STEROIDAL ALKALOIDS

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SEVERAL alkaloids now recognised to possess the characteristic steroidal carbon framework have been known for nearly a century. Little progress however could be made in earlier investigations with these bases owing to lack of fundamental knowledge of the better known steroids. The elucidation of the molecular structures of cholesterol and cholic acid in 1932 made the way clear for rapid and successful researches with other classes of steroids of great interest, and in 1936 Soltys and Wallenfels,[1] observing that the potato alkaloid solanidine in alcohol formed an insoluble adduct with digitonin, dehydrogenated the related base solanthrine with selenium, and obtained the well-known Diels hydrocarbon, 3′-methyl-1 : 2-*cyclo*-pentenophenanthrene (I). Other *Solanum* and *Veratrum* alkaloids were subsequently also demonstrated to be steroids, and in 1948 conessine and related *Holarrhena* bases were shown to belong to the same class.[2] Interest in these alkaloids has increased considerably within the past few years; until recently the structural formula could not be written with certainty for any of them, but the position has now been reached where the structure of most of the important bases are either well established or likely to require modification only in detail.

The work up to 1948 has been comprehensively reviewed by Henry [3] and by Fieser and Fieser.[4] The present Review is not intended to be comprehensive, and emphasis is focused on the more important recent developments.

Classification.—Steroidal alkaloids may be divided into three groups on the basis of botanical source: (*a*) solanum alkaloids, obtained from *S. tuberosum* (potato), *S. lycopersicum* (tomato), and other species; (*b*) veratrum alkaloids usually from *V. album* and *V. viride* (European and American "hellebore") or from sabadilla (*V. sabadilla*) seeds; (*c*) kurchi or holarrhena alkaloids from "kurchi" (*H. antidysenterica*), a small Indian shrub, and from other Indian and African species of *Holarrhena*.

All the kurchi alkaloids of well-authenticated structure contain a carbon framework of twenty-one atoms similar to that of the steroid hydrocarbon pregnane (II); owing however to the presence of *N*-methyl groups the number of carbon atoms in the molecules of these alkaloids may rise to twenty-four (the alkaloid conkurchinine may contain twenty-five carbon atoms in the molecule; see p. 253).

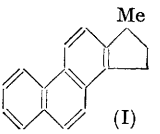
[1] *Ber.*, 1936, **69**, 811.

[2] Haworth, McKenna, and Singh, *Nature*, 1948, **162**, 22; *J.*, 1949, 831.

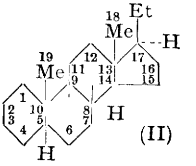
[3] "The Plant Alkaloids", J. and A. Churchill, Ltd., London, 4th Edn., 1949, pp. 661—672, 700—715, 742—749, where full references to the earlier work are given.

[4] "Natural Products related to Phenanthrene", Reinhold Publ. Corp., New York, 3rd Edn., 1949, pp. 597 *et seq.*

The solanum and veratrum alkaloids include glycosidic and ester types as well as the simple bases (alkamines); the parent bases, also readily obtainable by hydrolysis of the corresponding esters or glycosides, all contain twenty-seven carbon atoms in the molecule.* The carbon framework is usually that of cholestane (III), but there is strong evidence that at least two important veratrum alkaloids contain the modified cholestane framework illustrated by formula (IV). The aconite, delphinium, and erythrophloeum alkaloids, in which the existence of a steroid nucleus (even in a modified form) has not been demonstrated, are excluded from this Review;



(I)



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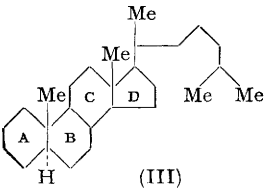

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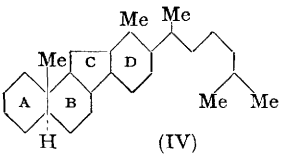


(IV)

these bases are probably more closely related to the diterpenoids. However, the Fritillaria alkaloids (ref. 3, pp. 732—734) of the Chinese drug "pei-mu" may ultimately prove to be steroids.

General Methods of Structural Investigation.—Hofmann, Emde, and cyanogen bromide degradations are among the most typical procedures for investigating alkaloid structures, but only in the case of conessine have these methods been applied with success. As with other polycyclic hydroaromatic products, dehydrogenation by selenium has been of outstanding value, not only for identification of the carbon framework, but also, with the veratrum and solanum alkaloids, for the provision of information about the heterocyclic portion of the molecule. Diels's hydrocarbon (I) is not obtained by dehydrogenation of all the steroidal alkaloids: in some cases presence of a substituent at or near $C_{(18)}$ results in the production of a closely related 1 : 2-*cyclo*pentenophenanthrene; and the alkaloids possessing the modified cholestane framework (IV) naturally cannot yield the normal product (I). The more important kurchi bases are notable both as natural steroids and as alkaloids not containing oxygen; many veratrum and solanum alkaloids, however, contain the 3β-hydroxy-group and 5 : 6-double bond so characteristic of other steroids, and the presence of this composite

* Two alkaloids, veratrobasine and geralbine, recently isolated by Stoll and Seebeck (*J. Amer. Chem. Soc.*, 1952, **74**, 4728) from *V. album* have the molecular formulæ $C_{24}H_{37}O_3N$ and $C_{22}H_{33}O_2N$ respectively, and thus constitute an exception to this rule. Each alkaloid contains one *N*-methyl group, likewise an exception among the veratrum and solanum alkaloids; geralbine may thus be related to the kurchi alkaloids.

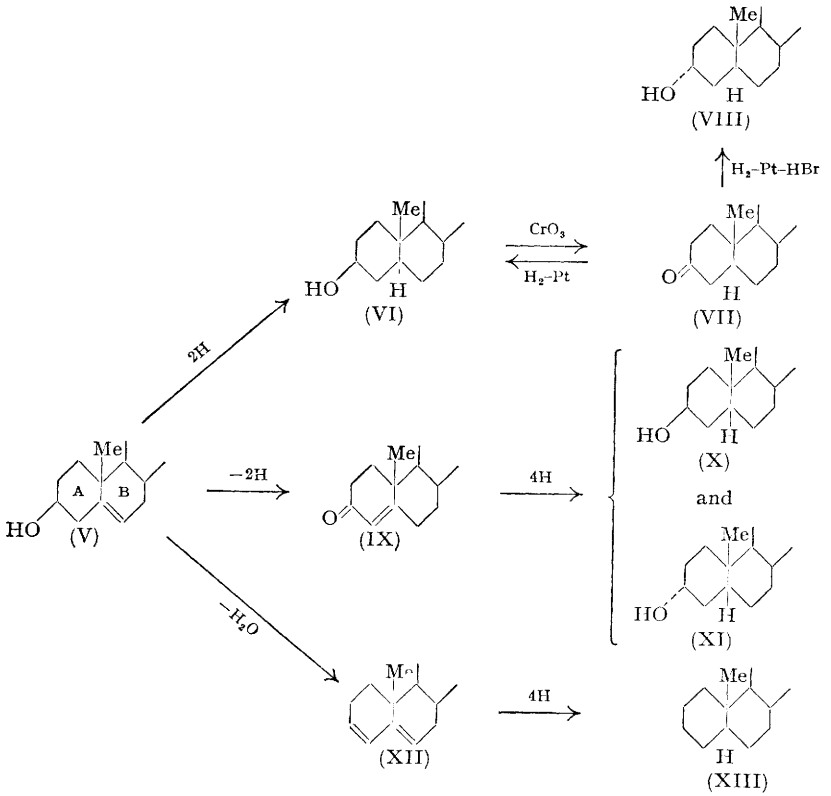
group is readily demonstrable in most cases by precipitation of the alkaloid with digitonin, and by dehydration, oxidation, and reduction. In some cases valuable information has been obtained by removal of the heterocyclic portion of the molecule by oxidation, or by otherwise establishing a close connection with a different type of steroid.

Solanum Alkaloids.—*Solanidine.* This base, of molecular formula $C_{27}H_{43}ON$, is obtained by acid hydrolysis of the glycoalkaloid solanine, $C_{45}H_{73}O_{15}N$, the usual source of which is potato shoots. The sugar portion of the solanine molecule is a glucosylgalactosylrhamnose, as shown by identification of the component monosaccharides and by partial hydrolysis ; [5, 6] the aglycone solanidine is glycosidically linked to the glucose unit of this unusual oligosaccharide. The correct molecular formula for solanidine was first given by Schöpf and Hermann.[7] Solanidine may readily be shown to contain a secondary alcoholic function, a double bond, and a tertiary amino-group. The alkaloid does not contain a *N*-methyl or *N*-ethyl group, an indication that the nitrogen atom is common to two rings, and the resistance of the base to Hofmann degradation * [1, 7, 8] has been regarded as additional evidence for this supposition. The secondary hydroxyl group is eliminated as water when solanidine hydrochloride is heated [7] and a doubly unsaturated base solanthrene or solanidiene, $C_{27}H_{41}N$, is produced ; some of this base (in which the double bonds are in conjugation) is also formed during acid hydrolysis of the glycoalkaloid. Solanidine gives a precipitate with digitonin [1] and (like solanthrene) yields the Diels hydrocarbon (I) on selenium dehydrogenation.[9] A steroidal structure for the alkaloid is thus indicated.

Additional valuable information is afforded by the reactions of the double bond and secondary hydroxyl group [10] in solanidine, which are closely analogous to well-known characteristic reactions in rings A and B of cholesterol. Some of these transformations are shown in the annexed Scheme, and similarities in specific rotation among compounds of each series are shown in the Table. All values of $[\alpha]_D$ in the Table are for solution in chloroform, and most of them are quoted by Prelog and Szpilfogel.[10] The relation between molecular rotation ($M[\alpha]_D/100$) and structure in the steroid field has recently been studied in detail, particularly by Barton and his co-workers (for a general account see Barton and Klyne) ; [11] in the present instance a simple comparison of specific rotations illustrates the point.

