ro-γ-valerolactone required for the synthesis of γ-hydroxyproline.

The preparation of α-amino-γ-butyrolactone by hydrolysis of β-chloroethylacetamidocyanoacetic ester is described.

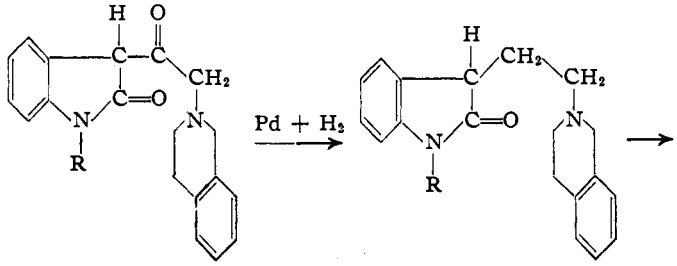
RENSSELAER, N. Y. RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM DE PAUW UNIVERSITY AND FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. VIII. Yohimbine (Part 1). The Mechanism of Dehydrogenation of Yohimbine and Related Compounds[1]

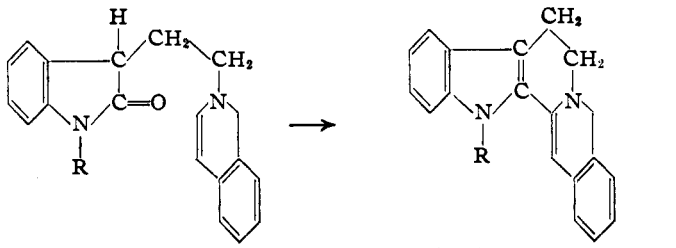
BY PERCY L. JULIAN, ARTHUR MAGNANI, JOSEF PIKL[2] AND WILLIAM J. KARPEL

The work reported in this communication had its origin in attempts to synthesize the basic ring structure of yohimbine by a procedure presented schematically with formulas I → IV.



(Ia) R = H
(Ib) R = CH₃

(IIa) R = H
(IIb) R = CH₃



(IIIa) R = H
(IIIb) R = CH₃

(IVa) R = H
(IVb) R = CH₃

At the time this investigation began, which was more than a decade ago, the successful preparation of the desired 3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ia) from oxindole and ethyl N-tetrahydroisoquinolyl acetate,[3] as well as the reduction of Ia to 3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIa) could be predicted[4] and indeed was ultimately realized in practice. Sufficient information was also available then and later to indicate that, once compound IIIa were available, enolization of the hydrogen atom at position 3 of the oxindole nucleus could be used for ring closure. The crux of the whole synthesis, however, rested upon the ability to dehydrogenate IIa to IIIa, and this in turn directed closer attention to the end-products from the dehydrogenation of yohimbine and indeed to the mechanism of this dehydrogenation.

When the synthesis of the yohimbine ring structure outlined above was projected the accepted formula for yobyrine, one of the principal dehydrogenation products of yohimbine, was IVa.[5] This structure, like IIIa, is that of a 1,2-dihydroisoquinoline and repeated efforts to prepare 1,2-dihydroisoquinolines hitherto have resulted in failure.[6] Only one case of such a preparation is reported in the literature, namely, that of Cooke and Gulland[7] who claim dehydrogenation of 2-methyltetrahydroisoquinoline to 2-methyl-1,2-dihydroisoquinoline with palladous chloride. Their evidence, however, is poor and subject to question. Our early failures to dehydrogenate IIb to 1-methyl-3-(2-N-dihydroisoquinolylethyl)-oxindole (IIIb) threw grave doubt upon the validity of IVa as representing the structure of yobyrine, despite the fact that the continuous conjugation in IVa might presumably favor the formation of a 1,2-dihydroisoquinoline in the case of the dehydrogenation of yohimbine to yobyrine. Moreover, Pruckner and Witkop[8] in the meantime proposed a new structure for yobyrine, involving a mechanism for the dehydrogenation of yohimbine more consistent with our experiences and those of others. Their results we have substantiated by a complete synthesis of yobrine.[9]

Both 1-methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib) and its unmethylated analog, (Ia), on catalytic reduction gave material whose empirical analyses correspond to substances IIb and IIa, respectively. There seems to be no fundamental difference in this case between reduction of the unmethylated and methylated acyl oxindoles such as Horner has indicated.[10]

(1) Presented in part as Indole Paper VIII before the Spring Meeting of the American Chemical Society at Boston, in April, 1939. For Paper IX in this series, see THIS JOURNAL, **67**, 1203 (1945).

(2) Present address: Jackson Laboratory, du Pont Company, Wilmington, Delaware.

(3) Wedekind and Oechslen, *Ber.*, **36**, 1161 (1903).

(4) Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).

(5) Barger and Scholz, *Helv. Chim. Acta*, **16**, 1343 (1933).

