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

Studies in the Indole Series. XI. The Reduction of Certain Oxindoles with Lithium Aluminum Hydride

BY PERCY L. JULIAN AND HELEN C. PRINTY

This investigation had its origin in the need for rather large quantities of N-methylyobyrine[1] and certain 5-ethoxylated indole derivatives. To secure the necessary starting materials, namely, 1-methylindole and 1-methyl-5-ethoxyindole, it seemed appropriate to study the reduction of the corresponding and very readily accessible oxindole analogs[2] with lithium aluminum hydride.[3] The method has been applied to several N-methylated oxindoles, and appears generally applicable for the reduction of these derivatives to indoles.

Even with the reverse addition of one mole of lithium aluminum hydride in ether to two moles of the oxindole suspended or dissolved in the same solvent, there always arose about 10–15% of the corresponding indoline. Easily removed from the indole by washing with dilute acid, its presence, nevertheless, gave another example of the reduction of isolated double bonds by lithium aluminum hydride.[4]

In view of the ease with which the reduction of N-substituted oxindoles and indoles took place, it was surprising that the reaction was an almost complete failure with unsubstituted oxindoles. Little or no indole could be obtained from oxindole even when the reaction was carried out at elevated temperatures in butyl ether, dioxane, or tetrahydrofuran. Likewise, unsubstituted indoles were not reduced to indolines by the reagent, a fact we have been able to utilize in the selective reduction of certain groups in more complex indole derivatives.[5]

Analogous results were noted in the behavior of dioxindoles: dioxindole was reduced to oxindole, with small amounts of indole resulting, whereas 1-methyldioxindole was reduced to 1-methylindole.

With ample quantities of 1-methylindole at our disposal, the preparation of 1-methyltryptamine was carried out according to the elegant method of Snyder and Eliel[6]; however, we were able to improve the yield by catalytic reduction[7] of the 1-methylindolylacetonitrile. N-Methylyobyrine was prepared from 1-methyltryptamine by the method already described for yobyrine.[8]

Experimental[9]

Reduction of 1-Methyloxindoles with Lithium Aluminum Hydride.—Twelve grams of lithium aluminum hydride in 600 ml. of anhydrous ether was added in forty minutes to a stirred suspension of 100 g. of 1-methyloxindole in 1 liter of anhydrous ether. The mixture was stirred another ten minutes, 250 ml. of water was added slowly, then 250 ml. of 4% hydrochloric acid. The reaction products were shaken out with ether, and the ether washed with 1 liter of 3% hydrochloric acid. The ether extract was concentrated, then steam-distilled until 4 liters of distillate was obtained. This was extracted with ether, dried over sodium sulfate, and the ether distilled. Fifty-five grams (61.8%) of 1-methylindole, a pale yellow oil, was obtained. This gave a red picrate, m. p. 146–147° dec. (lit.[10] 150°).

The residue from steam-distillation was extracted with ether, washed, dried and concentrated. Fourteen grams of 1-methyloxindole, m. p. 82–85°, was obtained.

The acid washes were treated with sodium hydroxide pellets until strongly alkaline, then steam-distilled until 1 liter of distillate was obtained. This was extracted with ether, which was dried over sodium sulfate, and the ether was distilled. Eleven grams (12%) of pale yellow oil was obtained. This oil distilled at 100–102° at 14 mm., and gave a picrate, shiny yellow plates, m. p. 171–172° dec. Carrasco[11] reports a melting point of 165° for 1-methylindoline picrate.

1,3-Dimethyloxindole was reduced by the metal hydride to 1,3-dimethylindole, b. p. 132–139° (16 mm.), picrate m. p. 141–142° dec., in 85.8% yield. A 13% yield of 1,3-dimethylindoline, a yellow oil, was also obtained. This gave a yellow picrate which crystallized from methanol, m. p. 111–112° dec.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.28. Found: C, 51.06; H, 4.15.

1-Methyl-5-ethoxyoxindole was reduced in 60% yield to 1-methyl-5-ethoxyindole; 6% of 1-methyl-5-ethoxyindoline was obtained, and 27% of 1-methyl-5-ethoxyoxindole, m. p. 88–90°,[12] recovered. 1-Methyl-5-ethoxyindole was, surprisingly, a higher-melting compound than we expected. It was obtained, on recrystallization from methanol, as shiny white plates, m. p. 86–87°.

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.39; H, 7.47. Found: C, 75.74; H, 7.70.

This compound gave a very soluble picrate which crystallized from methanol in fine red needles, m. p. 95–96° dec.

