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.

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[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

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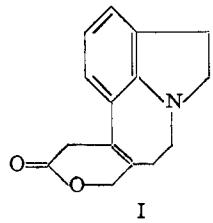
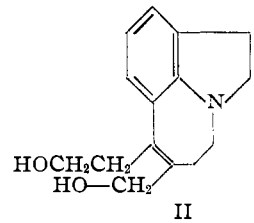
It is shown that the arrangement of the lactone ring in apo-β-erythroidine, as was previously assumed, is correctly represented by structure I. The proof for this is based on the conversion of the corresponding deoxygenated derivative XII, *via* a Hofmann decomposition, to XIV which, on ozonolysis, gives 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.




I




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-

(1) Aided by a grant from the United Cerebral Palsy Association.

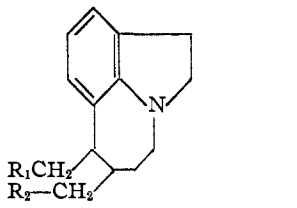
(2) Paper VI in this series; for the preceding communication see M. F. Grundon and V. Boekelheide, THIS JOURNAL, **75**, 2537 (1953).

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

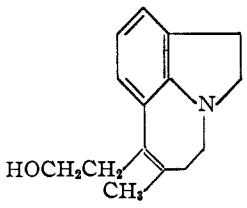
(4) G. L. Sauvage and V. Boekelheide, *ibid.*, **72**, 2062 (1950).

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

erythroidine was converted to the corresponding diol II by reduction with lithium aluminum hydride and the diol, in turn, was subjected to hydrogenolysis using a palladium-on-charcoal catalyst. Unfortunately, the hydrogenation of II gave mainly dihydroapo-β-erythroidinol (III). Although a small amount of the desired desoxy compound IV was isolated as its hydrochloride, the yield of IV was too low to permit its employment in an extended degradative scheme. Removal of the allylic oxygen was also attempted by reducing apo-β-erythroidine in alkaline solution with Raney nickel as catalyst. In this case the major product was the hitherto unknown hydroxy acid V derived from dihydroapo-β-erythroidine. This hydroxy acid, on heating to 115–120°, readily lactonized to give dihydroapo-β-erythroidine (VI) and this two-step sequence appears to be the best available method for preparing dihydroapo-β-erythroidine. Actually, a small amount of dihydroapo-β-erythroidine was isolated directly from the Raney nickel hydrogenation.



III, $R_1 = -CH_2OH$; $R_2 = -OH$
V, $R_1 = -CO_2H$; $R_2 = -OH$
VI, $R_1$ and $R_2 = -C(=O)-O-$



IV

XVIII, $R_1 = -CH_3$; $R_2 = -OH$

In view of these unsuccessful attempts at hydrogenolysis, the conversion of apo-β-erythroidinol to the corresponding dihalide was next investigated. When apo-β-erythroidinol was treated with thionyl chloride, the sole product of the reaction was a compound of empirical formula $C_{15}H_{13}NO$. The infrared spectrum of this derivative lacked an absorption peak in the region characteristic of a hydroxyl group and this molecule has, therefore, been assigned the cyclic ether structure shown by formula VII. That the cyclic ether structure is undoubtedly correct was brought out, quite unexpectedly, during a study of the apo-rearrangement of β-erythroidinol. Thus, when β-erythroidinol (VIII) was heated with phosphoric acid, rearrangement to the apo-derivative was accompanied by dehydration and the resulting product was identical with that obtained from the reaction of apo-β-erythroidinol with thionyl chloride. Apparently, the planar nature of the apo-β-erythroidinol molecule makes cyclic dehydration an extremely easy reaction, and so attempts to convert it to the corresponding dihalide were abandoned as impractical.

