydo*-galactose pentaacetate ethyl hemiacetal.

Summary

1. Acetylation of the semicarbazone of galactose produces appreciable amounts of the corresponding *aldehydo* acetate.

2. Acetylation of glucose semicarbazone produces mainly *aldehydo*-glucose semicarbazone pentaacetate, accompanied by smaller amounts of a semicarbazone tetraacetate, hexaacetate and an isomeric pentaacetate.

3. Acetylation of the sirupy oxime of β-glucose tetraacetate produces *aldehydo*-glucose oxime hexaacetate.

4. The O-acetyl group on the oximes of *aldehydo*-glucose and galactose hexaacetates may be selectively hydrolyzed.

5. A new synthesis of *aldehydo* sugar acetates is established for glucose and galactose by the action of nitrous acid on the *aldehydo*-pentaacetates of their oximes and semicarbazones.

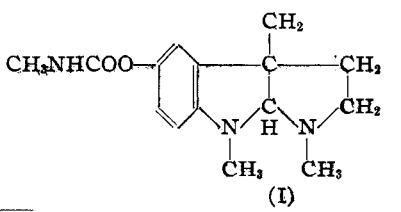
COLUMBUS, OHIO RECEIVED MAY 28, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

Studies in the Indole Series. II. The Alkylation of 1-Methyl-3-formyloxindole and a Synthesis of the Basic Ring Structure of Physostigmine[1]

BY PERCY L. JULIAN, JOSEF PIKL AND DOYLE BOGGESS

The literature records no efforts at direct alkylation of oxindoles, and this gap in our knowledge of these substances appears to us decidedly embarrassing in view of (1) recent attempts to effect a smooth and complete synthesis of the alkaloid, physostigmine, (I),[2] (2) the existing doubt as to the structure of the amino acid, oxytryptophane, for which formula (II) is a possibility.[3] It was with a view toward contributing to the solution of these two problems that the present work was undertaken.

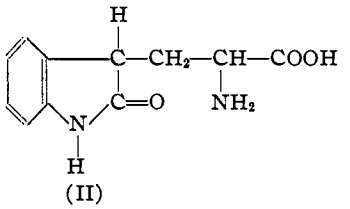


(I)

(1) This paper is an abstract of a portion of a thesis presented by Doyle Boggess to the Graduate Council of DePauw University in May, 1934, in partial fulfilment of the requirements for the degree of Master of Arts.

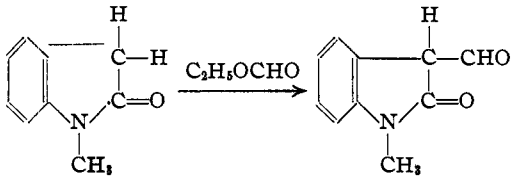
(2) King, Robinson and Suginome, *J. Chem. Soc.*, 298–336; 1433 (1932). (Reference there to earlier papers.) Hoshino and Tamura, *Proc. Imp. Acad. Japan*, **8**, 17 (1932); *Ann.*, **500**, 42 (1933).

(3) Abderhalden and Kempe, *Z. physiol. Chem.*, **52**, 212 (1907); Abderhalden and Sickel, *ibid.*, **138**, 108–117 (1924); Fischer and Smeykal, *Ber.*, **56**, 3470 (1923).



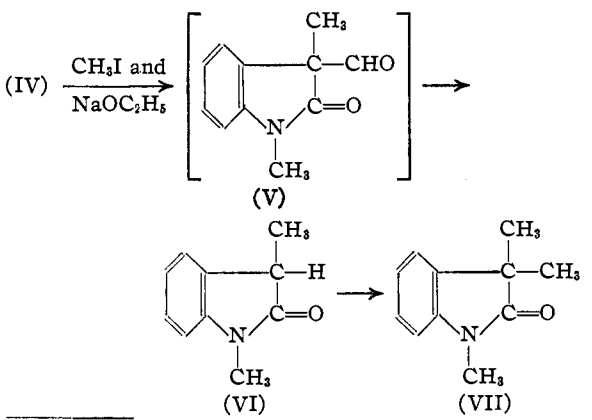
(II)

Our experiments began with 1-methyl-3-formyl oxindole (IV). This aldehyde was discovered by Friedländer,[4] who isolated it by hydrolytic cleavage of the dye, N-Methyl-thioindigo Scarlet. We found that this troublesome and costly method could be replaced advantageously by a condensation of ethyl formate with N-methyloxindole (III), which latter substance, thanks to the method of Stollé,[5] is readily available.



