

*Ajmaline. Part I.*

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[Reprint Order No. 4734.]

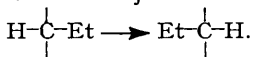
The most abundant alkaloid of *Rauwolfia serpentina*, Benth., namely, ajmaline,  $C_{20}H_{26}O_2N_2$ , has been further investigated.

On vigorous decomposition (soda-lime or zinc dust distillation) it affords *ind-N*-methylharman, carbazole, and simpler indole derivatives. A benzene nucleus represents the sole unsaturated group (hexahydroajmaline) and a dihydroindole structure is indicated by colour reactions and the ultra-violet absorption.

A group  $\cdot N\cdot CH(OH)\cdot$  is recognised (*a*) by transformation of the oxime into a nitrile (infra-red and hydrolysis), (*b*) by study of *N*-methylajmaline (CO infra-red band) which by a series of processes can be converted into monodeoxyajmaline,  $C_{20}H_{26}ON_2$  ( $\cdot N\cdot CH_2$ ), and (*c*) by application of Huang-Minlon's modification of the Wolff-Kishner reduction process to ajmaline and some of its derivatives, whereby  $\cdot N\cdot CH(OH)\cdot$  yields  $\cdot NH\ CH_3\cdot$  (deoxydihydroajmaline from ajmaline, deoxyoctahydroajmaline from hexahydroajmaline, and so on). This  $\cdot N\cdot CH(OH)\cdot$  group confers properties on the base which are not those hitherto associated with carbinol-amines: *e.g.*, ajmaline is a strong base and the hydroxyl group can be acylated.

The second oxygen is also contained in a hydroxyl group (diacetylajmaline, infra-red absorption of deoxydihydroajmaline, etc.), and the stability of deoxyoctahydroajmaline towards chromic acid suggests that the second hydroxyl is tertiary—this point is not certainly established. On oxidation of deoxydihydroajmaline with chromic acid, a significant quantity of ethyl methyl ketone was obtained: this proves that the reduced base contains the group  $-CHMeEt$  and, as the *C*-Me value was notably increased on passage from ajmaline to deoxydihydroajmaline, ajmaline must contain  $\cdot N\cdot CH(OH)\cdot CHEt$ .

Such a unit in the structure is strongly suggestive of a Woodward fission of ring  $\epsilon$  (yohimbine skeleton), and a consideration of congeneric alkaloids as well as the degradation to a harman derivative shows that ajmaline falls in the  $\alpha$  (yohimbine) rather than the  $\beta$  (strychnine) class of indole alkaloids. A structure is tentatively advanced, but further work is necessary in order to determine the points of attachment of the second hydroxyl group, and carbon atoms numbered 2 and 3, in the benzene ring of the presumed phenylalanine progenitor. *isoAjmaline*, obtainable from ajmaline by the action of heat or alkalis, and also of natural occurrence, affords a series of derivatives similar to those of ajmaline. It is regarded as a stereoisomeride of ajmaline:



ALTHOUGH more than forty *Rauwolfia* species have been described, *R. serpentina*, Benth. (syn. *Ophioxylum serpentinum*, Willd.) is the only one with a long history of medical use.

It is mentioned in the older Indian literature (Charaka) as a febrifuge, a remedy for snake-bites, and a cure for dysentery. Its reputation extended to Europe by 1690 (Rumphius) and in the "Herbarium Amboinense" (1741), it was stated that *serpentina* root "valet contra anxietatem." There is no mention of this hypnotic and sedative property in the older Indian literature but the drug has long been popularly used in Bihar as a hypnotic for children. Its most important action, in reducing the blood pressure, was established in 1931—1933 by Indian pharmacologists (Chopra, Gupta, and Mukherjee, *Indian J. Med. Res.*, 1933, 21, 261; cf. *ibid.*, 1937, 24, 1125; 1941, 29, 763; 1942, 30, 319; 1943, 31, 71). The drug has acquired a reputation, especially in India, as a remedy for insomnia, hypochondria, and even for some forms of insanity, and more recently the

intensification of the study of its chemistry and pharmacology has led to important results.

It had already been noted that extracts made from plants grown in Bihar were more active as a sedative than those originating in Dehra Dun, whereas the reverse was held to be true in respect of the treatment of insanity. This indicated the specific action of one or more variable constituents and it is now known that the roots contain at least fifteen different alkaloids. Recently the alkaloidal constituent (reserpine) claimed to be chiefly responsible for the sedative and hypertensive actions has been examined (Müller, Schlittler, and Bein, *Experientia*, 1952, **8**, 358. Full paper; Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Müller, Schlittler, Schwyzer, and St. Audré, *Helv. Chim. Acta*, 1954, **37**, 59). The pharmacology of the group has also been closely studied by Raymond-Hamet (*Compt. rend.*, 1935, **201**, 1050; 1939, **209**, 384, 599; *Compt. rend. Soc. biol.*, 1938, **129**, 462; 1939, **132**, 213).

A chemical investigation of *R. serpentina* was made by van Itallie and Steenhauer (*Arch. Pharm.*, 1932, **270**, 313) who isolated rauwolfine,  $C_{21}H_{26}O_2N_2$ , and two other bases, from the roots. Rauwolfine on distillation with zinc dust in a stream of hydrogen was stated to yield ammonia, scatole, quinoline, and carbazole, but these claims were substantiated only by a few colour reactions and ultra-violet spectra.

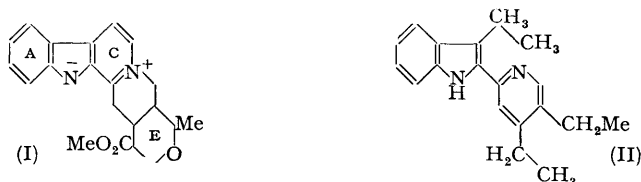
Approximately simultaneously, Siddiqui and Siddiqui (*J. Indian Chem. Soc.*, 1931, **8**, 667; 1932, **9**, 539; 1935, **12**, 37; R. H. Siddiqui, Inaug. Diss., Aligarh, 1934) made important contributions and isolated ajmaline,  $C_{20}H_{26}O_2N_2$ , and five other bases from the same botanical material.

There can be no doubt but that ajmaline is the rauwolfine of van Itallie and Steenhauer and the name rauwolfine should be reserved for the alkaloid,  $C_{20}H_{26}O_3N_2$ , isolated by Koepfli from *R. caffra*, Sonder (*J. Amer. Chem. Soc.*, 1932, **54**, 2412). This conclusion follows from a comparison of the properties of the rauwolfine of van Itallie and Steenhauer and the ajmaline of the Siddiquis as well as those of *isorauwolfine* and *isoajmaline*. R. H. Siddiqui (*op. cit.*) reproduces a sketch of a single crystal of rauwolfine hydrochloride made by Dr. L. H. Sitter (van Itallie and Steenhauer, *Pharm. Weekblad*, 1932, **14**, 341) which he states entirely agrees in form with his ajmaline hydrochloride.

In our own investigations no base,  $C_{21}H_{26}O_2N_2$ , resembling ajmaline,  $C_{20}H_{26}O_2N_2$ , has been encountered. *isoAjmaline* has been found by S. Siddiqui as a constituent of *R. serpentina* collected in the Dunn valley (*J. Indian Chem. Soc.*, 1939, **16**, 421) and this was accompanied by *neoajmaline*,  $C_{20}H_{26}O_2N_2$ .

A specimen of *neoajmaline* hydrochloride was kindly given to us by Dr. Siddiqui but we are unable to distinguish it from ajmaline with any certainty. One recrystallisation gave ajmaline hydrochloride and the m. p. 205—207°, quoted for *neoajmaline*, is that of anhydrous ajmaline.

A survey of *Rauwolfia* and closely related genera of the apocynaceae shows that the most usual skeleton of their indole alkaloids is of  $\alpha$ -type (yohimbine) rather than of  $\beta$ -type (strychnine).\*



In particular a major alkaloid of *R. serpentina* is serpentine and a recent study (Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463; Bader and Schwarz, *ibid.*, 1952, **35**, 1594) has shown that this base is  $C_{21}H_{22}O_3N_2$  (replacing the  $C_{20}H_{20}O_3N_2$  of Siddiqui and Siddiqui), that it contains a methoxycarbonyl group, and that it yields alstyrine (II) on selenium dehydrogenation. The constitution (I) was proposed (*loc. cit.*) for serpentine, with reservations in regard to ring E. In any case the formation of alstyrine

\* One of us (E. S.) has recently identified yohimbine itself as an alkaloid of *R. serpentina*.

(Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390; 1950, **33**, 100) demonstrates that serpentine is of  $\alpha$ -type and reference to this fact is made in the sequel.

The *R. serpentina* roots used in our work were collected in India through CIBA (Bombay). The material has been worked up on a considerable scale and new methods have been developed in this connexion. A brief account of the isolation of ajmaline is included in the Experimental section, and one of us (E. S.) with his colleagues is engaged in a comprehensive study of the alkaloids contained in the other fractions, as well as of those of different *Rauwolfia* species.

In general, the work of Siddiqui and Siddiqui has been confirmed although the interpretation of their results must often be changed. For example, their dibromoajmaline is bromoajmaline hydrobromide. Ajmaline exhibits colour reactions characteristic of alkylated anilines with a free *p*-position and its ultra-violet absorption (see Figure) resembles that of many 2 : 3-dihydroindole derivatives. It is, for example, closely similar to that of hexahydro-9 : 11-dimethylcarbazole examined by M. F. Millson (Thesis, Oxford, 1951).

On catalytic hydrogenation it affords a perhydro-derivative showing no characteristic ultra-violet absorption or colour reactions.

The benzene nucleus is remarkably easily reduced and this led us in our earlier work to suspect the presence of a double bond. However, there is no unsaturation apart from that of the benzene ring.

On the convention that N(*a*) is attached to the benzene ring, N(*b*) is the basic nitrogen. Thus ajmaline metho-salts exhibit the usual colour reactions, proving that N(*a*) has not been quaternised. As regards the functions of the oxygen atoms we were at first inclined to the view that a semiacetal group  $\cdot\text{O}\cdot\text{CH}(\text{OH})\cdot$ , was present (Mukherjee, Robinson, and Schlittler, *Experientia*, 1949, **5**, 215). This seemed to follow from the formation of ajmaline oxime, the power of ajmaline to reduce ammoniacal silver solutions, and the fact that ajmaline *appeared* to give a positive response in the Angeli-Rimini reaction for aldehydes. We have not, however, in later work established conditions under which this last test succeeds and we suspect the intervention of acetaldehyde, not on its own account, but as a link between ajmaline and the benzenesulphonylhydroxylamine.

This semiacetal hypothesis involved some special theory for diacetylajmaline, for example, that it contains  $\geq\text{C}\cdot\text{OAc}$  and  $\text{AcO}\cdot\text{CH}\cdot\text{C}<$ . However, diacetylajmaline shows no infra-red absorption band corresponding to the latter unsaturated structure, nor one for  $\text{:N}\cdot\text{COMe}$ . It is a weak base forming a N(*b*)-methiodide (colour reactions); its  $\text{p}K_{\text{a}}$  was found to be 4.9, which is close to that of *neostrychnidine* (4.6). It can be hydrolysed to ajmaline by acids or alkalis, or by treatment with lithium aluminium hydride, observations which tell against the assumption that  $\text{:N}\cdot\text{COMe}$  is contained in the diacetyl derivative. Similar observations were made with diacetylhexahydroajmaline and it is very significant that this substance could be prepared not only by acetylation of hexahydroajmaline but also by catalytic reduction of diacetylajmaline.

It seems certain that ajmaline contains two hydroxyl groups, capable of acetylation. R. H. Siddiqui (*op. cit.*) found by Zerewitinoff's procedure two active hydrogen atoms in ajmaline dried at 100° and one after drying at 150°. We have examined the methanol compound,  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2\cdot\text{CH}_4\text{O}$  and found three active hydrogen atoms.

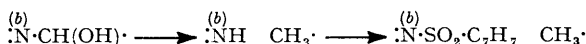
Further experiments have confirmed the presence of a reducing group but it is now regarded as  $\text{:N}\cdot\text{CH}(\text{OH})\cdot$ , though the carbinol-amine must be of a most unusual kind. The following three lines converge on this point.

