JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

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VOLUME 75 JUNE 11, 1953 NUMBER 11

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

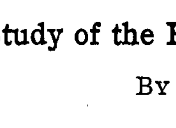
A Study of the Hofmann Degradation of Apo-β-erythroidine[1,2]

BY M. F. GRUNDON AND V. BOEKELHEIDE

RECEIVED NOVEMBER 21, 1952

By means of Hofmann degradation studies, it is demonstrated that there are two $-CH_2CH_2-$ groupings attached to the nitrogen atom of apo-β-erythroidine. This, in conjunction with other evidence, makes possible a complete assignment of structure for apo-β-erythroidine, as shown by formula II.

In a previous study on the degradation of apo-β-erythroidine,[2] it was shown that oxidation of the molecule with permanganate gave 7-carboxyisatin and 3,8-dicarboxy-4-hydroxyquinoline. Furthermore, apo-β-erythroidine was easily dehydrogenated to an indole derivative and, on the basis of these results, the molecule was assigned the partial structure I. The presence of a δ-lactone ring and an aliphatic double bond were also indicated from hydrogenation and spectral studies, but the relative positions of these groups were not specified. It is the purpose of this communication to provide evidence allowing a complete assignment of structure of apo-β-erythroidine.



I

In view of the successful use of the Hofmann decomposition reaction in a related study on β-erythroidine,[3] this method of degradation was chosen to determine the nature of the groups attached to the central nitrogen atom in apo-β-erythroidine. In the related study,[3] an ion-exchange technique was developed for preparing the quaternary hydroxides needed in the Hofmann decomposition; this procedure was found to be highly satisfactory in the present investigation as well. When apo-β-erythroidine methiodide was passed over a basic ion-exchange resin, it was converted to a crystalline compound which did not have the expected basic character of a normal methohydroxide. The infrared spectrum of this compound (see Fig. 1) lacks the characteristic absorption band of the lactone carbonyl, but instead has bands at 2.94 and 6.25 μ, corresponding to the absorption bands expected for a hydroxyl group and a carboxylate anion, respectively. Therefore, we have assigned the betaine structure IV to this molecule. It is of interest that this betaine derivative, when heated with methyl iodide, was readily reconverted to apo-β-erythroidine methiodide.[4] Treatment of either apo-β-erythroidine or its corresponding betaine with aqueous alkali effected a normal Hofmann decomposition and gave a crystalline methine base V in 54% yield.

Examination of the infrared spectra of many hydrocarbons has shown that terminal methylene groups of the type $RCH{=}CH_2$ absorb strongly in the 10.88–10.99 μ and 10.00–10.09 μ regions, whereas methylene groups of the type $RR'C{=}CH_2$ show a single strong absorption peak in the region of 11.21–11.27 μ.[5] The infrared spectrum of des-N-methylapo-β-erythroidine has a strong absorption peak at 10.82 μ, which is absent in the corresponding dihydro derivative VI obtained by reduction of the methine base over Adams catalyst. Unfortunately, apo-β-erythroidine and many of its derivatives absorb in the 10 μ region so that, in this series, only the peak in the 11 μ region provides useful information concerning the structure of the Hofmann decomposition products. However, it is clear from the peak at 10.82 μ that the terminal methylene group produced in the Hofmann decomposition is of the type $RCH{=}CH_2$, and apo-β-

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[1] Aided by a grant from the United Cerebral Palsy Association.

[2] Paper V in this series; for the preceding communication see M. F. Grundon and V. Boekelheide, THIS JOURNAL, **74**, 2637 (1952).

[3] J. Weinstock and V. Boekelheide, *ibid.*, **75**, 2546 (1953).

[4] Presumably, the reaction of the betaine derivative IV with methyl iodide first yields the methyl ester, which spontaneously lactonizes with loss of methanol to give apo-β-erythroidine methiodide.

[5] (a) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. Sutherland, *J. Chem. Soc.*, 915 (1950); (b) N. Sheppard and D. M. Simpson, *Quart. Rev.*, **6**, 1 (1952).