[5] Gerecs and Zemplen, *Ber.*, 1928, **61**, 2294.
[6] Caronna and Oddo, *Ber.*, 1934, **67**, 446. [7] *Ber.*, 1933, **66**, 298.
[8] Soltys, *ibid.*, p. 762.
[9] Rochelmeyer, *Arch. Pharm.*, 1936, **274**, 543 ; Craig and Jacobs, *J. Biol. Chem.*, 1943, **149**, 451.
[10] Geyer, Rochelmeyer, and Shah, *Ber.*, 1938, **71**, 226 ; Rochelmeyer, *Arch. Pharm.*, 1939, **277**, 340 ; Prelog and Szpilfogel, *Helv. Chim. Acta*, 1944, **27**, 390.
[11] *Chem. and Ind.*, 1948, 755.

* Solanidine has generally been recovered unchanged on attempted Hofmann decomposition of its metho-salts, but in one case an *iso*solanidine is reported to have been formed ; [8] this isomer may possibly result from recyclisation of an intermediate unsaturated base as in the case of *hetero*conessine (see p. 252).



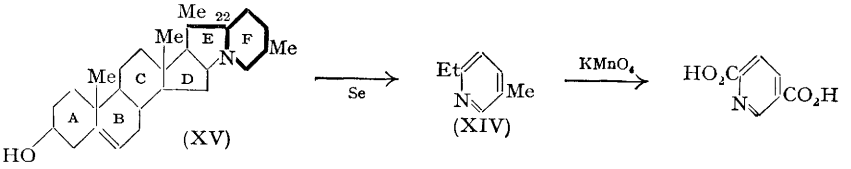
Partial formula	Compound, solanidine series	$[\alpha]_D$	Compound, cholesterol series	$[\alpha]_D$
(V)	Solanidine	− 27°	Cholesterol	− 37°
(VI) . . .	Solanidan-3β-ol*	+ 28	Cholestan-3β-ol	+ 28
(VII) . . .	Solanidan-3-one	+ 46	Cholestan-3-one	+ 40
(VIII) . . .	Solanidan-3α-ol*	+ 32	Cholestan-3α-ol	+ 32
(IX) . . .	Solanid-4-en-3-one	+ 89	Cholest-4-en-3-one	+ 89
(X)	5β-Solanidan-3β-ol†	+ 28	Coprostan-3β-ol	+ 28
(XI) . . .	5β-Solanidan-3α-ol	+ 35	Coprostan-3α-ol	+ 31
(XII) . . .	Solani-3 : 5-diene (solanthrene)	− 92	Cholesta-3 : 5-diene	− 123
(XIII) . . .	Solanidane	+ 33	Cholestane	+ 24

* An α-configuration for substituents or angular hydrogen atoms in rings A to D in steroids indicates a configuration *trans* to the $C_{(18)}$ methyl group ; a β-configuration is *cis*. These configurations are written with broken and full lines respectively in structural formulæ.

† The prefix "*allo*" has been widely used in the solanidine series to indicate *cis*-A/B ring fusion (5β-hydrogen) but is contrary to modern practice (see *J.*, 1951, 3528, rule 3.7).

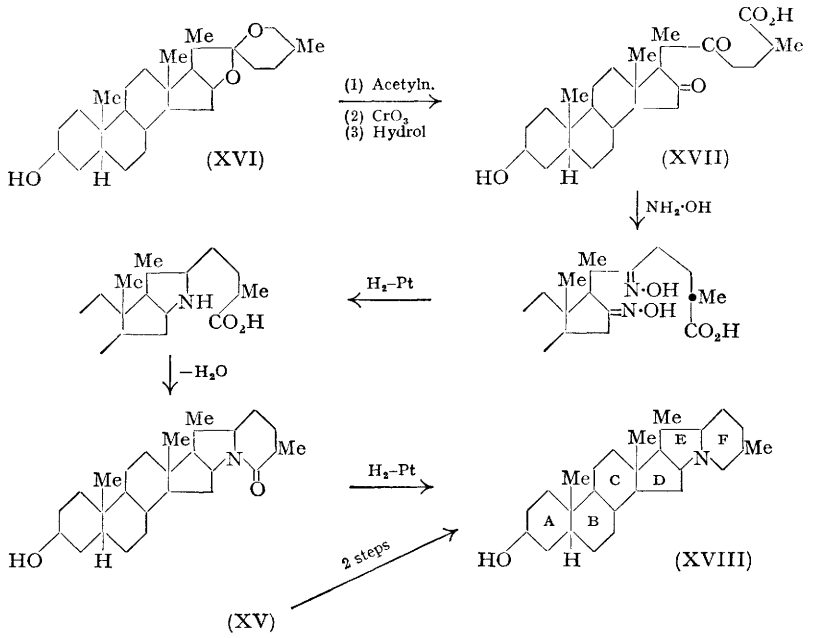
The chemical and physical properties of all the solanidine derivatives listed in the Table are in full accord with the partial structural formulæ

shown. All six 3β-hydroxy-compounds (but not the 3α-epimers) form precipitates with digitonin, and this is known to be the general rule with isomeric 3-hydroxy-steroids. The similarity between the two series of



derivatives strongly suggests that solanidine and cholesterol are structurally identical around rings A and B, and indeed among the various formulæ proposed for the alkaloid from time to time there has been no disparity on this point.

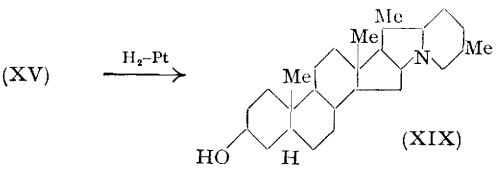
Earlier formulæ [1, 12] for solanidine showed considerable variations in the representation of the heterocyclic portion of the molecule, about which at first little information was available ; the demonstration by Rochelmeyer [12] that acetylsolanidine did not yield a $C_{(17)}$-ketone on oxidation with chromic acid suggested, however, that this part of the molecule is linked to ring D by more than one bond. In the absence of positive evidence from Hofmann degradations, the first definite indication of the structure of the heterocyclic ring was the isolation of 2-ethyl-5-methylpyridine (XIV) as a product of



[12] Clemo, Morgan, and Raper, *J.*, 1936, 1299 ; Rochelmeyer, *Arch. Pharm.*, 1942, **280**, 453.

selenium dehydrogenation.[13] This base had previously been encountered as a degradation product of the veratrum alkaloids, in the first instance by the distillation of cevine with zinc dust ; [14] its structure was proved by oxidation to pyridine-2 : 5-dicarboxylic acid, by the non-identity with the previously known 2-methyl-5-ethylpyridine, and by synthesis. On the strength of the additional evidence, and because of a possible structural analogy with the steroidal sapogenins, Prelog and Szpilfogel [10] proposed formula (XV) for solanidine, and suggested that a correlation with sarsasapogenin (XVI) might prove feasible. This possibility had independently become apparent to Jacobs and Uhle,[15] who converted sarsasapogenoic acid (XVII), an oxidation product of sarsasapogenin, into 5β-solanidan-3β-ol (XVIII) by the reactions indicated in the scheme on p. 235. This synthesis, the nearest approach so far * to the partial synthesis of any steroidal alkaloid from a steroid of different type, provides rigid proof for formula (XV) for solanidine. The formula is stereochemically certain so far as rings A—D are concerned ; the nitrogen linkage to ring D may be assigned the β-configuration because of the known β-configuration of the $C_{(17)}$ side-chain. Neither the orientation of substituents attached to the heterocyclic rings E and F nor the configuration at $C_{(22)}$ can be discussed at present for solanidine or any other steroidal alkaloid.

Demissidine. The glycoalkaloid demissine, $C_{50}H_{83}O_{20}N$, was isolated by Kuhn and Löw [16] from the leaves of the Mexican potato, *S. demissum.* On acid hydrolysis it yields glucose (2 mols.), xylose (1 mol.), galactose (1 mol.), and demissidine, $C_{27}H_{45}ON$. Demissidine is identical with solanidan-3β-ol (XIX), also obtainable from solanidine (XV) by catalytic hydrogenation, and is epimeric at $C_{(5)}$ with Craig and Jacobs's synthetic product (XVIII).



Tomatidine. The leaves of the red currant tomato (*Lycopersicon pimpinellifolium*) and of various species of wild tomato plants contain the glycoalkaloid tomatine, $C_{50}H_{83}O_{21}N$, which on acid hydrolysis yields tomatidine, $C_{27}H_{45}O_2N$, and a series of sugars identical with that obtained from demissine (above).[17] Tomatidine contains a hydroxyl group, an unreactive

[13] Prelog and Szpilfogel, *Helv. Chim. Acta*, 1942, **25**, 1306 ; Craig and Jacobs, *Science*, 1943, **97**, 122.

[14] Craig and Jacobs, *J. Biol. Chem.*, 1937, **119**, 141 ; 1937, **120**, 447 ; 1938, **124**, 659.

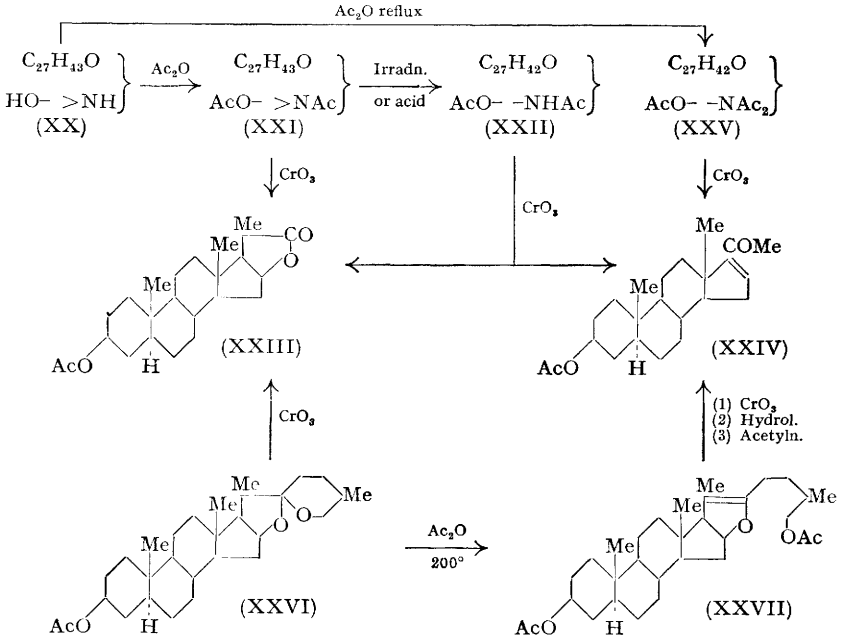
[15] *Ibid.*, 1945, **160**, 243.

