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The Stereochemistry of Tetrahydroalstonine and Related Indole Alkaloids *

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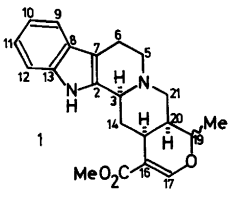
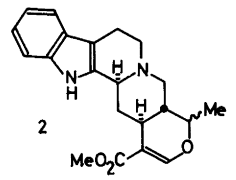
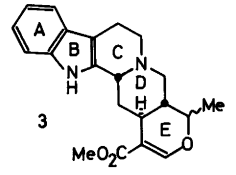
A chemical degradation of tetrahydroalstonine and correlation of a degradation product with one derived from ajmalicine has led to a reassignment of the C(20) stereochemistry of these and related alkaloids. ^{1}H NMR spectral analysis of these bases has yielded their full configurations.

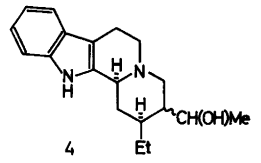
Preliminary experiments on model compounds during the period of active investigation of the stereochemistry of reserpine and related indole alkaloids in the middle 1950s showed that reactions designed to test the ease of electrophilic attack on the non-indolic nitrogen or ease of hydrogen abstraction from C(3) of natural bases of the yohimbine, ajmalicine and corynantheine types might reflect the stereochemistry of such substances.[2] Whereas differences of N_b reactivity were noticeable in pK_a measurements and N_b-oxide preparations, these observations remained unexploited up to the time of the development of an elegant method of stereochemistry analysis based on differences of N_b methiodide formation.[3,4] The observation of differences of ease of H(3) abstraction in palladium–maleic acid dehydrogenation of stereochemically different ring systems[2] was applied to a study of the configuration of ajmalicinoid alkaloids and led to the assignment of structures *1*, *2* and *3* to ajmalicine, tetrahydroalstonine and akuammigine, respectively.[5]

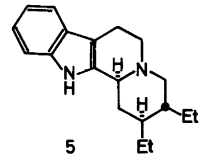
The involvement of heterogeneous catalysis in the H(3) abstraction process and the inherent difficulty of rigorous interpretation of reactions of such complexity made an alternative check of the configurational assignment of the ajmalicinoid alkaloids highly desirable. As a consequence, a degradation of tetrahydroalstonine, in a manner analogous to that of ajmalicine which had revealed the absolute configuration of the latter,[6] was contemplated but had to await the acquisition of sufficient quantity of the alkaloid. In the meantime, the conversion of the ajmalicine degradation product ajmaliciol *4*[6] to dihydrocorynantheane (*5*) by hydrogen bromide treatment and subsequent hydrogenolysis[7] shed serious doubt on the proposed relative configuration of the ajmalicinoid alkaloids[5] and made a reinvestigation of the











* For a preliminary account of this work see Ref. 1.

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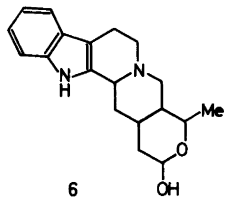
problem mandatory.*

Alkaline hydrolysis of tetrahydroalstonine, prepared by reduction of alstonine supplied kindly by Dr. J. Harley-Mason, and subsequent, short aqueous acid treatment yielded tetrahydroalstonial (*6*).** Wolff-Kishner reduction of the latter gave an isomer of the ajmalicine degradation product ajmaliciol *4*. Oppenauer oxidation of the isomeric alcohol under mild conditions produced a ketone which was isomeric with an analogue derived from ajmalicine. However, sodium methoxide-induced equilibration of the oxidation product transformed it into the ajmalicine-derived ketone [6] isomer. Since the latter thus had been shown to be the more stable 19-ketone, a substance expected to possess conformation *7*, it could be assigned the 18,19-dihydro-19-corynantheone (*8a*) structure and the tetrahydroalstonine-derived ketone the 19-corynantheidone (*8b*) formulation. As a consequence ajmaliciol (*4*)[6] could be attributed the 18,19-dihydro-19-corynantheol (*9a*) configuration, a structural detail reinforced by the observation of the isolation of this alcohol and its 19-epimer as products of sodium borohydride reduction of the stable 19-ketone. Finally, these results showed conclusively that tetrahydroalstonine possesses stereostructure *1* and ajmalicine *2*, in contrast to the previous structure assignments,[5] and that tetrahydroalstonine belongs to the H(15α) indole alkaloid family.[6]



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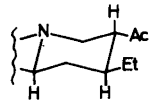

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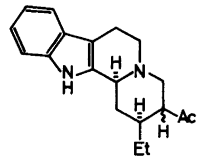