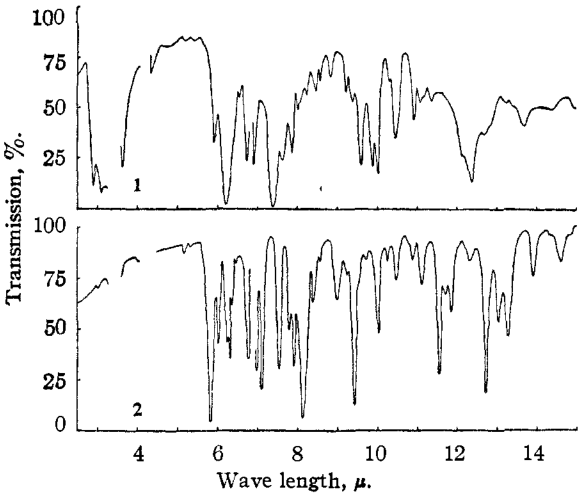
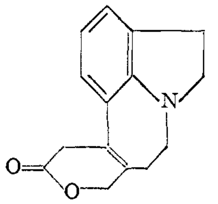


Fig. 1.—Infrared spectra of (1) the betaine derived from apo-β-erythroidine methiodide (IV), and (2) iso-des-N-methyl-apo-β-erythroidine (XI). Nujol mulls were employed for both samples.

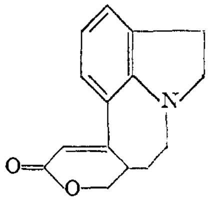
erythroidine must, therefore, have a $-CH_2-CH_2-$ grouping attached to the nitrogen atom.

Supporting evidence for the presence of the terminal methylene group was obtained in several ways. Ozonolysis of des-N-methylapo-β-erythroidine gave formaldehyde, isolated and identified as its 2,4-dinitrophenylhydrazone, in 27% yield. Also, a Kuhn–Roth determination on dihydro-des-N-methylapo-β-erythroidine gave an excellent yield of acetic acid, indicating the presence of one carbon-methyl group. This result is of significance in supporting the assigned structures, since apo-β-erythroidine and all of its other derivatives show the complete absence of a carbon-methyl grouping in the Kuhn–Roth determination.[6] As a further check on the significance of the ozonolysis and spectral experiments, dihydro-des-N-methylapo-β-erythroidine was reduced to the corresponding diol XIII with lithium aluminum hydride and it was demonstrated that this diol did not give formaldehyde on ozonolysis nor did its infrared spectrum have an absorption peak near 11.00 μ.

In view of these encouraging results, the exhaustive methylation of apo-β-erythroidine was carried through a second stage in order to determine the nature of the remaining N-alkyl substituent. When dihydro-des-N-methylapo-β-erythroidine (VI) was subjected to a Hofmann decomposition, there was obtained a light yellow methine base VII, whose infrared spectrum showed a strong absorption peak at 10.99 μ. The position of this peak indicates that again a terminal methylene group of the type $RCH{=}CH_2$ has been formed. As before, the presence of a terminal methylene group was confirmed by ozonolysis of the methine base to yield formaldehyde. Also, the methine base was hydrogenated over Adams catalyst to a dihydro derivative whose infrared spectrum showed no major peak in the 11.00 μ region. From this, it is evident that apo-β-erythroidine has two $-CH_2-CH_2-$ groups attached to the central nitrogen atom, and, therefore, the only logical structure which can be written for the molecule is II.[7]



