[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL CO., DIVISION OF CIBA CORPORATION, SUMMIT N. J., AND THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA]

Rauwolfia Alkaloids. XXXVIII.[1] Stereospecific Degradations Leading to the Absolute Configurations and Structures of Ajmaline, Sarpagine and Corynantheidine[2]

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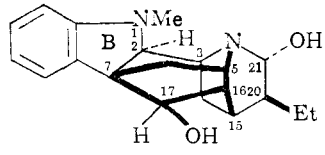
RECEIVED AUGUST 30, 1961

The alkaloid ajmaline (I) and its C-ethyl epimer, isoajmaline, were degraded to *l-cis-* and *d-trans*-2,3-diethyl-1,2,3,4-tetrahydro-12-methylindolo[2,3-a]quinolizinium (X) perchlorates which in turn were derived from corynantheidine on the one hand and corynantheine on the other. These correlations establish the absolute stereochemistry of corynantheidine (XI), as well as six of the nine asymmetric carbons of ajmaline. Chromic acid oxidation of deoxyajmaline O-acetate yielded the N_a-demethylindolenine (XVII) which upon reduction and N_a-methylation gave the C_2-epimer of deoxyajmaline (XXI). The stereochemistry at C_{17} followed from the course of the reduction of deoxyajmalone. The stereochemistry of the remaining center at C_{21} rests on conformational arguments. These conclusions were consistent with p.m.r. spectra of a number of derivatives. The detailed structure of sarpagine (XXV) was deduced from its transformation into deoxyajmalol-B (VI).

The Siddiqui base, ajmaline,[6] had been the subject of extensive study,[7] principally by the Oxford group,[8] before Schenker and Woodward[9] finally established the correct hexacyclic system and position of the C_{17}-hydroxyl in I.[10] Since then its stereochemistry has been the subject of discussion,[7c,11] although no experimental evidence to support these deductions has been presented.



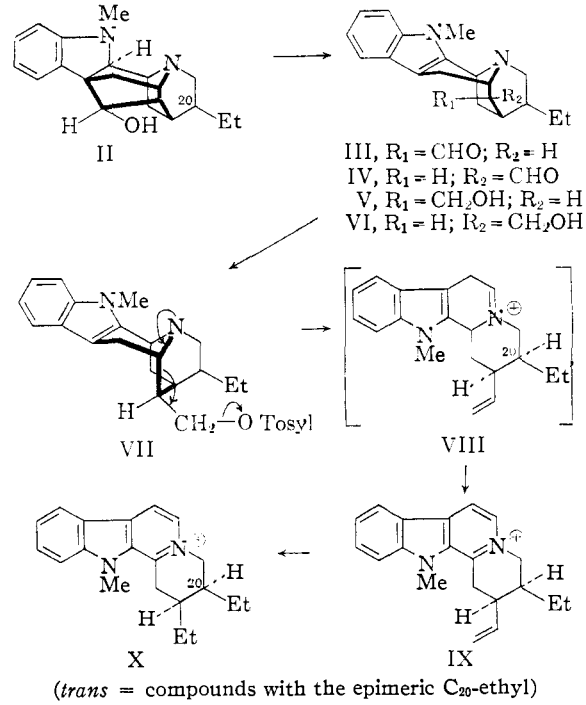
I

In connection with alkaloidal studies to be reported elsewhere, we saw in ajmaline chemistry a route to the preparation of compounds of a type which had been assigned to sarpagine (XXV), as well as a means of determining its structure. More important, there appeared to be a way of converting ajmaline into compounds of known configuration, which would afford not only a solution to its stereochemistry, but also a new and simple structure proof. The critical step in the proposed sequence was based on an elimination reaction involving a carbon–carbon bond fission,[12] *viz.*, VII → VIII. It was hoped that the dihydropyridinium salt VIII would either oxidize or disproportionate, during the reaction or work-up, into the stable β-carbolinium salt IX. To anticipate the sequel, these reactions went as expected, and this, coupled with other data, lead to I as a complete expression for the structure of ajmaline.

Ajmaline was first converted by two known steps into deoxyajmaline (II). According to Schenker and Woodward[9] as inferred from the published[13] analogous oxidation of dihydrosandwicine, deoxyajmaline is oxidized readily by lead tetraacetate in acetic acid to an indole aldehyde. In our hands, benzene was the solvent of choice,

CHART I

DEGRADATION OF DEOXYAJMALINE AND DEOXYISOAJMALINE



(*trans* = compounds with the epimeric C_{20}-ethyl)

(1) Preceding paper, Part XLII, *Tetrahedron Letters*, No. **11**, 363 (1961).

(2) For preliminary accounts of part of this work, see M. F. Bartlett, E. Schlittler, R. Sklar, W. I. Taylor, R. L. S. Amai and Ernest Wenkert, *J. Am. Chem. Soc.*, **82** 3792 (1960), and M. F. Bartlett, R. Sklar and W. I. Taylor, *ibid.*, **82**, 3790 (1960).

(3) Research Department, CIBA Pharmaceutical Products, Inc.

(4) The Department of Chemistry, Iowa State University.

(5) Public Health Service Predoctoral Research Fellow, 1960–1961.

(6) S. Siddiqui and R. H. Siddiqui, *J. Indian Chem. Soc.*, **8**, 667 (1931).

(7) For reviews of ajmaline chemistry: (a) J. E. Saxton, *Quart. Revs.*, **10**, 108 (1956); (b) A. Chatterjee, S. C. Pakrashi and G. Werner, *Forts. Chem. Org. Natur.*, **13**, 346 (1956); (c) R. Robinson, *Angew. Chem.*, **69**, 40 (1957).

(8) (a) B. Mukherji, R. Robinson and E. Schlittler, *Experientia*, **5**, 215 (1949); (b) F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1242 (1954); (c) R. Robinson, *Chemistry & Industry*, 285 (1955); (d) F. C. Finch, J. D. Hobson, R. Robinson and E. Schlittler, *ibid.*, 653 (1955).

(9) Schenker and R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956).

(10) Since ajmaline can be regarded as a derivative of an α-type indole, we have used the well known convention which assigns to its atoms the same numbers as their supposed equivalents in yohimbine.

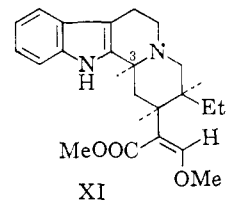
(11) S. K. Talapatra and A. Chatterjee, *Naturwiss.*, **45**, 58 (1958); W. Venkateswaran and A. Chatterjee, *J. Indian Chem. Soc.*, 35, 363 (1958).

(12) For summaries of such reactions in simpler systems see C. A. Grob, *Experientia*, **13**, 126 (1957); *Bull. soc. chim. France*, 1360 (1960).

(13) M. Gorman, N. Neuss, C. Djerassi, J. P. Kutney and P. J. Scheuer, *Tetrahedron*, **1**, 328 (1957).

and the base II was converted rapidly in high yield into deoxyajmalal-A (III). Under more vigorous conditions or by allowing the reaction mixture to stand for some time, it became contaminated with deoxyajmalal-B (IV). Quantitative conversion of the A- into the B-aldehyde[14] was accomplished by heating the former in alcoholic alkali, the driving force lying in the fewer resultant diaxial interactions in the quinuclidine moiety. Reduction of aldehyde-B with sodium borohydride furnished crystalline deoxyajmalol-B[14] (VI) which was used in preference to the amorphous alcohol-A (V). The efficiency of the above procedure is illustrated by the routine conversion of deoxyajmaline into O-tosyldeoxyajmalol-B[15] (VII) in 42% over-all yield without purification of the intermediates. After VII had been refluxed in collidine, it was observed upon cooling that there gradually developed a pronounced blue fluorescence, indicative of a β-carbolinium salt. This material was readily separable by chromatography, but for a satisfactory yield of a final product was better purified by conversion successively into its picrate, chloride and perchlorate. The yield of IX-perchlorate was never greater than 50% which would favor a disproportionation over an aerial oxidation, but this point has not been investigated. No other characteristic product could be isolated from the by-products obtained during the isolation of IX. Catalytic hydrogenation of IX chloride gave the diethyl derivative X isolated as its perchlorate. This proved identical in all respects with N_a-methyltetradehydrocorynantheidane perchlorate (*vide infra*) whose ethyl groups were known to be in a *cis* relationship,[16] but with an unknown absolute stereochemistry.

By an analogous series of reactions, deoxyisoajmaline (*trans*-II) was converted into *trans*-X perchlorate indistinguishable from the same salt of the N_a-methyltetradehydro derivative of dihydrocorynantheane XII (*vide infra*). Since the absolute configuration of *trans*-X is known,[17] the stereochemistry of ajmaline (I) is settled with the exception of three centers, C_2, C_{17} and C_{21}. Also in view of the experimental connection with corynantheidine, *via* the degradation product X, the last major uncertainty in the structure XI of that alkaloid is elucidated.[18]



XI

Two methods were used for the synthesis of *trans*-X from dihydrocorynantheane[19] (XII). By the first route, the latter compound was converted, without purification of the intermediates, successively into the tetradehydro compound, the anhydro base XIV, *trans*-X iodide and finally *trans*-X perchlorate. By the second method, which was also used for converting corynantheidane[20] into X, the potassium derivative of dihydrocorynantheane, for example, was prepared and methylated in benzene,[21] and the resultant mixture of tertiary and quaternary bases was pyrolyzed *in vacuo*, furnishing the pure N_a-methyl derivative XIII. This upon catalytic dehydrogenation gave the desired *d-trans*-2,3-diethyl-1,2,3,4-tetrahydro-12-methyl[2,3-a]quinolizinium perchlorate (*trans*-X).

