VERATRUM ALKALOIDS

By K. J. Morgan, M.A., B.Sc., D.Phil.
(Chemistry Department, The University, Birmingham)

and J. A. Barltrop, M.A., B.Sc., D.Phil.
(Brasenose College, and Dyson Perrins Laboratory, Oxford University)

The veratrum alkaloids, which form part of the steroid group of alkaloids, are obtained from liliaceous plants belonging to the sub-order Melanthaceæ. Those which have received most attention are *V. album* and *V. viride*, native to Europe and North America respectively, and *V. sabadilla* or *Schœnocaulon officinale*, but many other species of *Veratrum* and of the closely related *Zygadenus* genus have been investigated. Since the first recorded investigations [1] into this group, some forty alkaloids have been isolated and fully characterised; no fewer than twenty-five have been reported since 1951 (Table 1). Brief summaries [2] of the earlier investigations into the structure of these compounds have been supplemented by more recent and more extensive reviews by Jeger and Prelog,[3] McKenna,[4] and Stoll.[5] No attempt is made here to discuss in detail evidence already presented in these previous reviews.

Hydrolysis of the ester and glycosidic alkaloids gives the corresponding alkamines, but under the conditions normally employed for such hydrolyses several of the alkamines are unstable and suffer isomerisation. By using mild and controlled conditions the true alkamines can readily be obtained, Partial deacylation of many of the ester alkaloids occurs readily with methanol, catalysed by the basic centre in the molecule, and it may be that some of the esters, notably those of germine, isolated from natural sources are actually artefacts; this applies particularly to germerine, protoveratridine, germidine, germanidine, and possibly germbudine.

The glycosidic fraction of all three glycoalkaloids has been identified [6] as D-glucose. It is attached to the 3β-hydroxyl group in *iso*rubijervosine; a similar arrangement is inferred for *pseudo*jervine and veratrosine. The acids (I—VII) present in the ester alkaloids bear a marked relation to each other. The two aromatic acids, vanillic (VII) and veratric (VI), differ only

[1] Pelletier and Caventou, *Ann. Chim. Phys.*, 1819, **14**, 69.

[2] Henry, "The Plant Alkaloids", J. and A. Churchill, London, 1949; Fieser and Fieser, "The Natural Products related to Phenanthrene", Reinhold Publ. Corp., New York, 1949.

[3] Jeger and Prelog, "The Alkaloids", Vol. III, ed. Manske and Holmes, Academic Press Inc., New York, 1953.

[4] McKenna, *Quart. Rev.*, 1953, **7**, 231.

[5] Stoll, *Gazzetta*, 1954, **84**, 1190.

[6] Jacobs and Craig, *J. Biol. Chem.*, 1944, **155**, 565; Klohs, Draper, Keller, Malesh, and Petracek, *J. Amer. Chem. Soc.*, 1953, **75**, 2133.

in their degree of methylation and the aliphatic acids, with the exception of acetic acid, all possess the isoprene skeleton.

Extraction of the Alkaloids.—Alkaloids are probably present in all parts of *V. album* and *V. viride*,[7, 8] but the insecticidal action of dried sabadilla, characteristic of cevadine and veratridine, is found [9] only in the seeds. The usual sources are the roots and rhizomes of *V. album* and *V. viride* and the seeds of *V. sabadilla*. The alkaloids can be extracted from the appropriate parts of the dried and powdered plants by aqueous or alcoholic acid or by organic solvents. Subsequent separation of the bases from the crude extract has been achieved by fractional crystallisation, precipitation, or extraction [10] and by chromatographic separations on alumina,[11, 12] on silica gel,[13] on kieselguhr,[8] and on an ion-exchange resin.[14] Chromatography on paper [8, 15] has proved convenient for characterising the alkaloids. Perhaps the most significant advance in recent years in the separation of complex mixtures has been the application of liquid–liquid countercurrent extraction.[16] This has rendered possible the investigation of the amorphous alkaloidal residues that resisted other analytical techniques and has resulted[17] in the isolation of nearly all the recently discovered alkaloids.

Structural Investigations: General.—The more general methods of alkaloid degradation, notably Hofmann and Emde degradations, have not been widely or successfully used with the veratrum alkaloids. Such general methods as have been used are those normally associated with steroid chemistry. The nature of the carbon skeleton of the alkaloids has been elucidated largely from examination of the products of selenium dehydrogenation. It is found that the main reaction is a fission of the molecule into a hydrocarbon fraction and a nitrogenous fraction composed of substituted pyridines (Table 2). The essential basic product is 2-ethyl-5-methylpyridine (VIII). This is also obtained from the potato alkaloid, solanidine, and on the basis of this and certain other evidence it was concluded that the alkaloids of *Solanum* spp. and such alkaloids of *Veratrum* spp. as are tertiary bases contain a perhydropyrrocoline residue. The correctness of this

[7] Poethke, *Arch. Pharm.*, 1937, **275**, 357.

[8] Hegi and Flück, *Pharm. Acta Helv.*, 1956, **31**, 428.

[9] Allen, Dicke, and Harris, *J. Econ. Entomol*, 1944, **37**, 400.

[10] (*a*) See, *e.g.*, Wright and Luff, *J.*, 1878, 338; 1879, 405, 421; (*b*) Jacobs and Craig, *J. Biol. Chem.*, 1943, **148**, 41; 1945, **160**, 555; (*c*) Auterhoff, *Arch. Pharm.*, 1953, **286**, 69.

[11] Pelletier and Jacobs, *J. Amer. Chem. Soc.*, 1953, **75**, 3248.

[12] Kupchan, Lavie, Deliwala, and Andoh, *ibid.*, p. 5519.

[13] Hennig, Higuchi, and Parks, *J. Amer. Pharm. Assoc.*, 1951, **40**, 168; Svoboda and Parks, *ibid.*, 1954, **43**, 584.

[14] Edwards, *Chem. and Ind.*, 1953, 488.

[15] See, *e.g.*, Nash and Brooker, *J. Amer. Chem. Soc.*, 1953, **75**, 1942; Auterhoff, *Arch. Pharm.*, 1954, **287**, 380; Macek and Vejdelek, *Chem. Listy*, 1955, **49**, 539; *Nature*, 1955, **176**, 1173; Levine and Fischbach, *J. Amer. Pharm. Assoc.*, 1955, **44**, 543.

[16] Craig and Craig, "Technique of Organic Chemistry", Vol. III (2nd edn.), Part I, page 149, ed. Weissberger, Interscience Publ. Inc., New York, 1956.

[17] See, *e.g.*, Fried, White, and Wintersteiner, *J. Amer. Chem. Soc.*, 1949, **71**, 3260; 1950, **72**, 4621; Klohs, Arons, Draper, Keller, Koster, Malesh, and Petracek, *ibid.*, 1952, **74**, 5107; Myers, Morozovitz, Glen, Barber, Papineau-Couture, and Grant, *ibid.*, 1955, **77**, 3348; Stuart and Parks *J. Amer. Pharm. Assoc.*, 1956, **45**, 252.

TABLE 1. *Alkaloids of* Veratr n *spp.*

Alkaloid	Formula	M.p.	$[\alpha]_D$ in $CHCl_3$	$[\alpha]_D$ in C_5H_5N	$[\alpha]_D$ in EtOH	Source *	Esterifying † acid
Ester alkaloids							
(*a*) Esters of protoverine							
Protoveratrine A	$C_{41}H_{63}O_{14}N$	267—269°	−10·5°	−40·5°		Va Vv Zv	I(2), II, III
Protoveratrine B [a]	$C_{41}H_{63}O_{15}N$	268—270	−3·5	−37		Va Vv Zv	I(2), II, IV
Escholerine	$C_{41}H_{61}O_{13}N$	235—236	+7	−30		Ve	I(2), II, V
Deacetylprotoveratrine	$C_{39}H_{61}O_{13}N$	191—192		−15		Va	I, II, III
Deacetyl*neo*protoveratrine [b]	$C_{39}H_{61}O_{14}N$	182—183		−9·6		Va Vv	I, II, IV
(*b*) Esters of germine							
Germitetrine [c]	$C_{41}H_{63}O_{14}N$	229—230	−12	−74		Va	I(2), II, IV
Germitrine	$C_{39}H_{61}O_{12}N$	216—219	+4	−69		Vv	I, II, III
Germanitrine	$C_{39}H_{59}O_{11}N$	228—229	0	−61		Vf	I, II, V
Germinitrine	$C_{39}H_{57}O_{11}N$	175—176	+7·8	−36		Vf	I, V(2)
Germbudine	$C_{37}H_{59}O_{12}N$ [d]	160—164		−8		Vv	II, IV [e]
*neo*Germbudine	$C_{37}H_{59}O_{12}N$	149—152		−12		Va Vv	II, IV [e]
Germerine	$C_{37}H_{59}O_{11}N$	200—203	+6	−14·2		Va Vv Vn	II, III
*neo*Germitrine	$C_{36}H_{55}O_{11}N$	234—235	0	−78		Vv Vf Ve Zv Zp	I(2), II
Germidine	$C_{34}H_{53}O_{10}N$	230—231	+13	−11		Vv Zv	I, II
*iso*Germidine [f]	$C_{34}H_{53}O_{10}N$	221—223	−26	−63·2		Vv Zv Zp	I, II
Protoveratridine	$C_{32}H_{51}O_9N$	272—273		−9		Va Vv Zv	II
(*c*) Esters of veracevine							
Veratridine [g]	$C_{36}H_{51}O_{11}N$	160—180			+8	Va Vv Vs	VI
Vanilloylveracevine [h]	$C_{35}H_{49}O_{11}N$	256—257		+43·6		Vs	VII
Cevadine [i]	$C_{32}H_{49}O_9N$	206		+6·4	+12·5	Vv Vs	V
Cevacine	$C_{29}H_{45}O_9N$	205—207	−27			Vs	I
(*d*) Esters of zygadenine							
Veratroylzygadenine	$C_{36}H_{51}O_{10}N$	270—271	−27			Va Vf Ve Vn Zv Zp	VI
Vanilloylzygadenine	$C_{35}H_{49}O_{10}N$	258—259	−27·5			Zv Zp	VII
Zygacine	$C_{29}H_{45}O_8N$		−22			Zv Zp	I

