afford material of analytical purity in 80% yield; $\lambda_{max}^{CCl_4}$ 5.80 μ; n.m.r. (CCl_4) τ 4.83 (s), 5.17 (q), 7.92 (m), and 8.75 (t).

Anal. Calcd. for $C_{15}H_{22}O_2S_2$: C, 60.36; H, 7.43, S, 21.49. Found: C, 60.33; H, 7.39; S, 21.45.

Acknowledgment. We wish to express thanks to the National Institutes of Health, U. S. Public Health Service, for a grant (A4215) in support of this work, and the National Science Foundation for stipends for D. L. D., L. F., and V. L. S.[2] We are also grateful to Mr. A. O. Clouse for assistance with some of the n.m.r. determinations, and Mr. Steven W. Young of the Indiana University Research Computing Center for assistance with the computations.

General Methods of Synthesis of Indole Alkaloids. IV. A Synthesis of *dl*-Eburnamonine[1,2]

Ernest Wenkert[3] and Börje Wickberg

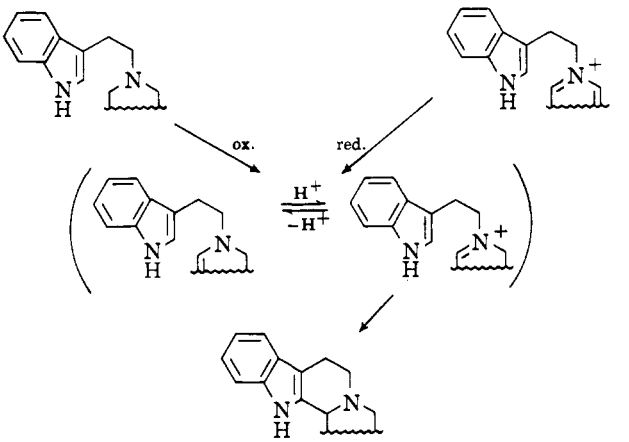
Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa. *Received November 2, 1964*

The hydrogenation of 1-[β-(3-indolyl)ethyl]-3-acetylpyridinium bromide to a tetrahydropyridine derivative is described. Transformation of the product into the alkaloid eburnamonine is discussed. The stereochemistry of the alkaloid and its possible biosynthesis are portrayed.

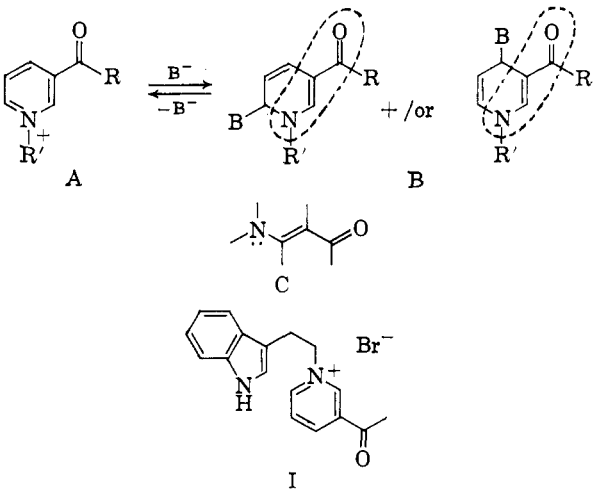
Previous reports[2,4] from this laboratory have illustrated three new methods of synthesis of indole alkaloids of the tetrahydrocarboline type, which were based on oxidative or reductive cyclizations of indole derivatives *via* Δ^1- and Δ^2-piperideine intermediates (*cf.* Chart I). The reductive cyclization scheme had involved hydride reductions of N-alkylpyridinium salts.[2,5] As a follow-up of this method a search for a scheme based on partial hydrogenation of the pyridinium salts was undertaken.

Since catalytic hydrogenation of N-alkylpyridinium salts yields N-alkylpiperidines,[6] it was clear from the beginning of our study that only a special experimental design might permit hydrogenation stoppage at the Δ^1- (or Δ^2-) piperideine stage. On the assumption that the presence of a pyridine substituent which would stabilize the double bond of the piperideine intermediate, while itself being impervious to hydrogen attack, might cause the desired interruption of the hydrogenation, a β-acyl group was chosen as the stabilizing substituent. Furthermore, reduction in alkaline medium was considered another important prerequisite of the reaction, since N-alkyl-β-acyl-

Chart I



pyridinium salts (A) would be expected to be transformed in this environment to compounds B which already possess the all-important vinylogous amide chromophore C (see dotted lines in B), on whose inertness to hydrogenation success of the reaction depended. The salt I, prepared from β-acetylpyridine and tryptophyl bromide,[2] was selected as the model for our study.



(1) This work was first presented as part of a lecture by E. W. at the 17th National Organic Chemistry Symposium of the American Chemical Society at Bloomington, Ind., June 26–29, 1961. The authors acknowledge gratefully herewith the financial support of the work by the U. S. Department of Health, Education, and Welfare (MY-5815) and the Swedish Natural Science Research Council.

(2) Part III: E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

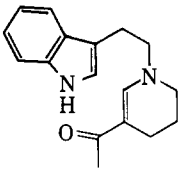
(3) Department of Chemistry, Indiana University, Bloomington, Ind.

(4) (a) E. Wenkert and J. Kilzer, *J. Org. Chem.*, **27**, 2283 (1962); (b) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

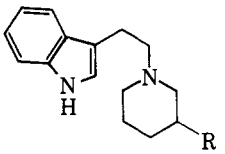
(5) For other recent syntheses of tetrahydrocarbolines by reductive cyclization, *cf.* (a) J. Thesing and W. Festag, *Experientia*, **15**, 127 (1959); (b) K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3066 (1963); (c) J. H. Supple, D. A. Nelson, and R. E. Lyle, *Tetrahedron Letters*, 1645 (1963).

(6) *Cf.*, *inter alia*, K. Hohenlohe-Oehringen, *Monatsh.*, **93**, 586 (1962).

Hydrogenation of an ethanolic solution of I and triethylamine over palladium-charcoal yielded predominantly the tetrahydro product II and some hexahydro product IIIa.[7] Lithium aluminum hydride reduction of II gave an alcohol mixture (IIIb) whose Oppenauer oxidation afforded the ketone IIIa. Wolff–Kishner reduction of the ketone yielded the known piperidine IIIc.[4b]

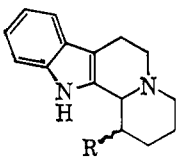


II



IIIa, R = Ac
b, R = CHOHMe
c, R = Et

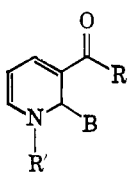
The crucial conversion of a pyridinium salt to a Δ^2-piperideine having been achieved, the latter was exposed to a Pictet–Spengler cyclization. Treatment of II with acid yielded a tetracyclic ketone IVa.[8] While only one of two possible diastereoisomers was isolated, the reaction appeared to yield two products. Thus, whereas sodium borohydride reduction of the pure ketone IVa gave two isomeric alcohols (IVb), reduction of the unrefined cyclization mixture produced yet one more alcohol, albeit in low yield. Presumably, the cyclization had afforded a mixture of two ketones, although the more labile ketone had isomerized (probably under the influence of the built-in base) on work-up to the one isolated.



IVa, R = Ac
b, R = CHOHMe
c, R = Et

As proof of the gross structure of ketone IVa, it was transformed into the salt V which, in turn, was prepared by independent synthesis. Wolff–Kishner reduction of the ketone gave IVc, also the end product of the treatments of IVb with hydrobromic acid and thereafter with hydrogen and palladium. As already reported previously,[4b] mercuric acetate oxidation of IVc yielded Va. The alternate synthesis of the latter followed the lines of the Janot synthesis of flavopereinine.[9] Diethyl ethylmalonate was alkylated with trimethylene bromide and the product treated with hydrobromic acid and subsequently with diazomethane.

(7) Formation of the piperidine derivative IIIa is probably not a consequence of slow reduction of the major product II. More likely, IIIa represents the product of hydrogenation of I or i.

