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

Syntheses of 14,15,16,17-Tetrahydroerythrinane[1,2]

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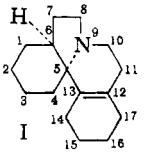
Two syntheses of 14,15,16,17-tetrahydroerythrinane (I) are described. Their potential value for the synthesis of derivatives of erythroidine is discussed.

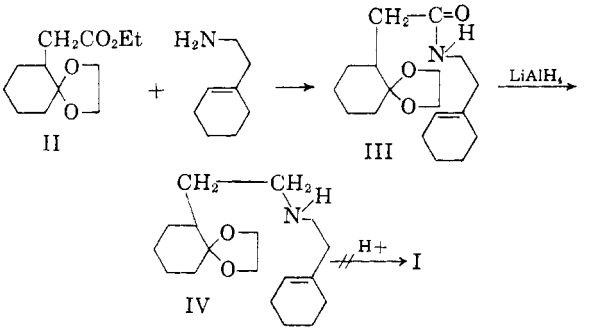
Since the spiro amine system was first deduced as being common to all of the erythrina alkaloids,[3-5] a number of methods have been explored for the synthesis of molecules of this type.[6-10] In the case of the aromatic derivatives, the syntheses of 15,16-dimethoxyerythrinane by Belleau[8] and by Mondon[10] are particularly elegant.

In our own work we have been concerned with the non-aromatic erythrina alkaloids, α- and β-erythroidine, and their possible synthesis. The present communication deals with syntheses of 14,15,16,17-tetrahydroerythrinane (I) and the accompanying paper[11] describes the synthesis and resolution of 14,15,16,17-tetrahydro-16-oxaerythrinane and the establishment of its identity with a compound derived from β-erythroidine.



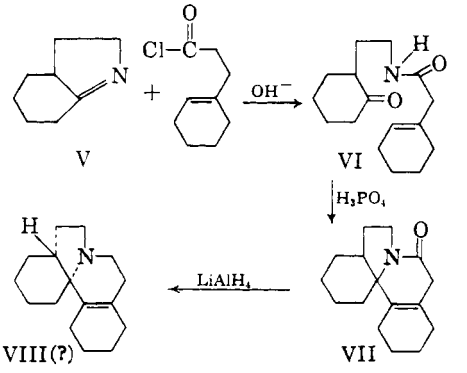
I

In considering ways of forming the spiro amine system present in I, we turned first to the procedure devised by Grewe and his colleagues[12] for the synthesis of 1,1-disubstituted octahydroisoquinoline derivatives. For this purpose, 2-carbethoxymethylcyclohexanone was converted to the corresponding ketal II and treated with cyclohexenylethylamine[13] to give the corresponding ketal lactam III. Reduction of III with lithium aluminum hydride gave the corresponding amine IV. Various attempts to effect the conversion of IV to I were without success. Removal of the ketal grouping with acidic reagents gave the free amino ketone as an unstable oil but this, likewise, gave no useful product in attempted cyclizations under acidic conditions.



II III IV

With the report of the synthesis of erythrinane by Belleau,[14] our attention turned toward carrying out the cyclization step with the corresponding keto amide rather than the keto amine. This was first done by preparing the keto amide VI, in strict analogy to Belleau's synthesis, and cyclizing it with polyphosphoric acid to VII. Reduction of VII with lithium aluminum hydride gave a product having the composition expected for the desired amine VIII. This reaction scheme has since been reported by Belleau[9] and our results are in good agreement with his. There seems little doubt from a comparison of physical properties that our final product (VIII) is identical with that which he obtained. The only point to be made in regard to our preparation as compared to Belleau's is that two new methods for preparing hexahydroindole (V) have been developed and these are described in the Experimental section. That utilizing the elegant enamine alkylation procedure of Stork, Terrell and Szmuszkovicz[15] appears to be the best procedure presently available for this interesting compound.



V VI VII VIII(?)

With the successful cyclization of VI, we returned to the ketal amide III, discussed previously, and subjected it to heating with polyphosphoric acid. Again, a cyclic amide (IX) was produced

(1) Paper XV in this series; for the preceding communication see V. Boekelheide and G. C. Morrison, THIS JOURNAL, **80**, 3905 (1958).

(2) Aided in part by grants from the United Cerebral Palsy Association and the Smith, Kline and French Laboratories.

