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STUDIES IN THE AJMALINE SERIES

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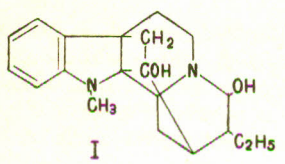
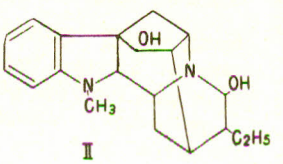
Out of the various bases isolated by Siddiqui and Siddiqui[1] from the roots of *Rauwolfia serpentina*, ajmaline, the principal alkaloid, was subjected by the authors to a more detailed study.[2] In the course of this study, it was found that ajmaline contains one N-methyl group, forms neutral nitrosoamine derivative and yields a tertiary methyl base through its methiodide. A secondary character was, therefore, concluded for one of its two nitrogen atoms. The presence of an olefinic double bond in the molecule was deduced from the fact that it took two atoms of bromine in the cold, giving a product which when crystallised from alcohol melted at 230°C. (decomp.) and analysed for dibromoajmaline. On the basis of their further studies in the chemical characteristics of ajmaline and the colour reactions of the zinc dust distillation products, already reported in the meanwhile by van Itallie and Steenhauer,[3] Siddiqui and Siddiqui further suggested a structure for ajmaline closely allied to strychnine.

Following these investigations, Robinson and his associates[4,5,6,7], carried out comprehensive studies in the constitution of ajmaline and assigned to it the structural formula I which was later slightly modified by Woodward as II.[8]



I



II

In their first communication on the subject, Robinson et al. generally confirmed the earlier findings of Siddiqui and Siddiqui, but disagreed with the interpretations they put forward for some of them. These points of disagreement may be summarised as follows:—

1. Dibromoajmaline is actually bromoajmaline hydrobromide, as its aqueous solution gave precipitate on the addition of an aqueous solution of silver nitrate, and monobromoajmaline on liberating the base with ammonia.

2. Ajmaline is di-tertiary and not secondary-tertiary in character, as it yields a quaternary base through its methiodide, and the action of nitrous acid on ajmaline hydrochloride in aqueous solution gives a basic C-nitroso and not N-nitroso derivative.

3. Neoajmaline reported by Siddiqui[9] could not be distinguished from ajmaline with any certainty as its hydrochloride gave ajmaline hydrochloride on recrystallisation, and the m.p. 205-207°C. recorded for neoajmaline as against 158-160°C. for ajmaline could be considered as that of anhydrous ajmaline.

The isolation of serpajmaline and other therapeutically significant alkaloidal complexes by Siddiqui[10] from the fresh undried roots of *Rauwolfia serpentina*, followed by the observation that the serpajmaline complex besides being hypotensive in character[11] also possessed antifibrillant action[12] on the isolated heart of the rabbit and dog, revived fresh interest in the chemistry and pharmacology of the alkaloidal constituents of *Rauwolfia*. Studies in this direction led to the finding that ajmaline, the main alkaloidal component of serpajmaline, has the same order of antifibrillant action as the complex as a whole and that serpentine also has this character although to a lesser degree, while serpentinine is inactive. In view of these findings, it was considered of interest to study the relationship between the chemical constitution of ajmaline and its cardiac action. As a result of this study it has been found that the reduction of the benzene ring in ajmaline (hexahydroajmaline) lowers its cardiac activity to about 1/1000. On the other hand, methyl-, acetyl- and dihydro-ajmaline, in all of which the benzene ring remains intact, were found to be devoid of any cardiac activity,[13] establishing the fact that the dynamic isomerism of the carbinolamine and imine-aldelyde structure, $=\overset{|}{N}.\overset{|}{C}H(OH) \rightleftharpoons =NH \quad \overset{|}{C}HO$, serving as what may be described as a 'cardiophoric' grouping, is essential for the cardiac action of the ajmaline molecule, and that the benzene ring in it has only a potentiating action.

In the course of these investigations the earlier work of Siddiqui and Siddiqui (loc. cit.) on ajmaline was repeated and their conclusions re-examined in the light of disagreement expressed by Robinson et al. and referred to at the outset.

