

and treated with 1.50 ml. of 0.963 *N* NaOH solution. Water was added to turbidity, and the reaction mixture was stirred for 8 hours at room temperature. An additional 0.80 ml. of 0.963 *N* NaOH solution was then added, and the reaction mixture was allowed to stand overnight at room temperature. The product was isolated by dilution with water and ether extraction, and after crystallization from ether-petroleum ether gave a substance (885 mg., 87%) melting at 115–117° with effervescence. The melting point was raised to 118–119° (effervescence) by several recrystallizations from ether-petroleum ether.

*Anal.* Calcd. for  $C_{23}H_{38}O_3 \cdot \frac{1}{2}C_4H_{10}O$ : C, 75.14; H, 10.85; ether, 9.28. Found: C, 74.93; H, 10.57; ether, 8.45 (by loss in weight).

The compound could not be satisfactorily crystallized from any other common solvent; removal of the solvent of crystallization led to the formation of an oil,  $[\alpha]_D +44.8^\circ$  (*c*, 2.12).

**Preparation of Pregnane-20 $\beta$ -ol-3-one Acetate.**—The hemietherate (260 mg.), obtained above, was dissolved in 5.00 ml. of acetic acid and treated with 3.00 ml. of 1.40 *N* chromic acid in dilute acetic acid. After standing overnight, the solution was diluted with water and extracted with ether. The ether extract was washed, dried, and evaporated. Crystallization of the residue from dilute methanol gave 225 mg. (87%) of ketone, m.p. 136.5–137.5°. The analytical sample melted at 138–138.5°,  $[\alpha]_D +51.0^\circ$  (*c*, 2.20).

*Anal.* Calcd. for  $C_{23}H_{36}O_3$ : C, 76.62; H, 10.07. Found: C, 76.72; H, 10.28.

Hydrolysis with 1% methanolic potassium hydroxide furnished pregnane-20 $\beta$ -ol-3-one,<sup>7</sup> m.p. 179–180°,  $[\alpha]_D +14.9^\circ$  (*c*, 1.34).

**Conversion of Pregnane-20 $\beta$ -ol-3-one Acetate into  $\Delta^4$ -Pregnene-20 $\beta$ -ol-3-one Acetate.**—The 20 $\beta$ -acetoxo ketone (1.94 g.) obtained by the procedure described above was dissolved in 25 ml. of acetic acid and treated with 5.38 ml. of a 1.10 molar solution of bromine in acetic acid. After the reaction was complete, water was added, and the mixture was extracted with ether. The ether extract was then washed successively with sodium thiosulfate solution, dilute sodium hydroxide, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solution was concentrated and diluted with petroleum ether. The crystalline product that separated weighed 1.55 g. and melted at 161–163.5° (dec.). Recrystallization of a small sample gave material that melted sharply at 164–165° (dec.). Analysis for bromine was high, however, and the substance was evidently contaminated by products of higher bromination.

The crude crystalline product was refluxed for 7 hours with 30 ml. of dry pyridine, and after crystallization from ether-petroleum ether material was obtained that melted at 148.5–152°; yield 370 mg. Four recrystallizations from ether-petroleum ether afforded a pure sample, m.p. 157–158°, that did not depress the melting point of  $\Delta^4$ -pregnene-20 $\beta$ -ol-3-one acetate derived from IVb.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

### $\beta$ -Erythroidine. III. A Study of the Hofmann Decomposition of Dihydro- $\beta$ -erythroidine<sup>1</sup>

BY V. BOEKELHEIDE AND EUGENE AGNELLO

The Hofmann decomposition of dihydro- $\beta$ -erythroidine has been found to yield an oxygen-free degradation product of molecular formula  $C_{18}H_{19}N$ . Oxidation experiments and infrared data have provided evidence that this degradation product contains a terminal methylene group and an ortho disubstituted benzene ring. A partial structure is suggested for the  $C_{18}H_{19}N$  product.