(3) M. Carmack, B. C. McKusick and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

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

(5) V. Boekelheide and V. Prelog, "Progress in Organic Chemistry," Vol. 3, edited by J. W. Cook, Butterworths, London, 1955, p. 242.

(6) K. Wiesner, Z. Valenta, A. J. Manson and F. W. Stonner, THIS JOURNAL, **77**, 675 (1955).

(7) V. Prelog, M. Ternbah and O. R. Rodig, unpublished work; *cf.* V. Prelog, *Angew. Chem.*, **69**, 33 (1957).

(8) B. Belleau, *Can. J. Chem.*, **35**, 651 (1957).

(9) B. Belleau, *ibid.*, **35**, 663 (1957).

(10) A. Mondon, *Angew. Chem.*, **68**, 578 (1956).

(11) M. Müller, T. T. Grossnickle and V. Bokelheide, THIS JOURNAL, **81**, 3959 (1959).

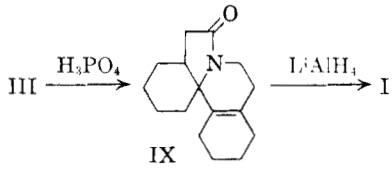
(12) R. Grewe, R. Hamann, G. Jacobsen, E. Nolte and K. Riecke, *Ann.*, **581**, 85 (1953).

(13) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).

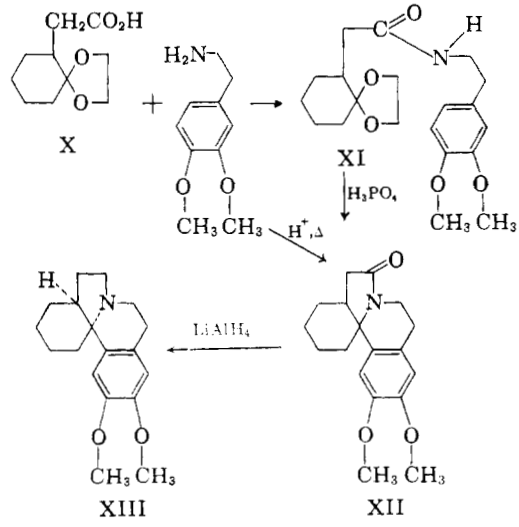
(14) B. Belleau, THIS JOURNAL, **75**, 5765 (1953).

(15) G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

and this, on reduction with lithium aluminum hydride, gave a product having the composition required by I. If the acid cyclization in this case had occurred to give the same type ring fusion as before, the final product in each case should be the same. However, the properties of the two amines and their picrates clearly demonstrated them to be different. It can be concluded therefore that either the two schemes are producing different diastereoisomers or there is an error in the structures assigned.



The second method of cyclization, in which the amide function is in the potential five-membered ring, corresponds to the scheme used by Mondon for the synthesis of 15,16-dimethoxyerythrinane[10] and conditions necessary for the cyclization are appreciably milder than those required in the Belleau procedure. It seemed conceivable, therefore, that under the mild conditions the cyclization proceeds in a concerted fashion to give the diastereoisomer having a *trans* ring fusion as shown by I, whereas under more drastic conditions the thermodynamically more stable ring fusion would predominate and the product isolated could be the *cis* isomer shown by VIII. If this were true, the Mondon and Belleau syntheses of 15,16-dimethoxyerythrinane should have led to different diastereoisomers of XIII rather than the same racemate. It seemed desirable to check this fact rigorously since identity had been assumed from melting point data and had not been established by direct comparison of the two products.

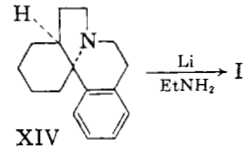


Repetition of the Mondon synthesis, as outlined above (X → XII → XIII), emphasized the mild conditions which serve for this remarkable cyclization. As originally described by Mondon, formation of the cyclic amide XII occurs simply by heating a mixture of the ketal-acid X and homoveratrylamine at 160°. It was our experience that under these conditions the main product was the ketal amide XI. However, when homoveratrylamine hydrochloride was used instead of homoveratrylamine under the same conditions, the desired cyclic amide XII formed in about 70% yield.[16]

The question of whether the ketal amide XI is an intermediate in the formation of XII under these conditions has not yet been settled. Since the ketal amide XI forms readily in high yield simply by heating a mixture of the ketal ester II and homoveratrylamine, it is a convenient compound for study. As would be expected, it is converted by the usual cyclization catalysts, such as polyphosphoric acid, to the corresponding cyclic amide XII. However, the mild conditions which suffice for this transformation are surprising. Thus, when the ketal amide XI was allowed to stand at room temperature in a solution of 1 *N* aqueous ethanolic hydrogen chloride for two days, it was converted in 75% yield to XII.

