-1.04 (1 = 2, c = 12, acetone). The infrared spectrum showed bands at 4.60 μ and 9.94 μ which were not present in the non-deuterated compound.

Anal. Calcd:[35] $C_{13}H_{15}DO_4$: C, 65.81; H, 6.79; D, 0.84. Found: C, 65.62; H, 7.02; D, 0.78.

(35) The carbon hydrogen values are regular combustion analyses; the theoretical hydrogen value is adjusted by assuming that one atom of deuterium per acid phthalate is present.

The combined acid phthalate fractions were hydrolyzed to neopentyl alcohol-1-*d*, which was purified as before to a product of unchanged properties. It was reconverted to the acid phthalate, $[\alpha]^{27}D$ -1.07 ± 0.03 (1 = 2, c = 15, acetone), m.p. 70. The average of all these acid phthalate rotations was $[\alpha]D$ -1.06 ± 0.04. Based on the deuterium analysis indicating 93% labelling, this corresponds to a rotation of $[\alpha]$ -1.14 for the product which would be 100% labelled.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.]

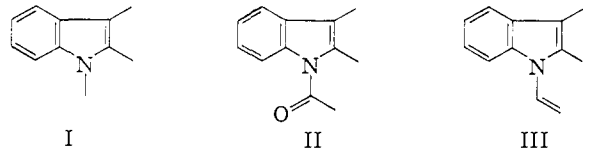
The Alkaloids of *Hunteria eburnea*. I. The Structures of Eburnamine, Isoburnamine, Eburnamenine and Eburnamonine and a Synthesis of *rac*-Eburnamonine[1]

BY M. F. BARTLETT AND W. I. TAYLOR

RECEIVED MAY 28, 1960

Eburnamine (XII) and its iso compound XII are shown to be interconvertible diastereoisomeric carbinolamines which upon oxidation afford the N-acylindole, eburnamonine (IV). Eburnamenine (XV), an N-vinyleneindole, is produced from the above alcohols by a mild acid-catalyzed dehydration. Reduction of eburnamonine yields the two alcohols as well as dihydroeburnamenine. Selenium dehydrogenation of eburnamonine furnishes 4-ethyl-4-propyl-4,5-dihydrocanthin-6-one, and 4-ethyl- and 4-propyl-canthin-6-ones. A general method is developed for the synthesis of these canthin-6-ones. Wolff-Kishner reduction of eburnamine furnishes *d*-1,1-diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3a]quinolizine which after racemization proves to be identical with a synthetic sample. From these and other results the structures and stereochemistry of the alkaloids are derived. A simple efficient seven-step synthesis of *dl*-eburnamonine is described.

During the course of an examination of the African apocynaceous plant *Hunteria eburnea* Pichon for substances of possible therapeutic value[2] several new alkaloids were isolated. Two of them, eburnamine and isoeburnamine, appeared analytically and spectrophotometrically to be trisubstituted pentacyclic indoles of type I, whereas eburnamenine

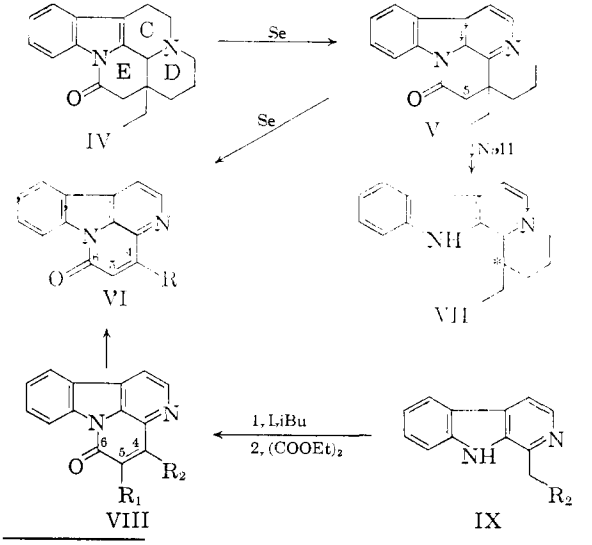


I II III

was an N_a-acylindole of type II, and eburnamenine had a spectrum which was not immediately recognized as being due to the chromophore (III). Since N_a-substituted indoles[3] were of rare occurrence and since this was the first occasion that an N-acylindole had been isolated it seemed that a more detailed investigation would yield some interesting results. It will be shown that these bases represent four representatives of a new class of pentacyclic indole alkaloid.

The position and hydroxylic nature of the oxygen in both eburnamine and its epimer was established by oxidation of the bases with chromic oxide in pyridine to eburnamonine in very high yield. Characterization of the chromophoric moiety of eburnamenine as III was made easily since it could be derived from the alcohols *via* mild acid-catalyzed dehydration; for example, it was sufficient to heat them in acetic acid on a steam-bath. The interrelationship was rounded off by the lithium aluminum hydride reduction of eburnamonine which gave a mixture of eburnamine, isoeburnamine and dihydro-eburnamenine.

Eburnamonine (IV) was chosen for further experimentation because of its stability and the potential usefulness of its N-acyl group not only for degradative purposes but also for the assistance it would provide in giving rise to chromophoric systems with characteristic spectral properties. Dehydrogenation of the base with selenium (5 minutes, 360°) gave an almost quantitative yield of the N-acyl-β-carboline[4] (V) in which ring C has been aromatized and ring D opened. This primary dehydrogenation product (V) after prolonged heating



(1) Part of this work has been the subject of two notes: (a) M. F. Bartlett, W. I. Taylor and Raymond-Hamet, *Compt. rend.*, **249**, 1259 (1959); (b) M. F. Bartlett and W. I. Taylor, *Tetrahedron Letters*, **20**, 20 (1959).