(1) Ajmaline oxime hydrochloride, treated with acetic anhydride, acetic acid, and hydrogen chloride at room temperature furnished a salt,  $\text{C}_{20}\text{H}_{25}\text{N}_3(\text{OAc})_2\cdot 2\text{HCl}$ . Alternatively this may be acetylanhydroajmaline dihydrochloride with 1AcOH of solvation. When treated with methanol and a little potassium hydroxide this salt gave a beautifully crystalline base, anhydroajmaline oxime,  $\text{C}_{20}\text{H}_{25}\text{ON}_3$ , which exhibits the characteristic infra-red absorption band for a  $-\text{CN}$  group (and absence of a CO frequency) and a band for OH or NH. On hydrolysis with concentrated hydrochloric acid it gave the salt,  $\text{C}_{20}\text{H}_{26}\text{O}_3\text{N}_2\cdot 2\text{HCl}$ , of an amphoteric base, as well as ammonium chloride. Lactamisation of this imino-acid was not found possible, probably because N(*b*) would be at the apex of a bridged-ring system in the hypothetical amide which would result. On reduction with

lithium aluminium hydride, anhydroajmaline oxime was reconverted into ajmaline, which is not itself reduced by this reagent. It is evident that ajmaline contains a latent aldehyde group which could on this evidence be  $\cdot\text{O}\cdot\text{CH}(\text{OH})\cdot$  or  $\cdot\text{N}\cdot\text{CH}(\text{OH})\cdot$ . But on treatment with methyl iodide, anhydroajmaline oxime was converted into anhydro-*N*-methylajmaline oxime hydriodide, which was not a quaternary salt since its aqueous solution gave an immediate precipitate of a base on the addition of dilute ammonia. Hence anhydroajmaline oxime appears to be a secondary base and the group  $\cdot\text{N}\cdot\text{CH}(\text{OH})\cdot$  is indicated as present in ajmaline.

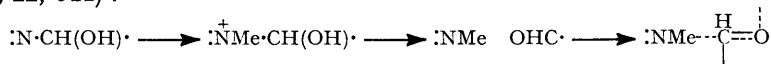
(2) When ajmaline was subjected to the Huang-Minlon modification of the Wolff-Kishner reduction method, it was converted in  $>90\%$  yield into a deoxydihydroajmaline ( $\text{p}K_a$  8.25; ajmaline, 8.15). Kuhn-Roth determinations show that ajmaline contains one *C*-Me group, and deoxydihydroajmaline two. The reduction product is also a secondary base: with methyl iodide it yields an *N*-methyl-hydriodide, giving a precipitate in aqueous solution with ammonia; it afforded an amorphous *N*-acetyl and a crystalline toluene-*p*-sulphonyl derivative ( $\text{p}K_a < 2.5$ ) which still exhibit the typical colour reactions showing that N(*a*) is not involved.

This evidence is almost conclusive in favour of the scheme:



Hexahydroajmaline was similarly reduced to deoxyoctahydroajmaline, which base was also prepared by catalytic reduction of deoxydihydroajmaline.

(3) Ajmaline methiodide behaves on titration as the salt of a strong base of  $\text{p}K_a$  9.2, rather than as a true quaternary salt. The glass obtained on distillation of this base gave a strong carbonyl band at  $5.80 \mu$  and a weak band at  $5.92 \mu$ , showing presence of a conjugated carbonyl group. In chloroform solutions the band at  $5.80 \mu$  became weak and that at  $5.93 \mu$  strong. This interesting behaviour is explicable on the hypothesis that  $\cdot\text{NMe}$  and  $\text{OHC}\cdot$  are present in the glass but that their approach for conjugation is hindered. This is facilitated by dissolution in chloroform (cf. Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 22, 944):



We were thus compelled to accept the carbinol-amine nature of ajmaline which was considered and rejected at an early stage because the base shows so little resemblance in its behaviour to other carbinol-amines, such as cotarnine or  $\psi$ -strychnine. For example, ajmaline is not reduced by zinc dust and boiling dilute hydrochloric acid and it forms *O*-acyl derivatives without fission. The base strength of ajmaline is much greater than would have been predicted.

The condensation reactions, occurring so readily in other cases, either do not occur or are difficult to interpret. Thus ajmaline forms a compound with methanol which is probably  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2\cdot\text{MeOH}$ . But it could be  $\text{C}_{20}\text{H}_{25}\text{O}(\text{OMe})\text{N}_2\cdot\text{H}_2\text{O}$ . It is proposed to devote further attention to this topic. With sulphur dioxide, a compound  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2\cdot\text{H}_2\text{SO}_3\cdot\text{H}_2\text{O}$  was obtained and it is similarly difficult to determine whether this is truly the betaine of a sulphonic acid:  $\cdot\text{N}\cdot\text{CH}(\text{OH})\cdot \longrightarrow \overset{+}{\text{N}}\text{H}_2 \bar{\text{O}}_3\text{S}\cdot\text{CH}(\text{OH})\cdot$ . It might be the hydrogen sulphite of the base. Neither ajmaline nor any of its derivatives responds to the test by *m*-dinitrobenzene and methanolic alkali. This we regarded as

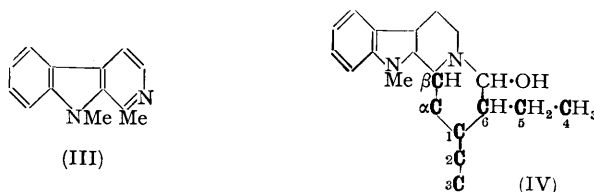
evidence that the group  $\cdot\text{N}\cdot\text{CH}(\text{OH})\cdot\overset{\text{C}}{\underset{\text{C}}{\text{C}}}$  was present in the molecule. For reasons

mentioned below we have now abandoned this deduction from negative evidence in favour of a different conclusion from positive evidence.

*iso*Ajmaline, which is produced from ajmaline by the action of heat or of hot alcoholic alkali, shows the same ultra-violet and infra-red absorption spectra as ajmaline and affords an entirely parallel series of derivatives. The substances are clearly stereoisomerides. Whereas deoxydihydro-*N*-methylajmaline could not be crystallised, the corresponding deoxydihydro-*N*-methyl*iso*ajmaline,  $\text{C}_{21}\text{H}_{30}\text{ON}_2$ , had m. p.  $129-130^\circ$ .

Although deoxyajmaline cannot be obtained by direct reduction of the base, we have made it indirectly, following methods used for the first preparations of *neostrychnidine* and *neostrychnine*. *N*-Methyl-*sec*.-ajmaline [ $\text{:NMe}(b) \text{OCH}\cdot$ ] was reduced by lithium aluminium hydride or potassium borohydride, and the product isolated as a hydriodide ( $\text{:NHMe}\{\text{I HO}\cdot\text{CH}_2\cdot$ ). This was converted by boiling aqueous hydrobromic acid into a quaternary salt ( $\text{:NMe}\cdot\text{CH}_2\cdot$ ), and the related chloride was pyrolysed to deoxyajmaline ( $\text{:N}\cdot\text{CH}_2\cdot$ ).

Degradations of ajmaline were undertaken in the early stages of our work. Heating with soda-lime at 280–300° gave some indolaceous material, the Ehrlich reaction of which suggested  $\beta$ -substitution, also a little crude carbazole, recognised by colour tests, and as main product *ind-N*-methylharman (III). A new synthesis of this substance was effected, in that harman was methylated by treatment with potassamide and then methyl iodide in liquid ammonia solution. The  $\text{:NMe}$  which ajmaline contains is therefore  $\text{:N}(a)\text{Me}$ . Distillation of ajmaline over zinc dust in a stream of hydrogen at about 380° afforded *ind-N*-methylharman and carbazole in about equal amounts. In this case the carbazole could be purified and characterised. These results have been mentioned in a preliminary account (Mukherjee, Robinson, and Schlittler, *loc. cit.*). More recently we have found that the oxidation of deoxydihydroajmaline or deoxydihydro*iso*ajmaline with chromic acid affords



ethyl methyl ketone. This enables us to write  $\cdot\text{CHMeEt}$  as a unit of the structure of deoxydihydroajmaline. Since the formation of the deoxydihydro-bases involves N–C fission and appearance of a new C–Me group, the only possibilities for ajmaline are (i)  $\text{:N}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CHMe}\cdot$  and (ii)  $\text{:N}\cdot\text{CH}(\text{OH})\cdot\text{CHEt}\cdot$ . For purposes of further discussion we adopt (ii) because it is in better accord than (i) with the usual indole-alkaloid skeleton and because it helps us to understand the ajmaline  $\rightarrow$  *iso*ajmaline transformation. The latter is plausibly an inversion of the group  $-\text{CHEt}-$  brought about by its direct union with the potential aldehyde group.

A part structure (IV) can now be set down on the basis of *ind-N*-methylharman and ethyl methyl ketone. The carbon atoms in heavy type are those of a phenylalanine progenitor on Woodward's hypothesis of strychnine biogenesis and they are numbered accordingly (cf. *Nature*, 1948, 162, 155).

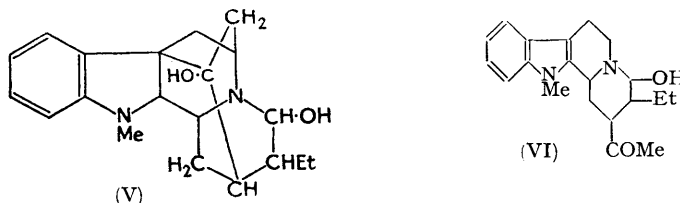
The second hydroxyl group of ajmaline is retained in deoxyoctahydroajmaline and it has been found that this substance can be recovered unchanged after treatment with chromic acid. This evidence, though not conclusive, tends to show that the hydroxyl group in question is tertiary. But this group is also resistant to thionyl chloride and several other reagents designed to replace it or to dehydrate the molecule. This behaviour recalls that of *apocamphan-1-ol* (Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, 61, 3185) and it is probable that, as in this substance, the second (tertiary) hydroxyl group of ajmaline is at the apex of a bridged-ring structure and is protected from inversion replacement.

Accepting this for the present we find that the hydroxyl group and the two additional rings can be accommodated in the structure (V), which is provisionally advanced as the best representation of the chemistry of the alkaloid possible at this date.

Biogenetically (V) could arise from (VI), or some such structure; and (V) gives a model in which the appearance of unsaturation between N(*b*) and CH(OH), *i.e.*, a group  $\text{:N}(b)\cdot\text{CH}\cdot$ , is seen to be difficult—this may account for the unusual character of the  $\text{:N}(b)\cdot\text{CH}(\text{OH})\cdot$  in ajmaline.

It remains to mention that A. Chatterjee and S. Bose have recently published a

discussion (*Experientia*, 1953, 9, 254) of the structure of ajmaline which is based on our preliminary account together with some new facts. These authors claim to have observed 20% carbonyl absorption in the infra-red region ( $5.82 \mu$ ). The conditions of their experiments may be different from ours, but neither in Nujol suspension nor in chloroform solution have we seen such a band. It is of course quite in line with our views, but we have not found it. We are also unable to confirm the alleged bands at  $7.24 \mu$  (CMe) and at  $9.0 \mu$  (ether bridge). The formula suggested by Chatterjee and Bose is one that we have considered and discarded. We had already disclosed (*loc. cit.*) the formation of *ind-N*-methylharman on drastic treatment of ajmaline; Chatterjee and Bose find that it is a product of dehydrogenation of ajmaline by selenium at  $300^\circ$ .



Finally it should be mentioned that stereoisomerism due to the secondary alcoholic group has not yet been observed. The cause could be either great lability or great stability and we propose to examine carefully this aspect of the chemistry of the base.

#### EXPERIMENTAL

*Isolation of Ajmaline.*—The ground bark of *Rauwolfia serpentina*, Benth. (300 kg.), was extracted with methanol and on removal of the solvent *in vacuo* gave a brown-yellow, viscous residue (30 kg.). This was mixed with "Hyflo" \* (20 kg.) and repeatedly triturated with water (total, 380 l.). The easily separated aqueous extract (*ca.* 300 l.) was dark brown and extremely bitter, and gave copious precipitates with reagents, such as Mayer's, for alkaloids. The extract was processed in batches of 20 l. An equal volume of ether, containing 10% of methanol, was added and the pH (glass electrode) adjusted to 7.0. The mixture was stirred for 0.5 hr. and then separated. The ethereal layer contained weak bases: all the ajmaline and certain quaternary bases remained in the aqueous solution. The latter was again mixed with ether (20 l.) containing 10% of methanol, and the pH was adjusted to 9.2 by the addition of ammonia. After being stirred again for 0.5 hr. the layers were separated and the aqueous layer was worked up for serpentine and other bases (*cf.* Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, 33, 1463). The filtered ethereal layer was extracted in portions of about 5 l. with 100 c.c. and then  $6 \times 50$  c.c. portions of 2N-hydrochloric acid.

Ajmaline hydrochloride crystallised from the first two or three extracts and the yield was about 0.1% but was not consistent. The salt (30 g.) was purified by dissolution in boiling water (charcoal) (200 c.c.), and about 25 g. were obtained on cooling of the filtered solution. Further small quantities were recovered from mother-liquors.

