the size of the substituent group. The introduction of 1,3-dimethyl groups also appeared to improve activity.

3. Although several of the uracils were effective in preventing chemoshock, there was no obvious relationship of structure to activity.

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The Alkaloids of *Rauwolfia serpentina* Benth*

By DONALD D. PHILLIPS† and MOHINDRA S. CHADHA‡

Rauwolfia **is an important genus of the plant family *Apocynaceae*. There are nearly one hundred and twenty-five species of *Rauwolfia* which are distributed all over the tropical regions of the world (1–8). The most important member of the genus is *R. serpentina* Benth; the crude drug was known to the ancient Indians as a useful febrifuge (8), a remedy for snake bite, and as a cure for dysentery. In more recent times it has been used for insomnia, hypochondria and insanity.**

The presence of alkaloidal principles in *R. serpentina* was first pointed out in 1890 by Greshoff (9). In 1933, Chopra, Gupta, and Mukherjee (10) reported the hypotensive activity of the material extracted from the plant and in 1931 Siddiqui and Siddiqui (11) isolated a series of crystalline alkaloids from *R. serpentina*. Active chemical and pharmacological interest in *R. serpentina* has resulted in the discovery of several new alkaloids (Table I). The isolation by Müller, Schlittler, and Bein (12) of reserpine, an alkaloid with pronounced hypotensive and sedative activity, has lent further impetus to the pharmacological and chemical study of the alkaloids of *R. serpentina*. A brief summary of the chemical aspects of *R. serpentina* will be presented in this review.[1]

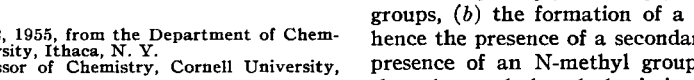
THE CHEMISTRY OF THE ALKALOIDS FROM R. SERPENTINA

THE alkaloids that have been isolated from *R. serpentina* to date are listed together with their pertinent physical properties in Table I. With the exception of thebaine and papaverine recently isolated by Hofmann (20), all of the known alkaloids from *R. serpentina* are indole bases. Included in the group are strong, moderately strong, and weak bases; the strongly basic alkaloids are deep yellow in color while the others are colorless. Schlittler, *et al.* (28), have found it convenient to subdivide the alkaloids of *R. serpentina* according to their chemical structures. In a similar manner, the alkaloids of *R. serpentina* will be considered in this review under the headings:

I. Tertiary indoline alkaloids
II. Quaternary anhydronium bases
III. Tertiary indole bases of the yohimbine type
IV. Tertiary indole bases of the tetrahydroalstonine type
V. Alkaloids of unknown ring structure
VI. Non-indole alkaloids

I. **Tertiary Indoline Alkaloids.**—The alkaloids belonging to this group are ajmaline, iso- and neoajmaline, and rauwolfinine. The available evidence indicates that ajmalinine belongs to this group but because of the limited chemical data it will be considered under Group V.

(*a*) *Ajmaline.*—Ajmaline, $C_{20}H_{26}O_2N_2$, was first isolated by Siddiqui and Siddiqui (11) and almost simultaneously by van Itallie and Steenhauer (13). The latter workers ascribed to it the molecular formula $C_{21}H_{26}O_2N_2$. The recent observations of Robinson and his coworkers (29) however, have confirmed the molecular formula, $C_{20}H_{26}O_2N_2$, originally proposed by Siddiqui and Siddiqui. The early Indian workers (11) reported: (*a*) the absence of hydroxyl, methoxyl, and methylenedioxy groups, (*b*) the formation of a monobenzoate and hence the presence of a secondary nitrogen, (*c*) the presence of an N-methyl group. They presumed that the methyl and the imino groups were both linked to the same nitrogen atom and proposed the partial betaine structure (I) for ajmaline.



I

In 1949, Robinson and collaborators (29) showed that ajmaline was a monoacidic, ditertiary base with strychnidine-like properties. One of the nitrogens was in the form of an N-methyl attached

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It is a pleasure to acknowledge the assistance of Sir Robert Robinson who supplied us with supplementary information on the structure of ajmaline prior to its publication. Our thanks are also extended to Mr. Murle Klohs of the Riker Laboratories, Los Angeles, who so kindly placed at our disposal a complete bibliography on the chemistry and pharmacology of *Rauwolfia serpentina*. The splendid cooperation of Drs. E. Schlittler, A. Stoll, A. Hofmann, and N. Neuss is also gratefully acknowledged.
[1] The chemistry and pharmacology of *Rauwolfia* alkaloids has been the subject of several recent reviews (15A, 28, 76, 177, 178, 92). Considerable progress in the field has resulted since the appearance of these articles making a more comprehensive review very desirable.

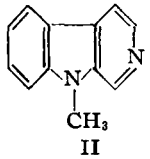
TABLE I.—ALKALOIDS OF *R. Serpentina Benth*

Name	Molecular formula	Sp. Rotation	m. p.	Derivatives	First Reported by
Ajmaline	$C_{20}H_{26}O_2N_2$	$[\alpha]_D^{33} = +128°$ ($CHCl_3$)	158–160°	B. HCl 253–255°; B. Picrate 126–127°	
Ajmalinine	$C_{20}H_{26}O_3N_2$	$[\alpha]_D^{33} = -97°$ ($CHCl_3$)	180–181°	B.HCl 240–245° (decompn); B. Picrate 200–205°	
Ajmalicine	$C_{21}H_{24}O_3N_2$	$[\alpha]_D^{23} = -48.5°$ (C_5H_5N)	250–252°	B. HCl 260–3° (decompn.); B. Picrate 212–215° (decompn.)	S. Siddiqui and R. H. Siddiqui (11)
Serpentine	$C_{21}H_{20}O_3N_2$	$[\alpha]_D^{40} = +188°$ (H_2O)	157–158°	B.HCl 260–261° (decompn.); B. Picrate 261–262° (decompn.)	
Serpentinine	$C_{21}H_{22}O_3N_2$ or $C_{21}H_{20}O_3N_2$		263–265°	B. HCl 260–262°; B. Picrate 225–227°	
"New Alkaloid"			220°		
"Amphoteric Alkaloid"			234°		
Isoajmaline	$C_{20}H_{26}O_2N_2$	$[\alpha]_D^{35} = +72.8°$ (C_2H_5OH)	264–265°	B. H_2PtCl_6 227–228° (decompn.)	S. Siddiqui (11A)
Neoajmaline	$C_{20}H_{26}O_2N_2$		205–207°		
Alkaloid C = ajmalinine		$[\alpha]_D = -76.4°$	177°	.....	
Rauwolfine = ajmaline		$[\alpha]_D = +131.1°$	160°	.....	L. vanItallie and A. J. Steenhauer (13)
Isorauwolfine = isoajmaline		$[\alpha]_D = +75°$	263–265°	.....	
Rauwolfinine	$C_{19}H_{26}O_2N_2$	$[\alpha]_D^{32} = -34.7°$	235–236°	B. HCl, 195° (decompn.)	A. Chatterjee and S. Bose (14)
Reserpine	$C_{33}H_{40}O_9N_2$	$[\alpha]_D^{33} = -117$ to $-118°$ ($CHCl_3$)	262–266° (corr. 277–278°)	B.HCl, H_2O 224° (decompn.); B. Picrate, H_2O 183–186° (decompn.)	J. M. Müller, E. Schlittler, and H. J. Bein (12)
Deserpidine (canescine)	$C_{22}H_{28}O_5N_2$	$[\alpha]_D^{25} = -137° \pm 1$ ($CHCl_3$)	228–232°	.....	E. Schlittler, P. R. Ulsafer, M. L. Pandow (77B)
Rescinnamine[a]	$C_{35}H_{42}O_9N_2$	$[\alpha]_D^{24} = -97° \pm 2$ ($CHCl_3$)	238–239°	.....	M. W. Klohs, M. D. Draper, and F. Keller (24)
Reserpinine		$[\alpha]_D^{20} = -98°$ ($CHCl_3$)	224–226°	.....	E. Haack, A. Popelak, H. Spingler, and F. Kaiser (23)
Sarpagine[a]	$C_{19}H_{22}O_2N_2$	$[\alpha]_D^{20} = +54°$ (C_5H_5N)	320°	B.HCl, 220° (decompn.)	A. Stoll and A. Hofmann (17)
Raupine	$C_{20}H_{26}O_3N_2$ ($C_{19}H_{22}O_2N_2 + CH_3OH$)	$[\alpha]_D^{20} = +63°$ (CH_3COOH)	325°	B. HCl, 239°	K. Bodendorf and H. Eder (18)
Serpenine			315°		S. Bose (16)
Substance I	$C_{22}H_{26}O_4N_2$	$[\alpha]_D^{20} = -123°$ ($CHCl_3$)	228°	B.HCl, 258–263° (decompn.)	A. Popelak, H. Spingler, and F. Kaiser (19)
= Raubasinine			228°		E. Haack, A. Popelak, H. Spingler, and F. Kaiser (23)
= Alkaloid C		$[\alpha]_D^{20} = -127°$ (C_5H_5N)	240°	B.HCl, 263–264° (decompn.)	A. Hofmann (20)
= New Alkaloid		$[\alpha]_D^{23} = -125°$ ($CHCl_3$)	240–241°		F. L. Weisenborn, M. Moore, and P. A. Diassi (21)
= Reserpinine[a]		$[\alpha]_D^{23} = -117° \pm 4$ ($CHCl_3$)	238–239°	B. HCl, 244–246°	E. Schlittler, H. Saner and J. M. Müller (22)
= Alkaloid A					N. Neuss, H. E. Boaz, and J. W. Forbes (26c)