(2) Some pharmacology of crude materials is already in the literature: Raymond-Hamet, *Compt. rend.*, **240**, 1470 (1955); A. E. Gelhardt and H. Gilbrecht, *Naturwiss.*, **45**, 547 (1958).

(3) On the contrary N_a-substitution of indolines is common; probably because of the greater electron density at the nitrogen, they can act as more efficient "traps" for activated alkyl and acyl groups.

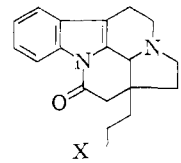
(4) The extensive work of Price and co-workers on the constitution of the canthin-6-ones from *Pentaceras australis* was very useful to us for the recognition of this and related systems and provided the basis also for the synthetic work; (a) H. F. Haynes, E. R. Nelson and J. R. Price, *Austral. J. Sci. Res.*, **5**, 387 (1952); (b) E. R. Nelson and J. R. Price, *ibid.*, **5**, 563 (1952); (c) **5**, 768 (1952).

with selenium was partially converted into a mixture of 4-ethyl- and 4-propyl-canthin-6-ones (VI, R = Et and R = Pr, respectively) separable by careful chromatography.

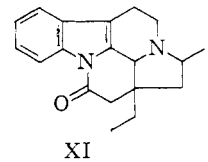
There was slight confusion at this point since the closely related canthinones did not differ very much in their analytical figures and both gave acetic and propionic acids upon oxidation by the modified Kuhn-Roth procedure[5] so that one might have been dealing with positional isomers rather than homologs. The molecular weights determined by mass spectroscopy[6] resolved this uncertainty and confirmed our ideas. The placing of the substituents at the 4-position was established by the results of another reaction on V which had its genesis in an attempt to test out a theory that ring E might be seven membered. It was reasoned that such a ring under appropriate basic conditions should split out an acrylic acid residue, leaving a β-carboline whose molecular formula would suffice to provide a considerable amount of information about substitution on ring E. In actual fact only after the use of drastic conditions there was obtained the β-carboline (VII) having two carbon atoms less. Its formation from V required the formal ejection of an acetate residue. If the results of this experiment were taken at face value ring E was six membered with no alkyl substituent on the 5-position.[7] The molecular weight of this compound was confirmed by mass spectroscopy[6] which also showed a trace of a substance two mass units of weight less, which may have been an olefin derived from VII. The mode of formation of VII which was optically active is obscure, but its structure was secured by a synthesis of the racemic compound (see Experimental).

For the synthesis of the canthin-6-ones an approach was designed to start from the readily available 1-alkyl-β-carbolines. Thus the appropriate β-carboline IX was converted into its dilithium derivative and condensed with diethyl oxalate[8] to furnish the hydroxy canthin-6-one (VIII, R_1 = OH) which after acetylation and reduction with zinc dust in acetic acid gave a mixture of the desired canthin-6-one and its 4,5-dihydro derivative. It was found simpler to convert the latter into the former by a selenium dehydrogenation of the mixture rather than to separate them. In this manner VI, R = ethyl and propyl, were synthesized as well as R = isopropyl, the first two agreeing in all respects with the appropriate degradation products. In order to round off this section of the work 5-hydroxy-canthin-6-one (VIII, R_1 = OH; R_2 = H) was made. Since Price[4] has prepared this phenol from 5-methoxycanthin-6-one, an alkaloid of *Pentaceras australis*, and reconverted it to the methoxy compound *via* its acetate[9] as well as eliminating the hydroxyl group to obtain canthin-6-one also a natural product, our synthetic method represents an efficient approach to these tetracyclic compounds.

The establishment of the structures of these degradation products does not lead to an unequivocal solution (IV) for the structure of eburnamonine, even if the possibility of rearrangement during dehydrogenation is ignored; that is, X and XI have to still be eliminated. In IV ring D is six membered and in

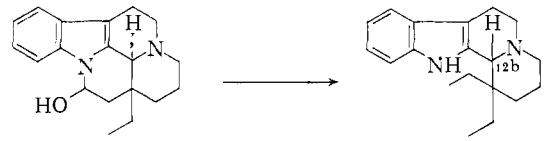


X



XI

preliminary dehydrogenation studies some of the chromatographic fractions had an ultraviolet spectrum suggestive of an α-pyridylindole which could only have arisen from X and XI by ring expansion; also eburnamonine has at least one C-ethyl as determined by the Kuhn-Roth procedure and analysis of the volatile acids, a result inconsistent with X unless it is assumed that all the butyric acid formed is converted into lower homologs. The structure XI cannot be eliminated with certainty since the Kuhn-Roth gives quantitative answers only in special cases. The skeleton implicit in IV was established by carrying out a Wolff-Kishner reaction on the carbinolamine eburnamine (XII) assuming that it would react *via* the theoretically tautomeric aldehyde. This it did, to give *d*-1, 1-diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3,a]-quinolizine (XIV). Racemization at 12b was effected by catalytic dehydrogenation[10] followed by



XII, α-OH(equatorial)
XIII, β-OH(axial)

XIV

sodium borohydride reduction of the resultant β-carbolinium salt. The product proved to be identical in all respects with a synthetic sample. This was prepared by reduction of the lactam formed by the condensation of 4-ethyl-4-formylhexanoic acid with tryptamine.

The stereochemistry of the pentacyclic system could now be considered. The spectral properties of both eburnamonine (IV) and eburnamenine (XV) pointed to a strain-free system. This conclusion was further supported by an examination of the hydrolysis product of eburnamonine, eburnamoninic acid, which recyclized very readily in

(5) Later paper chromatograms did show a small amount of a faster running acid (butyric ?) in the mixture of volatile acids derived from 4-propylcanthin-6-one.