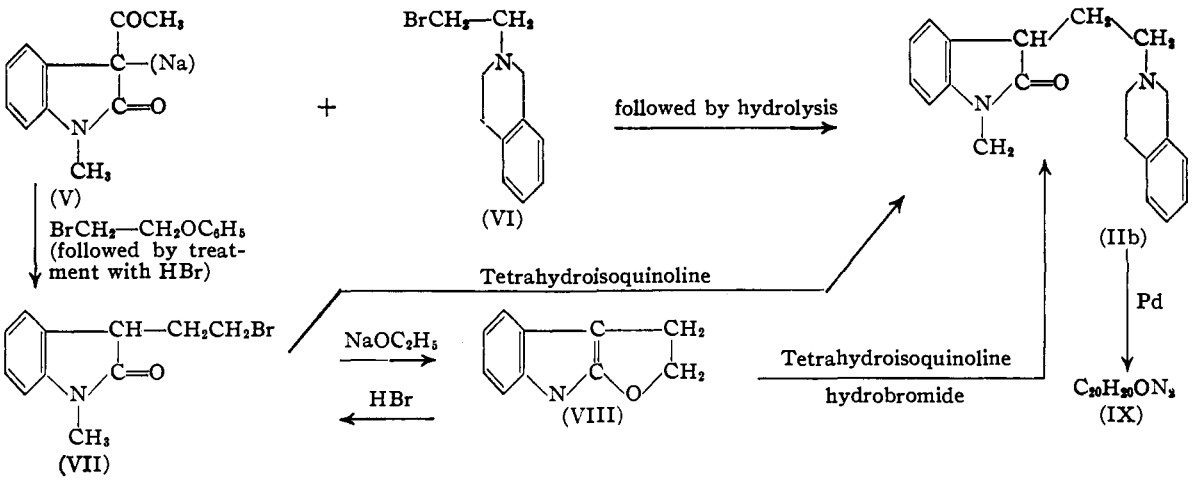
(6) Young and Robinson, *J. Chem. Soc.*, **275** (1933); Perkin, *ibid.*, 815 (1916); Reichert and Hoffmann, *Arch. Pharm.*, **274**, 281 (1936).

(7) Cooke and Gulland, *J. Chem. Soc.*, 872 (1939).

(8) Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

(9) See communication following this one, THIS JOURNAL, **70**, 180 (1948).

(10) Horner, *Ann.*, **548**, 119–120 (1941).



Because, up to quite recently 1-methyloxindole was more readily available to us than oxindole itself, and because the reduction of Ib led to two substances much more readily separable than the mixture obtained from reducing the unmethylated analog, we have employed Ib as a model in this study.

The reduction product of Ib is a fairly constant boiling oil in high vacuum and yields a hydrochloride that for a long time was thought to be a single entity. The recovered base from it, however, has been separated into two substances. The one of these is 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb), melting at 167°. The other is 1-methyl-2,3-dihydro-3-N-tetrahydroisoquinolylacetylindole (X), which we have been unable to induce to crystallize but which gave a pure crystalline hydrochloride. The formation of these two substances could be predicted by assuming, as a first reaction, 1,4-addition of hydrogen to each of the two possible enolic modifications of Ib.

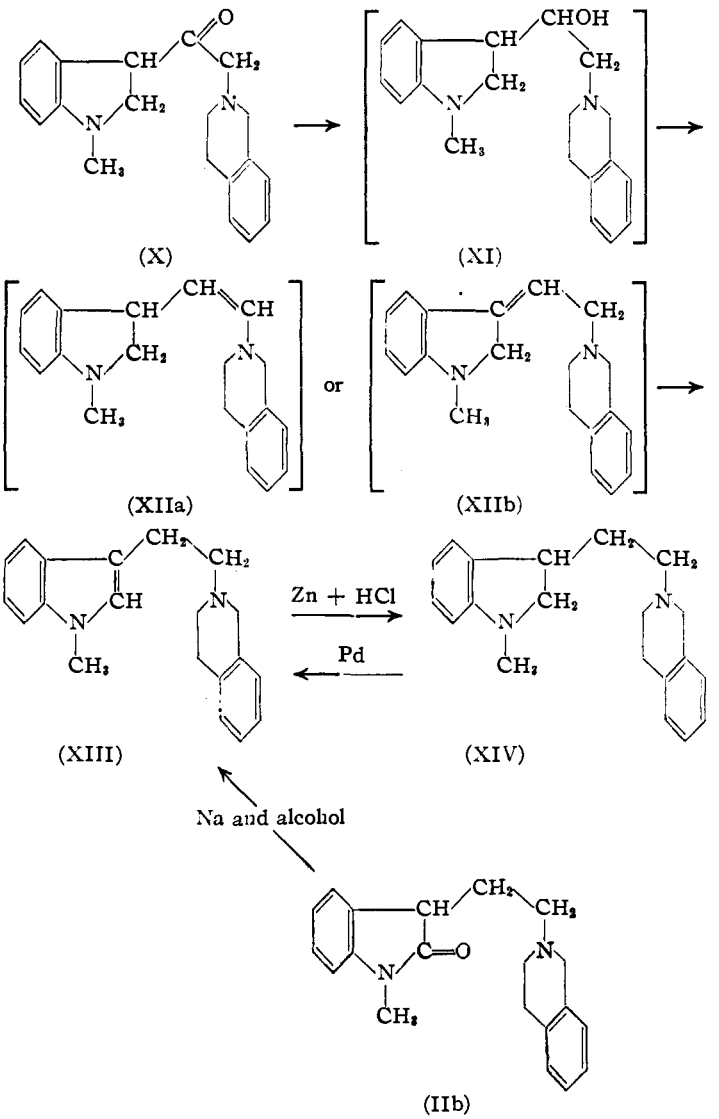
The constitution of our 167° melting compound (IIb) has been proved by two other unequivocal syntheses, schematically illustrated by formulas V → IIb and VII → VIII → IIb. Neither synthesis however proved to be an improvement over the reduction of Ib as far as yield is concerned. The reaction of the sodium salt of 1-methyl-3-acetyloxindole (V) with 1-bromo-2-N-tetrahydroisoquinolylethane (VI) resulted in poor yields of IIb, primarily because of the tendency of VI to condense with itself at elevated temperatures. The reaction of 1-methyl-3-(2-bromoethyl)-oxindole (VII) with tetrahydroisoquinoline in the cold led to 2,3-dihydro-8-methylfuro[2,3-b]indole (VIII) in quantitative yield. Heating the latter, however, with tetrahydroisoquinoline hydrobromide or heating the original mixture of VII and tetrahydroisoquinoline, resulted in a difficultly separable mixture of IIb and another substance whose constitution is not certain but the empirical analyses of which show the formula $C_{20}H_{20}ON_2$ (IX).