Glycosidic alkaloids						
*pseudo*Jervine	$C_{33}H_{49}O_8N$	304—305	−13 [j]			Va Vv Vf Ve
Veratrosine	$C_{33}H_{49}O_7N$	242—243	−53 [j]			Vv Ve
*iso*Rubijervosine	$C_{33}H_{53}O_7N$	279—280		−20		Ve
Alkamines						
Protoverine	$C_{27}H_{43}O_9N$	195—200		−12	−11	
Germine	$C_{27}H_{43}O_8N$	218—221			+5	Va Vv Zv
Veracevine	$C_{27}H_{43}O_8N$	181—183	−33		−24	Vs
Cevine [k]	$C_{27}H_{43}O_8N$	195—200			−17·5	
Zygadenine	$C_{27}H_{43}O_7N$	201—204	−45			Vn Zi Zv Zp Ze
Rubijervine	$C_{27}H_{43}O_2N$	240—242			+19	Va Vv Ve Vn
*iso*Rubijervine	$C_{27}H_{43}O_2N$	236—238			+9·2	Va Ve
Jervine	$C_{27}H_{39}O_3N$	243—244			−140	Va Vv Vf Ve Vl Vg Vst Vn
Veratramine	$C_{27}H_{39}O_2N$	205—206			−68	Vv Ve Vg Vst
Unclassified alkaloids						
Veralbidine	$C_{37}H_{61}O_{12}N$	181—183	+5·4	−11·7		Va
Veratrobasine	$C_{24}H_{37}O_3N$	285—288		−126	−77	Va
Geralbine	$C_{22}H_{33}O_2N$	221—223	0	0	0	Va
Veragermine	$C_{31}H_{53}O_{13}N$	262—264			−4·87	Vs

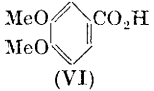
$Me{\cdot}CO_2H$ (I)

$CHMeEt{\cdot}CO_2H$ (II)

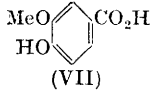
$HO{\cdot}CMeEt{\cdot}CO_2H$ (III)

$HO{\cdot}CHMe{\cdot}CMe(OH){\cdot}CO_2H$ (IV)

$Me{\cdot}CH{:}CMe{\cdot}CO_2H$ (V)



(VI)



(VII)

* Key to source of alkaloids: Va, *V. album*; Vv, *V. viride*; Vs, *V. sabadilla*; Vf, *V. fimbriatum* Gray; Ve, *V. escholtzii* Gray; Vl, *V. lobelianum*; Vg, *V. grandiflorum*; Vst, *V. stamineum*; Vn, *V. nigrum*; Zi, *Z. intermedius*; Zv, *Z. venenosus*; Zp, *Z. paniculatus*; Ze, *Z. elegans*.

† The roman numerals refer to the structural formulæ at the base of the Table; the arabic numerals in parentheses to the number of such residues present.

[a] Identical with *neo*protoveratrine and veratetrine. [b] Also known as germbutrine. [c] Identical with germitetrine B. [d] Not $C_{37}H_{59}O_{13}N$ as is reported in the literature. [e] These acids appear to be the *erythro-* and *threo*-isomers. [f] Identical with *neo*germidine. [g] Also called veratrine and amorphous veratrine by early workers. [h] Not vanilloylcevine as indicated in the literature. [i] Also called veratrine, crystallised veratrine, and pure veratrine by early workers. [j] Solvent is ethanol–chloroform. [k] Does not occur in Nature.

TABLE 2. *Dehydrogenation products*

Alkaloid	Nitrogenous products	Other products*
Cevine	β-Picoline 2-Ethyl-5-methylpyridine $C_9H_{13}N$ 2-2′-Hydroxyethyl-5-methylpyridine "Oxyethylmethylpyridine", C_8H_9ON† Cevanthridine, $C_{25}H_{27}N$ $C_{20}H_{19}N$ Veranthridine, $C_{26}H_{25}N$	4 : 5-Benzindane $C_{17}H_{16}$ (fluorene) $C_{18}H_{18}$ (fluorene) $C_{19}H_{20}$ (fluorene) $C_{24}H_{30}$ (fluorene) Cevanthrol, $C_{23}H_{24}O$
Germine	2-Ethyl-5-methylpyridine Cevanthridine	$C_{18}H_{18}$ (fluorene) Cevanthrol
Protoveratrine	2 : 5-Dimethylpyridine 2-Ethyl-5-methylpyridine C_8H_9ON Cevanthridine	Cevanthrol
Jervine	2-Ethyl-5-methylpyridine $C_8H_{11}ON$	$C_{14}H_{14}$ (benzindane) $C_{20}H_{22}$ (fluorene) $C_{21}H_{24}$ (fluorene) $C_{24}H_{30}$ (fluorene) $C_{20}H_{16}$ (benzofluorene) $C_{22}H_{20}$ (benzofluorene)
Veratramine	C_6H_7ON	$C_{22}H_{20}$ (benzofluorene)
Rubijervine	2-Ethyl-5-methylpyridine	$C_{18}H_{16}$ (phenanthrene) $C_{18}H_{16}O$
*iso*Rubijervine		$C_{17}H_{14}$ (phenanthrene)
Solanidine	2-Ethyl-5-methylpyridine	$C_{18}H_{16}$ (phenanthrene)
Solasodine	2-Ethyl-5-methylpyridine	$C_{18}H_{16}$ (phenanthrene)

* Names in parentheses indicate the spectral class to which the hydrocarbon belongs.

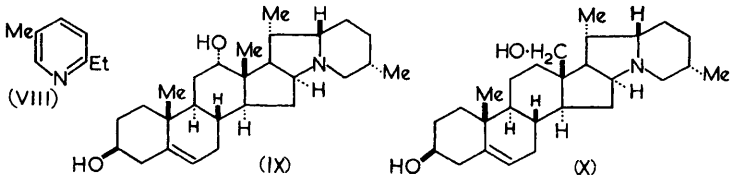
† Probably 4′ : 5′-dihydro-5-methylfurano(3′ : 3′ : 2 . 3)pyridine.

conclusion for the solanum alkaloids has been demonstrated by synthesis, but subsequent results have made it necessary to modify this view for the more highly hydroxylated veratrum bases.

The essential unity shown both by the formulæ of all the fully characterised alkamines (all, except veratrobasine and geralbine which may be related to the holarrhena alkaloids, are C_{27} compounds) and by the basic dehydrogenation products, is not found among the non-nitrogenous dehydrogenation products. Three types of hydrocarbon (and oxygenated derivatives) are formed. From cevine, germine, and protoverine, *cyclo*pentenofluorenes are obtained. Jervine, like cevine, gives 4 : 5-benzindane and *cyclo*pentenofluorenes but, together with veratramine, also yields 1 : 2-benzofluorenes. Phenanthrenes are produced by rubijervine and *iso*rubijervine but neither gives the Diels hydrocarbon which is formed by the solanum alkaloids. At least two distinct types of carbon skeleton are thus indicated. Subsequent

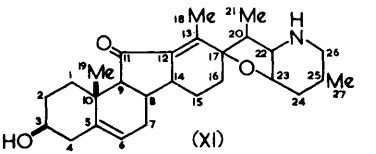
work has confirmed this and shown that the true steroid skeleton is to be found only in rubijervine and *iso*rubijervine ; in all the other alkaloids a modified steroid skeleton is found.

Rubijervine and *iso*Rubijervine.—The ring structure of these two alkaloids is that of the tertiary solanum alkaloids and both have been identified as hydroxysolanidines. Optical rotatory dispersions and molecular



rotations [18] have confirmed the view that rubijervine is 12α-hydroxysolanidine ; *iso*rubijervine has been identified as 18-hydroxysolanidine. The recent statement [19] of the full stereochemistry of solanidine enables complete structures (IX, X) to be written for these two veratrum alkaloids.

Jervine.—(a) *General.* Jervine, $C_{27}H_{39}O_3N$, is a secondary base which contains a hydroxyl group, an ether bridge, and a sluggishly reactive carbonyl group. These functions and the presence of a second double bond require that jervine be hexacyclic. The structure (XI) proposed by Fried, Wintersteiner, *et al.*[20] provides a satisfactory basis for interpreting the experimental evidence and will be used in the following discussion.



(i) The presence of the familiar steroidal 3β-hydroxy-$\Delta^{5:6}$-system, which was originally inferred from the formation of 3-oxo-$\Delta^{4:5}$-derivatives on oxidation, has been demonstrated by comparison of molecular-rotation differences with those of steroids and more recently by formation [21] of 3 : 5-*cyclo*-derivatives of certain degradation products of jervine.

(ii) The salient features of the carbon–nitrogen framework follow from the formation, on dehydrogenation, of a 4 : 5-benzindane and of *cyclo*penteno- and benzo-fluorenes which indicate that ring C is five-membered, and of 2-ethyl-5-methylpyridine which suggests the form assumed by the steroidal side chain in this alkaloid. The keto-group in jervine is inert and is thus presumably at position 11. Dihydrojervine (XVI) has an infrared absorption band [22] at 1730 cm.$^{-1}$, typical of a *cyclo*pentanone, and this confirms the nature of ring C.

[18] Pelletier and Locke, *J. Amer. Chem. Soc.*, 1957, **79**, 4531.

[19] Sato and Latham, *Chem. and Ind.*, 1955, 444 ; *J. Amer. Chem. Soc.*, 1956, **78**, 3146.

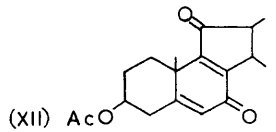
[20] Fried, Wintersteiner, Moore, Iselin, and Klingsberg, *ibid.*, 1951, **73**, 2970.

[21] Herz and Fried, *ibid.*, 1954, **76**, 5621.

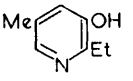
[22] Anliker, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 838.

(iii) The relationship demonstrated (see p. 44) between veratramine (XXXI) and jervine establishes that the latter has a six-membered ring D and a 13-methyl group.

(iv) The double bond conjugated with the keto-group has three possible locations. The 8 : 9-position is untenable because oxidation of 3-acetoxy-5 : 6-unsaturated steroids with chromic acid gives the corresponding 7-oxo-derivatives, and *ON*-diacetyl-7-oxojervine prepared [23] by this method did not have the ultraviolet spectrum expected for the extended conjugated system (XII). The 11-oxo-$\Delta^{12:14}$-structure has been ascribed to an isomer of jervine (see below), leaving the 12 : 13-position as the only possible location for the double bond in jervine. This assignment receives strong support



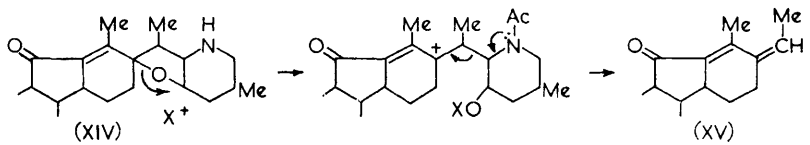
(XII)



(XIII)

from the fact that whereas in jervine and its derivatives possessing unsaturation in this position the ether bridge is readily cleaved, removal of the double bond by hydrogenation or by isomerisation to other positions gives molecules with much more stable bridges. This is a consequence of the allylic nature of the ethereal oxygen atom in jervine.