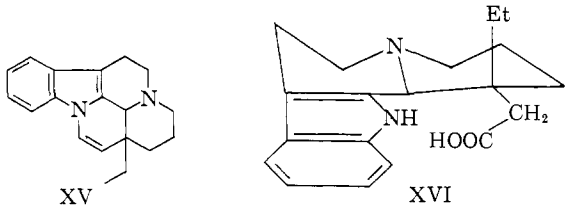
(6) We are grateful to Dr. K. Bieman of the Massachusetts Institute of Technology for running these measurements. The power of the method is shown by the fact that both of the samples submitted were found to be slightly contamined with each other. We are indebted to Professor G. Büchi for suggesting the use of this technique to us.

(7) In any event there could only have been one substituent on this atom as demanded by the known partial structure III for eburnamenine.

(8) The condensation of harman and diethyl oxalate using sodium ethoxide has been attempted previously without success; ref. 4b.

(9) By the prolonged action of diazomethane in moist ether on the acetate we have found it simpler to alkylate the hydroxy compound directly with diazomethane in methylene chloride. We have also made 4,5-dihydrocanthin-6-one by the palladium–charcoal-catalyzed dehydrogenation of the Hahn compound, 1,2,3,3a,4,5-hexahydrocanthin-6-one (G. Hahn and A. Hansel, *Ber.*, **71**, 2163 (1938)), in refluxing Dowtherm. The variability of the yields in our hands, however, did not lend itself to synthetic work.

(10) R. Majima and S. Murahashi, *Proc. Imp. Acad. (Tokyo)*, **10**, 341 (1934); E. Wenkert and D. K. Roychaudhuri, THIS JOURNAL, **80**, 1613 (1958).



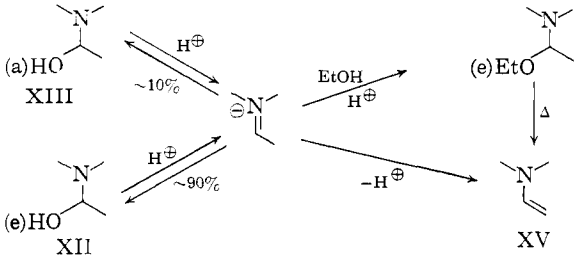
XV XVI

acidic solution also when one attempted the preparation of its ester using ethereal diazomethane. The best conditions for ester formation were found in the use of methylene chloride as the solvent but even then the lactam was often the sole product. Once the ester was formed it was stable, but surprisingly when methyl eburnamoninate was reduced with lithium aluminum hydride it gave eburnamine as the isolable product,[11] further support for the strain-free nature of the system. These conditions can only be met when eburnamoninic acid is represented as XVI which has di-equatorially placed indole and acetic acid residues. Thus, eburnamonine (IV) must have a *trans* D/E ring function. In the alternative possibility (XVI, Et- and CH_2-COOH interchanged) cyclization could only occur if rings C and D were considerably distorted.

The stability of the pentacyclic system is further illuminated in the reactions of eburnamine and its epimer. Neither of these compounds with the exception of the Wolff-Kishner reaction showed any properties which would indicate their being in equilibrium with the theoretically tautomeric aldehyde[12]; however, some reactions described below imply the intermediacy of another tautomer, the iminium ion. These reactions are summarized in Chart I.

CHART I

INTERRELATIONSHIPS OF EBURNAMINE, ISOEBURNAMINE AND EBURNAMENINE

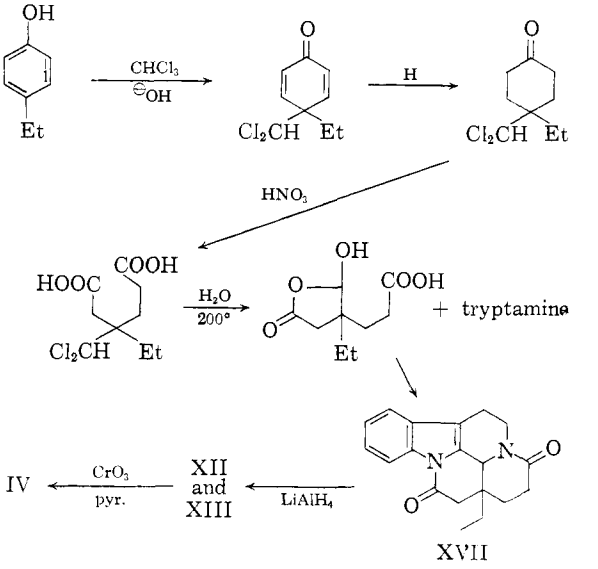


If either eburnamine or isoeburnamine was allowed to stand at room temperature in half normal sulfuric acid for a period they gave rise to a mixture of about 90% of the former and 10% of the latter, and if the solution was warmed briefly eburnamenine was obtained.[13] The driving force in the equilibration probably lies in the relief of strain (1,3-diaxial interaction of the hydroxyl and ethyl) in going from isoburnamine (XIII) to eburnamine (XII). In ethanolic picric acid both alcohols gave one and the same O-ethyleburnamine which if the solution was refluxed for a short period furnished eburnamenine in quantitative yield. Attempted acetylation of the alcohols under a variety of conditions led either to recovery of the bases or conversion into eburnamenine.