The constitution of the second product secured on the reduction of Ib, namely, X, has been demonstrated as diagrammatically outlined by reactions X → XIV, XIV → XIII, and IIb → XIII When the product (X) was reduced with sodium and alcohol it yielded a solid, m. p. 82°, containing no oxygen (XIII). This solid was identical with the compound secured on reducing IIb with sodium and alcohol. Considerable experience in this Laboratory (unpublished work) has convinced us that the transformation IIb → XIII is typical of oxindoles of this general character and compound XIII is therefore 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole and the mechanism of its formation from X is suggested in formulas XI and XIIb (or XIIa) of the diagram referred to above.

What is very significant for indole chemistry is the discovery here of a most interesting reduction of a 2,3-dihydro-3-acyl-indole (X) into a 3-alkyl indole (XIII) with sodium and alcohol. We hope to report later on the general application of this spontaneous rearrangement of XIIb or XIIa into XIII.

The dehydrogenation of IIb yielded considerable isoquinoline and about a 30% yield of a crystalline substance, m. p. 182°, of the formula $C_{20}H_{20}ON_2$ having the correct analysis for IIIb. All attempts to effect ring closure on this compound failed and we are loathe to assign to it the structure of a 1,2-dihydroisoquinoline (IIIb). Moreover, this dehydrogenation product is identical with the product (IX) which arises on treating IIb with tetrahydroisoquinoline hydrobromide. It is indeed difficult to explain how a 1,2-dihydroisoquinoline of structure IIIb would arise in such a reaction. The absorption spectrum of compound IX indicates that it is still an oxindole and does not give any additional peak which might be expected for the increased conjugation of a 1,2-dihydroisoquinoline. We have, therefore, concluded that dehydrogenation of yohimbine or compounds related to it like IIb does not lead to 1,2-dihydroisoquinolines and the projected synthesis of the yohimbine ring structure via IIIb is not possible.

Having failed to effect ring closure *via* IIIb →



IVb, we next attempted this through dehydrogenation of 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIII). If the initial dehydrogenation attack were at the 3,4-position of the tetrahydroisoquinoline nucleus, such a ring closure should be possible. On carrying out the reaction, however, quantitative cleavage of XIII took place, giving isoquinoline and 1-methyl-2-ethylindole. Likewise a selenium dehydrogenation of IIb gave quantitatively isoquinoline. These findings are of great significance as they indicate that cleavage at the nitrogen atom is the preferred reaction on dehydrogenation of these compounds related to yohimbine. It has been demonstrated clearly by Scholz[11] that the so-called "tetrahydroyobyrine," one of the two principal degradation products of yohimbine with selenium, is the product of just such a cleavage. Pruckner and Witkop[8] have suggested that similarly, in the case of formation of the other dehydrogenation product of yohimbine, namely, yobyrine, the focal point of dehydrogenation is at the other vulnerable linkage to the nitrogen atom, instead of at the 3,4-position of the tetrahydroisoquinoline nucleus, as suggested by Barger and Scholz.[5] Thus, instead of structure IVa, they suggest that yobyrine is 3-*o*-xylyl-4-carboline. Our findings certainly support such a view for the mechanism of dehydrogenation.

(11) Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).