Name	Molecular formula	Sp. Rotation	m. p.	Derivatives	First Reported by
Substance II		$[\alpha]_D^{20} = -61°$ ($CHCl_3$)	247–248° (corr. 255°)		(19)
= Raubasine					(23)
= δ-yohimbine	$C_{21}H_{24}O_3N_2$	$[\alpha]_D^{20} = -45°$ (C_5H_5N)	257°	B. HCl, 280–290° (decompn.)	(20)
= Alkaloid F		$[\alpha]_D^{20} = -37° \pm 6$ (CH_3OH)	253–254°	B. HCl, 264–265°	(26c)
= Ajmalicine[a] (*py*-tetrahydroserpentine)		$[\alpha]_D^{24} = -58.1° \pm 2$ ($CHCl_3$)	250°	B. HCl, 265–268°	(11), M. W. Klohs, M. D. Draper, F. Keller, W. Malesh. F. J. Petracek (62)
Reserpiline	$C_{33}H_{38}O_9N_2$	$[\alpha]_D^{24} = -40° \pm 2$ (C_2H_5OH)	amorphous	B. HCl, 205–207°	M. W. Klohs, *et al.* (24A)
Rauhimbine (corynanthine)	$C_{21}H_{26}O_3N_2$	$[\alpha]_D^{20} = -82°$ (C_5H_5N)	218–225°	B. HCl, $2H_2O$ 285°	A. Hofmann (20, 25)
Isorauhimbine	$C_{21}H_{26}O_3N_2$	$[\alpha]_D^{20} = -104°$ (C_5H_5N)	225–228°	B. HCl, 235–250° (decompn.)	A. Hofmann (25)
Yohimbine	$C_{21}H_{26}O_3N_2$	$[\alpha]_D^{20} = +105°$ (C_5H_5N)	235–237°	B. HCl, 300–302°	
Methyl reserpate	$C_{23}H_{30}O_5N_2$	$[\alpha]_D^{20} = -106°$ (C_5H_5N)	244–245°	B. HCl, 219–228°	A. Hofmann (20)
Thebaine	$C_{19}H_{21}O_3N$	$[\alpha]_D^{20} = -279°$ (C_5H_5N)	195°	B. Picrate, 217°	
Papaverine	$C_{20}H_{21}O_4N$		147°	B. HCl, 225–226°	
Serpine	$C_{31}H_{38}O_4N_2$	$[\alpha]_D^{20} = +70.1°$ (C_5H_5N)	213°	B. HCl, 263–264° (decompn.)	A. Chatterjee and S. Bose (27)
Alkaloid 3078[b]	$C_{21}H_{26}O_3N_2$	$[\alpha]_D^{26} = -96°$ (C_5H_5N)	125–128° and 181–183°	B. HCl, 235–240° (decompn.)	F. E. Bader, D. F. Dickel, R. A. Lucas, E. Schlittler (22A)
Chandrine	$C_{25}H_{30}O_6N_2$		230–231°	B. Picrate, 180°	B. Rakshit (179)

[a] Name suggested for future use (180). [b] Since shown to be identical with 3-epi-α-yohimbine (272).

to an aromatic nucleus with a free and reactive *para* position. Ajmaline gave seemingly positive chemical but negative spectral evidence for the presence of an aldehyde group, and a latent aldehyde group was assumed to be present. Evidence for a hydroxyl group and an isolated double bond was also presented. When distilled with soda lime or zinc dust, ajmaline produced Ind-N-methylharman (II) and carbazole (III).



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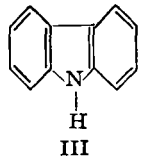

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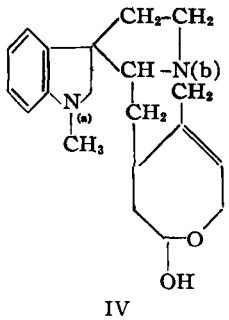
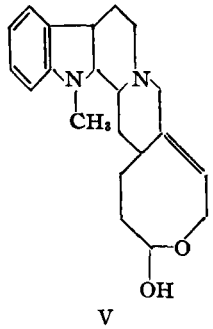


IV

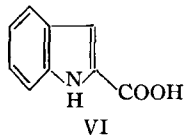


V

Reasoning from the above facts Robinson and collaborators suggested (IV) and (V) as possible structures for ajmaline. They favored structure (IV) as a working hypothesis for the reason that dihydroindoles such as (V) are very uncommon in nature and also because (IV) is related to strychnine and could arise biogenetically according to Woodward's scheme (30). The formation of Ind-N-methylharman (II) was rationalized as a migration of the type $-CRR_1-\overset{|}{C}-H \rightarrow -CR=CR_1-$, and carbazole (III) was said to be the result of a dehydrogenation of an open hexane chain to an aromatic system. Ind-N-methylharman (II) could arise from formula (V) without migration but the formation of carbazole (III) could not be readily explained.

Chatterjee and Bose (31, 32) have studied the infrared spectrum of ajmaline and have reported an absorption band at 5.82μ that indicated 15 to 20% carbonyl absorption, thus confirming the presence of the cyclic-acetal group suggested by Robinson and co-workers (29). The spectrum also contained the band at 7.24μ characteristic of a C-methyl group as well as the typical ether absorption at 9μ. On alkaline fusion of ajmaline, they obtained a crystalline base and two acids, one of which was shown to be indole-2-carboxylic acid (VI), a result that could not be rationalized on the basis of (IV) for ajmaline. Moreover, it was suggested (31, 32) that if structure (V) correctly represented

ajmaline, selenium dehydrogenation should produce Ind-N-methylalstyrine (VII, R′ = CH_3, R = C_2H_5), desethyl-Ind-N-methylalstyrine (VIII) or desmethyl-Ind-N-methylalstyrine (VII, R = R′ = CH_3). Chatterjee and Bose could not isolate any of these compounds from the dehydrogenation products of ajmaline but found only Ind-N-methyl-



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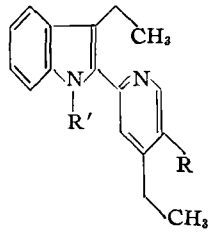
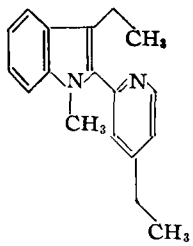
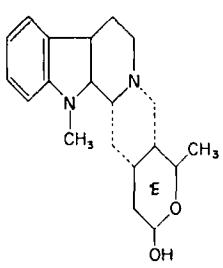


VII

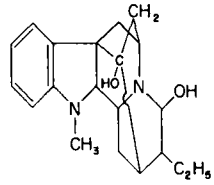


VIII

harman (II). For this reason, they suggested structure (IX) for ajmaline, ring D being involved in some undefined weak linkage, so that Ind-N-methylharman was easily formed.



