aluminum hydride in 50 ml. of ether, and stirred for one and one-half hours. Water was added, the aluminum hydroxide dissolved in 3% hydrochloric acid, and the ether layer washed, concentrated and steam-distilled. From the steam-distillate, 4.3 g. of indole was recovered. No indoline was formed. Under these same conditions both 1-methylindole and 1,3-dimethylindole were converted to the respective indolines in 25–30% yields.

Reduction of Dioxindoles.—From 3.72 g. of dioxindole, treated in essentially the same manner, 2.05 g. of oxindole, and, surprisingly, 0.41 g. of indole were obtained. On the other hand, 3.2 g. of 1-methyldioxindole on reduction yielded 1.2 g. of 1-methylindole and 0.5 g. of the oxindole.

Preparation of N-Methylyobyrine.—The following compounds were prepared as previously described.[8b]

o-Tolylacetyl-1-methyltryptamine crystallized from ether in creamy white plates, m. p. 103.5°.

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.39; H, 7.23. Found: C, 78.52; H, 6.97.

N-Methyldihydroyobyrine picrate, crystallized in yellow needles from benzene, m. p. 205–206° dec.

Anal. Calcd. for $C_{26}H_{23}O_7N_5$: C, 60.34; H, 4.48. Found: C, 60.72; H, 4.47.

N-Methylyobyrine (picrate, m. p. 233° dec.) crystallized from ether–methanol as shiny white needles, m. p. 106°.[1]

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.33; N, 9.78. Found: C, 83.72; H, 6.30; N, 9.85.

The over-all yield, in large (4 g.) runs of N-methylyobyrine from *o*-tolylacetyl-1-methyltryptamine, was 30%.

Summary

1-Methyloxindoles are reduced in good yields to the corresponding indoles with lithium aluminum hydride.

The preparation of N-methylyobyrine is described.

CHICAGO, ILLINOIS RECEIVED MARCH 2, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

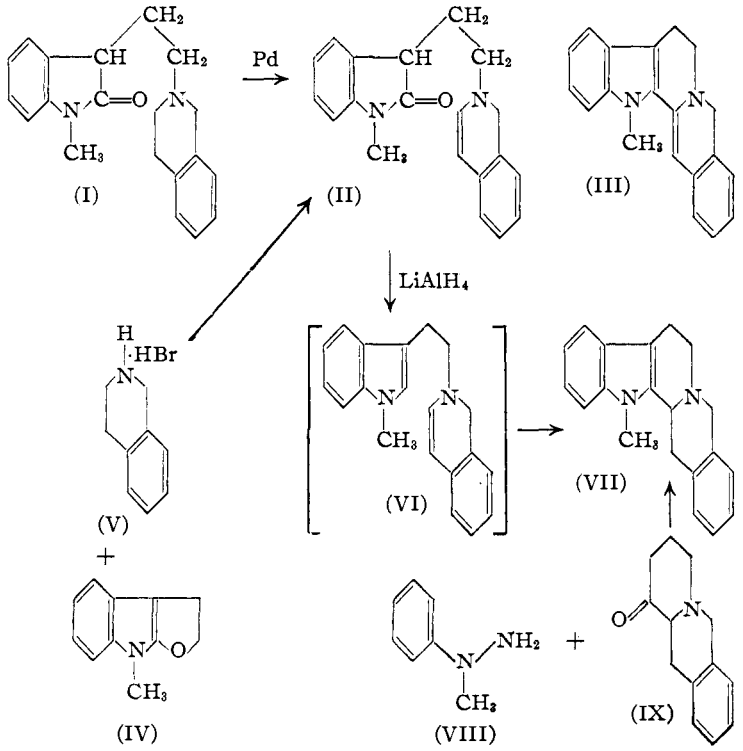
Studies in the Indole Series. XII. Yohimbine (Part 3). A Novel Synthesis of the Yohimbine Ring Structure

BY PERCY L. JULIAN AND ARTHUR MAGNANI

In an earlier communication dealing with the preparation and properties of 3-(N-tetrahydroisoquinolylethyl)-1-methyloxindole (I),[1] it was shown that dehydrogenation of I with palladium black yielded a 182° melting compound which could not be cyclicized, with the usual dehydrating agents, to III, a substance possessing the basic ring structure of yohimbine.

