[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, AND THE LABORATOIRE DE PHARMACIE GALÉNIQUE, FACULTÉ DE PHARMACIE, UNIVERSITÉ DE PARIS]

The Structure and Stereochemistry of Undulatine[1,2]

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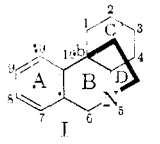
Evidence has been obtained for all features of the stercostructure III for the alkaloid undulatine.

Among the alkaloids found in an Amaryllis bella-donna hybrid was a base,[3] $C_{18}H_{21}NO_5$, m.p. 152°, $[\alpha]_D$ −32°, whose composition, melting point and methiodide melting point were remarkably similar to those of an alkaloid undulatine, $C_{18}H_{21}NO_5$, m.p. 149°, previously isolated by Boit and Ehmke from *Nerine undulata* (L.) Herb.,[6] *Nerine bowdenii*[7a] and later from *Nerine flexuosa*.[7b] At first the two compounds were not considered identical since the optical rotation reported by Boit ($[\alpha]_D$ 0°, $[\alpha]_D$+3°)[6,7a] differed markedly from that found in this Laboratory. Also undulatine was described[6] as having an N-methyl group, a function not found in the alkaloid isolated in this Laboratory. However, in more recent work[7b] Boit reported a negative N-methyl analysis and a rotation ($[\alpha]_D$ −22°) in better agreement with that found in the present work. The N-methyl anomaly was resolved when it was found that undulatine, although not possessing an N-methyl group, could give rise to an *N-ethyl* group under the conditions of the Herzig–Meyer analysis.[8] Finally a direct comparison of the two alkaloids demonstrated their identity.[9]

Structure.—Undulatine contained two methoxyl groups but no C-methyl group. A positive color test[10] for the methylenedioxy group was confirmed by the infrared spectrum which had the two characteristic absorption bands of this group at 9.58 and 10.66 μ.[11] Infrared OH or NH absorption was absent in agreement with a negative active hydrogen analysis. There was no absorption in the carbonyl region, but a strong peak appeared at 6.18 μ distinctive of the *vic*-trioxygenated benzene ring.[12] The ultraviolet absorption spectrum (λ_{max} 288 mμ, ϵ 1600) was also in accord with this formulation.[12] By analogy with other alkaloids of this series the aromatic oxygen functions were presumed to be a methoxyl and a methylenedioxy group.[12,13] Since undulatine did not absorb hydrogen and did not discolor permanganate solution, there was no evidence of unsaturation aside from that in the aromatic ring. The above facts served to characterize undulatine as a hexacyclic tertiary amine containing one aromatic ring and five ethereal oxygen atoms in the form of one methylenedioxy group, two methoxyl groups and a fifth cyclic oxide of unknown size.

It seemed likely that undulatine belonged to the group of alkaloids possessing the spiro crinane skeleton I[13] rather than the lycorane structure II or any other known skeleton[14–16] because: (a) the base contained no N-methyl or NH groups, (b) undulatine was not oxidized to an aromatic lactam by permanganate,[17] (c) the crystalline base was not oxidized to colored products on exposure to



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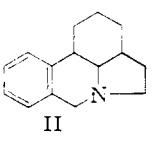


II

(1) Part XIII of the series Alkaloids of the Amaryllidaceae. Part XII, H. M. Fales and W. C. Wildman, THIS JOURNAL, **80**, 4395 (1958).

(2) A preliminary account of part of this work has appeared in *Chemistry & Industry*, 1293 (1958).

(3) The base, which was not readily separated by chromatography from an accompanying alkaloid, buphanidrine,[12] could be obtained pure by recrystallization of chromatogram fractions from ether, or, better, by conversion to the perchlorate with subsequent regeneration from the recrystallized salt and a final recrystallization from ether.

In this connection the alkaloid distichine,[4] m.p. 144°, $[\alpha]_D$ −39°, is in all probability undulatine contaminated with traces of buphanidrine since the infrared spectrum of distichine[5] is identical with that of a 3:1 mixture of undulatine and buphanidrine.

(4) A. N. Bates, J. K. Cooke, L. J. Dry, A. Goosen, H. Krüsi and F. L. Warren, *J. Chem. Soc.*, 2537 (1957).

(5) The authors would like to thank Professor Warren for providing a sample of distichine.

(6) H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956).

(7) (a) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 2093 (1956); (b) **90**, 369 (1957).

(8) Most of the alkaloids with the spiro skeleton I have been found to give appreciable, real N-methyl values in this determination if the pyrolysis was conducted repeatedly and for prolonged periods. For example, undulatine: calcd. 4.53, found 3.00, 3.48; dihydroundulatine: calcd. 4.50, found 3.75. Since the methoxyl values for these bases were slightly higher than the theoretical amount (same determination which gave the N-alkyl value), there was no contribution of methoxyl to the N-alkyl value. In a normal N-methyl analysis most of the volatile alkyl iodide is obtained in the first distillation of the procedure. In the case of the spiro alkaloids, however, the alkyl iodide was liberated only slowly on repeated distillations. It was found that the volatile iodide was actually ethyl iodide (see Experimental section). This could arise by cleavage of the bond connecting the ethano bridge to the spiro carbon atom to form an N-ethyl group which could then be converted to the iodide. In agreement with this view it was found that ambelline, an alkaloid with a hydroxyl at C$_{11}$ of the ethano bridge, gave a very low and probably insignificant N-alkyl value of 0.10% after correction for a blank run. Nevertheless the Herzig–Meyer analysis was significant in this series if carried out under mild conditions.

(9) The authors would like to thank Professor Boit for providing a sample of undulatine.

(10) J. A. Labat, *Bull. soc. chim. Biol.*, **15**, 1344 (1932).

(11) L. H. Briggs, L. D. Colebrook, H. M. Fales and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

(12) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 4807 (1955).

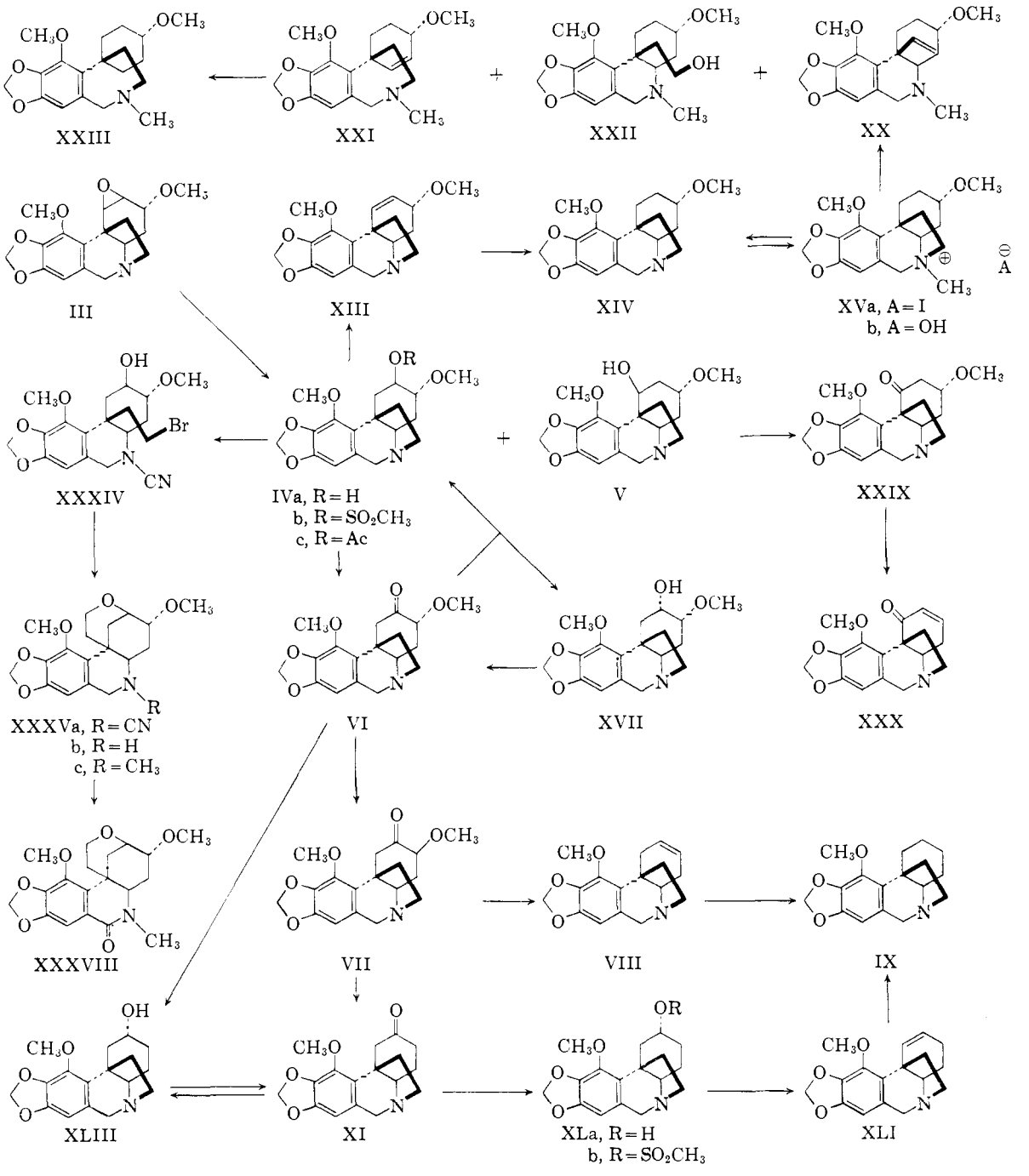
(13) W. C. Wildman, *ibid.*, **80**, 2567 (1958).

(14) C. K. Briggs, P. F. Highet, R. J. Highet and W. C. Wildman, *ibid.*, **78**, 2899 (1956).

(15) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

(16) S. Uyeo, Abs. Papers XVIth Int. Cong. Pure Appl. Chem., Paris, 1957, p. 209.

(17) *Cf.* the cases of (a) lycorine, K. Wiesner, W. I. Taylor and S. Uyeo, *Chemistry & Industry*, 46 (1954); and (b) caranine, E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **79**, 2192 (1957). Presumably the oxidation of alkaloids of type I to an aromatic lactam would at some stage require a double bond to the bridgehead nitrogen atom.



air,[18] (d) neither undulatine nor its dihydro derivative was oxidized by selenium dioxide,[19] and finally (e) the alkaloid gave a single methiodide.[20] The simplest test of this conclusion appeared to be the removal of the aliphatic oxygen functions of undulatine in an effort to relate its skeleton to that of a base of known structure.

With this purpose in mind attempts were made to cleave one of the aliphatic ether groups. Undulatine proved to be inert to refluxing sodium methoxide in methanol, boiling 20% ethanolic potassium hydroxide, boiling 10% hydrochloric acid[21] and catalytic hydrogenation in acetic acid over platinum. However, the cyclic oxide was readily opened by lithium aluminum hydride in ether to form two isomeric alcohols, dihydroundula-

(18) Amaryllidaceae alkaloids with the lycorane skeleton II slowly turn yellow to brown in the presence of oxygen, whereas none of the alkaloids with the spiro skeleton exhibits this behavior. This is readily rationalized if oxidative attack begins at the tertiary benzylic hydrogen atom in the former series of bases.

(19) Alkaloids with the lycorane skeleton II are easily aromatized by selenium dioxide; see (a) H. M. Fales, E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **77**, 5885 (1955); (b) H. M. Fales and W. C. Wildman, *ibid.*, **78**, 4151 (1956).

(20) *Cf.* lycorine and caranine (type I1) each of which gives two diastereoisomeric methiodides. With skeleton I only a single isomer is possible.

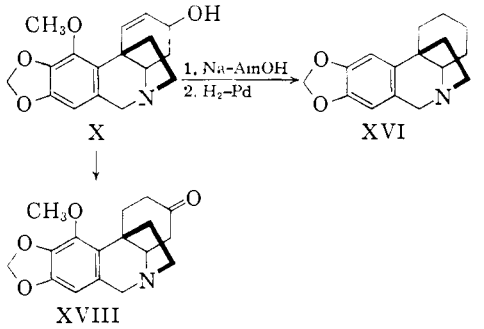
(21) The lack of reactivity toward acid supported placement of the methylenedioxy group on the aromatic ring.

tine (IVa), m.p. 251.5° dec., $[\alpha]_D$ −37°, and isodihydroundulatine (V),[22] m.p. 200.5°, $[\alpha]_D$ +21°, in the ratio of 11:1, respectively.

The modified Oppenauer oxidation of dihydroundulatine with fluorenone and potassium *t*-butoxide[23] at room temperature furnished a mixture of two isomeric ketones. Recrystallization from methanol containing a small amount of hydroxide ion converted the mixture almost entirely to one isomer, *epi*oxodihydroundulatine (VII), m.p. 223° dec., $[\alpha]_D$ −50°, whose infrared carbonyl absorption (5.78 μ) did not reveal whether the ketone was in a five- or six-membered ring.

The labile ketone, oxodihydroundulatine (VI), was obtained pure when it was found that dihydroundulatine, although containing no double bonds, was slowly oxidized by manganese dioxide to the extent of 30–50%.[24] A better yield (80%) of the ketone resulted from oxidation with the chromium trioxide–pyridine reagent. After purification to constant optical rotation by chromatography, conversion to the picrate and regeneration, the pure oxodihydroundulatine, $[\alpha]_D$ −15°, was still amorphous. Its infrared carbonyl peak (5.80 μ) also did not distinguish between a cyclopentanone or a cyclohexanone structure. The pure ketone VI was epimerized to the more stable *epi* isomer on recrystallization from methanol containing hydroxide ion. Reduction of oxodihydroundulatine with lithium aluminum hydride regenerated dihydroundulatine in 80% yield. Therefore the change of oxodihydroundulatine into *epi*oxodihydroundulatine cannot involve rearrangement of the carbon skeleton since both the *epi*-ketone VII and dihydroundulatine have been converted (see below) into derivatives known to have the same skeleton I.

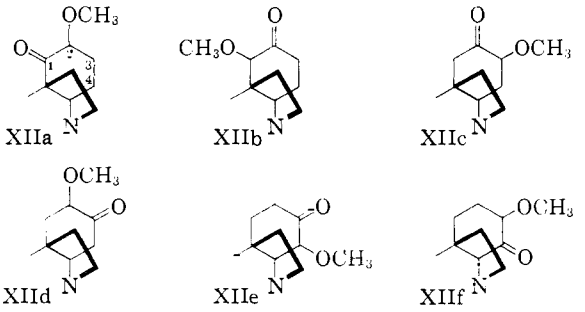
The removal of the aliphatic oxygen atoms from the *epi*-ketone VII proved easier than anticipated. When *epi*oxodihydroundulatine was subjected to a mild Wolff–Kishner reduction, both the carbonyl group and the aliphatic methoxyl group were lost and an unsaturated base VIII, $C_{17}H_{18}NO_3$, was produced. This behavior, although characteristic of α- and β-substituted ketones,[25] provides good evidence for an α-methoxy ketone in this case; *epi*oxodihydroundulatine cannot be a β-methoxy ketone in view of its stability to reflux with potassium *t*-butoxide.[26] The unsaturated compound absorbed one mole-equivalent of hydrogen over palladium-on-carbon catalyst to give the known (+)-powellane (IX) identical with a sample prepared from powelline (X).[13] Powelline has been reduced[27] to (−)-crinane (XVI) whose structure has been established by synthesis.[13] Therefore this conversion of the *epi*-ketone VII to IX served to



determine the carbon skeleton I of undulatine and to fix the position of the methylenedioxy group on ring A.

The structural problem had now been reduced to the location of the aliphatic oxygens and the aromatic methoxyl. Further evidence for the presence of an α-methoxy ketone in VII was provided by the reductive removal of the methoxyl of *epi*-oxodihydroundulatine with zinc and acetic acid[28] to give desmethoxyoxodihydroundulatine (XI) (alternative name, 2-oxopowellane), m.p. 209° dec., $[\alpha]_D$ +9.8°. The infrared carbonyl peak (5.84 μ) of this ketone finally provided proof of the presence of a cyclohexanone and therefore limited the aliphatic oxygen functions to ring C.