The resolution of XIII was accomplished using dibenzoyltartaric acid and the two enantiomorphs, as their crystalline picrates, were compared to the picrate of hexahydroapoerysotrine. The levorotatory enantiomorph was shown by melting point behavior and infrared spectral comparison to be identical with the natural material.[17] Since Belleau recently has made a similar resolution of his preparation of 15,16-dimethoxyerythrinane and established the identity of the levo enantiomorph with hexahydroapoerysotrine, there can be no doubt that the two schemes yield the same product. Further, from the mode of formation of hexahydroapoerysotrine,[18] it can be safely assumed that the ring fusion in XIII is as shown.

With the fact established that the Belleau and Mondon syntheses give identical products, at least in the case of 15,16-dimethoxyerythrinane, the question remained of why the two syntheses of 14,15,16,17-tetrahydroerythrinane resulted in different products. To try to resolve these difficulties a third synthesis of 14,15,16,17-tetrahydroerythrinane was undertaken. Erythrinane (XIV), pre-



pared by the Belleau procedure,[8,14] was reduced with lithium in ethylamine according to the procedure for reducing naphthalene to $\Delta^{9,10}$-octalin.[19] The resulting base was converted to the picrate and shown by melting point and infrared spectral comparison to be identical with the sample of I obtained through the cyclization of III. Thus, the

(16) In a private communication, Dr. Mondon has informed us that, independently of our work, he has also observed the necessity of mineral acid being present in order for cyclization to occur; *cf.* A. Mondon, Abstracts, Nordwestdeutsche Chemiedozenten Tagung, Munster, April, 1957.

(17) We are indebted to Professor Prelog for making the comparison of the synthetic samples with hexahydroapoerysotrine.

(18) V. Prelog, H. G. Khorana and G. W. Kenner, *Helv. Chim. Acta*, **32**, 453 (1949).

(19) R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, THIS JOURNAL, **77**, 3230 (1955).

formation of 14,15,16,17-tetrahydroerythrinane by these two different paths clearly establishes its over-all structure and most probably the mode of ring fusion is that indicated by I. As yet, we have been unable to obtain conclusive evidence to decide whether the product from the Belleau cyclization has the diastereoisomeric structure indicated by VIII or whether it differs in its over-all structure.

Experimental[20]

Ketal of Ethylene Glycol and 2-Carbethoxymethylcyclohexanone (II).—The preparation of 2-carbethoxymethylcyclohexanone was carried out both by the procedure of Chuang and Ma[21] and that of Stork, Terrell and Szmuszkovicz,[15] of which the latter was considerably more convenient. To a solution of 607.1 g. of the pyrrolidine enamine from cyclohexanone in 500 ml. of dry dioxane there was added dropwise with stirring 334.5 g. of ethyl bromoacetate. The reaction mixture was decomposed by the addition of cold aqueous acid and extracted with ether. Concentration of the ether extract followed by distillation of the residue gave 184.3 g. of 2-carbethoxymethylcyclohexanone as a colorless oil, b.p. 131–132° at 12 mm. For the preparation of the ketal, a solution of 61.5 g. of 2-carbethoxymethylcyclohexanone and 2.0 g. of *p*-toluenesulfonic acid in 500 ml. of benzene was boiled under reflux in an apparatus equipped with a water-separator. When water was no longer being evolved, the reaction mixture was cooled and washed successively with aqueous sodium bicarbonate and water. Concentration of the benzene extract followed by distillation of the residual oil gave 68.5 g. (90%) of a colorless oil, b.p. 106–109° at 0.5 mm., $n^{23}D$ 1.4640.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.37; H, 9.00.

