REVIEW ARTICLE

BIOLOGICAL ACTIVITY IN STEROIDS POSSESSING NITROGEN ATOMS

PART II. STEROIDAL ALKALOIDS‡

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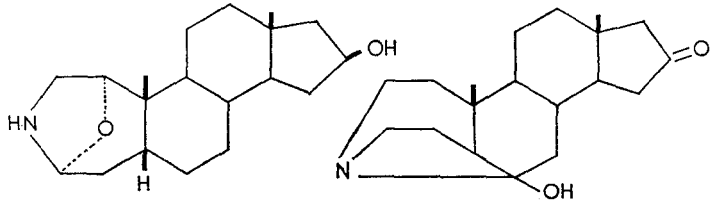
CHEMICALLY the steroidal alkaloids form a complex group, the individual members displaying much diversity in molecular structure (Fieser and Fieser, 1959; Goutarel, 1961; Jeger and Prelog, 1960; Morgan and Barltrop, 1958; Schöpf, 1961). Some occur unconjugated as the free alkamines in nature, but others occur as glycosides or esters. It has been customary to base classification of the group on botanical origin, but with the number of representatives now known, it is more convenient to consider them according to the nature of the skeleton of the alkamine. Such a classification in point of fact does not diverge too greatly from the botanical classification, but it should serve to give greater emphasis to possible structure-action relationships. Chemically, four main groups can be recognised.

3-Aza-A-homoandrostane derivatives.
Bases formally derived from the pregnane skeleton.
Bases formally derived from the unrearranged cholestane skeleton.
Bases possessing the "jervi" skeleton.

The first group is small and the only known representatives are the four salamander alkaloids samandarine (I), samandarone, samandaridine and cycloneosamandione (II) (Schöpf, 1961; Habermehl, 1962). Their pharmacological properties have been studied in detail by Gessner and his co-workers (1948 and earlier papers) who showed that these compounds exhibit analeptic activity, producing convulsions in mice and antagonising the narcotic effects of barbiturates, ethylurethane and tribromoethanol in salamander larvae and small fish.



I II

Their action on smooth muscle appears to be variable. Thus they produce vasoconstriction of the Löwen-Trendelenburg preparation of

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isolated frog vessels, relax the carotid artery of calves, relax the guinea-pig uterus and antagonise the action of adrenaline on certain preparations. Intracutaneous injection in man produces pain and hyperaemia.

Bases Formally Derived from Pregnane

The alkaloids of this group occur in various plants belonging to the family Apocynaceae and are characterised by the possession of amino functions at C(3) or C(20), or at both positions. Usually the members

TABLE I

MONOACID BASES DERIVED FROM PREGNANE

3-AMINOPREGNANES

Alkaloid	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Funtumine $C_{21}H_{35}NO$	3α-Amino-20-oxo-5α-pregnane	126	+95	*Funtumia latifolia*	1
Funtumidine $C_{21}H_{37}NO$	3α-Amino-20α-hydroxy-5α-pregnane	182	+10	*F. latifolia*	1
Holamine $C_{21}H_{33}NO$	3α-Amino-20-oxo-pregn-5-ene	135	+23	*Holarrhena floribunda*	2
Holaphyllamine $C_{21}H_{33}NO$	3β-Amino-20-oxo-pregn-5-ene	260 as HCl salt	+33 as HCl salt	*H. floribunda*	2, 3
Holaphylline $C_{22}H_{35}NO$	3β-Methylamino-20-oxo-pregn-5-ene	128	+23	*H. floribunda*	3
Paravallarine $C_{22}H_{33}NO_2$	3β-Methylamino-20α-hydroxypregn-5-en-18-carboxylic acid lactone	181	−52	*Paravallaris microphylla*	4

20-AMINOPREGNANES

Alkaloid	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Funtuphyllamine A $C_{21}H_{37}NO$	20α-Amino-3β-hydroxy-5α-pregnane	173	+13	*Funtumia africana*	5
Funtuphyllamine B $C_{22}H_{39}NO$	20α-Methylamino-3β-hydroxy-5α-pregnane	214	+24	*F. africana* and *Malouetia bequaertiana*	5, 6
Funtuphyllamine C $C_{23}H_{41}NO$	20α-Dimethylamino-3β-hydroxy-5α-pregnane	172	+24	*F. africana*	5
Funtumafrine B $C_{22}H_{37}NO$	20α-Methylamino-3-oxo-5α-pregnane	160	+43	*F. africana*	5
Funtumafrine C $C_{23}H_{39}NO$	20α-Dimethylamino-3-oxo-5α-pregnane	174	+45	*F. africana* and *M. bequaertiana*	5
Gluco-alkaloid $C_{27}H_{45}NO_6$	20α-Amino-3β-hydroxy-pregn-5-ene-β-D-glucoside	—	—	*Conopharyngia pachysiphon*	7
Holafebrine $C_{21}H_{35}NO$	20α-Amino-3β-hydroxy-pregn-5-ene	177	−61	*Holarrhena febrifuga* and *Kibatalia arborea*	8a

ALKALOIDS NOT FULLY CHARACTERISED

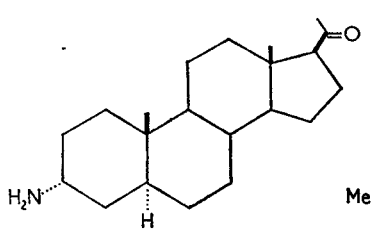
Alkaloid	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Holadysamine $C_{23}H_{37}NO$	—	173	−78	*Holarrhena antidysenterica*	8
Holadysine $C_{23}H_{37}NO$	—	120	−199	*H. antidysenterica*	8
Irehine $C_{23}H_{39}NO$	—	163	−30	*Funtumia elastica*	8
Latifoline $C_{23}H_{37}NO$	—	135	−4	*F. latifolia*	8*

1. Janot, Qui Khuong Huu and Goutarel (1959). 2. Janot, Cavé and Goutarel (1960). 3. Janot, Cavé and Goutarel (1959). 4. Le Men (1960). 5. Janot, Qui Khuong Huu and Goutarel 1960). 6. Janot, Lainé and Goutarel (1960). 7. Dickel, Lucas and MacPhillamy (1959). 8. Goutarel (1961). 8a. Janot and others (1962b)

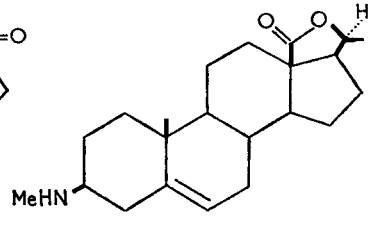
*Latifoline is now known to be the 3β-hydroxy compound corresponding to conamine (Table II) (Janot, Qui Khuong Huu and Goutarel, 1962).

of this group occur in nature as the free alkamine but at least one representative is found in glycosidic combination (Dickel, Lucas and MacPhillamy, 1959) and at least two others are found in the form of pyroterebate ester conjugates (Rostock and Seebeck, 1958).

The chemistry of the monoacid bases has recently been reviewed (Goutarel, 1961) and the known alkaloids belonging to this group are listed in Table I. Examples of the monoacid bases with the nitrogen atom in the 3-position are funtumine (III) (Janot, Qui Khuong Huu and Goutarel, 1959), and paravallarine (IV) (Le Men, 1960) which possesses a saturated lactone ring, and thus bears some structural resemblance to the dihydrocardenolides. A typical example of the monoacid bases possessing the nitrogen atom in the 20-position is afforded by funtuphyllamine A (V) (Janot, Qui Khuong Huu and Goutarel, 1960).