Of the asymmetric centers not yet defined by the above degradations, the configuration of the C_{17}-hydroxyl has been assigned that shown in I on the following grounds. Deoxyajmalone[9] (II, CHOH = CO), in which the side before the viewer is unhindered, yielded an epimeric alcohol upon catalytic reduction. The degree of hindrance to rearward attack must be quite severe, since it was also the only isolable product of sodium boro-

(14) This aldehyde is identical with that prepared by Schenker and Woodward (ref. 9). Among other compounds prepared by these authors and also described in this paper are deoxyajmalol-B, and its tosyl ester, deoxyajmalone, 17-epi-deoxyajmaline (Dr. K. Schenker, private communication).

(15) Tosyl is used throughout instead of *p*-toluenesulfonyl.

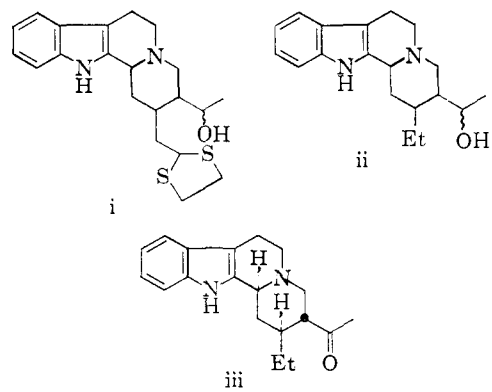
(16) E. E. van Tamelen, P. E. Aldrich and T. F. Katz, *J. Am. Chem. Soc.*, **79**, 6426 (1957), and references therein.

(17) This follows from: (a) the conversion of dihydrocorynantheol and cinchonamine into a common derivative [E. Wenkert and N. V. Bringi, *ibid.*, **81**, 1474, 6535 (1959)]; (b) the relating [E. Ochiai and M. Ishikawa, *Pharm. Bull. (Japan)*, **6**, 208 (1958)] of cinchonamine to cinchonine of known absolute configuration [V. Prelog and E. Zahn, *Helv. Chim. Acta*, **27**, 545 (1944)]. This result is in agreement with earlier work which was based on rotational evidence and the assumption of correctness of the assignment of the absolute configuration to yohimbine (van Tamelen, Aldrich and Katz, ref. 16).

(18) The configuration of the methoxymethylene in corynantheidine as well as corynantheine is that depicted in XI [E. Wenkert, B. Wickberg and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961)]. The stereochemistry of C_3 in corynantheidine was determined previously from molecular rotational differences of suitable derivatives [M.-M. Janot, R. Goutarel, A. Le Hir, G. Tsatas and V. Prelog, *Helv. Chim. Acta*, **38**, 1073 (1955)] and from infrared data [E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956)].

(19) Most of the dihydrocorynantheane was prepared from the more readily available ajmalicine (ref. 17). In the experimental, an improvement on the published procedure is given. The rest was obtained from corynantheine kindly supplied by Dr. Raymond Hamet.

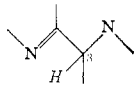
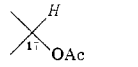
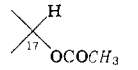
(20) As a follow-up of a previous study of the stereochemical interrelationship of indole alkaloids (ref. 17a) a direct conversion of ajmalicine to corynantheidane and hence a direct correlation of corynantheidine (XI) and alkaloids of known absolute configuration was sought. However, none of the ajmalicine degradation products proved suitable for this purpose: Ajmalicial thioacetal (i) (see Experimental) could not be desoxygenated. Similar attempts of oxygen removal of ajmaliciol (ii) by acetylation or laurylation and pyrolysis as well as by tosylation and lithium aluminum hydride reduction were of no avail. Finally, base-induced equilibration of 18,19-dihydro-19-corynantheone (iii) (see Experimental) proved it to be a 15,20-*trans* compound and thus of little value for conversion to corynantheidane



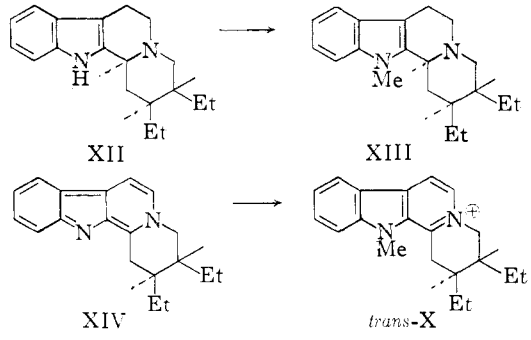
(21) This procedure was worked out using yohimbane as a model (see Experimental).

TABLE I

VALUES FROM THE P.M.R. SPECTRA OF AJMALINE DERIVATIVES

$-\delta$	Deoxyajmaline O-acetate	N_a-Demethyl-Δ^{-1} deoxyajmaline O-acetate	17- Epideoxyajmaline O-acetate	N_a-Demethyl-Δ^{-1} 17-epideoxyajmaline O-acetate
Aromatic (4-protons)	Multiplet 6.54–7.39	Multiplet 7.06–7.84	Multiplet 6.54–7.12	Multiplet 6.54–7.68 (different shape from others)
$N\text{-}CH_3$	Singlet 2.75		Singlet 2.78	
		Quartet centered at 4.20 (J 3.4, 8.8 c.p.s.)		Doublet centered at 4.20 (J 8.7 c.p.s.)
$-CH_2\text{-}CH_3$	Triplet centered at 0.93 (J 6.0 c.p.s.)	Triplet centered at 0.95 (J 6.0 c.p.s.)	Triplet centered at 0.91 (J 5.9 c.p.s.)	Triplet centered at 0.98 (J 6.0 c.p.s.)
	Doublet centered at 5.30 (J 1.8 c.p.s.)	Doublet centered at 5.00 (J 1.8 c.p.s.)	Doublet centered at 5.70 (J 8.9 c.p.s.)	Doublet centered at 5.76 (J 8.7 c.p.s.)
	Singlet 2.18	Singlet 2.15	Singlet 2.03	Singlet 2.80

hydride[22] or lithium aluminum hydride reductions. Support for this conclusion was to be found in the p.m.r. spectra of a number of ajmaline derivatives (Table I). The values for the coupling constants show that the C_{17}-proton in the five-membered ring is *trans* to that at C_{16} in the normal series and *cis* in the C_{17}-epi-compounds.[23]



XII XIII

XIV *trans*-X

Theoretically, the orientation at C_2 should be capable of solution provided that a suitable indolenine could be prepared. Thus given an indolenine, *e.g.*, XVII, it would be expected to reduce catalytically from the top side, rather than from the highly hindered under side. It was discovered that oxidation of deoxyajmaline O-acetate by chromium trioxide in pyridine gave a 2-hydroxy compound (XV). Structure proof followed from its physical properties and reaction with base to furnish deoxyajmalal-B (IV). With acid, no ionization of XV to the indoleninium salt was observed; in fact if forcing conditions were used the molecule decomposed into a mixture of indole aldehydes (III and IV). Attempted reductions with lithium aluminum hydride or sodium borohydride led only to indoles (probably V and/or VI). This approach was abandoned when there was discovered among the chromatographic fractions from the chromium trioxide oxidation of deoxyajmaline O-acetate, the indolenine[24] XVII. Its structure was established from its physical properties, and its conversion to the sarpagine derivative XXVIII, *via* the indole aldehyde XVIII. Catalytic reduction of XVII gave a high yield of a single indoline (XIX). This was hydrolyzed to the hydroxy indoline XX which was not identical with N_a-demethyldeoxyajmaline (II, Me = H), obtained in very poor yield by the pyrolysis of deoxyajmaline hydriodide. Provided that this demethylation has proceeded without rearrangement, and that the hydrogenation of the indolenine XVII took place on the "topside" the stereochemistry at C_2 in ajmaline is that depicted in I, *i.e.*, ring B is *cis* fused to the chair piperidyl moiety.

This conclusion was further supported by the following experiments. N_a-Methylation of XX gave a compound (XXI) isomeric and not identical with deoxyajmaline (II). The optical rotatory dispersion curves of deoxyajmaline O-acetate and its C_2-epimer XIX were in a mirror image relationship to one another inferring accurately the stereochemical change adjacent to the chromophoric moiety. Finally, comparison of the dissociation constants of the epimeric pair, II and XXI, showed that the former, where the proton in the conjugate acid was bonded to N_a, was a stronger base (pK_a' 8.44) than the latter (pK_a' 7.80).