*Ajmaline and its derivatives.* Ajmaline recrystallised from methanol, as colourless rods, m. p.  $158-160^\circ$  (previous swelling),  $pK_a$  8.15 (Found: C, 70.4; H, 8.5; N, 8.0; MeO, 8.0; MeN, 7.5; C-Me, 4.6, 4.6; active H, 0.91.  $C_{20}H_{26}O_2N_2 \cdot CH_4O$  requires C, 70.4; H, 8.4; N, 7.8; 1NMe, 8.1; 1C-Me, 4.2; 3 active H, 0.84%). After being heated above its m. p. it sometimes crystallised again, or did so on scratching or seeding, to give crystalline anhydrous ajmaline,  $[\alpha]_D^{20} +144^\circ$  (*c.* 0.8 in  $CHCl_3$ ), m. p.  $205-207^\circ$  (rapid heating), or  $200-202^\circ$  (slow heating). At about  $220^\circ$  there was almost complete conversion into *isoajmaline* which usually crystallised, and melted again at  $260-263^\circ$  (decomp.). The crystalline anhydrous ajmaline gave after recrystallisation from methanol a product showing a behaviour identical with that of the original ajmaline.

Ajmaline and all its derivatives (including those of the *isoajmaline* series), except the hexahydro-compounds and bromoajmaline, exhibit reactions similar to those of strychnidine. With ferric chloride in weakly acid solution a red colour is produced as the result of oxidation; nitric acid gives an immediate red colour. Diazobenzenesulphonic acid couples in acetic acid solution to an orange-yellow dye which is an indicator of methyl-orange type. The base

\* A heat-treated siliceous earth (*cf.* Strain, *J. Biol. Chem.*, 1924, 105, 123).

produced on reduction with sodium hydrosulphite (dithionite) shows the typical reactions of a *p*-dialkylaminoaniline.

An ethereal solution of dry hydrogen chloride was added to a solution of ajmaline (0.5 g.) in just sufficient anhydrous methanol (6 c.c.) until acid to Congo-red. Dry ether was then added to turbidity and *ajmaline dihydrochloride* soon crystallised in rectangular plates, which were washed with ether. The m. p. of an anhydrous sample was 305—306° (decomp.) (Found, in anhyd. material: C, 59.8; H, 6.9; Cl, 17.7, 17.6.  $C_{20}H_{26}O_2N_2 \cdot 2HCl$  requires C, 60.1; H, 7.0; Cl, 17.8%).

Attempts to crystallise ajmaline dihydrochloride (m. p. 250°) from water or dilute hydrochloric acid gave aggregates of prisms, m. p. 140° (decomp.). This, the hydrated *monohydrochloride*, was also obtained by boiling ajmaline with dilute hydrochloric acid for a few minutes (Found: loss at 100° *in vacuo*, 8.8.  $C_{20}H_{26}O_2N_2 \cdot HCl \cdot 2H_2O$  requires  $2H_2O$ , 9.0%) (Found, in anhyd. material: C, 65.8; H, 7.3; Cl, 9.6.  $C_{20}H_{26}O_2N_2 \cdot HCl$  requires C, 66.2; H, 7.4; Cl, 9.8%).

A solution of methyl iodide (0.5 c.c.) and ajmaline (0.5 g.) in chloroform (2 c.c.) was kept at room temperature for 24 hr. *Ajmaline methiodide*, which gradually separated in the form of prismatic needles, was collected, washed with chloroform, and dried (0.52 g.). The salt crystallised from aqueous methanol in minute prisms, m. p. 229° (decomp.) (anhyd.) (Found, in material dried at 100° *in vacuo*: C, 53.9, 53.7, 53.9; H, 6.2, 6.2, 6.4; I, 26.7, 26.8.  $C_{21}H_{29}O_2N_2I$  requires C, 53.9; H, 6.2; I, 27.1%). This substance did not titrate as a true quaternary salt, but as the salt of a base of  $pK_a$  9.2 (0.03M in  $H_2O$ ). It gave a negative reaction with *m*-dinitrobenzene and methanolic potassium hydroxide.

A solution of ajmaline methiodide (0.4 g.) in water (8 c.c.) was digested with an excess of freshly prepared silver chloride for 2 hr., then filtered and concentrated to a syrup, which deposited needles *in vacuo* over sulphuric acid. After contact with porous porcelain the colourless mass (0.2 g.) was crystallised from a few drops of water and dried over sulphuric acid; it had m. p. 215° if air-dried. The sulphuric acid-dried *methochloride*, crystallised from methanol-ether, had m. p. 288—290° (decomp.) (Found in material dried at 100° *in vacuo*: Cl, 9.6.  $C_{21}H_{29}O_2N_2Cl$  requires Cl, 9.4%). The methochloride gives the characteristic colour tests for ajmaline, *e.g.*, with diazotised sulphanilic acid it gives a methyl-orange type of azo-compound.

Ajmaline methiodide (0.3 g.), dissolved in water, was treated while hot with dilute aqueous ammonia, and the solution was extracted with chloroform. The heavy viscous oil which remained after removal of the solvent solidified on trituration with absolute methanol. It (0.17 g.) crystallised from aqueous ethanol in rectangular plates, m. p. 124° (Found, in material dried at 100° *in vacuo*: C, 70.6; H, 8.4.  $C_{21}H_{30}O_3N_2$  requires C, 70.4; H, 8.4%). This *methohydroxide* (or tautomer) is readily soluble in water, alcohol, or chloroform, less readily so in ether. The substance was distilled at 0.01 mm., a colourless hygroscopic glass being obtained (Found: C, 73.45; H, 9.0.  $C_{21}H_{28}O_2N_2$  requires C, 74.1; H, 8.3%). This proved to be *N-methylisoajmaline*, readily soluble in water to give an alkaline solution. On neutralisation with dilute hydrochloric acid and addition of potassium iodide, a gum was obtained which after two crystallisations from water afforded colourless prisms, m. p. 195° (ajmaline methiodide, similarly recrystallised, had m. p. 129—131°) alone or mixed with *isoajmaline* methiodide of m. p. 195—196°.

*Attempted Condensation of Ajmaline and Ethanedithiol.*—A solution of ajmaline (0.2 g.) in glacial acetic acid (5 c.c.) containing ethanedithiol (0.5 g.) was saturated with dry hydrogen chloride at 0° and then kept for 24 hr. at the room temperature. The clear orange solution was diluted with water, made alkaline with 10% sodium hydroxide solution, and then extracted with ether. The ethereal solution was shaken with 2% hydrochloric acid, and the acid solution made alkaline with ammonia and again extracted with ether. Evaporation of the solvent and crystallisation from aqueous methanol gave unchanged ajmaline, m. p. and mixed m. p. 158—160°.

A similar experiment with *isoajmaline* yielded unchanged *isoajmaline*, m. p. and mixed m. p. 260—265°.

*Bromoajmaline.*—A solution of ajmaline (0.34 g.) in dry chloroform (4 c.c.) was treated dropwise and with efficient ice-cooling with a solution of bromine (0.17 g.) in dry chloroform (10 c.c.) until the colour of bromine was permanent. Crystalline *bromoajmaline hydrobromide* gradually separated. Next day, this was collected, washed with dry ether, and dried (yield 0.3 g.). It crystallised from alcohol in plates or from water in prisms, the m. p. of anhydrous material being 295° (decomp.) (Found, in material dried at 120° *in vacuo*: C, 49.2; H, 5.3; Br, 33.4.  $C_{20}H_{25}O_2N_2Br \cdot HBr$  requires C, 49.4; H, 5.4; Br, 32.9%). A solution of the compound in distilled water gave a precipitate of silver bromide on addition of silver nitrate.

A solution of the hydrobromide (0.25 g.) in hot water (5 c.c.) was basified with dilute aqueous ammonia. The dense white precipitate of the bromo-base was washed with water and dried (0.11 g.). It crystallised from aqueous methanol in microscopic needles, m. p. 182° (decomp.) (Found, in material dried at 100° *in vacuo*: C, 59.1; H, 6.1; Br, 19.3.  $C_{20}H_{25}O_2N_2Br$  requires C, 59.3; H, 6.2; Br, 19.7%). Neither the bromo-hydrobromide nor the free bromo-base exhibited any of the colour reactions of ajmaline.

*Diacetyljmaline*.—Ajmaline (0.4 g.), dissolved in the minimum of boiling benzene (4 c.c.), was refluxed with acetic anhydride (4 c.c.) for 6 hr. The benzene and excess of anhydride were removed as completely as possible under reduced pressure, and the residue was taken up in water and made alkaline with dilute ammonia. The acetyl compound, which separated as a voluminous white mass, was taken up in ether. On evaporation of the solvent, a heavy viscous oil remained which solidified on trituration with a mixture of ether and light petroleum (b. p. 40–60°). The solid was collected and washed with light petroleum. It crystallised from ether–light petroleum (b. p. 40–60°) in minute prisms, or from aqueous alcohol in prismatic needles, m. p. of anhydrous sample 132° (Found, in material dried at 100° *in vacuo*: C, 70.2, 70.2; H, 7.4, 7.3; AcO, 22.5.  $C_{24}H_{30}O_4N_2$  requires C, 70.2; H, 7.3; 2AcO, 21.0%). The acetyl compound is very readily soluble in the usual organic solvents, responds to the colour tests for ajmaline, and is easily soluble in dilute acids. After some years the matter was reinvestigated and a more stable polymorph was then isolated.

Ajmaline (2 g.) was refluxed with benzene (25 c.c.) and acetic anhydride (10 c.c.) for 12 hr., then evaporated *in vacuo* to dryness and the residue taken up in a little ether. Careful addition of light petroleum (b. p. 40–60°) caused the separation of thick, colourless rods (1.27 g.), m. p. 187–189°. Sometimes a metastable form crystallised, m. p. 130–132° (with resolidification and then m. p. 187–189°), but this readily changed to the higher-melting form (Found: C, 70.2; H, 7.4; N, 7.1.  $C_{24}H_{30}O_4N_2$  requires C, 70.2; H, 7.4; N, 6.8%).  $[\alpha]_D$  was +16° (c 2.7 in  $CHCl_3$ ), and  $pK_a$  4.9. It dissolved readily in dilute acid, but it gave a neutral solution in aqueous alcohol.

Attempts to oxidise this compound with potassium permanganate in acetone gave mainly unchanged product; on prolonged treatment only a trace of a substance giving a violet Otto reaction was obtained.

*Hydrolysis of Diacetyljmaline*.—(a) Diacetyljmaline (0.1 g.) was refluxed with 0.1N-hydrochloric acid for 2 hr. in a stream of nitrogen. The solution was basified and extracted with ether. The ether was evaporated, leaving a colourless residue which when crystallised from a little methanol had m. p. 158–160°, undepressed by ajmaline.

(b) Diacetyljmaline (0.03 g.), dissolved in dry ether (10 c.c.), was added to an ethereal solution of lithium aluminium hydride (15 c.c. of 1%). After 5 hr. the mixture was carefully decomposed at 0° with water, and after addition of 5% potassium hydroxide (2 c.c.) the ethereal layer was decanted. The crystalline residue obtained on evaporation was recrystallised from aqueous methanol and had m. p. 154–156°, undepressed by ajmaline (yield 0.02 g.). The hydrochloride, crystallised from water, had m. p. 132–133°.

(c) Diacetyljmaline (0.05 g.) was dissolved in methanol (1 c.c.) containing potassium hydroxide (0.01 g.). The mixture was refluxed for 15 min. and then diluted with water, giving colourless crystals (0.03 g.), m. p. 158–160°, undepressed by ajmaline.

*Diacetyljmaline Methiodide*.—A solution of diacetyljmaline in methyl iodide was kept for 1 hr. It was then evaporated to dryness and the residue crystallised from water. Clusters of colourless prisms, m. p. 251–253° (decomp.), were obtained (Found, in material dried at 100° *in vacuo* over  $P_2O_5$ : C, 54.3; H, 5.7; N, 4.8; I, 23.4.  $C_{25}H_{33}O_4N_2I$  requires C, 54.4; H, 6.0; N, 5.1; I, 23.0%). The aqueous solution gave no precipitate with ammonia.

*Benzoyljmaline*.—Ajmaline (0.4 g.), dissolved in just sufficient dry benzene (4 c.c.), was refluxed with freshly distilled benzoyl chloride (0.8 c.c.) for 30 min. The hydrochloride of the benzoylated base very soon separated as a chalky powder, which was collected and washed repeatedly with dry ether and benzene. Very thorough washing is necessary in order to remove the last traces of benzoyl chloride, the presence of which hinders the subsequent purification by crystallisation. The hydrochloride (0.34 g.) crystallised from anhydrous methanol–ether in small needles, m. p. 267° (decomp.) (Found, in material dried at 120° *in vacuo*: C, 69.4, 69.3; H, 6.5, 6.5.  $C_{27}H_{30}O_3N_2.HCl$  requires C, 69.4; H, 6.5%). Like ajmaline hydrochloride, benzoyljmaline hydrochloride is insoluble in cold, but readily soluble in hot, water.

