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SYNTHESIS OF ISOAJMALINE*

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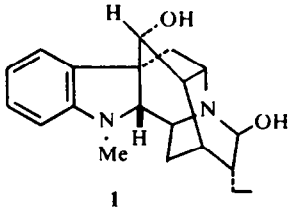
Abstract—As a preliminary for the synthesis of isoajmaline the known β-ketoester (**4**) was submitted to ketone fission to afford **5**. This was converted to the oxirane **6** by Corey's method, reduction of which with $HAlCl_2$ under specified conditions gave primary alcohol **7**. To extend the above result to the synthesis of isoajmaline, α-cyano-n-propyl side-chain was grafted to the ketone **5** to yield **9**, which was similarly treated as above to furnish **14** and **14a**. These compounds were found to belong not to the ajmaline series, but to isoajmaline series, through comparison with **19a** and **19** respectively prepared from isoajmaline by the known method. **19a** was now utilized as a relay, from which **23** was prepared via several steps. The latter was identified with an authentic specimen prepared from isoajmaline by Sir Robert Robinson's method, who also had succeeded to convert **23** to isoajmaline.

In some of the above intermediates was found reciprocal interconversion process between isoajmaline-ajmaline series, thus the present synthesis appears also to constitute an alternate synthesis of ajmaline.

THE structural study of ajmaline and isoajmaline, two important bases of ajmaline–sarpagine group of alkaloids, was carried out by Sir Robert Robinson *et al.*[1] and Woodward *et al.*[2] during 1956–1957, which culminated in elucidation of their plane structures. Later Taylor *et al.*[3] in 1962 and Shamma *et al.*[4] in 1963 worked out the stereostructure of ajmaline and isoajmaline as **2** and **1** respectively. The proposed structure **2** of ajmaline was fully supported through its total synthesis elaborated by Masamune *et al.*[5] in 1967.



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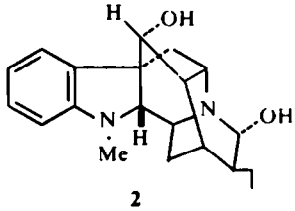

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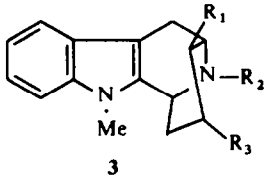


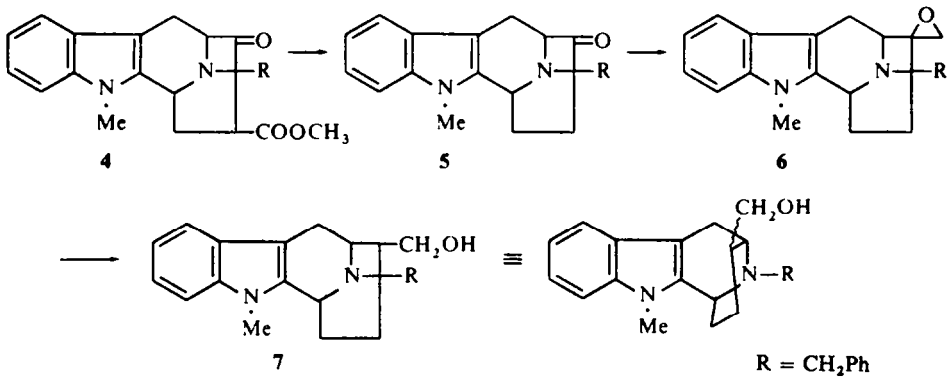
3

R_1 = CH_2OH, CHO
R_2 = H, CH_2Ph, COPh
R_3 = CH_2CN, $CHCH_2CH_3$ etc.
ĊN

For the past several years we also have been engaged independently in the synthesis of these alkaloids and succeeded in synthesizing isoajmaline. This paper will record our result together with some interesting informations obtained during the present work.

* For preliminary communications, see *Tetrahedron Letters* 901, 905 (1969).