Largely because of this failure at ring closure, and also because of the difficulties hitherto experienced by various workers in attempts to prepare 1,2-dihydroisoquinolines like II, we expressed the opinion that our dehydrogenation product did not have the constitution II, despite the correct analyses and molecular weight. Certainly its preparation from the dihydrofuroindole (IV) and tetrahydroisoquinoline hydrobromide (V) was, to say the least, not a comfortable basis for ascribing to it the constitution II.

Our subsequent investigations, however, have shown that failure to secure ring closure represents no criterion for or against structure II, and further that the 182° melting dehydrogenation product of I actually does have the structure II, despite the considerations recorded above and in an earlier communication.[1]



Moreover, reduction of II with lithium aluminum hydride, a procedure which we have demonstrated converts 1-alkyl oxindoles smoothly to the corresponding indoles,[2] resulted in spontaneous cyclization of the intermediate (VI) to VII, a compound possessing the basic ring structure of

(1) Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

(2) Julian and Printy, *ibid.*, **71**, 3206 (1949).

yohimbine. Thus a novel synthesis of this structure is revealed, the potential usefulness of which is far-reaching.

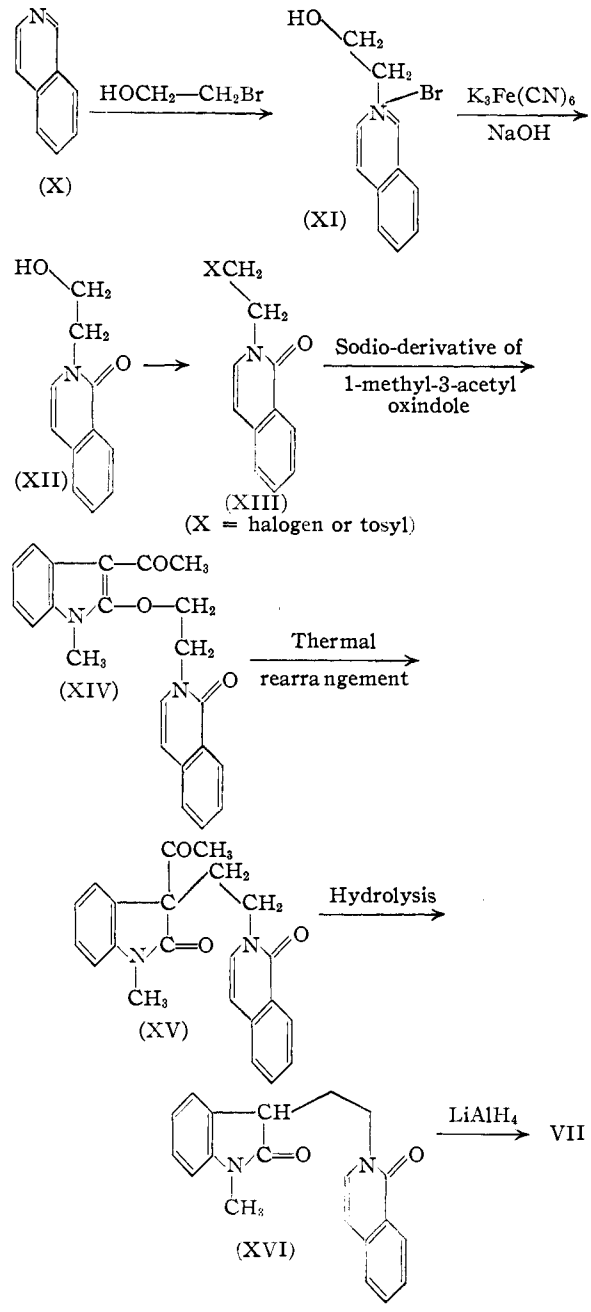
The structure of VII was demonstrated in several ways. First of all it was synthesized quite readily from VIII and IX by a procedure suggested by Clemo and Swan.[3]

The second verification of the structure of VII, demonstrated further the usefulness of this novel method of ring closure to yohimbine derivatives and afforded, in addition, some new insight into the 3-alkylation of oxindoles.[4] In an attempt to prepare compounds of the type represented by II and which indisputably possessed a double bond in the 3,4-position of the isoquinoline nucleus, we prepared the isoquinolone (XVI). All attempts to close the ring here through dehydration, involving enolization of the hydrogen atom in the 3-position of the oxindole, failed as had similar attempts on compound II. On reduction, however, with lithium aluminum hydride, XVI was readily converted into VII, the oxindole carbonyl being reduced as well as the carbonyl group of the isoquinolone.