A solution of benzoyljmaline hydrochloride (0.4 g.) in just sufficient hot water was made alkaline with dilute ammonia. The thick white precipitate which separated was taken up in ether. On evaporation of the solvent an amorphous powder remained which crystallised from



ether in colourless, microscopic needles, or from aqueous methanol in prisms (yield 0.2 g.), m. p. of anhydrous material, 219° (Found, in material dried at 100° *in vacuo* : C, 74.9, 74.9; H, 7.0, 7.1. Calc. for  $C_{27}H_{30}O_3N_2$  : C, 75.3; H, 7.0%). Benzoylajmaline is soluble in dilute acids with difficulty.\*

A solution of benzoylajmaline (0.2 g.) in anhydrous methanol (2 c.c.) was mixed with an ethereal solution of dry hydrogen chloride and further diluted with a little dry ether until just turbid. The *dihydrochloride* soon separated in minute needles, which, washed with dry ether and dried (0.11 g.), had m. p. 244—245° (decomp.) (Found, in material dried at 120° *in vacuo* : Cl, 14.5.  $C_{27}H_{30}O_3N_2 \cdot 2HCl$  requires Cl, 14.1%). This is very readily soluble in water.

*Ajmaline Oxime*.—Ajmaline (0.5 g.) was boiled for 10—15 min. with a solution of hydroxylamine hydrochloride (0.5 g.) in water (5 c.c.), then kept in the cold for 2—3 hr. *Ajmaline oxime hydrochloride* which separated (yield 0.25 g.) crystallised from water in colourless needles, m. p. (anhyd.) 218° (effervescence) (Found : loss at 100°, 4.1.  $C_{20}H_{27}O_2N_3 \cdot HCl \cdot 2H_2O$  requires  $1H_2O$ , 4.3. Found, in dried material : C, 60.4; H, 7.5; N, 10.4.  $C_{20}H_{27}O_2N_3 \cdot HCl \cdot H_2O$  requires C, 60.6; H, 7.6; N, 10.6%).

A solution of this hydrochloride (0.2 g.) in water (4 c.c.) was basified with ammonia, the free *oxime* being precipitated (yield 0.14 g.). It crystallised from methanol in minute prisms, m. p. 220° (Found, in material dried at 100° *in vacuo* : C, 70.6; H, 7.8; N, 12.1.  $C_{20}H_{27}O_2N_3$  requires C, 70.4; H, 7.9; N, 12.3%).

*Anhydroajmaline Oxime*.—Ajmaline oxime hydrochloride (0.67 g.) was suspended in a mixture of acetic acid (5 c.c.) and acetic anhydride (2 c.c.), and dry hydrogen chloride led in without cooling. All the solid went into the solution. When the mixture was kept at the room temperature for 3 hr. colourless needles separated. After cooling in ice the product was collected and dried at 100° (0.76 g.). Recrystallised from glacial acetic acid containing a little hydrogen chloride it had m. p. 202—205°, with previous sintering at 198—200° (Found, after drying at 100° *in vacuo* over  $P_2O_5$  : C, 57.1; H, 6.7; N, 8.6; Cl, 14.3; AcO, 18.2.  $C_{24}H_{33}O_4N_3Cl_2$  requires C, 57.8; H, 6.7; N, 8.4; Cl, 14.2; 2AcO, 17.2%). This substance has the composition of a *diacetylajmaline oxime dihydrochloride*. It was dissolved in methanol (20 c.c.) and treated with methanolic potassium hydroxide until alkaline. The solution was refluxed for 4 min. and then diluted with water (80 c.c.). Colourless needles of *anhydroajmaline oxime* separated (0.44 g.), having m. p. 254—255° unchanged by recrystallisation from aqueous methanol,  $[\alpha]_D^{25} + 29^\circ$  (c, 1.4 in  $CHCl_3$ ) (Found : C, 74.2; H, 7.7; N, 12.8; C-Me, 4.95; active H, 0.44.  $C_{20}H_{25}ON_3$  requires C, 74.4; H, 7.8; N, 13.0; C-Me, 4.65; 2H, 0.6%).

*Anhydro-N-methylajmaline Oxime Hydriodide*.—Anhydroajmaline oxime (0.110 g.) was refluxed with methyl iodide (2 c.c.) in acetone (5 c.c.) containing anhydrous potassium carbonate (1 g.) for 2 hr. The solution was filtered, the residue was washed with hot acetone, and the combined filtrates were evaporated to a small bulk and diluted with water. Boiling and scratching caused crystallisation. Recrystallisation from water with the addition of potassium iodide yielded the *N-methyl hydriodide* as colourless, elongated plates, m. p. 279—280°, with sintering at 275° (Found, in material dried at 100° *in vacuo* : C, 54.5; H, 6.2; N, 8.9; I, 26.8.  $C_{21}H_{27}ON_3 \cdot HI$  requires C, 54.2; H, 6.1; N, 9.0; I, 27.3%). Its aqueous solution gave an immediate precipitate with dilute ammonia, which did not dissolve even on boiling.

*Hydrolysis of Anhydroajmaline Oxime*.—Anhydroajmaline oxime (0.2 g.) was refluxed with 25% hydrochloric acid (4 c.c.) for 6 hr., then cooled in ice. Colourless prisms were slowly deposited. The product was collected and recrystallised from methanol-ether, colourless needles of *dihydrochloride* being obtained (0.15 g.), which sintered at 150° and softened and reddened above 250° but were not completely liquid until 275° (Found, in material dried at 100° *in vacuo* over  $P_2O_5$  : C, 57.8; H, 6.8; N, 6.9.  $C_{20}H_{26}O_3N_2 \cdot 2HCl$  requires C, 57.8; H, 6.8; N, 6.7%). The substance lost no weight at 140° *in vacuo*. The aqueous mother-liquor from the hydrolysis evolved ammonia when warmed with sodium hydroxide. This dihydrochloride was very soluble in water and could not be extracted from the solution by chloroform in either neutral or alkaline solution. It did not have any tendency to lactamise or lactonise in acid or neutral solution.

The free amino-acid has not been isolated. The constitution of anhydroajmaline oxime is discussed in the introductory section.

*Reduction of Anhydroajmaline Oxime with Lithium Aluminium Hydride*.—Anhydroajmaline oxime (0.05 g.) was dissolved in chloroform (2 c.c.) and added to lithium aluminium hydride (0.05 g.) in ether (20 c.c.). The mixture was set aside at room temperature for 2 hr., then

\* Dr. H. MacPhillamy has now prepared dibenzoylajmaline by treatment of the base with benzoyl chloride in cold pyridine. An account of this experiment will be submitted in Part II.

decomposed with water; dilute hydrochloric acid (5 c.c.) was added, and the solution warmed on a steam-bath for 10 min. After addition of potassium hydroxide the solution was extracted with chloroform. The extract was evaporated to dryness and the residue triturated with a little methanol; it crystallised, and had m. p. 154—158°, undepressed when mixed with ajmaline.

*Action of Sulphurous Acid on Ajmaline.*—On gentle warming of a suspension of ajmaline (0.2 g.) in saturated aqueous sulphur dioxide (8 c.c.) the colour changed to pale yellow and a crystalline precipitate separated. The mixture was mechanically stirred for 2 hr. The precipitated *product* was then collected, washed with cold water, and dried (0.2 g.). It was rather sparingly soluble in hot water but easily soluble in hot methanol and crystallised from a concentrated solution in methanol, with the addition of a drop of hot water, in shining colourless plates, m. p. 225° (when heated moderately quickly) (Found: C, 57.4; H, 7.1; S, 7.1, 7.2; loss at 100° *in vacuo*, 22.9.  $C_{20}H_{26}O_2N_2 \cdot H_2SO_3 \cdot H_2O$  requires C, 57.6; H, 7.0; S, 7.5;  $H_2SO_3 \cdot H_2O$ , 23.4%).

*isoAjmaline.*—(a) Ajmaline (1 g.) was added to a solution of potassium hydroxide (1 g.) in methanol (50 c.c.), and the mixture refluxed on the steam-bath for 6 hr. About three-fourths of the methanol were removed by distillation and the warm solution was diluted with water, a heavy viscous oil separating. This was again brought into solution by warming on the steam-bath and adding a few drops of methanol; on cooling, *isoajmaline* gradually separated as an amorphous powder which was collected, washed with water, and dried (0.85 g.). It crystallised from aqueous methanol in minute prisms or from ether in plates, m. p. 265° (decomp.) (Found, in material dried at 100° *in vacuo*: C, 73.5, 73.6, 7.35; H, 7.9, 7.9, 8.0; N, 8.3. Calc. for  $C_{20}H_{26}O_2N_2$ : C, 73.6; H, 8.0; N, 8.6%). The conversion was incomplete in less than 6 hr.; methanol could be replaced by ethanol without affecting the results.

(b) Ajmaline (0.2 g.) was heated at 200—220°/12 mm. for 4—5 hr. It sublimed in beautiful glistening plates. If, however, the temperature was raised above 250° a resinous mass distilled together with a small crystalline sublimate. The whole (0.1 g.) was washed with a little ether. It crystallised from dilute methanol in minute prisms, m. p. 265° alone or mixed with the previous specimen of *isoajmaline* (Found: C, 73.4, 73.5; H, 8.0, 7.9. Calc. for  $C_{20}H_{26}O_2N_2$ : C, 73.6; H, 8.0%).

*isoAjmaline*, recrystallised from aqueous alcohol and dried *in vacuo* over  $P_2O_5$  (Found: C, 73.9; H, 8.2; N, 8.5; C-Me, 5.7, 5.0, 4.9; active H, 0.61, 0.61.  $C_{20}H_{26}O_2N_2$  requires C, 73.6; H, 8.1; N, 8.6; C-Me, 4.6; 2H, 0.62%), had  $[\alpha]_D^{25} + 72^\circ$  (*c* 0.7 in  $CHCl_3$ ) and  $pK_a$  8.05.

*isoAjmaline Derivatives.*—*isoAjmaline* (0.1 g.), dissolved in the minimum quantity of hot methanol, was treated with ethereal hydrogen chloride until just turbid, then kept for some time in the cold. *isoAjmaline dihydrochloride* crystallised in glistening plates, m. p. 254° (decomp.) (air-dried), m. p. 310° (decomp.) (anhyd.) (Found, in material dried at 120° *in vacuo*: C, 59.9; H, 6.9; Cl, 18.1.  $C_{20}H_{26}O_2N_2 \cdot 2HCl$  requires C, 60.1; H, 7.0; Cl, 17.8%). Siddiqui and Siddiqui (*loc. cit.*) gave m. p. 238—249° (decomp. with previous frothing) for the amorphous dihydrochloride. The hydrochloride was recovered unchanged even on prolonged boiling with anhydrous methanol.

The dihydrochloride, m. p. 254°, on crystallisation from water gave a salt, m. p. 147° (decomp.). The same *hydrochloride*, m. p. 147°, was also obtained by boiling *isoajmaline* with dilute hydrochloric acid. It crystallised from water in prisms, m. p. 147° (anhyd.) (Found: loss at 100° *in vacuo*, 8.7.  $C_{20}H_{26}O_2N_2 \cdot HCl \cdot 2H_2O$  requires  $2H_2O$ , 9.0%). *isoAjmaline hydrochloride*, like ajmaline hydrochloride, is very sparingly soluble in cold water. *isoAjmaline picrate* was prepared by adding an ethereal solution of picric acid to a solution of the base in anhydrous methanol; it crystallised from alcohol as small yellow needles, m. p. 225° (decomp.) with previous frothing (Found, in material dried at 100° *in vacuo*: C, 56.0; H, 5.1; N, 12.3.  $C_{26}H_{26}O_9N_5$  requires C, 56.2; H, 5.2; N, 12.6%).

*isoAjmaline* (0.4 g.), dissolved in chloroform, was treated with excess of methyl iodide and left at the room temperature for 48 hr. A heavy oil gradually separated. This was collected, washed with chloroform, and then digested with methanol-ether, whereupon it solidified. The solid *methiodide* was dissolved in methanol and precipitated with dry ether. After repetition of this process, the material (0.22 g.) was crystallised from acetone-ether. It afforded minute, pale yellow prisms, which darkened at 185° and had m. p. 200—203° (Found, in material dried at 100° *in vacuo*: C, 53.5; H, 6.2; I, 26.8.  $C_{21}H_{29}O_2N_2I$  requires C, 53.9; H, 6.2; I, 27.1%). *isoAjmaline methiodide*, m. p. 194—195° (from acetone), behaved on titration with 0.1N-sodium hydroxide as the salt of a base of  $pK_a$  9.4. It gave no colour when warmed with pure *m*-dinitrobenzene in aqueous-methanolic potassium hydroxide.