Experimental

Tetrahydroisoquinoline.—The tetrahydroisoquinoline was prepared from distilled Eastman Kodak Co. "Practical" isoquinoline by catalytic hydrogenation[12] using copper chromite as described by Cromwell.[13] It distilled at 114–115° at 14 mm. pressure.

Ethyl N-Tetrahydroisoquinolylacetate.[3]—A mixture of 64.6 g. of tetrahydroisoquinoline, 50 g. of ethyl chloroacetate, 40 g. of finely powdered sodium carbonate and 200 cc. of benzene was refluxed vigorously for one hour on the steam-bath. Water was added, the benzene solution separated and distilled. The main fraction consisted of 72 g. boiling at 178–183°, 15 mm. Upon redistilling all fractions 74 g. of the ester was obtained, 180–182° (15 mm.).

1-Methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib).—To a solution of sodium ethylate from 5.5 g. of sodium in 60 cc. of absolute alcohol, a mixture of 37.5 g. of ethyl N-tetrahydroisoquinolylacetate and 24 g. of 1-methyloxindole[14] was added. After heating for one hour on the steam-bath, the mass was cooled and 55 g. of sodium salt was obtained after filtering and washing with absolute alcohol. The salt was suspended in 250 cc. of cold ethanol (ice-bath) dissolved by the addition of 5 *N* hydrochloric acid and then diluted with 600 cc. of ice water. Then the solution was made alkaline by the slow addition of sodium carbonate solution, and crystallization was induced by vigorous scratching. Yield was 42 g., m. p. 194–196°; on recrystallization from 95% ethanol, m. p. 199–200°.

Anal. Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.98; H, 6.31. Found: C, 75.32; H, 6.77.

Like other oxindole ketones of this type which we have prepared, the compound was cleaved readily by strong acids and bases.

3-(N-Tetrahydroisoquinolylacetyl)-oxindole (Ia).—This acyloxindole was prepared in the same manner as described above for the N-methyl analog. From 22 g. of oxindole and 38 g. of ethyl N-tetrahydroisoquinolylacetate there was obtained 30 g. of the acyloxindole after crystallization from ethanol, m. p. 268-270°.

Anal. Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92. Found: C, 74.63; H, 5.99.

Catalytic Reduction of 1-Methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib).—To 8.0 g. (0.025 mole) of the oxindole ketone dissolved in 80 cc. of glacial acetic acid was added 1.33 cc. of sulfuric acid followed by 0.8 g.

(12) We are indebted to Dr. Robert Baker and Mr. Ralph Olberg of Northwestern University for their coöperation in preparing a quantity of tetrahydroisoquinoline.

(13) Cromwell and Cram, THIS JOURNAL, **65**, 304 (1943).

(14) R. Stolle, *J. prakt. Chem.*, [2] **128**, 1-20 (1930).

of palladium oxide.[15] The solution was heated to 80° and hydrogenated at this temperature at 40–45 lb. pressure until two moles had been absorbed (four to six hours). While shaking, a precipitate usually separated which slowly went into solution as hydrogenation proceeded. The acetic acid was distilled under vacuum to a small volume, water was added, and if necessary hydrochloric acid added to give complete solution. The solution was extracted with ether to remove non-basic material, made basic with excess alkali, extracted with ether and the residue after evaporation of the ether subjected to distillation. Low boiling material proved to be tetrahydroisoquinoline (picrate, m. p. 199°) formed by cleavage. The main product distilled at 195–205° (bath temperature), 0.01 mm. pressure; yield 6.5 g., pale yellow oil. For analysis the oil was redistilled; b. p. 200–202° bath temperature (0.01 mm.).

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.09; H, 7.35.

Treating the oil in alcohol solution with concentrated hydrochloric acid and then adding ether to make an ether–alcohol solution consisting of 30% alcohol gave 4.8 g. of crystalline hydrochloride, m. p. 183–186°. Recrystallization from ether–alcohol gave 4.0 g. of the hydrochloride melting at 186–188°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.08, 69.89; H, 7.31, 6.80.

The oil obtained from the hydrogenation was believed to be a single compound until it was found that a concentrated ethereal solution of the oil on long standing deposited sandy crystals, m. p. 163–165°, which proved to be 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).

To separate the solid from the mixture, the hydrochloride of the mixture was repeatedly crystallized from ether–alcohol solution as described above. The hydrochloride of the solid, being more soluble, became concentrated in the mother liquors. The solid obtained from the mother liquors on rendering alkaline amounted to 5–7% of the weight of the original oil mixture, and crystallized readily from methanol, white prisms, m. p. 167°.

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.24; H, 7.25.

It readily formed a hydrochloride crystallizing from ether–alcohol as white needles, m. p. 238–239°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.39; H, 6.51.

The picrate of the solid was prepared by adding an equimolecular quantity of picric acid in benzene to a hot solution of the solid in benzene. It was sparingly soluble in alcohol and in benzene, crystallizing as yellow needles, m. p. 208–209° dec.