Further verification of the structure of VII was obtained by its conversion to N-methylyobyrine[2] by treatment with palladium black, a reaction now well identified with compounds containing the yohimbine ring skeleton.[5]

As stated above, the preparation of XVI gave us our first insight into the mechanism of 3-alkylation of 1-methyl-3-acetyloxindole, a type of alkylation we have frequently employed over the past several years.[1,4] The quaternary adduct from ethylene bromohydrin and isoquinoline was converted in good yield with alkaline potassium ferricyanide to the isoquinolone alcohol (XII). The tosylate of the latter or the corresponding chlor-compound (XIII) reacted with the sodio-derivative of 1-methyl-3-acetyloxindole to yield a readily crystallizable O-alkyl derivative, to which we tentatively ascribe formula XIV. The experimental basis for this structure is diffuse and will be the subject of a separate communication. Suffice it to say that structure XIV has been chosen primarily on the basis of analogy in ultraviolet spectrum and other properties to the 1-methyl-2-methoxy-3-formyl indole prepared several years ago.[6]

Thermal rearrangement of this O-alkyl derivative (XIV) yields a C-alkyl acetyl derivative (XV), which could not be induced to crystallize, but which on hydrolysis gave the crystalline 1-methyl-3-(1-oxo-isoquinolylethyl)-oxindole (XVI). Thus we have one of the relatively rare cases where the O-alkyl intermediate in C-alkylation of 1,3-dicarbonyl compounds can be cleanly isolated and thermally rearranged into its C-alkyl isomer.



The further exploitation of this interesting type of ring closure for the simplest type of synthesis of the yohimbine ring structure yet reported, involving the addition of β-indolylethyl bromide and β-N-methylindolylethyl bromide to isoquinoline, is being studied and will be reported in another communication.

Experimental

Reduction of 1-Methyl-3-[2-N-(1,2-dihydroisoquinolylethyl)]-oxindole (II) to the Yohimbine Ring Skeleton (VII) with $LiAlH_4$.—The dihydroisoquinolylethyloxindole (II) was obtained by dehydrogenating the tetrahydroisoquinolylethyloxindole (I) with palladium black.[1] The

(3) Clemo and Swan, *J. Chem. Soc.*, 617 (1946).
(4) Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).
(5) Clemo and Swan, ref. 3; Prelog, *Helv. Chim. Acta*, **31**, 588 (1948); Woodward and Witkop, THIS JOURNAL, **71**, 379 (1949).
(6) Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).

dihydroisoquinolylethyloxindole (0.45 g., m. p. 180–182°) was dissolved in 5 ml. of dry dioxane and diluted with 30 ml. of absolute ether. Over a five-minute period with agitation there was added a solution of 70 mg. of lithium aluminum hydride in 25 ml. of absolute ether. The reaction mixture was allowed to stand for one hour at room temperature, cautiously decomposed by the addition of water, and then acidified with dilute acid. The aqueous acidic solution was extracted with ether to remove any non-basic material. The basic fraction (0.4 g.) obtained by basifying and extracting with ether was distilled. The fraction distilling as a yellow oil at 180–185° bath temperature (0.008 mm.) was collected and amounted to 0.3 g. Upon treatment in methanol with picric acid, there was obtained 0.25 g. of orange picrate, m. p. 198–202° dec. It was identical with the picrate of the base VII obtained from the Fischer indole synthesis involving the ketone IX, and after crystallization from methanol melted at 205–207° dec. The picrate (0.18 g.) upon decomposition with alkali yielded the base VII (85 mg.) melting at 132–135°. By heating 60 mg. of the base with palladium black as described below, N-methylyobyrine was isolated as the picrate (44 mg., m. p. 230–233° dec.).

Fischer Indole Synthesis of the Base VII.—The method and procedure used were essentially those described by Clemo and Swan.[3] The hydrazone prepared from α-methylphenylhydrazine (VIII) and the ketone (IX) was crystallized from aqueous methanol as yellow plates, m. p. 93°.

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.83; H, 7.47; N, 13.45.

The phenylhydrazone (0.44 g.) was ring closed by heating for twenty minutes on the steam-bath with 15 ml. of 5% sulfuric acid. The red aqueous solution was diluted with water, made alkaline, and extracted several times with ether. The ethereal solution was washed with water, dried over sodium sulfate, and the solvent removed. The residual reddish oil could not be crystallized at this point. It was dissolved in methanol, treated with a methanolic solution of 0.30 g. of picric acid, and concentrated on the steam-bath until crystallization of the picrate began. After cooling, the picrate was filtered and washed with methanol. There was obtained 0.32 g. of the picrate of the ring-closed-base VII, m. p. 206–208° dec. Recrystallization from methanol gave yellow needles, m. p. 209° dec.