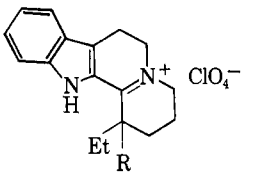


i

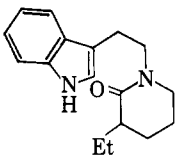
(8) For recent examples of analogous cyclizations, *cf.* R. N. Shut, *Chem. Ind.* (London), 1246 (1960); H. J. Teuber and U. Hochmuth, *Tetrahedron Letters*, 325 (1964); E. Winterfeld, *Chem. Ber.*, **97**, 2463 (1964).

(9) A. LeHir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958).

Interaction of the resultant methyl α-ethyl-δ-bromovalerate with tryptamine yielded lactam VI, whose exposure to phosphorus oxychloride led to the salt Va. The samples of Va prepared by the two different methods proved to be identical.

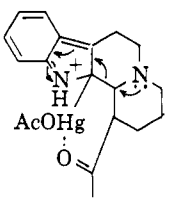


Va, R = H
b, R = CH_2CO_2Et



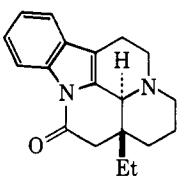
VI

In the two-step conversion of the aminoketone IVa to the immonium salt V, an oxidation had followed the initial reduction. In a tangential study of the feasibility of reversing the order of these steps, ketone IVa was exposed to mercuric acetate oxidation. Surprisingly, no oxidation took place. The reaction led largely to recovery of starting material and low yields of the vinylogous amide II. This unexpected reaction course is best interpreted on the basis of the intervention of an indole–mercury complex VII[4b] and its break-up in the manner of a *retro*-Pictet–Spengler process (arrows in VII).



VII

With a new, potentially general tetrahydrocarboline synthesis in hand, its application in the field of indole alkaloid chemistry became of interest. Since the substance Va appeared to be ideally suited for transformation into the ring system characteristic of several alkaloids of *Hunteria eburnea* Pichon,[10] the synthesis of the racemic form of one of these alkaloids, eburnamonine (VIII), was undertaken. An elegant structure analysis and rapid synthesis of the natural product had established its gross structure.[10] However, its stereochemistry lacked rigorous proof, though it had been suggested to be as depicted in VIII.



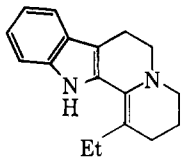
VIII

Alkali treatment of the immonium salt Va yielded a basic material (IX and/or X), whose exposure to ethyl iodoacetate under carefully controlled conditions and reaction work-up led to the salt Vb.[11] Heating of a buffered, aqueous solution of this salt produced the pentacyclic system XI. Extended manipulation of

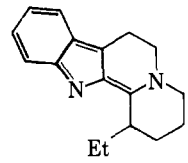
(10) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).

(11) The alkylation of IX with ethyl bromoacetate under a variety of conditions yielded mixtures of Vb, XI, and XII.

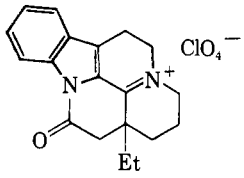
solutions of XI during its purification caused its transformation, presumably by air oxidation, into XII.



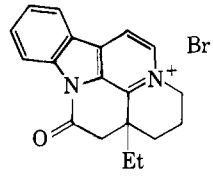
IX



X

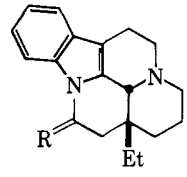


XI



XII

Reduction of the compounds XI and XII by chemical or hydrogenative means could be predicted with confidence to lead stereoselectively to the *trans* system VIII, since the angular ethyl group in the nearly planar substances would be expected to wield strong steric control. Hydrogenation as well as sodium borohydride reduction of both XI and XII yielded, indeed, exclusively one product (VIII), which, however, proved to be an isomer of eburnamonine.[12] On the basis of these data, the relative stereochemistry of the alkaloid can be represented now by XIIIa.[13] Moreover, vincamine, an alkaloidal plant constituent of various *Vinca* species which has been converted to *l*-eburnamonine,[14] must possess the relative configuration revealed in XIIIb.[14d]

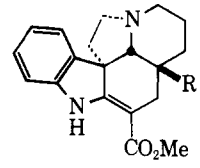


XIIIa, R = O
b, R = (OH)CO_2Me
c, R = H(OH)

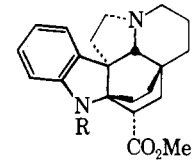
Hydrogenation or sodium borohydride reduction of Vb yielded mixtures of eburnamoninic and epieburnamoninic esters, alkali treatment of which led to the aforementioned eburnamonine isomer (epieburnamonine (VIII)) and eburnamonine (XIIIa).[12] While the borohydride reduction afforded a *ca.* 1:1 mixture of products, the hydrogenation yielded predominantly XIIIa. This completed the total synthesis of *dl*-eburnamonine, the racemate of the alkaloid from *Hunteria eburnea* Pichon,[10] and, as reported recently,[15] a naturally occurring base (isolated from *Vinca minor* L.) in its own right.

Biosynthetic Considerations. At the time of completion of our work on the stereochemistry of eburnamonine,[1] a theory of biosynthesis of the Aspidosperma alkaloids was introduced whose main contribution was the forging of a link between these structurally unique bases and those of the Iboga and classical corynantheine–yohimbine–strychnine types.[16] While it was already clear at that time that eburnamonine is closely related to the Aspidosperma alkaloids,[17] an explanation of the mechanism of its derivation from the latter had to await further structure developments.

The new structure patterns which have emerged as a consequence of the veritable deluge of reports of the last three years on structure determinations of Aspidosperma and structurally related alkaloids have been in full accord with the theory of biosynthesis. A multitude of compounds has been shown to possess the predicted, vitally important carboxy unit, *e.g.*, minovincine (XIVa), minovincinine (XIVb), and vincadifformine (XIVc),[18] which in the case of kopsine is even involved in the creation of a new ring. Compounds of greater ring complexity can be envisaged as being derived from those of type XIV. For example, intramolecular Mannich condensation of the conjugate acid of XIVa and the usual biochemical ketone reduction leads to kopsinine (XVa) and its relatives,[19] including pleiocarpine (XVb), an alkaloid found to cooccur with eburnamonine in *Hunteria eburnea* Pichon.[20,21] On the reasonable assumption that the vincamine (XIIIb) system constitutes the immediate precursor of eburnamine (XIIIc),[10,22] whose oxidation yields eburnamonine (XIIIa), a simple mechanistic rationale can now be given for the biosynthesis of eburnamonine. The transformations are presented in Chart II.



XIVa, R = Ac
b, R = CHOHMe
c, R = Et



XVa, R = H
b, R = CO_2Me

Perhaps the most exciting recent development from the point of view of alkaloid biosynthesis has been the assignment of structure XVI to pleiocarpamine,[23]

(12) The authors are indebted to Dr. M. F. Bartlett for a gift of comparison samples of ebunamonine and synthetic *dl*-eburnamonine.

(13) Our assignment of a *cis* configuration to eburnamonine was confirmed recently by independent evidence: J. Mokrý, M. Shamma, and H. E. Soyster, *Tetrahedron Letters*, 999 (1963).

(14) (a) J. Trojanek, O. trouf, J. Holubek, and Z. Čekan, *Tetrahedron Letters*, 702 (1961); *Collection Czech. Chem. Commun.*, **29**, 433 (1964); (b) J. Mokrý, I. Kompiš, and P. Sefčovič, *Tetrahedron Letters*, 433 (1962); (c) M. Plat, D. D. Manh, J. Le Men, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. soc. chim. France*, 1082 (1962); (d) *cf.* also M. E. Kuehne, *J. Am. Chem. Soc.*, **86**, 2946 (1964).

(15) J. Mokrý, I. Kompiš, P. Šefčovič, and S. Bauer, *Collection Czech. Chem. Commun.*, **28**, 1309 (1963).

(16) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).