(III) (IV)

The attempts to alkylate the aldehyde (IV) with methyl and ethyl iodide gave rather interesting results. On dribbling something in excess of two moles of sodium methylate into a boiling methyl alcoholic solution of (IV) containing somewhat in excess of two moles of methyl iodide, there was isolated in good yield 1,3,3-trimethyloxindole (VII). In the course of the alkylation, therefore, it seems that the intermediary C-methyl aldehyde (V) was cleaved to the dimethyloxindole (VI), which suffered further methylation to (VII). To test this latter assumption, which is obviously of great significance for the original object of this investigation, we attempted to alkylate 1,3-dimethyloxindole (VI)



(V) (VI) (VII)

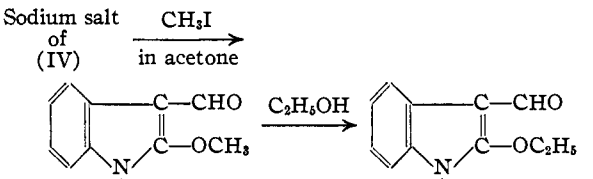
(4) Friedländer and Kielbasinski, *Ber.*, **44**, 3102 (1911).

(5) R. Stollé, *J. prakt. Chem.*, [2] **128**, 1–20 (1930).

with methyl iodide and sodium ethylate. It was quantitatively methylated to (VII).

Despite numerous attempts none of the C-alkylated aldehyde (V) could be obtained, quantitative cleavage occurring even in non-hydroxylic solvents.

When the sodium salt of (IV) is alkylated in dry and alcohol-free acetone with methyl iodide, the main product of the reaction is a double salt having the composition, $C_{11}H_{11}O_2N \cdot 0.5NaI$. On decomposing with water, it yields a colorless monomethyl derivative of (IV) which contains one methoxyl group. This O-methyl derivative, however, reduces ammoniacal silver nitrate much more rapidly than the parent aldehyde (IV) and further gives a crystalline bisulfite addition compound from which it is readily regenerated on decomposing with cold sodium carbonate solution. It is, therefore, still an aldehyde and has the composition represented by (VIII).



(VIII) (IX)

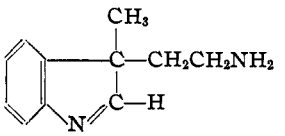
In neutral aqueous solutions and in glacial acetic acid (VIII) may be heated for hours without decomposition. Warmed with 3% hydrochloric acid or in dilute alkali, however, it is readily hydrolyzed to the original aldehyde (IV). It gives a semicarbazone, a phenylhydrazone, and an anil, but all these derivatives are identical with the corresponding derivatives of the original aldehyde (IV). Simultaneously with the aldehyde condensations, therefore, the ether group is hydrolyzed. This property may make possible several condensation reactions, which have been found not to proceed smoothly with the original aldehyde because of its enolic character,[6] and this is under investigation.

On boiling an ethyl alcoholic solution of (VIII) it is slowly converted into the corresponding O-ethyl derivative (IX) and when boiling is continued long enough, transformation is almost complete. This O-ethyl derivative, as well as its sodium iodide addition compound, was secured in exactly similar fashion as was the O-methyl compound.

(6) Compare Gränacher, *Helv. Chim. Acta*, **6**, 467–482 (1923).