A solution of the methiodide (0.3 g.) in hot water was treated with ammonia and allowed to cool. No solid separated even on long keeping. The solution was extracted with chloroform, and the extract washed with water and dried ( $\text{Na}_2\text{SO}_4$ ). After removal of the solvent, a heavy viscous oily *methohydroxide* remained which solidified on trituration with absolute ethanol (yield, 0.16 g.). It crystallised from aqueous alcohol in plates, which softened, with evolution of gas, at  $119^\circ$ , had m. p.  $121^\circ$  (Found, in material dried at  $100^\circ$  *in vacuo*: C, 70.2; H, 8.3.  $\text{C}_{21}\text{H}_{30}\text{O}_3\text{N}_2$  requires C, 70.4; H, 8.4%), and were readily soluble in water, alcohol, and methanol, less so in ethyl acetate, and difficultly so in ether.

*isoAjmaline Oxime*.—*isoAjmaline* (0.3 g.) was refluxed for 20 min. with a solution of hydroxylamine hydrochloride (0.3 g.) in water (3 c.c.). The oxime hydrochloride did not separate even at  $0^\circ$ . Addition of ammonia precipitated the *oxime* (0.2 g.) which crystallised from methanol as prisms, m. p. (anhyd.)  $185^\circ$  (Found, in material dried at  $100^\circ$  *in vacuo*: C, 70.3; H, 7.8; N, 12.2.  $\text{C}_{20}\text{H}_{27}\text{O}_2\text{N}_3$  requires C, 70.4; H, 7.9; N, 12.3%).

*Diacetylisoaajmaline*.—*isoAjmaline* (0.3 g.) was suspended in dry benzene (5 c.c.) and refluxed with freshly distilled acetic anhydride (4 c.c.) for 5 hr. The excess of anhydride and benzene were removed as completely as possible. The residue was taken up in water and made alkaline with ammonia. The precipitate was extracted with ether, washed with water, and dried ( $\text{Na}_2\text{SO}_4$ ). After removal of the solvent a crystalline *diacetyl* derivative (0.13 g.) remained, which crystallised from ether in thin plates, m. p. (anhyd.)  $224$ — $225^\circ$  (Found, in material dried at  $100^\circ$  *in vacuo*: C, 70.0; H, 7.4; AcO, 21.9.  $\text{C}_{24}\text{H}_{30}\text{O}_4\text{N}_2$  requires C, 70.3; H, 7.3; 2AcO, 21.0%). On titration the  $\text{pK}_a$  was found to be ca. 3.8.

*Benzoylisoaajmaline Hydrochloride*.—This was prepared from *isoajmaline* as described for benzoylajmaline. The *hydrochloride* (0.13 g.), crystallised from anhydrous methanol-ether, had m. p.  $258^\circ$  (decomp.) (anhyd.) (Found, in material dried at  $120^\circ$  *in vacuo*: C, 69.2; H, 6.6; Cl, 7.9.  $\text{C}_{27}\text{H}_{30}\text{O}_3\text{N}_2\cdot\text{HCl}$  requires C, 69.4; H, 6.6; Cl, 7.6%). It is more readily soluble in water than *isoajmaline hydrochloride*.

*Benzoylisoaajmaline* was prepared from the hydrochloride in the usual way and was obtained as an amorphous white powder, m. p.  $195^\circ$  with frothing from  $186^\circ$ , which could not be induced to crystallise.

*Bromoisoajmaline*.—A solution of *isoajmaline* (0.34 g.) in dry chloroform (4 c.c.) was treated drop-wise with a solution of bromine (0.2 g.) in dry chloroform (10 c.c.) with efficient ice-cooling, till the colour of bromine was permanent (bromine consumed, 0.17 g., ca. 1 mol.). A crystalline precipitate separated. The mixture was kept in the ice-chest and next day the *bromo-hydrobromide* was collected, washed with dry ether, and dried (0.29 g.). It crystallised from water in prisms, m. p. (anhyd.)  $288$ — $289^\circ$  (decomp.) (Found, in material dried at  $120^\circ$  *in vacuo*: C, 49.2; H, 5.4; Br, 33.4.  $\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}_2\text{Br}\cdot\text{HBr}$  requires C, 49.4; H, 5.4; Br, 32.9%), and was insoluble in cold water but readily dissolved in boiling water. It does not respond to any of the colour tests for *isoajmaline*.

A solution of this hydrobromide (0.2 g.) in hot water (5 c.c.) was basified with dilute ammonia. The dense white precipitate of the *bromo-base* (0.12 g.) which separated was collected, washed with water, and dried. It crystallised from aqueous methanol in minute needles, m. p. (anhyd.)  $192^\circ$  (decomp.) (Found, in material dried at  $100^\circ$  *in vacuo*: C, 59.2; H, 6.2; Br, 19.9.  $\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}_2\text{Br}$  requires C, 59.3; H, 6.2; Br, 19.8%).

*Cleavage of Diacetylisoaajmaline with Lithium Aluminium Hydride*.—Diacetylisoaajmaline (0.04 g.) in anhydrous ether (15 c.c.) was added to a solution of lithium aluminium hydride (0.04 g.) in ether (15 c.c.). After 4 hr. the excess of reagent was decomposed with ethyl acetate, and then water (10 c.c.) and 10% sodium hydroxide solution (5 c.c.) were added. The ethereal layer gave, after evaporation of the solvent, a colourless residue which readily crystallised from aqueous alcohol, m. p.  $260$ — $262^\circ$  with previous sintering at  $250^\circ$ , mixed m. p. with *isoajmaline*,  $260$ — $262^\circ$ .

*Anhydroisoajmaline Oxime*.—A solution of *isoajmaline oxime* (0.5 g.) in acetic acid (5 c.c.) and acetic anhydride (2 c.c.) was saturated with hydrogen chloride. After a day the mixture was evaporated to dryness *in vacuo* and the residue dissolved in methanol (10 c.c.). 5% Methanolic potassium hydroxide was added until the solution was alkaline, the mixture was then refluxed for 2 min., and more alkali was added to keep the solution alkaline. Dilution with water (100 c.c.) caused the separation of *anhydroisoajmaline oxime* (0.3 g.), m. p.  $218$ — $220^\circ$ . Recrystallisation from aqueous methanol gave long needles, m. p.  $219$ — $220^\circ$ ,  $[\alpha]_D^{19} + 74^\circ$  (c, 1.2 in chloroform) (Found: C, 74.2; H, 7.6.  $\text{C}_{20}\text{H}_{25}\text{ON}_3$  requires C, 74.4; H, 7.8%).

*Reduction of Anhydroisoajmaline Oxime with Lithium Aluminium Hydride*.—Anhydroisoajmaline oxime (0.05 g.) was dissolved in chloroform (2 c.c.) and added to a solution of lithium

aluminium hydride (0.05 g.) in ether (20 c.c.). The solution was kept at room temperature for 2 hr. and then decomposed with water and dilute hydrochloric acid (5 c.c.). The mixture was heated on a steam-bath for 10 min., cooled, made alkaline with potassium hydroxide, and extracted with chloroform. Evaporation of the solvent left a colourless glass which when moistened with methanol crystallised; several recrystallisations raised the melting point to 260—262° undepressed by admixture with *isoajmaline*.

*Some Negative Results.*—*isoAjmaline* was recovered from attempts to condense it with salicylaldehyde or piperonaldehyde in the presence of basic catalysts. Neither *ajmaline* nor *isoajmaline* could be reduced by lithium aluminium hydride in tetrahydrofuran or dioxan solution. *Ajmaline* was not reduced by zinc and boiling dilute hydrochloric acid.

*Experiments on the Degradation of Ajmaline.*—(I) *Ajmaline* (1 g.), intimately mixed with soda-lime (15 g.), was gradually heated in a metal-bath in a slow current of nitrogen until the temperature rose to 220° (after about  $\frac{1}{2}$  hr.). At this temperature, a liquid began to distil. The temperature was kept at 280—300° for 10—12 hr., after which no more liquid distilled. As a result or many trials it was found that the yield of the distillate depended mainly on the following factors: (i) In no case should the temperature be raised above 300° as otherwise no distillate could be obtained. (ii) The temperature must be raised slowly at a uniform rate. (iii) The quality of the soda-lime had a marked influence on the yield of the base. The soda-lime should be dried over phosphoric anhydride *in vacuo*.

The residue in the flask was exhaustively extracted with ether and the extract was added to the ethereal solution of the distillate. The combined ethereal extracts were washed with dilute hydrochloric acid, the yellow hydrochloride which separated being brought into solution by the addition of a few c.c. more of dilute hydrochloric acid. For the treatment of the acid washings (C) see below. The extract was washed with dilute alkali, then with water, and dried. The solvent was removed by evaporation and the residue distilled at low pressure, giving (A), b. p. 120—125°/0.2 mm. (bath-temp.), and a larger fraction (B), b. p. 190—200°/0.2 mm. (bath temp.).

The fraction (A) gave a positive pine-shaving test. With Ehrlich's reagent it gave a strong bluish-purple colour similar to that given by  $\beta$ -substituted indole derivatives. Fraction (B) gave reactions suggestive of the presence of carbazole, namely, a positive pine-shaving test but no response to Ehrlich's reagent, and a golden-yellow colour in concentrated sulphuric acid, changed to bluish-green on the addition of a trace of concentrated nitric acid (Blom, *Helv. Chim. Acta*, 1921, 4, 625). Furthermore, when warmed with acetaldehyde or formaldehyde in the presence of concentrated sulphuric acid the oil (B) gave a deep blue colour (Dische, *Biochem. Z.*, 1927, 189, 77). Further, the ultra-violet absorption spectrum of this fraction showed all the characteristic bands for carbazole. All attempts to induce the oil to crystallise, however, were unsuccessful.

The yellow acid washings (C) were boiled with animal charcoal and the filtered solution concentrated to a small bulk on the steam-bath. The crystalline *hydrochloride* which separated on cooling was collected and, recrystallised from dilute hydrochloric acid, had m. p. (anhyd.) 282° (decomp.) (yield, 0.32 g.) (Found, in material dried at 120° *in vacuo*: C, 66.9; H, 5.5; Cl, 15.4.  $C_{13}H_{12}N_2 \cdot HCl$  requires C, 67.1; H, 5.6; Cl, 15.3%).

The pure hydrochloride (0.3 g.) was dissolved in the minimum quantity of water and the solution made alkaline with concentrated aqueous sodium hydroxide; the precipitated base was extracted with a large volume of ether in which it was somewhat sparingly soluble. The ethereal extract was washed with water and dried ( $K_2CO_3$ ). On removal of the solvent, the residual oil was triturated with light petroleum (b. p. 40—60°); it then solidified and was purified by sublimation in a high vacuum. It then separated from ether in glistening needles (0.1 g.), m. p. (anhyd.) 102° (Found, in material dried at 80° *in vacuo*: NMe, 10.7; C-Me, 7.2.  $C_{13}H_{12}N_2$  requires NMe, 14.8; C-Me, 7.6%). The base, ind-*N-methylharman*, was readily soluble in the usual organic solvents, less readily in ether.

(II) An intimate mixture of *ajmaline* (3 g.) and zinc dust (32 g.), covered with a layer of zinc dust, was heated in a hard-glass tube at 380—400°. The tube was heated in a metal-bath, the temperature of which was recorded by a thermocouple. Hydrogen was passed through the tube for 10—15 min. before the heating, and the temperature was raised slowly and uniformly. When the temperature reached approx. 380°, volatile material was copiously evolved and immediately afterwards a liquid began to distil. The products of the distillation were led through a side-tube to a long tube, provided with a water-jacket, in which most of the liquid condensed. The end of this tube was connected to a series of bubblers, the first containing water, the second *N*-hydrochloric acid, and the third *N*-potassium hydroxide. The heating was

continued for 10—12 hr., after which no further liquid distilled. The tube was then allowed to cool slowly to room temperature and the residue in it was repeatedly digested with ether. The extract was added to an ethereal solution of the distillate. The combined ethereal solutions (A) were washed with *n*-hydrochloric acid, which became yellow (washing with hydrochloric acid was continued until the washings were colourless), and then with *n*-potassium hydroxide. For treatments of the acid-washings (B) and alkali-washings (C) see below.

The ethereal solution (A) was washed with water (until the washings were neutral), dried ( $\text{Na}_2\text{SO}_4$ ), and filtered. The solvent was then removed and the residual oil was distilled, giving fractions, (a) b. p. 80—90°/0.2 mm., (b) b. p. 110—120°/0.2 mm., and (c) b. p. 180—200°/0.2 mm. (all bath-temps.). The first two fractions, which were very small, were distilled from small bulbs. The distillate from the first two fractions showed a positive pine-shaving test and with Ehrlich's reagent gave a deep bluish-purple colour similar to that given by  $\beta$ -substituted indole derivatives. Solutions of the oils in organic solvents exhibited a dull, blue fluorescence in ultra-violet light, characteristic of some indole derivatives.