Preparation of the Ketal Amide III.—A mixture of 2.0 g. of cyclohexenylethylamine[13] and 3.6 g. of the ketal ester II was heated in a nitrogen atmosphere at 200° for 4 hours. The mixture was then taken up in benzene and chromatographed over alumina (Woelm, activity III). The benzene–ether eluate gave 1.75 g. (40%) of white crystals, m.p. 74–78°. A sample, recrystallized from ether–hexane, melted at 82–83°. The infrared spectrum showed absorption peaks at 6.04 μ (amide) and 9.2, 10.57 and 10.89 μ (ketal).

Anal. Calcd. for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.46; H, 9.53; N, 4.81.

Preparation of the Ketal Amine IV.—A solution of 3.0 g. of the ketal amide III in 100 ml. of anhydrous ether was added dropwise with stirring to a solution of 5 g. of lithium aluminum hydride in 100 ml. of ether. After the reaction mixture had boiled under reflux for 4 hours, it was decomposed by dropwise addition of a saturated, aqueous solution of sodium sulfate. The granular precipitate of metallic hydroxides was removed by filtration and the ethereal filtrate was concentrated. Distillation of the residue using a short path still gave 2.3 g. (80%) of colorless oil, b.p. (pot temperature) 130–140° at 0.01 mm. The infrared spectrum of the liquid film showed the absence of an amide band.

Anal. Calcd. for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.97; H, 10.89; N, 4.80.

The corresponding amino ketone could be obtained from the ketal-amine IV by allowing it to stand for 20 hours with 30% aqueous tartaric acid. When the solution was made basic, extracted with ether and the ether extracts were concentrated, a pale yellow oil resulted. A liquid film of this oil showed absorption in the infrared at 5.85 μ, as expected for the desired ketone. However, attempts to distil this oil or otherwise purify it led to decomposition. Various methods to effect cyclization of both the ketal amine IV and the amino ketone were tried without success. These included heating with polyphosphoric acid at 100–110°, standing with anhydrous hydrogen fluoride, and heating with zinc chloride.

Hexahydroindole (V). (A) From 2-(2′-Nitroethyl)-cyclohexanone.—The preparation of 2-(2′-nitroethyl)-cyclohexanone by the reaction of 2-dimethylaminomethylcyclohexanone and nitromethane has been described by Reichert and Posemann,[22a] King, Bovey, Mason and Whitehead,[22b] and Belleau.[8] In agreement with Belleau it was our experience that this reaction proceeds in poor yield. An alternate synthesis which was much more satisfactory involved the reaction of 2-dimethylaminomethylcyclohexanone with diethyl nitromalonate and then hydrolysis.

A solution of 40.0 g. of 2-dimethylaminomethylcyclohexanone and 53.0 g. of diethyl nitromalonate in 150 ml. of toluene was warmed with stirring until brisk evolution of diethylamine occurred. This began when the temperature of the reaction mixture reached 80° and the mixture was maintained at 80° until evolution of diethylamine ceased (14 hours). The solution then was cooled, 100 ml. of benzene added, and washed successively with 10% aqueous hydrochloric acid, water, 10% aqueous sodium carbonate solution, and finally with water again. Concentration of the organic layer gave 68 g. of a residual yellow oil. This was treated with 350 ml. of a 20% aqueous solution of potassium hydroxide and warmed at 50° for 2 hours. The resulting homogeneous, aqueous solution was cooled and acidified with 3 *N* hydrochloric acid. Vigorous evolution of carbon dioxide occurred and a yellow oil separated. This was extracted with ether, washed with water and dried. After concentration, the residual oil was distilled to give 20.0 g. of a colorless oil, b.p. 121–125° at 1.5 mm. This was shown to be 2-(2′-nitroethyl)-cyclohexanone by conversion to the corresponding semicarbazone, m.p. 147–148° (lit.[22a] gives 151°).

(B) From 2-Cyanomethylcyclohexanone.—Although Dornow and Fleischmann[23] recently have reported a convenient synthesis of 2-cyanomethylcyclohexanone utilizing the cyanohydrin of 2-dimethylaminomethylcyclohexanone, we have found it simpler to prepare this compound by the alkylation of the enamine of cyclohexanone and pyrrolidine. A mixture of 226.5 g. of N-(1-cyclohexeno)-pyrrolidine and 57.2 g. of freshly-distilled chloroacetonitrile in 500 ml. of dry dioxane was boiled under reflux for 3 hours. The reaction mixture was then cooled, poured onto ice, and extracted several times with ether. The combined ether extracts were washed with dilute acid, water, and dried. Concentration of the ether solution and then distillation of the residue gave 55.1 g. (53%) of a light yellow oil, b.p. 142–144° at 12 mm., $n^{20}D$ 1.4790.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.18; H, 8.29; N, 10.47.