[16] *Chem. Ber.*, 1947, **80**, 406.

[17] Doolittle, Fontaine, Irving, Ma, and Poole, *Arch. Biochem.*, 1948, **18**, 467 ; Doolittle and Fontaine, *Ind. Eng. Chem.*, 1948, **26**, 2440 ; Fontaine and Ma, *Arch. Biochem.*, 1950, **27**, 461 ; Kuhn and Löw, *Chem. Ber.*, 1948, **81**, 552 ; Gauthe, Kuhn, and Löw, *ibid.*, 1950, **83**, 448.

* *Added in Proof.*—This is no longer correct. See footnote on p. 239.

oxygen atom, and a secondary amino-group, but no double bond. Catalytic hydrogenation, or reduction with lithium aluminium hydride, gives dihydrotomatidine, $C_{27}H_{47}O_2N$, a base containing two hydroxyl groups. Tomatidine gives a precipitate with digitonin. The molecular formula and some of the reactions suggested a steroidal structure,[18] and this was confirmed in the following manner.[19] The base (XX) yields an *ON*-diacetyl derivative (XXI) containing the groups OAc and >NAc (infra-red absorption ; no active hydrogen), which on exposure to ultra-violet light or long boiling in acetic acid gives an isomeric diacetyl derivative (XXII) containing the groups OAc and NHAc (infra-red absorption ; one active hydrogen) ; during the isomerisation a nitrogenous ring has evidently been opened. Chromic acid oxidises the isomers (XXI) and (XXII) to, respectively, the acetoxylactone (XXIII) and a mixture of this with 3β-acetoxy*allo*pregn-16-en-20-one (XXIV). The same ketone is obtained by oxidation of a triacetyltomatidine (XXV) formed by acetylation under more drastic conditions ;

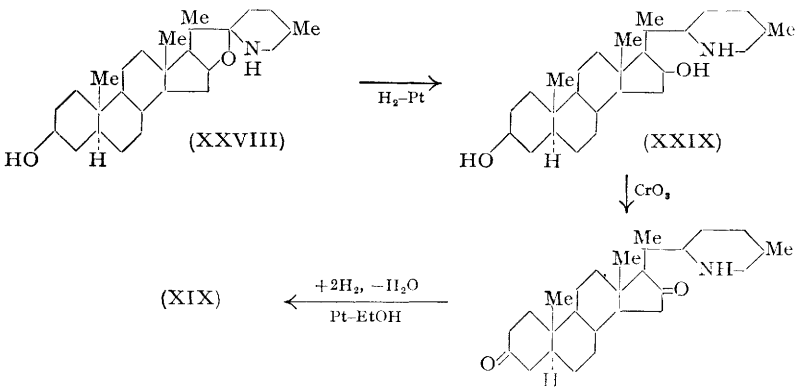


the triacetyl derivative contains the groups OAc and NAc_2 (infra-red absorption ; no active hydrogen). The lactone (XXIII) and the acetoxypregnenone (XXIV) had previously been encountered as oxidation products of acetyltitogenin (XXVI) and diacetyl-ψ-titogenin (XXVII) respectively. From these and other reactions a close structural analogy between tomatidine and the steroidal sapogenins was apparent, and formula (XXVIII)

[18] Ard, Fontaine, and Ma, *J. Amer. Chem. Soc.*, 1951, **73**, 879.

[19] Katz, Mossettig, and Sato, *ibid.*, p. 880 ; Kuhn and Löw, *Chem. Ber.*, 1952, **85**, 416.

was advanced for the alkaloid. This was confirmed by Kuhn, Löw, and Trischmann [20] by dehydrogenation of dihydrotomatidine to 2-ethyl-5-methylpyridine (XIV) and conversion of tomatidine into demissidine (XIX)



by the series of reactions illustrated. The reduction of tomatidine to dihydrotomatidine (XXIX) is paralleled by similar reactions of steroidal sapogenins, *e.g.*, (XXVI), in which one of the *spiro*ketal oxide linkages may likewise be opened by hydrogenolysis ; these reductions are possible because of the attachment of the second oxygen atom (or the nitrogen in tomatidine) to the *spiro*-carbon atom ($C_{(22)}$).

Solasodine. Hydrolysis of the glycoalkaloid solasonine, $C_{45}H_{73}O_{16}N$, from the green berries of the shrubs *S. sodomeum* (Dead Sea apple), *S. aviculare* (Maori " poro-poro "), and other species, yields solasodine, $C_{27}H_{43}O_2N$, together with one mol. each of glucose, galactose, and rhamnose. The order of the sugar units is probably the same as in solanine.[21, 6] The correct molecular formulæ for solasonine and its aglycone were established by Rochelmeyer [22] and by Briggs and his co-workers.[23] Solasodine has more recently been obtained by hydrolysis of solmargine,[24] $C_{45}H_{73}O_{15}N$, (from *S. marginatum*) in which the order of the sugar units (two of rhamnose and one of glucose) is indicated by partial hydrolysis to solasodine glucoside. Solasodine forms an insoluble adduct with digitonin and yields the Diels hydrocarbon (I) on dehydrogenation with selenium ; [25] one of the pyridine bases also formed in this reaction is probably 2-ethyl-5-methylpyridine (XIV) which has also been identified as a dehydrogenation product of solasodine glucoside.[24] These results indicate that the alkaloid has a steroidal structure with a heterocyclic arrangement probably closely related to that in solanidine. Two active hydrogen atoms are present, one of which is accounted for as a secondary hydroxyl group. The alkaloid also contains

[20] Kuhn and Löw, 1953, **86**, 372 ; *Angew. Chem.*, 1952, **64**, 397.
[21] Briggs and Carroll, *J.*, 1942, 17.
[22] *Arch. Pharm.*, 1939, **277**, 329.
[23] Briggs, Newbold, and Stace, *J.*, 1942, 3.
[24] Briggs, Brooker, Harvey, and Odell, *J.*, 1952, 3587.
[25] Rochelmeyer, *Arch. Pharm.*, 1937, **275**, 336.

a double bond, and the reactions of the hydroxyl group and the double bond, together with the spectral and rotational [26] characteristics of the products, give a strong indication of the presence of the familiar 5 : 6-unsaturated 3β-hydroxy- arrangement (as in solanidine and cholesterol). A series of derivatives corresponding to those listed in the Table on p. 234 may also be obtained from solasodine, *e.g.*, solasod-4-en-3-one and solasoda-3 : 5-diene with partial formulæ (IX) and (XII) respectively.

Erroneous conclusions were at first reached by Briggs and his co-workers [23] regarding the function of the second oxygen atom and the basic centre in solasodine, and the alkaloid was formulated as a carbinol-amine (XXX) related to an earlier structure for solanidine. The base, however, was later shown to be a secondary amine, and formula (XXXI) was proposed [27] by analogy with the structure of sapogenins such as diosgenin (XXXII). The properties and reactions of solasodine are readily explicable on the basis of formula (XXXI). Thus the alkaloid is a weak base,[28] difficult to acetylate owing to the inductive effect of the cyclic oxygen atom. Catalytic hydrogenation in the presence of palladium–charcoal gives solasodanol (dihydrosolasodine ; XXXIII) but when a platinum catalyst is employed a second mol. of hydrogen is taken up ; the product, dihydrosolasodanol (XXXIV), contains an additional hydroxyl group and yields a triacetate (cf. tomatidine and the steroidal sapogenins). The oxygen ring may also be opened by treatment with lithium aluminium hydride. Treatment of solasodine with acetic anhydride, followed by oxidation with chromic acid, hydrolysis with methanolic potassium hydroxide, and re-acetylation, gives a mixture [29] of 3β-acetoxypregna-5 : 16-dien-20-one (XXXV) and 3β-acetoxy-16α-methoxypregn-5-en-20-one (XXXVI) ; the methoxy-compound is evidently an artefact formed during the hydrolysis. Most of these reactions fail to distinguish unambiguously between the suggested structure (XXXI) for solasodine and the alternative (XXXVII). A preliminary claim,[27] not yet confirmed, of conversion of *N*-nitrososolasodine into diosgenin (XXXII) in low yield by treatment with aqueous acetic acid is equally inconclusive. However, dehydrogenation of the alkaloid or its glucoside to 2-ethyl-5-methylpyridine (XIV) seems decisive. Nevertheless, while the general nature of the heterocyclic arrangement in solasodine is clear, further evidence on the structure of this part of the molecule is desirable. For example, an established relation between solasodine and tomatidine (XXVIII) would be of great interest ; the tentative suggestion [27] that tomatidine and solasodanol (XXXIII) may be identical has not been confirmed, and indeed there are appreciable discrepancies in the physical properties of the two bases and their derivatives.*