(17) *Cf.* footnote 39 in ref. 16.

(18) M. Plat, J. Le Men, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. chim. soc. France*, 2237 (1962), and references therein.

(19) W. G. Kump, D. J. Le Count, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, **45**, 854 (1962), and references therein.

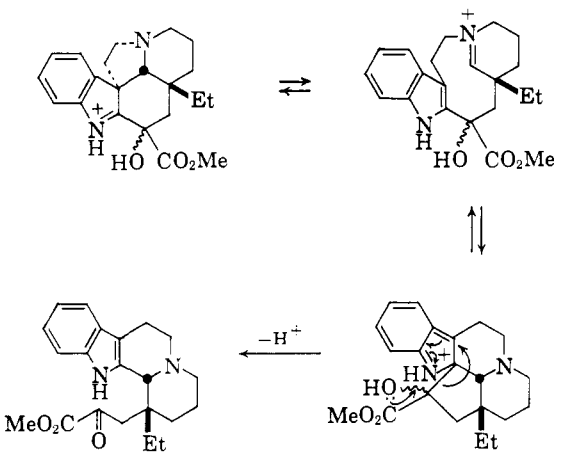
(20) M. F. Bartlett, R. Sklar, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 2197 (1963).

(21) Structure patterns represented by kopsine [T. R. Govindachari, B. R. Pai, S. Rajappa, N. Viswanathan, W. G. Kump, K. Nagarajan, and H. Schmid, *Helv. Chim. Acta*, **45** 1146 (1962); **46**, 572 (1963)] and tuboxenine [C. Kump, J. Seibl, and H. Schmid, *ibid.*, **47**, 358 (1964)] are further variants of skeleton XIV and are illustrative of the consequence of Nb oxidation, the resultant enamine condensing with the sterically proximate side chain.

(22) Nature abounds with α-keto acid decarboxylases.

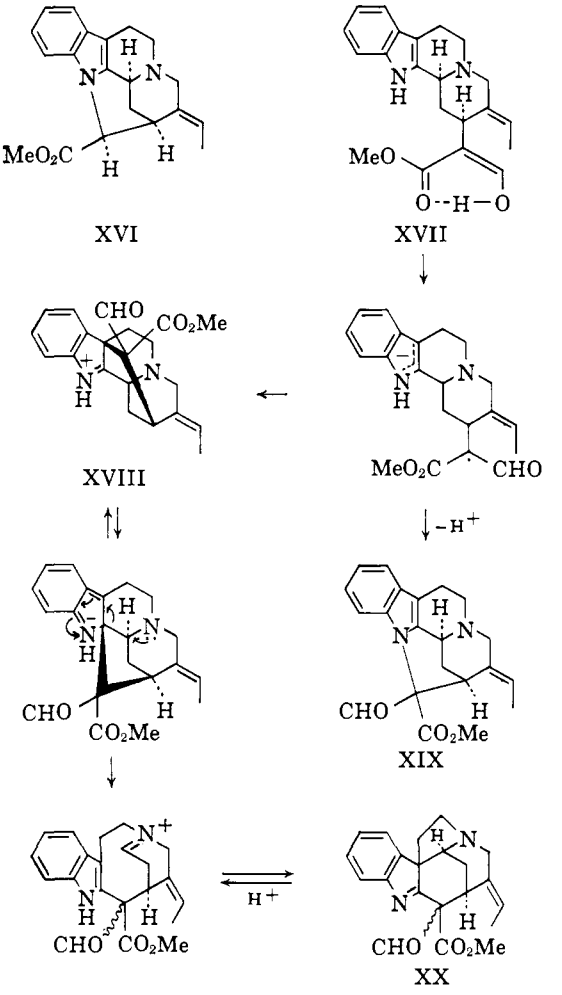
(23) M. Hesse, W. v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedman, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **47**, 878 (1964).

Chart II



another alkaloid of *Hunteria eburnea* Pichon.[20] This novel structure type offers a solution to the two heretofore puzzling biosynthetic mysteries, the genesis of the Akuamma[24] and of the Strychnos[25] bases. As Chart III illustrates, a simple oxidation of the corynantheinoid skeleton of geissoschizine (XVII)[26] links it with structures characteristic of the Akuamma (XVIII) and pleiocarpamine-like (XIX) bases,[27] while further changes of the Akuamma skeleton unite it with the structural framework of the Strychnos (XX) alkalids.[28] Thus it appears that *all indole alkaloids of the tryptamine + C_{10} structure type may be derived from corynantheinoid or closely related progenitors.*

Chart III



Experimental

General Procedures. Melting points were determined on a Kofler micro hot stage and are corrected. Unless stated otherwise, alumina used for chromatography was of a basic type with activity *ca.* III.

N-[β-(3-Indolyl)ethyl]-3-acetylpyridinium Bromide (I). Tryptophyl bromide[2] (3.29 g.) in 3-acetylpyridine (6 ml.) was heated at 70° for 12 hr. and then at 100° for 4 hr. under a nitrogen atmosphere. The crystalline mass was triturated with an ethanol–ether 2:1 mixture and the crude product recrystallized from 60% aqueous methanol, giving a nearly quantitative yield (4.9 g.) of 1-[β-(3-indolyl)ethyl]-3-acetylpyridinium bromide, m.p. 212–214° dec. This material, although essentially pure, failed to give a satisfactory analysis even after repeated recrystallizations from a variety of solvents. The presence of a trace impurity was further indicated by the infrared spectrum (Nujol mull), which showed a weak peak or shoulder at 5.77 μ in addition to the strong C=O band at 5.88 μ.

A sample (1.93 g.) of the pyridinium bromide salt in 50% aqueous methanol (25 ml.) acidified with a few drops of acetic acid was stirred for 1 hr. at room temperature with a slight excess of silver acetate (1.00 g.). After addition of acetic acid (5 ml.) the mixture was filtered, 2 *N* hydrochloric acid (1 ml.) was added to the filtrate, and the silver chloride was removed by filtration with Celite after 3 hr. After addition of 2 *N* hydrochloric acid (2.5 ml.), the solution was concentrated under reduced pressure and the crystalline residue recrystallized from water, giving the pyridinium chloride salt (1.60 g.), m.p. 191–195° dec. Further recrystallization from ethanol and acetonitrile–water raised the m.p. to 193–198° dec., but treatment with excess sodium bromide in formamide–water afforded the bromide salt, m.p. 212–216° dec., that still displayed the infrared band at 5.77 μ.

Recourse was had to chromatography of the chloride salt. A slurry of silica gel (13 g.) impregnated with 4.5 ml. of the stationary phase (85% aqueous formamide acidified with a trace of hydrochloric acid) in pre-equilibrated chloroform was filled all at once into a chromatographic tube and forced to settle by applying air pressure to the top of the tube. The chloroform

(24) A previous proposal for the biosynthesis of echitamine, a representative of the Akuamma type [G. F. Smith, *Chem. Ind.* (London), 1120 (1961)], suffers from the implausibility of its most crucial bond-forming step, an intramolecular Michael condensation between anhydroxymethylene acetic ester moiety and an α-acylindole unit at the site of the β-carbon of the indole. Indoles (even with electron-withdrawing side chains) would not be expected to be susceptible to nucleophilic attack.

(25) The previous scheme[16] required the joining of the tryptamine unit to the all-important C_{10} moiety at the former's glycosylideneanthranilic acid precursor stage. Since this implied that the Strychnos bases would be the only indole alkaloids not derived from tryptophan, it was the weakest link in the unifying theory of biosynthesis.[16]

(26) M.-M. Janot, *Tetrahedron*, **14**, 113 (1961); H. Rapoport, R. J. Windgassen, Jr., N. A. Hughes, and T. P. Onak, *J. Am. Chem. Soc.*, **82**, 4404 (1960).