The ring system in these alkaloids has been prepared[14] previously in connection with approaches to syntheses of possible curare alkaloids. The authors were not absolutely sure from their reaction sequence that rings D and E might not have been five and seven membered, respectively. This uncertainty has been resolved since we have found in model studies that whenever a choice exists for acid-catalyzed lactam formation onto either N_a or N_b of a tetrahydro-β-carboline the preference is always wholly toward the δ-lactam. This fact as well as the course of the lithium aluminum hydride reduction of eburnamonine paved the way to a third structure proof by a simple total synthesis (Chart II). Thus condensation of β-ethyl-β-formyladipic acid with tryptamine gave in one step *dl*-eburnamonine lactam (XVII) which upon reduction with lithium aluminum hydride followed by oxidation of the resultant *dl*-eburnamines (XII and XIII) with chromic oxide in pyridine afforded *dl*-eburnamonine. The desired aldehyde diacid was prepared in four steps from *p*-ethylphenol as indicated in Chart II. The poor-yielding steps were the abnormal Reimer-Tiemann (8%) and the ring closure (25%).

CHART II

THE TOTAL SYNTHESIS OF *dl*-EBURNAMONINE



The relationship between these indole bases and aspidospermine has been pointed out previously.[1a] Both these groups of bases like the Iboga alkaloids[15] do not appear to be formed from the same precursors as other known indole bases unless one assumes

(11) It is probably the intermediate aldehyde or complex which cyclizes and then like eburnamine is resistant to further reduction. For another example see S. Corsano and S. Algieri, *Ann. Chim. (Ital.)*, **50**, 75 (1960). 4-Ethyl-4-propylcanthin-6-one likewise was reduced to the corresponding alcohol (see Experimental) which can be converted into the dihydrocanthine *via* the canthine in a fashion analogous to the sequence eburnamine → eburnamenine → dihydroeburnamine.

(12) In the case of apogeissoschizine (H. Rapoport, R. S. Windgassen, N. A. Hughes and T. P. Onak, THIS JOURNAL, **81**, 3166 (1959)) which has a strained system corresponding roughly to the N-vinylindole moiety in eburnamenine, acid hydrolysis gives rise irreversibly to the aldehyde geissoschizine; H. Rapoport personal communication.

(13) Since mineral acid was used in the original isolation of the alkaloids it is quite possible that the ratios of the three bases was quite different in the plant.

(14) T. Wieland and E. Neeb, *Ann.*, **600**, 161 (1956).

(15) M. F. Bartlett, D. F. Dickel and W. I. Taylor, THIS JOURNAL, **80**, 126 (1958).

that rearrangements occur.[16] There is also an interesting proposal[17,1b] in which the hydroaromatic precursor is derived from an aromatic amino acid along the lines of the synthesis of eburnamonine. The contribution of the organic chemist to the biogenetic problems raised will continue to lie in the isolation and structure proof of new alkaloids. The actual solutions will come from those laboratories where biosynthesis is being studied *in vivo*.

Acknowledgments.—We are grateful to Dr. E. Schlittler for his constant interest and encouragement. We are indebted to Mr. Louis Dorfman and his staff for the analytical and spectral data. We wish also to acknowledge the capable assistance of Ann F. Smith, Mrs. Nina Raab, William Bappe and Robert Sklar.

Experimental

All melting points were uncorrected. Unless otherwise noted the optical rotations were recorded in chloroform at 25 ± 2°, the ultraviolet absorption spectra were measured in ethanol, the infrared were taken in Nujol mulls and the alumina used in chromatography was Woelm. Depending on circumstances the analytical samples were dried between 25–100° at 0.02 mm. for 12 hours.

O-Ethyleburnamine.—Attempted formation of the picrates of either eburnamine or isoeburnamine in ethanol gave one and the same O-ethyleburnamine picrate, m.p. variable 152–166° (bubbling), resolidification and re-melting at 186°.

Anal. Calcd. for $C_{27}H_{31}N_5O_8$: C, 58.6; H, 5.6. Found: C, 58.3; H, 5.7.

The free base generated from the picrate had m.p. 147–148° from alcohol (routinely melting points of 141° were observed), $[\alpha]_D$ +64°. The infrared spectrum in chloroform was transparent in the OH/NH stretching region.

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.6; H, 8.7; OEt, 13.4. Found: C, 77.3; H, 8.7; OEt, 11.0.

The base methiodide from water had m.p. 262° dec.

Anal. Calcd. for $C_{22}H_{31}N_2OI$: C, 56.7; H, 6.7. Found: C, 56.5; H, 6.9.

Eburnamenine (XV).—(a) Eburnamine (or isoeburnamine) (100 mg.) was heated on a steam-bath for 30 minutes in acetic acid (2 ml.). The isolated semi-solid free base was characterized as its picrate, m.p. 186° or 196° from alcohol depending on the conditions of crystallization.

Anal. Calcd. for $C_{25}H_{25}N_2O_7$: C, 59.2; H, 5.0; N, 13.8. Found: C, 59.2; H, 4.9; N, 13.9.

Eburnamenine regenerated from the picrate could not be crystallized and was sublimed for analysis.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 8.0. Found: C, 81.8; H, 8.1.

It was characterized further as its methiodide, m.p. 274° dec. from water.

Anal. Calcd. for $C_{20}H_{25}N_2I$: C, 57.2; H, 6.0. Found: C, 57.0; H, 6.1.

If the methiodides of either eburnamine or isoeburnamine were prepared and crystallized from water, eburnamenine methiodide was the only product.

(b) If either eburnamine or isoeburnamine was refluxed in ethanol in the presence of picric acid for several hours an almost quantitative yield of eburnamenine picrate, m.p. 186° or 196°, was obtained.

(c) If O-ethyleburnamine picrate is heated at 160° *in vacuo* until the bubbling ceased and resolidification was complete, the product was pure eburnamenine picrate, m.p. 186°, recrystallization being unnecessary.

