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 $\mu$ (lactam).

*Anal.* Calcd. for $C_{15}H_{23}NO_3$: 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.

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[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]

BY M. MÜLLER, T. T. GROSSNICKLE AND V. BOEKELHEIDE

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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

(1) Aided by a grant from the Smith, Kline and French Laboratories.

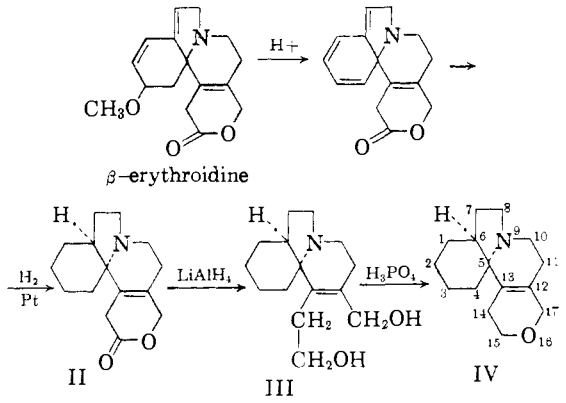
(2) Paper XVI in this series; for the preceding communication see V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle and M. Chang, THIS JOURNAL, **81**, 3955 (1959).

(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).

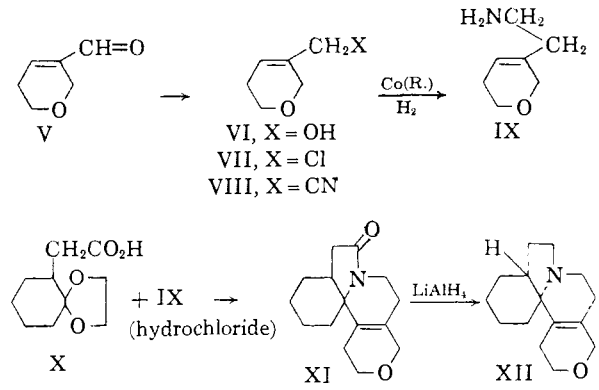
acid. The complete series of conversions leading from β-erythroidine to IV are




For the purposes of synthesis it was important to know the stereochemistry of IV with regard to the ring fusion at $C_5$–$C_6$. Fortunately, this can be deduced from reasonable assumptions about the mode of hydrogenation of I. From examination of molecular models it is clear that absorption of the triene system on a catalyst surface is readily possible only from the side opposite to the lactone ring. Therefore, the hydrogenation product as well as the succeeding derivatives should have the stereochemistry shown. Prelog, McKusick, Merchant, Julia and Wilhelm[6] have interpreted the mode of hydrogenation of erythraline in a similar fashion and the assignment of stereochemistry to synthetic[2,7,8] and natural (−)-hexahydroapoerysotrine[9] is based on the same argument.

The synthesis of IV was undertaken following a scheme similar to that which had been successful for 14,15,16,17-tetrahydroerythrinane and which in this case was known to give the desired stereochemistry.[2] The starting material, 2*H*-5,6-dihydropyran-3-carboxaldehyde (V),[10] was converted in a series of straightforward reactions to the corresponding alcohol VI, chloride VII and nitrile VIII. Reduction of the nitrile with lithium aluminum hydride in an attempt to obtain the corresponding amine IX yielded a complicated mixture and eventually we turned to catalytic hydrogenation using Raney cobalt.[11] This proceeded smoothly in excellent yield to give the desired product IX with the double bond in the ring still intact.

When the hydrochloride of IX was heated with the ketal acid X, the tetracyclic amide XI formed in good yield and was reduced directly with lithium aluminum hydride. The resulting racemic 14,15,16,17-tetrahydro-16-oxaerythrinane (XII), isolated as the picrolonate, was converted to the free base and its infrared spectrum as a film was similar to but not identical with that of IV.




Because the mechanism of the remarkable cyclization reaction by which XI was formed is not known, there existed the possibility that substitution of a dihydropyranyl ring for cyclohexenyl might affect the stereochemical outcome. The great similarity between the infrared spectra of IV and XII suggested they could be diastereoisomers. To settle this question our attention turned toward ways of obtaining a derivative in the natural series which would have the stereochemistry shown by XII. Fortunately, the solution to this was available from a prior observation that, by use of the Birch reduction, desmethoxy-β-erythroidine gives a series of derivatives which are diastereoisomeric with those from catalytic hydrogenation, the difference being in the mode of ring fusion.[5] A scheme for preparing XII in the natural series utilizing the Birch reduction was therefore undertaken.