(27) The free-radical coupling is an intramolecular analog of the tryptamine dimerization crucial to the biosynthesis of the calycanthaceous alkaloids [R. Robinson and H. J. Teuber, *Chem. Ind.* (London), 783 (1954); R. B. Woodward, N. C. Yang, T. J. Katz, V. M. Clark, J. Harley-Mason, R. J. F. Ingleby, and N. Sheppard, *Proc. Chem. Soc.*, 76 (1960); A. I. Scott, F. McCapra, and E. S. Hall, *J. Am. Chem. Soc.*, **86**, 302 (1964)].

(28) The *in vitro* conversion of compounds of the Akuamma series into Strychnos alkaloids has been performed recently (private communication from Professor J. Le Men).

was then displaced with the solvent to be used as the eluent (one part of a 1:3 mixture of 1-butanol–chloroform + nine parts of the same mixture, but equilibrated with the stationary phase). The pyridinium chloride salt (38 mg.) was dissolved in the eluent and added to the column. On continued elution it moved as a very wide yellow band. The fractions containing colored material (six 35-ml. portions) were concentrated separately and the pyridinium bromide salt precipitated by adding sodium bromide. Only the first fraction gave material (1.1 mg.), m.p. 207–212° dec., that showed a distinct infrared band at 5.77 μ. The combined product from fractions 4 to 6 (28 mg.), m.p. 214–217° dec., was recrystallized from acetonitrile and water and finally dried for 20 hr. at 80° and 0.1 mm., giving pure 1-[β-(3-indolyl)ethyl]-3-acetylpyridinium bromide (I), m.p. 214–216° dec.; spectra: infrared (Nujol mull), C=O 5.88 (s) μ; ultraviolet (0.1 *M* HCl in ethanol), λ_{max} 219 mμ (log ϵ 4.55), 268 (3.88), 288 (3.67), and 315 (very broad shoulder) (3.01), λ_{min} 242 (3.44) and 287 (3.66); ultraviolet (0.1 *M* NaOH in ethanol), λ_{max} 272 mμ (log ϵ 4.15), 279 (sh) (4.12), 288 (sh) (3.97), and 325 (4.04), λ_{min} 241 (3.43) and 298 mμ (3.78).

Anal. Calcd. for $C_{17}H_{17}ON_2Br$: C, 59.14; H, 4.96; N, 8.12. Calcd. for $C_{17}H_{17}ON_2Br \cdot H_2O$: C, 56.20; H, 5.27; N, 7.71. Found: C, 56.84; H, 5.25; N, 7.92.

Hydrogenation of Pyridinium Bromide I. A suspension of pyridinium salt I (2.14 g.) and 10% palladium–charcoal (0.40 g.) in ethanol (70 ml.) and triethylamine (4.3 ml.) was hydrogenated at room temperature and atmospheric pressure; the reaction ceased after 5.5 hr. (hydrogen uptake 360 ml.). Filtration and concentration of the filtrate under reduced pressure afforded a sirup that was dissolved in chloroform. The chloroform solution was shaken repeatedly with equal volumes of phosphate buffer (20% aqueous NaH_2PO_4, hydrochloric acid added to maintain pH *ca.* 3) until the latter gave only a faint cloudiness on addition of excess ammonium hydroxide. After subsequent washing with dilute hydrochloric acid (pH maintained at *ca.* 2; acid extract discarded) the chloroform solution was dried over potassium carbonate and concentrated under reduced pressure to give the crude tetrahydroketone II as a sirup (1.60 g.). Chromatography of the latter on alumina (80 g.) using chloroform as the eluent and crystallization from aqueous ethanol gave a crystalline product (1.00 g.), m.p. 131–133°. After repeated crystallizations from aqueous ethanol and from benzene–carbon tetrachloride, the tetrahydroketone II had m.p. 133–134.5°; spectra: infrared ($CHCl_3$), NH 3.02 (m) μ, vinylogous amide 6.17 (m), and 6.40 (s); ultraviolet (ethanol), λ_{max} 221 mμ (log ϵ 4.50) and 314 (4.41), λ_{min} 245 (3.43).

Anal. Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.82; H, 7.30; N, 10.23.

Addition of excess ammonium hydroxide to the combined phosphate buffer extracts and subsequent extraction with chloroform gave the crude hexahydroketone IIIa as sticky crystals (234 mg.); rapid sublimation at 0.1 mm and 180° (bath temperature) and recrystallization from aqueous methanol afforded pure IIIa (140 mg.), m.p. 129.5–131°; infrared spectrum ($CHCl_3$), NH 2.85 (m) μ, C=O 5.85 (s).

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.62; H, 8.01; N, 10.35.

Lithium Aluminum Hydride Reduction of II. A solution of tetrahydroketone II (150 mg.) and lithium aluminum hydride (500 mg.) in tetrahydrofuran (25 ml.) was refluxed under nitrogen for 12 hr. Excess hydride was decomposed by addition of moist sodium sulfate, the resulting slurry was filtered, and the filtrate and washings were combined and concentrated under reduced pressure to give an oil (171 mg.). This was chromatographed on alumina (23 g.). Chloroform–benzene 1:4 eluted some partly crystalline material (12 mg.) which might have been the hexahydroketone IIIa (ultraviolet spectrum of the simple indole type, infrared spectrum displaying a strong C=O absorption at 5.85 μ; not further investigated). Chloroform eluted the main fraction as an oil (120 mg.) which could not be induced to crystallize. It was presumably a mixture of diastereomeric alcohols IIIb; infrared spectrum ($CHCl_3$), hydrogen bonded NH and OH 2.78 (m) μ and *ca.* 3.0 (m, broad).

Oppenauer Oxidation of Alcohols IIIb. Amorphous alcohol(s) IIIb (120 mg.) was dissolved in benzene (18 ml.) and cyclohexanone (6 ml.) contained in a flask fitted with a Vigreux column. Part of the solvent (9 ml.) was distilled off slowly, aluminum phenoxide (0.75 g.) was added, and the mixture was refluxed for 10 hr. under dry nitrogen. After dilution with water dilute sulfuric acid was added until no solids remained. The acid solution was washed three times with chloroform, potassium acetate was added to make pH 4, the mixture was concentrated under reduced pressure, and the residue was dissolved in water (10 ml.) and ethanol (20 ml.). Excess potassium carbonate was added and the solution filtered. The filtrate was concentrated to a small volume, diluted with water, and extracted with chloroform. On concentration the chloroform extract afforded a sirup (94 mg.), which was chromatographed on alumina (23 g.). Elution with chloroform–benzene (1:4) gave crude ketonic material (44 mg.), m.p. 120–131°. Sublimation at 0.1 mm. and 150° (bath temperature) and recrystallization from carbon tetrachloride–cyclohexane gave pure ketone IIIa, m.p. 129–131°, identified by its infrared (Nujol mull) and ultraviolet (ethanol) spectra.

Wolff–Kishner Reduction of Ketone IIIa. Ketone IIIa (20 mg.) was heated with anhydrous hydrazine (0.25 ml.) and acetic acid (2 drops) in diethylene glycol (2.5 ml.) at 160° for 30 min. under nitrogen. After the addition of potassium hydroxide (0.28 g.) and hydrazine (0.2 ml.), the bath temperature was raised to 210° and kept there for 5 hr. After dilution with water the reaction mixture was extracted with chloroform, and the extract was washed with water, dried by filtration through a short alumina column, and concentrated to dryness. The crystalline residue (17 mg.) was sublimed at 0.1 mm. and 150° (bath temperature) and the sublimate repeatedly recrystallized from aqueous methanol and from cyclohexane to give the pure ethylpiperidine IIIc (7 mg.), m.p. 112–113.5°. The identity was confirmed by direct comparison with an authentic sample[4b] (m.p. 111–113.5°, infrared spectra in Nujol mull identical).

Pictet–Spengler Cyclization of Tetrahydroketone II.