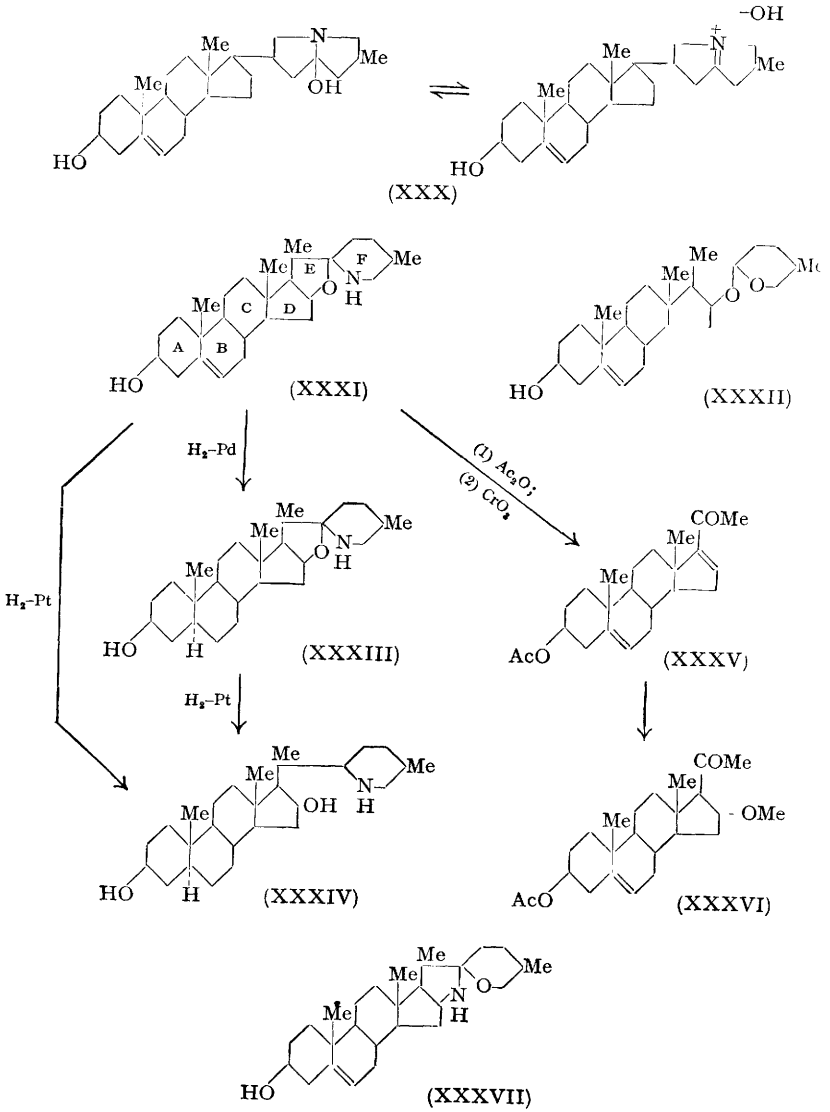
A stereoisomeric relation between solasodine and the aglycone

[26] Briggs and O'Shea, *J.*, 1952, 1654.

[27] Briggs, Harvey, Locker, McGillivray, and Seeyle, *J.*, 1950, 3013 ; Briggs and Locker, *ibid.*, p. 3020. [28] Cf. Bloom and Briggs, *J.*, 1952, 3591.

[29] Miller, Mosettig, and Sato, *J. Amer. Chem. Soc.*, 1951, **73**, 5009.

* *Added in Proof.*—The conversion of kryptogenin into solasodine recently reported by Uhle (*J. Amer. Chem. Soc.*, 1953, **75**, 2280) indicates that (XXXI) for solasodine is structurally correct ; tomatidine and solasodanol may thus be epimeric, *e.g.* at $C_{(22)}$.

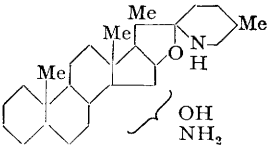


solauricidine (from *S. auriculatum*) has been suggested by Briggs and his co-workers,[30] but the data do not furnish clear evidence that these two bases are distinct individuals.

Solanocapsine. The leaves of *S. pseudocapsicum* contain the base solanocapsine, $C_{27}H_{46}O_2N_2$, apparently not in glycosidic combination. This alkaloid has been investigated by Barger and Fraenkel-Conrat,[31] and by Schlittler and Uehlinger.[32] Solanocapsine yields Diels's hydrocarbon (I)

[30] Bell, Briggs, and Carroll, *J.*, 1942, 12. [31] *J.*, 1936, 1537.
[32] *Helv. Chim. Acta*, 1952, **35**, 2034.

and 2-ethyl-5-methylpyridine (XIV) on selenium dehydrogenation, but differs from the other solanum alkaloids in giving no precipitate with digitonin, and in containing two basic centres. There are also present a hydroxyl group and an inert (ethereal) oxygen atom, but no double bond. Treatment with nitrous acid eliminates a primary amino-group (with the



(XXXVIII)

introduction of a double bond) and nitrosates the other basic centre, which is therefore secondary. The hydroxyl group cannot be acetylated, eliminated with acid reagents, or oxidised to a carbonyl group ; it is regarded as being tertiary in character. Although hydrogenolysis of the oxide ring has not been demonstrated satisfactorily, Schlittler and Uehlinger suggest structure (XXXVIII), analogous to that of the other secondary solanum bases. The behaviour of the hydroxyl group indicates that it is not in position 3, and it is thus possible that the amino-group may be situated there, as in some kurchi alkaloids.

Veratrum Alkaloids.—Three principal sources (*Veratrum* spp.) of this group of natural steroidal bases are named on p. 231 ; of these, each of the two " hellebores " contains almost all the more important alkaloids free or in combination, whereas sabadilla seeds yield mainly esters of cevine.

Rubijervine and iso*rubijervine.* These two isomeric tertiary bases $C_{27}H_{43}O_2N$, are neither epimers nor otherwise readily interconvertible as their names might suggest. Each base contains a double bond and two hydroxyl groups. The presence of the 5 : 6-unsaturated 3β-hydroxy-system is indicated [33] by positive digitonin reactions and by conversion of the bases, *via* the 4 : 5-unsaturated 3-ketones into the corresponding unsaturated 3-alcohols which give characteristic purple colours with trichloroacetic acid (Rosenheim reaction). Cholesterol behaves analogously. Dehydrogenation of *iso*rubijervine [33] yields 2-ethyl-5-methylpyridine (XIV) and 1 : 2-*cyclo*pentenophenanthrene (XLVIII). The alkylpyridine is also obtained from rubijervine, but in this case the neutral dehydrogenation product is a hydrocarbon, $C_{18}H_{16}$, which has not been conclusively identified but closely resembles 5′-methyl-1 : 2-*cyclo*pentenophenanthrene (for numeration see XLVIII) ; a phenol, $C_{18}H_{16}O$, possibly related, is also formed.[34] These results suggested that rubijervine and *iso*rubijervine were hydroxysolanidines, and this was confirmed by conversion of each base into solanidine (XV) and solanidan-3β-ol (XIX) by the reaction scheme [35, 36, 37] shown.

[33] Craig and Jacobs, *J. Biol. Chem.*, 1945, **159,** 617.

[34] *Idem, ibid.*, 1943, **148,** 41. [35] Jacobs and Sato, *ibid.*, 1949, **179,** 623.

[36] Jacobs and Pelletier, *J. Amer. Chem. Soc.*, 1952, **74,** 4218 ; Burn and Rigby, *Chem. and Ind.*, 1952, 668 ; *J.*, 1953, 963.

[37] Burn and Weisenborn, Abs. Amer. Chem. Soc. Meeting, Sept., 1952, No. 23L ; *J. Amer. Chem. Soc.*, 1953, **75,** 259.

The additional hydroxyl group in rubijervine (XXXIX) is regarded as being attached at the $C_{(12)}$ position (α-configuration) for the following reasons : [35] (*a*) all positions in rings A and B are ruled out since rubijervine is not an α-glycol, the corresponding dihydro-diketone (XL) is not a 1 : 3-diketone, and the 3-hydroxy-ketone (XLI) which yields solanidine (XV) on Wolff–Kishner reduction does not contain an $\alpha\beta$-unsaturated carbonyl group ; (*b*) the phenol, $C_{18}H_{16}O$ [probably a derivative of *cyclo*pentenophenanthrene (XLVIII)], rather than a hydroxypyridine (cf. jervine and veratramine, below), is formed on dehydrogenation of rubijervine ; this, together with the full carbonyl reactivity of the *basic* diketone (XL) exclude positions $C_{(11)}$ (authentic $C_{(11)}$-ketones are very inert), $C_{(15)}$ (also unlikely biogenetically), $C_{(23)}$, $C_{(24)}$, and $C_{(26)}$; (*c*) optical rotational data favour the assigned (12α-)position for the hydroxyl group. As it is not at all evident, however, how 5′-methyl*cyclo*pentenophenanthrene could be derived from (XXXIX), further investigation of the hydrocarbon $C_{18}H_{16}$ is desirable.