Dihydroeburnamenine.—Eburnamenine (870 mg.) in alcohol took up one mole-equivalent of hydrogen in the presence of pre-reduced platinum oxide (500 mg.). After filtration and addition of picric acid (0.9 g.) in alcohol the picrate (1.17 g.), m.p. 192–194° dec., was obtained, After recrystallization and drying for analysis it had m.p. 210–213° dec.

Anal. Calcd, for $C_{25}H_{27}N_5O_7$: C, 58.9; H, 5.3; N, 13.8. Found: C, 59.3; H, 5.2; N, 13.6.

Dihydroeburnamenine, regenerated from its picrate and crystallized from methanol–water, had m.p. 89–91°, $[\alpha]_D$ −1.5 ± 1°, pk_a' 6.9; λ_{max} (ϵ) 229 mμ (34.500), 284 (7,400) with shoulders at 278 (6,900) and 292 (6,400); λ_{min} 250 (2,400). A sample was sublimed at 130–150° *in vacuo* for analysis.

Anal. Calcd. for $C_{19}H_{24}N_2$; C, 81.4; H, 8.6; N, 10.0. Found: C, 81.4; H, 8.7; N, 9.9.

Chromium Trioxide Oxidation of (Iso)eburnamine.—Eburnamine (2.77 g.) in pyridine (35 ml.) was added slowly with ice cooling to chromium trioxide (2.8 g.) in pyridine (35 ml.). The resulting dark brown solution was allowed to stand for 10 minutes then filtered through alumina (activity III) using methylene chloride as an eluent. The eluate furnished crude eburnamonine (2.76 g.) which upon crystallization from alcohol gave eburnamonine (IV) (2.26 g.), m.p. 173–174°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.5; H, 7.5. Found: C, 77.0; H, 7.3.

A similar oxidation of isoeburnamine (140 mg.) furnished eburnamonine (90 mg.), m.p. 175–176°.

The Lithium Aluminum Hydride Reduction of Eburnamonine.—Eburnamonine (490 mg.) in ether (50 ml.) was refluxed with lithium aluminum hydride (50 mg.) for 2 hours and allowed to stand for 2 days at room temperature. After the work-up the product (480 mg.) was chromatographed over basic alumina (activity III). From the benzene–hexane (1:1) eluate dihydroeburnamenine was obtained. The benzene eluate furnished firstly isoeburnamine followed by eburnamine.

The Wolff-Kishner Reduction of Eburnamine.—Eburnamine (775 mg.), potassium hydroxide (500 mg.) and hydrazine hydrate (5 ml.) were heated in ethylene glycol (15 ml.) for 2 hours at 130° after which the bath temperature of the reaction mixture was raised over 2 hours to 260°. The cooled solution was extracted with ether which was washed several times with water, dried and concentrated to dryness. The residue (830 mg.) in hexane was filtered through neutral alumina (activity III) to afford *d*-1,1-diethyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a] quinolizine (XIV) (250 mg.), m.p. 106° from hexane, $[\alpha]_D$ +93°.

Anal. Calcd. for $C_{19}H_{26}N_2$ (sublimed sample): C, 80.8; H, 9.3. Found: C, 80.9; H, 9.3.

The dextrorotatory indolo [2,3-a] quinolizine (135 mg.) was heated for 3 days in an evacuated sealed tube with palladium black (100 mg.) and maleic acid (200 mg.) in water. The basified solution was extracted with methylene chloride and passed through alumina (activity III) to yield from the yellow eluate the crude anhydronium compound (35 mg.). This was reduced directly with sodium borohydride in methanolic solution and the racemic 1,1-diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine was crystallized from hexane to m.p. 132°, $[\alpha]_D$ +0.6 ± 2°.

Anal. Found (sublimed sample): C, 80.4; H, 9.3.

Selenium Dehydrogenation of Eburnamonine.—Eburnamonine (1.23 g.) and selenium (5.0 g.) were heated in a sealed evacuated tube for 12 hours at 340–350°. The contents of the tube were powdered and thoroughly extracted with methylene chloride–methanol, to afford a dark brown residue (1.09 g.). This was chromatographed over neutral alumina (activity II). Elution with benzene gave the fractions: (i) crude 4-ethyl-4-propyl-5,6-dihydrocanthin-6-one (340 mg.); (ii) oil (25 mg.); (iii) crude 4-propylcanthin-6-one (193 mg.); (iv) crude 4-ethylcanthin-6-one (125 mg.). A small quantity of a more polar material was eluted with methylene chloride but was not investigated.

***d*-4-Ethyl-4-propyl-5,6-dihydrocanthin-6-one (V).**[16]—The fraction i above was characterized as its picrate, m.p. 199–200° from alcohol.

Anal. Calcd. for $C_{25}H_{23}N_5O_8$: C, 57.6; H, 4.5; N, 13.4. Found: C, 57.2; H, 4.4; N, 13.5.

In one experiment there was obtained a picrate, m.p. 162° and 203°, which according to the analytical figures was approximately a dihydrate.

(16) E. Schlittler and W. I. Taylor, *Experientia*, **16**, 244 (1960).

(17) R. Robinson, *Tetrahedron Letters*, **18**, 14 (1959).

(18) If in the selenium dehydrogenation the time of heating (360°) was only 5 minutes the yield of this canthin-6-one was almost quantitative.

Anal. Calcd. for $C_{25}H_{23}N_5O_8 \cdot 2H_2O$: C, 53.9; H, 4.9; N, 12.6. Found: C, 54.2; H, 4.3; N, 12.1.