There were six possible arrangements of vicinal methoxyl and carbonyl functions in ring C of *epi*-oxodihydroundulatine represented by part formulas XIIa to XIIf. Certain of these could be dismissed from consideration. Since desmethoxy-



oxodihydroundulatine (XI) was not identical with a ketone of known structure, oxodihydropowelline (XVIII)[13] (alternative name, 3-oxopowellane), m.p. 166°, $[\alpha]_D$ −42°, structures such as XIId or XIIe with a 3-keto group were not permissible. A further limitation was imposed by exchange of the α-ketonic hydrogen atoms of *epi*-oxodihydroundulatine for deuterium. Three atoms of deuterium were incorporated into the molecule when VII was refluxed with O-deuterio-*t*-butyl alcohol and potas-

(22) The α and β designations used for these isomers in ref. 2 have been changed so that the prefixes α and β *preceded by a number* might be reserved to indicate configuration at a particular carbon atom, β designating a group above the plane of the molecule (the plane of the paper) and on the same side of ring C as the ethano bridge.

(23) (a) R. B. Woodward, N. L. Wendler and F. J. Brutschy, THIS JOURNAL, **67**, 1425 (1945); (b) W. E. Doering, G. Cortes and L. H. Knox, *ibid.*, **69**, 1700 (1947).

(24) For a similar observation see H. Bruderer, D. Arigoni and O. Jeger, *Helv Chim. Acta*, **39**, 859 (1956), footnote 16.

(25) See (a) N. J. Leonard and S. Gelfand, THIS JOURNAL, **77**, 3269 (1955); (b) T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1540 (1952); and (c) D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 2752 (1951).

(26) Further and conclusive evidence on this point (see below) is the oxidation of isodihydroundulatine (V) to a β-methoxy ketone. Since one β- and one α-methoxy alcohol must result from hydride reduction of a 1,2-epoxy-3-methoxy system, dihydroundulatine must be the α-methoxy alcohol which gives rise to an α-methoxy ketone. The marked difference of the infrared carbonyl peak wave lengths for the two ketones VI and VII compared to the desmethoxy derivative XI is also suggestive of an α-substituent.[27]

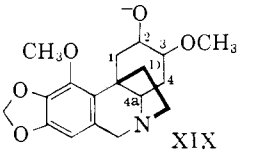
(27) H. M. Fales and W. C. Wildman, THIS JOURNAL, **80**, 4395 (1958).

(28) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

sium *t*-butoxide[29] under conditions which did not deuterate undulatine itself. Therefore, formulas XIIa and XIIf were excluded.[30] Of the two remaining possibilities XIIc was the one to be expected in consideration of the proposed biogenesis of amaryllidaceae alkaloids (see below).[31] A choice between XIIb and XIIc was facilitated by the possiblity of degrading XIIc, but not XIIb, to an optically inactive derivative.

The degradation required removal of one of the C-ring oxygen functions. For this dihydroundulatine was chosen since reductive removal of the carbonyl group of the ketone VII had resulted in concomitant loss of the methoxyl. The hydroxyl group of IVa was converted to the amorphous methanesulfonate IVb which formed in excellent yield[32] and was purified *via* its picrate. The elimination of methanesulfonic acid from the mesylate required the rather vigorous conditions of reflux with potassium *t*-amyloxide in *t*-amyl alcohol to achieve a reasonable reaction time.[33] There was obtained a 95% yield of a pure unsaturated product, $C_{18}H_{21}NO_4$, which was found to be identical with the alkaloid buphanidrine (XIII).[34] Hydrogenation of XIII with palladium-on-carbon gave an almost quantitative yield of amorphous dihydrobuphanidrine (XIV). This was purified *via* its picrate and transformed into the methiodide XVa. The quaternary ammonium hydroxide XVb was prepared with silver oxide and subjected to the Hofmann degradation at 135–155°. There was obtained a 96% crude yield of a mixture of products from which chromatography allowed the separation of four products: the two possible methines XX and XXI, dihydrobuphanidrine (from reversal of the Hofmann reaction) and the alcohol XXII formed by attack of hydroxide ion on C_{12}. The structure of the significant methine XXI (amorphous) rests on the following evidence. From its elemental analysis, $C_{19}H_{25}NO_4$, and in the absence of rearrangement the product had to be either XX or XXI. The infrared spectrum of the amorphous methine had no vinyl absorption[35] whereas the crystalline methine, m.p. 137.5°, did contain a vinyl group.[36] The ultraviolet spectrum of XXI had the normal methoxymethylenedioxyphenyl chromophore demonstrating that no rearrangement had taken place at the spiro carbon atom. Any such rearrangement would have led to a double bond conjugated with the aromatic ring. Finally and rigorously, the optically active methine absorbed one mole-equivalent of hydrogen with the formation of a dihydromethine whose crystalline methiodide was *optically inactive* from 350 to 589 mμ. The only dihydromethine derivable from a methoxypowellane skeleton which can be optically inactive is XXIII with the aliphatic methoxyl at the 3-position, for only then can the dihydromethine possess a plane of symmetry.[37] This result serves to exclude not only part formula XIIb but also XIIa, XIId and XIIe from consideration for *epi*oxodihydroundulatine since any of these would have given an optically active dihydromethine. Therefore, buphanidrine, undulatine and their derivatives all have the aliphatic methoxyl in the 3-position of the carbon skeleton. This being so, *epi*oxodihydroundulatine can only be represented by VII with a 2-keto group to account for the incorporation of three atoms of deuterium during exchange.[38] It follows that oxodihydroundulatine must be VI with the less stable configuration of the methoxyl at C_3 and dihydroundulatine is the corresponding alcohol IVa.

The other position of attachment of the oxide ring originally present in undulatine posed an interesting problem. The unknown size of this ring obliged consideration of attachment at the five structurally possible carbon atoms indicated by numbers in XIX. Infrared spectra of undulatine and derivatives were of no assistance. A

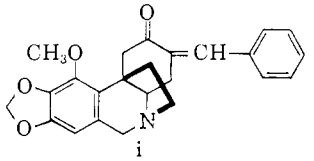


XIX

medium intensity peak at 10.85 μ in undulatine was absent in dihydroundulatine, buphanidrine and dihydrobuphanidrine, but this peak fell outside the observed values reported for all three possible types of oxide. Oxetanes have a strong characteristic band at 10.2–10.3 μ[39] while 1,4-epoxides

(29) These conditions were chosen because VII could not be recovered unchanged after reflux with sodium ethoxide in ethanol. Reduction of the carbonyl group apparently occurred.

(30) Before the deuterium exchange experiment structure XIIa or XIIf was strongly indicated since *epi*oxodihydroundulatine did not form a benzylidene derivative even under vigorous conditions, while in preliminary experiments the desmethoxy ketone XI formed a monobenzylidene derivative (now formulated as i). Apparently the free α-methylene group of the *epi*ketone is quite hindered. This is consistent with the structure VII.



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(31) D. H. R. Barton and T. Cohen, "Festschrift Arthur Stoll," ed. by E. Jucker, Birkhäuser, Basel, 1957, p. 117.

(32) Attempts to prepare the *p*-toluenesulfonate of IVa gave disappointingly capricious results. Previous to this, mild pyridine–phosphorus oxychloride dehydration of IVa had been tried. Dehydration took place, but the product was a mixture which was not readily separated.

(33) Refluxing collidine did not effect elimination of the mesylate, and potassium *t*-butoxide in boiling *t*-butyl alcohol required more than 48 hours to achieve complete elimination.

(34) Buphanidrine has been interrelated[13] with powelline (X) for which the position of the oxygen in ring C has been demonstrated. However, the acid hydrolysis (refluxing 10% hydrochloric acid) employed in the conversion of buphanidrine into powelline left the possibility of an allylic rearrangement from a 1-methoxy-$\Delta^{2,3}$-structure to the 3-hydroxy-$\Delta^{1,2}$ structure.

(35) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 49.

(36) Structur 1 evidence for XX and XXII is presented at the end of the present work.

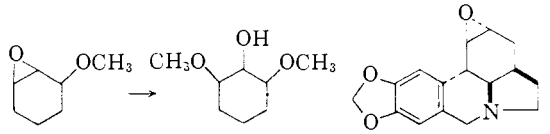
(37) For a similar application of the loss of optical activity see ref. 15.

(38) The other 3-methoxy structure XIIf with the 4-keto group is also excluded on other grounds. Thus the methochloride of *epi*oxodihydroundulatine was unaffected by zinc in refluxing acetic acid or acetic anhydride, conditions which would be expected to remove reductively a quaternary nitrogen on the α-carbon of a ketone. Also the pK_a of VII (6.14) was similar to that of undulatine (6.50) and only 1.5 units weaker than that of dihydroundulatine (7.67) whereas an α-aminoketone should be a much weaker base. Formula XIIf is also eliminated by the work described locating the oxide ring of undulatine.

(39) G. M. Barrow and S. Searles, THIS JOURNAL, **75**, 1175 (1953).

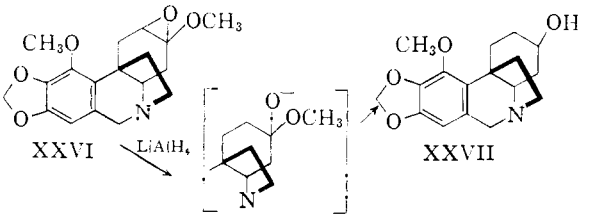
absorb strongly at 9.1–9.3 μ.[39] 1,2-Epoxides attached to six-membered rings have been reported[40] to absorb at both 11.22–11.4 μ and 12.3–12.5 μ although other workers found no characteristic peaks for this system.[41] The aromatic carbon–hydrogen absorption and the pronounced shoulder on the carbon–hydrogen stretching bands prevented detection of a 1,2-epoxide in this region.[42]

Chemical evidence was ambiguous. A normal 1,4-epoxide (C_2–O–C_{11}) would not react with acid, base or hydrogen, as observed, but also it would not be cleaved by lithium aluminum hydride.[43] An oxazolidine structure (C_2–O–C_{4a}) with the oxide joined to the carbon bearing the nitrogen should be reduced to dihydroundulatine, but it would also be expected to open with base, acid and hydrogen.[44] A 1,2-epoxide (C_1–O–C_2 or C_2–O–C_3) seemed unlikely in view of the unreactivity of undulatine toward base, aqueous acid and hydrogen. The inertness of undulatine to refluxing methanol containing sodium methoxide appeared to exclude a C_1–O–C_2 epoxide since a similar system, XXIV, was opened completely under these conditions to the dimethoxycyclohexanol.[45] Also the epoxide XXV derived from caranine was readily opened by this reagent as well as by acetic acid and by dilute sulfuric acid.[46] A 1,3-epoxide (C_2–O–C_4) seemed to fit the properties of undulatine somewhat better. Thus oxetanes with few substituents are usually cleaved by lithium aluminum hydride[47,48] but are not as reactive toward alkoxide or hydrogen as oxiranes.[49] However, oxetanes are readily opened by aqueous acid.[50]

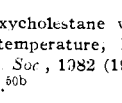


XXIV XXV

The point was finally decided by marking the unknown site of attachment of the oxide ring with a deuterium atom which was then located, a method generally applicable to epoxides which can be opened with lithium aluminum deuteride or a lithium–N-deuterioamine reagent. Undulatine was reduced with lithium aluminum deuteride to dihydroundulatine-*d* containing 0.86 atom of deuterium. This was oxidized by manganese dioxide to oxodihydroundulatine-*d* which was then epimerized in alkaline methanol solution. The *epi*-oxodihydroundulatine formed had only 0.01 atom of deuterium.[51] The deuterium atom lost during enolization of the ketone must have occupied one of the ketonic α-carbon atoms; therefore the original ethereal ring was a 1,2-epoxide. Formula XXVI with the C_2–O–C_3 oxide was untenable, although hydride reduction of XXVI would have produced dihydroundulatine,[52] because undulatine had none of the properties of a 1,2-epoxyether[53] and, conclusively, undulatine gave two *isomeric* products on hydride reduction. Even if the epoxyether XXVI could be opened at either carbon, the two products would differ by the elements of CH_2O since one of the dihydro derivatives would be a hemiketal which would lose methanol and be reduced further to XXVII. The only permissible structure remaining for undulatine is III with the C_1–O–C_2 epoxide.



Further confirmation for formula III was provided by oxidation of isodihydroundulatine (V), the minor isomer from reduction of undulatine, with the chromium trioxide–pryidine reagent. The crude product was a mixture of the expected ketone XXIX and an unsaturated ketone arising from elimination of the aliphatic methoxyl group. When the crude ketone was refluxed in pyridine–triethylamine–acetic acid solution, the cyclohexanone carbonyl absorption at 5.85 μ disappeared from the infrared spectrum while the cyclohexenone peak at 5.99 μ became more intense. A crystalline unsaturated ketone, $C_{17}H_{17}NO_4$ m.p. 210.5°, $[\alpha]_D$ −49°, was isolated and found to be identical with oxoisobuphanamine (XXX).[54] Subtraction of the ultraviolet spectrum of isodihydroundulatine from that of the unsaturated ketone left a typical conjugated cyclohexenone, λ_{max} 223 mμ (ϵ 8700). This ready loss of the methoxyl with formation of an α,β-unsaturated ketone under such mild conditions is only expected of β-methoxy ketones.



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(40) (a) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958); (b) W. A. Patterson, *Anal. Chem.*, **26**, 823 (1954); (c) J. Bomstein, *ibid.*, **30**, 544 (1958).

(41) Hs. H. Günthard, H. Heusser and A. Fürst, *Helv. Chim. Acta*, **36**, 1900 (1953).

(42) H. B. Henbest, G. D. Meakins, B. Nicholls and K. J. Taylor, *J. Chem. Soc.*, 1459 (1957).

(43) See for example H. L. Goering and C. Serres, THIS JOURNAL, **74**, 5908 (1952).

(44) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953), and references cited therein.

(45) (a) J. A. McRae, R. Y. Moir, J. W. Haynes and L. G. Ripley, *J. Org. Chem.*, **17**, 1621 (1952); (b) R. U. Lemieux, R. K. Kullnig and R. Y. Moir, THIS JOURNAL, **80**, 2237 (1958).

(46) K. Takeda and K. Kotera, *Pharm. Bull. Japan*, **5**, 234 (1957).

(47) S. Searles, K. A. Pollart and E. F. Lutz, THIS JOURNAL, **79**, 948 (1957).

(48) However, 3α,5α-epoxycholestane was unaffected by lithium aluminum hydride at room temperature, R. B. Clayton, H. B. Henbest and M. Smith, *J. Chem. Soc.*, 1982 (1957); *cf.* also the failure of *i* to be reduced even at 140°.[50b]

(49) S. Searles and C. F. Butler, THIS JOURNAL, **76**, 56 (1954). 3α,5α-Epoxycholestane is unaffected by boiling methanol containing methoxide ion.[48]

(50) (a) S. Searles, K. A. Pollart and F. Block, *ibid.*, **79**, 952 (1957); (b) G. Büchi, C. G. Inman and E. S. Lipinsky, *ibid.*, **76**, 4327 (1954).

(51) Dihydroundulatine-*d* was recovered without loss of deuterium after reflux under the same conditions which led to loss of deuterium from the deuterioketone.

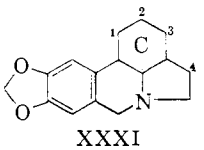
(52) Hydride attack takes place at the carbon atom bonded to two oxygen atoms in 1,2-epoxyethers; see C. L. Stevens and T. H. Coffield, THIS JOURNAL, **80**, 1919 (1958).

(53) 1,2-Epoxyethers are readily opened by mineral acid, organic acids, alkoxides and hydrogen; see ref. 52 and preceding papers.

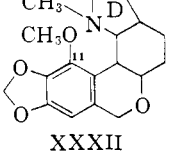
(54) H. M. Fales and W. C. Wildman, unpublished work; see also (a) W. C. Wildman, *Chemistry & Industry*, 1090 (1956); (b) L. G. Humber and W. I. Taylor, *Can. J. Chem.*, **33**, 1268 (1955).

Since the only position the hydroxyl group of isodihydroundulatine can occupy to produce a β-methoxy ketone is C_1, this constitutes additional proof of a C_1–O–C_2 epoxide in undulatine.