IX



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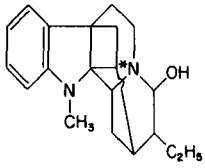
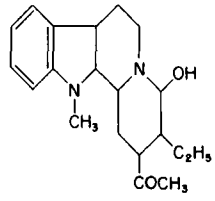


XI



XII

Structure (IX) represents a dihydroindole or dihydroindolenine derivative and similar compounds have been found in nature, e.g., the alkaloids of erythrina (33, 34). Furthermore, a possible biogenesis for such derivatives has been suggested by Schöpf, *et al.* (35). Ring E was presumed to be a six-membered heterocycle similar to that found in alstonine (36, 37) and serpentine (38). Chatterjee and Bose considered the possibility that the C-methyl was in ring B [*cf.* physostigmine (39) or calycanthidine (40)] but preferred to locate it in ring E as it is found in alstonine.

On the basis of more recent studies Robinson and co-workers (41, 41A) have modified their earlier structures (IV and V) and have advanced structure (X) as a better representation for ajmaline. The positive response in the Angeli-Rimini reaction has now been attributed to the intervention of acetaldehyde as a possible link between ajmaline and benzenesulfonylhydroxylamine. The reducing action of ajmaline has been ascribed to a :NCH(OH) group which was recognized by (*a*) the transformation of ajmaline oxime into a nitrile, (*b*) the conversion of N-methylajmaline (which showed a carbonyl band in the infrared spectrum) into monodesoxyajmaline, $C_{20}H_{26}ON_2$ (:N—CH_2—), (*c*) by the production of desoxydihydroajmaline (>NH CH_3—) and desoxyoctahydroajmaline in the Wolff-Kishner reduction of ajmaline and hexahydroajmaline respectively. The strong basic character of ajmaline and the acylable hydroxyl were attributed to the >NCH(OH) group, although these properties have not hitherto been associated with carbinol amines.

The formation of methyl ethyl ketone on chromic acid oxidation of desoxydihydroajmaline was taken as evidence for the presence of —$CH(CH_3)C_2H_5$ in the reduced base. The appreciable increase in the C-methyl value that occurred when ajmaline was converted to desoxydihydroajmaline further suggested the presence of the —NCH(OH)CHEt moiety in ajmaline.

The second active hydrogen was also shown to be part of a hydroxyl group by formation of diacetylajmaline and from a study of the infrared spectrum of desoxydihydroajmaline. The stability of desoxyoctahydroajmaline towards chromic acid suggested that the second hydroxyl was tertiary, and because of its resistance to dehydrating agents, it was placed at the apex of a bridgehead structure. Robinson and co-workers (41, 41A) could find no spectral evidence for the carbonyl group (5.82μ), the C-methyl group (7.24μ) or the ether bridge (9.0μ) that had been reported by Chatterjee and Bose (31, 32). Furthermore, Robinson and colleagues (41, 41A) have also offered a possible biogenetic scheme for the formation of (X) from (XII).

In a private communication (42) Robinson has further elaborated on the chemistry of ajmaline and has suggested a new structure for this alkaloid. The new facts which verified portions of the original structure and also allowed the extension to the new representation were the following:

(1) Ajmaline lost carbon monoxide when heated with Raney nickel in xylene resulting in the formation of a secondary base, decarbonoajmaline. This is undoubtedly best explained as >NCHOHCHEt → >NH + CO + CH_2Et, and in verification of this postulate, decarbonoajmaline gave *n*-butyric acid, less propionic and a trace of acetic acid on oxidation.

(2) Oxidation of ajmaline with permanganate in acetone afforded N-methylisatin thus confirming the presence of >N(a)—CH_3.

(3) The formation of a basic O-dibenzoylajmaline has been confirmed.

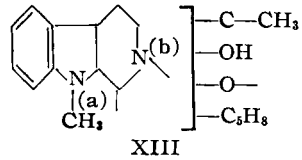
(4) C-Nitrosoajmaline, green prisms, m. p. >330° has now been prepared. This strongly suggests that ajmaline contains no >NH in acid solution. In basic solution, however some of the carbinolamine must be in the form >NH CHO because ajmaline is reduced by borohydride to dihydroajmaline, a secondary base. The hydrobromide of this latter base gave desoxyajmaline hydrobromide on heating. Furthermore, dihydroajmaline could be methylated to dihydro-N-methylajmaline which had been previously obtained (41, 41A) from the lithium aluminum hydride reduction of N-methylajmaline.

(5) When heated with palladium-charcoal catalyst, dihydrodesoxyajmaline [>NH CH$_3$ CHEt] afforded in small yield a base, $C_{20}H_{24}N_2$, whose ultraviolet absorption spectrum was of the alstyrine (VII, R′ = H, R = C_2H_5) type. On the basis of this new evidence, Robinson and coworkers now represent ajmaline as (XI), in which the asterisked carbon has a tertiary hydroxyl in place of a hydrogen. This unique structure avoids involvement of the tryptamine—CH_2CH_2— side chain in the bridge-ring structure, an undesirable feature of the earlier postulates (X).

(*b*) *Isoajmaline and Neoajmaline.*—These alkaloids were isolated by Siddiqui (11A) from a Dehra Dun variety of *R. serpentina*. Alcoholic potash or heat converted both neoajmaline and ajmaline to isoajmaline. Robinson and coworkers (41, 41A) found that isoajmaline gave derivatives that were similar to those from ajmaline and hence consider the former to be a stereoisomeride of ajmaline. The chemistry of isoajmaline and neoajmaline has not been thoroughly studied as yet and no definite structural conclusions can be drawn at this time.

(*c*) *Rauwolfinine.*—This alkaloid was recently isolated by Chatterjee and Bose (14) from a species of *R. serpentina* collected in the northwestern parts of India. The earlier observations of Siddiqui and Siddiqui (11) that *R. serpentina* specimens grown in different parts of India vary both quantitatively and qualitatively in alkaloidal content were confirmed by Chatterjee and Bose (14) and by Bose (15).

Preliminary investigations (15) showed that rauwolfinine was a monoacidic base containing an N—CH_3, C—CH_3 and two active hydrogens and no methoxy or methylenedioxy groups could be detected. The ultraviolet spectrum (15A, 15B) ($\lambda_{max.}$ 249 mμ, 292 mμ and $\lambda_{min.}$ 226 mμ and 272 mμ) resembled that of ajmaline (15A) and semperflorin (43) and for this reason the authors suggested that rauwolfinine was an indoline derivative. The absorption spectrum also resembled that of yohimbine (44), serpentine (38), and corynantheine (44), but only in the far ultraviolet region and not in the region of longer wavelengths. The infrared spectrum suggested the presence of a tertiary hydroxyl group (2.82μ) an indoline nucleus (intense bands at 6.2μ and 6.8μ), an ether bridge (9.0μ), and a C-methyl group (7.24μ). Absence of bands in the 5.75 to 6μ region nullified the possibility that carboxyl, ester, amide, betaine or carbonyl groups were present. The absorption ascribed to the ether linkage was similar to that observed in the spectrum of serpentine (38, 45). The spectral evidence for the presence of a C-methyl was substantiated by Kühn-Roth determination and the evidence for an indoline structure (XIII) was recently (15B) confirmed by the isolation of Ind-N-methylharman from zinc dust distillation. Alkali fusion of rauwolfinine produced indole-2-carboxylic acid (VI). The nature of a neutral moiety from the zinc dust distillation and a nitrogen-free acid from the alkali fusion is still under investigation. On the basis of the above degradative and spectral evidence Bose (15B) has proposed partial structure (XIII) for rauwolfinine.

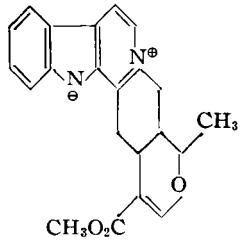


XIII

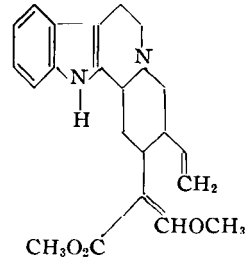
II. **Quaternary Anhydronium bases.**—The term "anhydronium base" was first advanced by Armit and Robinson (46). The structural determination of the Rauwolfia alkaloids in this class was greatly facilitated by the earlier work on harmala bases (47–49), sempervirine (50, 51) and the tetrahydroyohimbines (52).