However, this ease of dehydration does not hold generally for all diols derived from β-erythroidine. For example, treatment of β-erythroidinol (VIII) itself with thionyl chloride gave the hydrochloride of dichlorodesoxy-β-erythroidinol IX in 70% yield. This difference in behavior was quite fortunate, since the dichloro derivative, thus obtained, proved to be a useful starting material for preparing the desired desoxyapo-β-erythroidinol. This conversion was accomplished in the following way. Reduction of the dichloro derivative IX with lithium aluminum hydride eliminated one chlorine atom, presumably that in the allylic position, to give the monochloro derivative, X. This, on heating with phosphoric acid, underwent the apo-rearrangement to give a chlorodesoxyapo-β-erythroidinol XI. Removal of the remaining chlorine was then effected by prolonged heating of XI with a solution of lithium aluminum hydride in tetrahydrofuran. The resulting halogen-free product failed to crystallize but was characterized by analysis and by its conversion to a crystalline methiodide. There can be little doubt that this base is desoxyapo-β-erythroidinol (XII). Its infrared spectrum not only has the peaks characteristic of an aromatic compound but, in general, is in good correspondence with the infrared spectrum previously reported for apo-β-erythroidine. Furthermore, as is typical of all apo-β-erythroidine derivatives, the compound was weakly basic and gave a purple color with an acidic solution of ferric chloride.[4,6]

Desoxyapo-β-erythroidinol methiodide was converted to the corresponding methohydroxide, using the ion-exchange technique,[3] and this was heated in aqueous solution to accomplish a Hofmann decomposition. The resulting base, as would be expected for structure XIII, showed a strong absorption peak in the infrared at 11.16 μ, indicating the presence of a terminal methylene group of the type $RCH{=}CH_2$. Reduction of this Hofmann product over Adams catalyst gave a dihydro derivative XIV whose infrared spectrum no longer showed a peak in the 11.00 μ region. This reaffirms our previous observation that apo-β-erythroidine has no substituents in the seven-membered ring at either the α- or the β-positions with respect to the nitrogen atom.[2]

Ozonolysis of this dihydro derivative XIV gave methyl ethyl ketone, isolated and identified as its 2,4-dinitrophenylhydrazone in 34% yield. Since the ethyl group appearing in the methyl ethyl ketone has already been shown to be formed during the Hofmann decomposition, it is the acetyl portion which must be derived from the original lactone ring. As shown in Fig. 1, the reactions leading to the formation of methyl ethyl ketone follow logically from formula I for apo-β-erythroidine. It is fairly obvious that other possible structures, involving an alternate arrangement of the lactone ring or a different position for the aliphatic double bond, would not have led to methyl ethyl ketone. Thus, there can be little doubt that apo-β-erythroidine is correctly represented by structure I.

As discussed elsewhere,[7] the isomerization of apo-β-erythroidine on passage over alumina is considered to involve a shift of the aliphatic double bond into conjugation with the carbonyl group; isoapo-β-erythroidine is regarded as having structure XV. On reduction with lithium aluminum hydride, isoapo-β-erythroidine gave the corresponding diol XVI in good yield. If this diol could be treated in a suitable manner to effect removal of the

(6) E. Dietz and K. Folkers, *J. Am. Pharm. Ass., Sci. Ed.*, **35**, 48 (1946); see also, C. Lapiere, "Dissertation on Erythrina Alkaloids," University of Liege, 1952.