The 2,4-dinitrophenylhydrazone of 2-cyanomethylcyclohexanone readily formed and was obtained after recrystallization from ethanol as yellow crystals, m.p. 170–171°.

Anal. Calcd. for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.77; N, 22.07. Found: C, 53.34; H, 5.03; N, 22.27.

The conversion of 2-cyanomethylcyclohexanone to the corresponding ketal was carried out by heating a mixture of 55.0 g. of 2-cyanomethylcyclohexanone, 30.0 g. of ethylene glycol and 1.0 g. of *p*-toluenesulfonic acid in 200 ml. of benzene under reflux with continuous removal of water until no further water separated. The cold solution now was washed successively with aqueous base and water and then concentrated. Distillation of the residue gave 67.1 g. (92%) of a colorless oil, b.p. 147–152° at 15 mm., $n^{22}D$ 1.4772.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 66.43; H, 8.25.

The succeeding steps in the conversion of this ketal to hexahydroindole have been described by Belleau[8] and our results are in essential agreement with his.

2-(2′-Cyclohexenylacetamidoethyl)-cyclohexanone (VI).—To a mixture of 0.95 g. of hexahydroindole in 10 ml. of a 10% aqueous sodium hydroxide solution there was added 1.6 g. of cyclohexenylacetyl chloride. The exothermic reaction was controlled by shaking and cooling the reaction vessel with ice. Then the reaction mixture was poured onto ice and extracted with ether. After the ether extract had been washed successively with aqueous acid, base and water, it was dried and concentrated. The residual oil was taken up in benzene and chromatographed over alumina to give 1.5 g. of a pale yellow oil.

(20) Melting points are corrected. Analyses by Miss A. Smith and by the Micro-Tech Laboratories.

(21) C. Chuang and C. Ma, *Ber.*, **68**, 871 (1935).

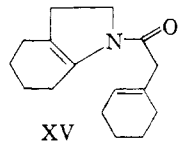
(22) (a) B. Reichert and H. Posemann, *Arch. Pharm.*, **275**, 65 (1937); (b) F. E. King, D. M. Bovey, K. G. Mason and St. D. Whitehead, *J. Chem. Soc.*, 250 (1953).

(23) A. Dornow and E. Fleischmann, *Chem. Ber.*, **88**, 1340 (1955).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57. Found: C, 73.16; H, 9.77.

When attempts were made to purify this oil by distillation using a short-path still heated at 145° at 1×10^{-2} mm., the distillate was a light yellow oil having a composition indicating that water was eliminated during distillation. Presumably, the distillate has structure XV.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.97; H, 9.38; N, 5.70.



XV

14,15,16,17-Tetrahydroerythrinane (VIII ?).—A mixture of 530 mg. of the above distillate XV in 20 g. of polyphosphoric acid was heated at 105–110° for 21 hr. The cold solution was poured into an excess of iced, aqueous sodium hydroxide and extracted with ether. The ether extracts were washed with water, dried and concentrated. The residual oil (0.32 g.) was taken up in 50 ml. of dry ether and added to a solution of 2.0 g. of lithium aluminum hydride in 50 ml. of ether. The resulting solution was boiled under reflux for three hours and then decomposed by addition of a saturated aqueous sodium sulfate solution. After removal of the granular precipitate, the ether solution was concentrated to give a residual, basic oil. This was taken up in ethanol and treated with picric acid. The solid, which separated, was recrystallized from ethanol to give yellow crystals, m.p. 186–188°.

Anal. Calcd. for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.06; H, 6.14; N, 12.22.