As a result of this re-examination the position may be stated as follows:—

The bromination product obtained on titration

of ajmaline with bromine in chloroform solution melts, as reported by Robinson et al. at 295°C. (decomp.), but on crystallisation from alcohol it shows m.p. 235-239°C. as recorded by Siddiqui and Siddiqui. That this variation in melting point is not due to the anhydrous state of the former is evidenced from the fact that on drying the bromo-product crystallised from alcohol *in vacuo* at 100°C., the melting point is not affected. In case of iso-ajmaline also the melting point recorded by Robinson for its bromination product is 288-289°C. (decomp.) but it has been found that on crystallisation from methanol it melts at 225-228°C.

Further, it has now been noted that, when the drop by drop addition of bromine in chloroform solution is carried on till there is a persistent turbidity, which occurs after the addition of only 1.7 atoms of bromine, and the addition product is worked up as described in the experimental, a bromo derivative is obtained which on crystallisation from methanol melts at 178-182°C. (decomp.), the melting point remaining unaffected on further crystallisations or drying *in vacuo* at 100°C. These findings suggest the formation of three isomeric bromo derivatives, of which the one melting at 296°C. is an unstable form.

The observations made in the course of the bromination studies, which were extended to a number of other derivatives of ajmaline, would appear to indicate that the carbinol amine tautomeric grouping induces a potential olefinic double bond in the complex ring system of ajmaline, presumably at the expense of the bridge ring provided in its structure by both Robinson and Woodward. This could account for the formation of a chloroform soluble, dibromo addition product from which HBr is secondarily eliminated, yielding a monobromo, chloroform insoluble hydrobromide, which on treatment with aqueous ammonia yields monobromoajmaline. This view gets a measure of support from the fact that dihydroajmaline fails to give a bromo derivative, and that secondary elimination of HBr from bromine addition products of bases containing an olefinic linkage has been reported earlier, e.g. in the case of the conessine series of alkaloids.[14] The fact that hexahydroajmaline is saturated to bromine would only show that the reduction of the benzene ring stabilises the bridge ring, rather than constitute an argument in favour of a straightforward bromine substitution reaction at the aromatic centre, under the experimental conditions of the reaction.

Again, methylajmaline, in which the carbinol-amine grouping is eliminated and the aldehyde group stabilised, takes up nearly 3 atoms of bromine, giving an amorphous powder which melts at 290°C., is difficultly soluble in water and gives a bromine-free product on liberation with aqueous ammonia, which could be identified with methylisoajmaline through its hydriodide (m.p. 195°C.; methylajmaline hydriodide, m.p. 129-131°C.). The formation of such a loose bromo compound might be explained by the enolisation of the aldehydic carbonyl of the base from which bromine is completely eliminated on treatment with ammonia, methylajmaline being converted into methylisoajmaline in the process.

In re-examining the alternatives of secondary or tertiary character of one of the two nitrogen atoms of ajmaline, the findings of Siddiqui and Siddiqui in regard to the formation of a neutral, N-nitroso derivative of ajmaline on treatment of the base with nitrous acid in acetic acid medium, and of a tertiary methyl base through the methiodide, have been repeatedly checked up and confirmed. It has, however, been noted that, as reported by Robinson et al., treatment of ajmaline in hydrochloric acid medium gives a C-nitroso basic product. The resolution of this point of disagreement, however, had in effect already emerged from a subsequent communication of Robinson et al. (loc. cit.) which formulated the tautomeric carbinol-amine and imine-aldehyde structure for ajmaline. In this context, the authors had concluded from their studies that ajmaline in neutral or acid soluti on contains $=N.\overset{|}{C}H(OH)$ 'the abnormal carbinol-amine group', but that in alkaline solution only a small proportion of the form $=NH\ \overset{|}{C}HO$ (aldehyde-imine) is probably present in equilibrium with the carbinol-amine. The fact that the N-nitroso derivative of ajmaline is smoothly obtained in nearly theoretical yield in acetic acid medium controverts such a conclusion.

Siddiqui and Siddiqui had concluded a mono- and a di-acid character for ajmaline and isoajmaline, respectively. This conclusion proved erroneous, because isoajmaline hydrochloride had been prepared by them in ethereal medium, and ajmaline hydrochloride by reacting the base with aqueous hydrochloric acid, in which the weakly basic nitrogen in both the bases fails to form a salt.