(*a*) *Serpentine.*—This bright yellow base was first isolated by Siddiqui and Siddiqui (11). They proposed the molecular formula $C_{20}H_{20}O_3N_2 \cdot 1^1/_2 H_2O$, but Schlittler and Schwarz (45), who undertook a more thorough examination of the alkaloid, revised the empirical formula to $C_{21}H_{22}O_3N_2$. The presence of two double bonds that could be hydrogenated, one active hydrogen and one methoxyl group, was readily established. Serpentine was further shown to be an indole alkaloid with a marked similarity to rauwolscine (53–55) and alstonine (36, 38, 56). The presence of an ester group in serpentine was indicated by its infrared spectrum, and was confirmed by the drastic hydrolysis to serpentinic acid, $C_{20}H_{20}O_3N_2$. On the basis of spectral evidence it was suggested that the third oxygen was present as an ether.

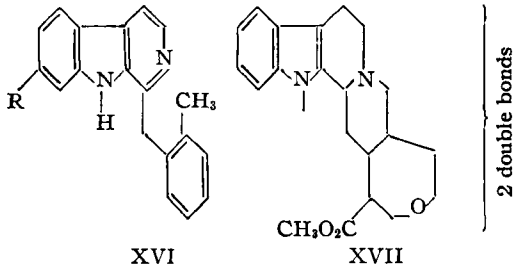
The Swiss workers (45) further established the basic character of one of the nitrogens and from spectral studies concluded that no >NH was present. Selenium dehydrogenation of serpentine produced an oxygen-free base alstyrine, $C_{19}H_{22}N_2$ (VII, R = C_2H_5, R′ = H), which had previously been characterized as a dehydrogenation product of alstonine (57, 58) (XIV), and corynantheine (59–61) (XV). Alstyrine and a carbomethoxy group accounted for all of the carbon atoms in serpentine. With the above evidence in hand, Schlittler and Schwarz (45) proposed the skeletal structure (XVII) for serpentine.



XIV



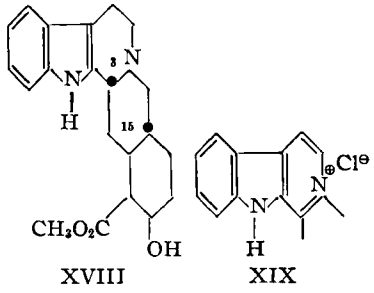
XV



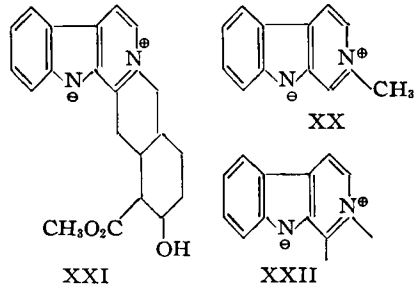
XVI XVII

Since no yobyrine (XVI, R = H) was obtained on dehydrogenation, Ring E was not assigned the normal carbocyclic structure found in yohimbine (XVIII).

Hydrogenation studies indicated the presence of six double bonds in serpentine and the yellow color of the base was considered to be a sign of conjugation. Bader and Schwarz (38) studied the infrared and ultraviolet absorption spectra of serpentine and its derivatives and confirmed this postulate. Moreover, the presence of an absorption band at 6.37μ in the infrared spectrum of serpentine hydrochloride and the absence of this band in *Py*-tetrahydroserpentine was cited as evidence for a conjugated —C=N— group in the hydrochloride and partial structure (XIX) was proposed for it. The ultraviolet spectra of serpentine and its hydrochloride were very similar to those of quaternary-β-carboline (XX) tetradehydroyohimbine (XXI) and their hydrochlorides, indicating the presence of a common chromophore (XXII).

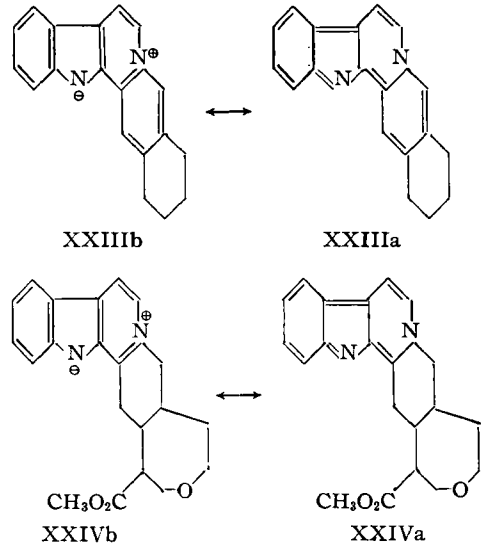


XVIII XIX



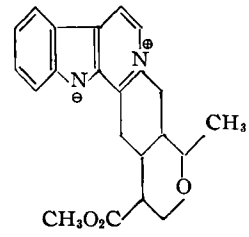
XXI XX XXII

Similar observations had led Woodward and Witkop (50) to propose structure (XXIII) for sempervirine, and because of a marked spectral similarity between sempervirine and serpentine Schlittler and Schwarz (45) proposed structure (XXIV) for the latter. The formation of salts of serpentine was then explained on the basis of the charge separation form (XXIVb).



XXIIIb XXIIIa XXIVb XXIVa

The first revision in the structure (XXIV) for serpentine was made by Bader and Schwarz (38). They proposed that ring E was six membered and contained a C-methyl group, this view being more compatible with the formation of alstyrine (VII, R = C_2H_5, R′ = H) on selenium dehydrogenation (45). The revised structure (XXV) was supposed to be identical with a stereoisomer of the unknown dihydroalstonine and in this connection it was shown that *py*-tetrahydroserpentine and *Py*-tetrahydroalstonine had identical ultraviolet absorption spectra.

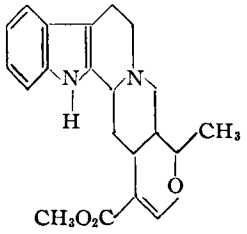


XXV

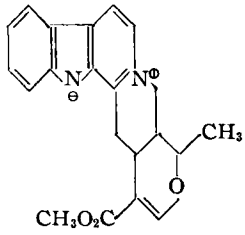
More recently Klohs and co-workers (62) have proposed what is undoubtedly a final revision of the serpentine structure. Analytical data for *py*-tetrahydroserpentine favored a molecular formula differing from that of Bader and Schwarz (38) by two less hydrogens, indicating an additional center of unsaturation. The view was supported by the infrared and ultraviolet absorption spectra of *py*-tetrahydroserpentine which were shown to contain the $H_3COOC—\overset{|}{C}=\overset{|}{C}—O—$ chromophore. The spectral characteristics of this group had been reported by Bader (63) and by Goutarel (64) in their work on alstonine (XIV) and corynantheine (XV) respectively. In addition to this, *py*-tetrahydroserpentine gave the corresponding alcohol, $C_{20}H_{28}O_2N_2$, on lithium aluminum hydride reduction, and the infrared spectrum indicated the presence of a hydroxyl group and an enol ether. The double bond absorption maximum had shifted from 6.2μ

in *py*-tetrahydroserpentine to 6.04μ because it was no longer in conjugation with an ester.

Klohs and co-workers (62) consequently have revised the molecular formula of *py*-tetrahydroserpentine and serpentine to $C_{21}H_{24}O_3N_2$ and $C_{21}H_{20}O_3N_2$ respectively and have proposed structures (XXVI) and (XXVII) for these compounds so that serpentine is in reality a stereoisomer of alstonine.



XXVI



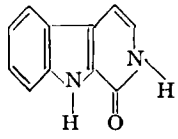
XXVII

(*b*) *Serpentinine.*—This alkaloid, accompanied by serpentine, was first isolated by Siddiqui and Siddiqui (11) and recently by Schlittler and co-workers (65). The Indian workers prepared a series of salts of serpentinine and from their analyses proposed the molecular formula $C_{20}H_{20}O_5N_2$ for the free base. In spite of great analytical difficulties Schlittler, *et al.* (65), have proposed the molecular formula $C_{21}H_{22}O_3N_2$ or $C_{21}H_{20}O_3N_2$ for serpentinine.

The infrared spectrum of serpentinine possessed two bands at 5.83 and 6.16μ that were similar to those found in alstonine at 5.88 and 6.11μ and in serpentine at 5.89 and 6.21μ, thus indicating the presence of the $RO_2CC{=}C{-}O{-}$ chromophore. In contrast to serpentine, however, the presence of a strong band at 2.99μ suggested an alcohol or >NH group. Moreover, several of the characteristic bands (6.38 and 6.28μ, for example) of serpentine (38) could not be detected in the serpentinine spectrum. The ultraviolet absorption spectrum of serpentinine was characteristic of both an indole and a quaternary β-carboline and Schlittler, *et al.* (65), have proposed that it is a base of the anhydronium type.