14,15,16,17-Tetrahydro-8-ketoerythrinane (IX).—A mixture of 300 mg. of the ketal amide III in 3.0 g. of polyphosphoric acid was heated at 100° for 4 hours. After the reaction mixture had been poured onto ice, it was extracted with methylene chloride and the methylene chloride extract was washed with dilute alkali and water. Concentration of the extract gave 146 mg. of a neutral brown oil which was taken up in a 1:1 benzene–petr. ether mixture and chromatographed over alumina (Woelm, activity II). From the eluate there was isolated 90 mg. of a white solid, m.p. 65–70°. After further recrystallization from an ether–hexane mixture, white crystals, m.p. 76–78°, resulted. The infrared spectrum of these crystals showed a band at 6.02 μ (lactam).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.22; H, 9.58.

14,15,16,17-Tetrahydroerythrinane (I). (a) From Erythrinane (XIV).—The erythrinane used in this experiment was prepared as described by Belleau[8] and in general our results, in terms of yields and properties of the various intermediates, are in good agreement with his. The chief discrepancy was our finding that erythrinane, previously obtained as oil, crystallizes to give white crystals, m.p. 56–58° (*Anal.* Calcd. for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.32; H, 9.67; N, 5.83). The picrate of the crystalline sample of erythrinane melts at 183–184° in agreement with Belleau's report.[8] The reduction of erythrinane was carried out following the procedure of Benkeser, Robinson, Sauve and Thomas.[19] A solution of 440 mg. of crystalline erythrinane (XIV) and 500 mg. of lithium in 30 ml. of anhydrous ethylamine was stirred in a nitrogen atmosphere and allowed to boil under reflux for 12 hr. After 3 hr., the solution had become gray in color and an additional 200 mg. of lithium was added to restore the blue color. At the end of the reaction time, ammonium chloride was added until there was no further evidence of reaction and the solvent was allowed to evaporate. The organic residue was extracted with ether, washed with a small amount of water, dried and the ether solution was concentrated. Distillation of the residue using a short-path still gave 340 mg. of a colorless oil, b.p. (block temperature) 85–120° at 10^{-4} mm. The ultraviolet absorption spectrum of this oil in ethanol containing 5% perchloric acid showed a single maximum at 208 mμ (log E 3.27). The presence of acid has been shown with various model compounds to remove the end absorption in the ultraviolet due to the tertiary nitrogen,[24] and the absorption band at 208 mμ can be attributed to the tetrasubstituted double bond in I.

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.05; H, 10.89. Found: C, 83.09; H, 11.06.

The picrate of 14,15,16,17-tetrahydroerythrinane (I) formed readily in ethanol and was obtained, after recrystallization from the same solvent, as yellow crystals, m.p. 147.5–148.5°.

Anal. Calcd. for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.24; H, 6.42; N, 12.14.

(b) From Reduction of IX.—To a solution of 270 mg. of 14,15,16,17-tetrahydro-8-keterythrinane (IX) in 30 ml. of anhydrous ether was added 270 mg. of lithium aluminum hydride. After the mixture had been heated under reflux for 4 hours, it was cooled and decomposed by the addition of a saturated aqueous sodium sulfate solution. Removal of the granular precipitate and then concentration of the ethereal filtrate gave 260 mg. of a colorless oil. This was dissolved in ethanol and treated with ethanolic picric acid solution. After the solution had stood overnight, there separated 170 mg. of yellow crystals, m.p. 143–146°. A further recrystallization from ethanol gave a sample melting at 147–148°, undepressed by admixture of the picrate of I obtained in (a) above. Also the infrared spectrum of these crystals was completely superimposable with that of the picrate of I from (a).

Anal. Calcd. for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13. Found: C, 57.83; H, 6.38.

Ketal of Ethylene Glycol and 2-Carboxymethylcyclohexanone, X.—A solution of 5.0 g. of the ketal ester II in 60 ml. of 4% methanolic potassium hydroxide was boiled under reflux for 1 hr. To the cold basic solution water was added and any remaining neutral material was extracted with ether. The aqueous layer then was brought to a *p*H 6.5 by addition of dilute phosphoric acid and the solution was extracted with chloroform. After the chloroform layer had been washed with water and dried over sodium sulfate, it was concentrated to give 4.7 g. of a colorless oil which, on standing, crystallized. Recrystallization from an ether–hexane mixture gave white crystals, m.p. 54–56°, whose only absorption in the carbonyl region of the infrared was at 5.88 μ.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.08; H, 8.20.