II



III

Although the Hofmann decomposition of apo-β-erythroidine might have been expected to yield two different products, only a single crystalline base was isolated. A consideration of structure II does not allow any *a priori* decision as to whether the five- or seven-membered ring would be the more susceptible to rupture during a Hofmann decomposition. Fortunately, though, it has been possible to take advantage of the apo-to-isoapo isomerization to prove that the crystalline base from the first Hofmann decomposition actually has structure V. As discussed elsewhere,[8] isoapo-β-erythroidine has been assigned structure III and the isomerization from apo- to isoapo-β-erythroidine, which occurs on passage over alumina, corresponds to a shift of the aliphatic double bond into conjugation with the lactone carbonyl. When des-N-methylapo-β-erythroidine was passed over alumina, it behaved in an analogous fashion to give a bright yellow crystalline isomer. The infrared spectrum of this isomer (see Fig. 1) is in full agreement with structure XI, which we have assigned to it. The compound no longer has the absorption peak at 10.82 μ, attributed to the terminal methylene group, and the lactone carbonyl peak appears at 5.89 μ, just as it does in isoapo-β-erythroidine. Furthermore, ozonolysis of the yellow isomer gave acetaldehyde, isolated and identified as its 2,4-dinitrophenylhydrazone, as required by formula XI. The isolation of acetaldehyde not only demonstrates the correctness of structure XI but serves as an independent proof that the seven-membered ring in apo-β-erythroidine has no substituents at the α- or β-positions with respect to the nitrogen atom.

To complete the proof for structure XI, the yellow isomer was reduced with lithium aluminum hydride to the corresponding diol XII and this was hydrogenated over Adams catalyst to give a dihydro derivative. The dihydro derivative, thus obtained, was identical in all respects with the diol XIII obtained previously by the lithium aluminum hydride reduction of dihydro-des-N-methylapo-β-erythroidine. The fact that the same product was obtained by these two different routes clearly shows

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(6) Although Koniuszy and Folkers (This Journal, **73**, 333 (1951)) have reported that apo-, isoapo- and octahydroapo-β-erythroidine all gave acetic acid in the Kuhn–Roth determination, we have submitted samples of apo-, isoapo-, dehydroapo-, dihydroapo- and octahydroapo-β-erythroidine to W. Manser of Zurich, Switzerland, who has reported that all of these derivatives failed to give any acetic acid in the Kuhn–Roth determination. Lapiere (Dissertation on Erythrina Alkaloids, University of Liege, 1952) has also reported a negative result for apo-β-erythroidine.

(7) The only assumption made in writing structure II is that the δ-lactone ring has the same arrangement as is true for the other β-erythroidine derivatives (see ref. 3). However, the correctness of this assumption is demonstrated experimentally in an accompanying paper (M. F. Grundon, G. L. Sauvage and V. Boekelheide, This Journal, **75**, 2541 (1953)).

(8) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello, *ibid.*, **75**, 2550 (1953).