With regard to neoajmaline which Robinson et al. have considered to be probably anhydrous ajmaline, it would appear from the present study that the two bases are quite distinct isomers. In the course of isolation of the alkaloidal complexes and individual bases from the fresh roots of *Rauwolfia*, it was observed that with identical procedure of isolation some batches of the drug yielded only neoajmaline while others gave the normal isomer,

ajmaline, depending on the age of the roots harvested from the same experimental farm. Moreover, neoajmaline was repeatedly obtained by slowly adding a warm aqueous solution of the hydrochloride to a strong, well-cooled solution of ammonia, and crystallising the precipitated base from dilute methanol. These conditions would not favour the formation of an anhydride, the more so because as reported by Siddiqui and Siddiqui the water of crystallisation tenaciously adheres to the ajmaline molecule, being completely eliminated only on heating *in vacuo* over a long period at 150°C. It has, however, been observed that the reduction of neoajmaline and ajmaline with borohydride results in the production of identical dihydroajmaline. The isomerism may, therefore, be due to the spatial arrangement of the H and OH of the carbinol amine group.

Taking into account the behaviour of ajmaline and its derivatives in respect of their cardiac action and the abnormal character of the carbinol-amine grouping in ajmaline, it was considered of great interest to study the stability of the carbinol-amine ring of the base, and the possible bearing of this factor on its cardiac action.

With this object in view, the von Braun reaction of cyanogen bromide[15] was carried out with ajmaline and hexahydroajmaline, after protecting the reactive hydroxyl groups and stabilising the carbinol-amine structure through acetylation. Under the conditions described in the experimental, a monocyano-monoacetyl derivative was readily obtained on treatment of diacetylajmaline with cyanogen bromide, while the same reaction takes about 24 hours for completion with hexahydrodiacetylajmaline. The comparative speed with which this reaction proceeds is a measure of the instability of the carbinol amine ring in ajmaline, and its considerable stabilisation through the reduction of the benzene ring, offering a co-relation of the stability of this ring with the intensity of cardiac action which, as referred to above, is 1000 times lower for hexahydroajmaline compared with that of ajmaline. It will be of interest to make a reference in this connection to the close relationship established by von Braun and his collaborators between the N-stability of the radicals attached to the basic nitrogen in the codeine series[16] and their action on respiration, and also to allied studies in the conessine series.[17,18] The cyanogen bromide reaction appears to proceed with the two bases on the pattern shown in Chart 1.

With the rupture of the carbinol amine ring in the case of both the diacetyl bases, the acetyl group attached to the ring is apparently eliminated as CH_3COBr, with the formation of a monoacetyl-

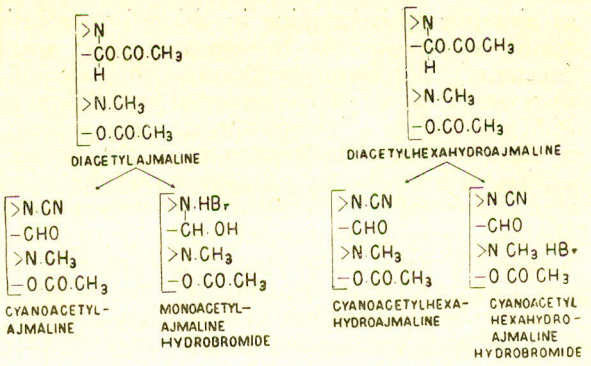


Chart 1

cyano derivative containing a free aldehyde grouping. As to the formation of the hydrobromides, it may be pointed out that a secondary elimination of HBr from the bromo alkyls resulting from the action of BrCN on tertiary amines has been noted by von Braun, and was also encountered with this reaction in the conessine series (loc. cit.). The formation of the monoacetylajmaline hydrobromide would indicate the comparative instability of the acetyl group attached to the carbinol amine ring and it is apparently hydrolysed off under the experimental conditions of this reaction, in which no special care was taken to completely free the reactants from moisture. It is also of interest to note that the reduction of the benzene ring in ajmaline brings about considerable increase in the basic strength of the indole nitrogen, with the result that a stable cyanohexahydroajmaline hydrobromide salt was found in the BrCN reaction with the base. It may be further stated that the use of chloroform employed by von Braun as a medium for the cyanogen bromide reaction (loc. cit.) proved altogether inadequate in the case of the ajmaline base, and that it proceeded smoothly in ethereal solution, as had also been observed with this reaction in the conessine series.