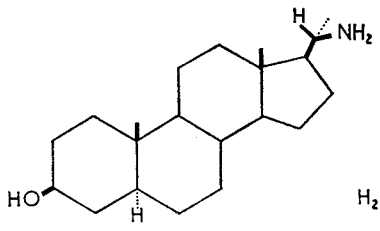


III

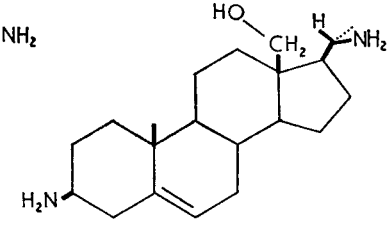


IV

The alkaloids containing two nitrogen atoms in the molecule can be subdivided into three main groups. Where the nitrogen atom on C(20) is not incorporated in a ring the alkaloids belong to the holarrhimine class, which is exemplified by holarrhimine itself (VI) (Černý, Lábler and Šorm, 1957). Where the nitrogen atom on C(20) forms a bridge to C(18) the conarrhimine and conkurchine groups result. In the conarrhimine group the nitrogen ring is fully saturated whilst in the conkurchine group the nitrogen ring possesses a double bond in the 17-20-position (Tschesche and Roy, 1956). The most extensively investigated alkaloids of the conarrhimine and conkurchine groups are conessine and conessidine respectively. The known diacid alkaloids of the pregnane group are listed in Table II.



V



VI

Two main pharmacological actions appear to be characteristic of the pregnane group of alkaloids. These are hypotensive activity and local

anaesthetic activity and both properties do not appear to be dependent upon either the number or the position of the nitrogen atoms. Thus hypotensive activity has been reported in kurchicine (Chopra, Gupta and Chopra, 1933) (later shown to be impure holarrhimine (Bertho, 1939)) and conessine (Bakhsh, 1936; Burn, 1915; Paris, 1938) as well as in funtumine, funtumidine and related alkaloids (Quévauviller and Blanpin, 1960, and earlier refs.) and in 20α-amino-3β-hydroxy-5-pregnene-β-D-glucoside (Dickel and others, 1959). The activity of this last compound inspired the synthesis of several related glycosides (Lucas and others, 1960) and some of these synthetic compounds also exhibited hypotensive activity when administered intravenously to dogs, although like the parent alkaloid, they were inactive by the oral route. For similar reasons the 20-glucoside of funtumidine (glucofuntumidine) was prepared synthetically for pharmacological studies (Quévauviller and Blanpin, 1960).

More detailed studies have indicated that the hypotensive properties stem from direct actions on the heart and blood vessels. Conessine and holarrhimine, in the anaesthetised cat (Bakhsh, 1936; Burn, 1915) show a preliminary rise in blood pressure before a prolonged depression and this has been attributed to an initial stimulation of the smooth muscle of the blood vessels, followed by slowing and incoordination of the heart. Section of the vagi has no influence on the drop in blood pressure (Bakhsh, 1936; Chopra and others, 1933) although the magnitude of the fall is smaller in decerebrate cats (Chopra and others, 1933), indicating that the medullary centres are playing some rôle.

Conessine and holarrhimine have been shown to produce a dilatation of the splanchnic vessels but to contract the renal vessels (Bakhsh, 1936; Chopra and others, 1933) whilst funtumine and funtumidine have been shown to dilate both peripheral and coronary vessels (Quévauviller and Blanpin, 1958), and to exhibit a positive inotropic and negative chronotropic action on the isolated rabbit heart. Conessine and holarrhimine have been reported to stimulate intestinal and uterine contractions (Bakhsh, 1936; Chopra and others, 1933) but later work (Stephenson, 1948) has shown that conessine has a quinidine-like action and antagonises the action of acetylcholine on skeletal, cardiac and smooth muscle. In this connection it is interesting that funtumidine has been reported to slightly inhibit peristalsis of the dog intestine *in situ* (Quévauviller and Blanpin, 1958).

The local anaesthetic activity exhibited by the pregnane group of alkaloids (Burn, 1915; Chopra and others, 1933; Quévauviller and Blanpin, 1958) is in most compounds more pronounced than that of cocaine (Quévauviller and Blanpin, 1960; Stephenson, 1948; Stephenson and Dutta, 1948; Trevan and Boock, 1927) but as the compounds produce necrosis on injection (Stephenson, 1948; Stephenson and Dutta, 1948) they are without clinical value.

Other actions which have been shown to be present in the group include antipyretic activity (Quévauviller and Blanpin, 1960; Paris, 1938) and ability to potentiate barbiturate hypnosis (Quévauviller and Blanpin, 1960). Holarrhimine and conessine exert a direct narcotic effect on frogs, but

this action is absent in mammals (Bakhsh, 1936; Burn, 1915). Although funtumidine has been classed as a tranquilliser on the basis of its ability to depress motility in rats (La Barre and Desmarez, 1959) it is possible that the effect could be produced by a direct paralysis of the peripheral motor nerves rather than by a reserpine-like action. Conessine has been shown to inhibit certain enzymes (Chopra and others, 1927; Kaushiva and Ghatak, 1956) and holamine on intraperitoneal administration gives rise to Parkinsonian-like tremors (Quévauviller and Blanpin, 1960).

The structural similarity of the funtumia alkaloids to the steroid hormones inspired an investigation of these agents for hormonal activity (Blanpin and Quévauviller, 1960). The results showed that all the alkaloids studied were devoid of positive hormonal properties, but there were some indications that the bases exhibited a degree of antagonism towards a limited number of specific effects of the natural hormones.

Conessine has been termed a general protoplasmic poison since it exhibits marked toxicity towards various micro-organisms, especially protozoans (Bertho, 1944b; Chopra and others, 1927; Goyal, 1935; Henry and Brown, 1923; Paris, 1938). It appears to have little or no activity against the malaria parasite (Stephenson, 1948) or helminths (Janot and Cavier, 1949; Mackie and others, 1955) although it has been reported to show weak antituberculous properties (Lambin and Bernard, 1953; Meissner and Hesse, 1930). Its toxicity towards *Entamoeba dysenteriae* has led to a limited clinical use (see for example Acton and Chopra, 1933; Lavier, Crosnier and Merle, 1948; Tanguy, Robin and Raoult, 1948) particularly on the Indian subcontinent and there have been several studies (see for example Durieux, Trenous and Tanguy, 1948; Kaushiva, 1957; Muhlpfordt and Martinez-Silva, 1956; Piette, 1950) in which its efficacy has been compared to that of emetine. The results indicate that it is inferior to emetine as an amoebicide, but not such a potent emetic. Studies have also been made on the distribution and fixing of conessine in the monkey (Auffret and Tanguy, 1950) and on its rate of elimination in man, which is very slow (Pluchon and Pille, 1950). Several reviews concerning the clinical potentialities of conessine in the treatment of amoebiasis have been published (Duviau, 1953; Kerny, 1948; Leake, 1932) and the authors all agree that conessine is not a suitable drug.

Alkaloids Formally Derived from Cholestane

Members of this group have been isolated as the free alkamines or as glycosides of mono-, di-, tri- and tetrasaccharides but it is possible that at least some of the alkamines and lower glycosides are produced by the hydrolysis of higher glycosides during the isolation procedure. The group embraces steroidal alkaloids occurring in various *Solanum spp.* and at least three alkaloids occurring in *Veratrum spp.*, namely rubijervine (12β-hydroxysolanidine), isorubijervine (18-hydroxysolanidine) and isorubijervosine, which is the 3-glucoside of isorubijervine. These alkaloids are all characterised by a hexacyclic skeleton incorporating a piperidine