The fraction (c) was distilled at  $4.9 \times 10^{-3}$  mm., giving two fractions (*d*) and (*e*). Only one or two drops of (*d*) were obtained boiling at 120—125° (bath-temp.). The rest of the liquid boiled at 140—150° (bath-temp.) and the oil gave a positive pine-shaving test but did not colour with Ehrlich's reagents; it also gave the characteristic colour tests for carbazole (Blom, Dische, *loc. cit.*). The oil, dissolved in light petroleum (b. p. 40—60°), was passed through a column of alumina. The solution then had a bluish fluorescence in ultra-violet light whereas carbazole itself has a strong violet fluorescence. On repeated chromatographic separation (seven columns) the impurity which imparted the bluish tinge to the fluorescence was held on the column and the characteristic violet fluorescence of carbazole appeared. Several fractions were collected and evaporated. The first two yielded heavy oils which showed the characteristic colour tests for carbazole. From the third and subsequent fractions solids were obtained. The solid residues from different fractions were combined and, crystallised from light petroleum (b. p. 40—60°), had m. p. 236°. By a mixed m. p. determination and a careful comparison of colour tests and absorption spectra the crystalline product (4 mg.) was found to be carbazole.

The acid-washings (B) were concentrated on the steam-bath to about 30 c.c. and boiled with animal charcoal. The filtered solution was basified with concentrated aqueous sodium hydroxide; the base was precipitated as a semi-solid viscous mass which was taken up by means of ether. After evaporation of the solvent the residual oil was distilled, b. p. 160—165°/0.2 mm. (bath-temp.). The distillate was dissolved in a little ether and treated with *n*-hydrochloric acid; a yellow hydrochloride which separated crystallised from dilute hydrochloric acid in pale yellow, silky needles, m. p. 282° (decomp.) (yield, 4.0 mg.). The solution in dilute hydrochloric acid had a strong violet fluorescence. The hydrochloride (4 mg.), dissolved in the minimum of water, was made alkaline with concentrated aqueous sodium hydroxide, and the precipitated base was taken up in ether. After evaporation the solid residue crystallised from aqueous methanol in glistening needles (3 mg.), m. p. (anhyd.) 102°. This base was identical with that obtained in the soda-lime distillation (mixed m. p. and ultra-violet absorption).

*ind-N-Methylharman.*—The harman that was required was prepared by the method of Kermack, Perkin, and Robinson (*J.*, 1921, **119**, 1617) from tryptophan (1 g.) (yield, 0.22 g.). The product melted at 237° after one crystallisation from aqueous methanol; it was dried *in vacuo* at 100° before use.

Potassium (0.14 g.) was dissolved in liquid ammonia (10 c.c.) in presence of a trace of ferric nitrate. Harman (0.65 g.) was then added; it very readily passed into solution imparting a dull fluorescence to the liquid. In a short time a yellow precipitate separated. The excess of ammonia was removed by cautious addition of ether and occasional shaking. When nearly all the ammonia had evaporated, the solution was gently warmed for  $\frac{1}{2}$  hr.; it was cooled at 18° and methyl iodide (0.24 c.c.), diluted with a large volume of ether, was slowly added. The mixture was slowly heated to 40° and kept at this temperature for 3 hr. The ethereal solution was carefully decanted and the residue in the flask exhaustively extracted with dry ether. The combined ethereal solutions were filtered and evaporated. The residue crystallised from ether in long silky needles or from acetone in plates, m. p. (air-dried) 95°, (anhyd.) 102° (yield, 0.59 g.) (Found, in material dried at 80° *in vacuo*: C, 79.4; H, 6.1; NMe, 12.1; C-Me, 7.6. Calc. for  $\text{C}_{13}\text{H}_{12}\text{N}_2$ : C, 79.6; H, 6.1; NMe, 14.8; C-Me, 7.6%). Späth and Lederer (*Ber.*, 1930, **63**, 2102) gave m. p. 102—103°.

The identity of the degradation product from ajmaline with *ind-N*-methylharman was

established by a careful comparison of properties including ultra-violet spectra, m. p., and mixed m. p.

The *hydrochloride* crystallised from dilute hydrochloric acid in long silky needles, m. p. 282° (Found, in material dried at 120° *in vacuo*: C, 66.8; H, 5.5; Cl, 15.1.  $C_{13}H_{12}N_2 \cdot HCl$  requires C, 67.1; H, 5.6; Cl, 15.3%).

*ind-N-Methylharmine*.—Treatment of a solution of potassium (0.12 g.) in liquid ammonia (10 c.c.) with harmine (0.65 g.) (see above) gave a solution with a deep violet fluorescence. A yellow precipitate soon separated. Removal of ammonia and treatment with methyl iodide (0.19 c.c.), etc., as above gave a viscous oil which solidified on trituration with acetone. The *ind-N-methylharmine* crystallised from acetone in glistening plates and after two recrystallisations had m. p. 117—118° (air-dried), 124—125° (dried over  $P_2O_5$ ) (yield, 0.42 g.) (Found, in material dried at 80° *in vacuo*: C, 74.1; H, 6.2; N, 12.6; *N*-Me, 10.5; OMe, 11.4. Calc. for  $C_{14}H_{14}ON_2$ : C, 74.3; H, 6.2; N, 12.4; *N*-Me, 12.8; OMe, 13.7%). Direct comparison showed that the specimen was identical with that obtained by Iyer and Robinson (*J.*, 1934, 1635). The hydrochloride, picrate, and methiodide were also identical in properties when made from the two sources.

*Hexahydroajmaline*.—(a) Ajmaline (0.7 g.), dissolved in 50% acetic acid (30 c.c.), was hydrogenated in presence of Adams catalyst (0.72 g.). Absorption was rapid and stopped sharply after the uptake of 3 mols. of hydrogen. The filtered solution was made alkaline with ammonia. After some time the amorphous precipitate crystallised and was then collected (0.58 g.; m. p. 145—150°). On recrystallisation from aqueous ethanol *hexahydroajmaline* was obtained as plates, m. p. 120—122° (frothing), or after drying at 100° *in vacuo*, m. p. 149—150° with slight previous sintering. It did not give the ajmaline colour reactions (Found, in material dried at 100° *in vacuo*: C, 72.1, 71.9; H, 9.5, 9.4; *C*-Me, 4.7.  $C_{20}H_{32}O_2N_2$  requires C, 72.2; H, 9.6; *1C*-Me, 4.5%) and had  $[\alpha]_D^{20} + 92^\circ$  (*c* 1.9 in  $CHCl_3$ ).

(b) Ajmaline dihydrochloride (0.5 g.) in anhydrous methanol (30 c.c.) was shaken with Adams platinum oxide (50 mg.) in hydrogen, which was rapidly absorbed (87 c.c. after 1 hr. Calc. for 3 mols., 93 c.c.). The filtered solution was concentrated to about 10 c.c. and mixed with dry ether; the *dihydrochloride* crystallised as long needles when kept in the ice-chest for 24 hr. The crystals, washed with dry ether and dried, had m. p. (anhyd.) 302° (decomp.) (Found, in material dried at 100° *in vacuo*: Cl, 17.9.  $C_{20}H_{32}O_2N_2 \cdot 2HCl$  requires Cl, 17.5%). The free base, generated from the hydrochloride in the usual way, melted at 150° after crystallisation from ethanol with the addition of a drop of water.

*Diacetylhexahydroajmaline*.—Hexahydroajmaline (0.5 g.) was refluxed with acetic anhydride (4 c.c.) and benzene (6 c.c.) for 6.5 hr. The solution was evaporated to dryness *in vacuo*, and the glassy residue dissolved in water. Addition of perchloric acid caused the separation of a crystalline perchlorate, which was washed with methanol [yield, 0.5 g.; m. p. 180° (frothing)]. It recrystallised from methanol-ether in colourless needles which sintered at 190° and decomposed at 265°.

The perchlorate was dissolved in water, and dilute aqueous ammonia was added. Extraction with ether gave a *diacetyl* derivative which after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 131—132°,  $[\alpha]_D + 66^\circ$  (*c* 2.4 in  $CHCl_3$ ) (Found: C, 69.45; H, 8.8.  $C_{24}H_{36}O_4N_2$  requires C, 69.2; H, 8.7%).

*Hydrogenation of Diacetylajmaline*.—Diacetylajmaline (0.201 g.) was hydrogenated in 50% acetic acid (20 c.c.) in presence of Adams catalyst (0.08 g.). After the uptake of 3 mols. of hydrogen, absorption ceased (1 hr.). The solution was filtered and made alkaline with ammonia. Extraction with ether gave a product, which on recrystallisation from light petroleum had m. p. 130—131°, undepressed by diacetylhexahydroajmaline.

On hydrolysis with methanolic potassium hydroxide it gave hexahydroajmaline, m. p. and mixed m. p. 150—151°.

*Deoxydihydroajmaline*.—Ajmaline (1.0 g.), hydrazine hydrate (3 c.c. of 90%), and diethylene glycol (8 c.c.) were refluxed for 10 min. Potassium hydroxide (0.4 g.) was then added and the temperature of the liquid raised to 195° by distillation. After 1.5 hr. at this temperature, the solution was cooled, diluted with water (50 c.c.), and, after 1 hr., filtered and the substance well washed with water, to give 0.82 g. (94%) of deoxydihydroajmaline, m. p. 182—184°. If the reaction is conducted in a stream of nitrogen the product is colourless, but in any case the *substance* is best purified by sublimation *in vacuo* followed by crystallisation from aqueous alcohol; it then has m. p. 185—186°,  $[\alpha]_D + 39^\circ$  (*c* 2.5 in  $CHCl_3$ ),  $pK_a$  8.25 [Found: C, 77.3, 77.1; H, 9.2, 9.1; N, 8.9, 9.0; *C*-Me, 7.85; active H (at 20°), 0.41.  $C_{20}H_{28}ON_2$  requires C, 76.9; H, 9.1; N, 9.0; *2C*-Me, 9.6; *2H*, 0.64%].

*Acetyldeoxydihydroajmaline*.—A solution of deoxydihydroajmaline (0.025 g.) in acetic anhydride (1 c.c.) was kept for 12 hr. The excess of anhydride was hydrolysed by water, and on further dilution a precipitate was formed, which was only slightly increased on neutralisation with dilute ammonia. The precipitated *acetate* was taken up in ether, but the residue left after evaporation of the solvent could not be crystallised. It gave a neutral solution in aqueous alcohol and only dissolved in moderately strong hydrochloric acid. It distilled as a colourless glass, b. p. 200°/0.005 mm., m. p. ca. 90° (Found: C, 74.9; H, 8.7.  $C_{22}H_{30}O_2N_2$  requires C, 74.6; H, 8.5%).

*Benzoyldeoxydihydroajmaline*.—Deoxydihydroajmaline (0.65 g.), benzoyl chloride (0.35 c.c.), and 5% sodium hydroxide solution (20 c.c.) were mixed and well shaken for 2 hr. The insoluble *benzoyl* derivative crystallised from aqueous methanol as colourless needles (0.6 g.), m. p. 250—255° (Found, in material dried at 100° *in vacuo*: C, 78.0; H, 7.8.  $C_{27}H_{32}O_2N_2$  requires C, 77.9; H, 7.8%). The substance reacts very slowly with methyl iodide in boiling acetone but the resulting methiodide could not be crystallised.

The quaternary reineckate was chromatographed from acetone solution on alumina and after conversion into the chloride exhibited none of the usual ajmaline colour reactions. Evidently N(a) has been quaternised in this case.

*Deoxydihydrotoluene-p-sulphonylajmaline*.—Deoxydihydroajmaline (0.1 g.) was dissolved in ether (5 c.c.) containing toluene-*p*-sulphonyl chloride (10% excess) and shaken overnight with 5% sodium hydroxide solution (1 c.c.). The ether was then separated and, after evaporation of the solvent, the residue crystallised from aqueous methanol as colourless needles (0.1 g.), m. p. 224—225°,  $pK_a$  2.5. The *toluene-p-sulphonyl* derivative was insoluble in 1% hydrochloric acid, even on boiling, but it dissolved in hot 10% hydrochloric acid and was reprecipitated on addition of dilute ammonia (Found, in material dried at 100° *in vacuo* over  $P_2O_5$ : C, 69.8; H, 7.3; S, 6.6; active H, 0.26.  $C_{27}H_{34}O_3N_2S$  requires C, 69.5; H, 7.4; S, 6.9; 1H, 0.22%).