The chemistry of ajmaline would indicate that in many cases it must be in tautomeric equilibrium with the open-chain aminoaldehyde. In the solid state, however, the infrared spectrum shows no carbonyl band and the C_{21}-hydroxyl has presumably taken up the more stable configuration *trans* to the neighboring ethyl substituent as shown in I. In the alternative structure there would result an increase in the steric strain due to an additional 1,2-diaxial interaction between the adjacent groups. In isoajmaline, for the same reasons, the C_{21}-hydroxyl would be expected to be *trans* to the C_{20}-ethyl. In this connection, it is not immediately clear why ajmaline, either by heating above its melting point or refluxing in alkali, should isomerize.

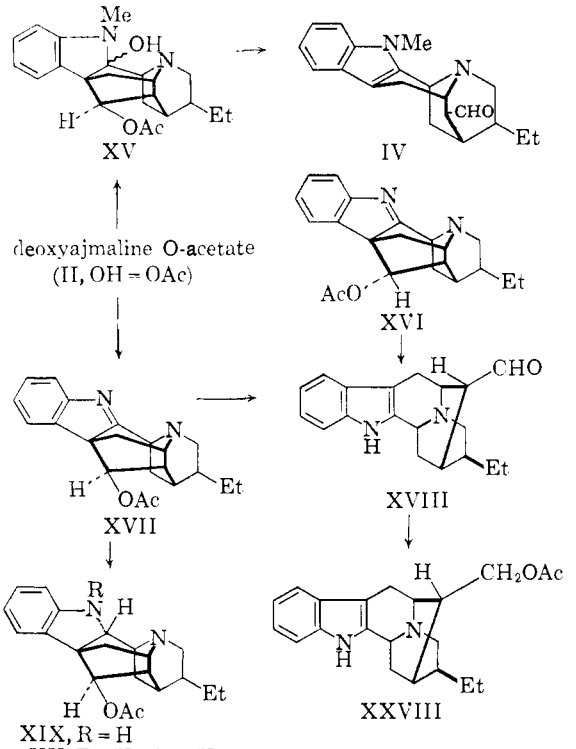
(22) Originally reported by Schenker and Woodward (ref. 9), but no details were given. A similar reduction of ajmalidine (ref. 27) is also on record.

(23) Analogous values for the spin–spin coupling constants of similarly oriented proton pairs were observed by F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

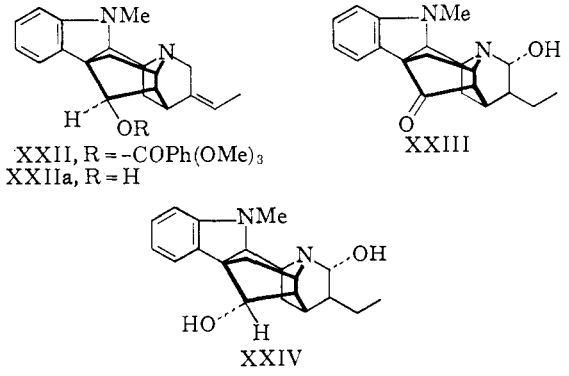
(24) Dealkylation of alkylanilines by a variety of oxidizing agents is well known. Its success here must be due to the comparative resistance of the quinuclidine portion to this type of oxidative attack.

CHART II

OXIDATION AND TRANSFORMATION PRODUCTS OF DEOXYAJMALINE O-ACETATE AND ITS C_{17}-EPIMER



The detailed structures of the known ajmaline congeners now can be written. Thus rauvomitine[25] (XXII) and tetraphyllicine[26] (XXIIa) have been converted into deoxyajmaline (II), and ajmalidine[27] (XXIII) and sandwicine[13] (XXIV) have been interrelated with ajmaline. Semperflorine, an indoline alkaloid isolated from *Rauwolfia semperflorens*,[28] has an infrared spectrum almost identical with tetraphyllicine, but since no sample is available for direct comparison some related possibilities cannot be excluded.



(25) E. Haack, A. Popelak and H. Springler, *Naturwiss.*, **42**, 627 (1955); J. Poisson, R. Goutarel and M.-M. Janot, *Compt. rend.*, **241**, 1840 (1955).

(26) C. Djerassi and J. Fishman, *Chemistry & Industry*, 627 (1955); C. Djerassi, M. Gorman, S. C. Pakrashi and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 1259 (1956).

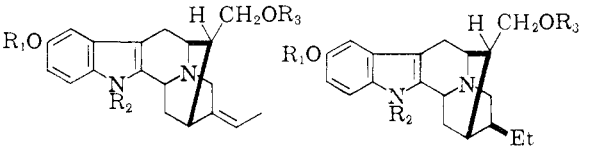
(27) S. C. Pakrashi, C. Djerassi, R. Wasicky and N. Neuss, *ibid.*, **77**, 6687 (1957).

(28) E. Schlittler and A. Furlenmeier, *Helv. Chim. Acta*, **36**, 996 (1953).

There is a group of 5-hydroxyindole alkaloids, *viz.*, sarpagine[29] (XXV), lochnerine (O-methylsarpagine)[30] and lochneram (lochnerine metho salt),[31] which are regarded as derivatives of a biogenetic precursor of ajmaline. Their structures, however, have been guessed solely from their interrelationships, determination of chromophoric moieties, functional group analysis and obtention of dehydrogenation products with the expected ultraviolet-absorbing properties. If the formula for sarpagine is correct, then its structure could be proved by its conversion into one of the four deoxyajmalols (V and VI). Tosylation of monoacetylsarpagine[32] (XXVI), followed by reductive cleavage,[33] gave O-acetyldeoxysarpagine (XXVIII), whose N_a-sodio derivative was methylated with methyl iodide in liquid ammonia. Unfortunately, attempted reduction of the ethylidene moiety under a variety of conditions, of either the N_a-methyl derivative XXIX or its hydrolysis product XXX, catalytically in the presence of either palladium or platinum, was unsuccessful.

CHART III

DERIVATIVES OF SARPAGINE



XXV,	$R_1 = R_2 = R_3 = H$	XXXI
XXVI,	$R_1 = H$; $R_2 = H$; $R_3 = Ac$	XXXII
XXVII,	R_1 = tosyl; $R_2 = H$; $R_3 = Ac$	XXXIII
XXVIII,	$R_1O = H$; $R_2 = H$; $R_3 = Ac$	XXXIV
XXIX,	$R_1O = H$; $R_2 = Me$; $R_3 = Ac$	XXXV
XXX,	$R_1O = H$; $R = Me$; $R_3 = H$	VI

It was decided to carry out the potentially troublesome reduction step first. After some trials, conditions were found to prepare dihydrosarpagine (XXXI). Its monoacetyl derivative XXXII was carried through the same sequence as described above for the sarpagine series yielding the amorphous acetyldeoxyajmalol-B (XXXV) which upon hydrolysis furnished deoxyajmalol-B (VI). Thus the stereochemistry of sarpagine is established, with the exception of the geometry of the ethylidine group.

The reason for our apparent difficulty in the reduction of the double bond in these sarpagine derivatives is not known. Caution should be exercised in deciding the course of the reduction of the double bond in such compounds. We would like to argue that reduction should proceed only on the side opposite to the projecting hydroxymethyl; the fallacy in this conclusion is shown up by the stereospecific reduction of normacusine-B[34] (XX-

(29) D. Stauffacher, A. Hofmann and E. Seebeck, *J. Am. Chem. Soc.*, **40**, 508 (1957); S. K. Talapatra and A. Chatterjee, *Sci. and Culture*, **22**, 692 (1957).

(30) J. Poisson, J. Le Men and M.-M. Janot, *Bull. soc. chim. France*, **24**, 610 (1957); W. A. Arnold, W. von Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **40**, 705 (1957).

(31) W. F. Arnold, F. Berlage, K. Bernauer, H. Schmid and P. Karrer, *ibid.*, **41**, 1505 (1958).

(32) We are grateful to Dr. A. K. Kiang for a generous sample of sarpagine which made this work possible.

(33) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 178 (1949).

(34) A. R. Battersby and D. A. Yoewell, *Proc. Chem. Soc.*, 17 (1961).

VIII, Ac = H) to deoxyisoajmalol-B (*trans*-VI) in acetic acid using a platinum catalyst.

One of the more important conclusions stemming from the above work is the extension of the rule[17a] of uniform absolute stereochemistry of the C_{15} equivalent of yohimbine to two more groups of indole alkaloids.

Acknowledgments.—We wish to express our thanks to Mr. L. Dorfman and his staff for the analytical and spectral data, and to Drs. M. J. Allen and C. R. Rehm for the pK_a's. We also are indebted to Professor R. K. Hill for the optical rotatory dispersion measurements. R. L. S. A., P. B., N. V. B. and E. W. are grateful to the National Institutes of Health, Public Health Service, for financial support.