In choosing a starting material for this scheme, we took advantage of the discovery that, when β-erythroidine is reduced with lithium aluminum hydride in methylal instead of ether, dihydrodesmethoxy-β-erythroidinol (XIII) is formed directly. Presumably, hydrogenolysis of the allylic methoxyl is followed by isomerization of the heteroannular diene to a homoannular diene system. The ultraviolet absorption spectrum of XIII shows an absorption maximum at 272 (log $E$ 3.63) in accord with the assigned structure.

When XIII was subjected to the Birch reduction, it was converted cleanly in good yield to tetrahydrodesmethoxy-β-erythroidinol (XIV). This, on treatment with phosphoric acid, gave the corresponding pyran derivative XV which, by catalytic reduction, then gave the desired anydro-α-hexahydrodesmethoxy-β-erythroidinol (XII).[12]

A comparison of the enantiomorph of XII, so obtained in the natural series, with the racemate of XII from the synthetic showed that they had identical infrared spectra when taken in chloroform solution. With this evidence of identity of the two samples, the comparison was extended further by resolving the racemic mixture using dibenzoyltartaric acid. The diastereoisomer obtained using dibenzoyl-D-(−)-tartaric acid showed good agreement in infrared spectrum, melting point and optical rotation with the dibenzoyl D-(−) tartrate of

(6) V. Prelog, B. C. McKusick, J. R. Merchant, S. Julia and M. Wilhelm, *Helv. Chim. Acta*, **39**, 498 (1956).

(7) B. Belleau, *Chemistry & Industry*, 410 (1956); *Can. J. Chem.*, **35**, 651 (1957).

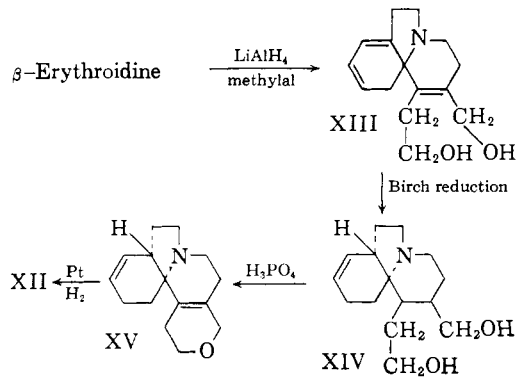
(8) A. Mondon, *Angew. Chem.*, **68**, 578 (1956).

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

(10) We wish to express our appreciation to Dr. T. J. Hall of the Carbide and Carbon Corp. and to Dr. F. B. Hilmer of the Shell Development Co. for generous gifts of this compound.

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

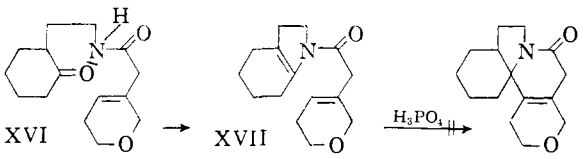
(12) Since the Birch reduction products are more dextrorotatory than their counterparts obtained by catalytic hydrogenation, the α-designation is assigned to the Birch series and β- to the series from catalytic hydrogenation.




the natural base. In addition the resolved and natural bases were compared as their crystalline picrates and shown to have identical melting points, undepressed by mixing, and identical infrared spectra.

The identity of the synthetic and natural samples of XII conclusively establishes the presence of the spiro amine system in β-erythroidine and there remains no doubt regarding the correctness of the structures postulated for this alkaloid and its various degradation products.[3,4,13] Since α-erythroidine recently has been converted to β-erythroidine,[14] the present synthesis also establishes the structures assigned to α-erythroidine and its derivatives.