The presence in serpentinine of two active hydrogen atoms (one probably due to solvent of crystallization) and of a C-methyl group was also reported (65). Serpentinine and serpentine both gave alstyrine (VII, R = C_2H_5, R′ = H) on selenium dehydrogenation. This base accounted for nineteen carbon atoms and the remaining two were presumed to be present as a carbomethoxy group. This ester was much more difficult to hydrolyze than that in serpentine but could be reduced with sodium and butyl alcohol to a compound of molecular formula $C_{20}H_{26}O_2N_2$. The properties of this latter alcohol were similar to those of hexahydroserpentinol (62, 66).

Hydrogenation of serpentinine over platinum failed in basic solution and in acetic acid it was slow and irregular, although a compound was obtained that was similar to *Bz*-tetrahydroserpentine in melting point and ultraviolet absorption spectrum. On alkaline fusion, serpentinine yielded indole-2-carboxylic acid (VI) and a compound that was shown to be identical to pyrid-3-4b-Indole-1(2)-one (67) (XXVIII). Similar treatment of alstonine resulted in the formation of harman (56).



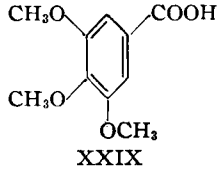
XXVIII

Schlittler and co-workers (65) could not postulate a reasonable structure for serpentinine from the evidence cited above and even the molecular formula remains somewhat obscure at the present time.

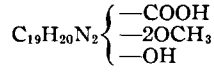
III. **Tertiary Indole Bases of the Yohimbine Type.**—The alkaloids in this group are reserpine, methyl reserpate, rescinnamine (reserpinine), deserpidine, yohimbine, isorauhimbine, serpine, sarpagine (raupine), "Alkaloid 3078," and rauhimbine.

(*a*) *Reserpine:*—The isolation of this base, which is pharmacologically the most important Rauwolfia alkaloid, was first reported by Müller, Schlittler, and Bein (12). Recently Steenhauer (91) has claimed that the alkaloid B reported earlier (13) is identical to reserpine. Reserpine has also been isolated from *R. heterophylla* Roem and Schult by Djerassi and co-workers (68) from *R. canescens* Linn by Klohs and his collaborators (69), from *R. hirsuta* by Vergara (175), from *R. micrantha* by Rao and Rao (181), and from *R. vomitoria* by Janot's group (184).

Reserpine has the molecular formula $C_{33}H_{40}O_9N_2$ and contains six methoxyl groups. The ultraviolet spectrum was quite different from that of other indoles suggesting that if an indole nucleus was present at all it must be a substituted one. The high oxygen content and the presence of a broad band in the ester region made it likely that reserpine was an ester alkaloid (70). Schlittler and co-workers (70, 71) and Neuss, *et al.* (26a, b), independently obtained 3,4,5-trimethoxybenzoic acid (XXIX) and reserpic acid, $C_{22}H_{28}O_5N_2$ (XXX) on alkaline saponification of reserpine. Klohs, *et al.* (72), originally assigned to reserpine the molecular formula $C_{35}H_{44}O_{10}N_2$ and named the hydrolysis product reserpinolic acid. Subsequent work (73) however, confirmed the molecular formula proposed by Schlittler and co-workers (70, 71) and the name reserpic acid has now been adopted for the nitrogenous saponification product.



XXIX

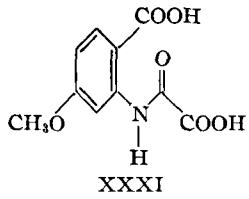


XXX

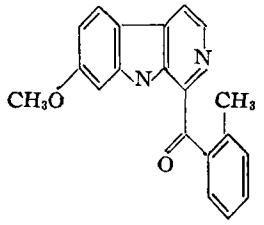
The chemistry of reserpine and reserpic acid was extensively investigated by the Ciba group (70, 71, 73, 74, 74A) and a total structure was proposed on the basis of the following facts. When treated with trimethoxybenzoyl chloride, methyl reserpate yielded a product identical to reserpine. Reserpic acid was shown to contain two methoxyl groups and the presence of a hydroxyl group was strongly indicated by the infrared spectrum. Acylation attempts, however, resulted in the formation of a γ-lactone. If reserpic acid was first esterified with diazomethane, methyl reserpate was obtained and the

hydroxyl group in the ester could be readily acylated or arylated. When reserpic acid was oxidized with permanganate (71), N-carboxyformyl-4-methoxyanthranilic acid (XXXI) was isolated as its dimethyl ester. This established the presence of a methoxyindole moiety in reserpine. Spectral evidence indicated that reserpic acid contained a monomethoxylated tetrahydro-β-carboline system and the assumption was substantiated by a positive Adamkewicz color test (74, 75).

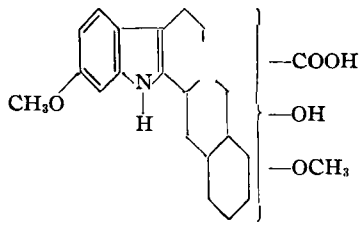
Reserpic acid yielded yobyrine (XVI, R = H) and 7-hydroxyyobyrine (XVI, R = OH) on selenium dehydrogenation. The structure of this yobyrine derivative was confirmed by selenium dioxide oxidation of its methyl ether to the ketone (XXXII) which was in turn compared with a synthetic sample. Reserpic acid was thus shown to contain a pentacyclic ring system and the partial structure was expanded to (XXXIII).



XXXI

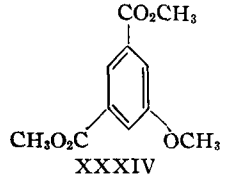


XXXII

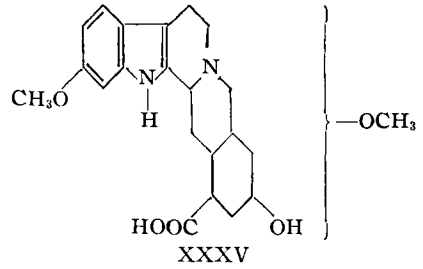


XXXIII

The potassium hydroxide fusion of reserpic acid resulted in the formation of 5-hydroxyisophthalic acid which was isolated as its monomethyl ether dimethyl ester (XXXIV). This degradation product as well as the lactone formed in acylation experiments were best explained by structure (XXXV) for reserpic acid. The remaining methoxyl group

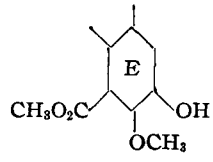


XXXIV

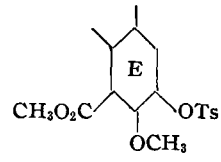


XXXV

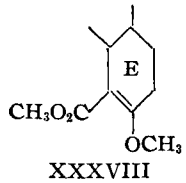
was placed at carbon 17 between the hydroxyl and the carboxyl groups (XXXVI) for the following reason (73). The tosylate of methyl reserpate (XXXVII) was treated with collidine and the reaction product was shown by its infrared absorption to contain the group $RO_2C-\underset{|}{C}=\underset{|}{C}-O$ (5.89 and 6.21μ); the ultraviolet absorption spectrum was in agreement with this conclusion. The structure of the detosylation product (XXXVIII) was further confirmed by the simultaneous acid hydrolysis and decarboxylation to the ketone, reserpone (XXXIX). From the degradations cited



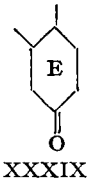
XXXVI



XXXVII

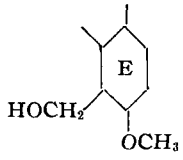


XXXVIII

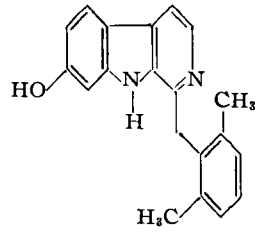


XXXIX

above Schlittler, *et al.* (74), could safely assume that all three substituents in Ring E were on adjoining carbons but the position of at least one of these groups had to be located exactly before the total structure of reserpine could be established. To this end the tosylate of methyl reserpate (XXXVII) was reduced (74A) with lithium alumi-