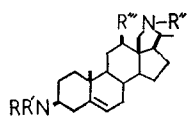
TABLE II

DIACID BASES DERIVED FROM PREGNANE

A. HOLARRHIMINE GROUP

Alkaloid	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Chonemorphine $C_{22}H_{40}N_2$	3β-Amino-20α-dimethylamino-5α-pregnane	145	+25	*Chonemorpha fragrans* *C. penangensis*	9
Holarrhidine $C_{21}H_{38}N_2O$	3α,20α-Diamino-18-hydroxy-pregn-5-ene	181–2	−23	*Holarrhena antidysenterica*	10
Holarrhimine (*syn* kurchicine) $C_{21}H_{36}N_2O$	3β,20α-Diamino-18-hydroxy-pregn-5-ene	183–6	−14·2	*H. antidysenterica*	11–13
Malouetine $C_{27}H_{52}N_2^{++}$	3β,20α-Bistrimethylammonium-5α-pregnane	264 (picrate)	+3 (chloride in water)	*Malouetia bequaertiana*	14
(3)-*N*-Methylholarrhimine $C_{22}H_{38}N_2O$	20α-Amino-18-hydroxy-3β-methylamino-pregn-5-ene	above 360 (dihydrochloride)	−28 (dihydrochloride in MeOH)	*H. antidysenterica*	15
(20)-*N*-Methylholarrhimine $C_{22}H_{38}N_2O$	3β-Amino-18-hydroxy-20α-methylamino-pregn-5-ene	163–164	−19	*H. antidysenterica*	15
NNN'N'-Tetramethylholarrhimine $C_{25}H_{44}N_2O$	3β,20α-Bis(dimethylamino)-18-hydroxy-pregn-5-ene	227–229	−35	*H. antidysenterica*	15, 16

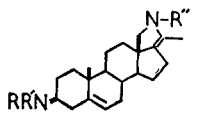
B. CONARRHIMINE GROUP



Alkaloid	R	R'	R''	R'''	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Conarrhimine $C_{21}H_{34}N_2$	H	H	H	H	Impure preparation	—	*H. antidysenterica*	13
Conimine $C_{22}H_{36}N_2$	Me	H	H	H	134	−30 (EtOH)	*H. antidysenterica*	17, 18
Conamine $C_{22}H_{36}N_2$	H	H	Me	H	130	−21	*H. antidysenterica*	13, 18
Conessimine $C_{23}H_{38}N_2$	Me	Me	H	H	100	−22·3	*H. antidysenterica*	19, 20
Isoconessimine $C_{23}H_{38}N_2$	Me	H	Me	H	92	+30 (EtOH)	*H. antidysenterica*	21
Conessine (*syn* wrightine) $C_{24}H_{40}N_2$	Me	Me	Me	H	125	−2	*Holarrhena spp.*	16, 22–24
Holarrhenine $C_{24}H_{40}N_2O$	Me	Me	Me	OH	198	−7	*H. congolensis*	25, 26
Holafrine $C_{29}H_{46}N_2O_2$	Me	Me	H	$OCOC_6H_9$	116–117	−19·1	*H. africana DC*	25
Holarrhetine $C_{30}H_{48}N_2O_2$	Me	Me	Me	$OCOC_6H_9$	74–75	−14·9	*H. africana DC*	25

TABLE II—*continued*

C. CONKURCHINE GROUP



Alkaloid	R	R'	R''	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Conkurchine $C_{21}H_{32}N_2$	H	H	H	152	−67·4	*H. antidysenterica*	27
Conessidine $C_{22}H_{34}N_2$	Me	H	H	123	−52·2	*H. antidysenterica*	18, 28
Trimethylconkurchine $C_{24}H_{38}N_2$	Me	Me	Me	125–127	+12·0	*H. antidysenterica*	18

D. ALKALOIDS INCOMPLETELY CHARACTERISED

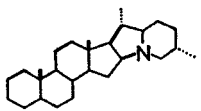
Alkaloid	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Base $C_{23}H_{34}N_2$	129·5	—	*H. antidysenterica*	29
Base $C_{22}H_{36}N_2$	87–88	—	*H. antidysenterica*	30
Conkurchinine $C_{25}H_{36}N_2$	161	−47 (EtOH)	*H. antidysenterica*	28
Holarrhessimine $C_{22}H_{36}N_2O$	160–164	−30	*H. antidysenterica*	20
Holarrhine $C_{20}H_{38}N_2O_3$	240	−17 (MeOH)	*H. antidysenterica*	19
α-Hydroxyconessine $C_{24}H_{40}N_2O$	—	−9 (EtOH)	*H. antidysenterica*	22
Kurchamine $C_{22}H_{36}N_2$	115–117	−16	*H. antidysenterica*	15
Kurchenine $C_{21}H_{32}N_2O_2$	335–336	−78 (H_2SO_4 in water)	*H. antidysenterica*	31
Kurchessine $C_{24}H_{40}N_2$	132–133	−36	*H. antidysenterica*	15
Kurchine (*syn* Curchine, nor-Conessine) $C_{23}H_{38}N_2$	75	−7	*H. antidysenterica*	12, 28, 32
Lettocine $C_{17}H_{25}NO_2$	350–352	—	*H. antidysenterica*	33
Malouphylline $C_{24}H_{40}N_2O_2$	259	−10	*M. bequaertiana*	34*

9. Janot and others (1962a). 10. Černý, Lábler and Šorm (1959). 11. Černý, Lábler and Šorm (1957). 12. Ghosh and Bose (1932). 13. Siddiqui (1936). 14. Janot, Lainé and Goutarel (1960). 15. Tschesche and Wiensz (1958). 16. Lábler and Černý (1959). 17. Siddiqui and Siddiqui (1934). 18. Tschesche and Roy (1956). 19. Siddiqui and Pillay (1932). 20. Tschesche and Petersen (1954). 21. Siddiqui (1935). 22. Bertho and Gotz (1958). 23. Favre and others (1953). 24. Siddiqui (1934). 25. Rostock and Seebeck (1958). 26. Uffer (1956). 27. Bertho (1951). 28. Bertho (1939). 29. Bertho (1947). 30. Bertho (1944a). 31. Bertho, von Schuckmann and Schönberger (1933). 32. Haworth (1932). 33. Peacock and Chowdhury (1935). 34. Goutarel (1961).

* The structure of malouphylline is now known to be 3β — acetamido-20α-dimethylamino-5α-pregnan-18-al (Janot, Lainé and Goutarel, 1962).

TABLE III

BASES DERIVED FROM SOLANIDANE



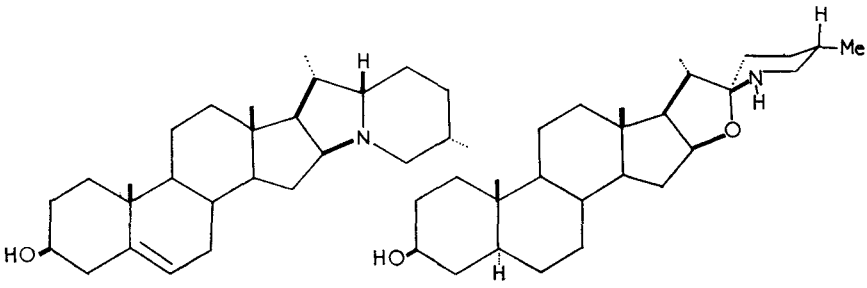
Alkamine	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived alkaloids	m.p. °C.	$[\alpha]_D$ in pyridine	Sugar	Source	Refs.
Acetylleptinidine $C_{29}H_{45}NO_3$	3β-Hydroxy-x-acetoxy-solanid-5-ene	192–196	—	Leptine I $C_{47}H_{75}NO_{16}$	230	−85	Trisaccharide of 2 moles L-rhamnose and 1 mole D-glucose	*Solanum chacoense*	35
				Leptine II				,,	
				Leptine III				,,	
				Leptine IV				,,	
Demissidine $C_{27}H_{45}NO$	3β-Hydroxy-5α-solanidane	220–222	+21	Demissine (*syn* Solanine d) $C_{50}H_{83}NO_{20}$	305–308	−20	Branched tetrasaccharide of 1 mole D-xylose 1 mole D-galactose and 2 moles D-glucose (lycotetraose)	*S. demissum*	36, 37
Leptinidine $C_{27}H_{43}NO_2$	3β,-x-Dihydroxy-solanid-5-ene	247–248	−24	Leptinine I $C_{45}H_{73}NO_{15}$	230	−90	Trisaccharide of 1 mole D-glucose and 2 moles L-rhamnose	*S. chacoense*	35
				Leptinine II $C_{45}H_{73}NO_{14}$	225	−62	Trisaccharide of 1 mole D-galactose 1 mole L-rhamnose and 1 mole D-glucose	,,	35
				Leptinine III	—	—	—	,,	35
				Leptinine IV				,,	35
Rubijervine $C_{27}H_{43}NO_2$	3β,12α-Dihydroxysolanid-5-ene	242–243	+8					*Veratrum album*	38, 39
Isorubijervine $C_{27}H_{43}NO_2$	3β,18-Dihydroxysolanid-5-ene	235–237	+6·5 (EtOH)	Isorubijervosine $C_{33}H_{53}NO_7$	279–280	−20	D-Glucose	*V. viride* *V. album*	38, 40, 41