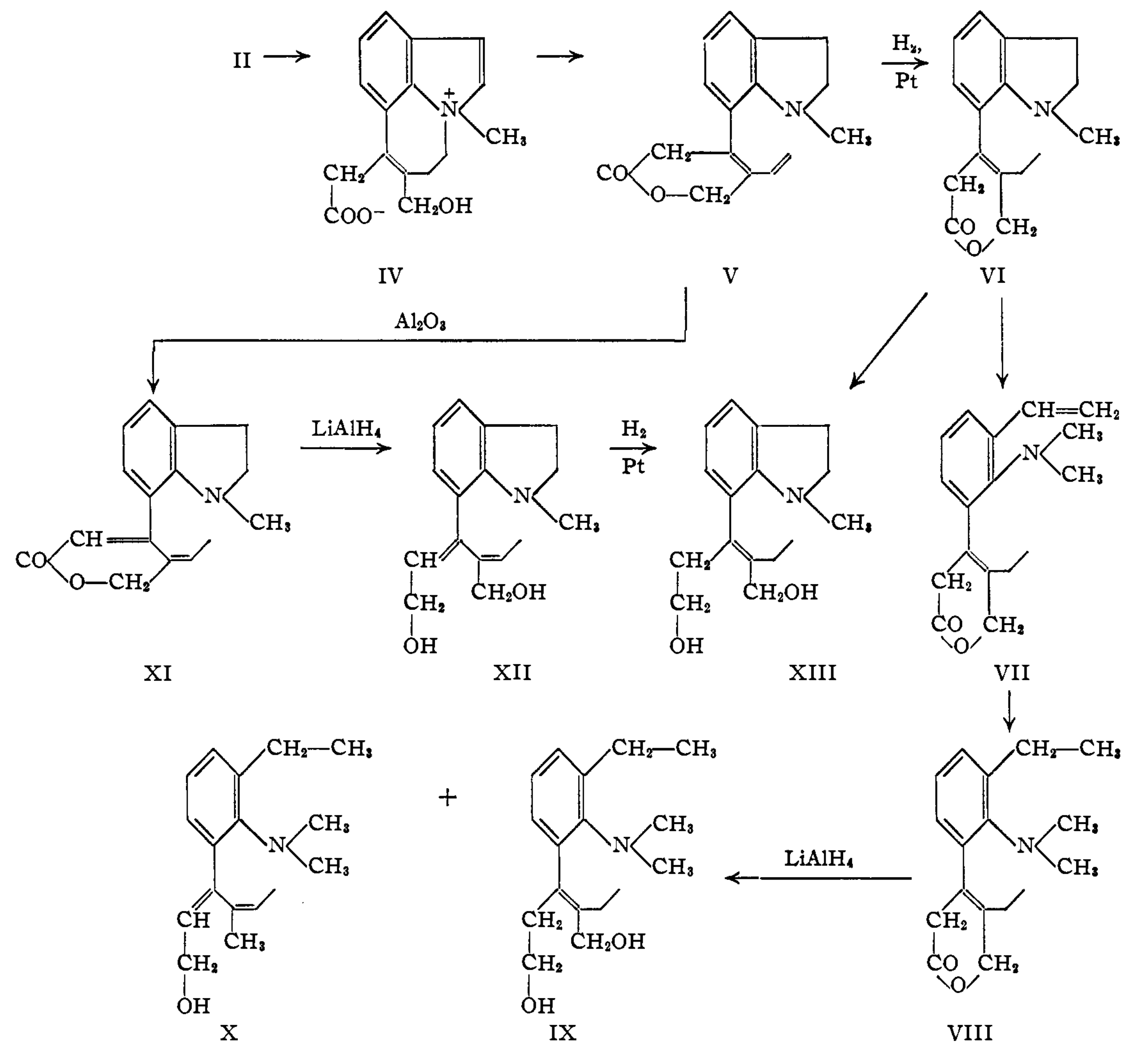

Fig. 2.

that no skeletal rearrangement was involved in the isomerization over alumina and, thus, formula XI is the only reasonable structure for the yellow isomer.

The reactions employed in the Hofmann degradation of apo-β-erythroidine are illustrated in Fig. 2. Brief mention should be made of the anomalous behavior encountered in the characterization of tetrahydro-des-N,N-dimethylapo-β-erythroidine (VIII). As shown, two products were obtained when VIII was reduced with lithium aluminum hydride. These were separated by fractional crystallization of their methiodide salts. Although one of these products showed the composition expected for the normal diol IX, the composition of the other corresponded to a derivative which had lost the elements of water. Tentatively, this abnormal product has been assigned structure X, since its infrared spectrum has a peak at 3.06 μ, attributable to a hydroxyl group, and no peak characteristic of a terminal methylene group.

Experimental[9]

Apo-β-erythroidine Methiodide.—The preparation of apo-β-erythroidine was described previously as giving white crystals, m.p. 189°.[10] This rather unstable compound has been prepared in some quantity for the present investigation and it has been possible to effect a more satisfactory purification as follows.

A solution of apo-β-erythroidine (1.40 g.) in ethanol (100 ml.) containing a large excess of methyl iodide was boiled under reflux for three hours. The solution, on cooling, gave 1.00 g. of yellow crystals, m.p. 196–198° dec. Concentration of the mother liquor gave an additional 0.45 g. (total yield 1.45 g., 66%) of a light brown solid, m.p. 191–193° dec. Although some decomposition occurred when the methiodide was taken up in boiling ethanol, recrystallization of the crude product from ethanol proved to be the best procedure for purification and gave a sample of colorless prisms, m.p. 203.5–204° dec.

Anal. Calcd. for $C_{16}H_{18}NO_2I$: C, 50.16; H, 4.73. Found: C, 50.50; H, 4.93.