Anal. Calcd. for $C_{26}H_{23}N_5O_7$: C, 60.34; H, 4.48; N, 13.54. Found: C, 60.40; H, 4.37; N, 13.26.

The free base VII was obtained from the picrate (0.3 g.) by shaking a suspension of it in ether with alkali until complete solution resulted. The ethereal solution was washed well with water, dried over sodium sulfate, and the solvent removed. The partially crystalline residue (0.14 g.) was distilled as a yellow oil (0.11 g.) collected at 0.002 mm. and 165–170° bath temperature. Slow crystallization from warm aqueous methanol gave the base VII as white plates; yield 88 mg., m. p. 135°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.72. Found: C, 83.20; H, 6.92; N, 9.66.

The base VII (30 mg.) was heated with 30 mg. of palladium black for twenty minutes at 215 to 225° and at 10–15 mm. pressure. The product was extracted with hot methanol and treated with norite. The methanol solution, upon treatment with 25 mg. of picric acid, yielded, on concentration, 25 mg. of the yellow picrate of N-methylyobyrine, m. p. 230–232° dec. After decomposition of the picrate with alkali, N-methylyobyrine (10 mg.) was readily obtained by crystallization from a concentrated solution in ether–petroleum ether as white rods, m. p. 105–106°. When this product was mixed with an authentic sample of N-methylyobyrine[2] (m. p. 105–106°), there was no depression of the melting point.

β-Hydroxyethyl-isoquinolinium Bromide (XI).—A mixture of 17.7 g. of ethylene bromohydrin and 20 g. of isoquinoline was heated on the steam-bath until an exothermic reaction darkened the solution and rapidly raised the temperature of the mixture to 190°. When allowed to cool slowly the reddish liquid set to a mass of crystals which was digested with acetone and filtered. The isoquinolinium bromide (34 g.) was dissolved in 34 ml. of hot methanol and crystallized by adding 340 ml. of hot acetone. There was obtained 26.2 g. of the isoquinolinium bromide, m. p. 154–156°. Further crystallizations raised the melting point to 157°.

Anal. Calcd. for $C_{11}H_{12}ONBr$: C, 51.99; H, 4.76; N, 5.51. Found: C, 51.86; H, 4.70; N, 5.42.

2-β-Hydroxyethyl-1-isoquinolone (XII).—The isoquinolinium bromide was oxidized to the isoquinolone in 60% yield with potassium ferricyanide by the method of Elpern and Hamilton.[7] The crude isoquinolone was isolated by filtration or by chloroform extraction and distilled. From 26 g. of the isoquinolinium bromide there was obtained 14.2 g. of a yellow oil which crystallized readily, b. p. 190–200°, bath temperature (2.5 mm.). The isoquinolone was dissolved in 10 ml. of methanol, 50 ml. of warm benzene was added and the solution concentrated to a volume of 35 ml. It crystallized as white plates; yield 11.8 g.; m. p. 114–116°. For analysis it was recrystallized from benzene, m. p. 116°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.73; H, 5.54; N, 7.31.

Tosylate of 2-β-Hydroxyethyl-1-isoquinolone (XIII).—The tosylate of the isoquinolone was best prepared by employing a large excess of tosyl chloride. To a suspension of 2.85 g. of the isoquinolone (finely divided) in 25 ml. of benzene was added 3.0 g. of tosyl chloride. The mixture was cooled in an ice-bath, and with vigorous agitation there was added 10 ml. of 30% sodium hydroxide over a period of five minutes. This mixture was agitated for five minutes, and the addition of tosyl chloride and sodium hydroxide was repeated twice. The slightly gummy precipitate of the tosylate changed to a finely divided precipitate which was collected on a filter and washed well with water and ether. There was obtained 4.0 g. of the tosylate, m. p. 160–164°. It is sparingly soluble in ether or benzene. For recrystallization, it was dissolved in a small amount of chloroform, diluted with hot benzene, and then concentrated until crystallization began, m. p. 166°.

Anal. Calcd. for $C_{18}H_{17}O_4NS$: C, 62.96; H, 4.99; N, 4.08. Found: C, 63.06; H, 4.96; N, 4.14.