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

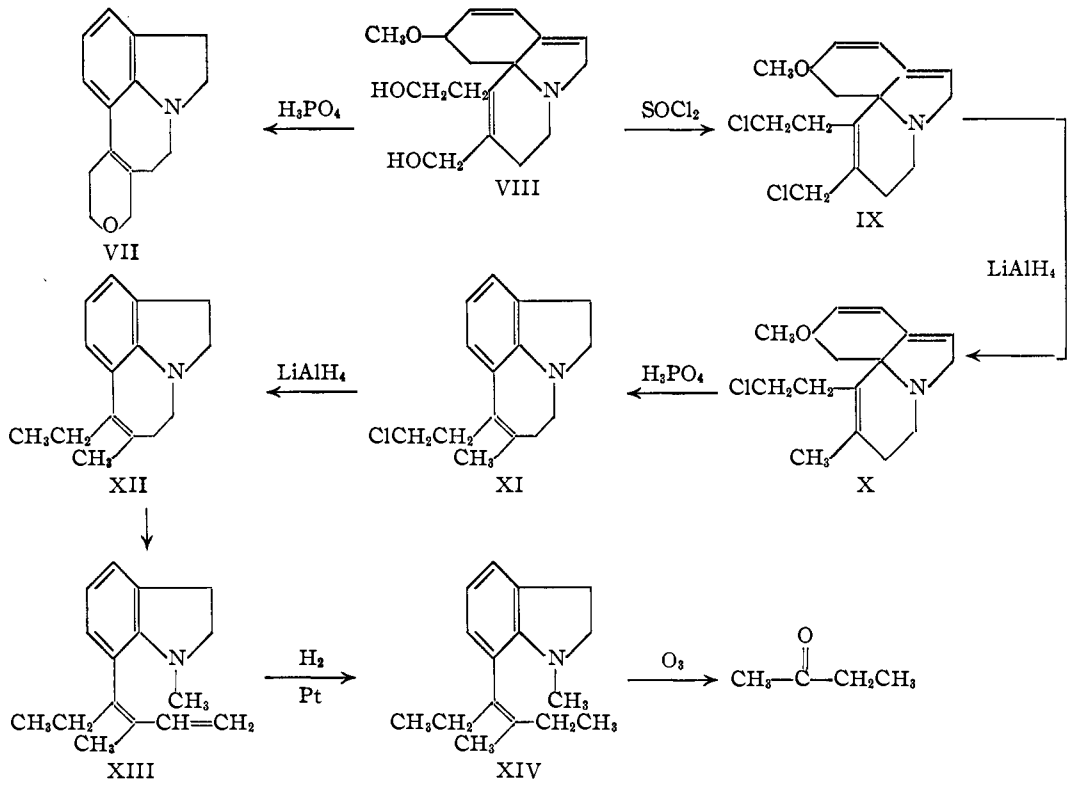
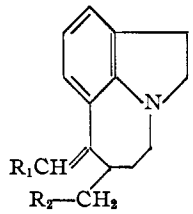



Fig. 1.

allylic hydroxyl, it would provide a convenient approach for establishing chemically the nature of the apo- to isoapo-transformation. For this reason, the reduction of isoapo-β-erythroidinol (XVI) over palladium-on-charcoal was investigated in the hope that hydrogenolysis might occur. However, the principal product isolated was dihydroapo-β-erythroidinol (III), identical in all respects with that obtained by hydrogenation of apo-β-erythroidinol. As a side-product there was also isolated a small amount of a base, whose hydrochloride had the composition required for that of dihydrodesoxyisoapo-β-erythroidinol (XVIII).



XV, $R_1$ and $R_2$ = $-\overset{O}{\overset{\|}{C}}-O-$
XVI, $R_1$ = $-CH_2OH$; $R_2$ = $-OH$
XVII, $R_1$ and $R_2$ = $-CH_2-O-$

Similarly, an attempt to replace the allylic hydroxyl with chlorine under mild conditions was unsuccessful. When isoapo-β-erythroidinol (XVI) was treated with concentrated hydrochloric acid in the cold, the only product to be isolated had the correct properties and composition for the cyclic ether XVII. It is quite reasonable that isoapo-β-erythroidinol should undergo dehydration with comparable ease to that exhibited by apo-β-erythroidinol.

## Experimental[8]

**Apo-β-erythroidinol (II).**—Apo-β-erythroidine (2.80 g.) was placed in a soxhlet apparatus and extracted with 800 ml. of a 0.03 *M* ethereal solution of lithium aluminum hydride. After the extraction was complete, the excess lithium aluminum hydride was decomposed with moist ether. The inorganic hydroxides were separated, and the ether solution was concentrated and cooled. This gave 0.68 g. of colorless crystals, m.p. 111–112°. When the inorganic hydroxides were extracted with 50 ml. of warm ethanol followed by concentration to 5 ml. and addition of 200 ml. of ether, a further quantity of apo-β-erythroidinol separated as a crystalline solid. This, on recrystallization from a benzene–hexane mixture, gave 1.40 g. of colorless plates, m.p. 112–112.5°. The total yield was 2.08 g. (74%).

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.01; H, 7.88.