It is apparent from the preceding discussion that caution must be exercised in using analogy to assign stereochemical relationships to fused spiro amines produced by acid-catalyzed cyclization of keto amides. In the case of 15,16-dimethoxyerythrinane, the same, *trans* fused product results whether the compound used for cyclization has the amide function in the potential six-membered ring (Belleau)[7] or in the potential five-membered ring (Mondon).[2,8] However, in syntheses directed toward 14,15,16,17-tetrahydroerythrinane, the Belleau and Mondon procedures give different final products, presumably due to stereochemical differences.[2] Since, in the present case, the stereochemistry of the 14,15,16,17-tetrahydro-16-oxaerythrinane corresponds to *cis* fusion, rather than *trans* as expected by analogy, it was of interest to repeat the synthesis utilizing the Belleau procedure to compare the stereochemical outcome in this case. Belleau has described such an approach but, unfortunately, he was unable to prepare the keto amide XVI necessary for the cyclization.[15] In our work, which




was carried out independently and prior to his publication, the synthesis of a compound having the expected physical and spectral properties for XVI was accomplished. Its purification by distillation was accompanied by loss of the elements of water, presumably due to formation of the cyclic enamide XVII. However, an attempt to effect cyclization of XVII under the usual conditions was unsuccessful and so a comparison of the stereochemical outcome of these alternate routes could not be made in this case.

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

(14) V. Boekelheide and G. C. Morrison, *ibid.*, **80**, 3905 (1958).

(15) B. Belleau, *Can. J. Chem.*, **35**, 663 (1957).

## Experimental[16]

**Anhydro-β-hexahydrodesmethoxy-β-erythroidinol (IV).**—A solution of 300 mg. of β-hexahydrodesmethoxy-β-erythroidinol (III)[5] in 4.5 ml. of 85% phosphoric acid was heated at 115° for 3 hr. under a nitrogen atmosphere. After the mixture had been poured onto ice and neutralized with sodium carbonate, it was extracted first with ether and then with benzene. Concentration of the extracts gave 245 mg. (88%) of an oil which was converted directly by treatment with ethanolic picrolonic acid to the corresponding crystalline picrolonate, m.p. 245–247° dec. A sample of the picrolonate was dissolved in chloroform and passed over alumina to regenerate the free base. The oil obtained by concentration of the eluate was distilled in a short-path still as a clear yellow oil, b.p. 120° at $10^{-4}$ mm. Its infrared spectrum showed no absorption in the 2.8–3.0 μ region.

*Anal.* Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.57; H, 9.89; N, 5.91.

**The picrolonate of IV** was prepared as indicated above and obtained, after recrystallization from ethanol, as yellow crystals, m.p. 245.5–247° dec., $[\alpha]^{25}$D +9.6° (*c* 0.92, chloroform).

*Anal.* Calcd. for $C_{25}H_{31}N_5O_6$: C, 60.34; H, 6.28; N, 14.08. Found: C, 60.73; H, 6.46; N, 14.34.

**The picrate of IV**, prepared in ethanol and recrystallized from the same solvent, melted at 185–186° dec.

*Anal.* Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.56; H, 5.64; N, 11.87.

**2*H*-5,6-Dihydropyranyl-3-acetonitrile (VIII).**—The reduction of 2*H*-5,6-dihydropyran-3-carboxaldehyde (V)[10] to the corresponding alcohol VI was carried out in 92% yield using lithium aluminum hydride in ether and gave a colorless oil, b.p. 108° at (11 mm.), $n^{20}$D 1.4889.[7,17] For characterization, the 3,5-dinitrobenzoate of VI was prepared giving white crystals, m.p. 90–91°, after recrystallization from alcohol.

*Anal.* Calcd. for $C_{13}H_{12}N_2O_7$: C, 50.65; H, 3.92. Found: C, 50.87; H, 4.17.

The conversion of the alcohol VI to the corresponding chloride VII and then to the nitrile VIII has been described by Belleau[7] and our results are in accord with his. As an alternate procedure, the nitrile VIII was prepared by the method of Breckpot.[18] A mixture of 20.0 g. of the alcohol VI, 16.0 g. of cuprous cyanide and 15 ml. of concentrated hydrochloric acid was heated on the steam-bath and, when the initial exothermic reaction had subsided, it was boiled under reflux for 0.5 hour. After the mixture had cooled, the organic layer was extracted with ether. Then, the aqueous phase was saturated with sodium chloride and again extracted with ether. The combined ether extracts were washed with water, dried, and concentrated to give 18.6 g. (86%) of the nitrile as a colorless oil, b.p. 105–108° at 11 mm., $n^{20}$D 1.4808.