2-β-Chloroethyl-1-isoquinolone (XIII).—Thionyl chloride (4 ml.) was cautiously added to 2.1 g. of the hydroxyethylisoquinolone covered with 6 ml. of petroleum ether (30 to 60°) and the resulting yellow layers allowed to stand for twenty minutes. This mixture was heated on the steam-bath until a homogeneous solution resulted, and the remaining petroleum ether and excess thionyl chloride were removed *in vacuo*. The residual yellow oil was dissolved in ether, and the solution washed with dilute alkali and water. The chloroethylisoquinolone was crystallized from ether–petroleum ether; yield 2.2 g., m. p. 102–105°. Recrystallization from the same solvents gave white needles, m. p. 109°.

Anal. Calcd. for $C_{11}H_{10}ONCl$: C, 63.62; H, 4.85; N, 6.74. Found: C, 63.88; H, 4.77; N, 6.62.

The same chloroethylisoquinolone was prepared from the tosylate. To 250 mg. of the tosylate in 10 ml. of dry alcohol-free acetone 50 mg. of lithium chloride was added and the mixture refluxed for one hour. The acetone was removed *in vacuo* and the residue was dissolved in ether and washed with water. The chloroethylisoquinolone (120 mg.) thus isolated melted at 107–109°.

2-β-Bromoethyl-1-isoquinolone (XIII).—Reaction of hydroxyethylisoquinolone with thionyl bromide yielded a mixture of products and very little of the bromoethylisoquinolone. The latter, however, was readily prepared from the tosylate as described for the chloroethylisoquinolone. From 0.5 g. of the tosylate and 0.5 g. of lithium bromide there was obtained 0.4 g. of the bromoethylisoquinolone, m. p. 109–110°. Recrystallization from ether–petroleum ether gave white needles, m. p. 112°.

(7) Elpern and Hamilton, THIS JOURNAL, 68, 1436 (1946).

Anal. Calcd. for $C_{11}H_{10}ONBr$: C, 52.40; H, 4.00. Found: C, 52.65; H, 4.10.

Reaction of Isoquinolones (XIII) with Sodio-derivative of 1-Methyl-3-acetyloxindole (a) with Tosylate of 2-β-Hydroxyethyl-1-isoquinolone.—A mixture of 2.5 g. of the tosylate and 2.1 g. of the sodium salt of the acetyloxindole in 50 ml. of alcohol-free acetone was refluxed vigorously for one hour under anhydrous conditions. The thick paste first formed was gradually replaced by a fine precipitate of the sodium salt of the sulfonic acid. This mixture was diluted with ether and washed with water. The reddish ethereal solution was concentrated and the last of the solvents removed *in vacuo*. The remaining oil was then crystallized from acetone–ether yielding 1.45 g. of the compound XIV resulting from O-alkylation of the acetyloxindole, m. p. 157–160°. Recrystallization from acetone–ether gave white needles, m. p. 161°.

Anal. Calcd. for $C_{22}H_{20}O_2N_2$: C, 73.31; H, 5.60; N, 7.77. Found: C, 73.37; H, 5.82; N, 7.40.

The compound XIV is sparingly soluble in ether and in the extraction described above will precipitate from the ethereal solution if all of the acetone is removed by washing.

(b) **With 2-β-Chloroethyl-1-isoquinolone.**—A mixture of 7.0 g. of the chloroethylisoquinolone, 14.0 g. of the sodio-derivative of 1-methyl-3-acetyloxindole, 1.0 g. of sodium iodide, and 70 ml. of dry dioxane was heated for 17 hours on the steam-bath with frequent shaking. The thick paste of solids slowly thinned as the reaction progressed. After cooling, water was added to dissolve the unchanged sodium salts and the mixture was extracted with ether. From the aqueous portion 5.6 g. of the acetyloxindole was recovered by acidification. The ethereal solution was washed free of alkali with water, small amounts of acetone being added to prevent precipitation of the sparingly soluble O-alkyl product. The product (XIV) was isolated and crystallized as previously described; yield, 3.1 g.; m. p. 158–160°.

(c) **With 2-β-Bromoethyl-1-isoquinolone.**—The same O-alkyl product (XIV) was obtained by refluxing 1.1 g. of the bromoethylisoquinolone, 2.2 g. of sodio-derivative of acetyloxindole, and 0.3 g. of sodium iodide in 25 ml. of dioxane for five hours. The work-up was the same as that described in (b); yield 0.35 g., m. p. 158–160°.