The free base was generated from the picrate by decomposition on an alumina column using methylene chloride–methanol (99:1) as eluant. The oil was sublimed at 95–120° (0.01 mm.) for analysis; $[\alpha]_D$ +36°, pK_a, 3.0; λ_{max} (ϵ) 222 mμ (43,400), 262–264 (16,600), 273 (14,600), 283 (16,700), 314–316 (8,600), 327 (10,000), shoulder at 229 (37,000); λ_{min} 242–243 (8,200), 271 (13,900) and 279 (10,000); λ_{max}^{acid} 229–231 (38,400), 256–261 (10,500), 298–299 (23,400), 346–352 (8,400); λ_{min} 244–246 (7,700), 269–271 (8,200), 316–318 (5,000); $\nu_{C=O}$ 1700 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.1; H, 6.9. Found: C, 77.9; H, 6.8.

4-Propylcanthin-6-one (VI, R = Pr).—Fraction iii from the selenium dehydrogenation of eburnamonine gave from benzene–hexane a product (41 mg.), m.p. 117–120°, which was raised upon recrystallization to m.p. 127–128°, and to 128–129° after sublimation; λ_{max} (ϵ) 257 mμ (16,000), 265 (16,700), 293–296 (9,000), 343–344 (9,000), 360 (15,200), 379 (14,500), shoulders at 236 (18,900) and 244 (14,700); λ_{min} 248 (13,100), 261 (14,900), 274 (5,300), 318 (3,700), 346 (8,900) and 370 (9,900). The ultraviolet spectrum was unchanged in dilute acid or base.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4; N, 10.7. Found: C, 77.7; H, 5.3; N, 10.5.

4-Ethylcanthin-6-one (VI, R = Et).—Fraction iv from the selenium dehydrogenation of eburnamonine gave crystals (72 mg.), m.p. 167–168° from benzene–hexane, raised to m. p. 170–172° after further crystallization from the same solvent and methanol. It was sublimed for analysis at 140° (0.003 mm.). The ultraviolet spectrum was identical with the above 4-propylcanthin-6-one.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.7; H, 5.1; N, 10.9.

The Action of Sodium Hydride on 4-Ethyl-4-propyl-4,5-dihydrocanthin-6-one.—The dihydrocanthin-6-one (115 mg.) and a 52% dispersion of sodium hydride in mineral oil (220 mg.) was refluxed in toluene for 6 hours. An addition of the sodium hydride dispersion (150 mg.) was made and the refluxing continued for 16 hours. After the addition of water the aqueous solution was strongly acidified (H_2SO_4). The toluene was separated and, after basifying, the bases were recovered from the aqueous solution by extraction into methylene chloride to furnish a residue (36 mg.). This was chromatographed over basic alumina (activity III). The benzene–hexane (1:2) eluate yielded crude *l*-1-(1-ethylbutyl)-β-carboline (VII) (24 mg.), m.p. 140–141° from hexane raised to m.p. 142–143°, $[\alpha]_D$ −7° after sublimation at 140° (0.005 mm.); λ_{max} (ϵ) 233–235 mμ (37,000), 288 (17,700), 338–340 (5,700) 350–351 (6,000) and shoulders 240 (36,000), 249 (24,400) and 283 (11,900); λ_{min} 270–271 (7,900), 305–306 (1,400), 341–345 (5,700); λ_{max}^{acid} 227–237 (23,100), 249–251 (30,200), 303 (20,900), 372 (6,500) and shoulder 260 (24,400); λ_{min} 275–277 (6,800), 328–330 (2,800).

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0. Found: C, 80.5; H, 7.7.

Eburnamenine Glycol.—Eburnamenine (430 mg.) and osmium tetroxide (1 mole equiv.) in pyridine (5 ml.) was allowed to stand at room temperature for 16 hours. After evaporation to dryness an aqueous suspension was treated with excess sulfur dioxide, basified and extracted with ether. The product (400 mg.) was amorphous, m.p. 100–120°, and for analysis was dried for 12 hours *in vacuo*.

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.0; H, 7.7. Found: C, 73.3; H, 8.2.

Hydroxyeburnamonine.—The amorphous eburnamenine glycol (100 mg.) stood for 20 minutes in pyridine containing chromium trioxide (100 mg.). Filtration through alumina using methylene chloride as an eluant gave the lactam, m.p. 192–194° from alcohol; λ_{max} (ϵ) 244 mμ (20,060), 301 (5,000), plateau 261–264 (10,080) and shoulder 279 (2,630).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.5; H, 7.1. Found: C, 73.4; H, 7.3.

This lactam was readily hydrolyzed to an amino acid which was recyclized upon treatment with hot dilute acids or ethereal diazomethane.

4-Ethyl-4-propylcanthine.—4-Ethyl-4-propyl-4,5-dihydrocanthin-6-one (320 mg.) and lithium aluminum hydride (320 mg.) were refluxed in ether (30 ml.) for 6 hours. Water was added and the ether layer was dried and concentrated to furnish a glass (315 mg.) which was heated in acetic acid (13 ml.) on a steam-bath for 2 hours. After basifying and extraction with methylene chloride the base (293 mg.) was chromatographed over basic alumina (activity III). The benzene–hexane (1:1) eluate furnished the canthine (280 mg.), m.p. 103–104° from hexane unaltered upon further crystallization. For analysis it was sublimed at 120–130° (0.005 mm.); λ_{max} (ϵ) 246 mμ (40,600), 267 (16,700), 280–282 (12,800), 290 (13,300), 372 (5,200), 384–388 (4,800), plateau 241–243 (39,600); λ_{min} 220 (16,400), 263–264 (16,300), 277 (12,400), 288–289 (11,600) and 310 (2,900); λ_{max}^{acid} 243 (43,700), 252 (29,800), 307 (16,600), 420–424 (4,900), shoulder at 293 (13,100); λ_{min} 272 (5,500) and 333–335 (180).