Isodihydroundulatine and its derivatives also furnished information with regard to the remaining structural point of undulatine—the position of the aromatic methoxyl group. In the methoxymethylenedioxyphenyl alkaloids the ultraviolet absorption maximum at 286–288 mμ is due to the substituted benzene ring and has a relatively constant molar extinction coefficient of about 1700–1800. It will be noted from Table I (1-26) that the extinction coefficients of all the derivatives in the present work together with additional values, but exclusive of salts and N-cyano derivatives,[55] fall between 1650 and 1900 with the exception of those derivatives with a substituent larger than hydrogen at C_1. In these latter cases the extinction coefficient falls in the range 1500–1320 with undulatine itself a borderline case (ϵ 1600). The only explanation for the lowered intensity of absorption is a disturbance of the aromatic chromophore. This must be steric in origin since transmission of electronic effects from ring C to ring A does not take place as evidenced by the constancy of absorption for the variously substituted C-ring derivatives of Table I. Molecular models with the stereochemistry to be demonstrated below show clearly that there can be no influence of a C_1-substituent on the aromatic ring except by non-bonded interaction with a group bulkier than hydrogen (in this case methoxyl) occupying the C_{10}-position.[56] Confirmatory evidence for this conclusion was provided by spectra of alkaloids having only a methylenedioxyphenyl skeleton, *e.g.*, XVI or XXXI. In these examples (numbers 27–40, Table I), where there is no possibility of interaction of a C_1-substituent with anything but an aromatic hydrogen, the ultraviolet spectrum has a maximum at 292–297 mμ with an extinction coefficient of 4600–5200 whether there is a substituent at C_1 or not (numbers 35–40 have a C_1-substituent). A second manifestation of the interference effect is found in trioxyaryl alkaloids of skeleton XXXII.[14] In these (numbers 41–42)



XXXI



XXXII

where the pyrrolidine D-ring is attached so as to interfere markedly with a C_{11}-substituent on the aromatic ring, the extinction coefficients are lower than those of alkaloids of skeleton IX where this type of interaction is not possible. In view of the consistency of these observations the aromatic methoxyl is assigned to C_{10} in undulatine (and to the analogous position in other methoxymethylenedioxyphenyl alkaloids), although conclusive chemical evidence on the point is desirable.

TABLE I

ULTRAVIOLET SPECTRA OF AMARYLLIDACEAE ALKALOID DERIVATIVES

	Derivative	Mol. extinc. ϵ	λ_{max}^{EtOH} mμ	Ref.
1	Hydrocotarnine	1700	287	[a]
2	Dihydroundulatine (IVa)	1750	287	[a]
3	Dihydroundulatine acetate (IVc)	1830	286	[a]
4	*epi*Dihydroundulatine (XVII)	1760	286	[a]
5	Oxodihydroundulatine (VI)	1750	288	[a]
6	*epi*Oxodihydroundulatine (VII)	1780	288	[a]
7	Δ^2-Powellene (VIII)	1790	288	[a]
8	Powellane (IX)	1670	286	[a]
9	2-Oxopowellane (XI)	1750	287	[a]
10	Dihydroundulatine mesylate (IVb)	1720	286	[a]
11	Buphanidrine (XIII)	1695	288	[a]
12	Dihydrobuphanidrine (XIV)	1820	287	[a]
13	2α-Hydroxypowellane (XLIII)	1720	286	[a]
14	2β-Hydroxypowellane (XLIa)	1730	286	[a]
15	Vinyl methine (XX)	1695	286	[a]
16	Hydroxyethyl Hofmann base (XXII)	1710	286	[a]
17	Dihydrobuphanidrine methine (XXI)	1650	286	[a]
18	Δ^1-Powellene (XLI)	1750	286	[a]
19	Undulatine (III)	1600	288	[a]
20	Isodihydroundulatine (V)	1500	285	[a]
21	Oxoisobuphanamine (XXX)	1320	279	[a]
22	Buphanamine	1480	285	[d], 54b
23	Powelline (X)	17 × 10²	288	13
24	Dihydropowelline	17 × 10²	287	13
25	Oxopowelline	19 × 10²	280	13
26	Dihydrooöxopowelline (XVIII)	17 × 10²	287	13
27	Buphanisine	56 × 10²	295	[d]
28	Montanine	51 × 10²	297	[c]
29	Coccinine	44 × 10²	296	[c]
30	Manthidine	51 × 10²	294	[c]
31	Crinine	52 × 10²	296	[b]
32	Manthine	51 × 10²	294	[c]
33	Crinamine	51 × 10²	297	[b]
34	Haemanthamine	51 × 10²	297	[c]
35	Caranine	48 × 10²	296	[b]
36	α-Dihydrocaranine	4700	291	17b
37	β-Dihydrocaranine	4650	292	17b
38	α-Dihydrocaranine acetate	4770	293	17b
39	α-Dihydrocaranone	4600	289	17b
40	Lycorine 1-acetate	5000	292	[a]
41	Krigeine	1060	287	14
42	Tetrahydroneronine	1320	287	14

[a] Present work. [b] L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, **77**, 1253 (1955). [c] W. C. Wildman and C. J. Kaufman, *ibid.*, **77**, 1248 (1955). [d] J. Renz, D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955).

Stereochemistry.—In undulatine there are five asymmetric centers of which two are the points of attachment of the 1,2-epoxide ring. This must be a *cis*-oxide and, furthermore, it must be on the same side of ring C as the hydroxyl of dihydroundulatine which arises from this oxide on reductive cleavage. Consequently the stereochemical problem was simplified to a consideration of the stereochemistry of dihydroundulatine (IVa) with only four asymmetric centers. In the determination of the stereostructure the only assumption made was that ring C of dihydroundulatine exists in the chair form. This is quite reasonable in the light of previous work[57] and in view of the fact that four

(55) The electronic effect of a positive charge or a highly polar cyano group on nitrogen in derivatives of these bases is apparently transmitted to the aromatic ring since it results in a shift of the ultraviolet maximum to 280–281 mμ and/or a decrease in absorption (ϵ 1220–1500). For this reason salts and N-cyano compounds are not included in the above discussion. It should be noted that removal of the N-cyano group of XXXVa gives a secondary amine with the normal ultaviolet absorption, λ_{max} 286 mμ (ϵ 1.7 × 10³).

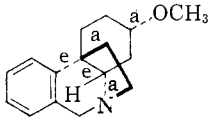
(56) It is interesting that the decrease in extinction coefficient is most marked in oxoisobuphanamine (XXX) whose more rigid C-ring (three adjacent trigonal carbon atoms) imposes the greatest interference of the C_1-substituent with a C_{10}-methoxyl group.

(57) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956), and references cited therein.

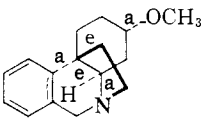
adjacent carbon atoms of the ring are free to assume the most stable conformation.

As a point of departure the C_3-methoxyl was confidently assigned the axial orientation in consideration of the ready epimerization of the methoxyl of oxodihydroundulatine (VI) to the more stable configuration (equatorial) in the presence of base. The C_3- methoxyl of oxodihydroundulatine has the same configuration as in dihydroundulatine since the ketone was reduced back to this same dihydroundulatine.

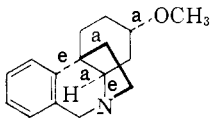
There are four conceivable arrangements (and their mirror images) for the fusion of rings B/C/D of the basic carbon skeleton with an axial C_3-methoxyl group (XXXIIIa, b, c and d). Of these only two could exist. Formula XXXIIIa involves the impossible attachment of the five-membered pyrrolidine ring to ring C through two *trans* diaxial bonds, while structure XXXIIIb has a forbidden fusion of the benzcyclohexane system to ring C through two *trans* diaxial bonds. Thus only XXXIIIc and d had to be considered. The net result is that, whatever the B/C/D fusion, the configuration at C_{4a} remains the same with the nitrogen atom attached to ring C through an equatorial bond. It follows that the direct determination of the manner of fusion of rings B/C/D was not necessary, but instead it was sufficient to find the configuration at C_{10b} relative to that of the other two asymmetric carbon atoms C_2 and C_3.



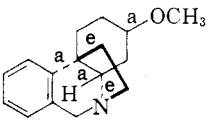
XXXIIIa



b



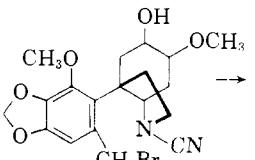
c



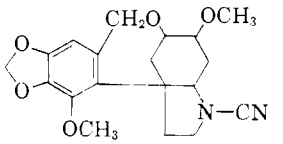
d

Fortunately a way to relate the orientation of the ethano bridge with respect to the C_2-hydroxyl was provided by a reaction useful in the determination of the stereochemistry of dihydrolycorine.[46] Von Braun degradation of dihydroundulatine with cyanogen bromide gave a bromo-N-cyano compound XXXIV, $C_{19}H_{23}N_2O_5Br$, which on treatment with potassium *t*-butoxide at room temperature formed the cyclic N-cyanoether XXXVa, $C_{19}H_{22}N_2O_5$, with loss of the elements of hydrogen bromide. The ether had no hydroxyl infrared absorption, or double bond absorption, and did not give a positive permanganate test for carbon–carbon unsaturation. The formation of an internal cyclic ether is sterically possible only if the C_{10b}-ethano bridge and the C_2-hydroxyl of XXXIV are *cis* with respect to ring C.

The cyanogen bromide adduct was proved not to have the alternative structure XXXVI, which would have resulted from cleavage at the benzylic carbon atom[58] and could have given rise to a seven-membered cyclic ether XXXVII, by degradation to the conjugated lactam with the following sequence of reactions: reductive removal of the N-cyano group of XXXVa by lithium aluminum hydride, methylation of the resulting secondary amine XXXVb by formaldehyde and formic acid, and permanganate oxidation of the N-methyl ether XXXVc. The major product from the oxidation was the slightly basic N-formyl derivative, but 3% of the neutral conjugated lactam XXXVIII was isolated.

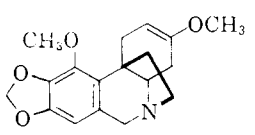


XXXVI

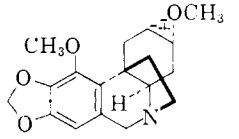


XXXVII

The last objective, the configurational correlation of C_2 with C_3, could be attained by deciding whether the C_2-hydroxyl possessed the axial or equatorial arrangement. The evidence presented so far is ambiguous. In hydride reductions of 1,2-epoxides the axial hydroxyl predominates[60] and this would favor the axial orientation of the hydroxyl in dihydroundulatine. On the other hand, hydride reduction of unhindered cyclohexanones produces mainly the equatorial isomer,[61] and reduction of oxodihydroundulatine (VI) regenerated dihydroundulatine in 80% yield. The fact that elimination of methanesulfonic acid from dihydroundulatine mesylate gave only buphanidrine (XIII) and no detectable amount of the enol ether XXXIX strongly suggests that the mesylate and methoxyl groups of IVb are *trans*, diaxially oriented preventing *trans* elimination of hydrogen and methanesul-



XXXIX



XLII

fonate toward C_3. The formation of the cyclic ether XXXVa does not have any conformational implication for the hydroxyl of IVa. While the C_2–O and C_{10b}–C_{11} bonds of the cyclic ether must be constrained in the axial positions with respect to ring C, this is not necessarily true of dihydroundulatine. Once the D-ring of IVa is broken in the cyanogen bromide reaction and regardless of whether the C_2-hydroxyl is axial or equatorial, ring C is free to assume any conformation neces-

(58) Although in the Von Braun reaction[59] a benzylic position is normally more reactive than a primary or secondary carbon atom, in both of the types of hydrophenanthridines I and II under discussion the secondary carbon of the pyrrolidine ring is apparently attacked exclusively. This is probably a reflection both of (a) the steric strain in the doubly fused five-membered ring which is relieved by the observed cleavage and (b) the greater energy necessary for displacement of the nitrogen from this particular benzylic carbon atom because the two atoms are held in close proximity by rings A and C preventing departure of the nitrogen atom.

(59) H. A. Hagemann, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. 7, 1953, p. 198.

(60) (a) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957); (b) A. Furst and Pl. A. Plattner, Abs. Papers XIIth Int. Cong. Pure Appl. Chem., New York, N. Y., 1951, p. 405. However, as pointed out in (a) there are exceptions (*e.g.*, 5β,6β-epoxycholestane) in which the equatorial isomer is the major product.

(61) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

sary for internal ether formation only provided that the hydroxyl and the ethano bridge are *cis*.[62]

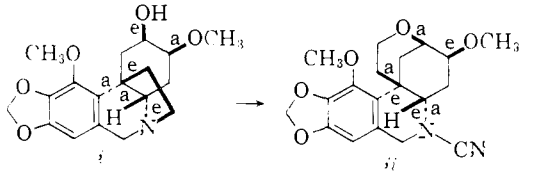
In order to obtain unequivocal evidence for the C_2 configuration, attempts were made to prepare the hydroxyl epimer of dihydroundulatine for direct comparison of the two epimers. Reduction of oxodihydroundulatine (VI) with lithium aluminum hydride, sodium borohydride and hydrogen–platinum was tried in hope that some of the epimeric alcohol would be formed. However, in each case apparently pure dihydroundulatine was isolated as judged from the infrared spectra of the crude products which had the same peaks as dihydroundulatine but slightly less well-defined. Finally the solvolysis of a derivative of dihydroundulatine seemed a possible route to *epi*dihydroundulatine. When the methanesulfonate IVb was refluxed in a mixture of acetic acid and acetic anhydride,[63] the infrared bands characteristic of the sulfonate ester at 8.50 and 11.08 μ[64] gradually disappeared and were replaced by strong carbonyl absorption at 5.76 μ. The crude product was not a mixture of the two epimeric C_2-acetates, but instead was found to be essentially pure dihydroundulatine acetate as judged by comparison of the infrared spectrum of the crude solvolysis product with that of an authentic sample. Deacetylation of the solvolysis product with lithium aluminum hydride gave dihydroundulatine. There were two possible explanations for the observed retention of configuration: (1) normal solvolysis with fission of the alkyl–oxygen bond but with solvent attack solely from the side of departure of the sulfonate anion, or (2) cleavage of the sulfur–oxygen bond only during solvolysis.

In order to eliminate the possibility of sulfur–oxygen cleavage[65] the desmethoxy alcohol, 2β-hydroxypowellane (XLa), m.p. 190.5°, $[\alpha]_D$ −15°, corresponding to dihydroundulatine was prepared by catalytic hydrogenation of 2-oxopowellane (desmethoxy oxodihydroundulatine)(XI). The alcohol was converted to the mesylate XLb which was solvolyzed under the identical conditions used for dihydroundulatine mesylate. It was not only found that the solvolysis was about three times slower than for IVb, but also the product had only a trace of infrared carbonyl absorption. Elimination had occurred and the solvolysis product, $C_{17}H_{19}NO_3$, was evidently Δ^1-powellene (XLI) because it absorbed one mole-equivalent of hydrogen with the formation of powellane (IX), and yet it was not identical with Δ^2-powellene (VIII) from the Wolff–Kishner reduction of *epi*oxodihydroundulatine.[66] Contrary to what was observed, there should have been no noticeable difference in the rate of loss of sulfonate ester from the two mesylates in the event of sulfur–oxygen fission during the solvolysis. Furthermore, the elimination product from solvolysis of the desmethoxy mesylate XLb can only arise from alkyl–oxygen fission. From these considerations the reaction with dihydroundulatine mesylate, which undoubtedly involves the same type of fission as for XLb, must also proceed by alkyl–oxygen cleavage.

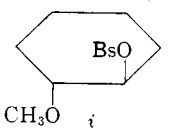
The difference in the nature of the products from the two solvolyses can only be explained by participation of the neighboring methoxyl in the case of IVb.[67] Formation of the intermediate bridged oxonium ion XLII would render elimination a less likely reaction path[68] than *trans* axial attack by solvent to yield a substitution product with over-all retention of configuration. The selective course of the solvolysis is all the more remarkable when it is noted that attack of solvent on the intermediate XLII occured on the side of the molecule strongly hindered by the ethano bridge. In contrast to this, during the solvolysis of 2β-hydroxypowellane mesylate (XLb), the approach of solvent even from the less hindered α-side of the molecule was less favored than loss of a proton from an adjacent carbon atom. Since the product of *trans* axial opening of the oxonium ion was the acetate of dihydroundulatine, the C_2-hydroxyl of this compound must be axial and *trans* with respect to the axial C_3-methoxyl group.

This assignment was confirmed when the optical rotations of the crude reduction products of oxodihydroundulatine mentioned earlier revealed the presence (later calculated to be 13–20%) of a second material. This was isolated by chromatography and proved to be *epi*dihydroundulatine (XVII),[69] m.p. 154°, $[\alpha]_D$ −61.5°, by oxidation back to oxodihydroundulatine with the chromium trioxide–pyridine reagent. The rate of oxidation[70] of dihydroundulatine in chromic acid–acetic acid was 2.8 times faster than that of *epi*dihydroundulatine. It has been amply demonstrated that the axial epimer is consumed at a greater rate than the equatorial epimer by this reagent[57,70] and, there-

(62) Thus i would give ii.