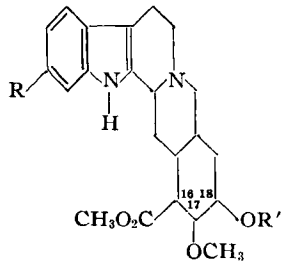


XL

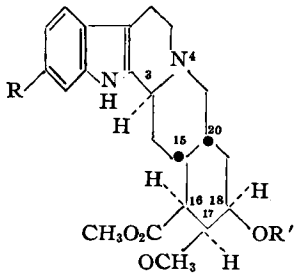


XLI

num hydride to reserpinol (XL) which in turn was dehydrogenated with selenium to give the methyl hydroxyyobyrine (XLI). In this way the carboxyl in reserpic acid was retained in the dehydrogenation product as a methyl group, the location of which was proved by the synthesis of the methyl ether of (XLI). This degradation placed the car-



XLII



XLIII

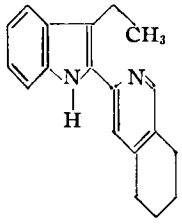
boxyl in reserpic acid at C_{16} and the total structure of reserpine could then be formulated as (XLII) (R = methoxy, R′ = 3,4,5-trimethoxybenzoyl).

(*b*) *Methyl Reserpate (XLII) (R = methoxy, R′ = H).*—The alkaloid was recently isolated from *R. serpentina* by Hofmann (20), who established its identity with the compound obtained from reserpic acid and methanol. It was further shown that methyl reserpate occurred as such in *R. serpentina* and was not a hydrolysis product of reserpine, since the latter was stable under the isolation conditions.

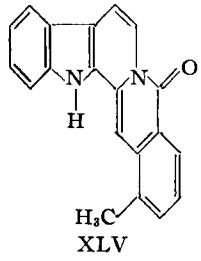
(*c*) *Rescinnamine.*—This base was recently isolated by Klohs, *et al.* (24), and shown by hydrolysis and spectral studies to be the 3,4,5-trimethoxycinnamic acid ester of methyl reserpate (XLII) (R = methoxy, R′ = trimethoxycinnamoyl). Independently, Haack, *et al.* (23), isolated the same alkaloid and gave it the name "reserpinine." "Reserpinine" was also the name given to a C_{22}-$H_{26}O_4N_2$ alkaloid (LIII, R = H) isolated by Schlittler, *et al.* (22). To avoid confusion, it is proposed (180) that the name rescinnamine be retained for the $C_{35}H_{42}O_9N_2$ alkaloid of Klohs and that reserpinine be reserved for Schlittler's C_{22} alkaloid.

(*d*) *Deserpidine:*[2]—Schlittler and coworkers (77B) have reported this base as a minor constituent of many Rauwolfia species including *R. serpentina* and have noted its similarity to reserpine both biologically and chemically. In a recent communication (77A), this similarity has been confirmed by the conversion of methyl deserpidate tosylate (XLIII) (R = H, R′ = $C_7H_7SO_2$—) to α-yohimbine [C_{16} epimer of (XVIII)]. They also proved that epimerization of C_3 occurred in the process so that deserpidine (XLIII) (R = H, R′ = 3,4,5-trimethoxybenzoyl) is a derivative of C_3-epi-α-yohimbine (83).

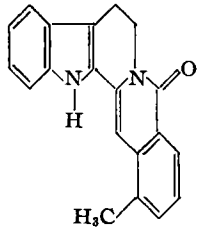
The formation of a γ-lactone from both reserpic acid and deserpidic acid (the acid corresponding to (XLIII) R = R′ = H)), together with the results (unpublished) of elimination reactions, indicate that all three groups in ring E of reserpine and deserpidine are cis. Hence (XLIII) (R = methoxy, R′ = 3,4,5-trimethoxybenzoyl) and (XLIII) (R = H, R′ = 3,4,5-trimethoxybenzoyl) are considered (77A) to represent the complete configuration of reserpine and deserpidine respectively.



XLIV



XLV



XLVI

The Squibb group have recently (182) confirmed these stereochemical assignments for C_{15}, C_{16}, C_{18}, and C_{20} in reserpine by the isolation of a quaternary tosylate containing a bond between N_4 and C_{18} (see XLIII). The formation of this compound by a concerted displacement mechanism requires a cis ring juncture at C_{15}—C_{20} and a β-tosyloxy group at C_{18}. Moreover, molecular rotation differences indicate (182) that (XLIII) (R = methoxy, R′ = 3,4,5-trimethoxybenzoyl) represents the absolute configuration of reserpine.[3]

(*e*) *Yohimbine.*—The isolation of yohimbine (XVIII) has been independently reported by Bader, *et al.*, (77), and by Hofmann (20). The identity of this alkaloid was shown by mixing melting point determination with an authentic sample of yohimbine and its hydrochloride and by comparison of infrared and ultraviolet absorption spectra.

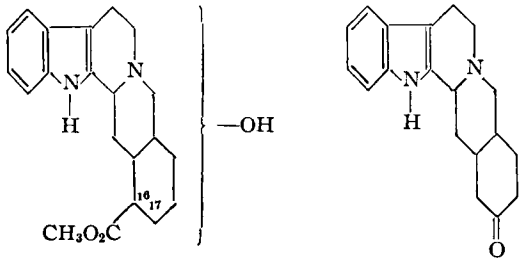
(*f*) *Isorauhimbine.*—This alkaloid was isolated from *R. serpentina* by Hofmann (25) and preliminary work (20, 25) indicated the molecular formula $C_{21}H_{26}O_3N_2$. The presence of two active hydrogen atoms and one methoxyl group was also established.

Further investigations (20, 78) on the constitution of isorauhimbine have indicated that it is probably an isomer of yohimbine (XVIII). Thus, the ultraviolet spectrum was characteristic of the indole chromophore and alkaline hydrolysis yielded isorauhimbic acid which regenerated isorauhimbine on esterification. The selenium dehydrogenation of isorauhimbine produced yobyrine (XVI, R = H), tetrabyrine (XLIV) and dehydroketobyrine (XLV). Yohimbine and its stereoisomers give compounds (XVI), (XLIV), and ketobyrine (XLVI) on selenium dehydrogenation (79, 80). Although a satisfactory explanation for the formation of (XLV)

[2] The same alkaloid (canescine) has been isolated from *R. canescens* by Stoll and Hofmann (174), Klohs, *et al.*, (257) and by the Lilly group (253a).

[3] This stereochemical representation for the reserpine molecule has recently been questioned (273) especially as to the configuration at C_3 (see XLIII).

has not been advanced, these dehydrogenation products establish the pentacyclic nature of the ring system as well as the location of the carbomethoxy group at C_{16}. Consequently, isorauhimbine can be represented by structure (XLVII). The oxidative decarboxylation of (XLVII) would be expected to yield a stereoisomer of yohimbone (XLVIII) if the hydroxyl were at C_{17}. This reaction has failed to yield a crystalline compound so that the position of the hydroxyl in isorauhimbine has not been finally established as yet.



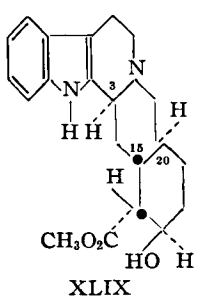
XLVII XLVIII

(*g*) *Serpine.*—Chatterjee and Bose (27) have recently isolated this alkaloid from a Cochin variety of *R. serpentina* that apparently contains no ajmaline.

Serpine was shown to be a weak, monoacidic tertiary base of empirical formula $C_{21}H_{26}O_3N_2$. Tests for the presence of a C-methyl, N-methyl, and methylenedioxy groups were negative. Sulfuric acid produced the characteristic color reaction of tetrahydro-β-carbolines and yohimbine.

The ultraviolet absorption spectrum was similar to that of yohimbine (44) and rauwolscine (55) with maxima at 227, 283, and 290 mμ. The infrared spectrum showed the characteristic absorption bands of an alcohol at 2.75 μ, an imino group at 2.95 μ, and an ester at 5.8 μ. When dehydrogenated in the presence of selenium, serpine produced yobyrine (XVI, R = H), tetrabyrine (XLIV), and ketoyobyrine (XLVI). These products served to establish the pentacyclic nature of serpine and the formation of ketoyobyrine located the carbomethoxy group at C_{16} as in yohimbine. The characteristic Oppenauer oxidation (81–83) product placed the hydroxyl at C_{17} so that serpine becomes a stereoisomer of yohimbine.