(v) The isolation of a base, probably 2-ethyl-3-hydroxy-5-methylpyridine (XIII), from the selenium dehydrogenation products suggests the position of one end of the ether bridge. The other end has been assigned to $C_{(17)}$ to account for its ready elimination and for the products of the jervisine rearrangement (see below). The partial structure (XIV) also affords, by analogy with the quinine-niquine transformation, a plausible explanation [24] of the remarkable scission which takes place [20, 25] when jervine is heated to 140° with acetic anhydride and zinc chloride :



(XIV) (XV)

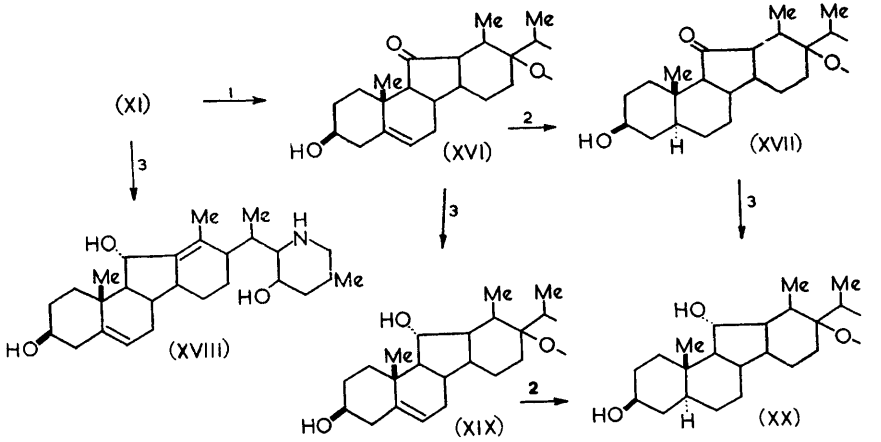
This evidence establishes the structure (XI) of jervine ; the transformations of jervine, discussed below, are interpreted in terms of this structure.

(b) *Reduction.* Jervine when hydrogenated over platinum under alkaline conditions gives dihydrojervine which, since it possesses a saturated C·C·CO·C·C grouping, must have the structure (XVI). Hydrogenation of jervine or of dihydrojervine under acidic conditions leads to tetrahydrojervine which, since it is still ketonic and forms an *ON*-diacetate, must be formulated as (XVII). The resistance shown by the carbonyl group to

[23] Wintersteiner, Moore, Fried, and Iselin, *Proc. Nat. Acad. Sci. U.S.A.*, 1951, **37**, 333.

[24] Fried and Klingsberg, *J. Amer. Chem. Soc.*, 1953, **75**, 4929.

[25] Mosher, Forker, Williams, and Oakwood, *ibid.*, 1952, **74**, 4627.



Reagents : 1, H_2–Pt–OH^-. 2, H_2–Pt–H^+. 3, Na–BuOH.

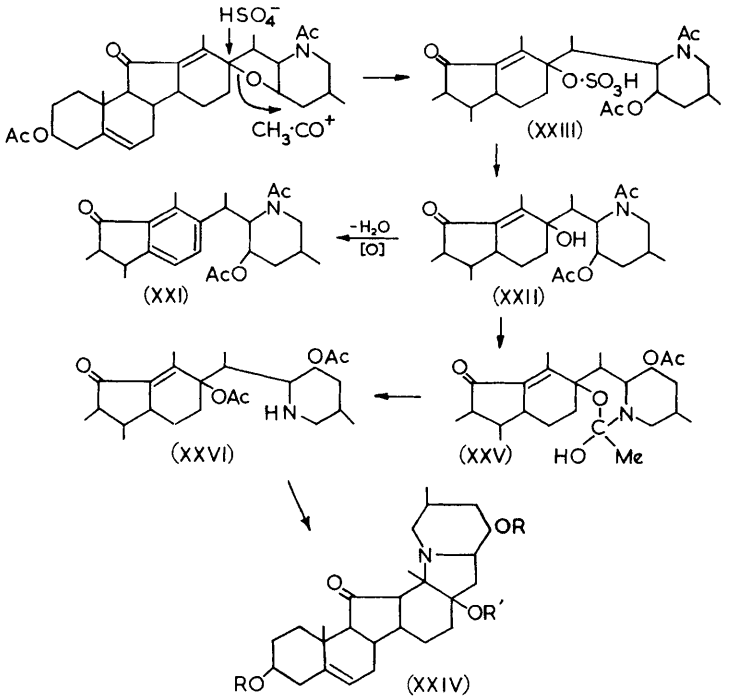
catalytic reduction is noteworthy ; however, it can be reduced chemically. Dihydrojervine (XVI), treated with sodium and butanol,[26] gives "β"-dihydrojervinol (XIX) in which the 11-hydroxyl group is α-orientated. Reduction of jervine under the same conditions was thought to give the 11-epimer, but it has now been shown [27] that the product, "α"-dihydrojervinol (XVIII), is a diene-triol in which the ether bridge has been broken. Further reduction of "β"-dihydrojervinol by catalytic methods or of tetrahydrojervine by sodium in butanol gives the same product, "β"-tetrahydrojervinol (XX), which contains an unhindered 11α-hydroxyl group. Lithium aluminium hydride reduces tetrahydrojervine to the hindered 11β-hydroxy-isomer. Di- and tetra-hydrojervine are much more stable than jervine to acidic reagents.

(c) *Acetolysis.* Jervine, when heated with zinc chloride and acetic anhydride, experiences scission to the doubly unsaturated ketone (XV). Acetolysis of jervine diacetate performed [28] at room temperature and catalysed by small amounts of sulphuric acid leads to a mixture of the "indanone" (XXI) and tertiary alcohol (XXII). The reaction has recently been interpreted [29] in terms of a concerted anionoid-cationoid attack on the $C_{(17)}$–O bond leading to an intermediate sulphate ester (XXIII) which has also been isolated. Hydrolysis will give the alcohol (XXII) which has been shown [28] to be converted under the conditions prevailing in the acetolysis into the indanone (XXI), presumably by dehydration to a diene followed by oxidation or dismutation to the indanone.

The triacetate (XXII) is transformed by alcoholic potassium hydroxide into jervisine monoacetate (XXIV ; R = H, R′ = Ac), the structure of

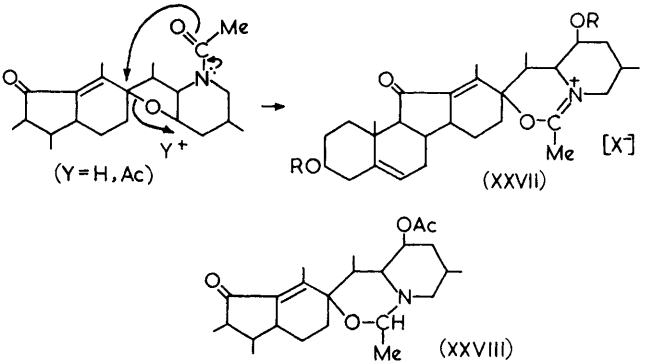
[26] Jacobs and Craig, *J. Biol. Chem.*, 1943, **148**, 51 ; Jacobs and Huebner, *ibid.*, 1947, **170**, 635.
[27] Iselin, Moore, and Wintersteiner, *J. Amer. Chem. Soc.*, 1956, **78**, 403.
[28] Wintersteiner and Moore, *ibid.*, 1953, **75**, 4938.
[29] *Idem, ibid.*, 1956, **78**, 6193.

which follows from the facts that it is a saturated ketone containing an *O*-acetyl but no *N*-acetyl group and that it is a weak tertiary base giving a basic triacetate ; its weakly basic nature may be ascribed to steric shielding of the nitrogen atom. It is thought [28] that the rearrangement proceeds *via* an intermediate (XXV) to an isomeric acetate (XXVI), the free amino-group of which can add to the $\alpha\beta$-unsaturated ketone.

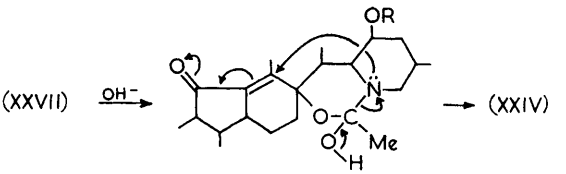


Acetolysis of jervine diacetate catalysed by perchloric acid gives yet another product,[29] a dihydro-1 : 3-oxazinium perchlorate (XXVII ; R = Ac, X = ClO_4), which when treated with weak bases rearranges to jervisine triacetate (XXIV ; R = R′ = Ac). The structure of the perchlorate rests on the following evidence. Analysis shows that it is derived from a hypothetical jervine triacetate by addition of the elements of perchloric acid. It is identified spectroscopically as an $\alpha\beta$-unsaturated ketone and, although it is a salt, the absence of an N–H band in the infrared spectrum indicates that the nitrogen atom must be quaternary. The crucial evidence comes from consideration of the related salt (XXVII ; R = H, X = Cl) which, together with *N*-acetyl*iso*jervine and jervisine 17-acetate (XXIV ; R = H, R′ = Ac), is formed when *N*-acetyljervine is treated with methanolic hydrogen chloride. This salt, the infrared spectrum of which indicates the absence of an *O*-acetyl group, does in fact contain such a group in a masked form since with sodium carbonate it forms jervisine 17-acetate. The dihydro-oxazinium salt structure, which provides the only reasonable inter-

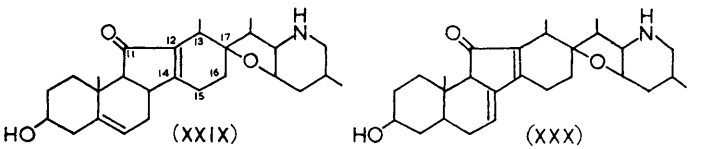
pretation of these results, is confirmed by catalytic reduction of the salt to a dihydro-derivative (XXVIII) from which acetaldehyde can be obtained. The dihydro-oxazinium salts are probably derived by a mechanism analogous to that invoked for the formation of the sulphate ester (XXIII); in the absence of any other anionoid reagent the oxygen atom of the *N*-acetyl group takes the place of the bisulphate ion :



The base-catalysed rearrangement of the dihydro-oxazinium salts to jervisine derivatives may be formulated as follows :



(d) *Jervine isomers.* Jervine has been found [30] to isomerise under the influence of hydrogenation catalysts to $\Delta^{12:14}$-jervine * (XXIX). The oxygen bridge, being no longer allylic, is much more resistant to acid-catalysed rearrangements. It withstands methanolic hydrogen chloride under conditions which transform jervine into *iso*jervine, and the substance can even be recovered partially unchanged from the perchloric acid–acetic anhydride acetolysis mixtures. However, under alkaline conditions, there is slow isomerisation into yet another compound (XXX).



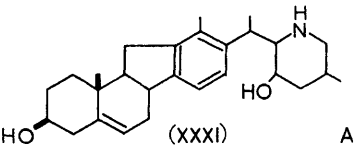
Acid hydrolysis of ψ-jervine, the naturally occurring glucoside of jervine, gives *iso*jervine. *iso*Jervine may also be obtained by treating jervine itself

* Iselin and Wintersteiner [30] designate this compound Δ^{13}-jervine.