In a previous communication<sup>1</sup> the behavior of  $\beta$ -erythroidine toward various acidic reagents was reported. In order to understand this behavior and to formulate the observed isomerizations on a rational basis, it was necessary that conclusive evidence be obtained regarding the carbon skeleton present in  $\beta$ -erythroidine. Of the various degradative procedures that one might apply to the molecule, the Hofmann method of exhaustive methylation appeared to be the most promising and was the first to be investigated. The present paper reports the initial results of this work.

Although Folkers and Koniuszy have stated that  $\beta$ -erythroidine possesses a nitrogen atom common to two rings,<sup>2,3</sup> experimental details supporting this have not yet appeared. In agreement with their results, though, we found in a preliminary study that the alkaloid could be carried through two stages of the Hofmann decomposition without loss of the nitrogen atom.<sup>4</sup> However, the results of this study were such as to indicate that a less highly unsaturated molecule might be better suited for carrying through the extended series of deg-

radation steps necessary for complete removal of the nitrogen atom. Because the preparation of tetrahydro- $\beta$ -erythroidine is complicated by the formation of stereoisomers whereas that of dihydro- $\beta$ -erythroidine is not,<sup>5</sup> the dihydro derivative was chosen for study.

The reduction of  $\beta$ -erythroidine using Raney nickel catalyst in the presence of aqueous base proceeded smoothly to give dihydro- $\beta$ -erythroidine in fairly good yield.<sup>5</sup> After purification by recrystallization of its hydrobromide salt, the dihydro derivative was converted, *via* its methiodide, to a crystalline methohydroxide base, m.p. 178–180° dec. When this base was heated at 170 to 190° in a molecular still, decomposition occurred and there were collected two fractions: a clear mobile oil boiling at 170–190° at 20 mm. and a thick viscous oil boiling at 190° at 0.05 mm. The two fractions formed in roughly equivalent amounts and both were characterized as tertiary amines.

The composition of the higher boiling oil, as indicated by analysis of its methiodide, was in agreement with that to be expected for a normal methine base formed by loss of a molecule of water. On the other hand the lower boiling oil appeared to be the result of a much more deep-seated de-

(1) Aided by a grant from the National Foundation for Infantile Paralysis. For the preceding paper, see Sauvage and Boekelheide, *THIS JOURNAL*, **73**, 2062 (1950).

(2) Folkers and Koniuszy, *ibid.*, **61**, 3053 (1939).

(3) Folkers and Koniuszy, Abstracts of Papers 97th Meeting of the American Chemical Society, April, 1939, Division of Organic Chemistry, page 17.

(4) Sauvage and Boekelheide, unpublished work.

(5) (a) Folkers and Koniuszy, U. S. Patent 2,370,651, March 6, 1945; (b) Major and Folkers, U. S. Patent, 2,280,837, April 28, 1942; (c) Folkers and Koniuszy, British Patent 596,976, Jan. 15, 1948.