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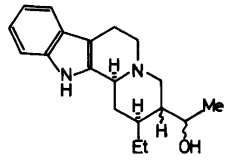
a, H(20β)
b, H(20α)



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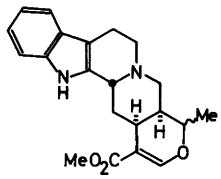
In the previous structure study [5] the ajmalicinoid alkaloid akuammigine had been oxidized to a ring C, tetradehydro product, which had appeared to be identical with alstonine. As confirmation of this correlation akuammigine was dehydrogenated again and the product exposed to Raney nickel-induced hydrogenation at high pH. This two-step procedure led to tetrahydroalstonine, corroborating the suggestion of akuammigine being 3-isotetrahydroalstonine and thus now possessing structure *10*.

Upon completion of the assignments of a *normal* configuration to ajmalicine (*2*) (and hence a *pseudo* structure to 3-isoajmalicine, *3* [5]), an *allo* configuration to tetrahydroalstonine (*1*) and an *epiallo* structure to akuammigine (*10*) only the C(19) stereochemistry of these alkaloids remained undetermined. Since a rapid solution of this problem appeared to reside in a ^{1}H NMR spectral analysis of the alkaloids, such a study on deuteriochloroform solutions of the bases was undertaken.

The *normal* and *pseudo* configurations of ajmalicine (*2*) and 3-isoajmalicine (*3*), respectively, limit these compounds to a rigid D/E *trans* framework possessing an axial H(20) conformation. Furthermore, the *pseudo* 3-isoajmalicine (*3*) has its H(3) limited to an equatorial conformation, a fact confirmed by the ^{1}H NMR spectrum of the compound exhibiting an H(3) multiplet at 4.45 ppm, a strongly downfield signal characteristic of equatorial H(3) substances.[10] The spectra of ajmalicine (*2*) and its 3-epimer (*3*) revealed H(19) pairs of quartets centered at 4.44 and 4.38 ppm, respectively, with H(19)-methyl coupling patterns of 6.0 and 7.0 Hz, respectively, and H(19)–H(20) coupling constants of 2.7 and 1.8 Hz, respectively. The *J* values for the H(19)-methyl interactions were obvious also from the splitting patterns of the 19-methyl doublets centered at 1.16 and 1.19 ppm, respectively. The weak coupling between H(19) and H(20) indicated the former hydrogen to be oriented equatorially and consequently the configuration of ajmalicine (*2*) and its 3-epimer (*3*) to be as depicted in

* At the end of their discussion of the stereochemistry of heteroyohimbine alkaloids Shamma and Richey [4] refer to a comment by van Tamelen at a 1961 American Chemical Society meeting on the total synthesis of ajmalicine purporting to prove a *trans* D/E ring fusion of the alkaloid. The absence of discussion of the stereochemistry in the later description of the ajmalicine synthesis [8] and the yet later proof of the presence of a mixture of C(20) epimers of a crucial, stereochemically determinant ketoester intermediate [9] in the total synthesis indicate this view to have been premature.

** This substance, reported m.p. 177 °C, was produced first by J. Harley-Mason and W. R. Waterfield.[15]



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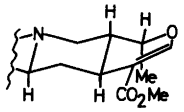

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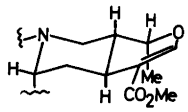

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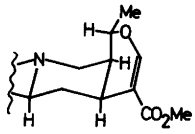

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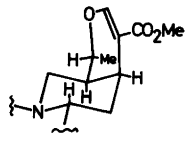

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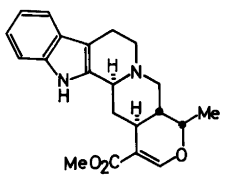
conformations *11* and *12*, respectively.

In view of the absence of a low-field signal, attributable to an equatorial H(3) substituent, in the ^{1}H NMR spectra of the D/E *cis*, 3-epimeric alkaloids tetrahydroalstonine (*1*) and akuammigine (*10*) their D and E ring conformations are limited to those portrayed in formulas *13* and *14*, respectively. The H(19) signals appeared as pairs of quartets centered at *ca.* 4.40 ppm, tetrahydroalstonine exhibiting H(19) – H(20) coupling of 10.2 Hz and akuammigine 5.9 Hz. These facts are compatible with a *trans* diaxial relationship of H(19) and H(20) in the former alkaloid and a *trans* diequatorial orientation in the latter base, as illustrated also in structures *13* and *14*, respectively.