(63) These conditions were used to solvolyze i at 75° by S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, **70**, 821 (1948).



(64) L. J. Bellamy, ref. 35, p. 364.

(65) It has been shown that sulfur–oxygen cleavage does not take place in the solvolysis of i, footnote 63, in acetic acid–acetic anhydride solution.

(66) A possible explanation for the preferential loss of the C_1-hydrogen during solvolysis of XLb, although both C_1 and C_3 have a hydrogen atom axial and *trans* to the leaving group, may be that the removal of the C_1-hydrogen is assisted by the nearby aromatic methoxyl at C_{16}.

(67) This appears to be the first case of neighboring methoxyl participation to result in an increase in the observed rate of solvolysis as compared with the desmethoxy analog. Doubtless this is due to the assisting and leaving groups being held in the most favored *trans* coplanar arrangement for assisted displacement.

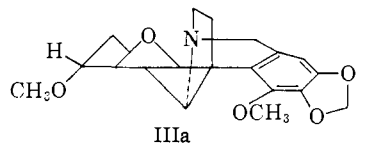
(68) Cleavage of 1,2-bridged oxonium salts, as in acid-catalyzed opening of 1,2-epoxides, generally leads to substitution rather than elimination reaction products.

(69) The infrared spectra of the two epimers, although distinctly different, were such that small amounts of one in the other could not be detected positively by this means.

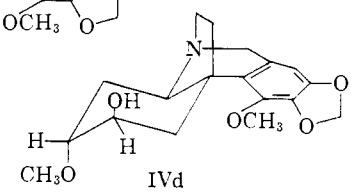
(70) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

fore, the axial configuration of the C_2-hydroxyl of dihydroundulatine was verified. From the above evidence the stereochemistry of dihydroundulatine is fixed as that shown in IVd. Undulatine itself is represented by IIIa. This carbon skeleton has the same stereostructure found for alkaloids of type I by a different approach.[71]

So far no direct evidence for the axial hydroxyl configuration of the hydrogenation product of 2-oxopowellane (XI) has been presented. This was obtained when the sodium amalgam reduction of 2-oxopowellane gave a different isomer, 2α-hydroxypowellane (XLIII), m.p. 200.5°, $[\alpha]_D$ +7°. Metal reductions usually produce predominantly the more stable (in this case equatorial) isomer.[57] This epimer was also the major product (along with some *epi*dihydroundulatine) from sodium amalgam reduction of oxodihydroundulatine in acetic acid solution where the anticipated loss of the adjacent methoxyl group occurred.[72] The assignments of configuration were confirmed by chromic acid oxidation experiments[70] in which the hydrogenation isomer XLa, m.p. 190.5°, was oxidized 4.5 times faster than the sodium amalgam isomer XLIII, m.p. 200.5°.



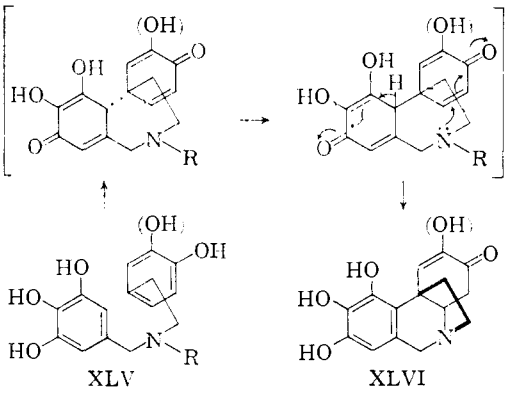
IIIa



IVd

Several reactions described above require comment in the light of the deduced stereochemistry of undulatine. The hydride reduction of oxodihydroundulatine to give mainly the axial hydroxyl is readily explained as a consequence of steric hindrance by C_{11} to attack of hydride on the β-side of the molecule. This is analogous to formation of axial 11β-hydroxysteroids by hydride reduction of 11-ketosteroids where the C_9–β-methyl group prevents approach of hydride from the β-side. The hydrogenation of oxodihydroundulatine and 2-oxopowellane to the axial alcohols is expected if absorption of the molecule on the catalyst is from the less hindered α-side with addition of hydrogen from this side. The lack of reactivity of the epoxide of undulatine toward methoxide is not so readily understood in view of the reactivity of XXIV and XXV toward this reagent. Conceivably the methoxyls at C_3 (axial) and C_{10} of III provide sufficient repulsion to α-approach of methoxide at C_1 (for diaxial opening) to prevent reaction in refluxing methanol.

The biogenesis of undulatine can be readily fitted into the scheme proposed by Barton and Cohen.[31] A precursor such as XLV formed from a 3,4,5-trihydroxyaryl derivative and dihydroxyphenylalanine (or *p*-hydroxyphenylalanine) on oxidative coupling could lead to XLVI from which undulatine would arise on methylation and epoxidation. Although undulatine occurs together with buphanidrine (XIII) which could possibly undergo



XLV XLVI

epoxidation to undulatine in the plant, there is an argument for the presence in a precursor of the oxygen which becomes the epoxide of undulatine. Introduction of the oxygen by epoxidation of the double bond of buphanidrine would be expected to take place from the less hindered side with formation of the α-oxide[73] rather than the β-oxide of undulatine.

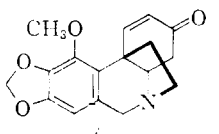
Finally the structural evidence for two of the Hofmann degradation products of dihydrobuphanidrine must be considered. In the case of the methine of m.p. 137.5°, the two infrared peaks at 10.22 and 11.10 μ characteristic of the vinyl group[35] were present. Curiously, the double bond could not be hydrogenated at room temperature and atmospheric pressure in ethanol solution with palladium-on-carbon or in acetic acid solution with platinum. However, the methine discolored permanganate solution whereas dihydrobuphanidrine did not.

The alcohol XXII, m.p. 156°, was not oxidized by manganese dioxide providing evidence that it was not the benzyl alcohol XLVII. Oxidation by the modified Oppenauer procedure gave an aldehyde XLVIII which gave positive Tollens and Fuchsin tests. The infrared carbonyl absorption of XLVIII at 5.92 μ was in better agreement with a conjugated aromatic aldehyde than a nonconjugated aldehyde.[74] Nevertheless, the ultraviolet spectrum, identical with that of the alcohol XXII, revealed that the aldehyde was not conjugated and, hence, must have structure XLVIII. An explanation for the anomaly was suggested by the observation that the perchlorate salt of the aldehyde had no infrared carbonyl absorption whatsoever, but instead had a strong hydroxyl peak. The aldehyde regenerated from the salt

(71) W. C. Wildman and H. M. Fales, THIS JOURNAL, **80**, 6465 (1958).

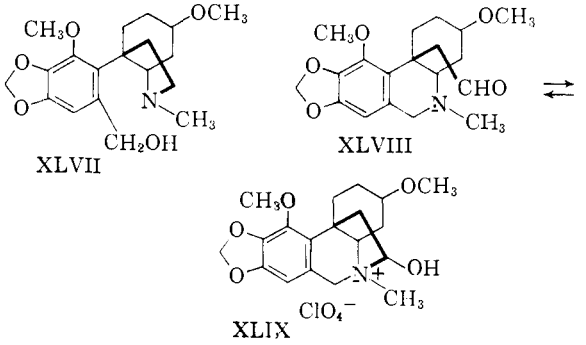
(72) See for example O. E. Edwards, L. Marion and K. H. Palmer, *Can. J. Chem.*, **36**, 1097 (1958).

(73) This has been observed in epoxidation of *i*, W. C. Wildman, unpublished work.



i

(74) L. J. Bellamy, ref. 35, p. 155.



XLVII XLVIII XLIX

had an infrared spectrum identical with the original aldehyde. Apparently the close proximity of the aldehyde carbonyl and the nitrogen permits pronounced interaction of these two functions resulting in a bathochromic shift of the infrared carbonyl peak.[75] In the case of the perchlorate evidently actual addition takes place with formation of a quaternary ammonium salt XLIX.[76]

Acknowledgment.—The authors are grateful to Mr. D. L. Rogerson (NHI) for assistance in the processing of plant material. E. W. W. is indebted to the National Science Foundation for a fellowship and to Professors M.-M. Janot, A. LeHir and Dr. R. Goutarel of the Faculté de Pharmacie de Paris and to Professor G. Büchi of the Massachusetts Institute of Technology for their generous encouragement.

Experimental[78]

Isolation of Alkaolids. (a) From an *Amaryllis Bella-donna* Hybrid (N-28-C) (3/4 *A. bella-donna* L. × 1/4 *Brunsvigea gigantea* Heist).—The bulbs[79] (41.6 kg.) were ground to a pulp and extracted at 60° with two 30-gallon portions of 95% ethanol for 1 hr. each. The first portion of ethanol contained 2 lb. of tartaric acid. The combined extracts were concentrated *in vacuo* to 8.5 l.

The concentrate was divided into four aliquots each of which was processed in the following manner. After dilution with water and acidification with 2 *N* hydrochloric acid, the aliquot was filtered through Super-cel. The filtrate was extracted with 200-ml. portions of chloroform. The chloroform extracts from all four aliquots were combined and concentrated to give 171.8 g. of a glassy brown material (fraction A).

The acidic aqueous solutions from above were combined, basified with solid sodium carbonate and divided into 200-ml. portions each of which was extracted with 15 portions of 4:1 chloroform–ethanol. The raffinates were combined and extracted continuously with chloroform until a negative silicotungstic acid test was obtained. All of the organic extracts were combined, dried and evaporated *in vacuo*. During the concentration a total of 20.2 g. of lycorine precipitated and was removed by filtration. Finally 154.6 g. of a dark brown resinous material (fraction B) was left after removal of solvent.

Fraction A was triturated with ethanol and filtered to give 48.4 g. of crystalline acetylcaranine hydrochloride from which was regenerated 38.8 g. of crystalline acetylcaranine. The ethanol filtrates containing 123 g. were concentrated to *ca.* 150 ml., basified with a solution of 50 g. of sodium hydroxide in 50 ml. of water, and refluxed under nitrogen for two hours.[80] Dilution with water and extraction with three portions of chloroform yielded 53.5 g. of a brown glassy gum after removal of solvent. The gum was triturated with ethyl acetate and filtered to remove 7.95 g. of ambelline. The alkaloids remaining in the ethyl acetate were extracted into 5% hydrochloric acid and then regenerated with sodium hydroxide solution. Chloroform extracted 38.4 g. of clear amber resin which was dissolved in benzene and chromatographed on 1000 g. of grade I alumina.

Eluent	Eluate
Benzene and 2% ethyl acetate in benzene	6.18 g. of belladine
2 to 5% ethyl acetate in benzene	13.5 g. of undulatine
5 to 50% ethyl acetate in benzene	3.28 g. of buphanidrine
Mixtures of ethyl acetate and methanol	Amorphous mixtures of alkaloids not investigated further

A mixture of fraction B, 200 ml. of methanol, 15 ml. of water and 40 g. of potassium hydroxide was refluxed under nitrogen for 2.5 hours, diluted with 1 l. of water and extracted with six portions of chloroform. Evaporation of the solvent left 63.8 g. of dark brown gum. This on reflux with benzene left undissolved 3.7 g. of ambelline. The benzene solution was chromatographed in three portions on grade I alumina (30:1 ratio).

Eluent	Eluate
5% ethyl acetate in benzene	3.0 g. of undulatine
10% ethyl acetate in benzene	12.4 g. of caranine
50% ethyl acetate in benzene and pure ethyl acetate	6.6 g. of ambelline

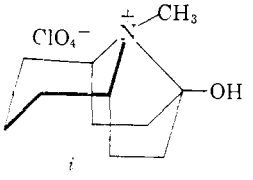
The total yields of alkaloids from the bulbs are given in Table II.

TABLE II

Alkaloid	Wt., g.	Yield from bulb, %
Acetylcaranine[81]	53.1	0.14
Lycorine	20.2	.048
Ambelline	18.2	.044
Undulatine	16.5	.040
Belladine	6.18	.015
Buphanidrine	3.28	.0079
Total	117.4	0.28

(75) For a discussion of transannular analogies see N. J. Leonard, *Rec. Chem. Prog.*, **17**, 243 (1956).

(76) There are several transannular examples of this behavior, *e.g.*, *i*.[77]



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(77) N. J. Leonard, D. F. Morrow and M. T. Rogers, THIS JOURNAL, **79**, 5476 (1957).

(78) All melting points are corrected and were taken on a Kofler microscope hot-stage. Optical rotations were taken in a 1- or 2-dm. tube with an O. C. Rudolph polarimeter on chloroform solutions unless otherwise specified. Analyses were performed by J. F. Alicino, Metuchen, N. J.; Drs. G. Weiler and F. B. Strauss, Oxford, England; and by the Scandinavian Microanalytical Laboratory, Copenhagen, Denmark. Deuterium analyses were by J. Nemeth, University of Illinois, unless otherwise specified. The pK_a determinations were carried out under the direction of Dr. W. Simon, E. T. H., Zürich. Ultraviolet spectra were recorded on a Cary model 11MS spectrophotometer and infrared spectra were recorded with a Perkin-Elmer model 21 or a Baird model B spectrophotometer by C. Monaghan, H. F. Byers, P. Wagner, N. F. Alvord, V. Seeman and Mme. C. Houelle. Molar extinction coefficients for the ultraviolet maxima are given in parentheses after the wave length. Various grades (Brockmann scale) of Merck neutral reagent alumina were used for chromatography. Organic solutions were dried over magnesium sulfate after being washed with saturated sodium chloride solution.

(79) From Oakhurst Gardens, 345 W. Colorado St., Arcadia, California.

(80) Each of the pure alkaloids finally isolated had been shown previously to be stable under these conditions except acetylcaranine which was saponified to caranine.

(81) Caranine is calculated as acetylcaranine since only traces of caranine were found in the unsaponified crude alkaloid mixture.

(b) **From** *Nerine flexuosa alba*.—The bulbs[82] (4.02 kg.) were ground to a pulp and aliquots of this were extracted continuously with methanol for 24 hours in a Soxhlet apparatus. The extracts were concentrated to a thick sirup, acidified with dilute sulfuric acid and washed with ether. The acid solution was basified with concentrated sodium hydroxide solution and extracted with ether and then with ethyl acetate. Evaporation of the solvent left 13.87 g. (0.34% of bulb wt., reported[7b] 0.3%) of a clear light amber resin which was dissolved in benzene and chromatographed on 450 g. of grade II alumina. The crystalline fractions eluted by benzene were combined to give 4.92 g. (0.012% of bulb wt.) of crude undulatine. Fractions eluted with more polar solvents were not investigated further.

From various extractions of various batches of bulbs the total amount of crude undulatine available for experimental work was 26.3 g.

Purification of Undulatine (III).—The crude alkaloid (1.066 g.), m.p. 125–150°, was dissolved in 20 ml. of ether containing a few milliliters of 95% ethanol. An excess of a solution of perchloric acid in ethanol was added dropwise with scratching. The gummy brown precipitate which formed soon crystallized. The mixture was filtered and the tan solid washed with ether–ethanol to give 1.238 g., m.p. 225–228° dec. This was dissolved in 95% ethanol, decolorized with carbon, filtered through Super-cel, and concentrated to yield 1.190 g. (85%) of pure **perchlorate**, m.p. 228.5–230° dec. Two more recrystallizations of a sample gave thin colorless prisms, m.p. 229.5–230.5° dec., $[\alpha]^{23}_{589}$ −22° (*c* 1.06, 95% ethanol); ultraviolet spectrum: λ^{EtOH}_{max} 280 mμ (1230); infrared spectrum: λ^{Nujol}_{max} 6.18 (trioxyaryl), 9.62 and 10.86 μ(methylenedioxy).[83]

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HClO_4$ (431.82): C, 50.06; H, 5.13; N, 3.24. Found: C, 50.03; H, 5.06; N, 3.30.