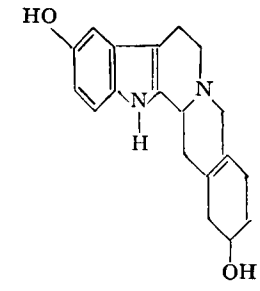
On the basis of experiments, the details of which were not disclosed, the authors further suggested that the carbomethoxy and hydroxyl groups were both axial and that the configuration in serpine (XLIX) at C_3, C_{15}, and C_{20} is the same as in ψ-yohimbine (81).



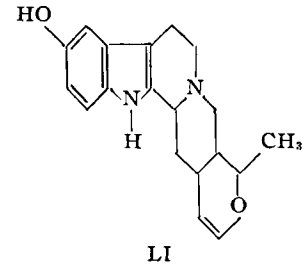
XLIX

(*h*) *Sarpagine* [*Raupine (18)*].—This alkaloid has recently been isolated by Stoll and Hofmann (17) and its identity with the alkaloid "raupine" of Bodendorf and Eder (18) has been established (18A).

Sarpagine was originally formulated as a 5-methoxyindole on the basis of its ultraviolet absorption spectrum (84). The alkaloid was soluble in sodium hydroxide solution however, and reduced ammoniacal silver nitrate and Fehling's solution, a behavior reminiscent of the phenolic alkaloid akuammine from *Picralima nitida* (Stapf) (85, 86). Consequently, Thomas (87) has postulated that sarpagine is a 5-hydroxyindole, because a complete yohimbine skeleton cannot be accommodated in the formula $C_{19}H_{22}O_2N_2$ if a methoxyl group is included. The two more likely structures for sarpagine that Thomas has proposed are the hydroxydehydroyohimbol (L) and the decarbomethoxyhydroxyserpentine (LI).



L



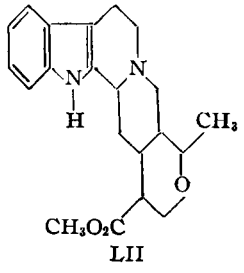
LI

(*i*) *Alkaloid 3078.*—This alkaloid has recently been isolated by Schlittler and coworkers (22A) and preliminary work suggests it to be an isomer of yohimbine.

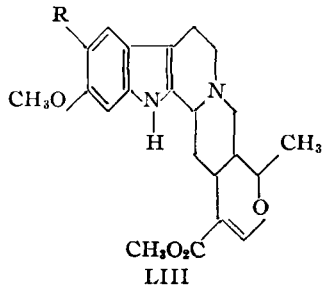
(*j*) *Rauhimbine* (corynanthine).—This base was isolated from *R. serpentina* by Hofmann (25) who later (20) established its identity with corynanthine, the C_{16} epimer of yohimbine (XVIII).

IV. **Tertiary Indole Bases of the Tetrahydroalstonine Type.**—(*a*) *Ajmalicine* (11) (*Py*-tetrahydroserpentine (62), δ-yohimbine (20, 21), alkaloid II (19), raubasine (23), alkaloid F (26)): Ajmalicine was first isolated by Siddiqui and Siddiqui (11) but no molecular formula was suggested for the compound. Klohs and co-workers (62) have recently isolated an alkaloid identical to the ajmalicine of Siddiqui and Siddiqui and to which they assigned the molecular formula $C_{21}H_{24}O_3N_2$. The infrared and ultraviolet spectra were found (62) to be the same as those of *Py*-tetrahydroserpentine as reported by Bader (63) and by Bader and Schwarz (38). The melting points and optical rotations were also found to be in good agreement.

Bader and Schwarz (38) had proposed structural formula (LII) for *Py*-tetrahydroserpentine but on



LII



LIII

the basis of spectral evidence discussed under serpentine, Klohs, *et al.* (62), proposed the structure (XXVI) for *Py*-tetrahydroserpentine and hence for ajmalicine.

Weisenborn, *et al.* (21), isolated from *R. serpentina* an alkaloid $C_{21}H_{24}O_3N_2$ which they showed to be identical with δ-yohimbine isolated from commercial yohimbine (88, 89). They independently assigned structure (XXVI) to δ-yohimbine and established its identity with the *Py*-tetrahydroserpentine of Bader and Schwarz (38). Confirmation of this assignment was provided by the lead tetraacetate dehydrogenation of δ-yohimbine to serpentine (XXVII).

Popelak, *et al.* (19), isolated from *R. serpentina* an alkaloid which they initially name "alkaloid II" and later "raubasine" (23). A molecular formula of $C_{21}H_{26}O_3N_2$ was originally suggested and later (90) corrected to $C_{21}H_{24}O_3N_2$. The identity with *Py*-tetrahydroserpentine (XXVI) was confirmed by the lead tetraacetate dehydrogenation of raubasine to serpentine (XXVII).

Hofmann (20) has also reported the isolation of δ-yohimbine from *R. serpentina*.

Neuss, *et al.* (26c) have isolated an alkaloid which was tentatively called "alkaloid F" but subsequent work has shown it to be identical to the ajmalicine (*Py*-tetrahydroserpentine) characterized by Klohs (62, 72).

(*b*) *Reserpinine* (22) [Alkaloid I (19), raubasinine (23), new alkaloid (21), alkaloid C (20), alkaloid A (26c)]: Reserpinine was first isolated by Schlittler, *et al.* (22), as a minor alkaloid of *R. serpentina* that accompanied reserpine. The molecular formula $C_{22}H_{26}O_4N_2$ was assigned and the presence of one C-methyl, two methoxyls and one active hydrogen was demonstrated.

The chemical and spectral evidence indicated that reserpinine was identical with "alkaloid I" (raubasinine) reported by Popelak, *et al.* (19, 23). The absorption maxima recorded for reserpinine were 229 and 298 mμ and for alkaloid I were 228–230 and 298 mμ. The infrared spectrum showed absorption bands at 2.96 (—NH), 5.87 and 6.24 μ (conjugated ester) and 12.05–12.5 μ (1,2,4-trisubstituted benzene ring). From this evidence, coupled with the results of other reactions, details of which are not yet published, Schlittler, *et al.* (22), proposed structure (LIII) (R = H) for reserpinine. Weisenborn, *et al.* (21), isolated a "new alkaloid" from *R. serpentina* and assigned to it the molecular formula $C_{22}H_{26}O_4N_2$. Independently they arrived at structure (LIII) (R = H) for this alkaloid.

The presence of a carbomethoxy group was demonstrated by alkaline hydrolysis followed by the regeneration of the alkaloid when the free acid was allowed to react with diazomethane. The position of second methoxyl group was shown to be C_{11} by comparison of the ultraviolet spectrum with that of methyl reserpate (XLII) (R = methoxy, R′ = H). The presence of the chromophore system $H_3COOC—\overset{|}{C}=\overset{|}{C}—O—$ was indicated by the characteristic infrared absorption at 5.85 and 6.21μ (63).

Hofmann (20) has reported the isolation of a base (alkaloid C) whose melting point, molecular formula and specific rotation are in close agreement with those of reserpinine (22), strongly suggesting their identity.

Neuss, *et al.* (26c), have shown that their "alkaloid A" is identical with Weisenborn's (21) reserpinine.

(*c*) *Reserpiline.*—This amorphous base has been reported recently by the Riker group (24A) as a minor alkaloid of *R. serpentina* and independently, Stoll's group (183) has isolated the same material from *R. canescens*. The molecular formula, $C_{22}H_{28}O_5N_2$, differed from that of reserpinine by the elements CH_2O, corresponding to an extra methoxyl group. This latter group was located in the 5-position of the indole moiety since the ultraviolet absorption spectrum of reserpiline was identical with that of 2,3-dimethyl-5,6-dimethoxyindole.

The infrared spectrum contained the two peaks at 5.99 and 6.20μ which are characteristic (63) of the $RO_2C—\overset{|}{C}=\overset{|}{C}—O—$ chromophore that occurs in ajmalicine, reserpinine and alstonine and the typical shift (62, 72A) of the enol ether band to 6.09μ in the lithium aluminum hydride reduction product was also observed.