Anal. Calcd. for $C_{26}H_{25}O_8N_5$: C, 58.32; H, 4.67. Found: C, 58.71; H, 4.54.

The other product of the hydrogenation, obtained as a colorless oil from its purified hydrochloride, is 1-methyl-2,3-dihydro-3-(N-tetrahydroisoquinolylacetyl)-indole (X). It distilled cleanly, b. p. 215–217°, (1 mm.).

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.43; H, 7.19. Found: C, 78.38; H, 7.48.

Its hydrochloride crystallized as fine white needles from ether–alcohol solution, m. p. 190–191°.

Anal. Calcd. for $C_{20}H_{23}ON_2Cl$: C, 70.07; H, 6.72. Found: C, 70.40; H, 6.99.

Catalytic Reduction of 3-(N-Tetrahydroisoquinolylacetyl)-oxindole (Ia).—The oxindole ketone (4.6 g.) was dissolved in 50 cc. of glacial acetic acid and there was added 1.5 g. of sulfuric acid and 0.5 g. of palladium oxide. The hydrogenation was carried out at 40–45 lb. pressure and at 75–80°. The time required for absorption of two moles of hydrogen was five hours. No precipitate formed in the solution. The reaction products were worked up as described above in the reduction of Ib. The acid soluble fraction distilled cleanly in high vacuum as a viscous pale yellow oil which slowly set to a glassy solid, b. p. 205–208° bath temperature (0.001 mm.).

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.05; H, 6.89. Found: C, 77.50; H, 6.72.

All attempts to crystallize the product from ether, alcohol, petroleum ether and combinations of these solvents failed. Likewise, although a hydrochloride and a picrate formed neither of these could be induced to crystallize. Further work on this compound was reserved for a later date and the work described in this paper was performed on the N-methyl analog which seemed to offer less complications in subsequent reactions.

Synthesis of 1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).—(a) From Sodium Salt of 1-Methyl-3-acetyloxindole (V) and 1-Bromo-2-N-tetrahydroisoquinolylethane (VI).—The sodium salt of the 1-methyl-3-acetyloxindole was prepared by adding a solution of sodium in absolute alcohol to a hot alcoholic solution of the acetyloxindole, care being taken to avoid an excess of sodium.

For the preparation of 1-bromo-2-N-tetrahydroisoquinolylethane, bromohydrin was treated with two moles of tetrahydroisoquinoline to yield 2-N-tetrahydroisoquinolylethanol,[16] b. p. 120–123° (2 mm.). This was converted into the bromo-compound by refluxing with 48% hydrobromic acid.[17] The bromo compound was isolated as the hydrobromide, insoluble white salt in acetone, and crystallized as white needles from acetone–alcohol mixture, m. p. 238–239°. It was analyzed by determining the amount of bromide ion in aqueous solution.

Anal. Calcd. for $C_{11}H_{15}NBr_2$: Br, 24.9. Found: Br, 25.4.

For use in the following condensation, the hydrobromide was suspended in ether and shaken with dilute alkali. The ethereal solution was washed with water, dried and the ether removed *in vacuo*.

A mixture of 6.0 g. of sodium salt of 1-methyl-3-acetyloxindole, 6.0 g. of 1-bromo-2-N-tetrahydroisoquinolylethane, 0.5 g. of sodium iodide, and 60 cc. of dry acetone was heated in a sealed tube at 100° for twenty-four hours. The resulting reddish solution was filtered to remove insoluble salts and the acetone removed. The residue was taken up in ether and washed with alkali to remove unchanged acetyloxindole. For deacylation, the remaining product was refluxed for twenty minutes in 20 cc. of absolute alcohol containing 1.0 g. of sodium, and poured into water. Washing the ether extract with water removed the greater portion of the reddish color. After removal of the ether and distilling there was obtained 2.1 g. of yellow oil distilling at 200–215° bath temperature (2 mm.). From the ethereal solution cooled overnight 0.25 g. of solid, m. p. 167°, was obtained. It was identical to the 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb) obtained by hydrogenation of the oxindole ketone (Ib). It also gave an identical picrate. On long standing the ethereal mother liquor deposited a further crop (0.2 g.) of the solid. A similar run heated at 140–150° gave the same results.

Upon heating the 1-bromo-2-N-tetrahydroisoquinolylethane alone on the water-bath, it quickly darkened and turned into a semisolid. A sample of the solid isolated from it melted over 300° and had no definite melting point. At lower temperatures the bromo compound did not react with the sodium salt of the 3-acetyloxindole. It was possible to run the reaction in dioxane heated at 80–90° for twenty-four hours. However, no increase in the yield of desired solid, m. p. 167°, was obtained.

(b) **From 1-Methyl-3-(2-bromoethyl)-oxindole (VII).**—1-Methyl-3-(2-phenoxyethyl)-oxindole was prepared by heating a mixture of 21.0 g. of sodium salt of 1-methyl-3-acetyloxindole, 100 g. of phenoxyethyl bromide. 15 cc.