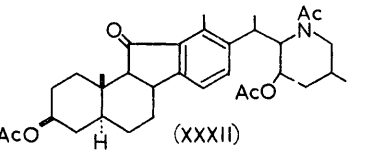
[30] Iselin and Wintersteiner, *J. Amer. Chem. Soc.*, 1955, **77**, 5318.

with methanolic hydrogen chloride. Since *iso*jervine forms a triacetate, the ether bridge has presumably been broken, but details of its structure remain to be established.

Veratramine.—This secondary base, closely related to jervine, is unique among the veratrum alkaloids in possessing a benzene ring in its skeleton. In addition, it contains a 5 : 6-unsaturated 3β-hydroxyl group and a second acylatable hydroxyl group. The isolation of 3-hydroxy-5-methylpyridine from the dehydrogenation products indicates that the second oxygen atom is located at $C_{(23)}$ in the nitrogenous ring. The similarity between the dehydrogenation products from jervine and veratramine led Tamm and Wintersteiner [31] to suggest that this evidence is best accommodated in the structure (XXXI). Confirmation is provided by oxidation of veratramine to benzene-1 : 2 : 3 : 4-tetracarboxylic acid and of *OON*-triacetyldihydroveratramine to an " indanone " (XXXII) identical with that obtained by reduction of the indanone (XXI) from jervine.

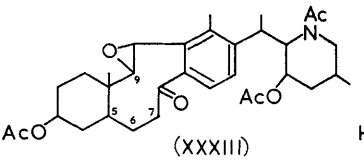


(XXXI)

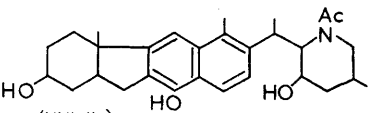


(XXXII)

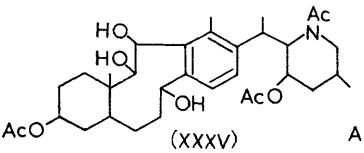
Further examination of the oxidation of triacetyldihydroveratramine has revealed that the indanone (XXXII) is not the major product. A substance, which has been assigned [32] the epoxy-ketone structure (XXXIII), is formed in 30% yield. This epoxy-ketone is readily transformed under both basic and acidic conditions into an α-naphthol (XXXIV), formed by attack of $C_{(7)}$ on the oxide ring at $C_{(9)}$, followed by aromatisation. Reduction of the epoxy-ketone by borohydride yields a trisecondary triol (XXXV) which is



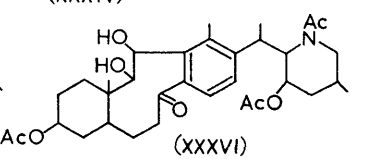
(XXXIII)



(XXXIV)



(XXXV)



(XXXVI)

stable to glycol-splitting reagents, has only one acylatable hydroxyl group, and is oxidised by chromic acid to the monoketone (XXXVI). It has been suggested that these surprising results can be explained conforma-

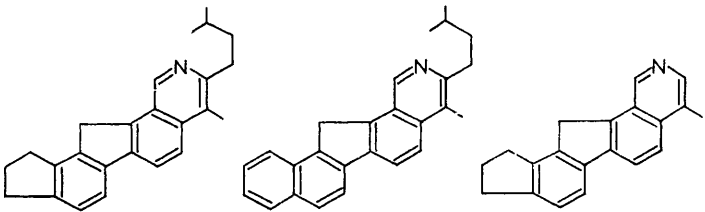
[31] Tamm and Wintersteiner, *J. Amer. Chem. Soc.*, 1952, **74**, 3842.
[32] Hosansky and Wintersteiner, *ibid.*, 1956, **78**, 3126.

tionally in terms of the steric factors operating within the nine-membered ring.

The Cevan Group.—The more highly hydroxylated alkamines, protoverine, veracevine, germine, and zygadenine are closely related structurally. Degradation of derivatives of the first three to identical compounds, and transformation of an ester of germine into an ester of zygadenine, have demonstrated this. Much of the structural investigation of these alkaloids has been conducted with cevine, the stable and more readily accessible isomer of veracevine, and it is from the determination of the structure of cevine that our knowledge of the structures of the other alkamines is derived.

Cevine, $C_{27}H_{43}O_8N$. This, first isolated by Wright and Luff,[10] is a tertiary base containing neither *N*-methyl nor *O*-methyl groups. Exhaustive chemical and spectral investigations showed that it contains neither carbonyl nor olefinic double bonds. It is therefore heptacyclic. The nature of the carbon–nitrogen skeleton has been established largely by dehydrogenation experiments. Selenium dehydrogenation gives a mixture of basic and non-basic substances (Table 2). The non-basic materials were identified spectroscopically and chemically as *cyclo*pentenofluorenes; the simpler basic fractions are 2 : 5-dialkylpyridines. Closely related pyridine and piperidine bases are formed by distillation of cevine with soda-lime and zinc dust. It is the more complicated bases, cevanthridine [33] $C_{25}H_{27}N$, veranthridine [34] $C_{26}H_{25}N$, and the substance [34] $C_{20}H_{19}N$, which reveal the structure of the cevan nucleus.

Cevanthridine, a tertiary base, is catalytically reduced to a tetrahydro-derivative which is a secondary amine. This suggests the presence of a quinoline or *iso*quinoline unit. Since the ultraviolet spectrum [35] of tetrahydrocevanthridine resembles closely those of the *cyclo*pentenofluorenes, it follows that the nitrogen atom cannot be directly attached to a benzene ring, since this would cause considerable spectral changes, and that, therefore, cevanthridine is in fact an *iso*quinoline derivative. Accordingly, cevanthridine can best be formulated [36] as a *cyclo*pentenoindeno*iso*quinoline (XXXVII). The presence of a fluorene nucleus has been confirmed [37] by



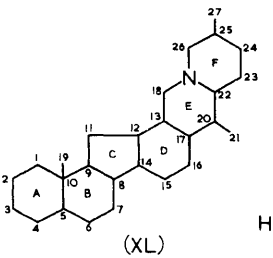
(XXXVII) (XXXVIII) (XXXIX)

[33] Blount, *J.*, 1935, 122; Jacobs and Craig, *J. Biol. Chem.*, 1939, **129**, 79.
[34] Craig and Jacobs, *ibid.*, 1941, **139**, 263.
[35] *Idem*, *ibid.*, p. 293.
[36] Jacobs and Pelletier, *J. Org. Chem.*, 1953, **18**, 765.
[37] Pelletier and Jacobs, *J. Amer. Chem. Soc.*, 1954, **76**, 2028; 1956, **78**, 1914.

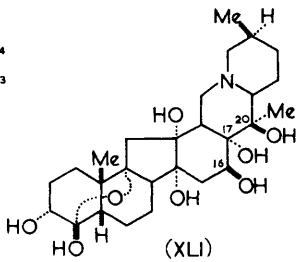
the ready and reversible oxidation of cevanthridine to the red *fluorenone*, oxycevanthridine.

Veranthridine has been formulated [36] as the analogous benzofluorene (XXXVIII). It can be reduced to an octahydro-derivative with the spectrum of a fluorene and oxidised to the red oxyveranthridine. The last substance, probably formed by autoxidation, has been isolated directly from the dehydrogenation mixture. The base $C_{20}H_{19}N$ then becomes (XXXIX).

On the basis of this evidence, Jacobs and Pelletier [36] suggested that cevan, the nucleus of cevine, was a C-nor-D-homo-steroid with the structure (XL). The alkamines veracevine, germine, protoverine, and zygadenine are oxygenated derivatives of this skeleton. The formation of *cyclo*pentenofluorenes on dehydrogenation is not inconsistent with this formulation, since jervine, under similar conditions, also gives a mixture of *cyclo*pentenofluorenes and benzofluorenes.



(XL)



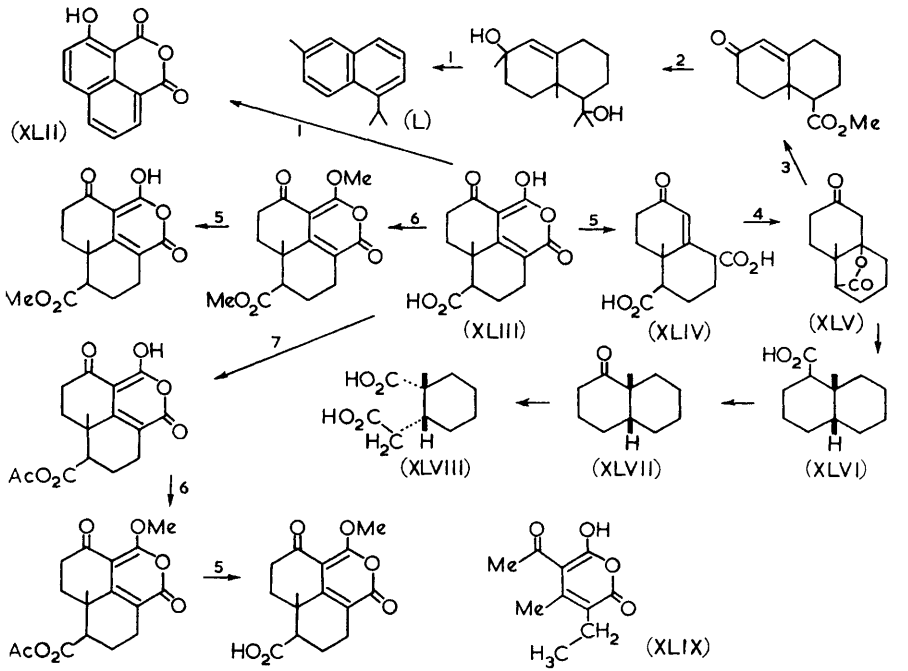
(XLI)

This modified steroid skeleton is further confirmed by oxidation of cevine and of its derivatives, studies of which lead also to determination of the position and nature of the eight oxygen atoms in the molecule. With chromic acid, cevine yields [38] a mixture of acids and lactams. From the acidic fraction, in addition to acetic acid, six acids have been isolated [39] as their methyl esters: (*a*) methylsuccinic acid, (*b*) αα-dimethylsuccinic acid, (*c*) a dicarboxylic acid $C_{11}H_{14}O_8$ or $C_{11}H_{16}O_8$, which also contains a lactone grouping, (*d*) a hexanetetracarboxylic acid $C_{10}H_{14}O_8$, (*e*) a heptanetetracarboxylic acid $C_{11}H_{16}O_8$, and (*f*) a tricarboxylic acid $C_{14}H_{18}O_8$, containing a lactone grouping. The most important of these is the acid (*f*), which, under the action of heat or alkali, loses the elements of water (2 mols.) to give decevinic acid, $C_{14}H_{14}O_6$. The properties and transformations of decevinic acid (scheme 1) have been extensively investigated by Craig and Jacobs.[39] Subsequent work by Gautschi, Jeger, Prelog, and Woodward [40] has extended the earlier results and led to the formulation of decevinic acid as an acylglutaconic anhydride (XLIII). A similar structure was proposed independently by Taylor, Barltrop, and Morgan [41] from an examination of the data provided by Jacobs and Craig.