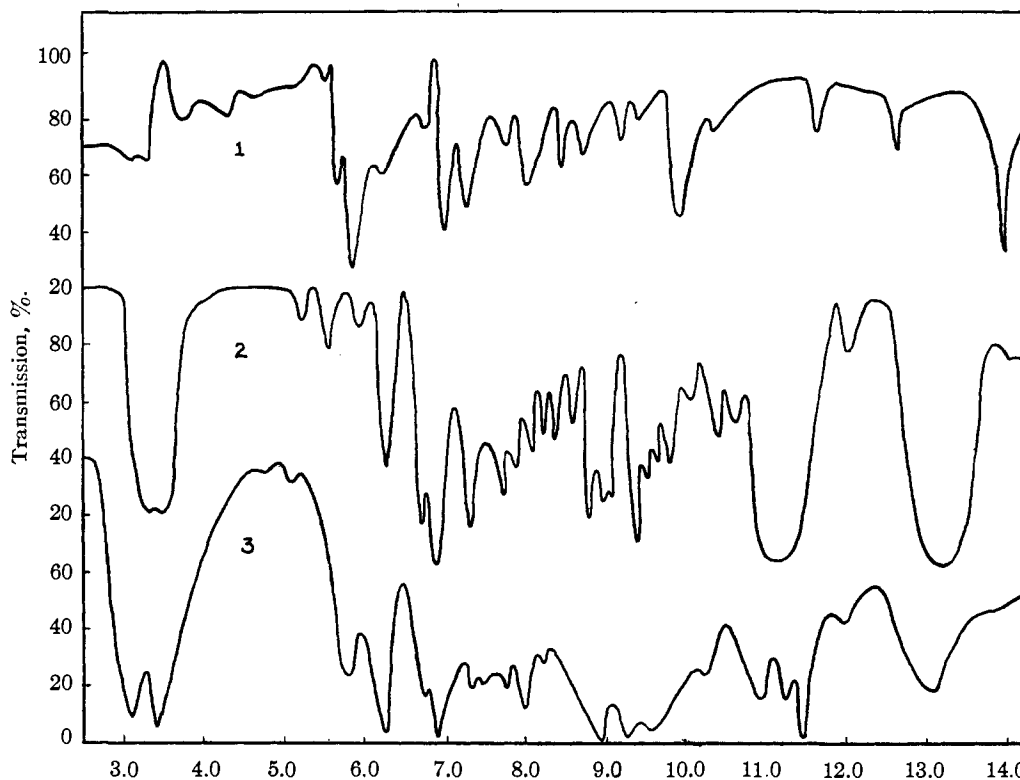


Fig. 1.—Infrared spectra of (1) N-methylphthalimide in nujol, (2) the  $C_{15}H_{19}N$  base, and (3) the  $C_{10}H_{22}NO_2$  base. The spectra of (2) and (3) were taken in the liquid state using a 0.025-mm. cell.

composition and its molecular formula, as arrived at from analyses of the oil, its picrate and its methiodide, was found to be  $C_{15}H_{19}N$ . Because it was believed that the abnormal degradation product represented a simpler molecule for identification than did the normal methine base, further work has been mainly concerned with the oxygen-free product.

The conversion of dihydro- $\beta$ -erythroidine methoxyhydroxide to the  $C_{15}H_{19}N$  base involves the loss of a  $C_2H_6O_4$  fragment. In view of the fact that dihydro- $\beta$ -erythroidine contains a methoxyl group and a lactone ring,<sup>2</sup> this transition would appear to involve a rupture of the parent molecule in which methanol, carbon dioxide and water are lost. If one assumes that a new double bond is formed for each simple molecule lost and that dihydro- $\beta$ -erythroidine originally contained only one olefin linkage,<sup>5</sup> the  $C_{15}H_{19}N$  product would be expected to have a total of four double bonds. However, the  $C_{15}H_{19}N$  base absorbed only one molar equivalent of hydrogen under mild reducing conditions and it appeared likely that three of the double bonds had become aromatized during the Hofmann decomposition. Evidence for this was obtained as follows.

The infrared spectrum of the  $C_{15}H_{19}N$  base (see Fig. 1) showed peaks at 6.28 and 6.72  $\mu$ , which are characteristic for the benzene ring.<sup>6</sup> Furthermore, a peak at 13.26  $\mu$  indicated that the benzene ring was ortho disubstituted,<sup>6</sup> and a peak at 11.12  $\mu$  indicated that there was also present a terminal methylene group of the type  $R_1R_2C=CH_2$ .<sup>6,7</sup>

(6) Williams, *Rec. Sci. Instruments*, **19**, 143 (1948).

(7) (a) Barnard, Bateman, Harding, Koch, Sheppard and Suther-

The presence of the terminal methylene group was confirmed when ozonolysis of the methiodide of the  $C_{15}H_{19}N$  base gave a 32% yield of formaldehyde, isolated as the dimedon derivative. This agrees well with the results of other investigators on the ozonolysis of terminal methylene groups.<sup>8</sup> Likewise, the presence of an ortho disubstituted benzene ring was established by permanganate oxidation studies on the methiodide salt. From the oxidation reactions, an acidic fraction was obtained which, after sublimation and treatment with methylamine, yielded N-methylphthalimide. The identity of the N-methylphthalimide was established by a mixed melting point determination with an authentic sample and also by the fact that the infrared spectrum of the authentic sample (see Fig. 1) was not affected by admixture of the material from the oxidation reaction.