The Betaine Derived from Apo-β-erythroidine Methiodide (IV).—A solution of apo-β-erythroidine methiodide (926 mg.) in 50 ml. of water was passed over an ion-exchange column (Amberlite, IRA-400), which had previously been treated with aqueous sodium hydroxide. The resulting eluate, which was neutral to litmus, was evaporated to dryness and the gummy residue, thus obtained, was crystallized from an ethanol–ether mixture. This gave 566 mg. (81%) of colorless irregular prisms, m.p. 189.5–191.5° dec., turning brown at *ca.* 160°.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot H_2O$: C, 65.98; H, 7.27; N, 4.81. Found: C, 66.26; H, 7.44; N, 4.97.

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[9] Analyses by Miss Claire King. The infrared spectra were recorded by Mr. Carl Whiteman using a Perkin-Elmer instrument, model 12-B.

[10] G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **72**, 2062 (1950).

Reaction of IV with Methyl Iodide.—To 50 mg. of the betaine derived from apo-β-erythroidine methiodide there were added 2 ml. of ethanol and 1 ml. of methyl iodide. The solution was allowed to stand for 9 hours at room temperature at which time the yellow prisms (42 mg.), which had separated, were collected. A sample of these crystals melted at 204–205°, dec., undepressed by mixing with an authentic sample of apo-β-erythroidine methiodide.

Anal. Calcd. for $C_{16}H_{18}NO_2I$: C, 50.16; H, 4.73. Found: C, 49.89; H, 4.63.

Des-N-methylapo-β-erythroidine (V). (a) From the Betaine (IV).—To a solution of 422 mg. of IV dissolved in 30 ml. of water there was added 5 ml. of an aqueous 40% solution of potassium hydroxide. After the solution had stood at room temperature for 24 hours, a slight excess of dilute hydrochloric acid was added and then the solution was made slightly alkaline with sodium bicarbonate. The yellow solid, which separated, was crystallized from benzene to give 193 mg. (52%) of pale yellow crystals, m.p. 165–168°. By further recrystallization from benzene a sample was obtained as almost white rods, m.p. 173.5–174°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.28; H, 6.71. Found: C, 75.07; H, 6.76.

(b) **From Apo-β-erythroidine Methiodide.**—When 7.0 g. of apo-β-erythroidine methiodide in 500 ml. of water was treated with 30 ml. of a 40% potassium hydroxide solution and the reaction mixture was worked up as described under (a), there was obtained 2.5 g. (54%) of pale yellow crystals, m.p. 169–171°, undepressed by admixture of a sample of the compound obtained in (a).

Ozonolysis of Des-N-methylapo-β-erythroidine.—A solution of 300 mg. of des-N-methylapo-β-erythroidine in 20 ml. of chloroform was subjected to a stream of oxygen containing ozone, until four equivalents of ozone was introduced. After removal of the chloroform at room temperature, the residue was treated with 20 ml. of water, 0.5 g. of zinc dust and a crystal of silver nitrate. The mixture was then warmed on a steam-bath for ten minutes, cooled and filtered. When the filtrate was added to an excess of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid, a precipitate separated. This was extracted with 30 ml. of benzene, the benzene solution was concentrated to 10 ml. and then was passed over a column of Florisil. Elution of the first yellow band was accomplished with benzene. Concentration of the eluate followed by crystallization of the residue from hexane gave 66 mg. (27%) of yellow needles, m.p. 159–161°. On further crystallization from hexane the sample gave needles melting at 164–165°. An authentic sample of the 2,4-dinitrophenylhydrazone of formaldehyde (m.p. 164–165°) was prepared and it was shown that a mixture of the synthetic and naturally-derived samples showed no depression of melting point.

Dihydro-des-N-methylapo-β-erythroidine (VI).—A solution of 1.62 g. of des-N-methylapo-β-erythroidine (V) in 150 ml. of ethanol containing two equivalents of hydrochloric acid was added to 100 mg. of prereduced Adams catalyst in 50 ml. of ethanol. Hydrogenation was carried out at room temperature and atmospheric pressure until one molar equivalent of hydrogen had been absorbed (35 minutes). After removal of the catalyst and solvent, the residue was dissolved in water, excess sodium bicarbonate was added, and the resulting precipitate was collected. Recrystallization of the crude product from hexane gave 1.50 g. (92%) of colorless prisms, m.p. 130–130.5°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.70; H, 7.44; –C–CH$_3$(1), 5.84. Found: C, 74.95; H, 7.71; –C–CH$_3$, 5.58.