TABLE III—*continued*

Alkamine	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived alkaloids	m.p. °C.	$[\alpha]_D$ in pyridine	Sugar	Source	Refs.
Solanidine (*syn* Solatubine Solanidine t) $C_{27}H_{43}NO$	3β-Hydroxysolanid-5-ene	219	−27	α-Chaconine $C_{45}H_{73}NO_{14}$	242	−85	α-L-Rhamnopyranosyl (1 → 2 glucose)-α-L-rhamnopyranosyl (1 → 4 glucose)-D-glucose	*Solanum tuberosum* *S. nigrum* *S. dulcamara* *S. chacoense*	42
				β-Chaconine $C_{39}H_{63}NO_{10}$	255	−61·5	α-L-Rhamnopyranosyl (1 → 4) D-glucose	"	42
				γ-Chaconine $C_{33}H_{53}NO_6$	243–244	−40	D-Glucose	"	42
				α-Solanine (*syn* Solanine Solanine t Solatunine) $C_{45}H_{73}NO_{15}$	285	−59	α-L-Rhamnopyranosyl (1 → 2 galatose)-β-D-glucopyranosyl (1 → 3)galactose) D-galactose	"	37, 43, 44
				β-Solanine $C_{39}H_{63}NO_{11}$	295	−31 (MeOH)	β-D-Glucopyranosyl (1 → 3) D-galactose	"	42
				γ-Solanine $C_{33}H_{53}NO_6$	240–250	−26 (MeOH)	D-Galactose	"	42
				Tetroside	—	—	Tetrasaccharide of 1 mole D-xylose 2 moles D-glucose 1 mole D-galactose	*S. acaulia*	45
				Solacauline $C_{52}H_{80}NO_{14}$	260–265	−30	Trisaccharide of 1 mole D-glucose and 2 moles D-xylose	*S. acaulia*	37
Soladulcamaridine $C_{27}H_{43}NO$	—	220–222	−78 (MeOH)	Soladulcamarine $C_{45}H_{79}NO_{17}$	193–197	—	Tetrasaccharide of 1 mole D-glucose 1 mole L-rhamnose 2 moles L-arabinose	*S. dulcamara*	46

35. Kuhn and Löw (1961 a,b). 36. Kuhn, Löw and Trischmann (1957). 37. Schreiber (1954). 38. Jacobs and Craig (1945). 39. Pelletier and Locke (1957). 40. Klohs and others (1953b). 41. Weisenborn and Burn (1953). 42. Kuhn, Löw and Trishmann (1955,b,c). 43. Kuhn, Löw and Trishmann (1955c). 44. Uhle and Jacobs (1945). 45. Schreiber (1957b). 46. Rasmussen and Boll (1958).

ring and they may be divided into two subclasses according to the immediate environment of the piperidino nitrogen atom. These subclasses are the solanidane and spirosolane groups and are exemplified by the alkamines solanidine (VII) and tomatidine (VIII) respectively. The known alkaloids belonging to the solanidane group are listed in Table III and those belonging to the spirosolane group are shown in Table IV.



VII VIII

The literature contains a number of references to the poisonous nature of various *Solanum spp.* and this can be attributed to the presence of cholestane-type alkaloids (see for example Griebel, 1923; Lowe, 1929; Rühl, 1951; Schowalter and Hartmann, 1924; Sirotina and Spirina, 1948). Potato sprouts and potatoes which have turned green through exposure above the ground develop a detectable amount of solanine and its aglycone solanidine and human consumption of such potatoes or potato shoots has led to a number of outbreaks of potato poisoning, several of which have been discussed by Willimott (1933). The most extensively investigated alkaloid of the cholestane group from a biological point of view is α-solanine (solanine), but it is to be noted that commercial samples of solanine have been shown to consist of 6 components (Kuhn, Löw and Trischmann, 1955b).

The cholestane group of alkaloids show certain similarities in their pharmacological properties to the pregnane group. Thus solanocapsine has been shown to slow the heart and induce incoordination by a direct action on cardiac muscle (Watt, Heimann and Epstein, 1932) and solanine, like conessine, has been shown to possess local anaesthetic properties (Weill, 1913). Rubijervine and several of its synthetic esters possess hypotensive properties (Poethke and Kuntze, 1958). Both solanine and solasonine induce haemolysis (de Lavergne and Kissel, 1935; Fischer, 1929; Macht, 1933) whilst solanine diminishes blood catalase (Levi, 1936), and inhibits non-specific cholinesterase (Pokrovskii, 1956). Solanine is also active as a mitotic poison (Danneberg and Schmähl, 1953) and has been shown to inhibit the oxygen uptake of mouse ascites tumour cells (Schmitz, 1951).

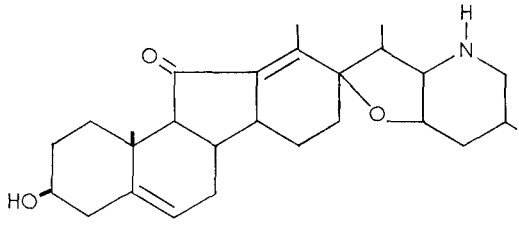
The discovery that extracts of tomato leaves exhibited antifungal and antibacterial activity led to the isolation of tomatine (Fontaine and

others, 1948) and similarly the observation that the leaves of *Solanum demissum* were resistant to the attacks of the larvae of the potato beetle *Leptinotarsa decemlineata* had as a result the isolation of demissine (Kuhn and Gauhe, 1947). Later work showed that other cholestane-type glycosidic alkaloids possessed the ability to prevent the ravages of the potato beetle and as tested on the leaves of solanum *tuberosum*, the order of potency was leptine I, then tomatine, then demissine, then α-solanine, and finally α-chaconine (Kuhn and Löw, 1961a). Independent work showed demissine to be more active than solacauline, which was more active than solanine (Shreiber, 1954). The insecticidal activity of various preparations of solanum steroidal alkaloids has, however, been shown to be but slight (Bergmann, Levinson and Mechoulam, 1958; Pollacci and Gallotti, 1940; Sievers and others, 1949).

Several studies have been devoted to the investigation of the antimicrobial properties of the group. Tomatine and several other alkaloids are antifungal (Chanussot, 1957; McKee, 1959; Sackman, Kern and Wiesman, 1959) and solanocapsine is claimed to possess *in vitro* activity against *Mycobacterium tuberculosis* (Boll and others, 1955–56). A number of synthetic solanine-type glycosides have been prepared, but they do not appear to have been investigated biologically (Schreiber, 1955).

Alkaloids possessing the "Jervi" Skeleton

The completely characterised alkaloids possessing the modified or "jervi" steroid skeleton in which ring C is 5-membered and ring D is 6-membered, are conveniently divided into two subclasses with the fritillaria alkaloids whose chemical constitution is as yet incompletely established, forming a third subclass. The first group consists of alkaloids whose alkamines possess a secondary nitrogen atom and contain only two or three atoms of oxygen. They occur in nature as the free alkamine or as D-glucosides and may be termed the "jerveratrum" alkaloids, as suggested by Fieser and Fieser (1959). Representative alkamines of this class are jervine (IX) and veratramine (X). The second subclass, which may be termed the "ceveratrum" group, consists of alkaloids whose alkamines are polyhydroxy tertiary bases possessing seven to nine atoms of oxygen and incorporating a quinolizidine ring system.