(15) Obtained from American Platinum Works, Newark, New Jersey. Platinum oxide was not found suitable for these reductions.

(16) Skita, *Ber.*, **57**, 1981 (1924).

(17) *Cf.* "Organic Syntheses," Coll. Vol. II, 91 (1943).

of dry acetone and 5.0 g. of sodium iodide under reflux in a metal-bath for fifteen hours at 150–160°. The reddish solution was diluted with ether and washed with alkali to remove unchanged acetyloxindole. Upon distillation at diminished pressure 84 g. of phenoxyethyl bromide was removed. The residue was boiled for thirty minutes in 100 cc. of absolute alcohol containing 5.0 g. of sodium to remove the acyl group and poured into water. The product was taken up in ether, washed with water to remove colored materials, and distilled after removal of the solvent. There was obtained 15.0 g. of pale yellow oil which on standing slowly crystallized. A sample crystallized from petroleum ether as silky needles, m. p. 57°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41. Found: C, 76.23; H, 6.36.

1-Methyl-3-(2-bromoethyl)-oxindole (VII) was obtained from the 1-methyl-3-(2-phenoxyethyl)-oxindole by treating with hydrobromic acid.[18] There was obtained 11.5 g. of colorless oil, b. p. 165–168° (2 mm.), which crystallized on standing as white needles from petroleum ether, m. p. 63°.

Anal. Calcd. for $C_{11}H_{12}ONBr$: C, 51.98; H, 4.75. Found: C, 52.23; H, 4.78.

2,3-Dihydro-8-methylfuro[2,3-b]indole (VIII) was obtained quantitatively from the bromoethyloxindole (VII); (a) by heating in benzene solution with tetrahydroisoquinoline, (b) by reaction with tetrahydroisoquinoline alone in the cold, and (c) by treating in alcoholic solution with sodium ethoxide. The reaction in each case was rapid and required only ten to fifteen minutes for completion. With tetrahydroisoquinoline, the hydrobromide of the base separated from the mixture. The dihydrofuroindole was dissolved in ether and the basic materials removed by washing with dilute acid. The residue after removal of the ether was either crystallized directly or distilled, b. p. 152–155° (12 mm.). It crystallized from petroleum ether as white prisms, m. p. 84°.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.30; H, 6.36. Found: C, 76.42; H, 6.38.

Upon refluxing with ten times its weight of 48% hydrobromic acid for six hours the bromoethyloxindole (VII) was formed, m. p. 52–53°.

To obtain 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb) 50.8 g. of the bromoethyloxindole (VII) (0.1 mole) and 26.6 g. of tetrahydroisoquinoline (0.2 mole) were mixed and heated gently on the steam-bath. The mixture solidified and was essentially a mixture of the dihydrofuroindole (VIII) and tetrahydroisoquinoline hydrobromide. This mixture was heated under nitrogen in a metal bath to 190° for three hours. The mixture was made alkaline and taken up in ether. A separation of basic from non-basic materials was made by washing with dilute acid. The basic fraction contained in the aqueous acidic washes was isolated in the usual manner and distilled. The low boiling fraction (5.0 g.) consisted of tetrahydroisoquinoline which was removed on the water pump. The main fraction was distilled in high vacuum. There was obtained 33.0 g. of yellow oil, b. p. 170–175° (0.005 mm.). It was dissolved in ether, concentrated, and allowed to crystallize. Two crops were obtained from ether; the ether was replaced with methanol and two further crops obtained. A total of 6.3 g. of solid was obtained, m. p. 146–150°, which proved to be a 50–50 mixture of the tetrahydroisoquinolylethyloxindole (IIb) and of a compound (IX), m. p. 182°.

The mixture was separated by fractional crystallization from ether and from methanol, and also mechanically. The compound (IX) is less soluble in methanol, but more soluble in ether than the tetrahydroisoquinolylethyloxindole (IIb) and crystallized in smaller prisms which when impure had a rose color. The tetrahydroisoquinolylethyloxindole (IIb) after crystallization from methanol melted at 166–167° and gave a picrate melting at 208° dec. The crude compound (IX) from the mixture melted at 172–178°. Treatment with norite in methanol removed all color and the compound crystallized as small colorless prisms, m. p. 182°.

Anal. Calcd. for $C_{20}H_{20}ON_2$: C, 78.92; H, 6.62; N, 9.19. Found: C, 78.71, 78.76; H, 6.76, 6.49; N, 9.19.

A picrate readily formed by admixing hot alcoholic solutions containing equimolecular quantities of the compound and picric acid; yellow prisms, m. p. 198° dec.

Anal. Calcd. for $C_{26}H_{23}O_8N_5$: C, 58.53; H, 4.34. Found: C, 58.42; H, 4.36.