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3; N, 10.1. Found: C, 82.7; H, 7.5; N, 10.0.

The compound rapidly took up one mole equivalent of hydrogen in the presence of Adams catalyst and the product which was not further characterized had the expected N_a-alkyl-β-carboline spectrum with maxima at 362, 347, 312 and 289 mμ.

Eburnaminic Acid (XVI).—Eburnamonine (1.18 g.) in methanol (80 ml.) containing 5 *N* sodium hydroxide (12 ml). was refluxed for 24 hours. After partial concentration, water was added and washed with methylene chloride. The aqueous solution was brought to *p*H 5–6 with acetic acid and extracted with methylene chloride. Concentration of this extract, after filtration through cotton wool, furnished the crystalline eburnamoninic acid (0.78 g.), m.p. 253° (*in vacuo*). A second crop (0.37 g.) was obtained upon further concentration. With dilute mineral acid, the amino acid reformed the lactam.

Treatment of the acid (43 mg.) in methylene chloride methanol (4 ml. of 1:1) with excess ethereal diazomethane gave the methyl ester (29 mg.), m.p. 138–139° (*in vacuo*) from hexane; λ_{max} (ϵ) 225 mμ (35,300), 280–283 (8,000), 290 (6,800) with shoulder at 275 (7,800); λ_{min} 247 (2,500) and 288 (6,700).

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.5; H, 8.1; N, 8.6.

Attempted preparation of the ester by treating a methanolic solution of the acid with ethereal diazomethane gave eburnamonine as the sole product. Reduction of either eburnamoninic acid or its methyl ester with lithium aluminum hydride gave a mixture of the alcohols eburnamine and isoeburnamine (paper chromatography) from which eburnamine was readily isolated.

Synthetic Work. 1,1-Diethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine.—Tryptamine (500 mg.) and 4-ethyl-4-formylhexanoic acid[19] (600 mg.) were heated at 120° for 1 hour and for 1 hour at the same temperature *in vacuo*. The residue was triturated with alcohol to afford the highly crystalline lactam, m.p. 291° (*in vacuo*), $\nu_{C=O}$ 1618 cm.$^{-1}$, which was soluble with difficulty in all common organic solvents. For analysis it was crystallized from a large volume of alcohol.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2. Found: C, 77.0; H, 8.2.

1,1-Diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (XIV).—The lactam was extracted for several days into ether containing excess lithium aluminum hydride to furnish the base, m.p. 132°, identical in all respects with the racemized Wolff-Kishner product from eburnamine.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.8; H, 9.3. Found: C, 80.8; H, 9.6.

1-(1-Ethylbutyl)-β-carboline (VII).—Ethylpropylacetyl chloride (0.92 g.) and tryptamine (1 g.) were heated on a steam-bath for 10 minutes in pyridine. After concentration, the residue was triturated successively with dilute hydrochloric acid, sodium hydroxide and water. The resulting crude amide (1.3 g.), m.p. 120°, was refluxed for 3 hours in phosphorus oxychloride to furnish the crude dihydro-β-carboline (750 mg.) which was dehydrogenated directly with selenium at 360° for 20 minutes in a sealed tube. The 1-(1-ethylbutyl)-β-carboline (550 mg.) had m.p. 144–145° from ether–hexane and had an infrared spectrum identical in all

(19) H. A. Bruson and T. W. Riener, THIS JOURNAL, **66**, 56 (1944). This compound is actually a low melting solid which exists as the lactone, $\nu_{C=O}$ 1711 cm.$^{-1}$ (liquid film).

respects with the corresponding optically active degradation product. A mixed melting point showed no depression.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0. Found: C, 80.7; H, 7.9.

5-Hydroxycanthin-6-one (VIII, R_1 = OH, R_2 = H).—Lithium butyl (1 mole-equiv. in hexane) was added with stirring under nitrogen to harman (1.17 g.) in absolute ether (200 ml.). There was an immediate yellow precipitate. After 5 hours, diethyl oxalate (940 mg.) in absolute ether (10 ml.) was added dropwise with stirring. As the addition continued the yellow precipitate turned orange and no other reaction was apparent. The stirring was continued overnight, water (20 ml.) was added and the lithium salt of 5-hydroxy-canthin-6-one (600 mg.) was filtered off. Trituration of the salt with aqueous acetic acid followed by crystallization of the residue from methylene chloride–ethanol gave 5-hydroxycanthinone, m.p. 258–259° dec. (lit.[4a] 259–261°). The ultraviolet spectrum was identical with that described in the literature.

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.2; H, 3.4. Found: C, 70.7; H, 3.5.

A solution of the hydroxy compound in methylene chloride containing excess diazomethane was allowed to stand overnight to furnish a quantitative yield of 5-methoxycanthinone, m.p. 238° (lit.[4a] 241–242° from ethanol–methylene chloride).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.0; H, 4.0. Found: C, 72.1; H, 4.1.

4-Propylcanthin-6-one (VI, R = Pr).—In the same way as described above *n*-butyl-β-carboline (2 g.), m.p. 171–172°,[20] gave 5-hydroxy-4-propylcanthin-6-one (1.43 g.) which upon acetylation with acetic anhydride furnished 5-acetoxy-4-propylcanthin-6-one, m.p. 201–202°.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.2; H, 5.0. Found: C, 71.3, 71.0; H, 5.2, 5.1.

The acetoxy compound (230 mg.) was refluxed for 25 minutes in acetic acid with the periodic addition of zinc dust and the resultant product (175 mg.) was heated *in vacuo* at 360° with selenium for 40 minutes. The benzene extract of the dehydrogenation mixture was filtered through alumina (activity III) to afford 4-propylcanthin-6-one, m.p. 131–132° from ether, raised to m.p. 132–133° upon vacuum sublimation. It was identical in all respects with the natural degradation product.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4. Found C, 77.7; H, 5.5.