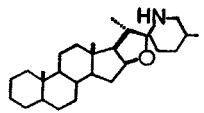


IX

The alkamine germine (XI) and the closely related alkamines, protoverine, veracevine and zygadenine possess a masked α-ketal system and

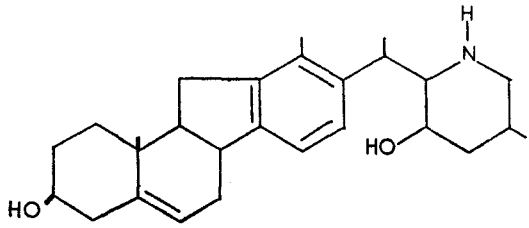
TABLE IV

DERIVATIVES OF SPIROSOLANE



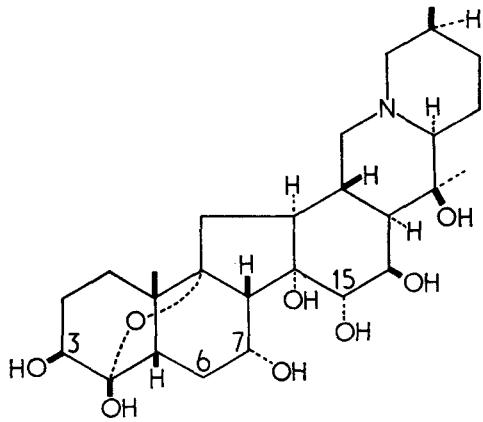
Alkamine	Structure	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived alkaloids	m.p. °C.	$[\alpha]_D$ in pyridine	Sugar	Source	Refs.
Solasodine (*syn* Solanidine s Solancarpidine Purapuridine) $C_{27}H_{43}NO_2$	3β-Hydroxy-22a, 25-L-spirosol-5-ene	202	−80 (MeOH)	Solasodamine $C_{51}H_{83}NO_{20}$	298–302	−72 (MeOH)	L-Rhamnosido-L-rhamnosido-D-galactosido-D-glucose	*Solanum sodomeum* *S. auriculatum* *S. marginatum* *S. aviculare*	47
				Solasonine (*syn* Solanine s Solancarpine Purapurine γ-solanigrine) $C_{45}H_{73}NO_{16}$	301–303	−88	L-Rhamnosido-D-galactosido-D-glucose	*S. aviculare* *S. sodomeum* *S. xanthocarpum* *S. nodiflorum* *S. torvum* *S. lacinlatum*	48–52
				Solamargine (*syn* δ-solanigrine) $C_{45}H_{73}NO_{15}$	301–310	−114	L-Rhamnosido-L-rhamnosido-D-glucose	*S. marginatum* *S. nigrum*	47, 48, 50, 52a
Tomatidine $C_{27}H_{45}NO_2$	5α,22b,25-L-Spirosolan-3β-ol	210–211	−8 (MeOH)	Tomatine $C_{50}H_{83}NO_{21}$	263–267	−19	Branched tetrasaccharide of 1 mole D-xylose 1 mole D-galactose and 2 moles D-glucose	*Lycopersicum pimpinellifolium* *L. esculentum* *L. peruvianum* *L. hirsutum*	52b, 53
				Trioside	—	—	Trisaccharide of 2 moles D-xylose and 1 mole D-glucose	*S. polyadenum*	52a
Solanocapsine $C_{27}H_{46}N_2O_2$	3α-Amino-x-hydroxy spirosolane	222	+25·5	—	—	—	—	*S. pseudocapsicum*	54
Solauricidine $C_{27}H_{43}NO_2$	—	219	−90 (MeOH)	Solauricine $C_{45}H_{73}NO_{16}$	270	—	L-Rhamnosido-D-galactosido-D-glucose	*S. auriculatum*	55
Solangustidine $C_{27}H_{43}NO_2$	—	amorphous (above 315 (HCl))	—	Solangustine $C_{33}H_{53}NO_7.H_2O$	235	—	D-Glucose	*S. angustifolium*	56
Soladulcidine $C_{27}H_{45}NO_2$	5α,22a,25-D-Spirosolan-3β-ol	206·5	−52·6	α-Soladulcine	—	—	—	*S. dulcamara*	57–59
				β-Soladulcine	—	—	—		
				γ-Soladulcine	—	—	—		
				Tetroside $C_{50}H_{83}NO_{21}$	268–270	−53	2 moles D-glucose, 1 mole D-galactose and 1 mole D-xylose	*S. dulcamara*	60
5,6-Dehydrotomatidine $C_{27}H_{43}NO_2$	3β-Hydroxy-22b, 25-L-spirosol-5-ene	206	−45	—	—	—	—	*S. tuberosum*	61

47. Briggs and Brooker (1958). 48. Boll (1958). 49. Briggs and Cambie (1958). 50. Kuhn, Löw and Trischmann (1955a). 51. Taylor (1958). 52. Uhle (1954). 52a. Schreiber (1957b). 52b. Fontaine and others (1948). 53. Kuhn, Löw and Trischmann (1957). 54. Boll and Lillevik (1959). 55. Briggs and Carroll (1942). 56. Tutin and Clewer (1914). 57. Briggs and O'Shea (1952). 58. Shreiber (1958). 59. Tuzson and Kiss (1957). 60. Alkemeyer and Sander (1959). 61. Shreiber (1957a).



X

undergo rearrangement with base. In veracevine, the rearrangement is particularly facile to yield first cevagenine and then cevine and for a time it was believed that cevine was the actual alkamine of the veracevine ester alkaloids. The ceveratrum alkaloids occur in various *Veratrum*, *Zygadenus* and *Schoenocaulon* species and are the agents responsible for the poisonous nature of these plants (Bealth and others, 1933; Reinhardt, 1909).



XI

The ceveratrum group have been isolated as the free alkamines or as mono-, di-, tri- or tetra- esters of various organic acids. Partial deacylation of the ester alkaloids occurs readily, however, and it is possible that some of the lower esters which have been isolated are in fact artefacts. It is the ceveratrum ester alkaloids, more particularly the tri- and tetra-esters which are the agents responsible for the hypotensive properties present in crude extracts of veratrum alkaloids. The known alkaloids of the ceveratrum group, together with the known jerveratrum alkaloids, are shown in Table V.

The jerveratrum alkaloids (both the alkamines and the glucosides) are characterised by an ability to antagonise the cardioaccelerator action of sympathetic nerve stimulation or of sympathomimetic amines (Krayer, 1952). This effect is thought to arise from a highly selective action upon the pacemaker of the heart and is not shown by adrenergic blocking agents. Accordingly the term "anti-accelerator agent" has been coined to describe

TABLE V

ALKALOIDS POSSESSING THE JERVI SKELETON

A. JERVERATRUM ALKALOIDS

Alkamine	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived alkaloids (3-glucosides)	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Source	Refs.
Jervine $C_{27}H_{39}NO_3$	240–245	−167·5	Pseudojervine $C_{33}H_{49}NO_8$	300–301	−131	*Veratrum album* *V. viride* *Schoenocaulon officinale*	62–66
Veratramine $C_{27}H_{39}NO_2$	204–207	−71	Veratrosine $C_{33}H_{49}NO_7$	242–243 (decomp.)	−55 ($EtOH/CHCl_3$)	*V. album* *V. viride*	67–69