**2*H*-5,6-Dihydropyranyl-3-acetic Acid.**—A mixture of 18.0 g. of the nitrile VIII in 15 ml. of concentrated hydrochloric acid was boiled under reflux for 2 hr. The cold solution then was extracted with ether and the combined ether extracts were extracted with aqueous sodium hydroxide. After acidification of the basic extract, it was saturated with sodium chloride and extracted with ether. After the ether extracts had been dried and concentrated, the residual oil was distilled to give 5.87 g. (27%) of an oil, b.p. 108–117° at 0.1 mm., $n^{20}$D 1.4905. Trituration with ether caused the oil to crystallize. After recrystallization from an ether–petr. ether mixture, there resulted 3.50 g. of white crystals,

(16) All melting points are corrected. Analyses by Miss A. Smith and by the Micro-Tech Laboratories.

(17) B. P. Geyer and R. H. Mortimer, U. S. Patent 2,514,156; *C. A.*, **44**, 8377 (1950).

(18) R. Breckpot, *Bull. soc. chim. Belg.*, **39**, 46 (1930); *cf.* J. W. E. Glattfield and E. Reitz, THIS JOURNAL, **62**, 974 (1940).

m.p. 67–68°. The ultraviolet spectrum of these crystals showed no absorption maximum above 210 mμ and the infrared showed the OH (3 μ) and carbonyl (5.92 μ, broad) absorption characteristic of an acid. The similarity between these spectra and those of cyclohexenyl-1-acetic acid was quite striking.

*Anal.* Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.88; H, 6.92.

**2*H*-5,6-Dihydropyranyl-3-ethylamine (IX).**—To a solution of 7.0 g. of 2*H*-5,6-dihydropyranyl-3-acetonitrile (VIII) in 40 ml. of methanol there was added 3 g. of Raney cobalt catalyst[11] and the mixture was subjected to hydrogenation at 60–65° and 100 atm. pressure. When two moles of hydrogen had been absorbed, the reaction was stopped and the catalyst and solvent were removed. The residual oil was dissolved in 2 *N* hydrochloric acid, extracted with ether, and the acidic solution made basic. After extraction of aqueous solution with chloroform, the chloroform extracts were washed, dried and concentrated. Distillation of the residue gave 3.5 g. of a colorless oil, b.p. 94–96° at 17 mm., $n^{20}D$ 1.4840. When tested with tetranitromethane, the oil gave a yellow color indicating an unconjugated double bond. In contrast, tetrahydrofuran gives no color with tetranitromethane and 2*H*-3,4-dihydropyran, having a conjugated enol ether, shows an orange color.

*Anal.* Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.06; H, 10.65; N, 11.29.

**The hydrochloride of IX** was prepared in ether using anhydrous hydrogen chloride and, after recrystallization from a methanol–acetone mixture, melted at 129–130°.

*Anal.* Calcd. for $C_7H_{14}NOCl$: C, 51.37; H, 8.29. Found: C, 51.13; H, 8.62.

**Tetrahydropyranyl-3-ethylamine Hydrochloride.**—To establish that a cyclic double bond still remained in IX, even though it was prepared by hydrogenation with Raney cobalt catalyst, its further hydrogenation over platinum was studied. A mixture of 175 mg. of the hydrochloride of IX and 70 mg. of prereduced Adams catalyst in 9.5 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. One mole of hydrogen was absorbed in 20 min. and then hydrogenation stopped. After removal of catalyst and solvent, the solid residue was crystallized from acetone to give 175 mg. of white crystals, m.p. 179–180°.

*Anal.* Calcd. for $C_7H_{16}NOCl$: C, 50.74; H, 9.74. Found: C, 51.00; H, 9.67.