Attempt to Dehydrogenate 1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIb).—One gram of the tetrahydroisoquinolylethyloxindole (IIb), m. p. 167°, was intimately mixed with 0.3 g. of palladium black[19] and the mixture heated at 60–80 mm. pressure for one hour at 190–200°. No further liberation of gas took place after forty minutes. The products of the reaction were then directly distilled. The low boiling fraction consisted of isoquinoline (picrate, m. p. 220°) indicating that some cleavage had occurred. The main fraction, 0.6 g. reddish oil distilled at 180–185° bath temperature (0.02 mm.). From a concentrated ethereal solution of the oil, there was obtained 0.25 g. of a solid compound, m. p. 172–175°. Recrystallized from methanol, it melted at 182° and gave no depression when mix-melted with compound (IX) obtained above.

Anal. Calcd. for $C_{20}H_{20}ON_2$: C, 78.92; H, 6.62; N, 9.19. Found: C, 78.78; H, 6.68; N, 9.07.

Its picrate, prepared as described above, melted at 198° dec.

All attempts to dehydrogenate at temperatures below 175° gave the tetrahydroisoquinolylethyloxindole back unchanged. Upon heating the tetrahydroisoquinolylethyloxindole alone at 200° for one hour 70% of it was recovered. The remainder was an uncrystallizable oil, but none of the 182° compound was isolated. However, when 0.3 g. was heated under identical conditions for the dehydrogenation with tetrahydroisoquinoline hydrobromide, a reddish oil was obtained from which 0.08 g. of the 182° compound was isolated with no recovery of the original.

Attempts to Ring Close Compound (IX).—Compound IX was at first thought to be 1-methyl-3-(2-N-dihydroisoquinolylethyl)-oxindole (IIIb) and several attempts at ring closure were made. Heating the compound in phosphorous oxychloride did not effect ring closure. Trials in which phosphorus pentoxide was added to a refluxing solution of the compound in xylene gave the compound back unchanged. In other attempts the compound was treated first with phosphorus pentachloride and then with aluminum chloride in nitrobenzene solution.[20] When the reactions were carried out at room temperature the solid was recovered unchanged. Similarly, at the temperature of the steam-bath, the solid was again recovered. Under more drastic conditions (175°) some of the solid was recovered and the remainder was converted into tar and halogenated products. Since all attempted ring closures failed, we felt that the compound was not a 1,2-dihydroisoquinoline.

Reduction of 1-Methyl-2,3-dihydro-3-N-tetrahydroisoquinolylacetylindole (X).—To a hot solution of 6.0 g. of the dihydro-tetrahydroisoquinolylacetyl-oxindole in 260 cc. of absolute ethanol was added 25.0 g. of sodium in portions over a period of two hours. The alcoholic solution, after removing the greater portion of the alcohol *in vacuo*, was diluted with water and the products were extracted with ether. The ethereal solution was washed with 10% hydrochloric acid to remove the basic materials. The basic fraction proved to be XIII which was crystallized directly from petroleum ether, yielding 3.1 g. of white prisms, m. p. 80–81°. A sample upon distillation gave a colorless oil, b. p. 190–192°, bath temperature (0.001 mm.), which solidified on cooling. Recrystallized from petroleum ether it melted at 82°.

(18) *Cf.* Boyd-Barrett and Robinson, *J. Chem. Soc.*, 320 (1932).

(19) Willstätter and Waldschmidt, *Ber.*, **54**, 123 (1921); *cf.* Späth and Lederer, *ibid.*, **63**, 120, 2102 (1930).

(20) *Cf.* Von Braun, *ibid.*, **57**, 908 (1924).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 83.02; H, 7.88.

The picrate prepared by admixing equimolecular portions of the compound and picric acid in benzene solution, first precipitated as an oil but crystallized when moistened with methanol. Recrystallization from benzene gave fine yellow needles, m. p. 161°.

Anal. Calcd. for $C_{26}H_{25}O_7N_5$: C, 60.11; H, 4.85. Found: C, 60.47; H, 4.85.

Reduction of XIII with Zinc and Hydrochloric Acid.—A Clemmensen reduction was attempted on the ketone X without success. The Clemmensen procedure was employed on XIII on the assumption at that time that we were dealing with the hydroxy compound (XI). To a solution of 1.5 g. of XIII in 40 cc. of 50% acetic acid, 10 cc. of concentrated hydrochloric acid and 10 g. of freshly amalgamated 20-mesh zinc were added. The mixture was heated on the steam-bath for five hours with a further addition of 5 cc. of hydrochloric acid every hour. The acetic acid was removed *in vacuo* and the material taken up in ether after the addition of enough strong alkali to solubilize the zinc hydroxide. The ethereal solution was washed with water, then with 10% hydrochloric acid and the basic material obtained from the acidic washings. On distilling, 1.4 g. of 1-methyl-2,3-dihydro-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIV) was obtained as a colorless oil, b. p. 190–195°, bath temperature (0.1 mm.).

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27. Found: C, 82.17; H, 8.25.

When the dihydroindole was treated with one mole of picric acid in methanol, a dark red colored monopicrate was obtained, m. p. 155°.