**Hydrogenation of Apo-β-erythroidinol with Palladium.**—A solution of 1.93 g. of apo-β-erythroidinol in 150 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 500 mg. of a 10% palladium-on-charcoal catalyst. A molar equivalent of hydrogen was absorbed in about 85 minutes. After removal of the catalyst and solvent, the residual oil was diluted with 30 ml. of ether and refrigerated. The solution deposited 771 mg. of a colorless solid, m.p. 144–150°, which, on crystallization from benzene, gave white prisms, m.p. 154–155°. This showed the correct composition for dihydroapo-β-erythroidinol (III).

*Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.56. Found: C, 72.94; H, 8.71.

The ether solution, from which the dihydroapo-β-erythroidinol had separated, was evaporated and the resulting residue was extracted with hot hexane. Evaporation of the hexane solution gave a residue, which was dissolved in 20 ml. of benzene–hexane (1:1) solution and purified by chromatography using a Florisil column. The column was eluted with hexane and the combined eluates were concentrated to give 492 mg. of a yellow oil. This was converted to a crystalline hydrochloride (231 mg.), m.p. 176–182°. This, on repeated crystallization from an ethanol–ether mixture, gave a sample of slightly pink needles, m.p. 177–180°, with softening at 175°. This corresponded to the hydrochloride of desoxyapo-β-erythroidinol (IV).

*Anal.* Calcd. for $C_{15}H_{20}NOCl$: C, 67.27; H, 7.59. Found: C, 67.16; H, 7.77.

(8) Analyses by Mrs. G. L. Sauvage and Miss Claire King. The infrared spectra were recorded by Mr. Carl Whiteman using a Perkin–Elmer instrument, model 12B.

**Hydrogenation of Apo-β-erythroidine with Raney Nickel.**—A solution of 520 mg. of apo-β-erythroidine (I) in 5 ml. of a warm 10% solution of aqueous sodium hydroxide was diluted with 50 ml. of water and hydrogenated in the presence of Raney nickel catalyst at room temperature and atmospheric pressure. Hydrogen absorption corresponded to about 0.9 molar equivalent in about 50 minutes. After the filtered solution had been acidified with hydrochloric acid, it was made basic with excess sodium bicarbonate and extracted three times with 20-ml. portions of ethyl acetate. The combined ethyl acetate extracts (A) were reserved for subsequent investigation. The aqueous solution was now acidified with acetic acid and extracted seven times more with 20-ml. portions of ethyl acetate. Evaporation of the ethyl acetate extracts followed by trituration of the residue with ether gave a white solid. This, on crystallization from an ether–hexane mixture, gave 141 mg. of colorless plates, m.p. 110–111°. In agreement with formula V, this compound was water-insoluble but readily dissolved in aqueous sodium bicarbonate. When a small portion of the crystals was heated at 115–120° for 10 minutes, the resulting solid crystallized from ethanol as colorless prisms, m.p. 150–152°, undepressed by admixture of an authentic sample of dihydroapo-β-erythroidine (VI).[9]

*Anal.* Calcd. for $C_{15}H_{19}NO_3$: C, 68.96; H, 7.33. Found: C, 69.12; H, 7.33.

The ethyl acetate extracts (A) were concentrated and the residue was crystallized from ethanol. This gave 43 mg. of colorless prisms, m.p. 148–149°, undepressed by admixture of dihydroapo-β-erythroidine. An additional 41 mg. of dihydroapo-β-erythroidine also was obtained from the ether wash used to triturate V.

**β-Erythroidinol (VIII).**—A solution of 10.0 g. of β-erythroidine in 1500 ml. of dry ether was treated with 50 ml. of 1 *M* ethereal solution of lithium aluminum hydride. After the reaction mixture had stood at room temperature for 12 hours, it was decomposed with moist ether, filtered immediately, and the ether filtrate was refrigerated. From the ether solution there was obtained 4.10 g. of white needles, m.p. 168°, with softening at 163°.

The inorganic precipitate from the reaction mixture was extracted with 100 ml. of hot methanol and the methanol extract, after concentration to 10 ml., was diluted with 300 ml. of ether. This caused the separation of an additional 3.70 g. (total yield 7.8 g., 76%) of faintly yellow needles, m.p. 161–165°.

*Anal.* Calcd. for $C_{16}H_{25}NO_3$: C, 69.24; H, 8.35. Found: C, 69.49; H, 8.27.