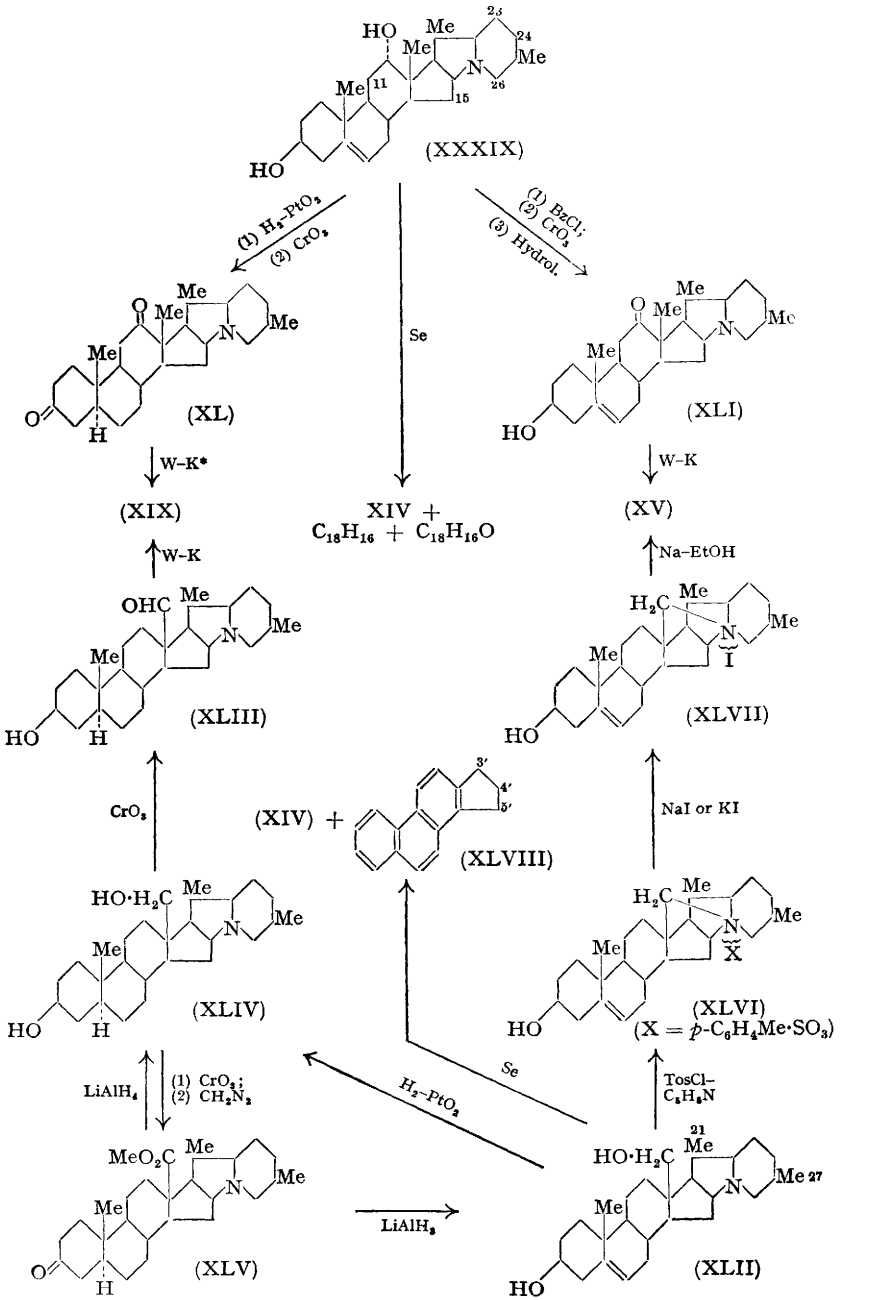
The additional hydroxyl group in *iso*rubijervine (XLII) is primary : dihydro*iso*rubijervine (XLIV) gives the aldehyde (XLIII) or a corresponding keto-acid on oxidation with chromic acid. The methyl ester (XLV) of the keto-acid is very resistant to hydrolysis,[38] indicating that it may be the ester of a tertiary carboxylic acid. [Strophanthidin derivatives carrying an angular carbomethoxy-group between rings A and B in place of the usual angular methyl group are more readily saponified than the ester (XLV).] The reaction product (XLVI) of *iso*rubijervine and toluene-*p*-sulphonyl chloride, and the corresponding iodide (XLVII), were formulated as the normal 18-toluene-*p*-sulphonate and primary halide respectively by Pelletier and Jacobs,[36] but the infra-red spectra and *neutral* character of these compounds show them to be quaternary ammonium salts ; [37] the alkaline reduction of the quaternary iodide to solanidine is a kind of Emde degradation. The formation of these quaternary salts indicates that the site of the primary hydroxyl group in *iso*rubijervine is within bonding distance of the nitrogen atom and, of the three possible positions [$C_{(18)}$, $C_{(21)}$, $C_{(27)}$; see (XLII)], $C_{(18)}$ is the most favoured stereochemically. As the same position (adjoining the tertiary $C_{(13)}$) also appears very likely on other grounds (see above), formula (XLII) for *iso*rubijervine may be regarded as well established.

Jervine. This interesting base occurs as the glucoside ψ-jervine,* $C_{33}H_{49}O_8N$, and as the free alkamine, $C_{27}H_{39}O_3N$, the correct molecular formula for which was established by Craig and Jacobs.[39] Jervine is a heterocyclic secondary amine, and contains a hydroxyl group and two double bonds, one of which is $\alpha\beta$ to a carbonyl group. The third oxygen atom is present as a cyclic ether linkage. The presence in the alkaloid of C:C·CO is reflected in the characteristic ultra-violet absorption curve which has $\lambda_{max.}$ 250 mμ(log ε 4·2). Partial hydrogenation of jervine gives

[38] Jacobs and Sato, *J. Biol. Chem.*, 1951, **191,** 63.

[39] *Ibid.*, 1943, **148,** 51. For further details of jervine chemistry see Craig, Jacobs, and Lavin, *ibid.*, 1941, **141,** 51 ; Huebner and Jacobs, *ibid.*, 1947, **170,** 635 ; Jacobs and Sato, *ibid.*, 1948, **175,** 57.

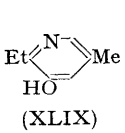
* Acid hydrolysis of ψ-jervine gives *iso*jervine, owing to isomerisation during the reaction. Hydrolysis of dihydro*pseudo*jervine, however, gives dihydrojervine.



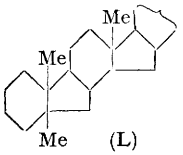
* The reduction of the 3-keto-group to a secondary alcoholic rather than a methylene group is abnormal. W–K = Wolff–Kishner.

dihydrojervine, the absorption of which ($\lambda_{max.}$ 295 mμ ; log ε 1·6) is typical of compounds containing an *isolated* carbonyl function. It follows that in the formation of dihydrojervine the double bond originally in conjugation with the carbonyl group is reduced preferentially ; further catalytic hydrogenation of dihydrojervine gives a tetrahydro-compound, $C_{27}H_{43}O_3N$. The ketonic group in jervine is unreactive towards most of the usual reagents but reduction of dihydrojervine with sodium and butanol yields dihydrojervinol (isomeric with tetrahydrojervine), a compound containing an additional acylatable hydroxyl group.

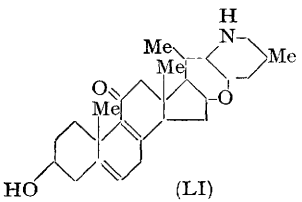
Jervine does not form an insoluble digitonide. While this may be connected with the modified steroid skeleton described below, it is of interest that the closely related alkamine veratramine gives a positive digitonin reaction (see p. 246). Nevertheless, evidence for the presence of the familiar 5 : 6-unsaturated 3β-hydroxy-steroid structure is provided by Barton's method of molecular rotation differences. For example, the changes in molecular rotation on *O*-acetylation and *O*-benzoylation of *N*-acetyljervine, and on hydrogenation of the double bond in dihydrojervinol, are — 27°, + 91°, and + 228°, respectively, compared with average values of — 35°, + 81°, and + 243° for authentic 5 : 6-unsaturated 3β-hydroxy-steroids such as cholesterol. Oxidation of jervine, dihydrojervine, and dihydrojervinol gives 4 : 5-unsaturated 3-ketones, recognisable as such by their ultra-violet spectra,* and by reduction with aluminium *iso*propoxide to 4 : 5-unsaturated 3-hydroxy-amines which give positive Rosenheim reactions.



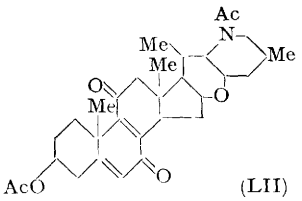
(XLIX)



(L)



(LI)



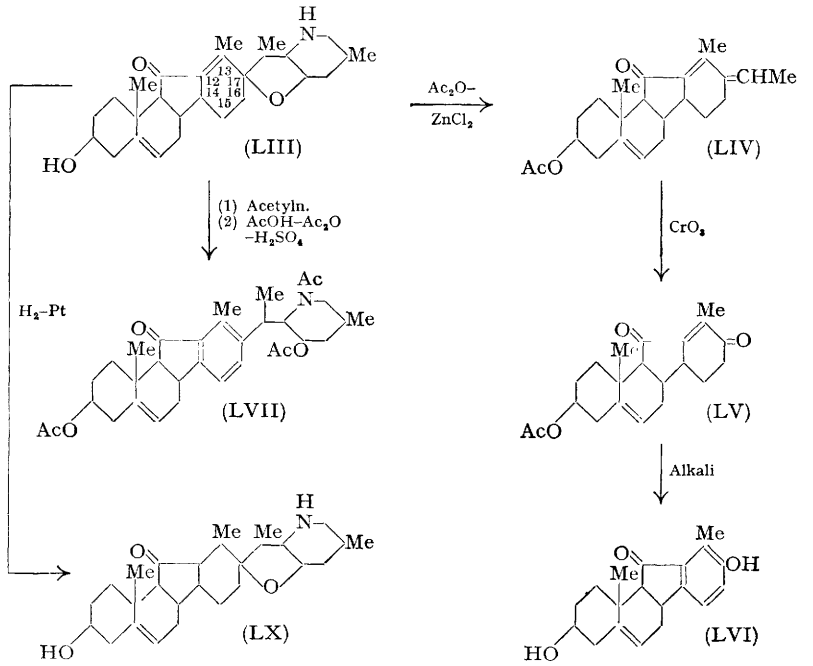
(LII)

Dehydrogenation of jervine with selenium yields 2-ethyl-5-methylpyridine (XIV) and a hydroxy-base, $C_8H_{11}ON$, the ultra-violet absorption and colour reactions of which indicate that it is a β-hydroxypyridine, possibly 2-ethyl-3-hydroxy-5-methylpyridine (XLIX). By the same reaction there is also formed a mixture of unidentified hydrocarbons, many of which appear on the basis of their ultra-violet absorption to be fluorene derivatives, *i.e.*, to contain *non-terminal* five-membered rings. The formation of fluorene

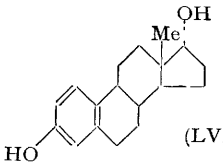
* The newly introduced chromophore is an $\alpha\beta$-unsaturated carbonyl system, similar to that originally present in jervine, so that the change in ultra-violet absorption on oxidation is particularly evident with the reduced bases.

rather than phenanthrene hydrocarbons on dehydrogenation at first led Jacobs and his collaborators to consider the possibility that ring B in jervine was five-membered as in the partial formula (L) but subsequent proof for the presence of the 5 : 6-unsaturated 3β-hydroxy-grouping in rings A and B ruled out structures of this sort and led instead to the development of formula (LI). The lack of carbonyl reactivity in jervine and its derivatives suggested that the ketonic group was at $C_{(11)}$; on this basis and on the assumption of a normal carbon skeleton, the 8 : 9-position is the only one possible for the conjugated double bond. Jacobs and Sato's formula [39] (LI), however, was not in satisfactory accord with the neutral dehydrogenation products of jervine, and it was later shown to be untenable by Wintersteiner and his collaborators.[40] Oxidation of 5 : 6-unsaturated 3-acetoxy-steroids with chromic acid yields the corresponding 7-ketones, and *ON*-diacetyl-7-ketojervine, prepared by this method, had not the spectral characteristics expected of the unsaturated diketone (LII) with its extended conjugated system. Nevertheless, the properties of this and related oxidation products leave no doubt whatever about the position of the newly introduced keto-group.