*Deoxydihydro-N-methylajmaline Hydriodide*.—Deoxydihydroajmaline (0.08 g.) was kept for 2 hr. with methyl iodide (0.5 c.c.) and chloroform (2 c.c.). The mixture was then evaporated and the residue crystallised from methanol-ether, giving colourless prisms (1 g.), m. p. 260—264°. Recrystallised from the same solvent the *N-methyl hydriodide* was obtained as fine colourless needles which after drying at 100° *in vacuo* had m. p. 262—264° (Found: C, 55.3; H, 6.6; N, 6.3; I, 27.7.  $C_{21}H_{30}ON_2HI$  requires C, 55.5; H, 6.9; N, 6.2; I, 27.9%). An aqueous solution of this salt gave an immediate precipitate with dilute ammonia, and this was completely soluble even in light petroleum but did not crystallise. The base dissolved readily in dilute hydrochloric acid and addition of potassium iodide caused crystallisation of the hydriodide, m. p. and mixed m. p. 262—264°.

*Oxidation of Deoxydihydroajmaline to Ethyl Methyl Ketone*.—Deoxydihydroajmaline (0.5 g.) in water (10 c.c.) and concentrated sulphuric acid (10 c.c.) was heated, under nitrogen, almost to the b. p. after chromium trioxide (5 g.) in water (10 c.c.) had been added. The distillate was collected in a saturated solution (15 c.c.) of 2:4-dinitrophenylhydrazine in dilute hydrochloric acid. After  $\frac{1}{2}$  hr. more chromium trioxide (5 g.) was added and the distillation continued slowly for a further  $\frac{1}{2}$  hr. The crystalline precipitate (37 mg.) was collected (m. p. 109—111°). The product, purified by chromatography on alumina from a benzene solution, and finally by crystallisation from aqueous methanol, had m. p. 115—116°, or 114—115° when mixed with authentic ethyl methyl ketone 2:4-dinitrophenylhydrazone of m. p. 114—115° (Found: C, 47.7; H, 5.0. Calc. for  $C_{10}H_{12}O_4N_4$ : C, 47.6; H, 4.8%).

*Deoxydihydroisoajmaline*.—*isoAjmaline* (0.26 g.) was refluxed in an atmosphere of nitrogen, with diethylene glycol (6 c.c.) and 85% hydrazine hydrate (2 c.c.) for 10 min. Potassium hydroxide (0.2 g.) was then added and the temperature raised to 190° by distillation. After 2 hr. at this temperature the solution was diluted with water and boiled until the precipitate crystallised. The mixture was cooled and filtered, giving deoxydihydroisoajmaline (0.22 g.), m. p. 152—153°. After sublimation *in vacuo* and crystallisation from aqueous methanol it had m. p. 153—154°,  $[\alpha]_D^{20} + 30^\circ$  (c, 2.3 in  $CHCl_3$ ) (Found: C, 76.2, 76.9, 77.4; H, 8.9, 9.4, 9.1; N, 9.0; C-Me, 8.4, 8.5; active H, 0.43.  $C_{20}H_{28}ON_2$  requires C, 76.9; H, 9.1; N, 9.0; 2C-Me, 9.6; 2H, 0.64%).

*Deoxydihydro-N-methylisoajmaline Hydriodide*.—Deoxydihydroisoajmaline (0.3 g.) was dissolved in benzene (15 c.c.), and methyl iodide (0.5 c.c.) added; crystals were deposited overnight. After decantation the *product* was recrystallised from methanol-ether, affording colourless needles (0.35 g.), m. p. 284—287° (decomp.) (Found: C, 55.6; H, 6.9; I, 28.0.  $C_{21}H_{30}ON_2HI$  requires C, 55.5; H, 6.9; I, 27.6%). An aqueous solution of this salt gave an immediate precipitate with dilute ammonia. The *base* so obtained was recrystallised twice

from aqueous methanol and had m. p. 129—130°,  $[\alpha]_D^{20} +100^\circ$  (*c*, 2.4 in  $\text{CHCl}_3$ ) (Found: C, 77.2; H, 9.1; N, 8.9.  $\text{C}_{21}\text{H}_{30}\text{ON}_2$  requires C, 77.3; H, 9.3; N, 8.6%). Addition of potassium iodide to a solution of the base in dilute hydrochloric acid regenerated the hydriodide, m. p. and mixed m. p. 284—287°.

*Oxidation of Deoxydihydroisoajmaline to Ethyl Methyl Ketone.*—Deoxydihydroisoajmaline (0.2 g.) was oxidised as was the corresponding ajmaline derivative. The crude 2:4-dinitrophenylhydrazone (10 mg.) had m. p. 108—109°. After chromatography on alumina, orange crystals were obtained, having m. p. 114—115°, undepressed by admixture with authentic ethyl methyl ketone 2:4-dinitrophenylhydrazone of the same m. p.

*Deoxyoctahydroajmaline.*—A mixture of hexahydroajmaline (0.3 g.), diethylene glycol (4 c.c.), and 90% hydrazine hydrate (1 c.c.) was refluxed for 5 min., and then potassium hydroxide was added. The product (0.27 g.), isolated as in the previous experiment, had m. p. 187—189°; it sublimed readily, even at atmospheric pressure, and then had m. p. 188—189°,  $[\alpha]_D^{20} +89^\circ$  (*c*, 1.8 in  $\text{CHCl}_3$ ). It showed only end-absorption in the ultra-violet (Found: C, 75.6; H, 10.9; N, 9.0; active H, 0.45, 0.44; C-Me, 9.15.  $\text{C}_{20}\text{H}_{34}\text{ON}_2$  requires C, 75.7; H, 10.8; N, 8.8; 2H, 0.66; 2C-Me, 9.7%).

*Deoxyoctahydroajmaline* was also prepared by catalytic reduction of deoxydihydroajmaline. Experiments with palladised charcoal in neutral solution showed no absorption of hydrogen, and only very slow absorption in the presence of acetic acid, but Adams catalyst gave satisfactory results. Deoxydihydroajmaline (0.117 g.) was dissolved in 50% acetic acid (40 c.c.) and hydrogenated at room temperature and pressure in the presence of Adams catalyst (0.08 g.). Absorption of 3 mols. of hydrogen took place in 25 min. after which there was no further uptake. The filtered solution was made alkaline with ammonia and then extracted with ether. The residue, on evaporation of the solvent, crystallised (m. p. 184—188°), and after recrystallisation from aqueous methanol was obtained as long fine needles, m. p. 188—189° undepressed by deoxyoctahydroajmaline prepared from hexahydroajmaline.

*Attempted Oxidation of Deoxyoctahydroajmaline.*—Deoxyoctahydroajmaline (0.1 g.), dissolved in glacial acetic acid (4 c.c.), was treated with a solution of chromium trioxide (0.1 g.) in water (0.5 c.c.) and acetic acid (2 c.c.). The mixture was set aside at room temperature for 30 hr., then made strongly alkaline and extracted with chloroform. The residue after evaporation of the solvent was passed in benzene through a column of alumina. Elution did not occur with ether alone, but ether containing 2% of methanol eluted starting material, which after crystallisation from aqueous methanol had m. p. and mixed m. p. 189—190°.

*Action of Bromine on Deoxyoctahydroajmaline.*—Deoxyoctahydroajmaline (0.1 g.) was dissolved in hydrobromic acid (1 c.c.) containing bromine (1 c.c.). The dark red mixture was set aside overnight, then diluted with water and boiled to expel the bromine, the last traces of which were removed with a little sodium sulphite. On addition of ammonia crystalline unchanged starting material, m. p. and mixed m. p. 188—189°, was obtained.

*Action of 50% Sulphuric Acid on Deoxyoctahydroajmaline.*—Deoxyoctahydroajmaline (0.2 g.) was heated on a steam-bath with 50% sulphuric acid (10 c.c.) for 1 hr. The base, obtained in the usual way and crystallised from acetone, was unchanged starting material (m. p. and mixed m. p. 188—189°).

*Action of Thionyl Chloride on Deoxyoctahydroajmaline.*—A solution of this base (0.1 g.) in concentrated hydrochloric acid (1 c.c.) was evaporated to dryness *in vacuo*, and the residue dissolved in a mixture of chloroform (5 c.c.) and thionyl chloride (5 c.c.). After refluxing for 4 hr., the solution was evaporated to dryness and the solid crystallised from methanol-ether. The colourless needles of *deoxyoctahydroajmaline dihydrochloride* had m. p. *ca.* 350° (with frothing) (Found: C, 61.1; H, 9.3; Cl, 20.0.  $\text{C}_{20}\text{H}_{34}\text{ON}_2 \cdot 2\text{HCl}$  requires C, 61.5; H, 9.3; Cl, 18.1%). The base had m. p. 188—189°, undepressed by deoxyoctahydroajmaline.

*Hexahydroisoajmaline.*—Hexahydroajmaline (0.5 g.) was refluxed in methanol (25 c.c.) with sodium hydroxide (0.5 g.) for 5 hr. The solution was evaporated to a small bulk *in vacuo*, water was added, and the oil was extracted with ether. The dried ( $\text{Na}_2\text{SO}_4$ ) extract left *hexahydroisoajmaline* as an oil on evaporation; this did not crystallise readily, but when an ethereal solution was kept at 0° large, colourless, elongated prisms, containing ether of crystallisation, gradually separated. The crystals had m. p. *ca.* 110° (frothing), or *ca.* 210° solvent-free. For analysis the substance was sublimed *in vacuo*, then having m. p. 208—210° with sintering at 206°,  $[\alpha]_D^{20} +73^\circ$  (*c* 2.15 in  $\text{CHCl}_3$ ) (Found: C, 72.4; H, 9.7.  $\text{C}_{20}\text{H}_{32}\text{O}_2\text{N}_2$  requires C, 72.3; H, 9.7%).

*Deoxyoctahydroisoajmaline.*—Hexahydroisoajmaline (0.05 g.) was reduced in the usual way, with diethylene glycol (1 c.c.), hydrazine hydrate (0.2 c.c.), and potassium hydroxide (0.1 g.).



The *deoxy*-compound obtained on dilution of the reaction mixture was crystalline and after sublimation *in vacuo* formed colourless prisms, m. p. 184—186.5°, mixed m. p. with deoxy-octahydroajmaline 175—180°,  $[\alpha]_D^{19} + 115^\circ$  (*c.* 1.0 in  $\text{CHCl}_3$ ) (Found : C, 75.3; H, 10.6.  $\text{C}_{20}\text{H}_{34}\text{ON}_2$  requires C, 75.7; H, 10.8%).

*Wolff-Kishner Reduction of Ajmaline Methiodide.*—Ajmaline methiodide (0.5 g.) was reduced in the usual way with diethylene glycol (5 c.c.), hydrazine hydrate (1.5 c.c.), and potassium hydroxide (0.5 g.). The product obtained by dilution with water and ether-extraction was a colourless glass (0.35 g.). On dissolving in dilute hydrochloric acid it readily gave crystalline *deoxydihydro-N-methylajmaline hydrochloride*, m. p. 272—277°,  $[\alpha]_D^{18.5} + 61^\circ$  (*c.* 2.3 in  $\text{H}_2\text{O}$ ) (Found : C, 69.6; H, 8.5; Cl, 10.0.  $\text{C}_{21}\text{H}_{30}\text{ON}_2\cdot\text{HCl}$  requires C, 69.5; H, 8.6; Cl, 9.8%).

The *base*, regenerated from the hydrochloride was sublimed *in vacuo*, then forming a colourless glass,  $[\alpha]_D^{18} + 66^\circ$  (*c.* 2.43 in  $\text{CHCl}_3$ ) (Found : C, 77.2; H, 9.3; active H, 0.29.  $\text{C}_{21}\text{H}_{30}\text{ON}_2$  requires C, 77.3; H, 9.3; 1H, 0.31%).

The hydriodide, obtained from an aqueous solution of the hydrochloride on addition of potassium iodide, formed colourless needles, m. p. 262—264°, unchanged by admixture with deoxydihydro-*N*-methylajmaline hydriodide.