Although the small amount of reserpiline available precluded extensive degradative studies, structure (LIII) (R = OCH_3) has been assigned to this base with reasonable certainty (24A, 183).

V. **Alkaloids of Unknown Ring Structure.**—(*a*) *Ajmalinine.*—This alkaloid, $C_{20}H_{26}O_3N_2$, was isolated by Siddiqui and Siddiqui (11), who proved it to be a tertiary base containing a methoxyl and a hydroxyl group. No methylimino group could be detected. When ajmalinine was heated to 200° in an atmosphere of nitrogen, apoajmalinine, $C_{13}H_{17}O_3N_2$, was formed. The ultraviolet absorption spectrum suggests the presence of a 5-methoxyindole moiety (84) but incomplete chemical information negates the possibility of assigning a reasonable structure to this alkaloid.

(*b*) *Serpenine.*—The isolation of this alkaloid was first reported by Chatterjee and Bose (27), and in a recent communication, Bose (16) has elaborated somewhat on the chemistry of this minor constituent. Analysis indicated the formula $C_{20}H_{24}$-

ON_2 or $C_{21}H_{26}ON_2$ for the base which melts and sublimes at 315–317°.

The alkaloid contains no methoxy, methylenedioxy or phenolic groups, feebly reduces ammoniacal silver nitrate and fails to give the typical color reaction of β-carbolines. The ultraviolet ($\lambda_{max.}$ 250, 293 mμ) and infrared spectrum are suggestive of the indoline structure found in ajmaline. The low yield (20 mg. per 75 Kg. of roots) has made degradative studies impossible to date.

(*c*) *Chandrine.*—The isolation of this alkaloid, $C_{25}H_{30}O_3N_2$, has recently been reported but no experimental details were given (179).

(*d*) *A "New Alkaloid" and an Amphoteric Alkaloid.*—These two alkaloids were isolated by Siddiqui and Siddiqui (11) and no evidence except for the melting points was reported. It is likely that these two alkaloids correspond to some of the alkaloids isolated in later years that have been reported under other names.

VI. **Non-indole Alkaloids.**—Hofmann (20) has reported the isolation of two non-indole alkaloids from *R. serpentina* and by mixed melting point determinations coupled with a comparison of ultraviolet and infrared spectra has shown them to be thebaine and papaverine.

PHARMACOLOGY

Because of the prodigious volume of literature concerned with the pharmacology[4] of Rauwolfia serpentina alkaloids, no attempt will be made to discuss the matter in detail, but instead, a few salient characteristics of the drug, its possible mode of action, and its uses in medicine will be described and a substantially complete bibliography on the subject will be supplied for the interested reader.

Prior to the discovery of reserpine (12) the principal alkaloids that had been studied as chemical individuals were ajmaline (10, 11, 76, 93, 112, 129–131, 132e, g, h, 133, 137, 138), iso- and neoajmaline (76, 134), rauwolfinine (14, 137), serpentine (10, 11, 76, 93, 112, 131, 132c, d, g, 137, 138, 170), serpentinine (10, 11, 76, 93, 112, 131, 132f, g, 137, 138), ajmalinine (11, 76, 131, 132a, b), and ajmalicine (132a, 136). An excellent review that clarifies the conflicting results of the early Indian investigators has been published (92). With the possible exception of serpentinine, the above-mentioned alkaloids were found to be hypotensive in nature.

The use of *Rauwolfia serpentina* in hypertension was first reported outside of India by Vakil in 1949 (100) and in the few years since then an almost unprecedented amount of work has been published on the pharmacology of the drug. Because various preparations have been used in these experiments the results are at times confusing. There is general agreement, however, that the powdered root, the alseroxylon fraction, and the pure component reserpine all have hypotensive activity (10, 12, 76, 93–129, 144–150, 153–172, 176, 185–218, 244, 246–249, 258, 259) and the mechanism of this action has been the subject of wide investigation both for reserpine (12, 76, 119, 135, 142–149, 154, 157–159, 165, 167, 168, 189, 192, 204, 207, 210, 215, 217, 219, 221–225, 228, 229, 231, 233, 238, 250, 251, 255, 260–262) and for various other forms of the drug (10, 11, 14, 18, 23, 24, 93–95, 97, 111, 115, 116, 119, 122, 131–136, 152, 173, 188, 193, 195, 202, 216, 220, 226, 227, 230, 232, 252–254, 256, 263).

Another outstanding property of most Rauwolfia preparations (10, 13, 97, 98, 103, 107, 108, 110, 113, 115, 118, 122, 126, 127, 138, 140, 152, 196, 207, 209, 220, 230, 236, 243) and of reserpine especially (12, 76, 139, 141–144, 146, 151, 160, 165, 166, 204, 206, 210, 215, 229, 238, 242, 250) is a marked sedative action on the central nervous system which apparently is independent of the hypotensive activity (190, 204, 217, see however, 210) and is in sharp contrast to the barbiturates in its mode of action (123, 141, 143, 144, 146, 152, 254). The sedation produced by the mixed alkaloids (98, 105, 122, 150, 197, 234–236, 241) and by reserpine (151, 237–240, 264, 269) seems to be of considerable importance in the treatment of various mental disorders and if the long-range results bear out the findings of short-range observations, it is claimed (238) that the drug will represent the most important therapeutic development in the history of psychiatry.[5]

Although Rauwolfia preparations have been used most widely in the treatment of hypertension and mental disorders, various reports indicate that the drug has potentialities in the field of geriatrics (160, 200, 206, 243, 271) and to a lesser extent in the treatment of psoriasis (171, 245), angina (190, 270), constitutional leanness (171), and gynecologic disorders (242).

Rauwolfia serpentina preparations and the pure alkaloid reserpine possess two properties that greatly increase their therapeutic utility. These are an apparent low toxicity (125, 168, 256, 259) and freedom from serious side effects. The most common complaints have been reported by Moore, *et al.* (218), as lethargy and muscular relaxation, drowsiness, nasal congestion or stuffiness, rhinorrhea, increased frequency of bowel movements, diarrhea, dizziness, decreased libido and potentia, tendency to gain weight, nightmares or disturbing dreams, agitated depression and dyspnea at rest. Many of these reactions have been substantiated by other investigators for various forms of the drug (24, 119, 127, 129, 144, 146, 147, 149, 151, 156, 160, 165, 168, 177, 186, 188–190, 194, 196, 197, 200, 206, 211, 215, 217, 249, 252, 259, 270, 271) along with bradycardia (24, 119, 127, 129, 142, 146–151, 156, 168, 190, 206, 211) and miosis (164, 189). Moyer (119) has recently shown that there is very little difference in the incidence of these side reactions when reserpine and Rauwiloid (an alkaloidal extract of *R. serpentina*) are compared. It should be noted that doses above the normal therapeutic level have on occasion caused parkinsonism (105, 215, 239, 266, 269) but the effect disappeared when the drug was discontinued.

The actual mechanism involved in the hypotensive and sedative action of Rauwolfia serpentina preparations is still not clear, although there is general agreement that the effects observed are mainly due to actions within the central nervous system. This has been suggested on the basis of

[4] For reviews on this subject see references 15A, 28, 76, 92, 101, 151, 177, 207, 217, 218, 230, 265.

[5] A symposium on the use of reserpine in the treatment of neuropsychiatric, neurological, and related clinical problems was recently held and the results are now available in published form (274).

experiments with reserpine (12, 28, 119, 135, 142–150, 157, 165–168, 190, 204, 217, 222, 224, 228, 230, 250, 255) and also with other forms of the drug (111, 127, 136, 150, 190, 195, 202, 207, 216, 217, 230, 254, 256). The complex pattern often observed suggests receptors other than those commonly recognized (148) so that a duality of mechanism, including a direct peripheral reaction (142A, 225), is a distinct possibility. It is beyond the scope of this paper to discuss the conflicting pieces of evidence which have recently been reviewed (217, but see 267).

It should be mentioned that until recently, reserpine has been considered the most potent chemical individual in Rauwolfia serpentina preparations. However, two other alkaloids, rescinnamine (23, 24, 173b, 220, 252) and canescine (deserpidine) (77B, 174, 176, 253a, b, 268) produce essentially the same pharmacological effects as does reserpine and results of further tests on these two compounds will be awaited with considerable interest.

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