The chemical degradations and ^{1}H NMR special interpretations led to stereostructures *15*, *16a* and *16b* for ajmalicine, tetrahydroalstonine and



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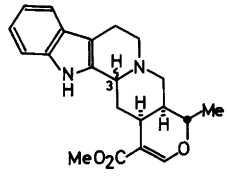

16a, H(3α)
b, H(3β)

akuammigine, respectively, in accord with data from recent syntheses of these natural substances.[11] The identity of the non-aromatic region of the ^{1}H NMR spectrum of tetraphylline[12] (with the exception of the signal of an extra *O*-methyl group) with that of ajmalicine (*15*) established this ajmalicinoid base as 11-methoxyajmalicine. Similar spectral comparison revealed aricine[13] to be 10-methoxytetrahydroalstonine and reserpinine[14] 11-methoxytetrahydroalstonine.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian V-4300 B instrument equipped with a Varian V-4365 field homogeneity control unit. The measurements were made at 24 °C using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Melting points were determined on a micro hot stage (Reichert) and are uncorrected. All reactions were carried out under nitrogen; concentrations of solutions were performed under reduced pressure or under nitrogen.

Tetrahydroalstonial (6). A solution of tetrahydroalstonine (750 mg) and KOH (2.0 mg) in absolute ethanol (10 ml) was refluxed for 5 h. The solution was adjusted to pH 10 with dilute HCl, water was added to dissolve precipitated salts, and non-acidic impurities were removed by two extractions with chloroform. After concentration of the aqueous phase, aqueous HCl was added to give a solution (50 ml) which was 0.8 M with respect to excess acid. The mixture was refluxed for 5 h, then made alkaline with excess K_2CO_3, extracted with chloroform and the chloroform solution concentrated to dryness. The amorphous residue (600 mg) was dissolved in hot benzene and the solution immediately filtered through alumina (1 ml, act. IV). Crude *6* (407 mg) crystallized upon cooling. It dissolved readily in hot benzene (6 ml), but upon continued heating pure tetrahydroalstonial (*6*) separated as prisms (280 mg), m.p. 210 – 214 °C, $[\alpha]_D^{28}$ −122° (*c* 1.5, chloroform). Reported[15] m.p. 177 °C, $[\alpha]_D$ −137°. Found: C 72.34, H 7.78, N 8.83. Calc. for $C_{19}H_{24}N_2O_2$: C 73.04; H 7.74, N 8.97. IR ($CHCl_3$): OH 3620 (w), NH 3480 (m), no band attributable to C=O.

The high-melting modification (or 19-epimer) obtained from hot benzene could be transformed into the low-melting form by dissolving a sample in a small volume of methanol, quickly removing the methanol by evaporation with benzene, dissolving the amorphous residue in cold benzene and seeding it with a sample of m.p. 177 °C (kindly provided by Dr. Harley-Mason). Tetrahydroalstonial now separated as needles, m.p. 173 – 177 °C with rapid resolidification and new m.p. 209 – 213 °C. No

mutarotation attributable to hemiacetal epimerization was observed.

*19-Corynantheidol (*9b*).* A solution of tetrahydroalstonial (340 mg), anhydrous hydrazine (2.9 ml) and acetic acid (0.15 ml) in diethylene glycol (11 ml) was refluxed for 30 min. After addition of KOH (1.16 g) refluxing was continued for 30 min, then water and excess hydrazine were distilled off until the temperature in the solution reached 200 °C and this temperature was maintained for 3 h. Dilution with water and repeated extractions with chloroform afforded crude 19-corynantheidol (300 mg) as an oil, after concentration of the extracts. On adding a slight excess of picric acid in methanol (10 ml), crystalline 19-corynantheidol picrate (370 mg) separated; m.p. 216–222 °C, d. Found: C 57.07, H 5.62, N 13.63. Calc. for $C_{25}H_{29}N_5O_8$: C 56.92, H 5.54, N 13.28. IR (Nujol): OH 3570, NH 3360. After liberation from its pure picrate, 19-corynantheidol (*9b*) failed to crystallize, $[\alpha]_D^{25}$ −121° (*c* 2.0, pyridine).