Further work on problems arising out of the present study is in progress with particular refernce to the synthesis of simpler compounds with a carbinol-amine grouping on the general model of the ajmaline molecule.

Experimental

Reduction of Ajmaline and Neoajmaline with Borohydride.—Ajmaline (1 g.) was dissolved in ethyl alcohol, freshly distilled over lime (10 ml.) and an aqueous solution of borohydride (0.5 g. in 10 ml.) was added to it, when the reaction mixture became slightly turbid. More ethyl alcohol was then added drop by drop and shaken

until a clear solution was obtained, and the reaction mixture was allowed to stand overnight at room temperature (25°C.). Any excess of borohydride was decomposed by cautious addition of dilute acetic acid. The solvent was removed on water bath, and the residue rubbed with ammonia and crushed ice. The crystalline precipitate thus obtained was filtered and washed with cold dilute ammonia (yield 0.9 g., m.p. 200-201°C.). Crystallised from methanol (rhombic plates) it melted at 203-205°C. Robinson et al. carried out the reduction in boiling aqueous methanol with potassium borohydride and obtained dihydroajmaline prisms, m.p. 200°C. Neoajmaline treated with borohydride in the same manner gave an identical dihydro product.

Reduction of Isoajmaline with Borohydride.—Isoajmaline was also treated with borohydride as in the case of ajmaline. The dihydro base finally obtained (yield 90%) crystallised from dilute methanol in rectangular plates which melted at 190-92°C. Robinson et al. recorded 188°C. as the melting point of dihydroisoajmaline.

Attempted Isomerisation of Dihydroajmaline.—Dihydroajmaline (0.25 g.) was refluxed in methanolic caustic potash (25 ml., 2% solution w/v) for 5 hours. The solvent was removed on the water bath and the thick viscous residue rubbed with crushed ice. The crystalline product thus obtained was filtered and washed free of alkali with ice-cold water. On re-crystallisation from methanol it melted at 203-205°C. (undepressed on admixture with dihydroajmaline).

On further refluxing for 12 hours with stronger methanolic caustic potash solution also (25 ml., 4% w/v), dihydroajmaline was recovered unchanged.

Borohydride Reduction of Hexahydroajmaline.—Hexahydroajmaline (0.2 g.) was dissolved in warm ethyl alcohol (freshly distilled over lime) and was treated with sodium borohydride (0.2 g.) in the manner already described. The product obtained on basification with ammonia became crystalline on standing. It was filtered, washed and crystallised with dilute methanol (prismatic rods), darkened at 210°C. onwards, shrank at 225°C. and melted at 228-30°C.

Catalytic Hydrogenation of Dihydroajmaline.—Dihydroajmaline (0.25 g.) was taken up in 50% acetic acid (20 ml.) and hydrogenated in the presence of Adams catalyst (0.025 g.). The reduction was complete in one hour. After filtering off the catalyst, the filtrate was concentrated to half the volume *in vacuo*. The precipitate obtained on the addition of ammonia crystallised from dilute methanol in prismatic rods which melted at 230°C. and showed no depression in m.p. on admixture with the product obtained by the borohydride reduction of hexahydroajmaline.

Bromination of Ajmaline.—Ajmaline (0.3 g.) in dry chloroform (4 ml.) was titrated with bromine solution in dry chloroform (1.5% w/v) with ice cooling. Absorption was very rapid and the reaction mixture gave test for free bromine when 11.5 ml. of the bromine solution had been added (4.9 ml. = 1 Br.). The solvent was removed *in vacuo* at room temperature. The micro-crystalline residue obtained on complete removal of the solvent darkened at 210°C. onwards and frothed up at 298-300°C. with decomposition (295°C. recorded by Robinson as the m.p. (decomp.) for anhydrous bromoajmaline). On crystallisation from ethyl alcohol it showed m.p. 235-39°C. with shrinking at 225°C. Siddiqui and Siddiqui recorded 230°C. as the melting point (decomp.) of the bromo derivative. After drying *in vacuo* over P_2O_5 at 100°C., this melting point remained unaffected.