**14,15,16,17-Tetrahydro-16-oxaerythrinane (XII).**—A mixture of 1.85 g. of the hydrochloride of IX and 1.70 g. of the ketal acid X[2] was heated at 160–170° in an atmosphere of nitrogen for 4 hr. Water and ice added were then and the mixture was extracted with chloroform. The chloroform solution was washed successively with aqueous acid, aqueous base, and water. On concentration it gave 1.80 g. of a neutral oil. This was taken up in benzene–petr. ether mixture and chromatographed over alumina (Woelm, activity II). After elution with benzene–petr. ether and then benzene–ether, there was obtained 400 mg. of an oil (XI) which showed lactam absorption (6.02 μ) in the infrared and whose spectrum over-all was very similar to that of 14,15,16,17-tetrahydro-8-ketoerythrinane.[2] The oil was taken up in anhydrous tetrahydrofuran and reduced directly by adding 800 mg. of lithium aluminum hydride and boiling the mixture under reflux for 4 hr. The reaction mixture was decomposed by the addition of a saturated aqueous sodium sulfate solution. When the granular precipitate of metallic hydroxides had been removed, the ether solution was extracted with a solution of 2 *N* hydrochloric acid. After the solution was made basic, it was extracted with ether and the ether extracts were dried and concentrated to give 380 mg. of a basic oil. As a precaution to avoid contamination by double bond isomers, the basic oil was taken up in a mixture of 10 ml. of dioxane and 6 ml. of concd. hydrochloric acid and allowed to stand overnight. The mixture then was made basic and extracted with chloroform. The chloroform solution was dried and concentrated to give 320 mg. of oil. This was treated with ethanolic picrolonic acid to give 350 mg. of a brownish-yellow solid, m.p. 194–196°. After several recrystallizations from ethanol, there was isolated yellow crystals, m.p. 200–201°.

*Anal.* Calcd. for $C_{25}H_{31}N_5O_6$: C, 60.34; H, 6.28; N, 14.08. Found: C, 60.33; H, 6.43; N, 14.21.

**Resolution of 14,15,16,17-Tetrahydro-16-oxaerythrinane.**—A solution of 125 mg. of the picrolonate of 14,15,16,17-tetrahydro-16-oxaerythrinane (XII) in chloroform was passed over alumina to liberate the free base. Concentration of the chloroform eluate gave 60 mg. of XII which was taken up in 2 ml. of acetone and treated with 140 mg. of dibenzoyl-D-(−)-tartaric acid in ethyl acetate. When the solution was allowed to stand overnight, there separated 54 mg. of the crystalline dibenzoyl D-(−)-tartrate, m.p. 145–147°. After recrystallization from methanol–acetone, the crystals melted at 151–152°, $[\alpha]^{20}D$ −42° (*c* 0.87 in chloroform).

*Anal.* Calcd. for $C_{33}H_{37}NO_9$: C, 66.99; H, 6.30. Found: C, 67.07; H, 6.38.

**The picrate of (−)-14,15,16,17-tetrahydro-16-oxaerythrinane** was prepared by dissolving 45 mg. of the dibenzoyl D-(−)-tartrate of XII in chloroform and passing the solution over alumina. Concentration of the eluate gave 21 mg. of a colorless oil. This was treated with ethanolic picric acid to give 25 mg. of nice yellow needles, m.p. 200°. These, after recrystallization from methanol–acetone, melted at 203–204°.

*Anal.* Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.64; H, 5.96; N, 12.06.

**Dihydrodesmethoxy-β-erythroidinol (XIII).**—A solution of 40.0 g. of β-erythroidine in 500 ml. of methylal was treated with 10 g. of lithium aluminum hydride and boiled under reflux for 8 hours. Then the reaction mixture was decomposed by adding a saturated aqueous solution of sodium sulfate, the granular precipitate was separated and the solution concentrated. The residual solid was a mixture which was taken up in chloroform and chromatographed over alumina. Concentration of the first eluate fractions gave 8.5 g. of a white solid which after crystallization from methanol melted at 193–194°. This showed the absence of methoxyl and had an absorption maximum in the ultraviolet at 272 mμ (*E* 4,240). On this basis it has been assigned structure XIII. Further elution of the column using chloroform–methanol gave an additional 25.2 g. of crystals, m.p. 165–168°, undepressed by admixture of authentic β-erythroidinol.[19]

*Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.77; H, 8.82.