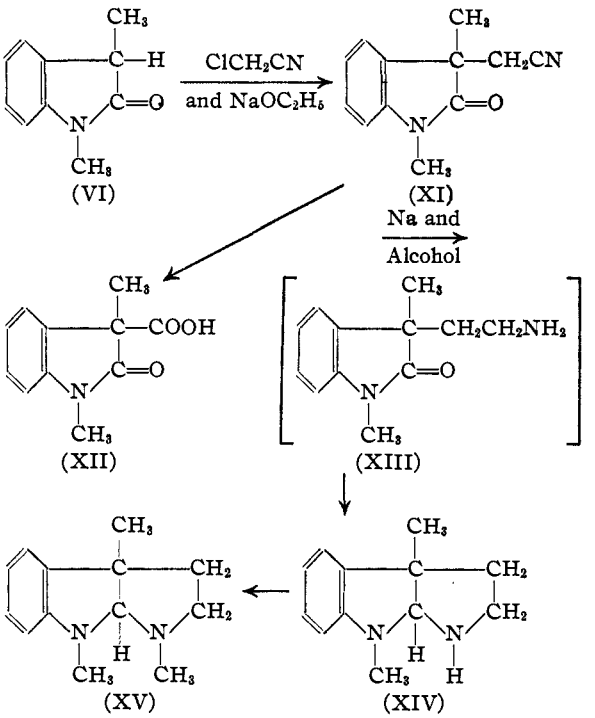
Attempts to convert these O-alkyl compounds into the C-alkyl derivatives (V) or cleavage products of the latter were unsuccessful.

Returning to the original object of this investigation it is obvious that the results on alkylation with methyl iodide and sodium methylate suggest a remarkably simple route to the ring structure found in physostigmine (I). Methods hitherto employed[2] have depended mainly upon transformation of difficultly accessible indolenine derivatives like (X) into compounds containing this ring structure.



(X)

The tremendously large number of steps and expensive material employed in arriving at compounds like (X) are all obviated by our new synthesis of this ring structure according to the following series of reactions



(VI) (XI) (XII) (XIII) (XV) (XIV)

The nitrile (XI) was characterized by hydrolysis to the corresponding acid (XII). Since, moreover, this nitrile is obtained in 90% yield and (VI) is a very cheap substance, the way is opened to a ready synthesis of the drug itself and even of homologs, containing other groups in the 3-position of the indole nucleus. Such substances may be of pharmacological interest in suggesting which particular portion of the ring structure of physostigmine is responsible for its peculiar physiological action.

We were surprised at the ease with which the nitrile (XI) was converted into desoxynoreseroline (XIV). On reduction with sodium and alcohol, the product consists mainly of the closed ring compound (XIV). Robinson,[7] who secured by a very involved route the 5-methoxylated derivative of (XIII), abandoned reduction experiments on this substance, after several such attempts failed to yield the corresponding indolinol or the ring structure represented by (XIV).

Our desoxynoreseroline (XIV) is characterized by a crystalline picrate and benzoate. In the Grignard "machine"[8] the presence of only one active hydrogen is indicated and one mole of reagent is consumed. Its structure appears, therefore, beyond doubt. On methylation with methyl iodide it yields desoxyeseroline (XV) characterized by a crystalline picrate. Thus a complete and extremely simple synthesis of the physostigmine ring structure is accomplished.

We hope soon to communicate the complete synthesis of the drug itself by this same procedure.

Experimental Part

1-Methyl-3-formyloxindole (IV).—A mixture of 30 g. of ethyl formate and 44 g. of 1-methyloxindole (III)—prepared by the method of Stollé[5]—was poured into a hot solution of 10 g. of sodium in 130 cc. of absolute alcohol. Almost immediately the mass set solid. The contents of the flask was taken up in water, and acidified with hydrochloric acid, whereupon the aldehyde separated in almost colorless crystals, which were filtered and washed with little alcohol and ether; yield 46.5 g. or 90% of the theoretical; recrystallized from dilute alcohol, m. p. 192° (Friedländer gives 186°); mixed m. p. with the aldehyde prepared by the Friedländer method[4] gives no depression.

Methylation in Alcohol with Sodium Methylate and Methyl Iodide.—Into a solution of 14 g. of 1-methyl-3-formyloxindole (IV) in 150 cc. of water-free methyl alcohol and 27 g. of methyl iodide, a solution of 4 g. of sodium in 60 cc. of water-free methyl alcohol is slowly dribbled under constant shaking. The whole is boiled for three hours, after which water is added and the aqueous solution extracted with ether. On distillation of the residue remaining after evaporation of the ether, the main portion boiled at 131–136° (11 mm.). This straw-colored oil almost completely crystallized on standing. The crystals were filtered, washed with petroleum ether and recrystallized from low boiling petroleum ether, m. p. 50°.