The pure perchlorate (937 mg.) was partitioned between ether and dilute sodium hydroxide solution. The aqueous layer was washed once with chloroform. Evaporation of the dried organic solutions left 723 mg. (100% recovery from the perchlorate) of undulatine, m.p. 149.5–151.° Recrystallization from ether gave 590 mg. of long colorless needles, m.p. 151–152° (reported[6] 148–149°), $[\alpha]^{25}_{589}$ −31.8° (*c* 0.99), $[\alpha]^{25}_{589}$ −32.3° (*c* 0.65), $[\alpha]^{22}_{589}$ −22° (*c* 0.31, 95% ethanol) (reported,[7b] $[\alpha]^{25}_{D}$ −22° (*c* 0.6, chloroform)). Apparently the alkaloid can exhibit polymorphism because some specimens melted partially at 138–140° followed by resolidification before melting again at the higher temperature; ultraviolet spectrum: λ^{EtOH}_{max} 288 mμ (1600); infrared spectrum: $\lambda^{CHCl_3}_{max}$ 6.18, 9.58 and 10.66 μ.

Anal. Calcd. for $C_{18}H_{21}NO_5$ (331.36): C, 65.24; H, 6.39; N, 4.23; 2 OCH_3, 18.73; 1 (C)CH_3, 4.53; 1 (N) C_2H_5, 8.77; 1 active H, 0.30. Found: C, 65.36; H, 6.41; N, 4.22; OCH_3, 18.49, 18.93; (C)CH_3, none; (N)C_2H_5, 0.00, 5.80, 6.73; active H, none; neut. equiv., 332; mol. wt. (Rast), 291.

A sample of undulatine kindly supplied by Professor H.-G. Boit had m.p. 149–151°. On admixture with material prepared as described above the melting point was undepressed. The infrared spectra of both samples in chloroform solution were identical.

Undulatine did not discolor permanganate in acetone at room temperature. When heated with selenium dioxide in ethanol at 80°, undulatine caused no precipitation of selenium.

From 50 mg. of undulatine in ethanol there was obtained 77 mg. (91%) of picrate, m.p. 224–226° dec. Three recrystallizations from chloroform–ethanol gave matted yellow needles, m.p. 226–227° dec. Samples from later preparations had m.p. 234–235° dec.

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot C_6H_3N_3O_7$ (560.46): C, 51.43; H, 4.32; N, 9.99. Found: C, 51.48; H, 4.43; N, 10.02.

Undulatine Methiodide.—To a solution of 100 mg. of undulatine in 2 ml. of benzene was added 1 ml. of redistilled methyl iodide. After one hour at room temperature 148 mg. (103%) of crude methiodide, m.p. 260–270° dec., $[\alpha]^{24}_{589}$ −19° (*c* 0.649, water–dimethylformamide 1:1) was obtained. Three recrystallizations from 95% ethanol gave colorless matted needles, m.p. 268–270° dec. in an evacuated capillary tube (reported[7a] m.p. 268–270° dec.), $[\alpha]^{24}_{589}$ −23° (*c* 0.73, water–dimethylformamide 1:1); ultraviolet spectrum: λ^{EtOH}_{max} 280 mμ (1280); infrared spectrum: λ^{Nujol}_{max} 6.17, 9.60 and 10.80 μ.

Anal. Calcd. for $C_{19}H_{24}NO_5I$ (473.41): C, 48.21; H, 5.11; N, 2.96. Found: C, 48.08; H, 5.22; N, 3.22.

Attempts to Open the Oxide Ring. Acid.—Undulatine was recovered in 72% yield after reflux with 10% aqueous hydrochloric acid for 1.5 hr.

Base (a) Undulatine was recovered in 98% yield after reflux with 20% ethanolic potassium hydroxide for 1 hour.

(b) Undulatine (150 mg., m.p. 148.5–151°) was refluxed for 24 hr. in a solution of 0.10 g. of sodium metal in 10 ml. of dry methanol. Evaporation of the methanol and partition of the residue between ether and water resulted in the recovery of 147 mg. (98%) of undulatine, m.p. 147.5–151°.

Hydrogenation.—There was no uptake of hydrogen when a solution of 93 mg. of undulatine in 6 ml. of glacial acetic acid was stirred under hydrogen with 100 mg. of platinum oxide at atmospheric pressure. Undulatine was recovered in 88% yield.

Oxidation.—Undulatine was recovered in 77% yield from attempted oxidation with potassium permaganate at 40° in acetone solution. There was no neutral material formed.

In each of the above experiments the infrared spectrum of the recovered material in chloroform was identical with that of undulatine.

Dihydroundulatine (IVa) and Isodihydroundulatine (V).—A solution of 3.037 g. of undulatine, m.p. 149–151°, in 300 ml. of anhydrous ether was refluxed with 1.5 g. of lithium aluminum hydride for 48 hours. The excess hydride was destroyed with water and dilute hydrochloric acid. The clear acid solution (*ca.* 250 ml.) was washed with ether before addition of 25 g. of sodium potassium tartrate crystals. The aqueous solution was then basified with concentrated sodium hydroxide solution and extracted with three portions of chloroform–ethyl acetate. The dried organic solutions were concentrated to incipient crystallization to yield 2.142 g. (70%) of iridescent white flakes of **dihydroundulatine**, m.p. 248.5–249.5° dec. Two recrystallizations from ethyl acetate gave the analytical sample, m.p. 250–251.5° dec., $[\alpha]^{25}_{D}$ −39° (*c* 2.13), $[\alpha]^{25}_{589}$ −37° (*c* 0.56); ultraviolet spectrum: λ^{EtOH}_{max} 287 mμ (1750); infrared spectrum: $\lambda^{CHCl_3}_{max}$ 2.75 (OH), 6.18, 9.57 and 10.67 μ.

Anal. Calcd. for $C_{18}H_{23}NO_5$ (333.37); C, 64.85; H, 6.95; N, 4.20; 2 OCH_3, 18.62; 1 (N)C_2H_5, 8.71. Found: C, 64.81; H, 6.98; N, 4.21; OCH_3, 18.72; (N)C_2H_5, 7.25.

From the mother liquors of the first crop was obtained a second crop of 278 mg., m.p. 238–242° dec., $[\alpha]^{24}_{D}$ −29.5° (*c* 2.10). The filtrates from the second crop were evaporated to dryness to yield 476 mg., $[\alpha]^{26}_{D}$ −16.7° (*c* 2.03). The total recovery of material from the reduction was 2.896 g. (95%). The 278 mg. of the second crop was recrystallized from benzene to give 146 mg. (4.8%) of pure dihydroundulatine, m.p. 248–250° dec.

The 476 mg. from the mother liquors was chromatographed on 15 g. of activity IV alumina. Benzene–ethyl acetate (49:1 to 9:1) eluted 168 mg. (5.5% from starting material), m.p. 170–195°. Three recrystallizations from ether gave short colorless prisms of **isodihydroundulatine**, m.p. 199–200.5°, $[\alpha]^{26}_{D}$ +20.8° (*c* 2.06); ultraviolet spectrum: λ^{EtOH}_{max} 285 mμ (1500); infrared spectrum: 2.74 (OH), 6.18, 9.56 and 10.57 μ.

Anal. Calcd. for $C_{18}H_{23}NO_5$ (333.37): C, 64.85; H, 6.95; N, 4.20. Found: C, 64.61; H, 6.83; N, 4.43.

Further elution of the column with benzene–ethyl acetate (3:1 and 1:1) and with pure ethyl acetate gave 182 mg. which was recrystallized from ethyl acetate–chloroform to yield 104 mg. (3.4%) of dihydroundulatine, m.p. 247–250° dec.

Although the total yield of pure dihydroundulatine isolated was only 78% and that of isodihydroundulatine only 5.5%, it was calculated from the optical rotation of the pure isomers and of various fractions above that the hydride reduction gave about 92% of dihydroundulatine and 8% of isodihydroundulatine.

Dihydroundulatine did not discolor potassium permanganate in acetone–water solution at room temperature nor did it cause precipitation of selenium when heated with an

(82) From C. G. van Tubergen, Zwanenburg Nurseries, Koninginneweg 86, Haarlem, Holland.

(83) These three peaks appear in this region of the infrared spectra of all the compounds prepared and their wave lengths are listed without comment in succeeding spectra.

ethanolic solution of selenium dioxide at 80°. The dihydro compound was recovered from (a) reflux for 1 hour in 10% hydrochloric acid, and (b) reflux for 1.3 hours in 10% ethanolic potassium hydroxide.

Dihydroundulatine Acetate (IVc).—The alcohol IVa (50 mg.) was refluxed with 2 ml. of dry pyridine and 0.5 ml. of acetic anhydride for 1 hour. The reaction mixture was diluted with potassium bicarbonate solution and extracted with chloroform. The crude acetate crystallized on standing in ether. Sublimation at 140° (0.01 mm.) and three recrystallizations from ether–hexane gave colorless prisms, m.p. 134–135.5°; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1830); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.76 (acetate C=O), 6.17, 9.53 and 10.58 μ.

Anal. Calcd. for $C_{20}H_{25}NO_5$ (375.41): C, 63.98; H, 6.71. Found: C, 64.10; H, 6.80.

Oxodihydroundulatine (VI). (a) **Manganese Dioxide Method.**—A solution of 230 mg. of dihydroundulatine in 10 ml. of chloroform was stirred with 1.8 g. of active manganese dioxide[84] for 94 hours. Filtration of the reaction mixture and washing of the dioxide with chloroform gave a colorless solution which on evaporation left 230 mg. of partially crystalline residue. When this was triturated with benzene, 44 mg. of dihydroundulatine, m.p. 234–240° dec., remained undissolved. The benzene solution was chromatographed on 7 g. of activity IV alumina. Benzene and benzene:ethyl acetate (49:1) eluted 76 mg. (33%) of oxodihydroundulatine as a colorless glass. Ethyl acetate eluted 82 mg. of dihydroundulatine, m.p. 235–240° dec. The total recovery of starting material was 126 mg. (55%).

For purification the 76 mg. of ketone was dissolved in a small amount of ethanol and treated with an excess of ethanolic picric acid to give 127 mg. (98%) of picrate, m.p. 234–235° dec., after washing with ethanol and drying. Two recrystallizations from acetone–ethanol gave felted yellow needles, m.p. 234–236.5° dec.

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot C_6H_3N_3O_7$ (560.46): C, 51.43; H, 4.32; N, 9.99. Found: C, 51.52; H, 4.27; N, 9.95.

The base was regenerated in 92–100% yields by percolation of the picrate in chloroform solution through thirty times its weight of alumina. The pure ketone which resisted various attempts at crystallization was evaporatively distilled at 135° (1μ). Samples from two different preparations had $[\alpha]^{24}_{589}$ −15.6° (*c* 1.22) and $[\alpha]^{25}_{589}$ −14.6° (*c* 1.06); ultraviolet spectrum: λ_{max}^{EtOH} 288 mμ (1750); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.80 (ketone C=O), 6.17, 9.56 and 10.65 μ.

Anal. Calcd. for $C_{18}H_{21}NO_5$ (331.36): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.21; H, 6.30; N, 4.20.

To demonstrate that no change had taken place on distillation of the ketone a 24.3-mg. sample which had been used for measurement of the optical rotation was treated with ethanolic picric acid to give 35 mg. (85%) of picrate, m.p. 233.5–235° dec., after washing with ethanol. On admixture with the picrate of oxodihydroundulatine there was no melting point depression.

(b) **Pyridine–Chromium Trioxide Method.**[85]—A solution of 250 mg. of dihydroundulatine in 3.5 ml. of pyridine was added to a mixture of 308 mg. of chromium trioxide in 3 ml. of pyridine. The reaction mixture was allowed to stand undisturbed for 12 hours. Then the gel was diluted with water and chloroform and filtered through Celite. The aqueous solution was extracted with five portions of chloroform. Evaporation of the combined dried organic extracts left 207 mg. (83%) of amber colored glass. The color was removed by dissolution in ether, filtration and evaporation to leave colorless **oxodihydroundulatine** whose chloroform infrared spectrum was identical with the analytical sample prepared above.

Reduction of Oxodihydroundulatine. (a) **Lithium Aluminum Hydride.**—A solution of 106 mg. of pure ketone VI in 20 ml. of anhydrous ether was refluxed for 12 hours with 140 mg. of lithium aluminum hydride. The reaction mixture was worked up as for the reduction of undulatine. Evaporation of the dried organic extracts left 93 mg. (87%) of material which crystallized on trituration with ethyl acetate, $[\alpha]^{27}_D$ −43° (*c* 0.93). The chloroform infrared spectrum was virtually identical with that of dihydroundulatine.

(b) **Sodium Borohydride.**—A solution of 90 mg. of the ketone VI and 250 mg. of sodium borohydride in 10 ml. of methanol was allowed to stand at room temperature for 20 hours. Evaporation of the methanol, dilution with water and extraction with chloroform gave 89 mg. (90%), $[\alpha]^{27}_D$ −41° (*c* 0.85), whose chloroform infrared spectrum was virtually identical with that of dihydroundulatine.

(c) **Hydrogen.**—A solution of 102 mg. of oxodihydroundulatine in 7 ml. of 95% ethanol with 80 mg. of platinum oxide absorbed one mole-equivalent of hydrogen in 10 minutes at atmospheric pressure and room temperature. Removal of catalyst and solvent left 96 mg. (94%) of dihydro compound, $[\alpha]^{28}_D$ −43° (*c* 0.92), whose chloroform infrared spectrum was virtually identical with that of dihydroundulatine.

The products of the above three reductions (266 mg.) were combined and recrystallized from chloroform–ethyl acetate to yield 125 mg. (47%) of **dihydroundulatine**, m.p. 249–251° dec. Evaporation of the mother liquors left 129 mg. which was chromatographed on 4.5 g. of grade IV alumina. Benzene and benzene–ethyl acetate (99:1 and 49:1) eluted 70 mg. of colorless material which crystallized on trituration with methanol. Recrystallization from methanol gave 42.5 mg. (14%) of solvated crystals, m.p. 87–102° before drying and m.p. 150–151.5° after drying at 90° (0.1 mm.). Two further recrystallizations from ethyl acetate gave colorless rhombs of *epi***dihydroundulatine**, m.p. 153–154°, $[\alpha]^{26}_D$ −61.5° (*c* 0.83); ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1760); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 2.76 (OH), 6.18, 9.56 and 10.62 μ.

Anal. Calcd. for $C_{18}H_{23}NO_5$ (333.37): C, 64.85; H, 6.95; 2 OCH_3, 18.62. Found: C, 64.69; H, 6.76; OCH_3, 18.57.

Calculations based on the optical rotations of the crude reduction products show that the amount of *epi*dihydroundulatine formed was about 20% in reductions (a) and (c) and about 13% in reduction (b).

Epimerization of Oxodihydroundulatine (VI).—The ketone VI, 67 mg., $[\alpha]^{25}_{589}$ −14.6° (*c* 1.06), regenerated from the pure picrate was dissolved in 3 ml. of methanol. After the addition of two drops of 10% aqueous potassium hydroxide the solution was concentrated to 1.5 ml. by boiling for 5 minutes. On cooling, 42 mg. (62%) of *epi***oxodihydroundulatine** separated, m.p. 220–223.5° dec., $[\alpha]^{25}_{589}$ −51° (*c* 0.95). The mixture melting point with the *epi*oxoketone prepared by the Oppenauer oxidation (see below) was undepressed. The infrared spectra of the two specimens were identical.

epi-**Oxodihydroundulatine** (VII).—Potassium *t*-butoxide was prepared from 0.45 g. of potassium and 20 ml. of dry *t*-butyl alcohol. The excess alcohol was removed by distillation and the residue was heated at 120° (5 mm.) for 15 minutes. To the butoxide was added 700 mg. (2.10 mmoles) of dihydroundulatine, 2.00 g. (11.1 mmoles) of fluorenone, 50 ml. of dry benzene and a magnetic stirring bar. The reaction mixture was stirred under nitrogen for 1.3 hours at room temperature. Water was added, the layers separated and the basic aqueous solution was washed with two portions of ethyl acetate. The combined organic layers were washed with three portions of 5% hydrochloric acid. After two washings with ether the combined acid solutions were basified with concentrated sodium hydroxide solution and extracted with three portions of ethyl acetate. The dried organic solutions were evaporated to give 698 mg. (100%) of a partially crystalline residue, $[\alpha]^{24}_{589}$ −26° (*c* 0.54). The crude mixture was crystallized from methanol containing a few drops of 10% potassium hydroxide solution. A first crop of 466 mg., m.p. 218–221° dec., and a second crop of 57 mg., m.p. 218–221° dec., brought the total yield of *epi*-oxodihydroundulatine to 75%. A sample for analysis was recrystallized thrice from methanol to afford colorless prisms, m.p. 219–223° dec., $[\alpha]^{22}_{589}$ −50° (*c* 0.78); ultraviolet spectrum: λ_{max}^{EtOH} 288 mμ (1780); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.78 (ketone C=O), 6.17, 9.57 and 10.66 μ.