B. CEVERATRUM ALKALOIDS

Alkamine	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived ester alkaloids	Esterifying acids—position of substitution in brackets	m.p. °C.	$[\alpha]_D$ in pyridine	Source	Refs.
Germine $C_{27}H_{43}NO_8$	218–221	+4 (EtOH)	Germanitrine $C_{39}H_{59}NO_{11}$	Acetic (7): (−)-2-Methylbutyric (15): Angelic (3)	228–229	−61	*Veratrum fimbriatum*	70–72
			Germbudine $C_{37}H_{59}NO_{12}$	(−)-2-Methylbutyric (15): (+)-*threo*-2,3-Dihydroxy-2-methylbutyric (3)	160–164	−8	*V. viride*	73, 74
			Neogermbudine $C_{37}H_{59}NO_{12}$	(−)-2-Methylbutyric (15): (−)-*erythro*-2,3-Dihydroxy-2-methylbutyric (3)	149–152	−12	*V. album* *V. viride*	75, 76
			Germerine $C_{37}H_{59}NO_{11}$	(−)-2-Methylbutyric (3) (+)-2-Hydroxy-2-methylbutyric (15)	200–203	−14	*V. album* *V. viride* *V. nigrum*	77–81
			Germidine $C_{34}H_{53}NO_{10}$	Acetic (3) (−)-2-Methylbutyric (15)	230–231	−11	*V. viride* *Zygadenus venenosus*	78, 81, 82
			Isogermidine (*syn* neogermidine) $C_{34}H_{53}NO_{10}$	Acetic (7) (−)-2-Methylbutyric (15)	221–223	−63	*V. viride* *Z. paniculatus* *Z. venenosus*	78, 79, 81, 83
			Germinitrine $C_{39}H_{57}NO_{11}$	Acetic Angelic Tiglic	175–176	−36	*V. fimbriatum*	63, 70
			Germitetrine (*syn* germitetrine B) $C_{41}H_{63}NO_{14}$	Acetic (7): (−)-2-Methylbutyric (15): 2-Hydroxy-2-methyl-3-acetoxybutyric (3)	229–230	−74	*V. album*	75, 84, 85, 92
			Deacetylgermitetrine $C_{39}H_{61}NO_{13}$	(−)-2-Methylbutyric (15): 2-Hydroxy-2-methyl-3-acetoxybutyric (3)	143–149	−8	*V. album*	75, 76
			Germitrine $C_{39}H_{61}NO_{12}$	Acetic (7): (−)-2-Methylbutyric (3): (+)-2-Hydroxy-2-methylbutyric (15)	216–219	−69	*V. viride*	77, 78
			Neogermitrine $C_{36}H_{55}NO_{11}$	2 moles Acetic (3,7): (−)-2-Methylbutyric (15)	234–235	−78	*V. viride* *V. fimbriatum* *V. escholtzii* *Z. paniculatus* *Z. venenosus*	78, 82, 86, 92
			Protoveratridine $C_{32}H_{51}NO_9$	(−)-2-Methylbutyric (3)	272–273	−9	*V. album* *V. viride* *Z. venenosus*	78, 83

TABLE V—*continued*

Alkamine	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived ester alkaloids	Esterifying acids—position of substitution in brackets	m.p. °C.	$[\alpha]_D$ in pyridine	Source	Refs.
Protoverine $C_{27}H_{43}NO_9$	195–200	−11 (EtOH)	Escholerine $C_{41}H_{61}NO_3$	2 moles Acetic (6,7): (−)-2-Methylbutyric (15): Angelic (3)	235–236	−30	*V. escholtzii*	87, 88
			Deacetylprotoveratrine $C_{39}H_{61}NO_{13}$	Acetic (6): (−)-2-Methylbutyric (15): (+)-2-Hydroxy-2-methyl-butyric (3)	191–192	−15	*V. album*	76, 89
			Deacetylneoprotoveratrine (*syn* germbutrine deacetylprotoveratrine B protoveratetrine) $C_{39}H_{61}NO_{14}$	Acetic (6): (−)-2-Methylbutyric (15): (+)-*threo*-2,3-Dihydroxy-2-methylbutyric (3)	182–183	−9	*V. album* *V. viride*	73, 89, 90
			Protoveratrine A $C_{41}H_{63}NO_{14}$	2 moles Acetic (6,7): (−)-2-Methylbutyric (15): (+)-2-Hydroxy-2-methyl-butyric (3)	267–269	−40	*V. album* *V. viride* *Z. venenosus*	85, 91–93
			Protoveratrine B (*syn* neoprotoveratrine veratetrine) $C_{41}H_{63}NO_{15}$	2 moles Acetic (6,7): (−)-2-Methylbutyric (15): (+)-*threo*-2,3-Dihydroxy-2-methylbutyric	268–270	−37	*V. album* *V. viride* *Z. venenosus*	79, 85, 91, 93, 94
Neo-Sabadine $C_{27}H_{43}NO_8$	140–150	−33 (EtOH)	Sabadine $C_{29}H_{45}NO_9$	Acetic	120–140	−9·5 (EtOH)	*V. sabadilla*	95
Sabine $C_{27}H_{45-47}NO_7$	173–176	—	Sabatine $C_{29}H_{47-49}NO_8$	Acetic	256–258	—	*Schoenocaulon officinalie*	96

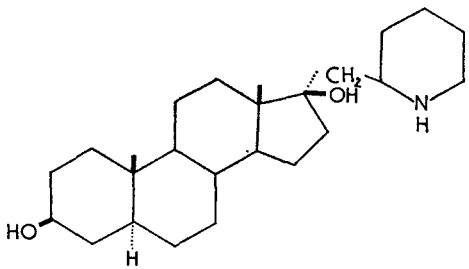
[*continued overleaf*

TABLE V—*continued*

Alkamine	m.p. °C.	$[\alpha]_D$ in $CHCl_3$	Derived ester alkaloids	Esterifying acids—position of substitution in brackets	m.p. °C.	$[\alpha]_D$ in pyridine	Source	Refs.
Veracevine (*syn* protocevine) $C_{27}H_{43}NO_8$	181–183	−33	Cevacine $C_{29}H_{45}NO_9$	Acetic (3)	205–207	−27 ($CHCl_3$)	*V. sabadilla*	97–100
			Cevadine (*syn* α-veratrine crystalline veratrine pure veratrine) $C_{32}H_{49}NO_9$	Angelic (3)	208–215	+6	*V. sabadilla* *V. viride*	101, 102
			Vanilloylveracevine $C_{36}H_{49}NO_{11}$	Vanillic (3)	256–257	+43	*V. sabadilla*	103
			Veratridine (*syn* amorphous veratrine) $C_{36}H_{51}NO_{11}$	Veratric (3)	160–180	−19 ($CHCl_3$)	*V. album* *V. sabadilla* *V. viride*	100, 101, 104
Zygadenine $C_{27}H_{43}NO_7$	201–204	−45	Angeloylzygadenine $C_{44}H_{69}NO_{11}$	Angelic (3)	222–224	−35 ($CHCl_3$)	*V. album*	105, 106
			Vanilloylzygadenine $C_{36}H_{49}NO_{10}$	Vanillic (3)	258–259	−27 ($CHCl_3$)	*Z. paniculatus* *Z. venenosus*	107
			Veratroylzygadenine $C_{36}H_{51}NO_{10}$	Veratric (3)	270–271	−27 ($CHCl_3$)	*V. album* *V. fimbriatum* *V. escholtzii* *V. nigrum* *Z. paniculatus* *Z. venenosus*	105, 108, 109
			Zygacine $C_{29}H_{45}NO_8$	Acetic (3)	Amorphous	−22 ($CHCl_3$)	*Z. paniculatus* *Z. venenosus*	110, 111

62. Jacobs and Craig (1944). 63. Klohs and others (1953a). 64. Okuda and Tsuda (1961). 65. Poethke (1938). 66. Tsukamoto and Kishimoto (1954). 67. Jacobs and Sato (1949). 68. Klohs and others (1953b). 69. Tamm and Wintersteiner (1952). 70. Klohs and others (1952b). 71. Kupchan and Afonso (1959). 72. Kupchan and Narayanan (1959). 73. Myers and others (1955). 74. Kupchan and Gruenfeld (1959b). 75. Kupchan and Ayres (1959). 76. Myers and others (1956). 77. Fried, White and Wintersteiner (1950). 78. Kupchan (1959a). 79. Myers and others (1952). 80. Poethke (1937). 81. Weisenborn and Bolger (1954). 82. Fried, Numerof and Coy (1952). 83. Kupchan and Deliwala (1952b). 84. Glen and others (1952). 85. Nash and Brooker (1953). 86. Klohs and others (1954). 87. Klohs and others (1952c). 88. Kupchan and others (1960). 89. Kupchan, Ayres and Hensler (1960). 90. Klohs and others (1953c). 91. Kupchan and Ayres (1960). 92. Kupchan and Deliwala (1953). 93. Stoll and Seebeck (1953a). 94. Klohs and others (1952a). 95. Möhrle and Auterhoff (1959). 96. Mitchner and Parks (1959). 97. Barton and others (1954). 98. Kupchan, Johnson and Rajagopalan (1959). 99. Kupchan and others (1953). 100. Vejdelek, Macek and Kahac (1956). 101. Ikawa and others (1945). 102. Kupchan and Afonso (1960). 103. Morgan and Baritrop (1958). 104. Blount (1935). 105. Kupchan (1959b). 106. Suzuki and others (1957). 107. Kupchan and Deliwala (1952a). 108. Klohs and others (1953a). 109. Stoll and Seebeck (1953b). 110. Kupchan, Lavie and Zonis (1955). 111. Shimizu (1958).