An indication of the relationship between the benzene ring and the terminal methylene group can be had from examinations of the ultraviolet spectrum of the  $C_{15}H_{19}N$  base. As shown in Fig. 2 the spectrum has high values for the extinction coefficient throughout the range from 220 to 280  $m\mu$  and the curve has no fine structure. This is typical for conjugated systems such as substituted styrenes or indenenes,<sup>9a</sup> but is rather different from that of non-conjugated systems such as allyl-

land, *J. Chem. Soc.*, 915 (1950); (b) Thompson, *ibid.*, 328 (1948); (c) Thompson and Torkington, *Trans. Faraday Soc.*, **41**, 246 (1945).

(8) Clemo and Macdonald, *J. Chem. Soc.*, 1294 (1935).

(9) (a) Nat. Bureau of Standards, A. P. I. Project 44, Serial No. 120; Marvel and Peppel, *This Journal*, **61**, 895 (1939). (b) Ramart-Lucas and Amagat, *Bull. soc. chim.* **61**, 965 (1932).

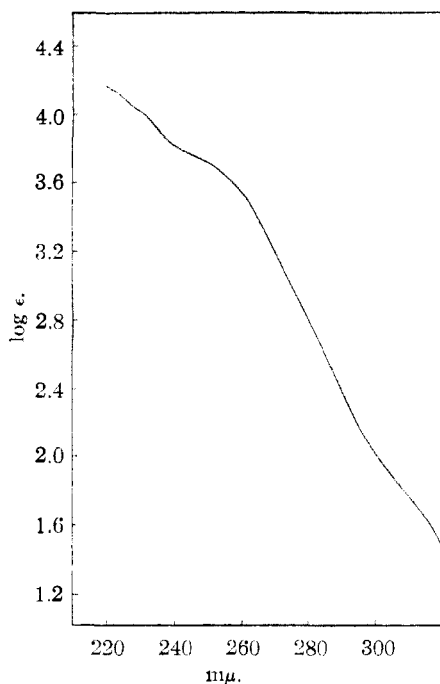
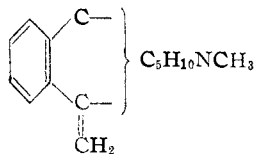


Fig. 2.—Ultraviolet spectrum of the  $C_{15}H_{19}N$  base in ethanol.

benzene,<sup>9b</sup> which shows a much lower extinction coefficient in this range. We therefore suggest the partial structure I for the  $C_{15}H_{19}N$  base.



In considering possible mechanisms to account for the formation of the abnormal degradation product, it seemed possible that the loss of carbon dioxide was necessary before loss of the methoxyl group could occur. If this were the case, the formation of the abnormal degradation product might represent a similar type of cleavage to that observed in the conversion of  $\beta$ -erythroidine to desmethoxy- $\beta$ -erythroidine. However, this supposition was found not to be correct.

Dihydro- $\beta$ -erythroidine was reduced with lithium aluminum hydride in order to eliminate the lactone ring, and the resulting dialcohol, which we have named dihydro- $\beta$ -erythroidinol, was subjected to the same exhaustive methylation procedure as before. In this case distillation of the methoxyhydroxide base gave a single product, a crystalline solid, whose composition is in agreement with the molecular formula  $C_{16}H_{23}NO_2$ . From its formula and from the fact that it showed a negative result in the methoxyl determination, the Hofmann decomposition product in this case also is clearly the result of loss of the elements of methanol and water. Therefore, no matter what mechanism one invokes to account for the loss of methanol, it certainly cannot require prior loss of carbon dioxide and it seems quite unlikely that there is prior introduction of any double bond other than that from the usual type of Hofmann decomposition.