**Dehydroxyapo-β-erythroidinol (VII).** (a) **From Apo-β-erythroidinol.**—Apo-β-erythroidinol (500 mg.) was added in small portions with cooling to 1 ml. of purified thionyl chloride. After 15 minutes, the reaction mixture was diluted with 50 ml. of cold ether and the solid, which precipitated, was collected. This was dissolved in 10 ml. of water; the solution was made alkaline with sodium bicarbonate and then extracted five times with 5-ml. portions of ether. Concentration of the ether extract gave a gum which was extracted with boiling pentane. The pentane solution, on evaporation, gave 105 mg. (25%) of a white solid, m.p. 89–91°. When this was recrystallized from ethanol, it yielded white needles, m.p. 93–94°.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 79.25; H, 7.53. Found: C, 79.03; H, 7.68.

(b) **From β-Erythroidinol.**—A solution of 200 mg. of β-erythroidinol (VIII) in 3 ml. of sirupy phosphoric acid was heated at 105–120° for 3 hours in a nitrogen atmosphere. The cold solution was diluted with water, neutralized with sodium hydroxide, and extracted with benzene. After concentration, the benzene solution was introduced on an activated alumina column. Elution of the column with ethanol followed by concentration gave an oil which, after crystallization from pentane, yielded 38 mg. (20%) of colorless needles, m.p. 89–90°. A mixed melting point determination showed the identity of the samples from (a) and (b). Both samples gave a violet color with an acidic solution of ferric chloride.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 79.25; H, 7.53. Found: C, 79.37; H, 7.41.

(9) M. F. Grundon and V. Boekelheide, THIS JOURNAL, **74**, 2637 (1952).

**Dichlorodesoxy-β-erythroidinol (IX).**—β-Erythroidinol (2.10 g.) was added in portions with cooling to 3 ml. of purified thionyl chloride. After 3 hours the excess thionyl chloride was removed under reduced pressure and the residue was triturated with ether to give a colorless solid. This, on recrystallization from ethanol, gave 1.83 g. (70%) of colorless plates, m.p. 222–223°. This compound has the correct composition for the hydrochloride of dichlorodesoxy-β-erythroidinol (IX).

*Anal.* Calcd. for $C_{16}H_{22}NOCl_3$: C, 54.79; H, 6.33. Found: C, 54.74, 55.08; H, 6.57, 6.51.

A solution of 3.2 g. of the hydrochloride of IX in 100 ml. of water was made basic with sodium bicarbonate and extracted 3 times with 30-ml. portions of ether. After concentration of the ether extracts, the residue was extracted with hot pentane, the pentane solution was concentrated to 20 ml., and this was refrigerated. From the pentane there separated 2.18 g. (77%) of colorless needles, m.p. 74–75°.

*Anal.* Calcd. for $C_{16}H_{21}NOCl_2$: C, 61.15; H, 6.71. Found: C, 60.87; H, 6.86.

**Hydrochloride of Chlorodesoxy-β-erythroidinol (X).**—A 1 *M* ethereal solution of lithium aluminum hydride (20 ml.) was added to a solution of 2.15 g. of dichlorodesoxy-β-erythroidinol (IX) in 50 ml. of tetrahydrofuran. After removal of all of the easily-volatile solvent, the remaining solution was boiled under reflux for 2 hours, treated with moist ether, and filtered. When the filtrate was concentrated, a colorless oil resulted which was taken up in an ethanol–ether mixture and converted to its hydrochloride. Recrystallization of the solid hydrochloride from ethanol–ether gave 1.82 g. (85%) of colorless plates, m.p. 233–233.5° (dec.).

*Anal.* Calcd. for $C_{16}H_{23}NOCl_2$: C, 60.96; H, 7.35. Found: C, 61.41; H, 7.46.

**Chlorodesoxyapo-β-erythroidinol (XI).**—A solution of 690 mg. of chlorodesoxy-β-erythroidinol (X) in 10 ml. of sirupy phosphoric acid was heated at 115–120° for 1 hour. After the cold solution had been diluted with 100 ml. of water, sufficient sodium hydroxide was added to completely precipitate the product which, in turn, was removed by extraction with ether. Concentration of the ether gave a brown gum which was again extracted with 50 ml. of boiling pentane. When the pentane extract was concentrated to 5 ml. and cooled, there separated 305 mg. (56%) of crystals, m.p. 69–70.5°. A sample, on crystallization from ethanol, gave colorless prisms, m.p. 72–73°.