The hydrochloride of VI was prepared using an ethanol–ether solvent mixture and, on crystallization from the same mixture, was obtained as stout colorless prisms, m.p. 152–154°.

Anal. Calcd. for $C_{16}H_{20}NO_2Cl$: C, 65.40; H, 6.86. Found: C, 65.46; H, 7.01.

Dihydro-des-N-methylapo-β-erythroidinol (XIII).—To a solution of 3.60 g. of dihydro-des-N-methylapo-β-erythroidine (VI) in 300 ml. of dry ether there was added dropwise 16 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. The mixture was kept at room temperature for 6 hours, then boiled under reflux for two hours, and finally decomposed with moist ether. After removal of the precipitated hydroxides, the ether solution was concentrated to yield 2.85 g. of a colorless solid, m.p. 65–67°.

An additional 0.38 g. of product was obtained by extracting the inorganic hydroxides with ethanol, making a total yield of 3.23 g. (89%). A sample of the diol crystallized from hexane as colorless plates, m.p. 59–60°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.51; H, 9.07. Found: C, 73.81; H, 8.97.

The perchlorate of XIII was prepared using a mixture of ethanol–ether as solvent and, on recrystallization from the same solvent pair, it was obtained as colorless plates, m.p. 132.5–134°.

Anal. Calcd. for $C_{16}H_{24}NO_6Cl$: C, 53.11; H, 6.69. Found: C, 53.51; H, 6.82.

When a solution of XIII in chloroform was subjected to ozonolysis as described for the ozonolysis of V, no crystalline material corresponding in properties to the 2,4-dinitrophenylhydrazone of formaldehyde could be isolated.

Dihydro-des-N,N-dimethylapo-β-erythroidine (VII).—The methiodide of dihydro-des-N-methylapo-β-erythroidine (VI) was prepared by treating the free base with an excess of methyl iodide at room temperature and was obtained in 85% yield as colorless crystals, m.p. 171–173°. A solution of 1.40 g. of this methiodide in 50 ml. of water was passed over an ion-exchange column (Amberlite IRA-400, previously converted to the corresponding hydroxide) and the combined eluate, including 100 ml. of water used to wash the column, was evaporated to dryness. The residual oil was distilled twice to give 354 mg. of a light yellow oil, b.p. 125–132.0° (air bath temperature) at 1.5 mm.

A higher boiling fraction, obtained in the distillation, was dissolved in hexane and purified by chromatography over Florisil. In this way it was possible to isolate an additional 172 mg. of oil whose infrared spectrum was identical with that of the oil from the first fraction. The total yield, therefore, was 526 mg. (55%).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.23; H, 7.80. Found: C, 74.92; H, 7.98.

Ozonolysis of Dihydro-des-N,N-dimethylapo-β-erythroidine.—A stream of oxygen containing three molar equivalents of ozone was passed into a solution of 300 mg. of VII in 15 ml. of ethyl chloride at ice-bath temperatures. After the ethyl chloride had been allowed to evaporate at room temperature, a mixture containing 0.5 g. of zinc dust, a crystal of silver nitrate and 20 ml. of water was added. The resulting mixture was heated on the steam-bath for 5 minutes, and then filtered. The filtrate was combined with the hot aqueous washings of the precipitate and to this an excess of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid was added. The yellow-orange precipitate which formed, amounted to 152 mg. This was taken up in benzene and chromatographed over Florisil. The solid, obtained from the first eluate, was crystallized from hexane to give 30 mg. (13%) of fine yellow needles, m.p. 163–164°. This was shown to be the 2,4-dinitrophenylhydrazone of formaldehyde by mixed melting point determination and infrared spectral comparison with an authentic sample.