When the infrared spectrum of the  $C_{16}H_{23}NO_2$  product was compared to that of the  $C_{15}H_{19}N$  base (see Fig. 1), it was found that the same benzene ring absorption peaks (6.25, 6.73 and 13.12  $m\mu$ ) were present. If on this basis one makes the reasonable assumption that the  $C_{16}H_{23}NO_2$  product also contains an aromatic ring, it is of interest that the material shows no phenolic properties. This behavior would suggest that the lactone ring of dihydro- $\beta$ -erythroidine is not joined directly to the portion of the molecule that becomes aromatized during the Hofmann decomposition.

#### Experimental<sup>10</sup>

**Dihydro- $\beta$ -erythroidine Hydrobromide.**—The procedure employed is essentially that described by Folkers and Koniuszy.<sup>5a</sup> To a solution of 6.2 g. of  $\beta$ -erythroidine hydrochloride in 40 ml. of water there was added 2.6 g. of solid sodium hydroxide and 1.5 g. of Raney nickel catalyst. The mixture was subjected to hydrogenation at room temperature using 3 atm. pressure of hydrogen, and the expected amount of hydrogen was absorbed in 80 minutes. After removal of the catalyst, the solution was made acidic to a pH of 3.6 with concentrated hydrochloric acid and allowed to stand overnight. Solid sodium bicarbonate was then added until a pH of 8 was attained, whereupon the solution was extracted eight times with 50-ml. portions of chloroform. The chloroform extracts were combined, dried and the chloroform was removed *in vacuo*. The residual brown oil was taken up in 10 ml. of absolute ethanol and treated with 15 ml. of a saturated solution of anhydrous hydrogen bromide in absolute ethanol. After the solution had been refrigerated overnight, there was collected 3.7 g. (52%) of white crystals, m.p. 219–229° (dec.). Further recrystallizations from ethanol gave a sample having a narrow decomposition range at about 229°,<sup>11</sup> but the initial product was sufficiently pure for further work.

**Dihydro- $\beta$ -erythroidine Methoxyhydroxide.**—A solution of 3.7 g. of dihydro- $\beta$ -erythroidine hydrobromide in 40 ml. of water was brought to a pH of 8.0 by addition of solid sodium bicarbonate and then extracted nine times with 75-ml. portions of benzene. The solvent was removed from the combined extracts under reduced pressure, and the residual oil, after addition of 15 ml. of absolute methanol, was treated with 10 ml. of methyl iodide. After the resulting solution had boiled under reflux for three hours, the volatile material was removed *in vacuo* and the residue was washed with ether by decantation. There remained a light brown, glassy solid which could not be recrystallized satisfactorily and so was converted directly to the methoxyhydroxide. A solution of the residue in 20 ml. of water was added to the moist precipitate of silver oxide resulting from treatment of 13 g. of silver nitrate with an excess of sodium hydroxide solution. After the mixture had been allowed to stand for 24 hours with occasional stirring, it was filtered and the filtrate was concentrated *in vacuo* by warming at 40 to 50°. The residue crystallized to a semi-solid mush (seeding was sometimes necessary to induce crystallization), which was taken up in a small amount of absolute ethanol and reprecipitated by slow addition of ethyl acetate. The light tan solid, which was collected, weighed 1.7 g. (53%) and melted at 172–175° (dec.). Although yields as high as 84% were obtained in some runs, the above represents the usual result. Further recrystallization from an ethanol-ethyl acetate mixture gave white needles, m.p. 178–180° (dec.), that always appeared to retain a trace of water or solvent.

*Anal.* Calcd. for  $C_{17}H_{25}NO_4$ : C, 66.42; H, 8.20. Found: C, 65.60; H, 8.62.

**Hofmann Decomposition of Dihydro- $\beta$ -erythroidine Methoxyhydroxide.**—The decomposition was carried out by heating the crystalline methoxyhydroxide in a molecular still under reduced pressure. The character of the distillate depended to some degree on the manner of heating. For example, from 2.4 g. of methoxyhydroxide, subjected to heating at 0.04 mm. pressure, there was obtained an initial fraction

(10) Analyses by Mrs. G. L. Sauvage and by the Micro-Tech Laboratories.