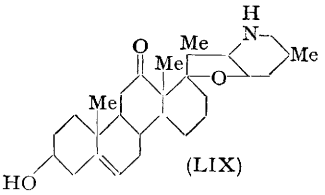
Further studies [41] with jervine led to formula (LIII) which accommodates adequately all the above reactions as well as those now to be described. Treatment of jervine with acetic anhydride and zinc chloride gives a product



[40] Fried, Iselin, Moore, and Wintersteiner, *Proc. Nat. Acad. Sci.*, 1951, **37**, 333.
[41] Fried, Iselin, Klingsberg, and Moore, *J. Amer. Chem. Soc.*, 1951, **73**, 2970.



(LVIII)



(LIX)

Unfortunately a 6-keto-group has been omitted from formula (LVIII).

(LIV) which on oxidation with chromic acid yields acetaldehyde and the yellow 1 : 4-diketone (LV) with the expected absorption characteristics. This diketone on treatment with alkali gives the phenol (LVI), the ultra-violet absorption of which is closely similar to that of the œstrane derivative (LVIII). Milder acetolysis of *ON*-diacetyljervine gives a product formulated as (LVII), the indanone structure in which may also be demonstrated spectroscopically. These acetolysis reactions indicate that the carbonyl group in jervine is directly attached to a six-membered ring D, but a poly-hydrochrysene structure (LIX) may be excluded as follows : (*a*) the keto-group in (LIX) would be expected to behave like an ordinary (reactive) steroidal $C_{(12)}$-ketone ; (*b*) the infra-red spectrum [42] of dihydrojervine (LX) has a band at 1730 cm.$^{-1}$, typical of a keto-group in a five-membered ring ; (*c*) biogenetically (LIII) is more probable (see p. 254) ; (*d*) the established relation between jervine and veratramine (see p. 247) indicates that jervine has a methyl group attached at $C_{(13)}$ in ring D (Wintersteiner's numbering). The oxide linkage to ring D is considered to be attached to $C_{(17)}$ rather than to $C_{(16)}$ (as, *e.g.*, in tomatidine) because of the ease of double-bond formation at this centre in the acetolysis reactions. Some further work on this point is desirable, as well as confirmation of the structure of the nitrogen-free acetolysis products, but formula (LIII) for jervine seems reasonably well established.

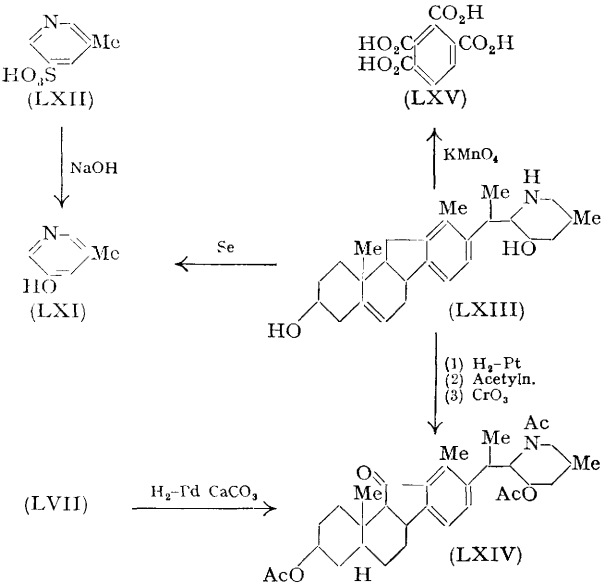
Jervine is isomerised to *iso*jervine by methanolic hydrochloric acid. The isomeric base contains a second acylatable hydroxyl group, and its ultra-violet absorption is considerably modified, but a profitable discussion of structure is hardly possible at present.

Veratramine. Structurally related to jervine is the secondary base veratramine,[43] $C_{27}H_{39}O_2N$, which contains two alcoholic hydroxyl groups, a double bond, and a benzene ring. Veratramine occurs free or as the glucoside veratrosine. The presence of the aromatic ring is shown by the ultra-violet absorption curve ($\lambda_{max.}$ 268 mμ ; log ε 2·8) and by the preparation of an aromatic nitro-compound from *OON*-triacetyldihydroveratramine. The ultra-violet absorption maximum of veratramine is not altered on hydrogenation to the dihydro-derivative, and the double bond is therefore not in conjugation with the benzene ring. Veratramine forms a precipitate with digitonin, and the presence of a 5 : 6-unsaturated 3β-hydroxy-grouping

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

[43] Craig and Jacobs, *J. Biol. Chem.*, 1945, **160**, 555 ; Jacobs and Sato, *ibid.*, 1949, **181**, 55 ; 1951, **191**, 71.

may be demonstrated by conventional methods. Dehydrogenation yields a hydrocarbon, $C_{22}H_{20}$, probably a chrysene or fluorene derivative, and 3-hydroxy-5-methylpyridine (LXI), identified by its reactions [which resemble those of the base (XLIX) from jervine] and by its synthesis from the corresponding picolinesulphonic acid (LXII). The presence of the aromatic ring in veratramine rules out a conventional steroidal structure, and led Tamm and Wintersteiner to propose [44] the formula (LXIII) by analogy with jervine (LIII). Strong support for this structure was obtained by oxidation of *OON*-triacetyldihydroveratramine to the indanone (LXIV) containing an *unreactive* carbonyl function; the same ketone may be obtained [45] by catalytic hydrogenation of the acetolysis product (LVII) obtained from *ON*-diacetyljervine as described above. The permanganate oxidation of



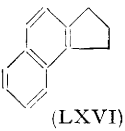
veratramine to benzene-1 : 2 : 3 : 4-tetracarboxylic acid (LXV) recently reported [46] is further proof of the assigned structure. Incidentally, the relation demonstrated between jervine and veratramine (which contains a preformed aromatic ring D) rules out the possibility that the six-membered ring in the acetolysis products of jervine described above arises from molecular rearrangement during acetolysis.

Cevine, germine, and protoverine. These three highly hydroxylated bases may be obtained by alkaline hydrolysis of a series of veratrum ester-alkaloids, together with various organic acids, *e.g.*, tiglic, angelic, veratric, acetic, or substituted acetic acids. In spite of extensive investigations [47]

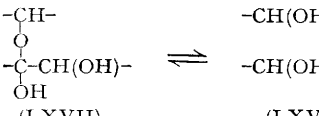
[44] Tamm and Wintersteiner, *J. Amer. Chem. Soc.*, 1952, **74**, 3842.
[45] Hosansky and Wintersteiner, *ibid.*, p. 4474.
[46] Hosansky, Moore, and Wintersteiner, *ibid.*, 1953, in the press.
[47] Ref. 3, pp. 702—705, 709—711.

little is known about their structure, and only brief mention is possible in this Review. Cevine and germine are isomeric and have the formula $C_{27}H_{43}O_8N$; protoverine contains an extra oxygen atom. All three alkaloids give similar products on dehydrogenation, including 2-ethyl-5-methylpyridine (XIV), a base cevanthridine, $C_{25}H_{27}N$, and a phenol cevanthrol, $C_{17}H_{16}O$. A series of hydrocarbons has also been obtained by dehydrogenation of cevine, and of these one has been identified as 4 : 5-benzindane (LXVI). Among the chromic acid oxidation products of cevine and germine is a hexanetetracarboxylic acid, which in spite of its simple molecular formula and obvious interest has not yet been conclusively identified.[48] None of the three bases contains a double bond or gives a positive digitonin reaction.

Cevine is not the parent base of the " veratrine " ester-alkaloids, but is formed by alkaline isomerisation of a precusor cevagenin.[49] Cevagenin, unlike cevine, contains a carbonyl group; cevine, however, has strong reducing properties, gives a dihydro-derivative on treatment with sodium and alcohol, and is represented by Barton and Eastham [50] as containing the masked α-ketol system (LXVII) possibly derived by isomerisation and lactolisation from the corresponding hydroxy-ketone arrangement (LXVIII)



(LXVI)



(LXVII) (LXVIII)

in cevagenin. A similar relation may exist between germine and protoverine and their respective ketonic alkaline-isomerisation products, *iso*germine and *iso*protoverine.