Dehydrogenation of decevinic acid under such mild conditions that

[38] Craig and Jacobs, *J. Amer., Chem. Soc.*, 1939, **61**, 2252.
[39] *Idem, J. Biol. Chem.*, 1940, **134**, 123; 1941, **141**, 253.
[40] Gautschi, Jeger, Prelog, and Woodward, *Helv. Chim. Acta*, 1954, **37**, 2280.
[41] Morgan, Thesis, Oxford University, 1952.

major structural changes can be discounted yields 2-hydroxynaphthalic anhydride (XLII). This at once fixes the relative positions of twelve of the fourteen carbon atoms. Decevinic acid is a dibasic acid possessing a carboxyl group and a weaker acidic function associated with the acylglutaconic anhydride system. When the acid is heated with N-alkali the anhydride



SCHEME 1

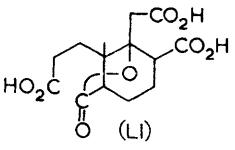
Reagents : 1, Se. 2, MeMgBr. 3, OH^-, then H^+, then CH_2N_2. 4, Heat. 5, OH^-. 6, CH_2N_2. 7, Ac_2O.

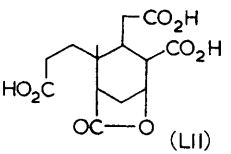
ring opens with the consumption of a further equivalent of alkali, giving a β-keto-acid which suffers decarboxylation. The resultant dicarboxylic acid (XLIV) is itself a vinylogue of a β-keto-acid and on further heating is decarboxylated with simultaneous lactonisation, giving the compound (XLV) ; the infrared spectrum confirms the ketonic ring as six-membered and the lactone ring as five-membered. Hydrolysis and methylation of this keto-lactone gives a keto-ester which can be reduced by the Clemmensen method to an acid identified synthetically as (+)-9-methyl-*cis*-decalin-1-carboxylic acid (XLVI). All these results are adequately accommodated in the structure (XLIII) proposed for decevinic acid. Strong confirmatory evidence is provided by comparison [42] of the ultraviolet and infrared spectra of decevinic acid and of α-acetyl-α'-ethyl-β-methylglutaconic anhydride (XLIX). However, it is not possible from these results alone to discriminate

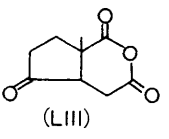
[42] Barltrop and Morgan, unpublished results.

between the structure (XLIII) and one which contains the carboxyl group in the other *peri*-position. The alternative formulation is excluded by consideration of the cevan skeleton and by the structure of the hexanetetracarboxylic acid and of the precursor acid *f*. Direct evidence for the position of the carboxyl group has been provided [43] by conversion of the keto-lactone (XLV) into 2-methyl-5-*iso*propylnaphthalene (L).

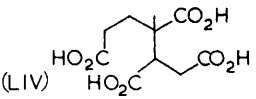
The precursor, acid (*f*), of decevinic acid yields a triester and is the γ-lactone of a monocyclic, saturated, hydroxy-tetracarboxylic acid. Its ready conversion into decevinic acid eliminates all but two positions (LI, LII) for the site of the lactonised hydroxyl group ; the second formulation does not satisfy the structural requirements of the cevine molecule and may be discarded. From the nature of the substitution on the carbocyclic ring of the precursor acid it follows that this ring must have originated as ring B in cevine. Further degradation of the acid (XLVI) to (+)-9-methyl-*cis*-1-decalone (XLVII) and thence to the *cis-cyclo*hexane acid (XLVIII) has been achieved [44] and consequently links the stereochemistry of cevine at $C_{(10)}$ with that of the steroids and terpenes.[45]

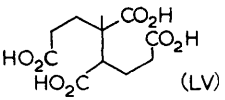

(LI)


(LII)


(LIII)

The hexanetetracarboxylic acid, on being heated, gives first a dicyclic anhydride in which one ring is five-membered and then a keto-anhydride in which the carbocyclic ring is five-membered.[38, 46] This keto-anhydride (LIII) has been synthesised [47] and shown to be derived from the expected hexane acid (LIV). The homologous heptane tetracarboxylic acid may then be written as (LV).


(LIV)


(LV)

In the carbon skeleton adopted for cevine, fission to the precursor acid suggests that there are oxygen atoms at position 4 and possibly also at position 3. There can be only one more oxygen atom in rings A and B, and that, from the structure of the precursor acid, must be located at position 9. The side chain $CH_2 \cdot CO_2H$ in the precursor confirms the writing of ring C as five-membered : a conventional steroid would almost certainly suffer fission between $C_{(11)}$ and $C_{(12)}$.

Cevine consumes two mols. of lead tetra-acetate or of periodic acid and

[43] Prelog, unpublished results.

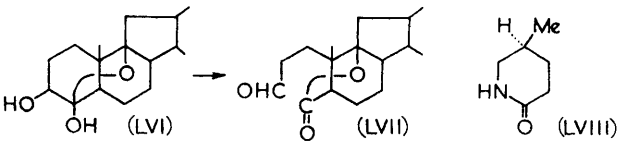
[44] Gautschi, Jeger, Prelog, and Woodward, *Helv. Chim. Acta*, 1955, **38**, 296.

[45] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

[46] Elming, Vogel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 2022.

[47] Jeger, Mirza, Prelog, Vogel, and Woodward, *ibid.*, 1954, **37**, 2295.

hence possesses at least two α-glycol systems. It is weakly acidic, giving salts with alkali-metal alkoxides ; it is methylated[10c] by methanolic hydrogen chloride ; it reduces Fehling's solution and silver oxide, and can be reduced by sodium in ethanol. These reactions all suggest that one of the glycol groups is actually an α-ketol or acyloin. Since cevine has been shown not to contain a free carbonyl group it was further suggested that the ketonic function was masked in a hemiketal group [41, 48] (cf. LVI), thus providing the seventh ring required by the analytical figures for cevine. Confirmation of such a structure was obtained by the periodate fission of one of the glycol systems to an aldehydo-γ-lactone.[49, 50] This recalls the γ-lactonic function of the precursor acid and suggests the formulation (LVII).



The other α-glycol grouping is ditertiary because, while cevine triacetate is stable to chromic acid, it still consumes one mol. of lead tetra-acetate. Although 2-dialkylaminoethanols are inert to lead tetra-acetate, α-dialkylamino-ketones undergo oxidative fission. Since cevine triacetate consumes only one mol. of lead tetra-acetate neither of the hydroxyl groups of the ditertiary glycol can be situated β with respect to the nitrogen atom, for such a circumstance would lead to the formation of an α-dialkylamino-ketone as an intermediate and hence to the consumption of more than one mol. of oxidising agent. Also the absence of carbinolamine properties in cevine requires that there be no hydroxyl group located α with respect to the nitrogen atom. These considerations leave the C/D ring junction at $C_{(12)}$ and $C_{(14)}$ as the only available site for the second glycol system.

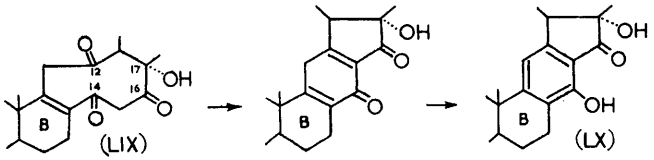
Five oxygen atoms have now been accounted for : the remaining three must be located in rings D, E, and F and they can be placed by a process of elimination. One of the lactams formed in the chromic acid oxidation of cevine is optically active and has been shown by synthesis [51] to be L(−)-5-methylpiperidone (LVIII) ; there can thus be no oxygen atom situated between $C_{(23)}$ and $C_{(27)}$. There are no primary CH_2·OH groups. $C_{(13)}$ and $C_{(15)}$ are excluded as sites bearing the hydroxyl groups because they are adjacent to the tertiary glycol ; $C_{(18)}$ and $C_{(22)}$ by the absence of carbinol amine properties. This leaves available only the positions 16, 17, and 20. Accordingly, the structure (XLI) can be written [52] for cevine (the stereochemical aspects are considered below).

It is noteworthy that this structure contains a 1 : 2 : 3-triol which must be inert to glycol-splitting reagents. Hydroxyl groups held rigidly in

[48] Barton and Eastham, *J.*, 1953, 424.
[49] Barton and Brooks, *Chem. and Ind.*, 1953, 1366.
[50] Barton, Brooks, and Fawcett, *J.*, 1954, 2137.
[51] Jeger, Prelog, Sundt, and Woodward, *Helv. Chim. Acta*, 1954, **37**, 2302.
[52] Barton, Jeger, Prelog, and Woodward, *Experientia*, 1954, **10**, 81.

hindered positions are known [53] to show such inactivity. It may be noted that titration of cevine with glycol reagents shows a slow continuing uptake of the reagents after the initial fast reaction is complete ; epimerisation [54] or oxidation [55] of the 16-hydroxyl group makes attack on the $C_{(16)}$-$C_{(17)}$-$C_{(20)}$ system more rapid.

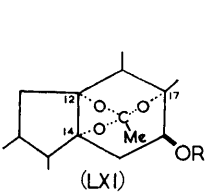
A sophisticated confirmation of the nature of the C/D ring system has been provided by chromic acid oxidation [56] of the ester alkaloid cevadine (see below). The primary product is the 12 : 14-*seco*-$\Delta^{8:9}$-4 : 12 : 14 : 16-tetrone (LIX) which cyclises and aromatises under the experimental conditions to a compound in which a 7-hydroxyindan-1-one unit was identified spectrally and chemically (cf. LX). It follows that ring C must be five-membered, that there is a hydroxyl group at position 16, and that there can be no hydrogen atom at position 17.