In another experiment ajmaline (0.5 g.) dissolved in chloroform (8 ml.) was treated with bromine in chloroform (1.58 % w/v), drop by drop with ice cooling. After about one atom of bromine had been added, slight turbidity started appearing on further addition which vanished on stirring. When 13.3 ml. had been added (equivalent 1.7 Br) the addition of a further drop of bromine solution gave a persistent turbidity with a tendency to partial crystallisation. Bromine addition was stopped at this stage and the solvent removed *in vacuo*. The white semi-crystalline residue was freed from any unreacted ajmaline by repeated extraction with ethyl acetate and repeatedly crystallised from methanol when it formed stout prismatic hexagonal plates melting at 278-82°C. as against 235-39°C. recorded for the bromo derivative crystallised from methanol in the preceding experiment. The product was fairly soluble in water from which it crystallised in cauliflower-like aggregates of silky needles melting at 230°C. (decomp.), which on crystallisation from methanol reverted to the prismatic form and showed m.p. 268-70°C. (decomp.).

Monobromoajmaline.—Bromoajmaline, m.p. 239°C. (decomp.), dissolved in dry ethyl acetate, was saturated with dry ammonia gas. The precipitated ammonium bromide was filtered off and the solvent removed on the water bath. The solution of the residue in methanol gave on slow evaporation fine colourless needles which melted at 182°C. (decomp.). The melting point was identical with that of the product obtained after Robinson's

method on treatment of the bromination product with aqueous ammonia. (In the case of conessine, it was possible to obtain a dibromo base on treatment of the bromine addition product (dibromoconessine dihydrobromide) with dry ammonia in organic solvents).

Bromination of Isoajmaline.—Isoajmaline (0.206 g.) in dry chloroform was titrated with bromine solution in dry chloroform (1.58% w/v) with ice cooling. The reaction mixture showed the presence of free bromine (tested with starch-potassium iodide paper) when 0.13 g. had been added (0.11 g. = 1 mole). The solvent was removed under reduced pressure at room temperature (25°C.). The residue crystallised on rubbing with methanol in triangular plates, m.p. 225-228°C. (decomp.). (Robinson et. al. recorded 288-289°C. (decomp.) as the melting point for'anhydrous' bromoisoajmaline).

Action of Bromine on Dihydroajmaline.—A well-cooled solution of dihydroajmaline (0.24 g.) in dry chloroform was treated with bromine in dry chloroform (1.58% w/v). The absorption of bromine appeared to be very slow as judged by the disappearance of the yellow colour. One mole of bromine was however added and the mixture kept in the cold for about an hour. The solvent was then removed *in vacuo* at room temperature (25°C.) and the residue which became powdery on rubbing with ether was filtered and washed well with ether. The amorphous powder decomposed with charring at 220-222°C. It was sparingly soluble in water and the aqueous solution produced a precipitate with aqueous silver nitrate. The amorphous powder, which failed to crystallise from methanol or dilute methanol, was treated with ammonia in aqueous medium, and the liberated base crystallised from methanol, when it melted at 200-201°C. showing no depression in melting point on admixture with dihydroajmaline.

Bromination of Methylajmaline.—Methylajmaline (0.33 g.) in dry chloroform was titrated with bromine in dry chloroform (1.38%w/v) with ice cooling. The reaction mixture showed the presence of free bromine when 16.5 ml. (ca. 3 Br) had been added. The supernatant liquid was decanted from the precipitate which formed with the addition of bromine. On rubbing with ether the yellowish sticky residue turned into a nearly colourless powder, which when washed well with ether darkened from 180°C. onwards, and melted with decomp. at 290°C. The bromo product was then treated in dry ethyl acetate suspension with dry ammonia gas, the resulting solution of the liberated base filtered off from ammonium bromide and the filtrate freed of the solvent *in vacuo*. The residue on complete removal of the solvent melted at 120°C. but failed to crystallise. It was characterised as methylisoajmaline through its hydriodide, which on crystallisation from methanol melted at 198°C. (decomp.). (Robinson et al. have recorded m.p. 195-96°C.).