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.43; H, 7.43. Found: C, 75.26; H, 7.56.

(7) King and Robinson, *J. Chem. Soc.*, 1434 (1932).

(8) Kohler, Stone and Fuson, THIS JOURNAL, 49, 3181 (1927).

For comparison, 1,3,3-trimethyloxindole (VII) was synthesized as follows. To a well cooled solution of 24.4 g. of methylaniline in 100 cc. of dry benzene, 22.9 g. of bromisobutyryl bromide was added with constant shaking. The mixture was allowed to stand overnight, after which the methylaniline hydrobromide was filtered off, the benzene filtrate shaken several times with 2% hydrochloric acid, and dried over sodium sulfate. After removal of last traces of benzene, 26 g. of sublimed aluminum chloride was added in small portions to the residual anilide with cooling. Reaction with formation of the double compound proceeds vigorously at ordinary temperature, complete liquefaction of the mixture resulting. On heating in a metal bath at 100°, hydrogen bromide evolution begins and reaction is over after ten minutes of heating at 120–125°. Ice and water were added and the oil taken up in ether. The ethereal solution is shaken with 2% hydrochloric acid, then with sodium carbonate and dried over sodium sulfate. The 1,3,3-trimethyloxindole distilled at 131–132° (11 mm.) and crystallized immediately, m. p. 50°; yield 14 g. The mercuric chloride double compound, prepared from equimolecular quantities of the reactants in alcoholic solution, with addition of a trace of water to facilitate crystallization, melted at 122.5°. A mixed melting point of it with the same derivative prepared from the oxindole secured in alkylation of (IV) above, showed no depression. Likewise were both samples of the oxindole identical.

When the same procedure in alkylation as outlined above is employed, except that one mole of alcoholate is used, 1,3-dimethyloxindole (VI) is secured in almost quantitative yield. It boils at 136–138° (11 mm.). The metastable modification melts at 27°, changing on standing into the higher melting modification, 55°.

Anal. Calcd. for $C_{10}H_{11}ON$: C, 74.53; H, 6.83. Found: C, 74.06; H, 7.03.

For comparison and use in later experiments described in this paper, 1,3-dimethyloxindole (VI) was synthesized from bromopropionyl bromide and methylaniline in essentially the same manner as described under the trimethyl derivative. Here hydrogen bromide evolution took place at 160–170°. From 180 g. of α-bromopropionyl bromide, 124 g. (92% of theoretical) of 1,3-dimethyloxindole was obtained. It boiled at 136–138° (11 mm.), showed the same dimorphism recorded above, and gave no depression in melting point when mixed with the sample secured on methylating the aldehyde (IV). Likewise were the two mercuric chloride double salts, m. p. 125°, identical.

Methylation of 1,3-Dimethyloxindole (VI) to 1,3,3-Trimethyloxindole (VII).—To a warm solution of 10.7 g. of 1,3-dimethyloxindole in 30 cc. of water-free alcohol and 20 g. of methyl iodide, a solution of 2.4 g. of sodium in 50 cc. of water-free alcohol was added in the course of two hours. The solution was refluxed gently for one hour, the alcohol taken off under diminished pressure and the residue taken up with water and ether; yield on distillation 9.5 g.; m. p. on recrystallization, 50°; mixed melting point with samples prepared by the two other methods already described showed no depression.

Alkylation in Acetone with Methyl and Ethyl Iodides.—For preparation of the sodium salt of 1-methyl-3-formyloxindole (IV), a warm solution of 35 g. of the aldehyde in 300 cc. of absolute alcohol is added to a warm solution of 4.6 g. of sodium in 150 cc. of absolute alcohol. The sodium salt, which separates in snow-white flakes after a few minutes, is filtered, washed well with absolute alcohol and ether and dried under diminished pressure at 100°; yield 33 g. Conversion into the sodium salt constitutes the best method for purification of the aldehyde.