Experimental

The melting points were taken in evacuated capillaries and are uncorrected. Unless otherwise stated, the ultraviolet absorption spectra were measured in alcohol and are expressed as $m\mu$ (ϵ), the infrared spectra in Nujol mulls, the potentiometric titrations in 80% methyl Cellosolve–water, optical rotations in methanol at *ca.* 25°, $c \approx 1$, and the analytical samples were routinely dried at 80° for 12–24 hours *in vacuo*. Sodium sulfate was normally used for drying the organic solvents and Woelm alumina activity III was used throughout.

Deoxyajmaline O-Acetate.—Deoxyajmaline (5.1 g.) was allowed to stand in pyridine (130 ml.) and acetic anhydride (40 ml.) over a weekend. The solution was evaporated to dryness *in vacuo* and chromatographed on alumina (37 × 60 mm.). The materials (5.1 g.) eluted with hexane–benzene (1:1, 100 ml.) and benzene (150 ml.) were combined and crystallized from methanol–water yielding the O-acetate (4.5 g.), m.p. 102–108°. For analysis it was recrystallized from benzene–hexane and dried at 25° *in vacuo;* m.p. 146–147°, $[\alpha]_D$ + 13.9° (5 MeOH–2$CHCl_3$), $\gamma_{C=O}$ 1749 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.96; H, 8.01; N, 7.95. Found: C, 75.15; H, 8.16; N, 7.61.

Deoxyajmalone.[35]—Deoxyajmaline (3.0 g.) and fluorenone (4.1 g.) were dried *in vacuo* in a 1-l. round-bottomed flask containing a magnetic stirring bar. Freshly sublimed potassium *t*-butoxide (~4 g.) was added to the flask, then 500 ml. of benzene which was dried by filtering through activity I alumina directly into the flask. The solution rapidly turned dark brown in color. The atmosphere was replaced by dry nitrogen and the solution was refluxed with stirring for 45 minutes. After cooling, dilute sulfuric acid was added and the resulting light yellow solution was extracted with excess dilute sulfuric acid which was then made basic with concentrated sodium hydroxide and extracted with methylene chloride. After drying, the solvent was removed and the residue crystallized from acetone yielding deoxyajmalone (2.54 g.), m.p. 154–156°, $[\alpha]_D$ +350° ($CHCl_3$), $\nu_{C=O}$ 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.83; H, 7.88; N, 9.23.

17-Epi-deoxyajmaline.—Deoxyajmalone (2.0 g.) in alcohol (80 ml.) and sodium borohydride (2.0 g.) were stirred at room temperature overnight. After the addition of water to dissolve a white precipitate, it was extracted into methylene chloride. The residue from the dried organic phase was crystallized from methanol to furnish 17-epi-deoxyajmaline (1.31 g.), m.p. 262–264°, $[\alpha]_D$ +347° ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.51; H, 8.54; N, 9.33.

Deoxyajmalone either extracted into an ethereal solution of lithium aluminum hydride or catalytically hydrogenated in methanol in the presence of platinum, gave the same epi-alcohol.

17-Epi-deoxyajmaline O-Acetate (XVI).—The above epi-alcohol (200 mg.) was allowed to stand at room temperature overnight in acetic anhydride and pyridine. After evaporation, the residue was chromatographed over neutral alumina (18 × 80 mm.). The benzene eluted material was crystallized from ether; m.p. 168–169°, $[\alpha]_D$ + 178° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.96; H, 8.01. Found: C, 74.59; H, 8.12.

Deoxyajmalal-A (III).—To a stirred suspension of deoxyajmaline (5.0 g.) in benzene (400 ml.), lead tetraacetate (7.1 g.) was added portionwise over a 3-minute period. The suspended material dissolved rapidly to give a yellow solution and a gummy green-brown precipitate. The benzene solution was decanted and washed successively with water, dilute sodium hydroxide and finally water. The gummy precipitate was dissolved in water and extracted with benzene which was washed with dilute sodium hydroxide and water. The combined benzene extracts were dried and evaporated yielding the crude oxidation product (3.83 g.), which crystallized from ethyl acetate giving deoxyajmalal-A (3.0 g.), m.p. 177–179°. For analysis, the aldehyde was recrystallized from the same solvent, m.p. 180–181° (after drying), $[\alpha]_D$ + 40°, pK_a' 5.89; λ_{max} 226–228 (37,600), 283 (8,560); shlds. 275 (8,000), 288 (7,700), 293 (7,100); λ_{min} 248–250 (3,900); $\nu_{C=O}$ 1706 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.97; H, 7.97; N, 9.00.

Deoxyajmalal-B (IV).—Deoxyajmalal-A (4.2 g.) was dissolved in methanol (250 ml.) and 0.1 *N* sodium hydroxide was added to bring the *p*H to *ca.* 12. After refluxing for 1 hour, the methanol was removed *in vacuo*, and the concentrate was extracted with methylene chloride. Evaporation of the dried solvent afforded the crude aldehyde-B (4.1 g.), purified by crystallization from ethyl acetate to m.p. 213–215°, $[\alpha]_D$ −1°, pK_a' 6.19; λ_{max} 226–229 (38,960), 283 (7,870); shlds. 278 (7,300), 292 (6,700); λ_{min} 249–250 (2,900); $\nu_{C=O}$ 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.90; H, 7.80; N, 9.01.

Deoxyajmalol-A (V).—Aldehyde-A (2.05 g.) in 90% aqueous methanol (50 ml.) was added to a stirred solution of sodium borohydride in 20% aqueous methanol (50 ml.) over a period of 15 minutes. Another 2 g. of sodium borohydride was added directly to the reaction mixture and the stirring was continued for 1.75 hours. The methanol was removed *in vacuo* and the residue was extracted into methylene chloride, dried and evaporated to yield the viscous alcohol (2.2 g.), characterized as its picrate, m.p. 219–221° (dried sample) from ethanol–ethyl acetate.

Anal. Calcd. for $C_{26}H_{29}N_5O_8 \cdot C_2H_5OH$: C, 57.43; H, 6.03; N, 11.97. Found: C, 57.35; H, 5.36; N, 12.15, 11.97.

The picrate (100 mg.) was decomposed by washing it through a short column of basic alumina in 5% methanol–methylene chloride. The resultant amorphous alcohol-A sublimed at 150–180° *in vacuo* yielding a glass, $[\alpha]_D$ −53°, λ_{max} 228 (36,700), 284 (7,100); plat. 289-91 (6,500); λ_{min} 249–250 (1,900).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 76.53, 76.25; H, 8.55, 8.60; N, 8.99.

Deoxyajmalol-A (120 mg.) in methylene chloride treated with methyl iodide furnished the methiodide (155 mg.), m.p. 244–247°, raised to m.p. 249–250° after crystallization from ethanol–ethyl acetate.

Anal. Calcd. for $C_{21}H_{29}IN_2O$: C, 55.76; H, 6.46; N, 6.19. Found: C, 55.76; H, 6.27; N, 5.99.

Deoxyajmalol-A O-Tosylate.—Tosyl chloride (220 mg.) was added to deoxyajmalol-A (184 mg.) dissolved in pyridine (1 ml.). The solution was kept at 5° for 3 days, then more tosyl chloride (200 mg.) was added and left for 1 more day. The reaction mixture was diluted with ice and water and extracted with methylene chloride. The aqueous phase was brought to *p*H 9–10 with 50% ammonium hydroxide and extracted with methylene chloride. The combined extracts afforded the crude tosylate (234 mg.). Crystallization from acetone–ether yielded needles of the pure ester (188 mg.), m.p. 118–120°. The sample was air-dried for analysis since it decomposed at 80° *in vacuo*.

Anal. Calcd. for $C_{27}H_{32}N_2O_3S$: C, 69.80; H, 6.94; N, 6.03. Found: C, 69.63; H, 7.00; N, 6.18.

Deoxyajmalol-B (VI).—Deoxyajmalal-B (2.0 g.) was reduced with sodium borohydride as described for alcohol-A. The amorphous product (2.0 g.) crystallized upon addition of

(35) This procedure is patterned after that used for the preparation of yohimbinone (A. Le Hir and E. Warnhoff, *Compt. rend.*, **246**, 1564 (1958)).

ether; m.p. 213–215°. After recrystallization from ethanol and drying it has m.p. 217–218°, $[\alpha]_D$ −3°; pK_a' 7.46; λ_{max} 228–229 (39,600), 284 (7,350); shld. 232 (34,600), 276 (6.480); plat. 289–293 (6,700); λ_{min} 250 (950); ν_{OH} 3378 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.35; H, 8.56; N, 9.29.

Deoxyajmalol-B O-tosylate (VII). (a).—Deoxyajmalol-B (8.5 g.) in pyridine (120 ml.) was cooled in an ice bath, tosyl chloride (16.2 g.) was added, and the solution was kept at 5° for 5 days. The reaction mixture was diluted with ice and water and extracted into methylene chloride furnishing the crude tosylate (16.8 g.) which gave the pure ester (7.4 g.), needles from acetone, m.p. 149–151°, pK_a' 6.11; λ_{max} 226 (46,600), 284 (7,000); shlds. 228 (46,500), 232 (40,200), 273 mμ (6,100), 293 (6,200); λ_{min}, 249 (2,600).