Tetrahydroketone II (800 mg.) was treated with 1 *M* hydrochloric acid (80 ml.) under nitrogen on a steam bath for 75 min. After the pH of the mixture had been brought to 2.5 by the addition of potassium carbonate, a small quantity (35 mg.) of weakly basic material was removed by extraction with chloroform (its ultraviolet spectrum indicated *starting material*). The aqueous phase, which contained a substantial amount of insoluble dark resin, was basified with potassium carbonate and extracted with chloroform under a protective layer of hydrogen. (Owing to the pronounced oxygen sensitivity of the tetracyclic ketone IVa, solutions of this compound had to be handled with exclusion of oxygen.) The chloroform extract was filtered through a short column of alumina and then concentrated to dryness. The residue (670 mg.) was recrystallized from carbon tetrachloride to give needles of crude IVa (324 mg.), m.p. 163–169°. A second crop (133 mg.), m.p. 167–171°, was obtained on chromatography of the mother liquors on alumina (11 g.) using chloroform–benzene as the eluent. Interestingly enough, the tail fractions (50 mg.) from this column deposited stout prisms (m.p. 133–136°) in addition to the needles of the main product. A complete separation of these compounds did not appear promising, but on the assumption of the presence of a stereoisomeric pair of ketones, the mixture was combined with remaining mother liquors and subjected to isomerizing conditions (2 hr. reflux in 20 ml. of 0.01 *M* sodium ethoxide in ethanol). The product (133 mg.) was chromatographed on alumina (20 g.) as before, giving a third crop of IVa (65 mg.), m.p. 167–171°, but none of the low-melting prisms. The combined material was recrystallized from 1-propanol to give pure tetracyclic ketone IVa (440 mg.), m.p. 171–173° with partial melting and resolidification at *ca.* 160°. An analytical sample was further purified by sublimation at 0.1 mm. and 155° (bath temperature) followed by crystallization from 1-propanol (melting point unchanged); infrared spectrum ($CHCl_3$), C=O 5.88 (s) μ.

Anal. Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.73; H, 7.73; N, 10.52.

Wolff–Kishner Reduction of Ketone IVa. A solution of ketone IVa (50.5 mg.), anhydrous hydrazine (0.7 ml.), and acetic acid (3 drops) in diethylene glycol (4 ml.) was kept at 170° (bath temperature) under nitrogen for 90 min. After the addition of potassium hydroxide (0.65 g.), the bath temperature was raised to 215° while water and excess hydrazine were removed by passing nitrogen through the reaction mixture until the boiling point of the latter exceeded 200°. Heating was continued at the same rate for 5 hr. Dilution with water and extraction with chloroform afforded a gum (55 mg.) which was chromatographed on alumina (7 g.). Benzene eluted a fraction (12.5 mg.) which upon recrystallization from hexane afforded pure IVc, m.p. 116–118°, identical with an authentic specimen[4b] as shown by mixture melting point and infrared spectra.

Sodium Borohydride Reduction of Ketone IVa. Sodium borohydride (0.9 g.) was added in portions over a period of 5 hr. to a methanolic solution (40 ml.) of crude ketone IVa (1.41 g.), as obtained by hydrochloric acid treatment of II. After standing at room temperature overnight, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with chloroform. The chloroform solution was washed with dilute aqueous sodium hydroxide and then extracted with 0.2 *M* hydrochloric acid (three 50-ml. portions). Methanol (40 ml.) was added to the acid extract, which was then slowly basified by the addition of 5% aqueous potassium carbonate to yield a crystalline fraction (fraction A, 890 mg.), m.p. 185–212°. Extraction of the mother liquors with chloroform and concentrations of the extract afforded a largely crystalline residue (fraction B, 236 mg.).

Fraction A was recrystallized from propanol yielding one of the stereoisomers IVb (280 mg.), m.p. 215–221°. Upon concentration the mother liquors afforded a second crop of the same material (84 mg.), m.p. 213–221°. Recrystallization of the combined crystalline batches from propanol, aqueous ethanol, and chloroform–carbon tetrachloride followed by sublimation in a tube with gradient heating afforded pure isomer IVb, m.p. 226–227.5°; infrared spectrum ($CHCl_3$), OH 2.76 (w) μ, NH 2.91 (m), and hydrogen bonded NH and OH 3.05 (m, broad).

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.43; H, 8.35; N, 9.91.

Upon standing, the final propanolic mother liquors of fraction A deposited a second stereoisomer of IVb as glistening flakes (37 mg.), m.p. 260–265° (with sublimation and decomposition). Recrystallization from aqueous propanol raised the m.p. to 265–270°; infrared spectrum ($CHCl_3$), OH 2.75 (w) μ, NH 2.87 (m), and hydrogen bonded OH and NH 3.05 (m, broad).

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.55; H, 8.40; N, 10.49.

Fraction B upon stepwise recrystallization from propanol afforded a third stereoisomer, IVb, in total yield of 80 mg., m.p. 193–196°. Sublimation at 0.1 mm. and 190° (bath temperature) followed by recrystallization from aqueous propanol afforded a pure isomer IVb (50 mg.), m.p. 195–196.5°; infrared spectrum ($CHCl_3$), OH and NH 2.87 (m) μ and 3.0–3.15 (m, broad, hydrogen bonding).

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.36; H, 8.22; N, 10.40.

All mother liquors were combined and concentrated to dryness, yielding a largely crystalline residue (630 mg.), the infrared spectrum of which (Nujol mull) indicated the isomer melting at 226–227.5° to be the main constituent.

Sodium borohydride reduction of pure ketone IVa (100 mg.) and general work-up as described above afforded isomer IVb, m.p. 226–227.5° (65 mg.) and isomer IVb, m.p. 195–196.5° (10 mg.). The highest-melting isomer was not detected.

Conversion of Alcohol IVb into IVc. A solution of alcohol IVb, m.p. 226–227.5° (75 mg.), in 48% aqueous hydrogen bromide (3 ml.) was heated under nitrogen in a sealed tube at 110° for 10 hr. The reaction mixture was concentrated under reduced pressure, finally with intermittent addition of absolute ethanol in order to remove most of the excess of hydrogen bromide. The residual sirup was dissolved in ethanol and the solution added to a prehydrogenated mixture of 10% palladium–charcoal (10 mg.) and potassium acetate

(300 mg.) in ethanol (2 ml.). Upon hydrogenation at room temperature and atmospheric pressure, the reaction subsided after 2.5 hr. and an uptake of 4.65 ml. of hydrogen (67% of theory). The solution was filtered, diluted with water, basified with potassium carbonate, and extracted with chloroform. Upon concentration the extract afforded a reddish oil (67 mg.) which was chromatographed on alumina (7 g.). Elution with benzene gave a crystalline material (37 mg.) which after purification by sublimation and crystallization from hexane could be identified as IVc by its melting point (115–118°) and infrared spectrum (Nujol mull).

Diethyl 3-Bromopropylethylmalonate. To a stirred solution of sodium (6.4 g.) in absolute ethanol (125 ml.) there was added a solution of diethyl ethylmalonate (54.9 g.) in ether (100 ml.) and then 1,3-dibromopropane (202 g.). After stirring overnight the mixture was heated under reflux for 2 hr. Solvents were distilled off under slightly reduced pressure; the residue was diluted with water and extracted with hexane. The extract was dried and distilled under water pump pressure in order to remove hexane and excess 1,3-dibromopropane, whereafter the residue was distilled at 5 mm. through a glass-helix-packed column (12 × 300 mm.) provided with an efficient still head. Diethyl 3-bromopropylmethylmalonate was obtained as an oil (32.5 g.), b.p. 145–148° (5 mm.), $n^{26.5}$D 1.4585.

Anal. Calcd. for $C_{12}H_{21}O_4Br$: C, 46.61; H, 6.85. Found: C, 46.97; H, 6.91.

Methyl α-Ethyl-δ-bromovalerate. A mixture of diethyl 3-bromopropylethylmalonate (10 g.) and 48% aqueous hydrobromic acid (40 ml.) was refluxed under nitrogen until the CO_2 evolution had subsided (16 hr.). The mixture was then extracted repeatedly with hexane; the extract was washed with aqueous sodium sulfate and dried over sodium sulfate. A slight excess of diazomethane in ether was added to the hexane solution. After 2 hr. at room temperature excess diazomethane was decomposed by the addition of acetic acid, and the solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated under slightly reduced pressure. The residue was distilled through a Vigreux column (12 × 270 mm.) at 5 mm. pressure. Methyl α-ethyl-δ-bromovalerate was collected in two fractions (b.p. 93–94° at 5 mm.), the first of which (3.0 g.) contained *ca.* 6% of a slightly more volatile impurity, whereas the second (1.5 g.), n^{25}D 1.4583, appeared to be of better than 99% purity, as estimated by g.l.c. (silicone rubber column).