Kurchi Alkaloids.—*Conessine.* The most abundant and important of the kurchi alkaloids is conessine, $C_{24}H_{40}N_2$, the correct molecular formula for which was first given by Warnecke.[51] Many workers have obtained conessine from the seeds or bark of *Holarrhena antidysenterica*; it may also be obtained from *H. africana*, *H. congolensis*, *H. Wulfsbergii*, or *H. febrifuga*. Conessine is an unsaturated diacid base, and on oxidation with potassium iodate in dilute sulphuric acid, or by other methods, yields the characteristic derivative dioxyconessine (more correctly dihydrodihydroxyconessine), $C_{24}H_{42}O_2N_2$. The presence of one double bond may be demonstrated by catalytic hydrogenation to dihydroconessine, $C_{24}H_{42}N_2$, and since the alkaloid is a ditertiary base containing three *N*-methyl groups, it follows that one of the nitrogen atoms is present as a dimethylamino- and the other as a cyclic methylimino-group.[52, 53] These results may be expressed as (LXIX), where the nucleus contains one double bond.

[48] For a recent discussion see Elming, Jeger, Prelog, and Vogel, *Helv. Chim. Acta*, 1952, **35**, 2541.

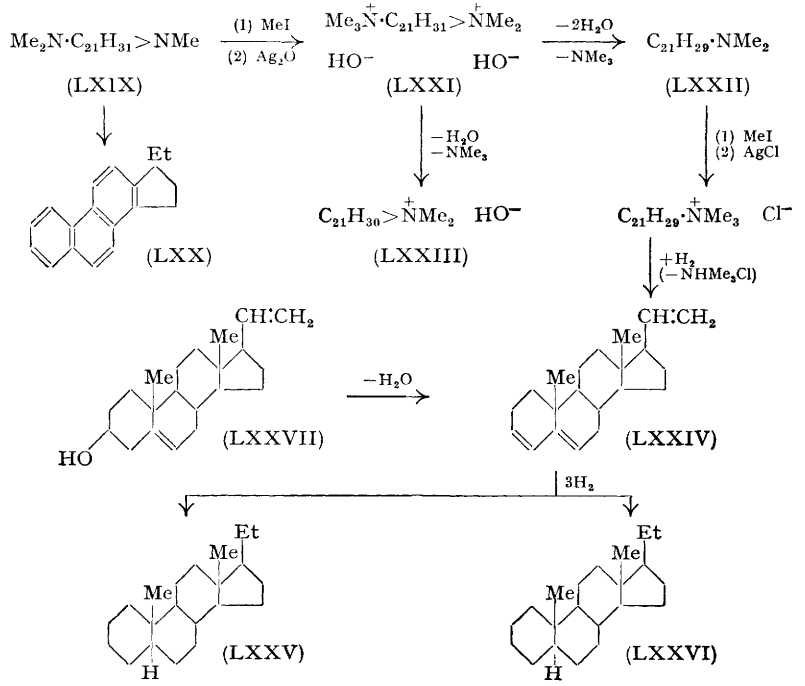
[49] Seebeck and Stoll, *ibid.*, p. 1270; cf., however, Jacobs and Pelletier, *J. Org. Chem.*, 1953, **18**, 765. [50] *J.*, 1953, 424. [51] *Ber.*, 1886, **19**, 60.

[52] Späth and Hromotka, *Ber.*, 1930, **63**, 126.

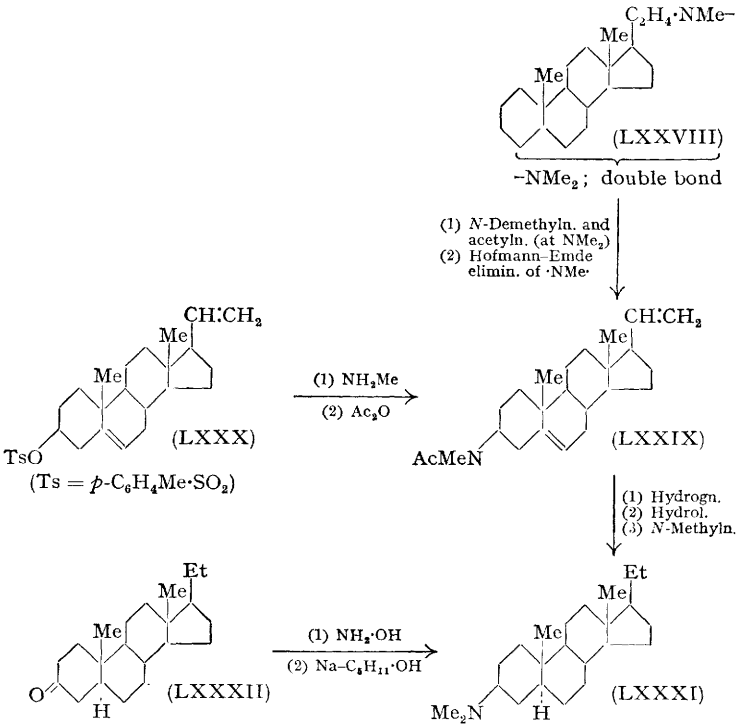
[53] Kanga, Ayyar, and Simonsen, *J.*, 1926, 2123.

Proof that conessine is a steroidal alkaloid was derived in the first instance [2] by selenium dehydrogenation of an unsaturated hydrocarbon or (more probably) a mixture of hydrocarbons, $C_{21}H_{30}$, obtained by dry distillation of conessine dihydriodide in a reducing atmosphere. From the dehydrogenation mixture was isolated 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (LXX) possibly in admixture with a little of Diels's hydrocarbon (I). The structure of the hydrocarbon (LXX) was demonstrated by its synthesis by methods analogous to those used for (I). The notable preponderance of the ethyl homologue in the dehydrogenation mixture is due in this case to special structural conditions (see below).

The detailed chemistry of conessine has been elucidated mainly by examination of products obtained on Hofmann decomposition of the alkaloid and its derivatives. Degradation of conessine by this technique was first investigated in detail by Späth and Hromatka,[52] following valuable earlier work by Kanga, Ayyar, and Simonsen.[53] When conessine dimethohydroxide (LXXI) is heated, water and trimethylamine are eliminated, and *apo*conessine (LXXII) is formed. This contains a dimethylamino-group (which is evidently derived from the methylimino-group in conessine) and three double bonds, of which two are introduced during the Hofmann decomposition : one is formed by fission of the conessine heterocyclic ring, and the other by elimination of the dimethylamino-group of the alkaloid as trimethylamine. Two of the three double bonds present in *apo*conessine are in conjugation. Partial Hofmann decomposition of conessine results in

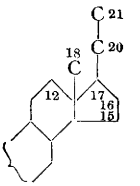


elimination of the dimethylamino-group as trimethylamine and yields metho-salts (*e.g.*, LXXIII) containing a heterocyclic ring and hence only two double bonds ; since these two double bonds are in conjugation (ultra-violet absorption as for *apo*conessine), the conjugated system in the metho-salts and in *apo*conessine is derived from the original conessine double bond and that formed by elimination of the dimethylamino-group as trimethyl-amine. The isolated double bond present in *apo*conessine is therefore formed by fission of the conessine heterocyclic ring.[54] Reductive scission of *apo*-conessine methochloride (Emde degradation) gives pregna-3 : 5 : 20-triene (LXXIV) identified by its reactions, including hydrogenation to pregnane (LXXV) and *allo*pregnane (LXXVI),[55] and by synthesis from pregna-5 : 20-dien-3β-ol (LXXVII).[56, 57] *apo*Conessine is therefore a dimethyl-aminopregna-3 : 5 : 20-triene and, having regard to the origin of the conju-gated diene system and isolated double bond in this derived base (see above), it is evident that conessine may be represented by the partial structural formula (LXXVIII), in which a double bond and dimethylamino-group are situated near $C_{(5)}$, and a methylimino-group is attached to the $C_{(17)}$-side chain and to some other carbon atom in the neighbourhood.

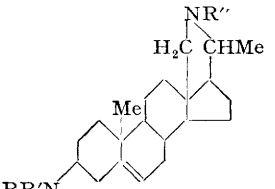


[54] Haworth, McKenna, and Whitfield, *J.*, 1949, 3127.
[55] Haworth, McKenna, Powell, and Woodward, *J.*, 1951, 1736.
[56] Haworth and McKenna, *Chem. and Ind.*, 1951, 312.
[57] Haworth, McKenna, and Whitfield, *J.*, 1953, 1102.

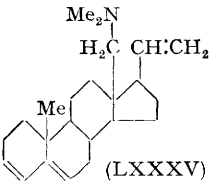
For the investigation of the position of the double bond and dimethylamino-group in conessine, a series of reactions was devised [57] to eliminate the heterocyclic methylimino-group, leaving the other two structural features intact. *N*-Demethylation of conessine gives the known subsidiary kurchi base *iso*conessimine (see p. 253) in which the dimethylamino-group of conessine is replaced by a methylamino-group. *N*-Acetyl*iso*conessimine is a monoacid base, and Hofmann degradation of the monomethohydroxide results only in fission of the heterocyclic ring; Emde elimination of the resultant dimethylamino-group then gives a *N*-acetyl-*N*-methylaminopregnadiene (LXXIX) in which one of the double bonds (formed by ring fission) is at the 20 : 21-position (side chain). The second double bond and the nitrogen atom in (LXXIX) obviously correspond to the double bond and dimethylamino-group in conessine. Since the physical properties (ultra-violet and infra-red spectra and molecular rotations) of conessine and a



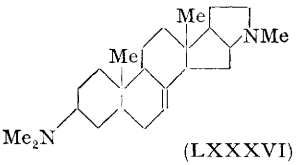
(LXXXIII)



(LXXXIV)



(LXXXV)



(LXXXVI)

number of its derivatives suggest that the double bond of the alkaloid is at the 5 : 6-position, with the dimethylamino-group at the adjacent 3β-position, 3β-*N*-acetyl-*N*-methylaminopregna-5 : 20-diene was synthesised from the toluene-*p*-sulphonate (LXXX) [58] and found to be identical with the conessine degradation product (LXXIX). The structure of (LXXIX) was confirmed by reduction, deacetylation, and *N*-methylation to 3β-dimethylamino-*allo*pregnane (LXXXI) which was synthesised [58] from *allo*pregnan-3-one (LXXXII). These experiments therefore indicate that conessine is a derivative of 3β-dimethylaminopregn-5-ene (see formula LXXXIV for conessine).