(11) Folkers and Koniuszy (ref. 5a) give 230° (dec.).

of 200 mg. of distillate, b.p. (pot temperature) 130–140°; and a second fraction of 400 mg., b.p. (pot temperature) 165–190°. On the other hand, when it was desired to obtain larger amounts of the more volatile fraction, it was found that from 2.0 g. of solid methohydroxide, subject to heating at 20 mm. pressure, there could be obtained an initial fraction of 600 mg., b.p. 170–190°. Then, when the pressure was lowered to 0.05 mm., a second fraction of 150 mg. of oil distilled at the same temperature. Through the preparation of the picrate and methiodide, respectively, of the lower and higher boiling fractions it was shown that the nature of the products was the same in each run.

When the lower boiling fraction from the second decomposition (600 mg.) was treated with picric acid in ethanol, there was obtained 650 mg. of yellow needles, m.p. 164–167°.

*Anal.* Calcd. for  $C_{21}H_{22}N_4O_7$ : C, 57.01; H, 5.01. Found: C, 56.86, 56.69; H, 4.90, 4.95.

To obtain the free base, 570 mg. of the picrate in 75 ml. of ether was extracted nine times with 10-ml. portions of 2% sodium hydroxide solution. After the ethereal solution had been dried, it was concentrated and the residue was subjected to molecular distillation at 100° and 1.5 mm. pressure. There was obtained about 220 mg. of a pale yellow, mobile oil. The infrared and ultraviolet spectra of this oil are shown in Figs. 1 and 2.

*Anal.* Calcd. for  $C_{15}H_{19}N$ : C, 84.45; H, 8.98; N, 6.57. Found: C, 84.58; H, 8.77; N, 7.28.

The methiodide of the  $C_{15}H_{19}N$  base was prepared in absolute ethanol and, after crystallization from absolute ethanol, was obtained as ivory-colored crystals, m.p. 224–225°.

*Anal.* Calcd. for  $C_{15}H_{22}NI$ : C, 54.09; H, 6.24. Found: C, 54.50; H, 6.25.

When the higher boiling fraction from either decomposition was treated with methyl iodide in absolute ethanol, there was obtained white crystals, m.p. 234–235°. As can be seen from the analysis, this material has the expected composition for the normal methine base.

*Anal.* Calcd. for  $C_{15}H_{22}NO_3I$ : C, 50.12; H, 6.08; N, 3.25. Found: C, 50.05; H, 6.55; N, 3.51.

**Hydrogenation of the  $C_{15}H_{19}N$  Base.**—When a mixture of 210 mg. of  $C_{15}H_{19}N$  base, 300 mg. of pre-reduced platinum oxide catalyst and 7 ml. of 1 *N* hydrochloric acid was subjected to hydrogenation at room temperature and atmospheric pressure, one molar equivalent of hydrogen was absorbed in 20 minutes and no more hydrogen was absorbed in an additional 20 minutes. Attempts to characterize the product of this reduction were unsuccessful.

**Ozonolysis of the Methiodide of the  $C_{15}H_{19}N$  Base.**—A solution of 250 mg. of the methiodide of the  $C_{15}H_{19}N$  base in 25 ml. of purified chloroform was subjected at room temperature to a stream of oxygen containing approximately 1% ozone for two hours with the effluent gases passing through two traps containing 15 ml. of water each. At the end of the ozonolysis, the water from the traps was added to a hot solution of 250 mg. of dimedon (dimethyldihydroresorcinol) in 50 ml. of a 50% water-ethanol mixture. The precipitate was collected and amounted to 65 mg. (32%) of a white solid, m.p. 191–193°. A mixed melting point determination with an authentic sample of the dimedon derivative of formaldehyde showed no depression of melting point.