4-Ethylcanthin-6-one (VI, R = Et).—*n*-Propyl-β-carboline (2 g.) gave, as described above for the parent compound, 5-hydroxy-4-ethylcanthin-6-one (800 mg.), m.p. 230–231° from methylene chloride–alcohol.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.7; H, 4.6. Found: C, 72.9; H, 4.7.

The hydroxycanthin-6-one upon refluxing in acetic anhydride yielded the O-acetyl derivative, m.p. 211–212° from acetic anhydride.

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.6. Found: C, 70.2; H, 4.6.

The acetoxy derivative (100 mg.) was refluxed for 15 minutes in acetic acid with periodic addition of zinc dust. The crude reduction product (90 mg.) and selenium (200 mg.) were heated at 360° for 20 minutes *in vacuo* and furnished after chromatography and crystallization from benzene–hexane 4-ethylcanthin-6-one (20 mg.), m.p. 177°, which was raised to m.p. 179–180° upon vacuum sublimation. It was identical in all respects with the natural degradation product.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.4; H, 4.9. Found: C, 77.0; H, 5.0.

4-Isopropylcanthin-6-one (VI, R = *i*-Pr)—1-Isobutyl-β-carboline (655 mg.), m.p. 200°, was converted into 5 hydroxy-4-isopropylcanthin-6-one (300 mg.) which upon acetylation gave the acetoxy compound, m.p. 196–197°.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.2; H, 5.0. Found: C, 71.2; H, 5.1.

After reduction with zinc and acetic acid and selenium dehydrogenation, the acetoxy compound (80 mg.) furnished 4-isopropylcanthin-6-one (10 mg.), m.p. 118° from benzene–hexane.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4. Found: C, 77.5; H, 5.5.

4-Dichloromethyl-4-ethylcyclohexadienone.—Sodium hydroxide (200 g.) in water (250 ml.) was added dropwise over 1.5 hours to a well stirred solution of *p*-ethylphenol (113 g.) in chloroform (162 ml.) maintained at 60°. After some initial foaming the reaction proceeded smoothly. The cooled reaction mixture was filtered and the solid washed well with ether. The combined filtrates were concentrated and steam distilled to furnish directly from the distillate the crystalline cyclohexadienone (7.2 g.), m.p. 61–62°. For analysis the compound was sublimed *in vacuo*.

Anal. Calcd. for $C_9H_{10}OCl_2$: C, 52.7; H, 4.9. Found: C, 53.0; H, 5.0.

4-Dichloromethyl-4-ethylcyclohexanone.—The cyclohexadienone in ethanol took up 2 mole equivalents of hydrogen in the presence of palladium-on-carbon. The product had m.p. 58° from hexane, $\nu_{C=O}$ at 1709 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}OCl_2$: C, 51.6; H, 6.7. Found: C, 51.5; H, 6.8.

β-Dichloromethyl-β-ethyladipic Acid.—The cyclohexanone (7 g.) was dissolved in concentrated nitric acid (25 ml.) and warmed gently until an exothermic reaction commenced. After this had subsided the solution was boiled for 10 minutes. The diacid (3 g.), m.p. 125°, crystallized directly upon cooling. For analysis it was recrystallized from concentrated nitric acid.

Anal. Calcd. for $C_9H_{14}O_4Cl_2$: C, 42.1; H, 5.5. Found: C, 41.9; H, 5.5.

β-Formyl-β-ethyladipic Acid.—The above dicarboxylic acid (500 mg.) was heated at 210° in a sealed tube in water (10 ml.) for 3 hours. Removal of the water by distillation yielded the crude compound which was isolated as the lactone (450 mg.), m.p. 102–103° from ether–methylene chloride. It had $\nu_{C=O}$ 1779 cm.$^{-1}$ (γ-lactone carbonyl) and 1717 cm.$^{-1}$ (carboxyl).

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.5; H, 7.0. Found: C, 53.4; H, 7.0.

***dl*-Eburnamonine Lactam (XVII).**—The lactone (126 mg.) and tryptamine (100 mg.) were heated at 100° in acetic acid (0.5 ml.) for 12 hours and concentrated to dryness. The oily product was heated in polyphosphoric acid (5 ml.) at 100° for 15 minutes. Dilution with water afforded a precipitate which was triturated with dilute sodium hydroxide. The residue after crystallization from alcohol furnished *dl*-eburnamonine lactam (57 mg.), m.p. 215°, with $\nu_{C=O}$ 1712 cm.$^{-1}$ (N_a-lactam) and 1664 cm.$^{-1}$ (N_b-lactam).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.5. Found: C, 73.7; H, 6.7.

In dilute hydrochloric acid the same reactants at 100° gradually produced a lower yield (5–10% of the theoretical) of the same lactam. At room temperature no neutral product was formed.

***dl*-Eburnamonine (IV).**—The dilactam (35 mg.) was refluxed for 1 hour in ether (20 ml.) containing lithium aluminum hydride (150 mg.). A little water was added and the solution filtered and evaporated to dryness. The residue (30 mg.) was treated for 5 minutes with chromium trioxide (30 mg.) in pyridine (5 ml.) then filtered through alumina (activity III) using methylene chloride as eluant. The product (20 mg.), m.p. 203–204 from alcohol, had an infrared spectrum superimposable upon that of eburnamonine.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.5; H, 7.5. Found: C, 77.3; H, 7.7.

(20) K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2033 (1958), give m.p. 166°.