*Anal.* Calcd. for $C_{15}H_{18}NCl$: C, 72.70; H, 7.32. Found: C, 72.60; H, 7.41.

**Desoxyapo-β-erythroidinol (XII).**—A solution of 1.20 g. of chlorodesoxyapo-β-erythroidinol (XI) in 30 ml. of tetrahydrofuran was treated with 20 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. All readily volatile solvent was removed, and then the reaction mixture was boiled under reflux for 20 hours. The excess lithium aluminum hydride was decomposed by addition of moist ether, the solution was filtered, and the filtrate was concentrated *in vacuo*. Distillation of the residual oil at 2 mm. pressure gave 949 mg. (92%) of a colorless oil, b.p. 140–155° (bath temperature) at two mm.

*Anal.* Calcd. for $C_{15}H_{19}N$: C, 84.45; H, 8.98. Found: C, 84.07; H, 8.88.

The methiodide of XII was prepared by treating a solution of 770 mg. of desoxyapo-β-erythroidinol (XII) in 20 ml. of ethanol with 5 ml. of methyl iodide. After 12 hours the solution was concentrated to 5 ml. and diluted with ether. The colorless solid (m.p. 169–170°), which separated, weighed 1.018 g. (80%). A sample crystallized from ethanol as colorless crystals, m.p. 170–171°.

*Anal.* Calcd. for $C_{16}H_{22}NI$: C, 54.09; H, 6.24. Found: C, 54.19; H, 6.21.

**Des-N-methyldesoxyapo-β-erythroidinol (XIII).**—A solution of 1.40 g. of the methiodide of desoxyapo-β-erythroidinol (XII) in 50 ml. of water was passed over a basic ion-exchange resin (Amberlite, IRA 400). The resulting eluate, when warmed on the steam-bath for two hours, precipitated a yellow oil which was removed by extraction with ether. Concentration of the ether extract gave 748 mg. of a pale yellow oil. This was characterized by converting a portion to the corresponding methiodide. When 48 mg. of the oil in 2 ml. of ethanol containing 1 ml. of methyl iodide

was allowed to stand for 12 hours and was then diluted with ether, there separated 56 mg. (72%) of colorless needles, m.p. 206–207°. Recrystallization of this sample from ethanol–ether gave needles, m.p. 220–221°.

*Anal.* Calcd. for $C_{17}H_{24}NI$: C, 55.29; H, 6.55. Found: C, 54.95; H, 6.71.

**Dihydro-des-N-methyldesoxyapo-β-erythroidinol (XIV).**—A solution of 700 mg. of des-N-methyldesoxyapo-β-erythroidinol (XIII) in 30 ml. of ethanol containing 0.7 ml. of concentrated hydrochloric acid was hydrogenated over prereduced Adams catalyst at room temperature and atmospheric pressure. Hydrogen absorption became slow after 1.2 molar equivalents of hydrogen was absorbed (17 minutes). When the filtered solution was concentrated to 5 ml. and diluted with 100 ml. of ether, 640 mg. (77%) of pink crystals, m.p. 135–137°, was obtained. This corresponded to the hydrochloride of XIV and, after crystallization from an ethanol–ether mixture, it was obtained as faintly yellow prisms, m.p. 138–140°.

*Anal.* Calcd. for $C_{16}H_{24}NCl$: C, 72.32; H, 9.10. Found: C, 72.12; H, 9.44.

The free base (XIV) was obtained from the hydrochloride in quantitative yield by dissolving the hydrochloride in water, neutralizing the aqueous solution with sodium bicarbonate, and extracting with ether. The free base was a pale yellow oil and so it was characterized by converting it to its methiodide. The solid methiodide of XIV was obtained as colorless plates, m.p. 201–202°, after one crystallization from an ethanol–ether mixture.

*Anal.* Calcd. for $C_{17}H_{26}NI$: C, 54.99; H, 7.06. Found: C, 55.20; H, 7.36.