compounds exhibiting this particular pharmacological action (Krayer, 1950). Since antiaccelerator activity is absent in the tertiary veratrum alkaloids, it was concluded that such activity was associated with a secondary nitrogen atom incorporated in a piperidine ring (Krayer, Uhle and Ourisson, 1951) and attention was devoted to the preparation of synthetic steroids possessing a piperidine ring in the side chain (Krayer and Briggs, 1950; Uhle, 1951), among which were included several compounds prepared by cleavage of the ether link in derivatives of spirosolane These compounds indeed proved active, but later work showed antiaccelerator activity to be present both in tertiary amino-steroids (Gould, Shapiro and Herschberg, 1954) and in secondary amino-steroids in which the nitrogen atom was not part of a piperidine ring (Gould and others, 1954; Margolin and others, 1954). These observations serve to emphasise the dangers of postulating structure-action relationships from a consideration of an inadequate number of compounds of insufficient chemical diversity. Quinidine was also shown to possess dual anti-accelerator and antifibrillatory activity and in this connection it is interesting that certain nitrogenous steroids (Gould and others, 1954; Robson and Trounce, 1955; Schallek and others, 1957) such as 17α-(2-piperidylmethyl)-3β,17β-dihydroxyandrostane (XII) and 16α-cyclohexylamino-3β-hydroxy-20-oxopregn-5-ene show quinidine-like properties.



XII

Detailed investigations have shown that veratramine decreases the oxygen consumption of atrial tissue without any initial augmentation of uptake (Reiter, 1950). In high doses veratramine produces excitation of the central nervous system (Krayer, 1949) whilst it is claimed that jervine in high doses produces hypotension in dogs (Wood, 1906).

Preparations of the ceveratrum ester alkaloids of varying purity have been employed medicinally from the time of the ancient Greek herbalists until the present day, the modern interest lying in their hypotensive properties, but as their pharmacology is covered in standard texts and has been extensively reviewed elsewhere (Krayer and Acheson, 1946; Stoll, 1954), a relatively brief summary will suffice in the present article. No attempt will be made to cover the literature pertaining to each individual ceveratrum ester.

Much of the earlier work was done with a preparation known as veratrine, which was first obtained by Pelletier and Caventou (1820),

but as this proved to be a complex mixture (Auterhoff, 1955; Blount, 1935), care must be taken in assessing this work owing to the great variation in potency exhibited by the alkamines and their esters (Krayer and Acheson, 1946; Krayer, Moe and Mendez, 1944). Other mixtures of alkaloids which have been employed in biological studies or medicinally, are cevadilline (also called sabadilline), cryptenamine (Kupchan and Gruenfield, 1959), protoveratrine, sabadine and sabatrine. As a broad generalisation it would appear that the alkamines are almost devoid of hypotensive activity, the naturally-occurring monoesters are feebly active, the diesters more active and the tri- and tetra-esters very active (Wintersteiner, 1953). In this connection it is to be noted that the highly active ester alkaloid germitetrine, although giving rise to four molecules of organic acids per molecule on hydrolysis, is really only a triester, as one of the esterifying acids is 2-hydroxy-2-methyl-3-acetoxybutyric acid (Kupchan and Ayres, 1959). Similar potency relationships have been found amongst synthetic esters of germine, where it was also discovered that several synthetic tetraesters were virtually inactive (Weisenborn and others, 1954).

More recent structure-action studies of a large number of synthetic esters of protoverine (Kupchan, Hensler and Weaver, 1961) have shown that esterification at positions 3 and 15 is necessary for high activity and that esterification at position 16 is accompanied by a profound loss of activity. Positions 6 and 7 need not be esterified for high activity. Esterification by a branched chain acid is advantageous at position 15, of no great import at position 3 and disadvantageous at position 7. Moreover, these relations were found to be broadly true for both the naturally-occurring and the previously prepared synthetic esters of germine (Weisenborn and others, 1954) whose structures were unknown at the time of the original experiments.

The pharmacological actions exhibited by the ceveratrum ester alkaloids are complex, making it difficult to analyse the exact contribution each makes to the total response, but there would now seem to be general agreement that in low doses they act by triggering reflex mechanisms.

The most pronounced pharmacological effect of the ceveratrum esters at therapeutic doses is the production of a rapid fall in arterial pressure, which is mediated by a reflex general vasodilatation, and a fall in heart rate. Thus they act in a unique fashion, differing from all other hypotensive agents. They are without any direct action on the blood vessels. The drop in blood pressure is also accompanied by respiratory depression. These effects have been demonstrated in various species of animals as well as in man and the experiments have indicated the existence of species differences (Rothlin and Cerletti, 1954), rodents being much more resistant to the hypotensive effect than man, the dog, or the cat.

The experimental evidence indicates that the afferent sensory receptors, upon which the ceveratrum esters act to produce the reflex fall in blood pressure, lie in the lungs and the heart (Heymans and Neil, 1958), with their afferent fibres lying in the vagi. Elicitation of the Benzold-Jarisch reflex (Aviado and Schmidt, 1955; Jarisch and Richter, 1939; von

Benzold and Hirt, 1867) as it is now known, however, is not the only reflex action produced by the ceveratrum esters, as vagotomised animals may still show a fall in blood pressure, indicating that other receptors are also involved (Heymans and Vleeschhouwer, 1950; Wang, Ngai and Grossman, 1955). The most important of these other receptors appear to be the baroreceptors situated in the region of the carotid bifurcation (see for example Aviado and others, 1955; Martini and Calliauw, 1955). Experiments with dogs would seem to indicate that stimulation of receptors within the nodose ganglion are responsible for the production of emesis (Borison and Fairbanks, 1952).

In higher concentrations the ceveratrum esters induce vasoconstriction and so exert a pressor effect. This action is mediated in part at least by the liberation of adrenaline from the adrenal medulla (Krayer, Moe and Mendez, 1944; Mendez and Montes, 1943).

At high doses the ceveratrum esters also produce changes in the electrophysiological state of nerve and muscle (see for example Shanes, 1958) which manifest themselves in the elicitation of a series of repetitive responses to a single stimulus—the so-called "veratrinic" response (see for example Acheson and Rosenbleuth, 1941; Gregor, 1904). It is thought that these electrophysiological changes result from alterations in the concentration of calcium ions on the cell membrane (Gordon and Welsh, 1948; Straub, 1954) with disruption of the normal ion transport mechanisms across the membrane (Shanes, 1952 and earlier papers; Straub, 1956) although muscle and nerve do not show the same changes in ionic migration when exposed to ceveratrum esters. Thus there is an increase of potassium ion efflux from nervous tissue (Shanes, 1952) and cardiac muscle (Lister and Lewis, 1959; Vick and Kahn, 1957) but no increase from skeletal muscle (Lister and Lewis, 1959). In view of the general assumption that ionic exchange occurs by similar mechanisms in all tissues (Davson and Danielli, 1952; Heilbrunn, 1956; Hodgkin, 1951) these facts are disturbing. It has also been shown that the ceveratrum esters do not promote potassium ion influx into potassium-poor cold-stored human erythrocytes (Kahn, Acheson and Cohen, 1955).