Anal. Calcd. for $C_8H_{15}O_2Br$: C, 43.06; H, 6.78. Found: C, 42.93; H, 6.81.

Condensation of Methyl α-Ethyl-δ-bromovalerate with Tryptamine. A mixture of tryptamine (12.0 g.), methyl α-ethyl-δ-bromovalerate (6.75 g.), finely powdered anhydrous potassium carbonate (4.8 g.), and anhydrous butanol (750 ml.) was refluxed under nitrogen for 10 hr. After filtration and concentration of the filtrate under reduced pressure, the residue was dissolved in benzene and this solution repeatedly extracted with 10% aqueous acetic acid in order to remove unchanged tryptamine. After a final washing with water, the benzene solution was dried over sodium sulfate and concentrated to dryness. The solid residue was recrystallized from benzene–hexane and then from 65% aqueous ethanol to give lactam VI (5.10 g.), m.p. 124–126°; a second crop (0.63 g.), m.p. 117–123°, was recovered from the mother liquors. An analytical sample was prepared by sublimation in a tube with gradient heating; infrared spectrum (CCl_4), C=O (amide) 6.12 (s) μ.

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20. Found: C, 75.34; H, 8.37.

Bischler–Napieralsky Cyclization of Lactam VI. Lactam VI (5.73 g.) and phosphorus oxychloride (15.5 ml.) were mixed in benzene (500 ml.) and the mixture refluxed under nitrogen for 3.5 hr. After cooling, water (150 ml.) was added and the heating resumed for 1 hr. The phases were separated while still hot and the benzene solution was washed with a small volume of water. Sodium perchlorate (6 g.) was added to the combined aqueous phases, precipitating the crude product Va (6.52 g.), m.p. 168–176°. Crystallizations from acetone and from acetone–ethanol afforded a total of 5.82 g. of the immonium perchlorate Va, m.p. 174–177°. An analytical sample had m.p. 175–177.5°; ultraviolet spectrum (0.001 *M* HCl in ethanol), λ_{max} 247 mμ (lot ε 4.02), 251 (sh) (4.00), and 353 (4.39), λ_{min} 233 (3.89) and 278 (2.53).

Anal. Calcd. for $C_{17}H_{21}O_4N_2Cl$: C, 57.87; H, 6.00; N, 7.94. Found: C, 57.92; H, 6.10; N, 8.19.

Mercuric Acetate Treatment of Ketone IVa. A solution of ketone IVa (80 mg.) and mercuric acetate (390 mg.) in 5% aqueous acetic acid (7.5 ml.) was heated at 80° under nitrogen for 3 hr. The mixture was diluted with water (15 ml.), acidified with 2 *M* hydrochloric acid (1.10 ml.), refluxed for 3 min. with introduction of hydrogen sulfide, and then filtered with Celite. The filter cake was washed with aqueous methanol; the combined filtrates were made alkaline by addition of potassium carbonate and extracted with chloroform. The chloroform solution was extracted with dilute hydrochloric acid (two 15-ml. portions, pH adjusted to 2), washed with water, dried, and concentrated to give a residue of neutral material (*ca.* 6 mg.). On conventional work-up the combined acid extracts gave back impure ketone IVa (65 mg.).

The neutral fraction was chromatographed on neutral alumina (8 g., activity III). Benzene–chloroform (1:2) eluted material which on treatment with Norit in ethanol and recrystallization from aqueous ethanol and from benzene–chloroform gave pure vinylogous amide II (2.8 mg.), m.p. 132.5–134.5°, undepressed on admixture with authentic material; the respective ultraviolet (ethanol) and infrared spectra (Nujol mull) were identical.

In view of the possibility that acid treatment alone might reconvert IVa into II, samples of ketone IVa were kept for 1 hr. at 100° in 0.5 *M* hydrochloric acid and 5% acetic acid solutions, respectively, and the products isolated as above. In neither case could II be detected.

Since the acid conditions during the mercuric sulfide precipitation above no doubt caused some recyclization of liberated II, samples of the latter were boiled with 0.1 *M* hydrochloric acid for various lengths of time. By observing the decrease of the ultraviolet absorption band of II at 314 mμ, the recyclization of II during the mercuric sulfide precipitation was estimated at *ca.* 10%.

Conversion of Va into Vb. To a solution of Va (200 mg.) in dimethyl sulfoxide (0.5 ml.) and toluene (1.0 ml.) contained in a nitrogen-flushed centrifuge tube equipped with a stirrer were added 2 *M* sodium hydroxide (0.4 ml.) and water (1.5 ml.).[29] The mixture was diluted with toluene (1 ml.), the aqueous phase was withdrawn, and the toluene phase was washed with water (2 ml.) and then filtered through a layer of potassium carbonate into a small nitrogen-filled flask. The solvent was removed under reduced pressure and ethyl iodoacetate (0.3 ml.) added to the residue. The flask was then flushed with nitrogen, evacuated, and sealed, and the mixture was allowed to react at 110° for 4 hr. After the addition of acetic acid (5 drops) it was triturated with hexane in order to remove the excess iodoacetate. The undissolved salt mixture was dissolved in acetic acid (1 ml.), chloroform (1 ml.), and benzene (3 ml.), and stirred with finely powdered silver acetate (200 mg.) for 15 min. at room temperature. The mixture was left in a refrigerator for 1 hr., and filtered with Celite; the filtrate was carefully concentrated under reduced pressure at a temperature not exceeding 30°. Most of the excess acetic acid was removed by repeated evaporation with small quantities of toluene. The residual material was partly crystalline.

The reaction product was separated by partition chromatography on a Celite column with a 2:1 mixture of formamide–acetate buffer (30 ml. of acetic acid and 3 g. of potassium acetate in 70 ml. of water) as the stationary phase. Celite (3.5 g.) moistened with stationary phase (2.8 ml.) was dispersed evenly in pre-equilibrated benzene–chloroform (3:7) and the thin slurry added to a chromatographic tube (i.d. 12 mm.). The Celite was forced to settle by applying air pressure (*ca.* 6 p.s.i.), care being taken not to let the column top run dry. The upper layer was further packed with a plunger. The sample was dissolved in benzene–chloroform (3:7, 10 ml.) and saturated with the stationary phase and the solution added to the column. Elution was carried out with consecutively benzene–chloroform in the ratios 3:7 (20 ml.), 4:1 (10 ml.), and 9:1 (30 ml.) and chloroform (50 ml.), all solvents being equilibrated with the stationary phase. The eluate was investigated by circular paper chromatography (*cf.* ref. 4b) using the same stationary phase as above and with chloroform as the mobile solvent.

After a forerun of dark resinous material, benzene–chloroform (4:1 and 9:1) eluted chromatographically pure Vb and then, with but little overlapping, Va, presumably as the acetate salts. The last chloroform fractions apparently contained the pentacyclic salt XI. The proper fractions were combined, acidified with a few drops of acetic acid in order to minimize base-catalyzed lactam formation, and concentrated at water pump pressure below room temperature. The respective residues were dissolved in water and precipitated by addition of aqueous sodium perchlorate. The precipitated perchlorate salts were washed with ice-cold water.

(29) The solution momentarily assumed a deep orange color which rapidly faded to yellow. On concentration the toluene phase left an orange residue which gave deeply yellow solutions in polar solvents like methanol but pale yellow solutions in hexane. This may indicate that the initial proton abstraction occurs at N_a to give the polarized *o*-quinonoid structure X which should also be favored more in polar than in nonpolar solvents. In the latter solvent, tautomer IX may be the predominating form.