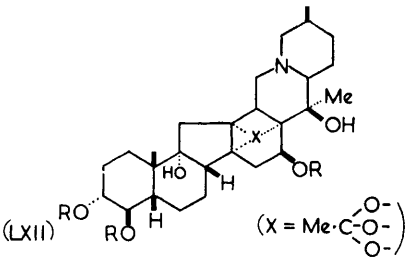
The extensive evidence which has accumulated through the preparation of a large number of esters fully supports the structure ascribed to cevine. The alkamine is readily diacylated (at positions 3 and 16), and in the presence of pyridine is triacylated. Triacylation must give protection to both hydroxyl groups in ring A since cevine triacetate is inert to chromic acid. Although the remaining hydroxyl groups are all tertiary, acetylation of cevine triacetate in the presence of perchloric acid results in the introduction of a fourth acetyl group and the concomitant loss of a molecule of water. The product, anhydrocevine tetra-acetate, exists in aqueous acetic acid in equilibrium with cevine tetra-acetate, and it has been shown spectroscopically [50] to be cevine triacetate orthoacetate. The presence of an orthoacetate system has also been demonstrated chemically [12, 57] by the existence in the analogous derivative of the ester alkaloid cevadine (see below) of an acetyl residue stable to alkali but readily hydrolysed by acid. Hydrogenation of cevine triacetate orthoacetate gives cevine triacetate " dihydro-orthoacetate ", formulated as an acetal since hydrolysis yields acetaldehyde ; re-oxidation of the " dihydro-orthoacetate " with chromium trioxide regenerates [55] the orthoacetate. The unique formation of an orthoester in this way demands the presence of three suitably orientated tertiary hydroxyl groups. At least one of the hydroxyl groups in the tertiary glycol is bound in the orthoester because although cevine triacetate is oxidised by periodic acid cevine triacetate orthoacetate is stable. This fixes the general location

[53] Criegee, Kraft, and Rank, *Annalen*, 1935, **507**, 159 ; Criegee, Büchner, and Walther, *Ber.*, 1940, **73**, 571 ; Wintersteiner and Moore, *J. Amer. Chem. Soc.* 1950, **72**, 1923.
[54] Kupchan and Johnson, *ibid.*, 1956, **78**, 3864.
[55] Barton, Brooks, and de Mayo, *J.*, 1954, 3950.
[56] Mijovic, Sundt, Kyburz, Jeger, and Prelog, *Helv. Chim. Acta*, 1955, **38**, 231.
[57] Stoll and Seebeck, *ibid.*, 1954, **37**, 824.

of the orthoacetate group and models indicate that the 12-, 14-, and 17-hydroxyl groups are suitably placed (LXI ; R = Ac). This provides additional evidence for the existence of a hydroxyl group at position 17 ; the necessity for such substitution is further indicated by the spectra of the 16-ketones obtained by oxidising cevine 3 : 4-diacetate and cevine 3 : 4-diacetate orthoacetate, the differences between which require [55] that there be a hydroxyl group adjacent to the ketone in the simple diacetate.



(LXI)



(LXII)

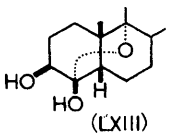
Cevine triacetate orthoacetate can be reduced at the hemiketal grouping by lithium in liquid ammonia, to give dihydrocevine orthoacetate (LXII ; R = H), readily convertible into the triacetate (LXII ; R = Ac). The last triacetate is stable to chromic acid and so the hydroxyl group (which is bound as an ether in the hemiketal and must be γ with respect to the potential carbonyl group in ring A) is tertiary, and therefore must be located [55] at position 9 as had been suggested above.

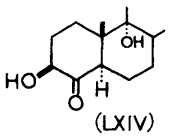
Veracevine. Hydrolysis of the ester alkaloid cevadine with 20% alcoholic potassium hydroxide gives cevine as its potassium salt. When milder conditions are used, a ketonic isomer of cevine, cevagenine, is obtained.[58] It is apparent that cevagenine cannot be the true alkamine of cevadine since the latter contains no ketonic carbonyl group. Use of very dilute alkali and very mild conditions gives a second isomer [11, 12, 59] of cevine. The new isomer, veracevine, is non-ketonic. Its status as the true alkamine of the cevan alkaloids is established by the synthesis [60] of the naturally occurring esters cevacine and veratridine from it. In the presence of alkali, veracevine is isomerised irreversibly, first to cevagenine and then, with more concentrated alkali, to cevine. Apart from its instability to alkali, veracevine is chemically very similar to cevine : entirely analogous esters and orthoesters have been prepared [59] and the oxidation of it and its derivatives parallels that of the corresponding cevine compounds.[61]

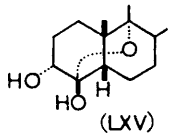
The isomerism of the triad veracevine (LXIII), cevagenine (LXIV), and cevine (LXV) is that of hemiketal, hydroxy-ketone, and *epi*hemiketal.[12] That ring A is the seat of these changes has been established by the oxidation of all three bases by bismuth oxide to the same product, cevilinic lactone.[61] This substance, a hydroxy-δ-lactone (LXVII), appears to be formed by a

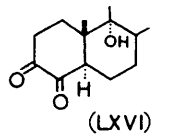
[58] Stoll and Seebeck, *Helv. Chim. Acta.*, 1952, **35**, 1270.
[59] *Idem*, *ibid.*, 1953, **36**, 189.
[60] Macek, Vanecek, Pelcova, and Vejdelek, *Chem. Listy*, 1956, **50**, 603.
[61] Kupchan and Lavie, *J. Amer. Chem. Soc.*, 1954, **76**, 314.

benzilic acid rearrangement of the initially formed α-diketone (LXVI). The structure of the lactone was confirmed by reduction with sodium

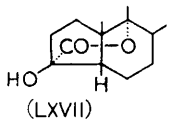

(LXIII)

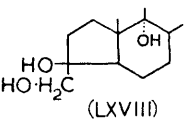

(LXIV)

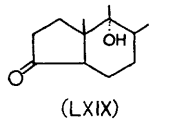

(LXV)


(LXVI)

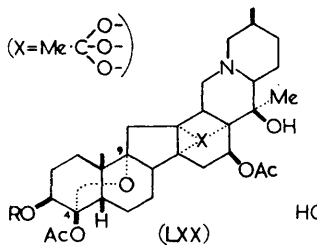
borohydride to the glycol (LXVIII), which was oxidised by periodate, after protection of the rest of the molecule by orthoester formation, to a *cyclo*-pentanone (LXIX).

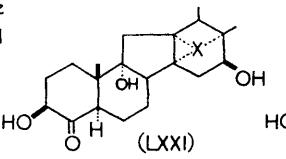

(LXVII)

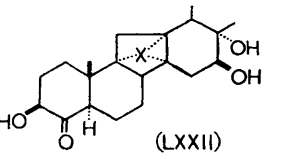

(LXVIII)


(LXIX)

The chemistry of cevagenine (LXIV) differs in some respects from that of the two hemiketals. It is readily diacetylated at positions 3 and 16. The absence of any simple triacyl derivatives further supports the tertiary nature and hence 9-position of the hydroxyl group masked as an ether in the hemiketals. The presence of a free 9-hydroxyl group provides a second triol system which can give orthoesters, and two distinct cevagenine ortho-acetates have been prepared. Hydrolysis of cevadine orthoacetate diacetate (LXX ; R = angeloyl) by alkali gives cevagenine D-orthoacetate (LXXI) which in dilute acid rearranges [62] to the isomeric cevagenine C-orthoacetate (LXXII). These structures have been assigned by comparison of the


(LXX)


(LXXI)


(LXXII)

spectra and molecular rotations of these compounds with the orthoacetates derived from the hemiketal alkamines. The stability of the C-orthoacetate to 20% potassium hydroxide solution, which converts the D-orthoacetate into cevine orthoacetate, may be attributed to the non-availability of the 9-hydroxyl group.

There are present in veracevine fourteen asymmetric centres. It is possible with our present knowledge to assign to many of these centres their appropriate configuration.[52, 55] The $C_{(4)}$-O-$C_{(9)}$ bridge demands that the A/B ring junction be *cis* and that the bridge be α-orientated. The assignment of configuration at $C_{(3)}$ is based on the concept that the driving

[62] Kupchan, *J. Amer. Chem., Soc.*, 1955, **77**, 686.

force for the veracevine–cevine transformation is the thermodynamic instability of an axial hydroxyl group with respect to its equatorial counterpart; *i.e.*, in veracevine and cevine, the 3-hydroxyl groups are orientated β and α respectively. Cevagenine must possess *trans*-fusion of the A and B rings to account for the lack of interaction between the 4-carbonyl and the 9-hydroxyl group, which with an A/B-*cis* arrangement would lead immediately to the construction of a hemiketal system. Since cevagenine is prepared under enolising conditions, the 3-hydroxyl group must lie in the equatorial, *i.e.*, β-direction. The B/C-ring junction in normal steroids is invariably *trans* and the configuration of the 8-hydrogen atom invariably β. The C-orthoacetate of cevagenine requires that the 12- and the 14-hydroxyl group have the same α-orientation as that at position 9, and the formation of the D-orthoacetates extends this requirement to position 17. The inertness of the triol system to periodic acid suggests that the 17- and the 20-hydroxyl group are diaxial and therefore have the α- and β-configuration respectively, and that the D/E-ring junction is *trans*. Since 16-*epi*cevagenine C-orthoacetate is split more readily than its isomer by periodic acid (suggesting that here we have a *cis*-16 : 17-glycol), we may assign a β-orientation to the 16-hydroxyl group in the alkaloids. The ready methanolysis of the 16-esters finds a simple interpretation [54] in terms of the neighbouring-group effect of the 20-hydroxyl if both groups are β and axial. The synthesis of the lactam (LVIII) has shown that the 27-methyl group is β-orientated. Thus an almost complete structure may be written for veracevine: it is 4α : 9α-epoxycevan-3β : 4β : 12α : 14α : 16β : 17α : 20β-heptaol. The configurations at $C_{(8)}$ and $C_{(13)}$ require to be confirmed and that at $C_{(22)}$ to be determined.

The four naturally occurring alkaloids, cevadine, veratridine, cevacine, and vanilloylveracevine, are respectively the angelic, veratric, acetic, and vanillic esters of veracevine, with the acyloxy-group at position 3.

Germine. Of the alkaloids found in *Veratrum* and *Zygadenus* spp. the most common are esters of germine. First isolated by Poethke,[7, 63] germine, $C_{27}H_{43}O_8N$, was shown to be linked structurally with its formal isomer, cevine, by dehydrogenation to cevanthridine.[64] Although germine does not contain a carbonyl group [65] it is reduced by sodium and butanol.[66] The similarity of this behaviour to that of cevine suggested [52] that germine might also contain a masked α-ketol system. This has been confirmed by the isolation of the ketonic isomer *iso*germine [64, 65] and the non-ketonic isomer *pseudo*germine.[65] All three alkamines give *iso*propylidene derivatives on condensation with acetone under acidic conditions; [64, 67, 68] periodate oxidation of these derivatives of germine and *pseudo*germine gives the same aldehydo-γ-lactone and indicates the presence of a 3-hydroxyl, 4-hemiketal

[63] Poethke, *Arch. Pharm.*, 1937, **275**, 571.
[64] Craig and Jacobs, *J. Biol. Chem.*, 1943, **148**, 57.
[65] Jaffe and Jacobs, *ibid.*, 1951, **193**, 325.
[66] Craig and Jacobs, *ibid.*, 1943, **149**, 451.
[67] Kupchan, Fieser, Narayanan, Fieser, and Fried, *J. Amer. Chem. Soc.*, 1954, **76**, 1200.
[68] Kupchan and Narayanan, *Chem. and Ind.*, 1955, 251.

system similar to that found in cevine.[63, 69] The order of stability [70] of the isomers, *iso*germine < germine < *pseudo*germine, differs from that of the cevine triad; acylation [71] of germine to give germidine and monoacetyl-*neo*germitrine establishes that it is the true alkamine of the naturally occurring esters.