Anal. Calcd. for $C_{18}H_{21}NO_5$ (331.36): C, 65.24; H, 6.39; N, 4.23; 2 OCH_3, 18.73. Found: C, 65.39; H, 6.23; N, 4.34; OCH_3, 18.86.

The picrate was prepared in ethanol solution and was recrystallized from ethanol as matted yellow needles, m.p. 137–140°.

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot C_6H_3N_3O_7$ (560.46): C, 51.43; H, 4.32; N, 9.99. Found: C, 51.49; H, 4.49; N, 10.11.

(84) Prepared according to the procedure of J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

(85) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 427 (1953).

The 2,4-dinitrophenylhydrazone was prepared by heating 35 mg. (0.10 mmole) of ketone with 25 mg. (0.12 mmole) of 2,4-dinitrophenylhydrazine in 2 ml. of glacial acetic acid on the steam-bath for one hour. The solution was diluted with water and the acid neutralized with 10% potassium carbonate solution. The dark orange gum which precipitated crystallized on standing. It was filtered, washed with water and dried to give 50 mg. (92%). Three recrystallizations from chloroform–ethanol yielded flat orange blades, m.p. 234.5–235° dec. The derivative had to be dried at 140° (0.05 mm.) to remove chloroform of solvation; ultraviolet spectrum: $\lambda_{max}^{CHCl_3}$ 370 mμ (21,800); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 3.05 (NH), 6.16, 9.57 and 10.66 μ.

Anal. Calcd. for $C_{24}H_{25}N_5O_8$ (511.48): C, 56.35; H, 4.93. Found: C, 56.47; H, 4.88.

From the crude product of another such oxidation of 1.00 g. of dihydroundulatine there was separated by recrystallization and chromatography 59% of pure *epi*oxoketone and 7% of pure oxodihydroundulatine.

Reactions of *epi*Oxodihydroundulatine. (a).—To a solution of 160 mg. of potassium in 5 ml. of dry *t*-butyl alcohol was added 100 mg. of ketone VII, m.p. 218–221° dec. The mixture was refluxed under nitrogen for 30 minutes and then evaporated to dryness. The addition of water followed by extraction with ethyl acetate gave 83 mg. (83% recovery) of ketone whose infrared spectrum was identical with starting material. Recrystallization from methanol gave 35 mg. of VII, m.p. 204–210° dec.

(b).—When 90 mg. of the *epi*-ketone VII was refluxed under nitrogen with a solution of 128 mg. of sodium in 5 ml. of absolute ethanol, the solution became yellow. Workup gave 78 mg. of an amber glass whose infrared spectrum was almost the same as that of the starting material except for a decrease in the intensity of the carbonyl peak at 5.78 μ and the appearance of a hydroxyl peak at 2.80 μ.

(c).—*epi*-Oxodihydroundulatine could not be induced to condense with (a) benzaldehyde in refluxing ethanol in the presence of piperidine,[86] (b) ethyl formate in refluxing benzene in the presence of sodium methoxide[87] or (c) benzaldehyde in refluxing *t*-butyl alcohol in the presence of potassium hydroxide.

Desmethoxy Oxodihydroundulatine (2-Oxopowellane) (XI).—A mixture of 770 mg. (2.33 mmoles) of *epi*oxo ketone VII, 12 g. of activated[88] 30-mesh zinc and 15 ml. of glacial acetic acid was refluxed for 90 hours. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in dilute hydrochloric acid. The acid solution was washed once with ether, basified with concentrated sodium hydroxide solution and extracted with five portions of chloroform. The dried organic solutions were evaporated leaving 672 mg. of a colorless amorphous material. A sample was distilled at 165° (2μ) for methoxyl analysis.

Anal. Calcd. for $C_{18}H_{21}NO_5$ (331.36): 2 OCH_3, 18.73. Found: OCH_3, 14.59.

Chromatography on alumina did not separate the products completely. The fractions (437 mg.) containing the ketonic material were dissolved in ethanol and converted to the picrate, 477 mg. (38% from starting material), m.p. 204–212° dec. Three recrystallizations of a sample from chloroform–ethanol gave feathery yellow needles of the **picrate of 2-oxopowellane**, m.p. 217–218.5° dec.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot C_6H_3N_3O_7$ (530.43): C, 52.07; H, 4.18; N, 10.56. Found: C, 52.20; H, 4.15; N, 10.13.

A sample of pure picrate (315 mg.) was dissolved in chloroform and passed through a column of 15 g. of activity I alumina. Elution with chloroform gave 172 mg. (96% recovery) of colorless glass which crystallized on trituration with methanol. Three recrystallizations from ether yielded long colorless prisms of **2-oxopowellane**, m.p. 206.5–209° dec., $[\alpha]^{23}_{589}$ +9.8° (*c* 0.66). On admixture with *epi*oxodihydroundulatine the melting point was depressed to 180–195° dec. The pure ketone was sublimed at 140° (1 μ) for analysis; ultraviolet spectrum: λ_{max}^{EtOH} 287 mμ (1710); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.84 (6-ring C=O), 6.17, 9.60 and 10.70 μ.

Anal. Calcd. for $C_{17}H_{19}NO_4$ (301.33): C, 67.76; H, 6.36; N, 4.65; 1 OCH_3, 10.29. Found: C, 67.88; H, 6.35; N, 4.81; OCH_3, 10.91.

The perchlorate was prepared by addition of one drop of ethanolic perchloric acid to an ethereal solution of 5 mg. of the ketone. The solid was recrystallized twice from ethanol–ether to constant m.p. 216–218° dec. There was not enough for analysis.

Benzylidene 2-Oxopowellane (i, Ref. 30).—A solution of 50 mg. of desmethoxy ketone XI in 3 ml. of dry *t*-butyl alcohol was refluxed under nitrogen with 145 mg. of freshly distilled benzaldehyde and 138 mg. of potassium hydroxide for 17 hours. The excess benzaldehyde and alcohol were removed by steam distillation. The residue, 63 mg., λ_{max}^{EtOH} 290 mμ (10,000), was chromatographed on 3 g. of alumina. Benzene–ethyl acetate eluted 36 mg. (55%) of a colorless glass which decomposed on attempted distillation at 150° (1 μ); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.98 (conjugated C=O), 9.63 and 10.68 μ.

***epi*-Oxodihydroundulatine Methochloride.**—A solution of 204 mg. of the ketone VII in 6 ml. of benzene was treated at room temperature with 1 ml. of redistilled methyl iodide. The white precipitate was centrifuged, washed twice with benzene by decantation and dried to leave 294 mg. of methiodide. An aqueous slurry of this was stirred with silver chloride prepared from 275 mg. of silver nitrate and dilute hydrochloric acid. After 15 minutes the silver halides were removed by filtration and the filtrate was concentrated to dryness to leave 239 mg. (100%) of methochloride which crystallized when triturated with boiling benzene containing a little ethanol, m.p. 240–250° dec. Two recrystallizations from ethanol–benzene gave hygroscopic colorless needles which decomposed at 245°, $[\alpha]^{24}_{589}$ +11° (*c* 0.68 ethanol); ultraviolet spectrum: λ_{max}^{EtOH} 280 mμ (1220); infrared spectrum λ_{max}^{Nujol} 5.80 (ketone C=O), 6.17, 9.60 and 10.83 μ.

Anal. Calcd. for $C_{19}H_{24}NO_5Cl$ (381.81): C, 59.76; H, 6.33; N, 3.67. Found: C, 59.53; H, 6.41; N, 3.49.

A solution of 403 mg. of the above methochloride in 11 ml. of glacial acetic acid was refluxed with 6.0 g. of activated[88] 30-mesh zinc for 40 minutes. The reaction mixture was filtered and the zinc washed twice with hot acetic acid. The filtrates were evaporated to dryness, dissolved in water and basified with concentrated ammonium hydroxide. Extraction with ether–chloroform gave only 7 mg. of oily material. The aqueous solution was acidified with hydrochloric acid and evaporated at reduced pressure to recover the methochloride. When the recovered material was stirred and refluxed with 1.6 g. of zinc dust in 10 ml. of acetic anhydride for 1 hour, there was no basic product formed either.

Δ^2-Powellene (VIII).—A mixture of 12 ml. of diethylene glycol, 1.85 g. of potassium hydroxide, 4 ml. of anhydrous hydrazine (98$^+$%) and 550 mg. (1.66 mmoles) of *epi*-oxodihydroundulatine, m.p. 213–220° dec., was refluxed under nitrogen for two hours (oil-bath 155°). The solution was cooled, diluted with water and extracted with ether. The ethereal solutions were dried and evaporated to leave 168 mg. (0.59 mmole, 35%) of a colorless glass whose infrared spectrum had no trace of carbonyl absorption. The product was chromatographed on activity IV alumina. Benzene eluted 112 mg. which was dissolved in ethanol and converted to the picrate, 128 mg., m.p. 155–162°. Several recrystallizations from chloroform–ethanol gave yellow prisms of **Δ^2-powellene picrate**, m.p. 168–170°.

Anal. Calcd. for $C_{17}H_{19}NO_3 \cdot C_6H_3N_3O_7$ (514.44): C, 53.69; H, 4.31; N, 10.89; 1 OCH_3, 6.03. Found: C, 53.81; H, 4.60; N, 10.65; OCH_3, 6.57.

Twice recrystallized picrate, 94 mg., m.p. 161–165°, was dissolved in chloroform and passed through a column of 4 g. of activity I alumina. Elution with chloroform gave 50 mg. of colorless Δ^2-powellene as a glass which partially crystallized, m.p. 104°. A sample was evaporatively distilled at 150° (10 μ) for analysis; ultraviolet spectrum: λ_{max}^{EtOH} 288 mμ (1790); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.17, 9.61 and 10.69 μ.

Anal. Calcd. for $C_{17}H_{19}NO_3$ (285.33): C, 71.56; H, 6.71; 1 OCH_3, 10.87. Found: C, 71.64; H, 6.64; OCH_3, 11.95.

(+)-Powellane (IX).—A solution of 54 mg. of Δ^2-powellene in 6 ml. of 99% ethanol was stirred under hydrogen with 80 mg. of 10% palladium-on-carbon (Baker) at room tempera-

(86) These conditions were sufficient to convert dihydroöxocrinine into a dibenzylidene derivative.[18]

(87) α-Dihydrocaranone readily formed a hydroxymethylene derivative under these conditions.[17b]

(88) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, THIS JOURNAL, **75**, 3504 (1953), footnote 22.

ture and atmospheric pressure. In 15 minutes 4.8 ml. (94% of 1 mole-equivalent) of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was treated with ethanolic picric acid to yield 73 mg. (74%), m.p. 206–210°. Three recrystallizations from acetone–ethanol gave yellow prisms of (+)-**powellane picrate**, m.p. 214–215.5°, $[\alpha]^{24}_{589}$ +29.5° (*c* 0.915). The mixture melting point with a sample of (+)-powellane picrate, m.p. 213–215°, $[\alpha]^{24}_{589}$ +28.2°, prepared from powelline[13] was 213–215.5°.

Anal. Calcd. for $C_{17}H_{21}NO_3 \cdot C_6H_3N_3O_7$ (516.45): C, 53.49; H, 4.68; N, 10.85. Found: C, 53.64; H, 4.62; N, 10.86.

(+)-Powellane regenerated from 9 mg. of the pure picrate by percolation of its chloroform solution through 2 g. of activity I alumina was crystallized from ether, m.p. 113–114.5°. There was no depression of melting point on admixture with authentic powellane,[13] m.p. 113.5–115°. The chloroform infrared spectra of the two samples were identical; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1670); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.18, 9.58 and 10.68 μ.

O-Deuterio-*t*-butyl Alcohol.—Potassium *t*-butoxide was sublimed in *ca.* 5-g. batches at 200° (10 μ) and the sublimation tubes sealed *in vacuo*. The contents of six sealed tubes were transferred to a tared, stoppered flask and weighed, 25.6 g. (0.228 mole). Then 4.8 ml. (0.24 mole) of deuterium oxide (99.7%)[89] was added and the lumps of *t*-butoxide were crushed with a stirring rod. After 45 minutes the sludge was distilled to dryness (metal-bath, air-cooled condenser). The distillate, 15.5 g. (92%), was then distilled from 0.5 g. of potassium to remove any remaining deuterium oxide. The product was 92.5% O–D by infrared analysis[90]; infrared spectrum: λ_{max}^{liq} 4.12 μ (O–D).

Deuterium Exchanges.—(a) Undulatine, 50 mg., m.p. 151–152°, was refluxed under nitrogen in 2 ml. of O-deuterio-*t*-butyl alcohol with 150 mg. of freshly sublimed potassium *t*-butoxide for 45 minutes. The alcohol was evaporated at reduced pressure and the *t*-butoxide destroyed with 1 ml. of deuterium oxide. The organic material was extracted with benzene and recrystallized from ether to give 38 mg., m.p. 150–151°, whose infrared spectrum was identical with starting material and had no indication of C–D absorption.

Anal. Calcd. for $C_{18}H_{20}DNO_5$ (332.36): D, 4.76 atom %. Found: D, 0.00 atom %.

(b) A solution of 110 mg. of *epi*oxodihydroundulatine, m.p. 212–217° dec., in 2.5 ml. of O-deuterio-*t*-butyl alcohol (92.5% O–D) was refluxed under nitrogen with 100 mg. of freshly sublimed potassium *t*-butoxide for 30 minutes. The alcohol was evaporated under reduced pressure and 2 ml. more of the O-deuterio alcohol was added. After a 30-minute reflux the alcohol was again evaporated. To the residue was added 1.5 ml. of deuterium oxide. Several extractions with benzene yielded 70 mg. which was recrystallized from benzene to yield 31 mg., m.p. 215–219° dec.; infrared spectrum: λ_{max}^{KBr} 4.80 μ (C–D) (conc., 5.5% in KBr).

Anal. Calcd. for $C_{18}H_{18}D_3NO_5$ (334.38): D, 14.28 atom %. Found: D, 14.07 atom %.[90,91]

A 10-mg. sample of the deuterated ketone was refluxed for 4 minutes in 0.5 ml. of methanol containing several drops of 2% aqueous potassium hydroxide and then crystallized. The treatment was repeated and followed by a crystallization from methanol. The infrared spectrum of the 4.0 mg., m.p. 211–219° dec., thus obtained had no C–D stretching absorption in a 5% potassium bromide pellet.

Dihydroundulatine Methanesulfonate (IVb).—A solution of 911 mg. (7.99 mmoles) of methanesulfonyl chloride in 4 ml. of pyridine freshly distilled from barium oxide was added to a chilled slurry of 825 mg. (2.48 mmoles) of dihydroundulatine, m.p. 249–251° dec., in 4 ml. of the dry pyridine. The reaction mixture was then allowed to stand at room temperature for 48 hours. The brown solution was poured into a mixture of ice and concentrated ammonium hydroxide and extracted with four portions of chloroform. Evaporation of the dried chloroform extracts left 1.044 g. of a brown amorphous foam which was chromatographed on 30 g. of grade IV alumina. Benzene and benzene–ethyl acetate mixtures eluted 1.006 g. of almost colorless material which did not crystallize. This was dissolved in ethanol and converted to the **picrate**, 1.383 g. (87% from dihydroundulatine), m.p. 205.5–211°. Recrystallization from chloroform–ethanol gave 1.351 g. of yellow needles, m.p. 209.5–211°. A polymorphic form, m.p. 145–147°, was also encountered.

Anal. Calcd. for $C_{19}H_{25}NO_7S \cdot C_6H_3N_3O_7$ (640.57): C, 46.87; H, 4.40; S, 5.00. Found: C, 47.17; H, 4.49; S, 4.58.

The mesylate IVb was regenerated by passage of a chloroform solution of 1.236 g. of the picrate, m.p. 208.5–211°, through a column of 30 g. of activity I alumina. Elution with chloroform gave 753 mg. (95% recovery) of a colorless amorphous solid. Since this could not be evaporatively distilled at 1 μ without decomposition, a sample was dried at 80° (0.1 mm.) for 30 hours, $[\alpha]^{26}D$ −25.8° (*c* 2.56); ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1720); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.18, 8.50 and 11.08 (sulfonate ester), 9.55 and 10.70 μ.

Anal. Calcd. for $C_{19}H_{25}NO_7S$ (411.46): C, 55.46; H, 6.12. Found: C, 55.13; H, 6.21.