Whatever the detailed mechanism, it would appear safe to conclude that the ceveratrum esters interfere with the functioning of the cell membrane and it is probable that similar changes occur at the sensory afferent receptors (Jarisch and Zotterman, 1948) which would appear to have a far greater sensitivity than nerve or muscle cells.

Experimentally veratrine has been used to induce auricular arrhythmias in order to screen drugs for antifibrillatory activity (Scherf and Chick, 1951).

Other Actions of Ceveratrum Esters

Pronounced insecticidal activity is present in the ceveratrum group and dusts and extracts prepared from the seeds of *Schoenocaulon spp.* (sabadilla seed) have been tried as insecticides (see for example Anderson, 1945; Frazier, 1945; Filmer and Smith, 1946; Ikawa and others, 1945; Walton, 1946), over eighty publications dealing with their efficacy against

various insect species appearing in the years 1944–1956. These studies have also been extended to include ceveratrum alkaloid preparations from *Veratrum spp.* (see for example Fisher, 1940; Jaretzky and Janecke, 1940; Krupp, Lendle and Stapenhorst, 1952; Seiferle, Johns and Richardson, 1942). A particularly active preparation is produced by treating sabadilla seed with lime (Allen and Brunn, 1945; Walton, 1945). As is true for hypotensive activity, the alkamines appear virtually inactive as insecticides (Allen and others, 1945). In attempts to elucidate the exact mechanism by which the ceveratrum esters act upon the insect, several studies have been concerned with their effect on various enzyme systems (Collias, McShan and Lilly, 1952; Hartley and Brown, 1955).

Other studies have been concerned with their ability to induce mutations in *Drosophila funebris* (Tinyakov, 1947) and their ability to produce C-mitotic effects (Burroni, 1955).

TABLE VI

FRITILLARIA ALKALOIDS

Alkaloid	m.p. °C	$[\alpha]_D$ in $CHCl_3$	Refs.
Alginine $C_{28}H_{39}NO_3$	271–272	+108 (EtOH)	112
Amianthine $C_{27}H_{41}NO_2$	251–253	−87	113
Base $C_{27}H_{45}NO_3$	256	—	114
Beilupeimine $C_{27}H_{43}NO_2$	155–157	−53 (EtOH)	114
Chinpeimine $C_{27}H_{43}NO_2$	247–248	−21	114
Fritiminine	258–260	—	114
Imperoline $C_{27}H_{45}NO_3$	237–238	−8	115
Imperonine $C_{27}H_{43}NO_3$	239	−65	115
Peimidine $C_{27}H_{45}NO_2$	222	−74 (EtOH)	116
Peimine (*syn* Peimunine Verticine apo Verticine) $C_{27}H_{45}NO_3$	223–224	−26 (EtOH)	117–120
Peiminine (*syn* Peimiphine Peimitidine Verticilline Fritillarine) $C_{27}H_{43}NO_3$	212–213	−78	116, 120, 121
Peimissine $C_{27}H_{43}NO_4$	270	−51 (EtOH)	116
Sipeimine (*syn* Imperialine) $C_{27}H_{43}NO_3$	267	−36	122–124
Sonpeimine $C_{27}H_{43}NO_4$	256–258	—	114

112. Yunusov, Konovalova and Orekhov (1939). 113. Neuss (1953). 114. Chu and Loh (1956b). 115. Paul and Boit (1958). 116. Chou (1947). 117. Chou and Chu (1941). 118. Chu and Loh (1956a, b, and earlier papers). 119. Ito and others (1961). 120. Wu (1944). 121. Chi, Kao and Chang (1940). 122. Bauer and others (1958). 123. Boit (1954). 124. Chu and Loh (1955).

The Fritillaria Alkaloids

The fritillaria group on present indications would appear to possess the same skeleton as the ceveratrum group, but to possess only two or three hydroxyl groups (Chu and Loh, 1956b and earlier papers). The group deserves more research, especially on the inter-relations of the

alkaloids which are claimed to be individual entities. These alkaloids are listed in Table VI.

The pharmacology of the group is also in need of re-investigation with modern techniques. The Chinese drug pei-mu (Chou, 1954), from which many of the alkaloids have been isolated, was used quite irrationally for widely diverse conditions (Chi, Kao and Chang, 1936). Claims (Liu, Chang and Chang, 1936) that one of the alkaloids, peimine (also called peimunine) resembles atropine in its pharmacological properties seem surprising, as do claims of veratrine-like activity (Narumi, 1935), since these alkaloids do not possess the ester groups now known to be essential for this activity. On the other hand, reports (Chen, Chen and Chou, 1933; Narumi, 1936) that peimine and peiminine possess hypotensive properties and induce incoordination in the heart are more in line with the known activity of the pregnane group of alkaloids and may further illustrate the lack of dependence of these properties upon the position and configuration of the nitrogen atom in nitrogenous steroids. Additional evidence on this point would be provided by the reports (Zolotukhina, 1945) that alginine, the alkaloid from *Fritillaria sewerzowii*, possesses pronounced local anaesthetic activity, comparable to that of cocaine and exhibits vasodilatatory properties—if one assumes that the originally proposed molecular formula (Yunusov, Konovalova and Orekhov, 1939) is in error and that alginine does indeed have a cevane skeleton.

Amianthine, whose admission to the group is by no means certain, is obtained from the plant known as staggergrass or fly poison (*Amianthium muscaetoxicum*) (Neuss, 1953). This alkaloid has been shown to depress respiration and lower blood pressure and to be definitely without a typical veratrinic action on muscle (Alsberg, 1914).

There are a number of other alkaloids which, in all probability, belong to the steroid group, but their purity, identity or chemical constitution, are still unknown. Three such alkaloids which would appear to be pure entities are geralbine (Stoll and Seebeck, 1952), which is a C_{22} compound and raddeanine (Aslanov and Sadykov, 1956) and veratrobasine (Stoll, Stauffacher and Seebeck, 1955), which are C_{24} compounds. Raddeanine has been shown to stimulate the central nervous system of cats, rabbits and dogs in small doses, but in larger doses to be a depressant (Zolotukhina, 1944).

Conclusions

Despite the shortcomings of current theories of drug action and the lack of a simple correlation of chemical structure and biological activity, it is nevertheless clear from the foregoing account that much of the recent interest in the biological properties of nitrogenous steroids has a rational basis. Two examples may be quoted. The first is the application of the conclusions drawn from the receptor theory to the synthesis of the anabolic steroidal [3,2-c] pyrazoles and [2,3-d] isoxazoles, and the second is the synthesis of new drugs suggested by the supporting moiety theory. Both represent significant steps forward. Only within the last ten years

has interest developed in the synthetic nitrogenous steroids and, in view of the encouraging progress in the field, it would seem that even greater attention will be devoted to these compounds in the future. This is especially true now that aza-steroid hormone analogues have been synthesised (Zderic, Carpio and Limon, 1962) and with the interesting demonstration that the anabolic steroid 17β-hydroxy-17α-methylandrostano-[3,2-c]-pyrazole loses its ability to promote nitrogen retention on introduction of a double bond into the 4-position whilst it is converted into an oestrogenic compound showing no anabolic or androgenic properties when the 4,-6-diene system is introduced (Beyler, Potts and Arnold, 1961). With the recent discoveries that anabolic properties are present in a number of steroidal Schiff's bases (Irmscher, 1962) and that hypotensive properties are present in certain steroidal enamines (Clinton and others, 1962), it can be confidently predicted that nitrogenous steroids will play a further rôle in studies of drug action.

Moreover, the nitrogenous steroids as a group faithfully reflect the biological properties of the steroids in general, affording a broad spectrum of biological action and emphasizing changes in pharmacological properties with species, and routes of administration. Certain individual members, notably the ceveratrum ester alkaloids, display a variety of pharmacological actions which in themselves have led the pharmacologist to disentangle basic mechanisms of action, thus contributing to a better understanding of biological phenomena. Nitrogenous steroids are not unique in this respect, but they do present a happy choice with which to illustrate the slow but certain development of the theoretical aspects of pharmacology.

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