Acetylation of all three isomers readily gives tetra-acetates, and germine under forcing conditions (acetic anhydride and sodium acetate) gives a penta-acetate.[70] This implies, first, the existence in germine of five non-tertiary hydroxyl groups and, secondly, that the bridge from $C_{(4)}$–O must be to a tertiary carbon atom and therefore presumably to position 9. The occurrence of a 7-oxygenated group is suggested by isolation of the hexanetetra-carboxylic acid formed in the oxidation of cevine, but not the precursor of decevinic acid, when germine is oxidised by chromic acid.[64] The remaining four oxygen atoms are to be accommodated in hydroxyl groups, two of which are secondary and two tertiary. While germine consumes three mols. of periodate, the consumption of only one mol. by *iso*propylidene-germine indicates that three of these hydroxyls form a 1 : 2 : 3-triol system.* The inertness of germine tetra-acetate to glycol fission suggests that the triol forms either a *sec.-sec.-tert.*- or a *tert.-sec.-tert.*-system. The absence of carbinolamine properties and the uptake of no more than three mols. of periodate lead to the exclusion of sites both α and β with respect to the nitrogen atom for the location of the triol. Since *iso*germine and dihydro-germine, neither of which possesses the $C_{(4)}$–O–$C_{(9)}$ ether bridge, consume only three mols. of periodate (like germine), there can be no hydroxyl group adjacent to $C_{(9)}$; the formation of the hexanetetracarboxylic acid on oxidation excludes the possibility of additional oxygenated groups in rings A and B. Consequently only positions 12, 14, 15, 16, and 17 remain available for the triol: amongst these a *tert.-sec.-tert.*-triol cannot be accommodated. The triol grouping has been placed [68] at positions 14, 15, and 16. Subsequent results support this arrangement rather than the alternative, 15 : 16 : 17. The residual hydroxyl group has been placed [70] at position 20, leading to the representation (LXXIII) as the structure of germine (the stereochemistry is discussed below).

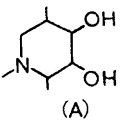
The presence of a *sec.-sec.-tert.*-triol is confirmed by hydrolysis of *OO-iso*-propylidenegermine diacetate, formulated as (LXXIV), to a diacetate which consumes one mol. of periodate with the formation of an unsaturated keto-aldehyde ($\lambda_{max.}$ 238 mμ). This was assigned [68] the structure (LXXV) at a time when it was believed that germine possessed a $C_{(4)}$–O–$C_{(7)}$ oxide structure. The alternative formulation (LXXVI) may perhaps be prefer-

[69] Kupchan, Fieser, Narayanan, Fieser, and Fried, *J. Amer. Chem. Soc.*, 1955, **77**, 5896.

[70] Kupchan and Narayanan, *Chem. and Ind.*, 1956, 1092.

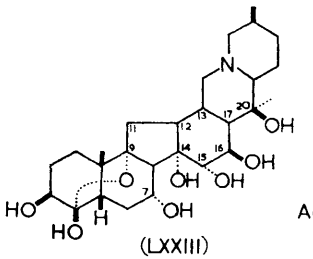
[71] Weisenborn and Bolger, *J. Amer. Chem. Soc.*, 1954, **76**, 5543.

* The possibility that germine contains a 1 : 2 : 3-dialkylamino-diol system such as (A) is excluded because acetylation of *OO-iso*propylidene-germine followed by hydrolysis gives a germine diacetate which consumes only one mol. of periodate, and not two as this formulation would require. (Ring F shown.)

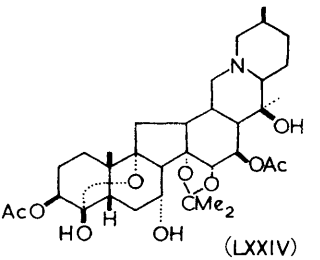


(A)

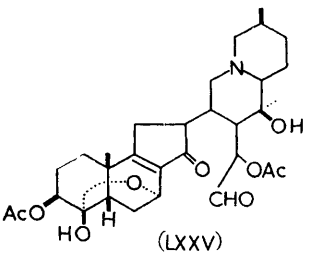
able. It is difficult to reconcile the ultraviolet spectrum of this product with the presence of a 15 : 16 : 17-triol system in germine.



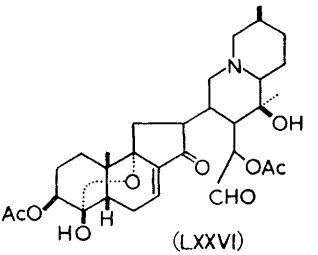
(LXXIII)



(LXXIV)

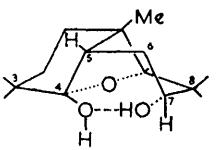


(LXXV)



(LXXVI)

The stereochemistry of the masked ketol system incorporates the pattern established in the cevine triad. The different sequence of stabilities among the germine isomers may be attributed [70] to a stabilisation of the hemiketal structures by hydrogen-bonding between the 4-hydroxyl and the α-orientated 7-hydroxyl groups (cf. LXXVII, where the dotted bonds have steroid



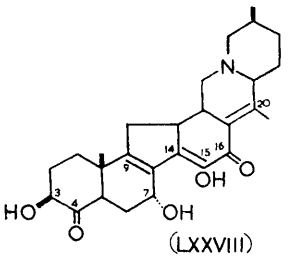
(LXXVII)

α-significance). That the 7-hydroxyl group is indeed α-orientated is suggested [70] (*a*) by borohydride reduction of 7-dehydro-14 : 15-*iso*propylidenegermine 3 : 16-diacetate to 14 : 15-*iso*propylidenegermine 3-acetate by attack from the relatively less hindered front face of the molecule, and (*b*) by acetylation of germine with acetic anhydride and pyridine to germine 3 : 7 : 15 : 16-tetra-acetate. This reagent, which acetylates the 4-hydroxyl group in veracevine, fails to do so with germine because prior 7-acetylation gives a 7-acetate which when α-orientated sterically hinders attack at the 4-position.

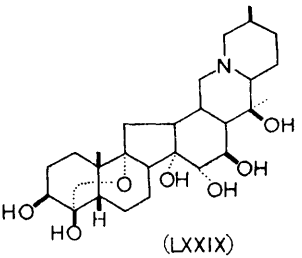
The tentative assignment of configurations to the hydroxyl groups in ring D is based on the resistance of *iso*propylidenegermine to acetylation of the 7-hydroxyl group. This suggests that the 14- and the 15-hydroxyl groups are both α-orientated : the failure of the disecondary 15 : 16-glycol to form an *iso*propylidene derivative suggests that these groups are *trans*. These notions find support in the ready methanolysis of the 7 : 16-acyl

groups, which indicates [54] that they bear a *cis*-1 : 3-relation to the 14- and 20-hydroxyl groups. A tentative structure for germine may accordingly be written as 4α : 9α-epoxycevan-3β : 4β : 7α : 14α : 15α : 16β : 20β-heptaol (LXXIII).

Some preliminary results [70] have been reported of attempts to establish the structure of the naturally occurring esters of germine. The three alkaloids germidine, *iso*germidine, and *neo*germitrine are all esterified in the same position by α-methylbutyric acid.[72] Germidine and *iso*germidine possess an additional acetyl group. Since germidine is stable to periodate it must have an acyl residue in ring A and another at position 15. *iso*-Germidine, consuming one mol. of periodate to give an aldehydo-γ-lactone, is therefore not acylated in ring A. It follows that the α-methylbutyric

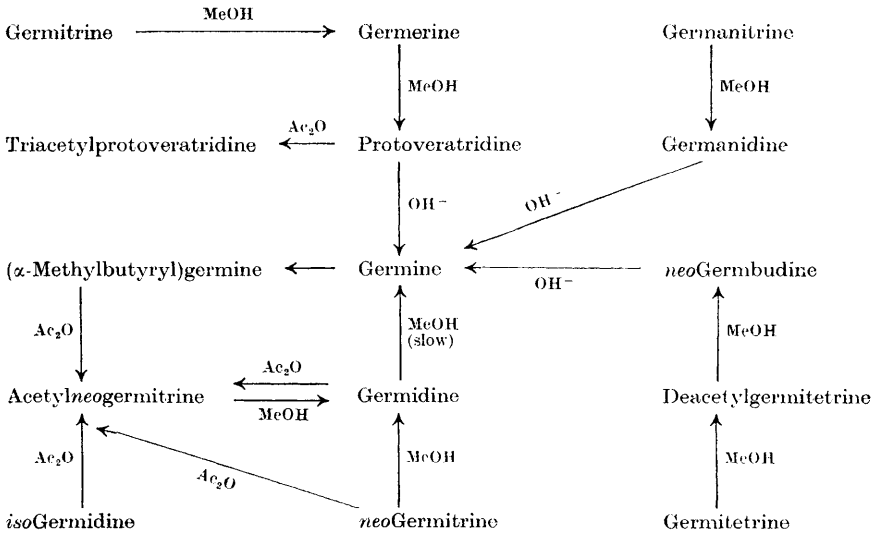


(LXXVIII)



(LXXIX)

acid moiety in all three esters must be at position 15. *neo*Germitrine may be oxidised by chromic acid to a ketone *neo*germitrone, which after hydrolysis gives a diosphenol, probably (LXXVIII). This suggests that the two



SCHEME 2. *Interrelationship of certain esters of germine.*

[72] Kupchan and Deliwala, *J. Amer. Chem. Soc.*, 1954, **76**, 5545.

acetoxyl groups in *neo*germitrine are at positions 3 and 7. Molecular-rotation evidence [70] indicates that the acetyl group in *iso*germidine is at position 16. These results and the recorded correlations (Scheme 2) and rotations [71] of other naturally occurring esters of germine enable tentative structures to be assigned (Table 3).

TABLE 3. *Germine esters*

Alkaloid	$[M]_D$ [a]	Position of acyl group [b]			
		3	7	15	16
Synthetic monoesters	−128°	—	x	—	—
Synthetic tetraesters	−636	x	x	x	x
Protoveratridine	−53	II	—	—	—
Germidine	−70	I	—	II	—
*iso*Germidine	−328	—	—	II	I
Germerine	−108	II	—	III	—
Germitrine	−518	II	I	III	—
*neo*Germitrine	−528	I	I	II	—
Triacetylprotoveratridine	—	II	I	I	I
Germbudine	−53	x	—	x	—
*neo*Germbudine	−84				
Germitetrine	−582	x	I	x	I
Germanitrine	−438	x	I	x	—

[a] In pyridine. [b] Roman numerals refer to formula numbers on p. 37; the symbol "x" is used when the acid radical is not specified.