Anal. Calcd. for $C_{27}H_{32}N_2O_3S$: C, 69.80; H, 6.94; N, 6.03. Found: C, 69.38; H, 7.20; N, 5.88.

(b).—The crude extract (9.2 g.) from the lead tetraacetate oxidation of deoxyajmaline (15 g.) was refluxed in methanol (250 ml.) and 0.1 *N* sodium hydroxide (50 ml.) for 1 hour. After cooling, sodium borohydride (20 g.) was added and the solution was stirred at room temperature overnight. Water was added, the excess methanol removed *in vacuo* and the product extracted with methylene chloride yielding deoxyajmalol-B (8.46 g.). The crude alcohol was dissolved in pyridine along with tosyl chloride (16.2 g.) and kept at 5° for 5 days. Ice, water, methylene chloride and 50% ammonium hydroxide (to bring the *p*H to 9–10) were added, the product was extracted into methylene chloride, washed with water, dried, and the solvent evaporated affording a residue (16.8 g.) which crystallized from acetone giving O-tosyldeoxyajmalol-B (9.4 g.), m.p. 146–147°.

Deoxyajmalol-B O-tosylate (50 mg.) was allowed to stand in the dark at room temperature with methyl iodide (1 ml.) in methanol (2 ml.). After evaporating the solution to dryness, the quaternary salt was crystallized from acetone to m.p. 168–169°.

Anal. Calcd. for $C_{28}H_{35}IN_2O_3S$: C, 55.44; H, 5.81; N, 4.61. Found: C, 55.71; H, 5.84; N, 4.59.

1-*cis*-3-Ethyl-1,2,3,4-tetrahydro-12-methyl-2-vinylindolo[2,3-a]quinolizinium Perchlorate (IX).—O-Tosyldeoxyajmalol-B (3.4 g.) was dissolved in 2,4,6-collidine (70 ml.) and refluxed for 2.5 hours. The solution gradually turned dark and an oil precipitated. At the end of the reflux period and while the solution was cooling, an intense blue fluorescence was observed under ultraviolet light which increased in intensity during the cooling period. The solution was diluted with methylene chloride, washed with 0.1 *N* sodium hydroxide, water, dried and evaporated *in vacuo*. The residue (3.6 g.) was chromatographed on a column of neutral alumina (4 × 27 cm.). Methylene chloride (400 ml.) and methylene chloride–methanol (99:1, 750 ml.) eluted 910 and 120 mg. of a colorless oil, respectively; methylene chloride–methanol (49:1, 900 ml.) eluted a number of green fluorescent bands weighing 770 mg. A broad brilliant blue fluorescent band (1.07 g.) was eluted with methylene chloride–methanol (32:1, 1600 ml.). This was immediately treated with picric acid to yield the *cis*-quinolizinium picrate (710 mg.), m.p. 149–151°, increasing to m.p. 151–152° upon recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{25}N_5O_7$: C, 60.11; H, 4.85; N, 13.48. Found: C, 59.92; H, 4.91; N, 13.25.

The picrate (600 mg.) was converted to its corresponding chloride by filtering it through a column of Amberlite CG45 (Cl^-) resin (3 × 7 cm.) in methanol. The chloride was crystallized from methylene chloride–acetone to m.p. 264–265°. A sample was dried *in vacuo* at 25° for analysis; $[\alpha]_D$ −39°, λ_{max} 257–260 (28,900), 264–265 (29,700), 309–310 (19,340), 375–379 (4,600); λ_{min} 230 (11,600), 284 (7,300), 328 (1,200).

Anal. Calcd. for $C_{20}H_{23}ClN_2\cdot H_2O$: C, 69.65; H, 7.30. Found: C, 70.20; H, 7.39.

The perchlorate was prepared by adding ethanolic perchloric acid to an ethanolic solution of the above chloride. After two crystallizations from aqueous ethanol and drying for analysis the melting point was 201–202°, $[\alpha]_D$ −27°.

Anal. Calcd. for $C_{20}H_{23}N_2\cdot ClO_4$: C, 61.45; H, 5.93. Found: C, 61.21; H, 6.04.

1-*cis*-2,3-Diethyl-1,2,3,4-tetrahydro-12-methyl-indolo[2,3-a]quinolizinium Perchlorate (X).—The above vinyl-β-carbolinium chloride (518 mg.) was hydrogenated in alcohol (15 ml.) in the presence of prereduced Adams catalyst (155 mg.). Uptake of hydrogen ceased after 1 mole equivalent and the isolated chloride had m.p. 256–257°, $[\alpha]_D$ −27°, from methylene chloride–ether.

Anal. Calcd. for $C_{20}H_{25}N_2Cl\cdot H_2O$: C, 69.24; H, 7.84. Found: C, 69.46; H, 8.17.

The perchlorate from ethanol had m.p. 212–213°, $[\alpha]_D$ −26°. The ultraviolet absorption spectrum was identical with that of the corresponding 2-vinyl derivative.

Anal. Calcd. for $C_{20}H_{25}N_2\cdot ClO_4$: C, 61.14; H, 6.41. Found: C, 61.06; H, 6.61.

Deoxyisoajmaline (*trans*-II).—Potassium borohydride (1 g.) was added slowly to a hot solution of isoajmaline (6.4 g.) in aqueous ethanol. After 18 hours the crystallized dihydroisoajmaline (3 g.), m.p. 192–194° (mixed m.p. with dihydroajmaline was 175°), $[\alpha]_D$ +35° (EtOH), was filtered off. The m.p. was unchanged upon recrystallization from methanol–water.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59. Found: C, 72.88; H, 8.60.

Dihydroisoajmaline (4.0 g.) was converted into its hydrobromide and heated at 295° for 25 minutes *in vacuo* (15 mm.). The product was dissolved in aqueous methanol, made basic with potassium hydroxide and the dried precipitate crystallized by dissolving it in methylene chloride, adding methanol and boiling off the first solvent. The deoxyisoajmaline (2.5 g.) had m.p. 295°, $[\alpha]_D$ +158.5° (MeOH–$CHCl_3$).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 77.53; H, 8.58.

Deoxyisoajmalal-A (*trans*-III).—Deoxyisoajmaline (1.0 g.) was oxidized with lead tetraacetate, in the same way as described for deoxyajmaline, to yield deoxyisoajmalal-A (510 mg.), m.p. 137–139°. Recrystallization from ethyl acetate–ether raised the melting point to 143–144°, $[\alpha]_D$ +126°, pK_a' 6.17. A sample was dried *in vacuo* at 25° for analysis.

Anal. Calcd. for $C_{20}H_{24}N_2O\cdot 0.5H_2O$: C, 75.67; H, 7.94. Found: C, 76.23; H, 7.83.

Deoxyisoajmalol-A (*trans*-V).—Deoxyisoajmalal-A (100 mg.) was reduced with sodium borohydride (2 × 200 mg. at 1-hour intervals) in 90% aqueous methanol. After removing the solvent, the residue was extracted with methylene chloride and water. After washing, drying and evaporating the methylene chloride, a white foam (100 mg.) was obtained that crystallized from ethanol–ether to afford deoxyisoajmalol-A (56 mg.), m.p. 172–174°, which after recrystallization from ethanol–ether and drying for analysis melted at 175–176, $[\alpha]_D$ +55.3°; λ_{max} 228–229 (37,150), 284–285 (7,300), shld. 277 (6,630), plat. 291–292 (6,570); λ_{min} 251 (2,000).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 76.83; H, 8.15.

Deoxyisoajmalal-B (*trans*-IV).—Epimerization of deoxyisoajmalal-A (453 mg.) gave deoxyisoajmalal-B, m.p. 179–180°, $[\alpha]_D$ +80°.1°, pK_a' 6.17.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84. Found: C, 78.09; H, 7.94.

Deoxyisoajmalol-B (*trans*-VI).—Deoxyisoajmalal-A (453 mg.) was refluxed in methanol (50 ml.) and 0.1 *N* sodium hydroxide (10 ml.) for 1.5 hours. After cooling, methanol (50 ml.) and sodium borohydride (1.0 g.) was added. After stirring 1 hour, sodium borohydride (1 g.) again was added, and the stirring was continued for 1 hour. After dilution with water and partial evaporation of the methanol, the product was extracted into methylene chloride, dried and the solvent evaporated yielding a product (500 mg.) crystallizing from ether to give deoxyisoajmalol-B (440 mg.), m.p. 243–245°. Recrystallization from methanol and drying for analysis raised the m.p. to 245–247°, $[\alpha]_D$ +86°, pK_a' 7.52; λ_{max} 228 (38,200), 283–285 (7,400); shlds. 230 (37,700), 293 (6,600); plat. 289–291 (8,200); λ_{min} 250 (2,000).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.54; H, 8.63; N, 9.28.

Deoxyisoajmalol-B O-tosylate (*trans*-VII) was prepared from deoxyisoajmalol-B as described for the tosylation of deoxyajmalol-B and had m.p. 167–168°.