Buphanidrine (XIII).—Potassium (263 mg., 5.75 mg. atoms) was dissolved in 10 ml. of *t*-amyl alcohol distilled from lithium aluminum hydride. A solution of 242 mg. of mesylate IVb (0.59 mmole) in 10 ml. of the dry *t*-amyl alcohol was added to the base and the colorless solution was refluxed (oil-bath 140°) for 26 hours. The alcohol was removed at reduced pressure and the residue was partitioned between ether and water. The aqueous solution was extracted with three additional portions of ether. The dried ethereal solutions were distilled to leave 176 mg. (95%) of colorless oil whose chloroform infrared spectrum was identical in every respect with that of buphanidrine. The crude product was chromatographed on 5 g. of activity IV alumina. The first benzene eluates, 139 mg., were recrystallized thrice from ether–hexane to give 65 mg. of colorless prisms, m.p. 90.5–92°, $[\alpha]^{26}D$ −2.4° (*c* 2.39) (reported[13] $[\alpha]^{23}_{589}$ −6.9° (*c* 1.01)). The mixture melting point with authentic buphanidrine,[93] m.p. 91–92.5°, was 90–91.5°. A solution of buphanidrine in acetone turned permanganate solution brown immediately; ultraviolet spectrum: λ_{max}^{EtOH} 288 mμ (1695).

Anal. Calcd. for $C_{18}H_{21}NO_4$ (315.36): C, 68.55; H, 6.71. Found: C, 68.66; H, 6.90.

When the mesylate IVb was heated with γ-collidine in toluene[92] at 130–135° for 14 hours, 96% of the starting material was recovered. When the mesylate was refluxed with potassium *t*-butoxide in *t*-butyl alcohol for 48 hours, the buphanidrine isolated in almost quantitative yield still contained about 5% of IVb.

Dihydrobuphanidrine (XIV).—Buphanidrine[93] (5.116 g., 16.2 mmoles) was dissolved in 35 ml. of 95% ethanol and hydrogenated at atmospheric pressure in the presence of 500 mg. of 10% palladium-on-carbon (Baker) catalyst. In 5 hours 97% of one mole-equivalent of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was evaporated to leave 5.011 g. (97%) of dihydrobuphanidrine as a colorless glass. Part of this, 2.989 g., was converted to the picrate, 4.978 g. (97%), m.p. 274–276° dec. Recrystallization from chloroform–acetone gave two crops totaling 4.832 g. (97% recovery) of flat golden plates, m.p. 281–283° dec. (reported[13] 281–283° dec.). The free base was regenerated by passage of a chloroform solution through 200 g. of activity I alumina. Elution with 600 ml. of chloroform gave 2.731 g. (100% recovery) of colorless, amorphous dihydrobuphanidrine. A sample was evaporatively distilled at 120° (1 μ), $[\alpha]^{18.5}D$ −7.0° (*c* 3.30); ultraviolet spectrum: λ_{max}^{EtOH} 287 mμ (1820); infrared spectrum: $\lambda_{max}^{CCl_4}$ 6.18, 9.53 and 10.60 μ. The dihydro compound in acetone did not discolor permanganate solution at room temperature.

Anal. Calcd. for $C_{18}H_{23}NO_4$ (317.37): C, 68.12; H, 7.31. Found: C, 68.00; H, 7.43.

Dihydrobuphanidrine Methiodide (XVa).—A solution of 2.335 g. of pure dihydrobuphanidrine in 30 ml. of benzene was added slowly to 2.65 g. of redistilled methyl iodide in

(89) Obtained through the courtesy of Professor M.-M. Janot and the Commissariat d'Energie Atomique de France.

(90) The authors would like to thank Miss A. W. P. Jarvie, Dept. of Chemistry, The University, Glasgow, for her kindness in performing the deuterium analysis.

(91) This figure is corrected for the 92.5% purity of the O-deuterio-*t*-butyl alcohol.

(92) *Cf.* K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952).

(93) The authors would like to thank Drs. J. Renz, E. Seebeck and D. Stauffacher of the Sandoz Co., Basel, for a generous gift of buphanidrine perchlorate.

10 ml. of benzene. After several hours at room temperature the white precipitate was filtered, washed with benzene and dried to yield 3.330 g. (98%), m.p. 277–280° dec. Recrystallization from 95% ethanol gave 3.135 g. of large colorless flat plates, m.p. 289–290.5° dec., $[\alpha]^{18.5}D$ −16° (*c* 1.64, water–ethanol 1:1). Further recrystallization did not raise the melting point; ultraviolet spectrum: λ_{max}^{EtOH} 281 mμ (1360); infrared spectrum: λ_{max}^{Nujol} 6.17, 9.71 and 10.80 μ.

Anal. Calcd. for $C_{19}H_{26}NO_4I$ (459.32): C, 49.68; H, 5.70. Found: C, 49.54; H, 5.67.

Hofmann Degradation of Dihydrobuphanidrine Methiodide.—A slurry of 6.210 g. (13.5 mmoles) of the methiodide in 40 ml. of distilled water was stirred by means of a magnetic stirring bar with the neutral silver oxide freshly prepared from 2.965 g. (17.4 mmoles) of silver nitrate until a test portion of the solution gave no precipitate with silver nitrate–nitric acid solution. The insoluble silver salts were removed by filtration through Super-cel. The clear yellow filtrate was evaporated to dryness at reduced pressure. Then the flask containing the residual sirup was immersed in an oil-bath at 135–155° for 1 hour. At the same time a vacuum of *ca.* 70 mm. was applied to the flask. At the end of the heating period the brown resin was triturated with benzene and filtered. Evaporation of the benzene filtrate left 4.227 g. (96% crude yield) of a clear amber resin which was dissolved in benzene–hexane (1:1) and chromatographed on 120 g. of activity I alumina.

Product	Eluent	Wt., mg.	Yield, %
Vinylmethine XX	Benzene	310	7
Dihydrobuphanidrine (XIV) and XXI	Benzene–ethyl acetate (99:1 to 19:1)	759	17
Hydroxyethylamine XXII	Benzene–ethyl acetate (9:1 to 1:1)	1223	26

The 310 mg. of crystalline **vinylmethine XX** was recrystallized four times from methanol to give colorless plates, m.p. 135–137.5°, $[\alpha]^{25}D$ −100° (*c* 1.25), which contained one molecule of methanol of solvation even after being dried at 75° (0.03 mm.) for 2 hours. Sublimation at 140° (1 μ) gave unsolvated crystals whose infrared spectrum no longer had hydroxyl absorption. An acetone solution of the vinylmethine turned permanganate solution brown immediately; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1695); infrared spectrum: λ_{max}^{Nujol} 2.90 (OH), 3.60 (NCH_3), 6.18, 9.66 and 10.73, 10.21 and 11.10 μ (CH=CH_2).

Anal. Calcd. for $C_{19}H_{25}NO_4 \cdot CH_3OH$ (363.44): C, 66.09; H, 8.04; 3 OCH_3, 25.62; 1 (N)CH_3, 4.13. Found: C, 66.00; H, 8.21; OCH_3, 26.85; (N)CH_3, 4.33.

The hydroxyethyl derivative XXII was recrystallized four times from methanol–water to afford long colorless prisms, m.p. 154–155.5°, $[\alpha]^{25}D$ −64.5° (*c* 2.25), $[\alpha]^{25}D$ −66.8° (*c* 1.84); ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1720); infrared spectrum: λ_{max}^{Nujol} 3.0–3.2 (H bonded OH), 3.61 (NCH_3), 6.16, 9.69 and 10.82 μ.

Anal. Calcd. for $C_{19}H_{27}NO_5$ (349.41): C, 65.31; H, 7.79; N, 4.01; 2 OCH_3, 17.76; 1 (N)CH_3, 4.31. Found: C, 65.52; H, 7.76; N, 4.2; OCH_3, 18.19; (N)CH_3, 4.47.

The perchlorate of XXII was prepared and recrystallized twice from 95% ethanol to give thin needles which decomposed turning black above 300°.

Anal. Calcd. for $C_{19}H_{27}NO_5 \cdot HClO_4$ (449.87): C, 50.72; H, 6.27. Found: C, 50.32; H, 6.15.

The 759 mg. of middle fractions containing the methine XXI from the above chromatogram was rechromatographed on 21 g. of activity I alumina. The change in composition of the eluate was followed by taking the optical rotation of each fraction. Benzene and benzene–ethyl acetate (99:1) eluted 90 mg. (2%) of pure **methine XXI** as a colorless glass, $[\alpha]^{27}D$ +12° (*c* 1.00); ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1650); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.16, 9.54 and 10.70 μ.

Anal. Calcd. for $C_{19}H_{25}NO_4$ (331.40); C, 68.86; H, 7.60. Found: C, 68.87; H, 7.55.

An additional 88 mg. of less pure material was obtained from earlier fractions to bring the total yield to 4%.

Benzene–ethyl acetate (19:1 and 9:1) eluted 209 mg. (4.9%) of impure **dihydrobuphanidrine (XIV)** which was converted directly into the methiodide with methyl iodide in benzene solution to yield 232 mg., m.p. 265–270° dec. Three recrystallizations from 95% ethanol gave white plates, m.p. 284–287° dec., whose infrared spectrum was identical with that of dihydrobuphanidrine methiodide and whose melting point was undepressed on admixture with authentic methiodide, m.p. 289–290.5° dec.

Dihydrobuphanidrine Dihydromethine (XXIII).—A solution of 82 mg. (0.24 mmole) of XXI in 5.5 ml. of 95% ethanol slowly absorbed 6.6 ml. (98% of 1 mole-equivalent) of hydrogen in the presence of 60 mg. of 10% palladium-on-carbon catalyst (Baker) during 10 hours. Removal of the catalyst and evaporation of the solvent left 74 mg. of a colorless oil that did not crystallize. This was dissolved in benzene–methyl iodide and converted to the methiodide, 95 mg. (90%), m.p. 185–215° dec. Three recrystallizations from absolute ethanol gave colorless prisms, m.p. 236.5–238.5° dec., $[\alpha]^{27}D$ 0° (*c* 1.62, water-ethanol 1:1), $[\alpha]^{25}_{350-589}$ 0° (*c* 0.18 water–ethanol 1:1); ultraviolet spectrum: λ_{max}^{EtOH} 281 mμ (1430); infrared spectrum: λ_{max}^{KBr} 6.18, 9.59 and 10.81 μ.

Anal. Calcd. for $C_{20}H_{30}NO_4I$ (475.37): C, 50.53; H, 6.36; 2 OCH_3, 13.05; 2 (N)CH_3, 6.32. Found: C, 50.64; H, 6.39; OCH_3, 12.86; (N)CH_3, 5.88.

Dihydroundulatine-1-*d*.—A solution of 1.020 g. of thoroughly dried undulatine, m.p. 150.5–151°, in 50 ml. of sodium-dried ether was refluxed with 0.50 g. of lithium aluminum deuteride for 15.5 hours. The excess reducing agent was destroyed with water and dilute hydrochloric acid. The reaction mixture was then worked up as for the preparation of dihydroundulatine. The product, 949 mg. (94%), was recrystallized from chloroform–ethyl acetate to give 680 mg., m.p. 243–246° dec. A small sample of the dihydro derivative was recrystallized a second time for deuterium analysis, m.p. 248–250° dec.; infrared spectrum: λ_{max}^{Nujol} 4.61 μ; $\lambda_{max}^{KBr\ 6\%}$ 4.63 μ (CD).

Anal. Calcd. for $C_{18}H_{22}DNO_5$ (334.37): D, 4.35 atom %. Found: D, 3.76 atom %.

A sample of the deuterated dihydro compound (43 mg.) was dissolved in 2 ml. of methanol containing 3 drops of 10% aqueous sodium hydroxide solution. The solution was slowly concentrated over a 5-minute period and then allowed to crystallize. This treatment was repeated and the product finally crystallized from methanol to give 23 mg., m.p. 250–251.5° dec., which still contained deuterium; infrared spectrum: $\lambda_{max}^{KBr\ 6\%}$ 4.63 μ (CD).

Oxidation of Dihydroundulatine-1-*d*.—A solution of 753 mg. of deuterio IVa in 20 ml. of chloroform was stirred with 6.0 g. of active manganese dioxide[84] for 92 hours. The mixture was filtered and the colorless filtrate evaporated to dryness. The benzene-soluble portion of the residue was chromatographed on 13 g. of grade IV alumina. Elution with benzene (100 ml.) gave 231 mg. (30%) of oxodihydroundulatine. This was converted to the picrate as described above for VI to yield 372 mg., m.p. 233–234.5° dec. The free base was regenerated as described above for VI.

A solution of 126 mg. of the pure oxoketone in 10 ml. of methanol containing 8 drops of 10% aqueous potassium hydroxide was boiled gently for 0.5 hour to concentrate the solution to about 3 ml. Then 5 ml. more of methanol was added and the solution again concentrated. Crystallization gave 100 mg. (79%) of colorless prisms of *epi*-oxodihydroundulatine, m.p. 210–215° dec. The infrared spectrum in 6% concentration in potassium bromide showed no C–D stretching absorption.

Anal. Calcd. for $C_{18}H_{20}DNO_5$ (332.36): D, 4.77 atom %. Found: D, 0.06 atom %.

Dihydroundulatine Cyanogen Bromide Adduct XXXIV.—A solution of 500 mg. (1.51 mmoles) of dihydroundulatine, m.p. 249.5–251.5° dec., and 1.05 g. (9.90 mmoles) of cyanogen bromide in 10 ml. of chloroform was refluxed 3 hours. The colorless solution was evaporated to dryness and the residue taken up in ethyl acetate. The organic solution was washed with two portions of 5% hydrochloric acid and dried. Evaporation left 578 mg. of colorless neutral material which on recrystallization from methanol deposited 443 mg. (67%) of prisms, m.p. 154.5–156.5° dec. Two recrystallizations from methanol raised the melting point to 156.5–158.5° dec., $[\alpha]^{27}D$ −70° (*c* 2.61); ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1450); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 2.76 (OH), 2.89 (H bonded OH), 4.50 (C≡N), 6.18, 9.60 and 10.70 μ. The compound gave a positive Beilstein copper wire flame test for halogen.

Anal. Calcd. for $C_{19}H_{23}N_2O_5Br$ (439.30): C, 51.97; H, 5.24; Br, 18.00. Found: C, 52.13; H, 5.56; Br, 17.61.

N-Cyanoether XXXVa.—To a solution of 204 mg. (5.2 mg. atoms) of potassium in 8 ml. of *t*-butyl alcohol distilled from sodium was added a solution of 159 mg. (0.362 mmole) of the cyanogen bromide adduct XXXIV in 7 ml. of dry *t*-butyl alcohol. A cloudiness (potassium bromide) developed immediately. After 0.5 hour the *t*-butoxide was destroyed with dilute hydrochloric acid, and the reaction mixture was evaporated to dryness. The residue was partitioned between water and ether. The ether solution was washed with dilute hydrochloric acid, saturated sodium chloride solution and dried. Evaporation of the ether left 145 mg. of a cloudy glass which was chromatographed on 5 g. of activity III alumina. Benzene eluted 113 mg. (86%) of colorless amorphous cyclic ether XXXVa, which was evaporatively distilled at 140° (<1 μ), $[\alpha]^{25}D$ −100° (*c* 1.42); ultraviolet spectrum: λ_{max}^{EtOH} 287 mμ (1450); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 4.51 (C≡N), 6.18, 9.56 and 10.70 μ. The Beilstein copper wire flame test for halogen was negative. The cyanoether gave a slight discoloration to a solution of potassium permanganate in acetone; however, the same discoloration was observed with the cyanogen bromide adduct XXXIV.

Anal. Calcd. for $C_{19}H_{22}N_2O_7$ (358.38): C, 63.67; H, 6.19. Found: C, 63.95; H, 6.38.