Ozonolysis of **Dihydro-des-N-methyldesoxyapo-β-erythroidinol (XIV).**—A stream of oxygen containing ozone was passed through an ice-cold solution of 480 mg. of dihydro-des-N-methyldesoxyapo-β-erythroidinol (XIV) in 15 ml. of ethyl chloride until 4 equivalents of ozone had been introduced (100 minutes, by previous standardization). The solution was then allowed to come to room temperature and the resulting brown gum was heated on a steam-bath for 15 minutes with a mixture consisting of 20 ml. of water, a crystal of silver nitrate and 1.0 g. of zinc dust. After this, the mixture was steam distilled and the first portion of distillate (5 ml.) was added to a solution of 600 mg. of 2,4-dinitrophenylhydrazine sulfate in aqueous ethanol. This gave 168 mg. (34%) of an orange solid, m.p. 108–111°. The solid was crystallized from ethanol to give orange needles, m.p. 115–115.5°. The crystals were shown to be the 2,4-dinitrophenylhydrazone of methyl ethyl ketone by their composition and by a mixed melting point determination and an infrared spectral comparison with an authentic sample of this derivative (m.p. 115–115.5°).

*Anal.* Calcd. for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80. Found: C, 47.44; H, 4.99.

**Isoapo-β-erythroidinol (XVI).**—Isoapo-β-erythroidine (4.0 g.) was placed in a soxhlet apparatus and extracted with 700 ml. of a 0.09 *M* ethereal solution of lithium aluminum hydride. When the extraction was complete (6 hours), the excess reagent was decomposed by addition of moist ether and the inorganic hydroxides were removed by filtration. The ether solution, on concentration, gave a yellow oil, which gave 1.36 g. of colorless prisms by treating it with an ether–hexane solution. A further crystallization from the same solvent gave prisms, m.p. 94.5–95.5°. Ethanol extraction of the inorganic hydroxides yielded an additional 1.55 g. (total yield 2.91 g., 73%) of slightly yellow prisms, m.p. 91–93°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81. Found: C, 73.61; H, 7.88.

**The methiodide of XVI** was prepared in ethanol and was obtained, after crystallization from the same solvent, as colorless prisms, m.p. 174–176°.

*Anal.* Calcd. for $C_{16}H_{22}NO_2I$: C, 49.60; H, 5.73. Found: C, 49.85; H, 5.78.

**Hydrogenation of Isoapo-β-erythroidinol (XVI).**—A solution of 300 mg. of isoapo-β-erythroidinol (XVI) in 50 ml. of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 200 mg. of a 10% palladium-on-charcoal catalyst. One molar equivalent of hydrogen was absorbed in 27 minutes. After removal of the catalyst and solvent, the residual oil was taken up in boiling ether, the ether solution was concentrated to 10 ml., hexane was added, and the solution was cooled. The solution deposited 133 mg. of colorless crystals, m.p. 146–152°. On recrystallization from benzene a sample was obtained as colorless prisms, m.p. 153–154°, undepressed by admixture of an authentic sample of dihydroapo-β-erythroidinol (III).

After removal of III, the ether–hexane mother liquors were concentrated and the residue was extracted with hexane. Evaporation of the hexane gave a yellow oil which was converted directly to its hydrochloride. The colorless solid, thus obtained, was crystallized from an ethanol–ether solution and yielded 52 mg. of colorless needles, m.p. 180–181°. This compound has the composition required for the hydrochloride of XVIII.

*Anal.* Calcd. for $C_{15}H_{22}NOCl$: C, 67.26; H, 8.28. Found: C, 66.51; H, 8.28.

**Dehydroxyisoapo-β-erythroidinol (XVII).**—A solution of 850 mg. of isoapo-β-erythroidinol in 7 ml. of concentrated hydrochloric acid was allowed to stand at 0° for 48 hours. The solution was then diluted with 50 ml. of water, made alkaline with sodium bicarbonate, and extracted five times with 20-ml. portions of ether. The yellow gum, obtained by evaporation, was crystallized from pentane to yield 215 mg. of colorless prisms, m.p. 103.5–104°. This compound exhibited the properties expected for XVII.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 79.25; H, 7.52. Found: C, 78.90; H, 7.71.

ROCHESTER, N. Y.