A mixture of 30 g. of dry sodium salt, 300 cc. of dry, alcohol-free acetone and 70 g. of methyl iodide was boiled until a test portion no longer showed color with ferric chloride (about five hours). The resulting clear solution was concentrated to less than half its volume. On cooling 10 g. of the double compound separated. Addition of ether to filtrate gives 18 g. more, but this is contaminated with excess sodium iodide. Difficult to purify, the double compound is obtained with sharp melting point of 213° only after several rapid recrystallizations from pure acetone.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot 0.5NaI$: C, 50.0; H, 4.17; Na, 4.35. Found: C, 50.55; H, 4.27; Na, 4.20.

On adding water to this double compound, it dissolves with separation of 1-methyl-2-methoxy-3-formylindole (VIII), melting at 138°, after recrystallization from methyl alcohol.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.80; H, 5.90; OCH_3, 16.40. Found: C, 69.54; H, 6.10; OCH_3, 16.78.

The bisulfite compound prepared in the usual way is decomposed by a cold concentrated solution of sodium carbonate and the aldehyde recovered unchanged. The semicarbazone, phenylhydrazone and anil, prepared in the usual way from equivalent quantities of the reactants in ethyl alcohol, melt at 245, 204 and 142°, respectively, but mixed melting points show them to be identical with the same derivatives prepared from 1-methyl-3-formyloxindole (IV).

When a solution of 4.2 g. of the O-methyl aldehyde (VIII) in ethyl alcohol is boiled for seventy-two hours, 4.2 g. of 1-methyl-2-ethoxy-3-formylindole (IX) is isolated on evaporation of the alcohol, the methyl group being quantitatively replaced by ethyl. The new substance melts at 78° after recrystallization from ether–petroleum ether.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.93; H, 6.45. Found: C, 70.87; H, 6.62.

The double compound of sodium iodide with the O-ethyl aldehyde, though more soluble in acetone than that of the corresponding O-methyl derivative, is secured much purer on concentration of the acetone solution. From 31 g. of sodium salt of (IV) and excess ethyl iodide, by exactly the same procedure as described for the O-methyl compound, 20 g. of addition compound was obtained. It melts at 167°.

Anal. Calcd. for $C_{12}H_{13}O_2N \cdot 0.5NaI$: C, 51.78; H, 4.71; OC_2H_5, 16.13; Na, 4.14; NaI, 26.95. Found: C, 51.68; H, 5.19; OC_2H_5, 16.11; Na, 3.96; NaI, 26.75.

When the O-ethyl aldehyde and sodium iodide, in the ratio represented by the above formula, are dissolved in hot acetone, and the acetone evaporated, the double salt is left behind in lustrous needles melting sharply at 167°. Identically the same semicarbazone, phenylhydrazone and

anil were obtained from the O-ethyl as from the O-methyl derivative.

Both the O-ethyl and the O-methyl aldehydes can be distilled in vacuum without decomposition. The latter was heated in vacuum for two days at 220° and recovered unchanged.

From the acetone filtrates, after removal of most of the O-alkyl double compounds, on distillation, there is always obtained a small quantity of 1,3-dimethyloxindole (VI).

1,3-Dimethyloxindolyl-3-acetonitrile (XI).—To a solution of 60 g. of 1,3-dimethyloxindole (VI), in 150 cc. of water-free alcohol and 42 g. of chloroacetonitrile, kept at a temperature around 60°, a solution of 9.4 g. of sodium in 150 cc. of water-free alcohol is added with stirring in the course of three hours. The alcohol is removed under diminished pressure, residue taken up in water and ether and shaken with 10% sodium hydroxide. The nitrile boils at 194–196° (14 mm.); yield 67.5 g. (90% of theoretical). On standing it crystallizes in colorless prisms, melting point after recrystallization from ether–petroleum ether, 58°.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.96; H, 6.10. Found: C, 71.93; H, 6.24.

1,3-Dimethyloxindolyl-3-acetic Acid (XII).—Two grams of nitrile (XI) was heated on the water-bath overnight with 20 cc. of concd. hydrochloric acid. On concentration of the solution, the acid separates; yield, 2 g.; recrystallized from water, m. p. 178°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.72; H, 5.98. Found: C, 65.88; H, 6.19.