**Permanganate Oxidation of the Methiodide of the  $C_{15}H_{19}N$  Base.**—To a solution of 400 mg. of the methiodide of the  $C_{15}H_{19}N$  base in 75 ml. of water, there was added dropwise with stirring at room temperature 90 ml. of a 2.5% potassium permanganate solution. After the addition was complete and the permanganate color continued to remain, the excess permanganate and manganese dioxide were destroyed by passing sulfur dioxide through the solution. Concentrated hydrochloric acid (7 ml.) was then added and the solution was extracted continuously for four hours

with ether. The ethereal extract was then concentrated *in vacuo*, leaving about 10 ml. of an aqueous residue to which there was added 10 ml. of a 10% ammonium hydroxide solution and enough aqueous calcium chloride to precipitate all the oxalic acid present. After removal of the precipitate, the filtrate was brought to a pH of 2 with concentrated hydrochloric acid and then extracted ten times with 50-ml. portions of ether. The combined ethereal extracts were dried, concentrated, and the residue was sublimed at atmospheric pressure. The sublimate (15 mg.) was then treated with an excess of aqueous methylamine and, after it had been heated at 100° for ten minutes, the solution was concentrated to dryness. Sublimation of the residue gave a white solid, m.p. 114–133°, which, after crystallization from an ethanol-water mixture, was obtained as white needles, m.p. 134.5–136°. A sample of this material, when mixed with an authentic sample of *N*-methylphthalimide, showed no depression of melting point. Likewise, a mixture of three parts of *N*-methylphthalimide to one of the oxidation product showed the same infrared spectrum as *N*-methylphthalimide alone.

**Dihydro- $\beta$ -erythroidinol.**<sup>12</sup>—To a solution of 1.00 g. of dihydro- $\beta$ -erythroidine in 250 ml. of ether there was added with stirring an excess of a 0.1 *M* ethereal solution of lithium aluminum hydride. After the reaction mixture had been allowed to stand at room temperature for 12 hours, it was decomposed by addition of moist ether. When the metallic hydroxides had been removed and the solution had been concentrated to one-half volume, the dihydro- $\beta$ -erythroidinol (750 mg.) separated as white crystals, m.p. 195–197°. These crystals showed the interesting property of being converted on recrystallization from ethanol to a crystalline form melting at 142–143°. The lower-melting form could be reconverted to the higher melting form by a further recrystallization from benzene.

*Anal.* Calcd. for  $C_{16}H_{23}NO_3$ : C, 68.78; H, 9.02. Found: C, 68.74; H, 9.15.

The methiodide of dihydro- $\beta$ -erythroidinol was prepared in ethanol and, after recrystallization from the same solvent, was obtained as white crystals, m.p. 180–181°.

*Anal.* Calcd. for  $C_{17}H_{26}NO_3I$ : C, 48.46; H, 6.69. Found: C, 48.69; H, 6.56.

**Hofmann Decomposition of Dihydro- $\beta$ -erythroidinol.**—A solution of 820 mg. of dihydro- $\beta$ -erythroidinol and 5 ml. of methyl iodide in 20 ml. of absolute methanol was heated at 50° for three hours. After removal of all volatile material, the residual glassy solid was taken up in 10 ml. of water and added to freshly prepared moist silver oxide (from 3 g. of silver nitrate). When the supernatant liquor no longer gave a positive halogen test the reaction mixture was filtered and the filtrate concentrated by heating at 50° under reduced pressure. The resulting thick, viscous oil was decomposed by heating at 140–170° in a molecular still under 0.02 mm. pressure. This gave 300 mg. of distillate as a pale yellow oil which solidified on standing. Recrystallization of the solid from hexane yielded white crystals, m.p. 96–99°. The solubility of this material in water was not affected by base, and no significant color change occurred when the solid was added to an acidic ferric chloride solution.

*Anal.* Calcd. for  $C_{15}H_{23}NO_2$ : C, 73.53; H, 8.87. Found: C, 73.50; H, 8.77;  $-OCH_3$ , negative.

The hydrochloride of the  $C_{15}H_{23}NO_2$  base was prepared in ether using anhydrous hydrogen chloride. After recrystallization from a dry ether-absolute ethanol mixture, it was obtained as a granular white solid, m.p. 174–175°.

*Anal.* Calcd. for  $C_{15}H_{23}NO_2Cl$ : C, 64.52; H, 8.12. Found: C, 64.19; H, 8.58.

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(12) We are indebted to Dr. G. L. Sauvage for the first preparation of this substance and its methiodide.