Oxoisobuphanamine (XXX).—A solution of 100 mg. of isodihydroundulatine (V) in 2 ml. of pyridine was added to a mixture of 126 mg. of chromium trioxide in 1 ml. of pyridine. The reaction was allowed to stand undisturbed at room temperature for 20 hours and was then worked up in the same way as for the preparation of oxodihydroundulatine. There was obtained 51 mg. of crude product with infrared absorption at 5.85 (6-ring ketone) and 5.99 μ (conjugated ketone). The crude material was dissolved in 8 ml. of a 2:1 mixture of triethylamine and pyridine to which was added 1 ml. of glacial acetic acid. After reflux for 2 days under nitrogen the solvents were evaporated and the residue taken up in dilute hydrochloric acid. The acid solution was washed with ether, basified with sodium hydroxide and extracted with ether. Evaporation of the dried organic solution left 38 mg. which was crystallized from ethyl acetate–hexane to give 23 mg., m.p. 185–199° dec. Three more recrystallizations from the same solvent gave colorless prisms, m.p. 208.5–210.5° dec., $[\alpha]^{24}D$ −49° (*c* 0.91). The melting point was undepressed on admixture with authentic oxoisobuphanamine.[54] The infrared spectra of the two compounds in potassium bromide were identical; infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.99 (conjugated ketone), 6.19, 9.60 and 10.70 μ; ultraviolet spectrum: λ_{max}^{EtOH} 279 mμ (1320). Graphical subtraction of the spectrum of isodihydroundulatine from that of the unsaturated ketone gave λ_{max}^{EtOH} 223 mμ (8700).

Anal. Calcd. for $C_{17}H_{17}NO_4$ (299.31): C, 68.21; H, 5.73; 1 OCH_3, 10.37. Found: C, 68.06; H, 5.83; OCH_3, 11.33.

2β-Hydroxypowellane (XLa).—A mixture of 70 mg. of pure 2-oxopowellane (XI), 3 ml. of 95% ethanol and 30 mg. of platinum oxide absorbed 93% of one mole-equivalent of hydrogen in 15 minutes at atmospheric pressure and room temperature. The catalyst and solvent were removed and the residue crystallized from ethyl acetate to give 35 mg. (50%), m.p. 172–189.5°. Three more recrystallizations from the same solvent gave colorless prisms of 2β-hydroxypowellane, m.p. 188.5–190.5°, $[\alpha]^{25}D$ −14.8° (*c* 1.35). The mixture melting point with 2α-hydroxypowellane, m.p. 198.5–201.5°, was depressed to 161–190°; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1730); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 2.73 (OH), 6.18, 9.58 and 10.68 μ.

Anal. Calcd. for $C_{17}H_{21}NO_4$ (303.35): C, 67.31; H, 6.98; 1 OCH_3, 10.23. Found: C, 67.19; H, 7.02; OCH_3, 11.23.

2α-Hydroxypowellane (XLIII). (a) From 2-Oxopowellane.—A solution of 5.0 mg. of the ketone XI in 2 ml. of 33% aqueous acetic acid was reduced at room temperature with 13 g. of 4% sodium amalgam. The solution was then basified with sodium hydroxide solution and extracted with ether. The residue left after evaporation of the ether was recrystallized from ethyl acetate to give 3.0 mg. (60%) of **2α-hydroxypowellane**, m.p. 195–199.5°. A second recrystallization raised the melting point to 198–200°. The mixture melting point with the product of sodium amalgam reduction of oxodihydroundulatine, m.p. 199–200.5°, was undepressed (199–201°). The infrared spectra of the two samples in potassium bromide were identical.

(b) From Oxodihydroundulatine.—A solution of 345 mg. of oxodihydroundulatine in 50 ml. of 33% aqueous acetic acid was chilled in an ice-bath and stirred with a magnetic stirring bar while 180 g. of 4% sodium amalgam was added in small pieces during 25 minutes. The solution was decanted from the mercury and basified with concentrated sodium hydroxide solution. Extraction with five portions of chloroform gave 336 mg. (97%) of colorless foamy material, $[\alpha]^{25}D$ −13.0° (*c* 1.15), whose chloroform infrared spectrum had no carbonyl absorption.

A 60-mg. aliquot of the crude material was chromatographed on 2.5 g. of activity IV alumina. Benzene–ethyl acetate (49:1) eluted 17 mg. (28%) of ***epi*dihydroundulatine** which crystallized on trituration with methanol. This was recrystallized twice from methanol and once from ethyl acetate–hexane to give 9 mg. of colorless rhombs, m.p. 151.5–153.5°, identical with the material isolated from hydride reduction of oxodihydroundulatine.

Benzene–ethyl acetate (3:1 and 1:1) and ethyl acetate–methanol eluted 20 mg. (33%) which crystallized on trituration with ethyl acetate. Two recrystallizations from ethyl acetate afforded **2α-hydroxypowellane**, m.p. 199–200.5°, $[\alpha]^{23}D$ +7.1° (*c* 1.40). The mixture melting point with isodihydroundulatine, m.p. 199–200.5°, was depressed to 162–193°; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1720); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 2.74 (OH), 6.17, 9.50 and 10.60 μ.

Anal. Calcd. for $C_{17}H_{21}NO_4$ (303.35): C, 67.31; H, 6.98; 1 OCH_3, 10.23. Found: C, 66.88; H, 6.94; OCH_3, 10.69.

Optical rotation calculations based on the assumption that only the two isolated compounds were present in the crude mixture gave its composition as 70% of 2α-hydroxypowellane and 30% of *epi*dihydroundulatine.

Oxidation of *epi*Dihydroundulatine (XVII).—A solution of 36 mg. of XVII in 0.6 ml. of pyridine was added to a slurry of 35 mg. of chromium trioxide in 0.3 ml. of pyridine and the mixture was allowed to stand 19 hours at room temperature. Dilution with water and extraction with chloroform gave a brown amorphous material which was dissolved in benzene and centrifuged to remove the insoluble chromium residue. Evaporation of the colorless supernatant liquid left 31 mg. (86%) of amorphous **oxodihydroundulatine (VI)**, $[\alpha]^{27}D$ −15° (*c* 1.47). The chloroform infrared spectrum was identical with that of VI.

Solvolyses. (a) Dihydroundulatine Methanesulfonate (IVb).—In a tube surrounded by the vapor (136°) from a refluxing xylene bath was placed a solution of 121 mg. (0.29 mmole) of pure dihydroundulatine mesylate in a mixture of 3 ml. of redistilled glacial acetic acid and 2 ml. of redistilled acetic anhydride. This solution was allowed to reflux for 29.5 hours and was then concentrated at reduced pressure. The residue was basified with 10% potassium bicarbonate solution and extracted with three portions of chloroform. The organic extracts were washed with 10% bicarbonate solution and dried. Evaporation of the chloroform left 114 mg. of a colorless glass now containing only about 10% of IVb as judged from its infrared spectrum. This material was redissolved in a mixture of 3 ml. of redistilled acetic acid and 2 ml. of redistilled acetic anhydride and refluxed as before during an additional 40.5 hours for a total solvolysis time of 70 hours. The reaction mixture was worked up as before to yield 105 mg. (95% from starting material) of colorless glass whose chloroform infrared spectrum was identical with that of **dihydroundulatine acetate** (25 peaks); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.76 (acetate C=O), 6.17, 9.53 and 10.62 μ.

A 49-mg. sample of the solvolysis product was dissolved in 10 ml. of ether and refluxed with 0.2 g. of lithium aluminum hydride for 1.5 hours. The work-up was the same as that described for the preparation of IVa. Evaporation of the chloroform extracts left 40 mg. (92%) of dihydroundulatine whose chloroform infrared spectrum (22 peaks) was identical with that of an authentic sample. Recrystallization from chloroform–ethyl acetate gave 25 mg. of colorless flakes, m.p. 247–250° dec. The mixture melting point with authentic dihydroundulatine, m.p. 250–251.5° dec., was 247–251° dec.

(b) 2β-Hydroxypowellane Methanesulfonate (XLb).—A solution of 65 mg. (0.17 mmole) of the mesylate in a mixture of 2 ml. of redistilled glacial acetic acid and 1.33 ml. of redistilled acetic anhydride was solvolyzed as described in (a) above for 29 hours and was then worked up as in (a) to yield 40 mg. The infrared spectrum still indicated consider-

able sulfonate ester present. The solvolysis was repeated for an additional 70 hours and worked up again. The crude product, containing no sulfonate and less than 5% of O-acetate, was refluxed in ether with lithium aluminum hydride as in (a). There was obtained 28 mg. (0.1 mmole, 59%) of crude **Δ¹-powellene (XLI)**. Chromatography on 1 g. of activity III alumina afforded 20 mg. of pure Δ¹-powellene on elution with benzene; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1750).

The 20 mg. was dissolved in ethanol and converted to the picrate, 30 mg. (83%), m.p. 195–200.5°. The picrate occurred in two forms: matted needles and stout prisms, but after five recrystallizations from acetone–ethanol matted yellow needles were obtained, m.p. 207–212° dec.

Anal. Calcd. for $C_{17}H_{19}NO_3 \cdot C_6H_3N_3O_7$ (514.44): C, 53.69; H, 4.31. Found: C, 53.70; H, 4.35.

The chloroform infrared spectrum of a sample of Δ¹-powellene regenerated from 9 mg. of the pure picrate was distinctly different from that of Δ²-powellene. The regenerated XLI in acetone solution discolored permanganate solution.

Hydrogenation of Δ¹-Powellene (XLI).—A solution of 18 mg. of XLI in 2.5 ml. of 95% ethanol absorbed one mole-equivalent of hydrogen in the presence of 16 mg. of 10% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After removal of catalyst by filtration the solvent was evaporated to leave 17 mg. of a colorless glass which yielded 15 mg. (50%) of picrate, m.p. 206–210°. Two recrystallizations from acetone–95% ethanol gave 12 mg. of yellow prisms of (+)-powellane picrate, m.p. 213–214.5°. The mixture melting point with an authentic specimen, m.p. 213–215°, was 211.5–214°, undepressed.

2β-Hydroxypowellane Methanesulfonate (XLb).—A mixture of 88 mg. of 2β-hydroxypowellane and 255 mg. of methanesulfonyl chloride in 4 ml. of dry pyridine was stirred at room temperature for 40 hours. The reaction mixture was worked up as described for dihydroundulatine mesylate to yield 65 mg. (59%) of colorless amorphous glass after chromatography. In view of the small amount of material the mesylate was solvolyzed directly as described above; infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.17, 8.51 and 10.93 (sulfonate ester), 9.54 and 10.61 μ.

Chromic Acid Oxidations.—The oxidations were carried out according to the procedure of Schreiber and Eschenmoser[70] in 90.7% (w./w.) acetic acid at 25 ± 0.5°. Samples of about 2 mg. were accurately weighed and dissolved in a standard solution containing 100 mg. of chromium trioxide in 500 ml. of 90.7% acetic acid. Then 90.7% acetic acid was added to make the concentration of alcohol 3.57×10^{-4} molar and the concentration of chromic acid 4.75×10^{-4} molar. The ultraviolet spectrum was then measured periodically between 340–360 mμ on a Cary model 11MS spectrophotometer with the hydrogen lamp. Oxidation did not cease after one equivalent presumably because of a slow oxidation of the tertiary nitrogen atom. Therefore a blank was run on undulatine and this was subtracted from each run. Rates were obtained by plotting optical density at the 348–349 mμ maximum *vs.* time elapsed and estimating the slope of the line formed during the first part of the reaction.

Compound	Relative rate of ox.
*epi*Dihydroundulatine (XVII)	1
2α-Hydroxypowellane (XLIII)	1.5
Dihydroundulatine (IVa)	2.8
2β-Hydroxypowellane (XLa)	6.9

Dehydration of Dihydroundulatine (IVa).—When dihydroundulatine (68 mg.) in 3 ml. of dry pyridine and 0.5 ml. of redistilled phosphorus oxychloride was refluxed for 10 minutes (oil-bath 132°), a mixture of dehydration products resulted. Under exactly the same conditions buphanidrine was recovered unchanged.

N-Methyl Cyclic Ether XXXVc.—A solution of 338 mg. of cyanoether XXXVa in 25 ml. of dry ether was refluxed for 18 hours with 0.5 g. of lithium aluminum hydride. The excess hydride was destroyed with water and dilute hydrochloric acid. The aqueous acid solution was washed with ether, and after addition of 10 g. of sodium potassium tartrate, was basified with concentrated sodium hydroxide solution. Extraction with chloroform yielded 289 mg. (92%) of colorless, amorphous **secondary amine XXXVb** which was not analyzed but used directly for the methylation; ultraviolet spectrum: λ_{max}^{EtOH} 286 mμ (1.7×10^3); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 2.96 (NH), 6.17, 9.58 and 10.61 μ.

The amine XXXVb (282 mg.) was dissolved in a mixture of 6 ml. of 98% formic acid and 5 ml. of 37% aqueous formaldehyde solution. The mixture was heated at 105° for 21 hours and then evaporated to dryness at reduced pressure. The residue was dissolved in dilute hydrochloric acid, washed with ether, and basified with concentrated sodium hydroxide solution. Extraction with chloroform gave 268 mg. (91%) of amorphous N-methyl ether XXXVc; infrared spectrum: $\lambda_{max}^{CHCl_3}$ 3.58 (NCH_3), 6.17, 9.64 and 10.62 μ.

From 17 mg. dissolved in methyl iodide there was obtained 21 mg. (88%) of methiodide, m.p. 260–263° dec., after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{20}H_{26}NO_5I$ (487.33): C, 49.29; H, 5.37. Found: C, 48.90; H, 5.74.

Lactam from N-Methyl Ether XXXVc.—To an ice-cold solution of 243 mg. of XXXVc in 8 ml. of acetone was added dropwise with stirring a cold solution of 160 mg. of potassium permanganate in 15 ml. of distilled water. When the permanganate had been reduced the manganese dioxide was removed by filtration. The acetone was distilled from the filtrate and the basic aqueous residue was extracted with ether. The ether solution was washed with 5% hydrochloric acid, saturated sodium chloride and dried. Evaporation of the ether left 8 mg. (3%) of neutral, amorphous lactam XXXVIII. There was not enough to purify for analysis; infrared spectrum: $\lambda_{max}^{CHCl_3}$ 6.08 (conjugated lactam), 6.20, 9.62 and 10.63 μ.

Basification of the acid extracts and extraction with ether allowed recovery of 223 mg. of a mixture of XXXVc and the N-formyl derivative of XXXVb as judged from the infrared spectrum.

Oxidation of Ethylol Derivative XXII. (a).—When a solution of 70 mg. of XXII in 3 ml. of chloroform was stirred with 420 mg. of active manganese dioxide for 24 hours, there was recovered 67 mg. of starting material whose infrared spectrum had no carbonyl absorption.

(b).—A mixture of 400 mg. (1.14 mmoles) of XXII, 1.10 g. of fluorenone and the dry potassium *t*-butoxide prepared from 0.29 g. of potassium was stirred in 20 ml. of sodium-dried benzene under nitrogen for 4 hours at room temperature. A deep brown color developed immediately. Water was added to destroy the butoxide and the color lightened to orange. The workup was exactly the same as for the oxidation of dihydroundulatine above. Evaporation of the dried organic solution left 348 mg. of colorless oil. Chromatography on 10 g. of activity I alumina gave 319 mg. (80%) of the colorless amorphous **aldehyde XLVIII.**

The perchlorate XLIX was prepared in 94% yield by addition of ethanolic perchloric acid to an ethereal solution of 135 mg. of the aldehyde. Four recrystallizations from 95% ethanol gave colorless needles, m.p. 320–322° dec.; ultraviolet spectrum: λ_{max}^{EtOH} 281 mμ (1300); infrared spectrum: λ_{max}^{Nujol} 3.05 (OH), 6.17, 9.49 and 10.70 μ.

Anal. Calcd. for $C_{19}H_{25}NO_5 \cdot HClO_4$ (447.86): C, 50.95; H, 5.85; N, 3.12; Cl, 7.91. Found: C, 50.82; H, 6.17; N, 3.30; Cl, 8.12.

The infrared spectrum of the aldehyde regenerated from the pure perchlorate was identical with the material purified by chromatography. A sample of the regenerated aldehyde was evaporatively distilled at 140° (< 1μ) for analysis. It gave positive Tollens and Fuchsin tests; ultraviolet spectrum: λ_{max}^{EtOH} 286 (1650); infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.92 (CH=O), 6.14, 9.60 and 10.66 μ.

Anal. Calcd. for $C_{19}H_{25}NO_5$ (347.40): C, 65.68; H, 7.25. Found: C, 65.79; H, 7.54.

N-Alkyl Analysis.—A 50-mg. sample of undulatine was subjected to a non-quantitative standard N-alkyl analysis. The O-methyl was first removed and then the volatile iodide from the N-alkyl residue was passed into a solution of trimethylamine in ethanol; no precipitation occurred. The solution was blown to dryness and the residue recrystallized from 95% ethanol to give large colorless prisms whose infrared spectrum in potassium bromide was identical with that of an authentic sample of ethyltrimethylammonium iodide but different from the spectrum of tetramethylammonium iodide.

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