Reaction of Bromine on Hexahydroajmaline.—Hexahydroajmaline (0.3 g.) was dissolved in an excess of chloroform (about 30 ml.) in which it is difficultly soluble. The solution was well cooled in ice and titrated with bromine solution (1.38% w/v). Absorption was rapid and the reaction mixture gave the test for free bromine when 6 ml. of the solution had been added (about 1 Br).

The residue obtained on complete removal of the solvent *in vacuo* at ordinary temperature was found to be readily soluble in water and gave a precipitate with silver nitrate. The base liberated from the aqueous solution of the product with dilute alkali and crystallised from ethyl alcohol (square plates) showed m.p. 150°C., as recorded for hexahydroajmaline by Robinson et al.

Action of Bromine on Diacetylhexahydroajmaline.—Diacetylhexahydroajmaline on treatment with bromine under conditions already described gave a water-soluble reaction product from which the base was recovered unchanged. It was characterised through its perchlorate m.p. 190-192°C., undepressed on admixture with an authentic sample of the salt.

Action of Cyanogen Bromide on Diacetylajmaline.—Diacetylajmaline (5 g.) was dissolved in ether (50 ml.) with the help of a little ethyl acetate, and the solution concentrated to about 120 ml. To the solution was added drop by drop a solution of 1.5 g. cyanogen bromide (1.15 mole) in ether (15 ml.) with efficient ice cooling and stirring. The gelatinous precipitate, which separated out during the addition in the course of about 10 minutes, turned into a granular powder on rubbing. After keeping in the cold for about 3 hours the ethereal solution was filtered, repeatedly washed with small quantities of water, dried over sodium sulphate and allowed to concentrate by slow evaporation overnight. The product thus obtained (5.0 g.) crystallised from ethyl acetate in colourless, stout, prismatic rods and hexagonal plates which were soluble in hot ethyl acetate, very sparingly so in ether and alcohol, insoluble in water, melted at 205-207°C. and analysed for monoacetylcyanoajmaline.

Calculated for $C_{23}H_{27}O_3N_3$: C, 70.23; H, 6.87; N, 10.88. Found on drying at 100°C. *in vacuo*: C, 69.57; H, 6.96; N, 10.75.

The granular precipitate obtained in the reaction (0.8 g.) melted at 250-252 °C. and when repeatedly crystallised from a large quantity of ethyl acetate helped with a little ethyl alcohol finally gave colourless crystals which showed m.p. of 266 °C., were soluble in water, very sparingly so in ethyl acetate, almost insoluble in ether or petroleum ether and analysed for monoacetylajmaline hydrobromide.

Caculated for $C_{22}H_{28}O_3N_2.HBr$: C, 58.79 ; H, 6.68; N. 6.46; Br, 17.81. Found on drying at 100 °C. *in vacuo*: C, 58.61; H, 6.11; N. 6.10; Br, 17.99.

The equeous solution of the hydrobromide was basified with ammonia and the liberated base on recrystallisation from dilute alcohol melted at 212-214°C. and analysed for monoacetylajmaline.

Calculated for $C_{22}H_{28}O_3N_2$: C, 71.73; H, 7.60; N, 7.60. Found on drying at 100°C. *in vacuo*: C, 71.77; H, 7.87; N, 7.52.

In the process of working up the reaction mixture small quantities of crystalline products, probably resulting from side reactions and melting at 194-196 °C. and 220-224 °C., were also obtained but were not followed up.

Hydrolysis of Monoacetylcyanoajmaline—Isoajmaline.—Monoacetylcyanoajmaline (0.5 g.) was refluxed over water bath with methanolic potassium hydroxide (5% w/v, 10 ml.). The hydrolysis proceeded at a very slow rate with the formation of sodium carbonate and evolution of ammonia. After about 50 hours, the reaction mixture gave on keeping in the cold for 48 hours, a bulky crop of colourless crystals which was filtered off from the supernatant liquid, washed with a little ice-cold methyl alcohol and then with water (yield, 0.18 g.). On crystallisation from methyl alcohol it gave colourless stout rods which melted at 256 °C. and analysed for isoajmaline (m. p. 265 °C.). On further refluxing, the mother liquor from the reaction crystallisate gave, after about another 40 hours, 0.17 g. of the hydrolysed base (total yield, 0.35 g.).