Desoxynoreseroline (XIV).—To a boiling solution of 20 g. of 1,3-dimethyloxindolyl-3-acetonitrile (XI) in 1500 cc. of water-free alcohol, 72 g. of sodium was added in fairly large lumps in the course of two to three hours. After all was dissolved, one liter of water was added and the alcohol taken off under diminished pressure. A few cc. of hydrochloric acid was added to the distilled alcohol and the alcohol again carefully removed under diminished pressure. The residues were combined and extracted with ether, from which ethereal solution the base was removed by shaking with 10% hydrochloric acid. The free base liberated in the usual way was separated into two fractions in the first distillation, 1 g. of material collected up to 146° and 7.65 g. from 146–161°. The latter fraction proved to be fairly pure desoxynoreseroline (XIV). The picrate prepared in methyl alcoholic solution was yellow in color and melted at 158°.

Anal. Calcd. for $C_{18}H_{19}O_7N_5$: C, 51.77; H, 4.60; N, 16.81. Found: C, 51.90; H, 4.79; N, 17.03.

The free base (XIV) was isolated from the picrate by decomposing the latter with 10% hydrochloric acid, shaking out twice with ether, making the aqueous solution alkaline and extracting with ether. The last traces of picric acid were then removed from the ethereal solution by extraction with dilute alkali. The pure desoxynoreseroline boiled at 154° (17 mm.).

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.56. Found: C, 76.41; H, 8.65.

Desoxynoreseroline (XIV) was further characterized by a monobenzoyl derivative made by treating the base with an excess of benzoyl chloride and sodium hydroxide. After recrystallization from 50% methyl alcohol, it melts at 168°.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.03; H, 6.91. Found: C, 77.80; H, 7.13.

On further examination of this base (XIV) in the Grignard machine the following figures were obtained: one mole of base (XIV) gives 0.92 and 0.87 mole methane; one mole of base (XIV) consumes 0.75 mole of reagent. There is no doubt that our base is desoxynoreseroline.

β-[1,3-Dimethyloxindolyl]-ethylamine (XIII).—From the lower boiling basic fraction secured in the reduction just described, the portion boiling at 110–120° gave a yellow picrate melting at 113°. Analyses show it to be the picrate of the homoamine (XIII).

Anal. Calcd. for $C_{18}H_{19}O_8N_5$: C, 49.86; H, 4.43. Found: C, 49.49; H, 4.44.

Desoxyeseroline (XV).—1.05 g. of desoxynoreseroline was dissolved in 20 cc. of absolute ether and 2 cc. of methyl iodide added. After a few minutes the solution becomes turbid and a sirup separates. The latter is, after some hours, freed from the ether by decantation, washed well with ether, dissolved in 20 cc. of water and filtered. To the filtrate a solution of 1.3 g. of sodium picrate in 20 cc. of water was added. Immediately an oil separated which soon crystallized. This picrate is difficult to purify and only after several recrystallizations from ethyl alcohol, in which it is difficultly soluble, it melted sharply at 177°; yield 1.3 g.

Anal. Calcd. for $C_{19}H_{21}O_7N_5$: C, 52.87; H, 4.92. Found: C, 52.92; H, 4.72.

The authors are eager to acknowledge their great indebtedness to Dr. W. M. Blanchard, Dean of the College of Liberal Arts and Senior Professor of Chemistry, without whose generous support, constant encouragement, helpful advice and criticisms, the completion of this work would have been impossible.

Summary

1. Both C- and O-alkylation take place with 1-methyl-3-formyloxindole, but the C-alkyl products are quantitatively cleaved to 3-alkylated oxindoles. The O-alkyl products are no longer oxindoles but 2-alkoxylated indole aldehydes.

2. Oxindoles containing a hydrogen atom in the 3-position are readily alkylated, with replacement of this hydrogen by an alkyl group.

3. The observation indicated in (2) has made possible the synthesis of the basic ring structure of the alkaloid, physostigmine, by a remarkably simple series of reactions.

GREENCASTLE, IND. RECEIVED JUNE 2, 1934