Hydrolysis of O-Alkyl Product (XIV).—Upon treatment of the O-alkyl product (XIV) with sodium ethoxide several products were obtained. To 1.45 g. of XIV in 10 ml. of ethanol a solution of 0.2 g. of sodium in 5 ml. of ethanol was added and the mixture heated for ten minutes on the steam-bath. The purple solution was diluted with ether and washed with water and dilute hydrochloric acid to remove most of the color. The ethereal solution was dried, concentrated, and taken to dryness. The residue (1.0 g.) crystallized readily from ether-petroleum ether to give 0.8 g. of crystals, m. p. 88–94°, which proved to be a mixture of two compounds. They were separated by fractional crystallization. One product crystallized as white plates, m. p. 116°, and proved to be 2-β-hydroxyethyl-1-isoquinolone. The other product crystallized as white rods, m. p. 110°, and by analysis appeared to be 2-β-ethoxyethyl-1-isoquinolone.

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.54; H, 6.77; N, 6.70.

Ether extraction of the acidified aqueous alkaline washes gave 1-methyl-3-acetyloxindole which crystallized as needles from aqueous methanol, m. p. 108–110°. By alkaline extraction of residues from the fractional crystallizations more of the acetyloxindole was obtained.

Thermal Rearrangement of the O-Alkyl Compound (XIV) and Hydrolysis to XVI.—The O-alkyl compound (1.3 g.) was heated in a metal-bath for ten minutes at 220–230° for the rearrangement. The red melt was allowed to cool and dissolved in ether but could not be induced to crystallize. By distillation (230–250° bath temperature, 0.5 mm.) there was obtained 1.1 g. of a red oil (XV) which again could not be obtained crystalline. It was dissolved in 5 ml. of ethanol and refluxed for ten minutes with a solution of 0.3 g. of sodium in 8 ml. of ethanol for deacetylation. After cooling and diluting with water, the product was extracted with ether and washed with water. Removal of the ether gave a reddish oil which crystallized readily from ether–petroleum ether yielding 0.7 g. of the 1-methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI), m. p. 120–124°. Recrystallization gave fine white needles, m. p. 126°.

Anal. Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.76; N, 8.95.

Attempts to Ring Close 1-Methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI).—A solution of 0.3 g. of the isoquinolylethyloxindole in 4 ml. of phosphorus oxychloride was refluxed for one hour. The oxychloride was removed *in vacuo* and the remaining viscous residue was dissolved by digestion with water. The acidic aqueous solution was rendered alkaline and extracted with ether. From the ethereal solution there was recovered 0.24 g. of the original compound, m. p. 121–124°. No other product was isolable. The same results were obtained when a longer refluxing time was used. Similarly, by using phosphorus pentoxide in xylene, the original compound was recovered. With phosphorus trichloride followed by treatment with aluminum chloride only the starting material was isolated from the halogen-containing products.

Reduction of 1-Methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI) with $LiAlH_4$ to VII.—Two grams of the oxo-dihydroisoquinolylethyl oxindole was dissolved in 10 ml. of dioxane and diluted with 50 ml. of absolute ether. There was added with agitation a solution of 0.4 g. of lithium aluminum hydride in 50 ml. of absolute ether over a five-minute period. After standing for one hour the reaction mixture was worked up as described for the reaction with the dihydroisoquinolylethyloxindole (II). The crude basic fraction (1.5 g.) was purified by distillation. The fraction distilling at 180–210° bath temperature and at 0.01 mm. (0.8 g.) was redistilled and the pale yellow oil (0.55 g.) distilling at 180–190° at 0.01 mm. collected. Upon treating the oil in methanol with 0.45 g. of picric acid there was readily obtained 0.75 g. of crude picrate melting at 180–190° dec. After two crystallizations from methanol, the picrate (0.3 g.) melted at 205–207° dec. and gave no melting point depression when admixed with the picrate of the base VII obtained by the Fischer indole synthesis. Upon decomposition of 100 mg. of the picrate with alkali there was obtained 40 mg. of the base VII (m. p. 132–135°) which upon treatment with palladium black gave N-methylyobyrine, isolated as the picrate (29 mg., m. p. 232–234° dec.).

Summary

A novel synthesis of the yohimbine ring structure is reported which comprises the spontaneous ring closure of a 3-[2-N-(1,2-dihydroisoquinolylethyl)]-indole.

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