Action of Cyanogen Bromide on Diacetylhexahydroajmaline. — Diacetylhexahydroajmaline (0.57 g.), obtained by treating the crystalline perchlorate of the base with ethereal ammonia in ether suspension, was dissolved in ether (3 ml.). To the ethereal solution of the base was added drop by drop, a solution of cyanogen bromide 0.2 g. (a little in excess of one mole) in dry ether (5 ml.) with efficient ice cooling and stirring. No immediate precipitation followed, as had happened in the case of this reaction with diacetylajmaline. The reaction mixture was then allowed to stand in the cold for about 24 hours, in the course of which a thick jelly-like mass separated out which was repeatedly triturated with ether. The combined ethereal extract was freed of the solvent on the water bath and the residue thus obtained was crystallised from methanol, out of which it came out in colourless needles which were readily soluble in ethyl alcohol and ethyl acetate, sparingly soluble in ether, less so in petroleum ether, melted at 146-148 °C. and analysed for monoacetylcyanohexahydroajmaline.

Calculated for $C_{23}H_{33}O_3N_3$: C, 69.17; H, 8.27; N, 10.52. Found on drying at 100 °C. *in vacuo*: C, 69.39; H, 8.40; N, 10.39.

The ether insoluble, gelatinous residue was completely freed of the solvent, taken up in water and extracted with small quantities of ethyl acetate. The colourless residue left on removal of the solvent from the aqueous layer on the water bath, crystallised from a mixture of absolute alcohol and ethyl acetate in colourless needles (m.p. 256-257 °C.) which were freely soluble in water and alcohol, almost insoluble in ethyl acetate and ether, and analysed for monoacetylcyanohexahydroajmaline hydrobromide.

Calculated for $C_{23}H_{33}O_3N_3.HBr.H_2O$: C, 55.42; H, 7.22; N, 8.42; Br, 16.06. Found on drying at 100 °C. *in vucuo*: C, 55.82; H, 7.03; N, 8.31; Br, 16.21.

The free base obtained from the hydrobromide salt on liberation with ammonia crystallised from methanol in colourless needles which melted at 146-148 °C. and showed no depression in the melting point on admixture with the cyano derivative obtained directly from the ether soluble portion of the reaction product.

The total yield of the cyano base was nearly theoretical, and derived in about equal proportions from the ether soluble and the ether insoluble fractions of the cyanogen bromide reaction product.

Acetylation of Ajmaline and Hexahydroajmaline.—*Diacetylajmaline and Diacetylhexahydroajmaline.*—In the preparation of diacetylajmaline needed for the BrCN reaction, considerable difficulty was experienced in following the method employed by Robinson et al. (refluxing with acetic anhydride in benzene solution for 12 hours). Apart from being time consuming and complicated in its working it was noted that slight impurities in the reactants or the solvent very adversely affected the yield, and a simpler method

was, therefore, worked out for the acetylation of these bases which consisted in heating the components directly for 5 minutes in the water bath, removing acetic anhydride completely *in vocuo* and crystallising the product when diacetylajmaline (hexagonal prismatic rods, m.p. 192-194°C.) and diacetylhexahydroajmaline (isolated as perchlorate needles, m.p. 190-192°C.) were obtained in about 70% yield.

Summary

The action of bromine on ajmaline and its various derivatives has been studied in detail to elucidate the mechanism of this reaction, and earlier points of disagreement in respect of the chemical characteristics of ajmaline have been experimentally checked up for clarification. Further, on the basis of studies in the action of cyanogen bromide on the diacetyl derivatives of ajmaline and hexahydroajmaline, the antifibrillant cardiac action of ajmaline has been co-related with the N-stability of the carbinol-amine structure, which appears to function as a 'cardiophore' grouping in the ajmaline molecule.

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