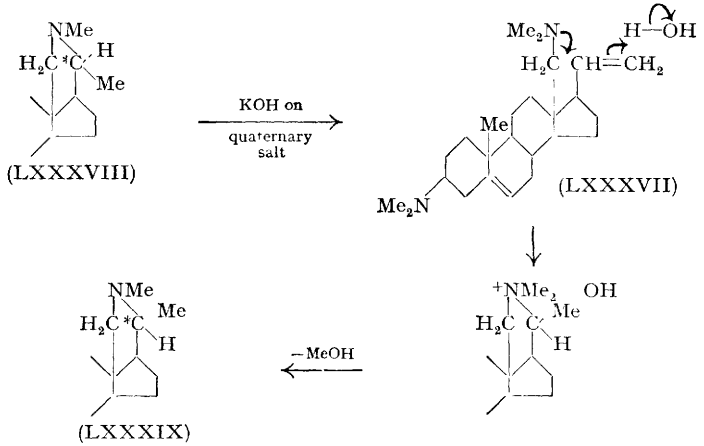
The structure of the heterocyclic part of conessine, *i.e.*, the positions of attachment of the heterocyclic methylimino-group to the pregnane framework, can be deduced as follows.[59] The methylimino-group involves $C_{(20)}$ or $C_{(21)}$ (see partial formula LXXXIII) and some other carbon atom in the neighbourhood to which is also attached the dimethylamino-group in *apo*conessine. Models show that the only possible positions are $C_{(12)}$ (β-orientated nitrogen linkage), $C_{(15)}$(β), $C_{(16)}$ (β), and $C_{(18)}$. Of these possibilities all

[58] Haworth, McKenna, and Powell, *ibid.*, p. 1110.

[59] Favre, Haworth, McKenna, Powell, and Whitfield, *ibid.*, p. 1115.

but $C_{(18)}$ may confidently be excluded : $C_{(15)}$ on, *inter alia*, biogenetic grounds (this is not a proved position of substitution in steroids) ; $C_{(16)}$ because of the relation between conessine and *hetero*conessine (see below) ; $C_{(15)}$, $C_{(16)}$, and $C_{(12)}$ because neither *apo*conessine nor its hexahydro-derivative gives a hydrocarbon on attempted Hofmann decomposition, indicating the probable absence of a β-hydrogen atom (to the nitrogen). {It is true that trimethylammonium groups attached by *equatorial* linkages [*i.e.*, linkages such as 3β (A/B *trans*) which are roughly in the same plane as the ring system as a whole] would not be readily eliminated by Hofmann degradation, but at least a small yield of hydrocarbon might be expected [58].} On the other hand, strong evidence in favour of $C_{(18)}$ as the position of attachment of the methylimino-group in conessine and the dimethylamino-group in *apo*conessine is obtained from Kuhn–Roth *C*-methyl analysis,* which also indicates that the other position of attachment of the methylimino-group in conessine is $C_{(20)}$ rather than $C_{(21)}$ (conessine, like *apo*conessine, has two *C*-methyl groups). Conessine and *apo*conessine may therefore be written with the structural formulæ (LXXXIV ; R = R′ = R″ = Me) and (LXXXV) respectively. There is no evidence in favour of the alternative structure (LXXXVI) for conessine previously proposed by Bertho.[60]

By heating conessine dimethiodide under carefully defined conditions in alkaline ethylene glycol,[54, 59] the isomeric base *hetero*conessine is obtained



The stereochemical representations at $C_{(20)}$* merely illustrate the isomerism ; the configurations are not shown.

instead of a Hofmann degradation product. *hetero*Conessine and conessine give the same product, conessimethine (LXXXVII), on partial Hofmann decomposition, and (LXXXVII) reverts to *hetero*conessine in hot aqueous

[60] *Annalen*, 1950, **569**, 1 ; 1951, **573**, 210.

* *C*-Methyl analyses are notoriously inaccurate, but precautions were taken here to avoid erroneous conclusions. *E.g.* 3α-dimethylamino*allo*pregnane (isomeric with hexahydro*apo*conessine) was shown to contain three *C*-methyl groups (*mols.* of acetic acid found : 2·17) whereas hexahydro*apo*conessine contains two (mols. of acetic acid found : 1·29).

glycol or ethanol. By these and other reactions it has been shown that conessine and *hetero*conessine are $C_{(20)}$-epimers (partial formulae LXXXVIII and LXXXIX), and that the reactions described may be represented as illustrated on p. 252.

On stereochemical grounds it is not possible to formulate conessine and *hetero*conessine with the methylimino-group engaging $C_{(16)}$, since apart from the evidence of *C*-methyl analysis (which shows unambiguously that *hetero*conessine, like conessine, contains two *C*-methyl groups), the existence of the isomerism shows that the heterocyclic ring in at least one base must be joined to $C_{(20)}$ as there cannot be $C_{(21)}$-epimers.

A second isomer, *neo*conessine, was first prepared by Siddiqui and Vashistha.[61] (Their " *iso*conessine " was probably a mixture.) The structure of *neo*conessine is not yet known; the base contains a double bond which cannot be hydrogenated catalytically,[55] and is probably fully substituted (infra-red spectrum).[59]

iso*Conessimine*. This base, $C_{23}H_{38}N_2$, which may also be obtained by demethylation of conessine with cyanogen bromide [62] (see p. 251), contains two *N*-methyl groups and reverts to conessine on *N*-methylation with formaldehyde and formic acid.[63] The demethylation reaction would be expected [62] to take place at the dimethylamino- rather than at the methylimino-group in conessine, and structure (LXXXIV; R = H, R′ = R″ = Me) is confirmed by the reactions described on p. 251 (degradation to 3β-dimethylamino*allo*pregnane).

Conessimine. This alkaloid, isomeric with *iso*conessimine, also contains two *N*-methyl groups, and yields conessine on *N*-methylation; [63] its structural formula is therefore (LXXXIV; R = R′ = Me, R″ = H).

Conimine. Demethylation of conessine or *iso*conessimine gives the di-secondary base conimine,[62] which contains one *N*-methyl group. Conimine is reconverted into conessine on methylation,[63] and evidently has the structure (LXXXIV; R = R″ = H, R′ = Me).

Holarrhimine. This interesting base, $C_{21}H_{36}ON_2$, has been isolated by several groups of workers.[59, 64] A hydroxyl and two primary amino-groups are present in the molecule, together with one double bond, and Siddiqui has suggested [65] that the nitrogen ring in the heterocyclic kurchi alkaloids may be formed by the condensation of the hydroxyl group in holarrhimine with one of the amino-groups. In agreement with this, Hofmann degradation of tetra-*N*-methylholarrhimine gives a cyclic ether, $C_{21}H_{30}O$, which appears to be a steroidal 3 : 5-diene (ultra-violet absorption).[59]

Conkurchine. According to Bertho,[66] acid decomposition of the base conkurchinine, $C_{25}H_{36}N_2$, yields conkurchine, $C_{21}H_{32}N_2$, and an unidentified

[61] *J. Sci. Ind. Res.* (*India*), 1945, **3**, 559.
[62] Siddiqui and Siddiqui, *J. Indian Chem. Soc.*, 1934, **11**, 787.
[63] Siddiqui, *ibid.*, p. 283.
[64] Siddiqui and Pillay, *ibid.*, 1932, **9**, 553; Bertho, *Chem. Ber.*, 1947, **80**, 316.
[65] *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 249.
[66] *Arch. Pharm.*, 1939, **277**, 237; *Annalen*, 1943, **555**, 214; *Chem. Ber.*, 1947, **80**, 316.

four-carbon compound. Conkurchine is stated to contain two double bonds, but no *N*-methyl groups. Hydrogenation gives successively di- and tetrahydroconkurchine, which on *N*-methylation yield respectively conessine and dihydroconessine. On the basis of this evidence conkurchine could be (LXXXIV; R′=R′=R″=H) with an additional double bond, which Bertho regards as being situated in the heterocyclic ring.

Holarrhenine. This hydroxy-base, $C_{24}H_{38}ON_2$, has been isolated only from the bark of the African species *H. congolensis.*[67] The alkaloid, like conessine, contains three *N*-methyl groups.

Other kurchi alkaloids. The isolation of many other subsidiary bases from extracts of various species of *Holarrhena* has been reported, but of these some have been inadequately characterised and the individuality of others is open to doubt.

In view of the well-established occurrence of solanum and veratrum alkaloids in glycosidic combination, confirmation of Irani's claim [68] to have obtained a crystalline glycoalkaloid from an extract of "kurchi" seeds would be of particular interest.

Biogenetic Considerations.—The structural analogy between solanum and veratrum alkaloids of known constitution and the steroidal sapogenins (which has been obvious to many investigators) is underlined by the conversion of sarsasapogenin into 5β-solanidan-3β-ol (p. 235), and is doubtless of biogenetic significance. An artificially prepared [69] rearrangement product of rockogenin has the modified skeletal structure (IV) of jervine and veratramine, and the relation between these alkaloids and others of more conventional structure is also apparent among other groups of natural products, *e.g.*, the triterpenes.

Pharmacology.[3]—The most important uses have been: (*a*) of conessine or kurchi extracts for the treatment (in India) of amœbic dysentery; and (*b*) of veratrum alkaloids as insecticides or (more recently) as hypotensive agents. It is interesting that wild tomato plants are protected by their alkaloid content (tomatine) against tomato wilt; [17] and similarly the Mexican potato (*S. demissum*, containing demissine) is not prone to attack by the potato beetle.[16]

The Reviewer thanks Professor R. D. Haworth, F.R.S., for his interest, and Professor L. H. Briggs, Dr. D. H. R. Barton, and Dr. O. Wintersteiner for prior information about recent work.

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[67] Pyman, *J.*, 1919, **115**, 163. [68] *Current Sci.* (*India*), 1946, **15**, 229.
[69] Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1952, **74**, 2693.