Zygadenine, $C_{27}H_{43}O_7N$, was first isolated [73] from *Z. intermedius* in 1913 and first identified [74] as a typical veratrum base in 1949. Subsequently, the isolation [72, 75] of germine esters from many *Zygadenus* spp. and of veratroylzygadenine from several *Veratrum* spp. confirmed the close relation between these species first suggested by the similarity of their pharmacological properties.[76] Zygadenine, a tertiary base, containing neither *O*-methyl nor *N*-methyl groups, possesses a typical masked α-ketol system.[74, 77] Alkaline isomerisation gives first the free α-ketol, *iso*zygadenine,[77] which can be oxidised to a diosphenol [78] and isomerised to the hemiketal, *pseudo*zygadenine.[77] The stabilities of the three isomers lie in the order, zygadenine < *iso*zygadenine < *pseudo*zygadenine, analogous to the veracevine triad.

Zygadenine yields a triacetate readily, a tetra-acetate under forcing conditions, and with acetone an *iso*propylidene derivative.[79] The presence [80] of a 1 : 2 : 3-triol in addition to the masked α-ketol group is indicated by

[73] Heyl, Hepner, and Loy, *J. Amer. Chem. Soc.*, 1913, **35**, 258.
[74] Heyl and Herr, *ibid.*, 1949, **71**, 1751.
[75] Kupchan and Deliwala, *ibid.*, 1952, **74**, 3202.
[76] Hunt, *Amer. J. Physiol.*, 1902, **6**, 19; Mitchell and Smith, *ibid.*, 1911, **28**, 318.
[77] Kupchan and Deliwala, *J. Amer. Chem. Soc.*, 1953, **75**, 1025.
[78] Auterhoff and Günther, *Arch. Pharm.*, 1955, **288**, 455.
[79] Kupchan, Lavie, and Zonis, *J. Amer. Chem. Soc.*, 1955, **77**, 689.
[80] Kupchan, *ibid.*, 1956, **78**, 3546.

periodate titrations. The structure (LXXIX) for zygadenine and its correlation with germine is proved [80] by the reduction of 7-dehydrogermine 3 : 16-diacetate to zygadenine 3 : 16-diacetate : condensation of the keto-group with propane-1 : 3-dithiol followed by desulphurisation with Raney nickel led to the elimination of the carbonyl group. Only monoesters of zygadenine have been isolated from natural sources ; the acid residues (acetyl, vanilloyl, and veratroyl) are presumed to be at position 3.

Protoverine, $C_{27}H_{43}O_9N$, is the most highly hydroxylated veratrum base. Apart from the presence of the cevan skeleton [81] and the characteristic masked α-ketol system,[78] little is known of its structure. The isomers *iso*-protoverine [82] and *pseudo*protoverine [78] have been isolated and shown to be the corresponding free ketol and the isomeric hemiketal respectively. Protoverine yields an *iso*propylidene derivative ; [82] this, and the presence of two readily methanolysed acyl groups in its tetraesters, suggest that it may prove to be a hydroxygermine. It is of interest that the three cevan bases, protoverine, germine, and zygadenine, which occur together in many *Veratrum* spp. appear to show in their fine structure close similarities which are not shared with veracevine.

Fritillaria Alkaloids.—The Chinese drug Pei-mu consists of extracts of the dried bulbs of the liliaceous plant, *Fritillaria roylei*. In the East it enjoys a considerable reputation as a general medical panacea.[83] A more precise evaluation [84] detected similarities between its pharmacology and that of veratrine. Recent structural investigations of the alkaloidal constituents of Pei-mu and other *Fritillaria* extracts have shown close chemical links between the principal alkaloids and those of *Veratrum* spp.

Imperialine, $C_{27}H_{43}O_3N$, was first isolated [85] from *F. imperialis* ; recently it has been shown [86] to be identical with sipeimine [87] obtained from the Chinese drug Si-pei-mu (*F. roylei*). It is a saturated, tertiary base containing a carbonyl group and two alcoholic hydroxyl groups, one of which is secondary and acylatable, the other tertiary ; it contains neither *N*-methyl nor *O*-methyl groups.[87, 88] The presence of the cevan skeleton has been established by dehydrogenation.[89] In addition to typical benzofluorenes (one of which, $C_{18}H_{14}$, has been identified as 8-methyl-1 : 2-benzofluorene) and 2 : 5-lutidine, there have been isolated veranthridine (XXXVIII) and a compound, $C_{26}H_{31}N$, which appears to be hexahydroveranthridine. Infrared spectra indicate that the carbonyl group, which readily yields an oxime, is located in a six-membered ring.[86] Oxidation of the secondary alcoholic

[81] Craig and Jacobs, *J. Biol. Chem.*, 1942, **143**, 427.

[82] *Idem*, *ibid.*, 1943, **149**, 271.

[83] (*a*) Liu, Chang, and Chang, *Chinese Med. J.*, 1936, **50**, 249 ; (*b*) Chi, Kao, and Chang, *J. Amer. Chem. Soc.*, 1936, **58**, 1306.

[84] Narumi, *Tohóku J. Exp. Med.*, 1935, **26**, 325.

[85] Franger, *Ber.*, 1888, **21**, 3284.

[86] Boit and Paul, *Chem. Ber.*, 1957, **90**, 723.

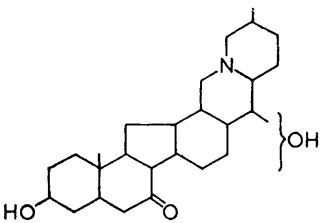
[87] Chu and Loh, *Acta Chim. Sinica*, 1955, **21**, 241 ; *Chem. Abs.*, 1957, **51**, 445.

[88] Boit, *Chem. Ber.*, 1954, **87**, 472.

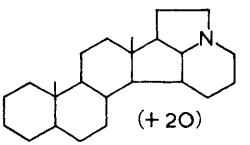
[89] Chu, Loh, and Hwang, *Acta Chim. Sinica*, 1955, **21**, 401 ; *Chem. Abs.*, 1957, **51**, 45 ; Chu and Loh, *Acta Chim. Sinica*, 1956, **22**, 210 ; *Chem. Abs.*, 1957, **51**, 445.

group to give imperialone (sipeimone) which is neither an α- nor a β-diketone introduces a keto-group into a second six-membered ring. Examination of the recorded rotations [90] of these compounds, the reduction products, and the esters suggests that the secondary hydroxyl group and the carbonyl groups may tentatively be placed at positions 3 and 7 respectively (cf. LXXX); this leaves positions 12, 13, 17 and 20 as possible sites for the tertiary hydroxyl group.

Peimine, $C_{27}H_{45}O_3N$, which may be identical with verticine, [83b, 91] apoverticine,[92] and peimunine [93] can be extracted from *F. roylei* or *F. verticillata* and forms the major part of the active principle of the drug Pei-mu. It is a saturated tertiary base containing neither *N*- nor *O*-methyl groups. Two of the oxygen atoms are present as acylatable secondary alcoholic groups.[94] On mild oxidation [94a] peimine is converted into the monoketone, peiminine $C_{27}H_{43}O_3N$, which accompanies it in Pei-mu (peiminine may be identical with verticilline,[91] peimiphine,[95] peimitidine,[95] and fritillarine [91]). Reduction of peiminine with sodium in ethanol regenerates peimine. The suggestion [96] that peimine is related to the veratrum alkaloids is confirmed by dehydrogenation to 2 : 5-lutidine and 1 : 2-benzofluorenes, identical with those from imperialine.[97] It has been further suggested [97] that peimine is a cevan-11 : x : y-triol, and peiminine the corresponding cevan-11-one, but the reactivity of the carbonyl group which yields an oxime seems to preclude position 11 for it.



(LXXX)



(LXXXI)

Raddeanine, $C_{24}H_{39}O_2N$, isolated [98] from *F. raddeana*, is a saturated tertiary base which contains no *N*-methyl group. Although the ultraviolet spectrum [99] suggests the presence of an unconjugated carbonyl group and

[90] Chu, Loh, and Hwang, *Acta Chim. Sinica*, 1956, **22**, 205 ; *Chem. Abs.*, 1957, **51**, 445.

[91] Fukuda, *J. Chem. Soc. Japan*, 1929, **50**, 74.

[92] *Idem*, *ibid.*, 1948, **69**, 167.

[93] Li, *J. Chinese Pharm. Assoc.*, 1940, **2**, 235.

[94] (*a*) Chu and Chou, *J. Amer. Chem. Soc.*, 1947, **69**, 1257 ; (*b*) Chu and Loh, *Acta Chim. Sinica*, 1955, **21**, 227 ; *Chem. Abs.*, 1957, **51**, 444.

[95] Chou, *J. Amer. Pharm. Assoc.*, 1947, **36**, 215.

[96] Wu, *J. Amer. Chem. Soc.*, 1944, **66**, 1778.

[97] Chu, Hwang, and Loh, *Acta Chim. Sinica*, 1955, **21**, 232 ; *Chem. Abs.*, 1957, **51**, 444.

[98] Lazur'evskii and Sadykov, *J. Gen. Chem. U.S.S.R.*, 1943, **13**, 159 ; Aslanov and Sadykov, *Zhur. obshchei Khim.*, 1956, **26**, 579.

[99] *Idem*, *ibid.*, p. 1790.

the action of phosphorus pentachloride gives a trichloride, acetyl or benzoyl chloride in pyridine gives the diacyl derivative. Isolation [100] of a base, $C_{22}H_{17}N$, and phenanthrene on dehydrogenation with selenium, coupled with a positive pyrrole pine-splint test given by the vapour of raddeanine (though not by the base $C_{22}H_{17}N$), are expressed [98] in a carbon-nitrogen skeleton (LXXXI). Hydroxyl groups have been tentatively placed at positions 3 and 5 to account for a positive Liebermann reaction, characteristic of 3-hydroxy-Δ^5-sterols, and for the formation of a compound $C_{24}H_{37}O_3NS$, formulated as a cyclic sulphite, with thionyl chloride.[99, 100] Mild oxidation of raddeanine gives raddeanone, but under more vigorous conditions [99] a hexanetetracarboxylic acid, m.p. 153 –157°, is obtained. On the basis of the melting point this has been identified with the hexanetetracarboxylic acid from cevine : this characterisation alone cannot be regarded as adequate, for at least seven of the known hexanetetracarboxylic acids melt between 150° and 161° ; it is difficult to see how the cevine acid could be formed from the proposed structure.

Other alkaloids. There have been many reports of the isolation of other fritillaria and veratrum alkaloids. Many of these refer to bases which have yet to be fully characterised, and many others to apparently impure specimens which may subsequently prove to be identical with other preparations. A profitable discussion of these products is not possible at present.

[100] Aslanov and Sadykov, *Zhur. obshchei Khim.*, 1956, **26**, 1794.