The crude ester perchlorate Vb crystallized spontaneously on trituration at −10° with a small volume of acetone acidified with a drop of acetic acid. Recrystallization from the same solvent gave pure Vb (59 mg.), m.p. 170–172.5°; spectra: infrared (KBr), NH 2.98 μ (m) and C=O (ester) 5.83 (s); ultraviolet (0.001 *M* HCl in ethanol), λ_{max} 247 mμ (log ϵ 3.98), 251 (sh) (3.95), and 352 (4.33), λ_{min} 230 (3.89) and 278 (2.55).

Anal. Calcd. for $C_{21}H_{27}O_6N_2Cl$: C, 57.46; H, 6.20; N, 6.38. Found: C, 57.73; H, 6.32; N, 6.26.

The crude Va crystallized sluggishly from dilute acetic acid, affording sticky crystals (39 mg.). After recrystallization from acetone at −70° it had m.p. 171–174° and gave an infrared spectrum indistinguishable from that of the starting material.

The material from the chloroform eluate afforded a crystalline perchlorate (16 mg.) from methanol, m.p. 208–212 dec. as compared to 215–220° dec. for pure XI. Its infrared spectrum (KBr) was nearly identical with that of the pentacyclic salt XI, the only significant difference being a weak absorption at 6.87 μ, indicative of contamination by the tetradehydro salt XII. This assumption was substantiated on comparison of the ultraviolet spectra (ethanol) of pure XI and the present preparation, the latter showing a shoulder at 306 mμ. The ultraviolet spectrum of XII exhibits a strong absorption in this region (see below). We have not been able to develop a chromatographic procedure for the separation of XI and XII.

Condensation of Va with Ethyl Bromoacetate. Isolation of XII. Whereas the condensation of IX with ethyl iodoacetate as described above was easily reproducible, preliminary attempts to alkylate with ethyl bromoacetate gave ambiguous results. Because of the lower reactivity of the latter reagent the reaction required more severe conditions (2–4 hr. at 150°). In view of the ready lactam formation of Vb it is not surprising that except for starting material, the pentacyclic salts XI and/or XII were usually the only identified products. In spite of normal precautions to prevent air oxidation, XII rather than XI was frequently the only product to be isolated.

Compound IX, prepared from 500 mg. of Va as described above, was heated with ethyl bromoacetate (2 ml.) at 150° for 2.5 hr. under nitrogen in a flask fitted with a reflux condenser. The salt mixture obtained after removal of excess ester by extraction with hexane was converted into acetate form by treatment with silver acetate (600 mg.) in acetic acid (0.5 ml.) and methanol (10 ml.). After removal of the solvents under reduced pressure below 30°, the residue was dissolved in benzene and the solution soaked up in Celite (2 g.). The Celite powder was dried and added to the top of a partition column prepared from Celite (22 g.) and buffer (12 ml.; 10 g. of potassium acetate and 24 ml. of acetic acid in 75 ml. of water) in benzene–hexane (4:1). Elution was started with the same solvent (180 ml.), followed by benzene–hexane (9:1, 250 ml.) and benzene (600 ml.). The collected eluate was acidified by brief treatment with dry hydrogen bromide. From the first half of the benzene eluate only starting material Va (93 mg.), m.p. 171–175°, was obtained. A careful paper chromatographic investigation of the mother liquors and of the pre-

ceeding fractions showed that only traces of Vb could have been present.

When concentrated, the second half of the benzene eluate gave a solid residue (80 mg.) which formed solvated crystals from chloroform. It was recrystallized by alternating treatment with chloroform and with acetone. The final product (50 mg.), m.p. 285–288° dec. (rapid heating), was assigned structure XII on the basis of chemical and spectral evidence; spectra: infrared (Nujol mull), C=O 5.81 (s) μ and 6.02 (s); ultraviolet (ethanol), λ_{max} 233 mμ (log ϵ 4.30), 256 (4.26), 305 (4.28), and 353 (3.65), λ_{min} 218 (4.24), 245 (4.13), 280 (3.86), and 325 (3.45); ultraviolet (0.05 *M* NaOH in ethanol), λ_{max} 223 mμ (log ϵ 4.24), 251 (4.07), 282 (sh) (4.59), 287 (4.69), 322 (3.96), 332 (4.05), and 429 (3.46), λ_{min} 240 (3.96), 256 (4.05), 303 (3.74), 326 (3.95), and 354 (2.70).[30]

Anal. Calcd. for $C_{19}H_{19}ON_2Br$: N, 7.55. Found: N, 7.26.

On one occasion a similar experiment yielded a crystalline product (70 mg. from 750 mg. of Va) whose spectral data indicated it to be a mixture of the ester Vb and a second compound with nearly the same ultraviolet absorption. On attempted fractional crystallization from water and methanol, Vb apparently cyclized eventually leading to the isolation of XI (30 mg.). In addition there was obtained a second perchlorate salt (9 mg.), m.p. 165–170°, 187–192° (dimorphous); spectra: infrared (Nujol mull), C=O 5.73 (s) μ and no band below 3.2; ultraviolet (0.001 *M* HCl in ethanol), λ_{max} 248 mμ (log ϵ 4.00), 253 (sh) (3.99), and 351 (4.36), λ_{min} 233 (3.86) and 279 (2.43). It is believed to be the product of N_a alkylation of Va by ethyl bromoacetate.

Conversion of Vb into XI. Four samples of the tetracyclic salt Vb (1 mg. each) in acetone (0.02 ml.) were mixed with 0.05-ml. portions of (a) ethanol, (b) 0.1 *M* potassium acetate in ethanol, (c) 0.1 *M* acetic acid in ethanol, and (d) 0.01 *M* hydrogen chloride in ethanol, respectively, and left at room temperature. Paper chromatograms indicated that in case b lactam formation was significant after 30 min. and nearly complete after 8 hr. Even subsequent heating at 75° for 10 min. failed to produce detectable amounts of XI in the neutral and acidic solutions.

A mixture of Vb (23 mg.) and 0.01 *M* potassium acetate–0.01 *M* acetic acid buffer (1 ml.) was heated at 100° for 2.5 hr. Paper chromatography indicated that the conversion to XI was then complete. Upon cooling, clusters of needles separated which were collected (18 mg.) and recrystallized from water to yield pure XI (15 mg.), m.p. 215–220° dec. (rapid heating); spectra: infrared (Nujol mull), C=O 5.80 (s) μ, 6.05 (m), and no band below 3.2; ultraviolet (0.001 *M* HCl ethanol), λ_{max} 219 mμ (log ϵ 4.28), 231 (4.25), 260 (3.84), and 354 (4.33), λ_{min} 226 (4.24), 254 (3.80), and 285 (2.92).

Anal. Calcd. for $C_{19}H_{21}O_5N_2Cl$: C, 58.09; H, 5.39; N, 7.13. Found: C, 57.91; H, 5.40; N, 7.14.

Epieburnamonine (VIII) by Reduction of XI. (*a*) A solution of the pentacyclic salt XI (30 mg.) in methanol (2 ml.) was treated with sodium borohydride (20 mg.) for 90 min. at room temperature. It was then acidified with acetic acid, made alkaline with ammonium hydroxide, and extracted with chloroform. The chloroform extract was dried over potassium carbonate and concentrated to give a crystalline residue, which was sublimed at 0.1 mm. and 130° (bath temperature) and recrystallized from hexane to give VIII as colorless needles (23 mg.), m.p. 132–135°. Further recrystallization from methanol followed by sublimation in a tube with gradient heating afforded pure epieburnamonine (VIII), m.p. 135.5–137°; spectra: infrared ($CHCl_3$), C=O 5.88 (s) μ, 6.04 (m), and no band below 3.2; ultraviolet (ethanol), λ_{max} 242 mμ (log ϵ 4.29), 2.66 (3.98), 295 (3.59), and 302 (3.60), λ_{min} 222 (3.94), 260 (3.96), 288 (3.53), and 298 (3.59).