**Birch Reduction of Dihydrodesmethoxy-β-erythroidinol (XIII).**—To a solution of 3.0 g. of dihydrodesmethoxy-β-erythroidinol (XIII) and 4 ml. of absolute ethanol in 100 ml. of liquid ammonia there was added small bits of sodium until the blue color of the dissolved sodium remained (40 min.). After the ammonia had been allowed to evaporate, water was added and the mixture was extracted with chloroform. Concentration of the chloroform extracts gave 2.4 g. of white crystals, m.p. 173–176°. By recrystallization from methanol–benzene, there was isolated 1.5 g. of nice white crystals, m.p. 184–187°, identical in all respects with the Birch reduction product (XIV) from β-erythroidinol described previously.[5]

**Anhydro-α-tetrahydrodesmethoxy-β-erythroidinol (XV).**—A solution of 1.20 g. of XIV in 10 ml. of 85% phosphoric acid was heated at 100° for 3 hr. It then was poured onto ice, neutralized with sodium carbonate and extracted with ether. Concentration of the ether extract gave 1.10 g. of a colorless oil. This was treated with ethanolic picrolonic acid and the resulting solid, after recrystallization from ethanol, gave 950 mg. of yellow crystals, m.p. 222–223°.

*Anal.* Calcd. for $C_{25}H_{29}N_5O_6$: C, 60.59; H, 5.90. Found: C, 60.41; H, 6.04.

**The picrate of XV** was obtained readily by treating a sample of the free base, regenerated from the picrolonate, with ethanolic picric acid. After recrystallization from ethanol, the yellow crystals melted at 160–161°.

*Anal.* Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25. Found: C, 54.98; H, 5.29.

**Anhydro-α-hexahydrodesmethoxy-β-erythroidinol (XII).**—A solution of 330 mg. of XV as the free base (obtained by decomposing 650 mg. of the corresponding picrolonate in the usual way) and 200 mg. of prereduced Adams catalyst in 20 ml. of ethanol containing 2 ml. of concd. hydrochloric acid was subjected to hydrogenation at room temperature

(19) M. F. Grundon, G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **75**, 2541 (1953).

and atmospheric pressure. When one mole of hydrogen had been absorbed, the reaction was stopped and the catalyst and solvent were removed. This afforded 320 mg. of a colorless oil which was taken up in a benzene–petr. ether mixture and chromatographed over alumina (*Woelm*, activity II). The principal eluate fraction yielded 245 mg. of a colorless oil which was dissolved in 5 ml. of acetone and treated with a solution of 500 mg. of dibenzoyl-D-(−)-tartaric acid in 5 ml. of ethyl acetate. When the resulting solution was allowed to stand overnight, there separated 490 mg. of crystals, m.p. 150–151°, unchanged by recrystallization from an acetone–methanol mixture, $[\alpha]^{20}D$ −45° (*c* 1.02, chloroform). A comparison of the dibenzoyl D-(−)-tartrate of XII, prepared in this way, showed it to have an infrared spectrum superimposable with that of (−)-14,15,-16,17-tetrahydro-16-oxaerythrinane (XII) obtained by synthesis. Also, a mixture of the two samples showed no depression of melting point.

For further proof of identity, 470 mg. of the dibenzoyl D-(−)-tartrate of anhydro-α-hexahydrodesmethoxy-β-erythroidinol was dissolved in chloroform and passed over alumina. The free base, obtained by concentration of the chloroform eluate, was treated with ethanolic picric acid to give 300 mg. of yellow crystals, m.p. 202°. These, after a further recrystallization from an acetone–ethanol mixture, melted at 204°. Comparison of this picrate of XII from the natural series with the picrate of (−)-14,15,16,17-tetrahydro-16-oxaerythrinane obtained by synthesis showed them to have identical infrared spectra and mixtures showed no depression of melting point.

A solution of 120 mg. of the pure picrate of anhydro-α-hexahydro-β-erythroidinol in chloroform was passed over alumina and the chloroform eluate was carefully concentrated. This gave 60 mg. of a colorless oil; $\alpha^{25}D$ −110° (*c* 0.6 in $CHCl_3$), b.p. (short path still) 110–120° at $10^{-4}$ mm.

*Anal.* Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 76.85; H, 10.04; N, 5.94.