Preparation of the Ketal Amide XI.—A mixture of 8.6 g. of the ketal-ester II and 4.1 g. of homoveratrylamine was heated in a nitrogen atmosphere for 9 hours. The temperature was initially at 110° and was raised slowly to 180° during the period of heating. The reaction mixture was then taken up in 60 ml. of a 10% methanolic potassium hydroxide solution and boiled under reflux for 0.5 hour to hydrolyze any unreacted ester. After dilution with water, the solution was extracted with chloroform and the chloroform extracts were washed successively with dilute acid and water. Concentration of the chloroform solution gave 7.4 g. of a light tan solid, m.p. 115–120°. Recrystallization from a mixture of acetone and isopropyl ether gave a sample of white crystals, m.p. 122–123°.

Anal. Calcd. for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.44; H, 8.04; N, 4.07.

When various experiments were carried out heating X and homoveratrylamine together in the temperature range between 110 to 200° as described by Mondon,[10] the main product isolated in each case was identical with the amide described above. In several instances, where an excess of the ketal-acid X was employed, there was found in addition the cyclic amide XII but in very poor yield.

15,16-Dimethoxy-10-ketoerythrinane (XII). (a) By Cyclization of X.—To a solution of 980 mg. of the ketal amide XI in 10 ml. of ethanol there was added 10 ml. of a 5% solution of aqueous hydrochloric acid and the mixture was allowed to stand for two days. After neutralization by addition of sodium bicarbonate, the solution was concentrated to remove most of the ethanol and the residual aqueous solution was extracted with chloroform. The chloroform extract was washed with water, dried and concentrated to give a colorless oil. This, on seeding, crystallized yielding 650 mg. of a white solid, m.p. 115–117°, which was taken up in a benzene–petr. ether mixture and chromatographed

(24) T. T. Grossnickle and V. Boekelheide, unpublished work.

over alumina to give white crystals, m.p. 117–118°, unchanged by recrystallization from ethyl acetate. In other runs, the concentration of acid varied from 1 to 6 *N* without affecting the yield. When the cyclization was carried out using polyphosphoric acid, as described in the preparation of VII, 15,16-dimethoxy-10-ketoerythrinane was obtained in yields of 60–70%. The infrared spectrum of XII using a KBr disk, showed an absorption band at 5.96 μ (lactam).

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.39; H, 7.72.

(b) **By the Reaction of XI with Homoveratrylamine Hydrochloride.**—A mixture of 435 mg. of homoveratrylamine hydrochloride and 450 mg. of the ketal acid X was heated at 150–155° in an atmosphere of nitrogen for 4 hours. The cold residue then was dissolved in chloroform and washed successively with aqueous acid, base, and water. After the chloroform solution was dried, it was concentrated to give a light yellow oil. This was taken up in a benzene–petr. ether mixture and chromatographed over alumina. From the eluate, there was isolated 210 mg. (70%) of white crystals, m.p. 116–117°, undepressed by admixture of a sample of XII from (a). A mixture of these crystals and a sample of the ketal-amide XI showed a strong depression of melting point.

Racemic 15,16-Dimethoxyerythrinane (XIII).—To a solution of 500 mg. of XII in 80 ml. of absolute ether there was added 500 mg. of lithium aluminum hydride and the resulting mixture was boiled under reflux for 4 hours. The excess lithium aluminum hydride was decomposed by adding ethyl acetate and then a saturated aqueous solution of sodium sulfate. After removal of the granular precipitate, the ether layer was extracted with a 2 *N* solution of hydrochloric acid, the aqueous layer was made basic, and the organic base was extracted with chloroform. When the chloroform solution had been dried, it was concentrated to give 450 mg. of a colorless oil. This was dissolved in ethanol and converted to the picrate. After recrystallization from an ethanol–acetone mixture, the picrate was obtained as yellow crystals, m.p. 186–187°.[25]

Anal. Calcd. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.85. Found: C, 56.30; H, 5.64; N, 10.89.

The hydrochloride of 15,16-dimethoxyerythrinane was prepared by passing an ethanolic solution of the picrate over an ion exchange column (Dowex 2-X4) and the product, after recrystallization from acetone, gave white crystals m.p. 228–229°.[25]

Anal. Calcd. for $C_{18}H_{26}NO_2Cl \cdot {}^1/_2H_2O$: C, 64.95; H, 8.17. Found: C, 64.75; H, 8.33.