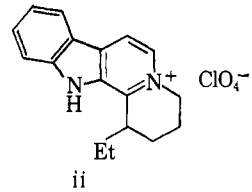
Anal. Calcd. for $C_{19}H_{22}ON_2$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.53; H, 7.55; N, 9.49.

(*b*) A mixture of XI (21 mg.), 10% palladium–charcoal (5 mg.), and potassium acetate (10 mg.) in ethanol (2 ml.) was hydrogenated at room temperature and atmospheric pressure until the reaction stopped (1 hr.) and the hydrogen uptake was 1 mole. Conventional work-up followed by recrystallization from hexane and aqueous methanol afforded epieburnamonine (12 mg.), m.p. 134–137°.

On careful inspection of the mother liquors from methods a and b by paper chromatography and infrared spectroscopy, no traces of eburnamonine (XIIIa) were detected.

Epieburnamonine (VIII) by Reduction of XII. A mixture of XII (17.8 mg.), 5% palladium–charcoal (14 mg.), and 0.097 *M* ethanolic sodium hydroxide (1.2 ml.) was hydrogenated at atmospheric pressure and room temperature for 17 hr. (hydrogen uptake 1.6 moles). The mixture was filtered, the filtrate was acidified with hydrochloric acid, basified with ammonium hydroxide, and extracted with chloroform, and the extract was concentrated to dryness. The residue (12 mg.) was chromatographed on alumina (4 g.). Elution with benzene–hexane (1:1) and crystallization of the solute from hexane and aqueous methanol afforded epieburnamonine (VIII) (7 mg.), m.p. and m.m.p. 135–137°; the infrared spectrum (KBr) was identical with that of authentic VIII. No eburnamonine (XIIIa) could be detected in the other fractions from the column or in the mother liquors.[31]

(30) Alkaline hydrolysis of XII apparently yields an anion containing the same chromophoric system as the conjugate base of ii[4b]; ultraviolet spectrum of ii (0.05 *M* NaOH in ethanol): λ_{max} 223 mμ (log ϵ 4.23), 250 (4.14), 280 (sh) (4.70), 286 (4.78), 322 (sh) (3.99), 331 (4.05), and 426 (3.49), λ_{min} 238 (4.01), 254 (4.13), 301 (3.73), and 352 (2.68).



ii

(31) It was deemed reasonable that the sodium salt of tetradehydroeburnamoninic acid, as obtained by alkaline hydrolysis of the lactam ring of XII under the conditions of the hydrogenation, would be hydrogenated in a nonstereospecific way. This is apparently not the case. Similarly, when a sample of XII in 0.1 *M* ethanolic sodium hydroxide was treated with sodium borohydride at room temperature overnight, followed by brief heating with ethyl acetate in order to achieve a gradual neutralization of the excess base, epieburnamonine (VIII) but no eburnamonine (XIIIa) was indicated by paper chromatography of the product.

Reduction of Vb. (*a*) A solution of Vb (49 mg.) in methanol (3 ml.) was added with stirring to an ice-cooled solution of sodium borohydride (30 mg.) in methanol (2 ml.). The yellow color of the salt Va disappeared immediately. Circular paper chromatograms[4b] (mobile phase, benzene–hexane (1:1); stationary phase, 5 g. of potassium acetate and 25 ml. of acetic acid in 75 ml. of water) of the reaction mixture indicated the presence of two products (potassium iodoplatinate spray reagent),[32] one of which was slower than eburnamonine. The othertr avelled much faster, with the same rate as epieburnamonine, but appeared with a violet rather than the grayish blue color of the latter compound. After brief heating to boiling, the mixture was acidified with acetic acid, diluted with water, basified with ammonium hydroxide, and extracted with chloroform. After drying over potassium carbonate, the extract was concentrated under reduced pressure to give a partly crystalline residue (34 mg.). On paper chromatograms it gave the same two spots as the methanolic reaction mixture. It was believed to be composed of epieburnamonine and the ethyl esters of eburnamoninic and epieburnamoninic acid. This assumption was supported by the infrared spectrum ($CHCl_3$): hydrogen bonded NH 2.88 (m) and 3.00 (m) μ, C=O 5.78 (sh) (s), 5.88 (s), and 6.04 (m).

The mixture was dissolved in 0.1 *M* ethanolic ethoxide (5 ml.) with gentle heating and then left at room temperature for 15 min. On paper chromatography, the solution now gave two spots indistinguishable from those given by eburnamonine and epieburnamonine, respectively. It was acidified with acetic acid and left at room temperature overnight. Basification with ammonium hydroxide and extraction with chloroform gave the crude bases (23 mg.) as an oil, which was chromatographed on alumina (4 g.). Benzene–hexane (1:3) eluted a crystalline material (11.5 mg.) which upon recrystallization from benzene–hexane and aqueous methanol gave pure epieburnamonine (VIII) (9 mg.), m.p. 134.5–136°, m.m.p. 134.5–136.5°; infrared spectra (KBr) identical.

Elution with benzene–hexane (1:1) gave a crystalline fraction (12 mg.) which on recrystallization from benzene–hexane and methanol afforded eburnamonine (XIIIa) (10 mg.), m.p. and m.m.p. 201–202°; infrared spectra (KBr) identical.

(*b*) A mixture of Vb (40 mg.) and 5% palladium–charcoal (20 mg.) in ethanol (3 ml.) was hydrogenated at room temperature and atmospheric pressure until after 14 hr. when the reaction had stopped and the initially yellow color of the starting material had disappeared. Paper chromatograms indicated that the product composition was qualitatively the same as in method a, but with the slow-moving compound in a large excess. The solution was filtered, diluted with water, basified with ammonium hydroxide, and extracted with chloroform. Concentration of the extract gave a partly crystalline residue (28 mg.) which spectral data indicated to be a mixture of the ethyl esters of eburnamoninic and epieburnamoninic acid; ultraviolet spectrum (ethanol), λ_{max} 227 mμ (log ϵ 4.33), 283 (3.73), and 290 (3.67), λ_{min} 247 (3.40) and 288 (3.66); infrared spectrum ($CHCl_3$), NH 2.89 (m) μ, and C=O 5.84 (s).

The ester mixture was treated with sodium ethoxide in ethanol and the product worked up as under method a to give epieburnamonine (VIII) (2 mg.), m.p. and m.m.p. 135–136.5°, and eburnamonine (16 mg.), m.p. and m.m.p. 200–202°; their identities were confirmed by comparison of infrared spectra (KBr).

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The Total Synthesis of the (±)-Furopelargones

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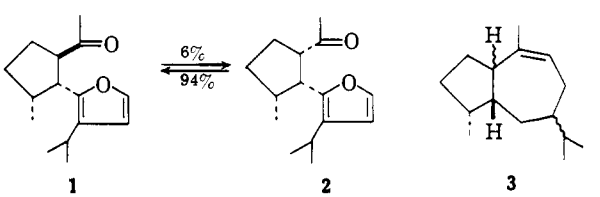
Photocitral-A (**9**), *whose configuration was elucidated, served as starting material in the synthesis of the naturally occurring sesquiterpene (?) ketone furopelargone-A* (**1**). *Reformatzky condensation with t-butyl α-bromoisovalerate followed by oxidation yielded a mixture of diastereomeric ketoesters* (**14**). *The latter was alkylated with allyl bromide and the resulting β-ketoester transformed to the dienone* **18** *by pyrolysis. Oxidation with ozone followed by dehydration in acetic acid solution completed the total synthesis of furopelargone-A* (**1**). *The epimeric furopelargone-B* (**2**) *was available by acid- or preferably base-catalyzed equilibration of the A isomer* (**1**).

The high boiling fractions of *Geranium Bourbon Oil*[1] contain the two isomeric furopelargones A and B ($C_{15}H_{22}O$). The structures of these two natural products were elucidated very recently and formulas **1** and **2** also represent their absolute configurations.[2,3] We have verified these structures by a total synthesis which is discussed in this paper.



1 **2** **3**

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(2) R. E. Wolff, J. C.-N. Ma, and G. Lukas, *Compt. rend.*, **257**, 1784 (1963).

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