Anal. Calcd. for $C_{26}H_{27}O_7N_5$: C, 59.88; H, 5.22. Found: C, 59.92; H, 5.20.

Upon treating the monopicrate in methanol with an additional mole of picric acid, a yellow dipicrate was obtained, m. p. 176°.

Anal. Calcd. for $C_{32}H_{30}O_{14}N_8$: C, 51.20; H, 4.03. Found: C, 51.30; H, 4.48.

This characteristic of such dihydroindoles to give red monopicrates and yellow dipicrates has been previously observed by Julian and Pikl.[21]

1-Methyl-3-(2-N-tetrahydroisoquinolylethyl)-indole (XIII). (a) Reduction of the Ethyloxindole (IIb).—The ethyloxindole (IIb) (2.0 g.) was dissolved in 50 cc. of absolute ethanol and over a period of two hours there was added 12.0 g. of sodium and 100 cc. of absolute ethanol in portions. The alcohol solution, after removal of part of the alcohol *in vacuo*, was diluted with water and the products extracted with ether. The ethereal solution was washed with dilute acid to remove the basic fraction which was isolated in the usual manner and was distilled. There was obtained 1.4 g. of pale yellow oil, b. p. 180–185° bath temperature which on exposure to air turned reddish, especially when warmed. A sample was redistilled for analysis, b. p. 180–182° (0.008 mm.).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 82.54; H, 8.10.

The picrate formed by heating equimolecular portions of the oil and picric acid in methanol was a red oil which on standing solidified, m. p. 155–157° dec. Recrystallization from methanol gave yellow needles, m. p. 161° dec.

Anal. Calcd. for $C_{26}H_{22}O_7N_5$: C, 60.11; H, 4.85. Found: C, 60.30; H, 4.64.

Struck by the similarity between this picrate and that of the sodium reduction product of X, we examined the two picrates and found them identical. On seeding the distillate, from which the picrate was formed, it crystallized and melted at 82°.

(b) Dehydrogenation of the Dihydroindole (XIV).—A mixture of 0.69 g. of the dihydroindole and 0.22 g. of palladium black was heated to 195–200° for forty minutes. The evolution of gas was quite vigorous during the first fifteen minutes. The mixture after heating was deeply colored. On distillation there was obtained 0.54 g. of yellow oil which becomes colored on standing, b. p. 175–180° bath temperature (0.006 mm.). A sample was redistilled for analysis, b. p. 175–177° at the same pressure.

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.63. Found: C, 82.46; H, 7.28.

This oil likewise crystallized on seeding with the 82° melting solid (XIII) and the two proved to be identical.

The picrate formed by adding an equimolecular quantity of picric acid to a solution of the base in benzene was an oil which crystallized from benzene–methanol, m. p. 153–156° dec. When recrystallized from methanol it gave yellow needles, m. p. 161°. A mixed melting point with the picrate obtained above from the reduction of the ethyloxindole (IIb) gave no depression.

Anal. Calcd. for $C_{26}H_{25}O_7N_5$: C, 60.11; H, 4.85. Found: C, 59.91; H, 4.74.

Attempted Ring Closure of XIII by Dehydrogenation with Selenium.—1.0 g. of the solid, m. p. 82°, was intimately mixed with 0.7 g. of selenium and heated in a distillation tube. At 290–300° reaction ensued. Heating was continued for ten minutes. Working up and distillation in the usual manner gave 0.45 g. (the theoretical quantity) of isoquinoline, identified by its picrate, m. p. 222°.

Attempted Ring Closure of IIb by Dehydrogenation with Selenium.—In exactly the same manner as above 1.0 g. of IIb gave almost quantitatively isoquinoline.

Summary

1. For attempted synthesis of the basic ring structure of yohimbine, 1-methyl-3-(2-N-tetrahydroisoquinolylacetyl)-oxindole and its unmethylated analog have been prepared.

2. On catalytic reduction 1-methyl-3-(2-N-tetrahydroisoquinolylacetyl)-oxindole yields two products, 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole and 1-methyl-2,3-dihydro-3-(2-N-tetrahydroisoquinolylacetyl)-indole. The constitution of each product has been proved.

3. The conversion of a 1,2-dihydro-3-acyl-indole into the corresponding 3-alkyl indole by reduction with sodium and alcohol (followed by loss of water and rearrangement) is recorded.

4. Attempts to prepare the basic ring structure of yohimbine by ring closure on the dehydrogenation product of 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole failed. The dehydrogenation product is therefore probably not the desired 1,2-dihydroisoquinoline.

5. The dehydrogenation of yohimbine and related compounds seems to result primarily in cleavage at the nitrogen atom of the tetrahydroisoquinoline nucleus.

CHICAGO, ILLINOIS RECEIVED[22] JULY 21, 1947

(21) Julian and Pikl, THIS JOURNAL, **57**, 539, 563 (1935).

(22) Original manuscript received September 9, 1946.