Anal. Calcd. for $C_{17}H_{16}O_8N_4$: C, 50.49; H, 3.98. Found: C, 50.90; H, 4.10.

For purposes of comparison, 1-methyl-5-ethoxyindole was prepared from pyruvic acid and *p*-ethoxyphenylmethylhydrazine.[13] The indole obtained this way was identical with that from 1-methyl-5-ethoxyoxindole.

1-Methyl-5-ethoxyindoline was an oil which was isolated as the picrate. This crystallized from methanol in shiny yellow plates, m. p. 142–144° dec.

Anal. Calcd. for $C_{17}H_{18}O_8N_4$: C, 50.24; H, 4.46. Found: C, 50.30; H, 4.61.

Dehydrogenation of the Indolines to Indoles.—This was effected by refluxing a solution of 4 g. of the indoline in 80 ml. of xylene with 7.5 g. of chloranil. The yields of indole were approximately 50%, the remainder of the material apparently forming a complex with chloranil.[14]

Reduction of Indoles with Lithium Aluminum Hydride.—A solution of 4.68 g. of indole in 50 ml. of anhydrous ether was added to a stirred suspension of 1.0 g. of lithium

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[1] Woodward and Witkop, THIS JOURNAL, **71**, 379 (1949).

[2] Stollé, *J. prakt. Chem.*, **128**, 1 (1930); Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).

[3] Nystrom and Brown, *ibid.*, **69**, 1197 (1947).

[4] Hochstein and Brown, *ibid.*, **70**, 3484 (1948).

[5] Julian and Magnani, *ibid.*, **71**, 3207 (1949).

[6] Snyder and Eliel, *ibid.*, **70**, 1703 (1948).

[7] *Cf.* Fluchaire and Chambret, *Bull. soc. chim.*, **11**, 22 (1944).

[8] (a) Clemo and Swan, *J. Chem. Soc.*, 617 (1946); (b) Julian, Karpel, Magnani and Meyer, THIS JOURNAL, **70**, 180 (1948).

[9] Carbon-hydrogen analyses by Mr. C. W. Beazley of Micro-Tech Laboratories, Skokie, Illinois.

[10] Fischer and Hess, *Ber.*, **17**, 562 (1884).

[11] Carrasco, *Gazz. chim. ital.*, **38**, 306 (1908).

[12] Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).

[13] Stedman, *J. Chem. Soc.*, 1373 (1924).

[14] *Cf.* Weitz and Schmidt, *J. prakt. Chem.*, **158**, 211–232 (1941).

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.

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

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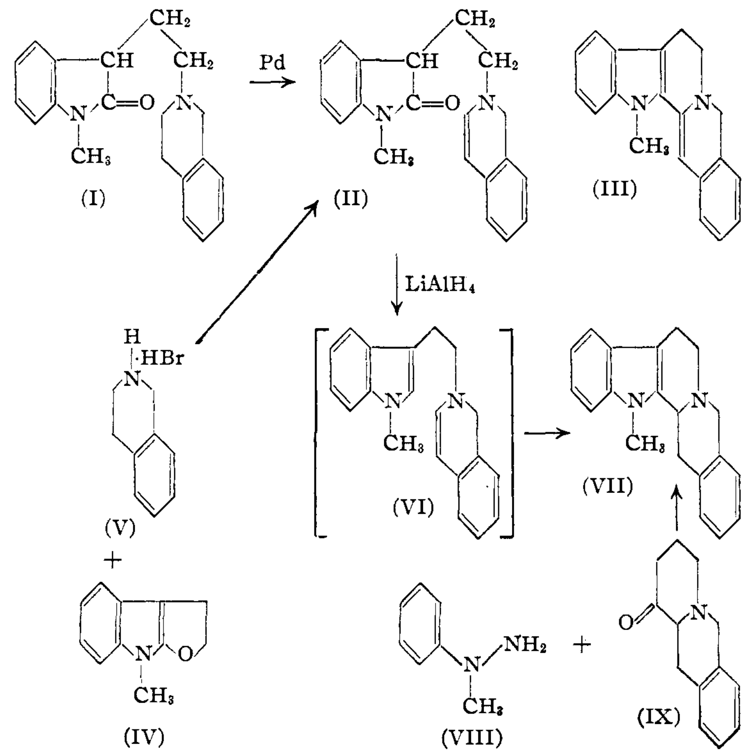
In an earlier communication dealing with the preparation and properties of 3-(N-tetrahydroisoquinolylethyl)-1-methyloxindole (I),[1] it was shown that dehydrogenation of I with palladium black yielded a 182° melting compound which could not be cyclicized, with the usual dehydrating agents, to III, a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

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

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