Anal. Calcd. for $C_{27}H_{32}N_2O_3S$: C, 69.80; H, 6.94. Found: C, 69.87; H, 7.16.

d-trans-**3-Ethyl-1,2,3,4-tetrahydro-12-methyl-2-vinylindolo[2,3-a]quinolizinium Perchlorate** (*trans*-**IX**).—The fission of deoxyisoajmalol-B O-tosylate was carried out as described for the normal series. Thus from the tosyl ester (400 mg.) there was obtained the picrate (150 mg.), m.p. 167–169° from ethanol.

Anal. Calcd. for $C_{26}H_{25}N_5O_7$: C, 60.11; H, 4.85; N, 13.48. Found: C, 59.98; H, 4.97; N, 13.30.

The picrate was converted into the hygroscopic chloride [*via* ion exchange using Amberlite CG45 (Cl^-)] then into the perchlorate, m.p. 167–169°, $[\alpha]_D$ +63.7°, after three crystallizations from ethanol.

d-trans-**2,3-Diethyl-1,2,3,4-tetrahydro-12-methylindolo-[2,3-a]quinolizinium Perchlorate** (*trans*-**X**).—The above chloride salt (80 mg.) was hydrogenated in the presence of Adams catalyst (40 mg.) in ethanol (10 ml.); the theoretical uptake was completed in 20 minutes. The hygroscopic chloride in ethanol was treated with dilute ethanolic perchloric acid and the resulting perchlorate was recrystallized from ethanol to m.p. 201–202°, $[\alpha]_D$ +16.4° and +10.8° (4MeOH–1$CHCl_3$).

Anal. Calcd. for $C_{26}H_{25}N_2 \cdot ClO_4$: C, 61.14; H, 6.41. Found: C, 60.97; H, 6.65.

The Chromium Trioxide–Pyridine Oxidation of Deoxyajmaline O-Acetate.—Deoxyajmaline O-acetate (1.24 g.) in pyridine (20 ml.) was added to chromium trioxide (1.47 g.) in pyridine (30 ml.) cooled in ice. After stirring for 16 hours at room temperature, the solution was diluted with methylene chloride (100 ml.) and passed through a column of basic alumina (38 × 60 mm.); the methylene chloride washings (800 ml.) yielded a residue (0.98 g.). Upon careful rechromatography of this over neutral alumina (28 × 120 mm.) nothing was eluted with methylene chloride. The first 100 ml. of methylene chloride–methanol (200:1) furnished N_a-**demethyl-Δ^1-deoxyajmaline O-acetate** (**XVII**), 181 mg., m.p. 184–185°, $[\alpha]_D$ −12°; λ_{max} 219 (20,800), 258 (5,000); shld. 224 (16,400); λ_{min} 235 (3,500); $\nu_{C=O}$ 1743 $cm.^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19. Found: C, 74.83; H, 7.10; OCH_3, 0.0; NCH_3, 0.0.

The second 100-ml. portion of methylene chloride–methanol (200:1) afforded an amorphous fraction (136 mg.), while the third 100-ml. portion yielded a residue (306 mg.) which furnished, from ether–hexane, **2-hydroxydeoxyajmaline O-acetate** (**XV**), 240 mg., m.p. 95–98° or 182–184°, $[\alpha]_D$ −108°; λ_{max} 244 (8,800), 292 (2,800); λ_{min}, 223 (2,800), 266 (700); $\nu_{C=O}$ 1742 $cm.^{-1}$.

Anal. Calcd. for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66. Found: C, 72.06; H, 7.98.

If this compound (200 mg.) was allowed to stand in dilute alcoholic sodium hydroxide for a few hours, it yielded after working up deoxyajmalal-B (IV), m.p. 208–211°. In qualitative experiments, 2-hydroxydeoxyajmaline O-acetate upon treatment with either lithium aluminum hydride or sodium borohydride gave indoles as judged by the qualitative ultraviolet absorption spectra.

Oxidation of Dideoxyajmaline.—The oxidation of dideoxyajmaline (700 mg.) with chromium trioxide in pyridine was carried out in the same way as described above. In this case, the indolenine came off the column in the methylene chloride eluate and was crystallized from ether–hexane to furnish pure *N_a-demethyl-Δ^1-dideoxyajmaline*, m.p. 188°; λ_{max} 219 (22,100), 256 (5,200); λ_{min} 235 (3,900); λ_{max}^{acid} 220 (16,600), 264 (5,600); λ_{min}, 236 (1,600).

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.67; H, 8.34; N, 10.13.

From the 1% methanolic methylene chloride eluate the amorphous **2-hydroxydideoxy-ajmaline** was isolated and characterized as its diperchlorate, m.p. 340°, from ethanol; λ_{max} 244 (10,900), 292 (3,800); λ_{min} 220 (2,900), 264 (900).

Anal. Calcd. for $C_{26}H_{26}N_2O.2HClO_4$: C, 46.97; H, 5.52; N, 5.48. Found: C, 46.98; H, 5.39; N, 5.15.

Oxidation of 17-Epi-deoxyajmaline O-Acetate.—The acetate (134 mg.) was oxidized in pyridine with chromium trioxide as described for its isomer. After chromatography, there was obtained N_a-**demethyl-Δ^1-17-epi-deoxyajmaline O-acetate**, m.p. 208–209°, from ethyl acetate-ether; λ_{max} 219 (21,800), 258 (4,800), λ_{min} 236 (3,600) λ_{max}^{acid} 221 (20,000), 268 (5,800); λ_{min} 239 (3,100); $\nu_{C=O}$ 1739 $cm.^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19. Found: C, 74.97; H, 7.46; NMe, 0.0.

N_a-**Demethyldeoxyajmalal-B.**—When N_a-demethyl-Δ^1-deoxyajmaline O-acetate (101 mg.) was dissolved in methanol and 2 *N* sodium hydroxide added there was an immediate precipitate. Filtration and crystallization of this product gave the aldehyde, m.p. 265–266°, $[\alpha]_D$ +12° (pyr.), which was sublimed for analysis.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53. Found: C, 77.49; H, 7.83; NMe, 0.0.

The aldehyde was recovered unchanged after refluxing for 1 hour in alcoholic sodium hydroxide.

Deoxydihydrosarpagine (**XXXI**).—Reduction of N_a-demethyldeoxyajmalal-B (420 mg.) with excess sodium borohydride in aqueous methanol gave deoxydihydrosarpagine (348 mg.), m.p. 247–249° from methanol, raised to m.p. 250–251° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 0.5H_2O$: C, 74.72; H, 8.25; N, 9.18. Found: C, 74.78; H, 8.39; N, 9.04.

The alcohol (220 mg.) was refluxed in acetic acid for 2 hours, concentrated to dryness *in vacuo* and put onto a column of alumina in benzene. The benzene and benzene–methylene chloride (1:1) eluates afforded the O-acetyl derivative, m.p. 252–254° from ethanol–ethyl acetate identical in all respects with the corresponding derivative prepared from sarpagine (*vide infra*).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.51; H, 7.94.

N_a-**Demethyl-2-epi-deoxyajmaline O-Acetate** (**XIX**).—N_a-Demethyl-Δ^1-deoxyajmaline O-acetate (1.19 g.) and platinum oxide (330 mg.) in methanol (70 ml.) was shaken in a hydrogen atmosphere under 46 lb. pressure for 2.5 hours. Chromatography of the product over alumina (28 × 100 mm.) gave a methylene chloride eluent (1.05 g.) which from ether yielded the indoline, m.p. 143°, increasing to m.p. 144–145° upon crystallization from ether–hexane. For analysis, a sample was sublimed at 140° *in vacuo*, m.p. 145–146°, $[\alpha]_D$ +3° (5MeOH–2$CHCl_3$); λ_{max} 242 (6,700), 292 (2,600); λ_{min} 222 (2,900), 265 (670).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.37; H, 7.78.

N_a-**Demethyl-2-epi-deoxyajmaline** (**XX**).—The above acetate (1.61 g.) in methanol (50 ml.) was refluxed for 2 hours with 4 *N* sodium hydroxide (20 ml.). After partial evaporation, the residue was extracted into methylene chloride which after concentration and crystallization from ether yielded N_a-demethyl-2-epideoxyajmaline, m.p. 206°, raised after recrystallization from ethanol–ether to m.p. 209–210°, $[\alpha]_D$ +94.3° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16. Found: C, 76.60; H, 8.29.

The methiodide crystallized from ethanol had m.p. 287–288°. The methochloride prepared from the methiodide by filtration through Amberlite CG45 (Cl^-) had m.p. 328–329° dec. from ethanol.

N_a-**Demethyldeoxyajmaline.**—Deoxyajmaline (2.3 g.) was dissolved in dilute hydriodic acid, concentrated to dryness and the salt pyrolyzed (*ca.* 300°) under nitrogen until the bubbling ceased. The resin was extracted into methylene chloride and chromatographed over neutral alumina. Deoxyajmaline (580 mg.) was eluted first followed by the demethyl derivative (80 mg.) which after several crystallizations from methanol had m.p. 307°. Its infrared spectrum was very similar to that of deoxyajmaline but there was an additional sharp band at 3320 $cm.^{-1}$.