Resolution of the Racemic 15,16-Dimethoxyerythrinane.—To a solution of 147 mg. of 15,16-dimethoxyerythrinane (recovered from the crystalline picrate by dissolving the picrate in chloroform and passing it over alumina) in 1 ml. of acetone there was added 360 mg. of dibenzoyl L(+)-tartaric acid in 3 ml. of ethyl acetate. When the solution was allowed to stand, there separated 300 mg. of white crystals, m.p. 135–138°. By repeated crystallization from acetone, there was obtained 120 mg. of white needles, m.p. 126–127°, $[\alpha]^{20}D$ −29° (*c* 1.11, chloroform).

Anal. Calcd. for $C_{36}H_{39}NO_{10}$: C, 66.96; H, 6.09. Found: C, 67.30, 66.03; H, 6.35, 6.48.

The corresponding picrate of (−)-15,16-dimethoxyerythrinane was prepared by passing the L-(+)-dibenzoyl tartrate over an ion exchange column to regenerate the free base and this was treated with ethanolic picric acid. This was obtained after recrystallization from ethanol as yellow crystals, m.p. 202°, undepressed by admixture of the picrate of hexahydroapoerysotrine.[17] Also, its infrared spectrum in chloroform was superimposable with that of hexahydroapoerysotrine.[17]

Anal. Calcd. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46. Found: C, 56.00; H, 5.54.

The dibenzoyl D-(−)-tartrate of 15,16-dimethoxyerythrinane was obtained by treating 100 mg. of the free amine (recovered from the mother liquors of the solution given above) in 1 ml. of acetone with 200 mg. of dibenzoyl-D-(−)-tartaric acid in 100 ml. of ethyl acetate. After standing, the solution deposited 110 mg. of white needles, m.p. 129–130°. After three recrystallizations from acetone, a sample was obtained as white needles, m.p. 126–127°, $[\alpha]^{20}D$ +30° (*c* 1.12 in chloroform).

Anal. Calcd. for $C_{36}H_{39}NO_{10}$: C, 66.96; H, 6.09. Found: C, 66.54; H, 6.52.

The picrate of (+)-15,16-dimethoxyerythrinane was prepared in the same manner as described for its enantiomorph and, after crystallization from ethanol, melted at 202°. A mixture of this picrate and that of hexahydroapoerysotrine began melting at 176°.[17]

Anal. Calcd. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.85. Found: C, 55.57; H, 5.51; N, 10.72.

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(25) Belleau (ref. 8) gives 186–189° as the melting point of the picrate and 225–227° for the hydrochloride.

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

A Synthesis of 14,15,16,17-Tetrahydro-16-oxaerythrinane and its Identity with Anhydro-α-hexahydrodesmethoxy-β-erythroidinol[1,2]

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The synthesis and resolution of 14,15,16,17-tetrahydro-16-oxaerythrinane (XII) are described. The identity of the levorotatory enantiomorph with anhydro-α-hexahydrodesmethoxy-β-erythroidinol conclusively establishes the spiro amine structures previously postulated for α- and β-erythroidine.

Although the degradative studies on β-erythroidine are by now quite extensive and the deduction of the spiro amine system for this alkaloid is convincing,[3,4] the experimental evidence has been obtained largely from products derived through skeletal rearrangement and there has been no direct evidence to prove the presence of the spiro amine function. For this reason a synthesis of a derivative of β-erythroidine containing the intact spiro amine system was desirable and the purpose of the present paper is to report the accomplishment of this synthetic goal with the accompanying proof of identity of synthetic and natural materials.

The compound first chosen for synthesis was anhydro - β - hexahydrodesmethoxy - β - erythroidinol (IV), which was readily obtainable in the natural series by treatment of the known β-hexahydrodesmethoxy-β-erythroidinol (III)[5] with phosphoric

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(2) Paper XVI in this series; for the preceding communication see V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle and M. Chang, THIS JOURNAL, **81**, 3955 (1959).

(3) V. Boekelheide and V. Prelog, "Progress in Organic Chemistry," Vol. 3, edited by J. W. Cook, Butterworths, London, 1955, p. 242.

(4) V. Boekelheide, *Record Chem. Progr.*, **16**, 227 (1955).

(5) V. Boekelheide, A. E. Anderson, Jr., and G. L. Sauvage, THIS JOURNAL, **75**, 2558 (1953).