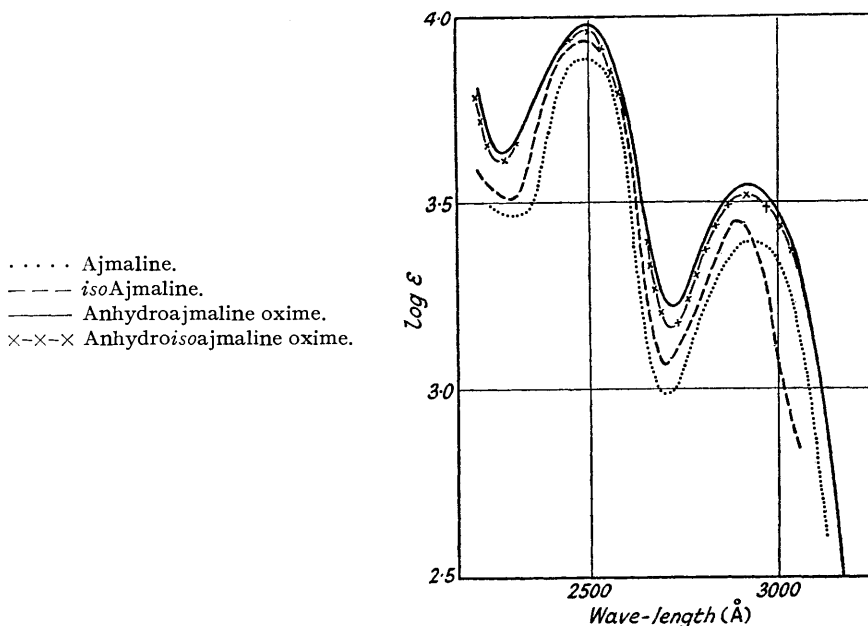
*Deoxydihydro-N-methylajmaline Methiodide.*—Deoxydihydro-*N*-methylajmaline, obtained by Wolff-Kishner reduction of ajmaline methiodide (5 g.), was dissolved in methyl iodide (20 c.c.) and kept for 2 days. The residue after evaporation crystallised slowly from methanol-ether as glistening, compact prisms (3.0 g.), m. p. 213—215° (frothing) and with previous sintering at 200° (Found : C, 55.6; H, 7.4; N, 5.5.  $\text{C}_{22}\text{H}_{33}\text{ON}_2\text{I}$ ,  $\text{CH}_4\text{O}$  requires C, 55.2; H, 7.5; N, 5.6%). The *methiodide* did not crystallise from aqueous solvents. Its aqueous solution gave no precipitate with ammonia. When pyrolysed over a free flame in a test tube at 15 mm. pressure it decomposed with vigorous gas evolution, leaving a colourless oil, which was identified as deoxydihydro-*N*-methylajmaline by conversion into the crystalline hydrochloride, m. p. and mixed m. p. 272—275°.

*Attempted Hofmann Degradation of Deoxydihydro-N-methylajmaline.*—The methiodide (1 g.) was treated with an excess of silver oxide in hot water (100 c.c.), and the glassy methohydroxide left after removal of water from the filtered solution was heated at 180°/20 mm. for 10 min. The colourless oil eluted by chloroform from an alumina adsorbate was dissolved in dilute hydrochloric acid and converted into its hydriodide by addition of successive portions of potassium iodide; some of the fractions crystallised (40 mg.; m. p. 235—240°) and after recrystallisation, had m. p. 250—255° alone or mixed with deoxydihydro-*N*-methylajmaline hydriodide (Found : C, 55.9; H, 7.1. Calc. for  $\text{C}_{21}\text{H}_{30}\text{ON}_2\cdot\text{HI}$ : C, 55.5; H, 6.9%). The infra-red spectra of the two specimens were identical. It is certain that the methohydroxide simply lost the elements of methanol but the yield was low and the process will be re-investigated.

*Anhydrohexahydroajmaline Oxime.*—Hexahydroajmaline oxime (0.55 g.) was dissolved in a mixture of acetic anhydride (1 c.c.) and acetic acid (2 c.c.). The mixture was saturated with dry hydrogen chloride without cooling, and set aside. Colourless needles (0.5 g.) of *O-acetyl-anhydrohexahydroajmaline oxime dihydrochloride* separated and after recrystallisation from methanol-ether had m. p. 350—352° (decomp.) (Found, in material dried at room temperature *in vacuo* over  $\text{P}_2\text{O}_5$ : C, 59.3; H, 8.1; Cl, 15.3.  $\text{C}_{22}\text{H}_{35}\text{O}_2\text{N}_3\text{Cl}_2$  requires C, 59.5; H, 8.0; Cl, 16.0%). It was boiled with potassium hydroxide (0.3 g.) in methanol (12 c.c.) for 3 min., then the mixture was diluted with water, causing the separation of beautiful, flat needles of *anhydrohexahydroajmaline oxime*, m. p. 199—200°. For analysis the substance was sublimed *in vacuo*; it then had  $[\alpha]_D^{17.5} + 44^\circ$  (*c.* 2.03 in  $\text{CHCl}_3$ ) (Found : C, 72.5; H, 9.4.  $\text{C}_{20}\text{H}_{31}\text{ON}_3$  requires C, 72.9; H, 9.5%).

*Action of Methyl Iodide on N-Methyl-sec.-ajmaline.*—Ajmaline methiodide (0.2 g.), dissolved in water (20 c.c.), was made alkaline with excess of 10% sodium hydroxide solution and then extracted with chloroform (4 × 10 c.c.). The extract, after drying ( $\text{Na}_2\text{SO}_4$ ), was evaporated *in vacuo* at as a low temperature as possible. The residue was freed from water and chloroform by distillation with benzene *in vacuo*. It was then dissolved in methyl iodide (5 c.c.) and the solution kept for 30 hr. The excess of the reagent was evaporated and the partly solid residue crystallised from hot water containing a little potassium iodide. The product was obtained as small prisms (0.15 g.), m. p. 250° (decomp.), which, after several recrystallisations from water with the addition of potassium iodide, and finally from water alone, had m. p. 251—252° (decomp.) (Found : C, 54.9; H, 6.5; I, 25.3; OMe, 8.0; NMe, 5.2.  $\text{C}_{22}\text{H}_{31}\text{O}_2\text{N}_2\text{I}$  requires C, 54.8; H, 6.5; I, 26.3; IOMe, 6.4; INMe, 6.0%). The *salt* showed true quaternary character, and could even be crystallised unchanged from concentrated potassium hydroxide solution. Further estimations of OMe and NMe combined gave values of 12—15% calculated as *N*-Me.

*Dihydro-N-methylajmaline Hydriodide*.—*N*-Methyl-*sec*.-ajmaline, prepared as before from ajmaline methiodide (1 g.) and dried by distillation with benzene *in vacuo*, was dissolved in tetrahydrofuran (30 c.c.), and the solution carefully added to a suspension of lithium aluminium hydride (0.5 g.) in the same solvent (20 c.c.). The mixture was refluxed for 2 hr. and then cautiously decomposed by the addition of water. The solution was filtered and the granular precipitate washed with tetrahydrofuran. The combined filtrate and washings, on evaporation to dryness, left a colourless oil, which did not crystallise but readily afforded a crystalline hydriodide (0.5 g.) on addition of potassium iodide to a solution in dilute hydrochloric acid. The *hydriodide* formed colourless needles, easily soluble in hot water, and had m. p. 224—226° (frothing) (Found, in material dried at 100°: C, 53.8; H, 6.4.  $C_{21}H_{30}O_2N_2, HI$  requires C, 53.6; H, 6.7%). The same product was obtained more easily by adding a concentrated aqueous solution of potassium borohydride (0.2 g.) to a warm solution of ajmaline methiodide (1.5 g.) in water (50 c.c.). The base was precipitated as an oil almost immediately. The mixture was acidified with dilute hydrochloric acid, and the hydriodide (1 g.) obtained by the addition of potassium iodide.



*Deoxyajmaline*.—Dihydro-*N*-methylajmaline hydriodide (1 g.) was refluxed with hydrobromic acid (20 c.c. of 50%) for 4 hr. The solution was then evaporated to dryness *in vacuo*, and the residue dissolved in water and mixed with a saturated solution of Reinecke's salt (5 g.). The amorphous precipitate was dried and adsorbed on alumina from an acetone solution. The most readily eluted and major fraction was concentrated *in vacuo*, and diluted with warm water; long needles separated on cooling. The reineckate was collected, dissolved in acetone, and converted into the chloride by successive treatments with silver sulphate and barium chloride. The filtered solution was evaporated to dryness *in vacuo* and the residue washed with boiling alcohol, which left the barium chloride undissolved. The alcoholic solution was diluted with ether, colourless needles of *deoxyajmaline methochloride* being deposited. The salt was recrystallised from methanol-ether and formed long, colourless needles, m. p. 305—310° (decomp.) (Found: C, 64.5; H, 8.7.  $C_{21}H_{29}ON_2Cl, CH_4O, H_2O$  requires C, 64.3; H, 8.6%). *Deoxyajmaline methobromide* was obtained on addition of sodium bromide to an aqueous solution of the methochloride. It crystallised from methanol-ether in colourless prisms, m. p. 320—325°,  $[\alpha]_D^{20} +132^\circ$  (*c*, 1.44 in  $H_2O$ ) (Found: C, 61.6; H, 7.4; Br, 19.0.  $C_{21}H_{29}ON_2Br, 0.5CH_4O$  requires C, 61.3; H, 7.4; Br, 19.0%).

*Deoxyajmaline methochloride* was pyrolysed in a test tube at 0.5 mm. pressure, over a free flame. Colourless crystals sublimed on the cold parts of the tube. The product, *deoxyajmaline*, recrystallised from aqueous methanol as colourless plates, m. p. *ca.* 310° (sublimation),  $[\alpha]_D^{20}$

+124° (*c*, 0.94 in MeOH-CHCl<sub>3</sub>, 5 : 2 by vol.) (Found : C, 76.9; H, 8.2. C<sub>20</sub>H<sub>26</sub>ON<sub>2</sub> requires C, 77.4; H, 8.4%).

*Physical Data.*—Values of p*K*<sub>a</sub> were determined in 80% Methylcellosolve except where stated otherwise, at 18–20°, with a glass electrode and Cambridge pH meter and at concentrations of about *M*/100. 0.1*N*-Hydrochloric acid was used in the titrations.

The ultra-violet absorptions of ajmaline and *iso*ajmaline (and their anhydro-oximes) were very similar (see Figure).

Hexahydroajmaline and deoxyoctahydroajmaline showed only end-absorption (at *ca.* 2000 Å).

Active-hydrogen values were determined at room temperature. Under these conditions the NH group usually affords about 30% of the theoretical value.

Infra-red absorption bands of paraffin-paste suspensions (Perkin-Elmer double-beam instrument; wave-lengths in microns) are tabulated below.

Substance	Selected bands or no band	Interpretation *	Substance	Selected bands or no band	Interpretation *
Ajmaline	3.00, 3.17 3.5–4.00 6.21	OH Bonded OH *	Deoxydihydro- <i>N</i> - methyl <i>iso</i> - ajmaline	3.05 6.20	OH *
<i>iso</i> Ajmaline	2.85, 3.27 3.5–3.8 — 6.21	OH Bonded OH No CO *	Ajmaline meth- iodide	2.98, 3.10 — 6.20	OH No CO *
Hexahydro- ajmaline	3.10 (wide) —	OH No CO or sub- stituted benzene	<i>iso</i> Ajmaline meth- iodide	2.77, 2.98, 3.27 — 6.20	OH OH No CO *
Ajmaline hydro- chloride	2.95, 3.03, 3.14 3.5–4.00 6.00 (weak) 6.19	Various OH ? ?	<i>N</i> -Methylajmaline hydrate	5.97, 6.04 6.20 2.97	† * OH
Do., 2H <sub>2</sub> O	2.83, 3.02, 3.06 3.15, 3.50— 4.00 (6.04 (medium) 6.20	OH " " ? *	<i>N</i> -Methylajmaline (distilled) (con- tains some methyl <i>iso</i> - ajmaline)	5.80 (strong) 5.92 (weak) 6.20 >7.0	Unconjugated CO Conjugated CO * Follows the curve of its hydrate
Ajmaline dihydro- chloride	3.10, 3.25 3.5–4.25 — —	OH " No CO No benzene band (!)	Do. in CHCl <sub>3</sub>	5.81 (weak) 5.93 (strong)	} As above As above
Diacetylajmaline	— 5.75 — 6.21	No OH CO of OAc No CO of NAc *	<i>N</i> -Methyl <i>iso</i> - ajmaline	Similar results	As above
Diacetylhexa- hydroajmaline	— 3.72, 5.76 — —	No OH CO of OAc No CO of NAc No benzene band	<i>iso</i> Ajmaline oxime	3.00, 3.05 — 6.20	OH No :C=N* *
Deoxydihydro- ajmaline	3.20 6.21	OH *	Ajmaline oxime hydrochloride	2.90, 3.00, 3.05 6.15	OH OH :C=N* (?)
Deoxydihydro <i>iso</i> - ajmaline	3.15 6.21	OH *	Hexahydro- ajmaline oxime	3.10, 3.30, 3.55 6.05	OH OH :C=N* No benzene band
Deoxyoctahydro- ajmaline	3.05, 3.23 —	OH No benzene band	Anhydroajmaline oxime	3.20 4.50 — 6.22	OH CN No CO *
			Anhydro <i>iso</i> - ajmaline oxime	3.0, 3.12 4.47 — 6.20	OH CN No CO *

\* In this column an asterisk denotes an aromatic benzene nucleus.

† Small separation to double peak, conjugated CO.

The authors thank Dr. F. Bader for assistance in the extraction and purification of ajmaline. They are also grateful to Dr. F. B. Strauss for examination of the infra-red absorption spectra and for his assistance in their interpretation.