Anal. Calcd. for $C_{12}H_{24}N_2O$: C, 77.0; H, 8.2. Found: C, 76.9; H, 8.1.

2-Epi-deoxyajmaline (**XXI**).—N_a-Demethyl-2-epi-deoxyajmaline (100 mg.) in methanol (1 ml.) was heated with methyl iodide (2 ml.) at 110° in a sealed tube for 18 hours. The residue after concentration gave, from ethanol–ethyl acetate, 2-epi-deoxyajmaline methiodide (111 mg.), m.p. 312–315°, constant m.p. 326–328° after two further crystallizations.

Anal. Calcd. for $C_{21}H_{29}IN_2O$: C, 55.76; H, 6.47; NMe, 6.65. Found: C, 55.65; H, 6.55; NMe, 5.03.

The methiodide (2 × 50 mg.) was pyrolyzed at 330° *in vacuo*. The product was resublimed at 195° *in vacuo*, dissolved in methylene chloride, washed with dilute ammonia,

dried and concentrated to dryness. Crystallization of the residue from ethanol–ethyl acetate gave 2-epi-deoxyajmaline (31 mg.), m.p. 241–242°, which upon recrystallization had m.p. 242–243°, $[\alpha]_D$ −9.6° (5MeOH–2$CHCl_3$), pK_a' 7.80.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 77.48; H, 8.46.

N_a-Demethyl-2-epi-dideoxyajmaline.—N_a-Demethyl-Δ^1-dideoxyajmaline (390 mg.) and platinum oxide (200 mg.) in methanol (50 ml.) were shaken for 2 hours in a hydrogen atmosphere under 47 lb. pressure. The crude product was chromatographed over neutral alumina (18 × 70 mm.). The material (260 mg.) eluted with benzene gave from ether–isopropyl ether the pure indoline (115 mg.), m.p. 84–89°, which was air-dried for analysis.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot H_2O$: C, 76.47; H, 8.78. Found: C, 76.59; H, 9.06.

Phenolic-tosyl-O-acetylsarpagine (XXVII).—Tosyl chloride (1.2 g.) was added to a cold solution of O-acetylsarpagine (600 mg.) in pyridine (6 ml.) and kept at 5° for 3 days, then at ambient temperature for 3 days. The pyridine solution was diluted with ice and water and extracted with methylene chloride. The aqueous phase was basified with ammonium hydroxide and extracted with methylene chloride. The combined organic phases were washed with water, dried and evaporated *in vacuo*. The product (929 mg.) gave the tosyl ester (443 mg.), m.p. 120–121° from acetone. From the mother liquors an additional 258 mg., m.p. 117–119°, was isolated.

Anal. Calcd. for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97. Found: C, 66.52; H, 6.28.

O-Acetyldeoxysarpagine (XXVIII).—The above tosyl derivative (474 mg.) in alcohol (25 ml.) was refluxed for 1.5 hours with Raney nickel catalyst (5 ml. of wet powder, *ca.* 3 g.). After filtration, the solvent was removed *in vacuo*. The residue was shaken up with methylene chloride–water and the aqueous phase after basifying was re-extracted with methylene chloride. The combined extracts were washed with water, dried, and evaporated *in vacuo*. The white foam (242 mg.) gave O-acetyldeoxysarpagine (163 mg.), m.p. 213–215°, $\nu_{C=O}$ 1744 cm.$^{-1}$, from ethyl acetate with an additional amount (19 mg.) being obtained from the mother liquors.

Anal. Calcd. for $C_{21}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 73.98; H, 7.24. Found: C, 74.21; H, 7.25.

N_a-Methyl-O-acetyldeoxysarpagine (XXIX).—Ammonia (*ca.* 35 ml.) was distilled from excess sodium into a dry 3-necked flask (50 ml.) containing a trace of ferric chloride (5–10 mg.). Freshly cut sodium (22 mg.) was inserted and after the solution became colorless, O-acetyldeoxysarpagine (282 mg.) was added, then a solution of methyl iodide (0.058 ml.) in ether (1 ml.). After several minutes stirring, a precipitate began to form. The ammonia was allowed to evaporate first at room temperature and finally under reduced pressure. The residue was separated from the inorganic material by extraction into methylene chloride and furnished a crude product (300 mg.) which upon crystallization from alcohol gave the N_a-methyl derivative (122 mg.), m.p. 171–173°. Sublimation for analysis raised the m.p. to 172–176°, $\nu_{C=O}$ 1746 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{26}N_2O_2 \cdot 0.25\ H_2O$: C, 74.44; H, 7.53. Found: C, 74.65; H, 7.42.

N_a-Methyldeoxysarpagine (XXX).—The above O-acetyl compound (183 mg.) stood overnight in alcohol (4 ml.) and 1 *N* sodium hydroxide (0.52 ml.). After concentration, the residue was extracted into methylene chloride, dried and evaporated. The product (176 mg.) gave from ethyl acetate the N_a-methyldeoxysarpagine (148 mg.), which softens and foams at 110–120° then resolidifies and melts at 190–192°.

Anal. Calcd. for $C_{20}H_{24}N_2O \cdot 0.25\ H_2O$: C, 76.74; H, 7.83. Found: C, 77.04; H, 8.10.

Dihydrosarpagine (XXXI).—Sarpagine (1.1 g.) was added to palladium black (2 g.) in alcohol (120 ml.) and shaken with hydrogen at 3 atmospheres pressure at room temperature for 65 hours and at 65° for 7 hours. After filtration and evaporation, the solid was filtered in 12.5% ethanol in methylene chloride through neutral alumina (3 × 6 cm.). The eluate (1.0 g.) crystallized from ethanol to furnish dehydrosarpagine (811 mg.), m.p. 350°, $[\alpha]_D$ +31°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2 \cdot C_2H_5OH$: C, 70.36; H, 8.44. Found: C, 70.26; H, 8.63.

Acetylation using acetic anhydride in pyridine gave O,O-diacetyldihydrosarpagine, m.p. 261–263° from benzene, $[\alpha]_D$ −22° (pyr.) (lit.[29] m.p. 268–271°, $[\alpha]_D$ −23°).

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12. Found: C, 69.48; H, 7.25.

O-Acetyldihydrosarpagine (XXXII).—Dihydrosarpagine (796 mg.) in acetic acid (40 ml.) was refluxed for 4.5 hours. Most of the acid was removed *in vacuo* and the residue was dissolved in water and brought to *ca.* *p*H 7 with sodium bicarbonate. The precipitated O-acetyldihydrosarpagine (655 mg.) was filtered off and crystallized from benzene; m.p. 272-273°. Recrystallization and drying raised the m.p. to 277–278°, $[\alpha]_D$ +29°.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39. Found: C, 70.85; H, 7.39.

O-Acetyldeoxydihydrosarpagine (XXXIV).—O-Acetyldihydrosarpagine (300 mg.) was tosylated as described for the analogous case above. The crude product (508 mg.) which crystallized from ethyl acetate afforded phenolic tosyl-O-acetyldihydrosarpagine (XXXIII) (337 mg.). This derivative (270 mg.) was refluxed with Raney nickel (3 ml., wet wt. 1.8 g.) in alcohol (15 ml.) for 1.75 hours. The catalyst was filtered off and the solvent removed *in vacuo*. Crystallization of the residue (130 mg.) from ethanol–ethyl acetate furnished O-acetyldihydrodeoxysarpagine (90 mg.), m.p. 243–247°, which after three further recrystallizations had m.p. 253–254°, $[\alpha]_D$ + 1.3°.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.71; H, 7.70.

Deoxyajmalol-B (VI).—O-Acetyldihydrodeoxysarpagine (70 mg.) was N_a-methylated by exactly the same method as that described for O-acetyldeoxysarpagine (see above). N_a-Methyl-O-acetyldihydrosarpagine was an oil (70 mg.) which could not be induced to crystallize. It was put down a column of neutral alumina (activity II), using benzene–methylene chloride (1:1) as eluent, to yield a non-crystallizable oil (50 mg.) with a $\nu_{C=O}$ 1740 cm.$^{-1}$. The oil was allowed to stand overnight in alcohol (2 ml.) containing one mole equivalent of 1 *N* sodium hydroxide. The solvent was removed and the residue extracted with methylene chloride, which gave the crude alcohol (47 mg.); crystallizing from ether yielding the deoxyajmalol-B (28 mg.), m.p. 211–213°. This was raised to m.p. 213–214°, $[\alpha]_D$ +2° from ethanol. The infrared spectrum of this alcohol was identical in all respects with deoxyajmalol-B prepared from ajmaline and their mixed m.p. showed no depression.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 76.52; H, 8.54.