Tetrahydro-des-N,N-dimethylapo-β-erythroidine (VIII).—A solution of 350 mg. of dihydro-des-N,N-dimethylapo-β-erythroidine (VII) in 20 ml. of ethanol containing 2 equivalents of hydrochloric acid was added to a small amount of prereduced Adams catalyst in 10 ml. of ethanol. Reduction proceeded readily at room temperature and atmospheric pressure until one molar equivalent of hydrogen was absorbed. Then, the catalyst and solvent were removed, the residue was dissolved in 30 ml. of water and an excess of sodium bicarbonate was added. Extraction of the solution with ether followed by concentration of the extracts gave a pale yellow oil. This was dissolved in hexane and purified by chromatography using a Florisil column. Concentration of the hexane eluate followed by distillation at 115–130° (air-bath temperature) at 0.3 mm. gave 145 mg. of a pale yellow oil. Elution of the column with a benzene–hexane (1:1) mixture followed by concentration gave an additional 93 mg. of oil whose infrared spectrum was identical with that of the previous sample of oil. The total yield of product, therefore, was 238 mg. (67%). It was not possible to obtain a crystalline hydrochloride or methiodide from VIII.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.68; H, 8.48. Found: C, 74.67; H, 8.45.

Reduction of VIII with Lithium Aluminum Hydride.—To a solution of 130 mg. of tetrahydro-des-N,N-dimethylapo-β-erythroidine (VIII) in 200 ml. of dry ether there was added 3 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. After the solution had stood for 48 hours, it was decomposed with moist ether, the inorganic precipitate was removed, and the ether solution was concentrated. This gave 116 mg. of a colorless oil, which did not crystallize nor give a solid hydrochloride. When 96 mg. of this oil was treated with an excess of methyl iodide and, after 24 hours, the solution was concentrated, there were deposited 83 mg. of crystals which melted over a range. Repeated crystallization of this solid from an ethanol–ether mixture gave a sample of colorless crystals, m.p. 167–168°. This compound has been tentatively assigned structure X.

Anal. Calcd. for $C_{18}H_{28}NOI$: C, 52.65; H, 6.87. Found: C, 52.85; H, 6.88.

Addition of ether to the mother liquors of the above preparation gave crystals melting at 121–124°. This, on repeated crystallization from ethanol–ether, gave long needles, m.p. 138–140°. This compound is assigned structure IX.

Anal. Calcd. for $C_{18}H_{30}NO_2I$: C, 51.55; H, 7.21. Found: C, 51.57; H, 7.12.

Iso-des-N-methylapo-β-erythroidine (XI).—A solution of 2.00 g. of the colorless des-N-methylapo-β-erythroidine (V) in 150 ml. of benzene was introduced on an alumina column. Immediately a yellow band appeared which could be eluted with benzene containing 5% ethanol. Concentration of this eluate followed by crystallization of the residue from ethanol gave 0.56 g. of deep yellow plates, m.p. 160–162°. This, on recrystallization from ethanol, gave a sample melting at 160.5–161°. After the alumina column had been allowed to stand for 48 hours, it was again washed with a benzene–ethanol solution and an additional 0.61 g. of the yellow compound was thus obtained, making the total yield 1.17 g. (59%).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.28; H, 6.71. Found: C, 75.05; H, 6.91.

Ozonolysis of Iso-des-N-methylapo-β-erythroidine.—A solution of 400 mg. of iso-des-N-methylapo-β-erythroidine (XI) in 20 ml. of chloroform was subjected to a stream of oxygen containing 5 molar equivalents of ozone. After removal of the solvent, a mixture of 20 ml. of water, 0.5 g. of zinc dust and a crystal of silver nitrate was added. After the solution had been heated on the steam-bath for five minutes, it was filtered and the precipitate was washed with hot water. Addition of an excess of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid to the aqueous filtrate gave an orange precipitate. This was extracted with benzene and the extract, after concentration to 10 ml., was introduced on to a Florisil column. The benzene eluate containing the first yellow band was concentrated and the residue, on trituration with hexane, yielded 93 mg. (27%) of orange crystals, m.p. 151–155°. Recrystallization of this from ethanol gave orange-yellow plates, m.p. 159–160°. This was shown by mixed melting point determinations and a comparison of infrared spectra to be identical with an authentic sample of the 2,4-dinitrophenylhydrazone of acetaldehyde.