**N-(2*H*-5,6-Dihydropyranyl-3-acetyl)-hexahydroindole (XVII).**—A mixture of 3.0 g. of 2*H*-5,6-dihydropyranyl-3-acetic acid and 2 ml. of thionyl chloride was boiled under reflux for 40 min. The solution was diluted with benzene and then concentrated to remove excess thionyl chloride. This was repeated once more and then the residue was distilled to give 2.48 g. of the acid chloride as a colorless oil, b.p. 96–98° at 9 mm., $n^{20}D$ 1.5953. Since the acid chloride was somewhat unstable, it was treated directly with a solution of 1.90 g. of hexahydroindole[2] and 15 ml. of dry pyridine in 30 ml. of benzene. The resulting mixture was heated at 60–70° for 45 min. and then poured onto ice. The two layers were separated and the aqueous layer was extracted further with benzene. After the benzene extracts were washed successively with dilute acid, dilute base and water, they were concentrated to give 2.53 g. of a reddish oil. The infrared spectrum of this oil showed carbonyl absorption (5.87 μ) and lactam absorption (6.12 μ) as would be expected for the keto amide XVI. Since attempts to crystallize the oil were without success, it was purified by two successive short-path distillations. This gave 2.0 g. of an oil showing strong absorption at 6.00 (double bond) and at 6.12 μ (lactam). The composition of the distillate was in accord with that required for the cyclic enamide XVII.

*Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.25; H, 8.88; N, 5.83.

A solution of 2.0 g. of XVII in 125 g. of polyphosphoric acid was heated at 120–130° for 24 hr. under an atmosphere of nitrogen. The mixture then was poured onto ice, neutralized and extracted with chloroform. Concentration of the chloroform extracts gave a thick red oil which did not crystallize. Attempts to purify it by chromatography or distillation were unavailing. A portion of the oil was reduced directly with lithium aluminum hydride but the product, so obtained, did not form crystalline derivatives and showed an absorption band at 3.0 μ (N–H or –OH) in the infrared.

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[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

# Synthesis of Potential Anticancer Agents. XIX. 2-Substituted $N^6$-Alkyladenines

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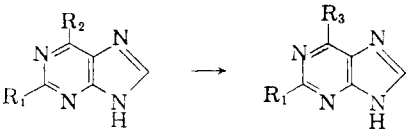
Several 2-substituted $N^6$-alkyladenines have been prepared from the corresponding 6-(alkylthio)-purines. Debenzylation of the $N^6$-alkyl-2-(benzylthio)-adenines has been effected by treatment with sodium in liquid ammonia.

Although a number of $N^2$-alkyl derivatives of guanine and 6-thioguanine have been prepared for screening as potential anticancer agents,[2] none of the isomeric derivatives of adenine has been reported, even though 6-amino-2-purinethiol, 2-(methylthio)-adenine and isoguanine have all shown some activity against Adenocarcinoma 755.[3] In order to investigate the possible anticancer activity of purines substituted in this manner, we have prepared some $N^6$-alkyladenines substituted in the 2-position by hydroxy, methylthio, benzylthio, and mercapto groups (Table I).

A number of $N^{2,6}$-alkyl derivatives of 2,6-diaminopurine, described in a previous paper of this series,[4] were obtained by stepwise aminations of 2,6-dichloropurine. Because acid hydrolysis of 2,6-dichloropurine gave xanthine, whereas basic hydrolysis gave 2-chloro-6-purinol,[5] one approach to the preparation of the 6-alkylamino-2-purinols IIa, b, c appeared to be acid hydrolysis of the corresponding $N^6$-alkyl-2-chloroadenines.[4] Although Davoll and Lowy[6] were able to obtain isoguanine



I II

Ia, $R_1$ = OH, $R_2$ = $SCH_2C_6H_5$
b, $R_1$ = $R_2$ = $SCH_3$
c, $R_1$ = $R_2$ = $SCH_2C_6H_5$
IIa, $R_1$ = OH, $R_3$ = $NHCH_3$
b, $R_1$ = OH, $R_3$ = $N(CH_3)_2$
c, $R_1$ = OH, $R_3$ = NH–*n*-$C_4H_9$
d, $R_1$ = $SCH_3$, $R_3$ = $NHCH_3$
e, $R_1$ = $SCH_3$, $R_3$ = NH–*n*-$C_4H_9$
f, $R_1$ = $SCH_2C_6H_5$, $R_3$ = $NHCH_3$
g, $R_1$ = $SCH_2C_6H_5$, $R_3$ = $N(CH_3)_2$
h, $R_1$ = $SCH_2C_6H_5$, $R_3$ = NH–*n*-$C_4H_9$

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Contract No. SA-43-ph-1740. Part XVIII, R. W. Balsiger, D. G. Jones and J. A. Montgomery, *J. Org. Chem.*, **24**, 434 (1959).

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