The Thioacetal from Ajmalicine Hemiacetal.—Hemiacetal (100 mg.) was dissolved in ethane dithiol (0.3 ml.) by trituration with a glass rod. BF_3-ether (0.3 ml.) was added and triturated to get a clear solution. The solution was kept at room temperature for an hour. Water and either potassium hydroxide or ammonia was added and extracted with chloroform. The chloroform layer was washed several times with dilute potassium hydroxide. The chloroform on removal gave a sticky, crystalline substance. Chromatography over alumina and elution with ether containing 2% methanol gave crystals (75 mg.), m.p. 225–230° dec. Two recrystallizations from dilute methanol yielded magnificent crystals of the thioacetal, m.p. 228–230°, $[\alpha]_D$ +7.3° (pr).

Anal. Calcd. for $C_{21}H_{28}S_2ON_2$: C, 64.93; H, 7.28; N, 7.21. Found: C, 64.84; H, 7.48; N, 6.99.

Dihydrocorynantheane from Ajmalicine.[36]—To ajmaliciol (75 mg.) in dry benzene (6 ml.) freshly distilled cyclohexanone (4 ml.) and aluminum phenoxide (0.5 g.) were added. After refluxing under nitrogen for 8 hours, the cooled solution was extracted with several portions of 2 *N* sulfuric acid which was then washed with ether, made basic and extracted with ether. After drying and concentration the residue was chromatographed over alumina. The benzene–ether (1:2) eluent

(36) This modification led to higher yields of dihydrocoryantheane than previously reported (ref. 17a). The oxidation is based on a milder procedure used by S. Kimoto, M. Okamoto and H. Kondo [*Chem. Pharm. Bull. Japan*, **7**, 650 (1959)] for their preparation of yohimbinone from yohimbine.

urnished 18,19-dihydro-19-corynantheone[37] (31 mg.), m.p. 223–25°. Further elution with ether–methanol (9:1) gave ajmaliciol (32 mg.).

The ketone so obtained was exposed to a Wolff–Kishner reduction as described previously[17a] except that the reaction time was reduced from 4 to 3.25 hours resulting in a consistent 62% yield of dihydrocorynantheane.

N_a-Methylyohimbane.[38]—To yohimbane (60 mg.) in dry benzene (4 ml.) potassium (10 mg.) was added and the mixture was stirred under reflux in a nitrogen atmosphere for several hours, until the metal was consumed. The suspension was cooled to room temperature and treated with an excess of methyl iodide in benzene. The reaction mixture was stirred overnight and the precipitate (120 mg.) of potassium iodide and N_a-methylyohimbane methiodide was collected and dried. When this mixture (40 mg.) was heated at 280–300° *in vacuo*, it gave a sublimate which afforded N_a-methylylohimbane, m.p. 178–179° (lit. 179°) from methanol. The total yield after processing all the salt mixture was 38 mg.

N_a-Methylylohimbane with excess methyl iodide in benzene gave the methiodide, m.p. 287–288° (lit. 288–289°). Repetition of the above vacuum pyrolysis at 280–300° regenerated the tertiary base.

N_a-Methyldihydrocorynantheane.—Following the procedure described above, dihydrocorynantheane (10 mg.) in dry benzene (4 ml.) was treated with potassium (6 mg.). Two additions of methyl iodide (0.5 ml.) at 45-minute intervals to the resulting potassium salt gave after 15 hours a white precipitate (20 mg.). Pyrolysis of this *in vacuo* at 340° gave a crystalline sublimate (6 mg.) which afforded N_a-methyldihydrocorynantheane, m.p. 109–110.5°, $[\alpha]_D$ −22°, from aqueous methanol.

Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. Found: C, 79.71; H, 9.52; N, 9.24.

N_a-Methylcorynantheidane.—Corynantheidane (60 mg.) was converted by the procedure above into its potassium derivative in dry benzene and alkylated with excess methyl iodide. A portion (50 mg.) of the crude salt mixture (127 mg.) was vacuum pyrolyzed at 280–320° to furnish an oily sublimate. This was dissolved in 5% acetic acid and treated with a few drops of perchloric acid to give N_a-methylcorynantheidane perchlorate (25 mg.), m.p. 208–210° after recrystallization from methanol.

Anal. Calcd. for $C_{20}H_{28}N_2 \cdot ClO_4 \cdot CH_3OH$: C, 57.78; H, 7.89. Found: C, 57.54; H, 7.48.

N_a-Methyl-3,4,5,6-tetradehydroyohimbane Perchlorate. (a).—N_a-Methylyohimbane (20 mg.) was catalytically dehydrogenated in an aqueous solution on a steam-bath by palladium black (10 mg.) using maleic acid (40 mg.) as an acceptor. The hot reaction mixture was filtered and gave upon addition of perchloric acid N_a-methyl-3,4,5,6-tetradehydroyohimbane perchlorate, m.p. 250–251°.

(b).—3,4,5,6-Tetradehydroyohimbane perchlorate (20 mg.) was dissolved in a small volume of methanol and treated with a few drops of 10% sodium hydroxide. The deep yellow solution was diluted with water until a precipitate began to form and then was extracted with ether. The extract was dried, evaporated and the residue in dry benzene was treated with 2 drops of methyl *p*-toluenesulfonate. The resultant precipitate (9 mg.) had m.p. 205°. It was dissolved in a minimum of methanol and treated with perchloric acid to furnish N_a-methyl-3,4,5,6-tetradehydroyohimbane perchlorate, m.p. 250–251° after crystallization from methanol. The perchlorate could also be obtained by passing a solution of the *p*-toluenesulfonate through a column of Amberlite resin [CG45 (ClO_4)].

Anal. Calcd. for $C_{20}H_{28}N_2 \cdot ClO_4$: C, 59.64; H, 6.43; N, 6.62. Found: C, 59.37; H, 6.24; N, 6.58.

***d-trans*-2,3-Diethyl-1,2,3,4-tetrahydro-12-methylindolo-[2,3-*a*]quinolizinium Perchlorate (*trans*-X).** (a).—N_a-Methyldihydrocorynantheane (5 mg.), maleic acid (10 mg.) and palladium black (4 mg.) were heated in water on a steam-bath with stirring for 13 hours. Filtration and then addition of perchloric acid to the cooled solution gave the perchlorate (4 mg.), m.p. 198–200°, $[\alpha]_D$ +15°, after crystallization from aqueous methanol.

(b).—Dihydrocorynantheane (90 mg.) was heated in a sealed evacuated tube with palladium black (90 mg.), maleic acid (200 mg.) and water (4 ml.) for 36 hours, when the ultraviolet absorption spectrum indicated that conversion to the tetradehydro compound was complete. After filtration and basifying with 25% sodium hydroxide, the anhydro compound was extracted into methylene chloride which was dried and evaporated. The residue was heated with methyl bromide for 10 minutes in a sealed tube at 100°, then dissolved in water and a drop of perchloric acid was added. The perchlorate recrystallized from aqueous ethanol had m.p. 200°, $[\alpha]_D$ +5° (4MeOH–1$CHCl_3$).

Anal. Calcd. for $C_{20}H_{28}N_2 \cdot ClO_4$: C, 61.14; H, 6.41. Found: C, 61.4; H, 6.5.

Both synthetic samples had infrared spectra identical with the degradation product of isoajmaline and the mixed m.p.'s showed no depression.

1-*cis*-2,3-Diethyl-1,2,3,4-tetrahydro-12-methylindolo[2,3-*a*]quinolizinium Perchlorate (X).—A portion (30 mg.) of the salt mixture obtained above from the methylation of corynantheidane was vacuum pyrolyzed at 300–340°. The oily sublimate was dissolved in alcohol and added to an aqueous solution of maleic acid (60 mg.) and suspended palladium black (20 mg.). The whole was heated on a steam-bath for 16 hours. The solution was filtered hot and the filtrate plus hot water washings were concentrated to remove most of the ethanol. The cooled solution was treated with perchloric acid to yield the β-carbolinium perchlorate (13 mg.). Recrystallization from aqueous methanol gave the pure salt, m.p. 212–214°, $[\alpha]_D$ −27° ($CHCl_3$). The infrared spectrum was identical with the degradation product derived from ajmaline and the mixed m.p. showed no depression.

(37) This ketone was refluxed in methanolic sodium methoxide and recovered unchanged. As a consequence, its previously assumed stereochemistry (*vide iii*) has been corroborated.

(38) Similar to a procedure described by B. Witkop [*J. Am. Chem. Soc.*, **76**, 3361 (1953)] for the same compound.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

The Preparation and Properties of Some Methoxypyrroles

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RECEIVED MAY 11, 1961

Using ethyl glycinate-1-^{14}C derivatives, a series of cyclizations by which these compounds yield 3-pyrrolidones has been shown to involve the carbonyl and not the methylene group of the glycine residue. Dimethyl ketals or methoxypyrrolines derived from these pyrrolidones give methoxypyrrolecarboxylic acids on catalytic dehydrogenation. From these acids and others, several unsymmetrical dipyrryl ketones also have been prepared. A comparison of the spectral properties of these compounds with those of the prodigiosin precursor showed that the prodigiosin precursor could not be a methoxydipyrryl ketone.

At one stage prior to the synthesis of prodigiosin,[2] we had considered various approaches to the synthesis of the then postulated tripyrrylmethene structure I, for prodigiosin. The key substance

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(2) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962).