Iso-des-N-methylapo-β-erythroidinol (XII).—To a solution of 140 mg. of iso-des-N-methylapo-β-erythroidine (XI) in 30 ml. of dry ether there was added 2 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. After two hours, moist ether was added, the inorganic precipitate was removed, and the ether solution was concentrated. The residual colorless oil was dissolved in an ether–hexane mixture and, on cooling, 68 mg. (48%) of colorless prisms, m.p. 94–95°, separated.

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.14; H, 8.17. Found: 73.75; H, 8.37.

Hydrogenation of Iso-des-N-methylapo-β-erythroidinol.—A solution of 340 mg. of iso-des-N-methylapo-β-erythroidinol (XII) in 50 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 300 mg. of a 10% palladium-on-charcoal catalyst. Hydrogen absorption stopped after 1.1 molar equivalents of hydrogen had been absorbed (20 minutes). After removal of the catalyst and solvent, the residual oil was taken up in an ether–ethanol solution and treated with perchloric acid. The solid, which separated, was crystallized from an ethanol–ether solution and gave 133 mg. (28%) of colorless plates, m.p. 131.5–133°. These crystals were shown to be identical with the perchlorate of dihydro-des-N-methylapo-β-erythroidinol (XIII) by a mixed melting point determination.

Anal. Calcd. for $C_{16}H_{24}NO_6Cl$: C, 53.11; H, 6.69. Found: C, 53.13; H, 6.86.

ROCHESTER, N. Y.

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

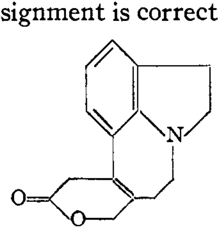
The Structure of Apo-β-erythroidine[1,2]

BY M. F. GRUNDON, G. L. SAUVAGE AND V. BOEKELHEIDE

RECEIVED NOVEMBER 21, 1952

It is shown that the arrangement of the lactone ring in apo-β-erythroidine, as was previously assumed, is correctly represented by structure I. The proof for this is based on the conversion of the corresponding deoxygenated derivative XII, *via* a Hofmann decomposition, to XIV which, on ozonolysis, gives methyl ethyl ketone. Several new examples of the apo-rearrangement are presented, including the formation of an interesting cyclic ether VII from β-erythroidinol.

In a previous communication,[2] evidence was presented which led to the assignment of structure I for apo-β-erythroidine. The arrangement of the lactone ring in structure I was assumed by analogy with the arrangement found for this portion of the β-erythroidine molecule, as deduced from Hofmann decomposition studies.[3] However, since the rearrangement of β-erythroidine to apo-β-erythroidine involves fairly drastic conditions,[4,5] it seemed desirable to obtain independent evidence establishing this point. In the present paper degradative evidence is provided showing that the lactone ring assignment is correct as given by structure I.



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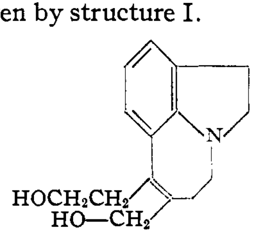

II

The initial experiments were directed toward removing the allylic oxygen function and establishing the lactone ring relationship by a Hofmann degradation, as was done in the case of des-N-methyldihydro-β-erythroidinol.[3] For this purpose, apo-β-

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[1] Aided by a grant from the United Cerebral Palsy Association.

[2] Paper VI in this series; for the preceding communication see M. F. Grundon and V. Boekelheide, THIS JOURNAL, **75**, 2537 (1953).

[3] J. Weinstock and V. Boekelheide, *ibid.*, **75**, 2546 (1953).

[4] G. L. Sauvage and V. Boekelheide, *ibid.*, **72**, 2062 (1950).

[5] F. Koniuszy and K. Folkers, *ibid.*, **73**, 333 (1951).