*19-Corynantheidone (*8b*).* A solution of 19-corynantheidol (250 mg) and cyclohexanone (14 ml) in benzene (50 ml) was made anhydrous by distilling off *ca.* 30 ml of benzene through a Vigreux column. Aluminum phenoxide (1.7 g) was then added and the clear solution kept at 100 °C for 8 h. The gelatinous reaction mixture was triturated with 1 M H_2SO_4 (2 × 45 ml), the extract was washed repeatedly with small portions of ether to remove cyclohexanone, then neutralized with K_2CO_3, made alkaline with NH_4OH and filtered with Celite. After dehydration of the filter cake with a small volume of methanol, both the filter cake and the combined filtrates were extracted with chloroform and the residue after concentrating the extracts was chromatographed on an alumina column (13 × 190 mm). Crude crystalline 19-corynantheidone (45 mg) and unreacted starting material (87 mg) were obtained by elution with benzene–chloroform (99:1 and 1:1, respectively). Recrystallization from benzene–cyclohexane and aqueous ethanol afforded pure 19-corynantheidone (*8b*); m.p. 152–153 °C, $[\alpha]_D^{28}$ −61° (*c* 1.5, chloroform). Anal. $C_{19}H_{24}N_2O$: C, H, N. IR (chloroform): NM 3480 (m), C=O 1710 (s). Mixed melting point with 18,19-dihydro-19-corynantheone (m.p. 225–228 °C): 143–215 °C, confirming nonidentity with the latter.

Alkaline epimerization of 19-corynantheidone. A solution of 19-corynantheidone (19 mg) in 2 M methanolic sodium methoxide (3 ml) was refluxed for 3 h. After dilution with water and extraction with chloroform the extract was filtered through a small quantity of alumina and concentrated to give a crystallizing oil. Recrystallization from benzene–cyclohexane and methanol gave 18,19-dihydro-19-corynantheone (*8a*) (15 mg); m.p. 225–228 °C, $[\alpha]_D^{28}$ −59° (*c* 1.5, chloroform). Lit.[6] 225–228 °C, $[\alpha]_D$ −57°. Mixed melting point and IR proved the identity with an authentic sample of *8a*.

*Ajmaliciol (*9a, 19S*) and 19-isoajmaliciol (*9a, 19R*) from* 8a. A solution of 18,19-dihydro-19-corynantheone (243 mg) and a large excess of $NaBH_4$ in 80% aqueous methanol (20 ml) was kept at 0 °C for 4 h and then at 50 °C for 30 min. The mixture was acidified with dilute HCl, made basic again with NH_4OH and then kept at 0 °C for 4 h to give needles of crude ajmaliciol (132 mg). Extraction of the mother liquors with chloroform and concentration of the extract gave a residue that afforded more ajmaliciol (25 mg) from aqueous methanol. Removal of the solvents from these mother liquors and recrystallization of the residue from benzene gave 19-isoajmaliciol (100 mg).

19-Isoajmaliciol apparently forms solvated crystals both from benzene and methanol, m.p. *ca.* 110 and 118 °C, respectively; on further heating it resolidifies and melts at *ca.* 175° and 185 °C with transient intermediary crystallization. A sample was distilled in a tube at 170 °C and 0.1 mm pressure and the amorphous distillate was kept for 15 min at 150 °C *in vacuo* to give the high melting modification of 19-isoajmaliciol as tetrahedral prisms, m.p. 195–197 °C, $[\alpha]_D^{28}$ −101° (*c* 1.5, pyridine). Found: C 76.02, H 8.82, N 9.16. Calc. for $C_{19}H_{26}N_2O$: C 76.47, H 8.78, N 9.39. IR (Nujol): OH 3570 (w), NH 3310 (m).

Ajmaliciol (lit.[6] m.p. 200–201 °C, $[\alpha]_D$ −25° in pyridine), prepared as described previously,[6] was now found to have $[\alpha]_D^{28}$ −109° (*c* 1.5, pyridine), and to exhibit multiple melting points when crystallized from methanol (m.p. 110–120 °C, 135–145 °C, 176–179 °C and 198–200 °C. From benzene only the high-melting modification was obtained (m.p. 198–200 °C).

*Tetrahydroalstonine (*16a*) from akuammigine (*16b*).* When dehydrogenated by the palladium–maleic acid method as described previously,[5] akuammigine gave a tetradehydro compound, the perchlorate of which melted at 227–229 °C. However, an authentic sample of alstonine perchlorate (m.p. 241–246 °C d.) could be converted to a low-melting modification (m.p. 228–230 °C) by seeding its methanolic solution with the present dehydrogenation product; the two preparations gave no melting point depression.

Tetradehydroakuammigine perchlorate (10.8 mg) was hydrogenated in 0.05 M methanolic KOH (2 ml) in the presence of Raney nickel W-2 (20 mg). The hydrogenation slowed down after an uptake of 1.8 molar equivalents of H_2. The reaction mixture was filtered after acidification with acetic acid, diluted with water, made alkaline with NH_4OH and extracted with chloroform. Concentration of the extract and recrystallization from aqueous ethanol gave tetrahydroalstonine (4.5 mg), m.p. 227–230 °C, undepressed on admixture with an

authentic sample (m.p. 229 – 230 °C). IR confirmed the identity of the two preparations.

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