For the synthesis of these unique structures of ajmaline and isoajmaline (3)-type of compounds appeared to be a suitable starting material and as a preliminary the synthesis of 7 was attempted.



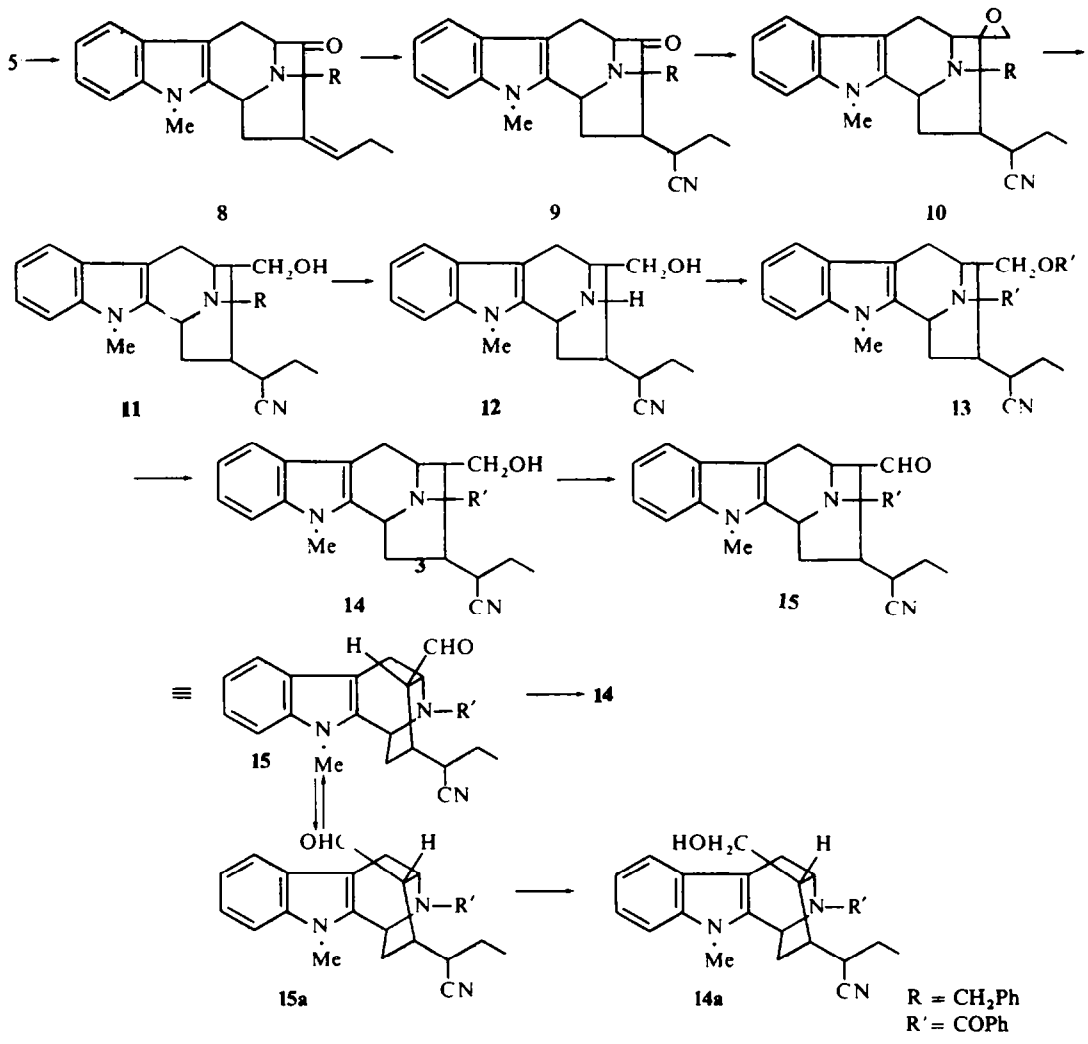
Thus β-ketoester (4), which had already been synthesized from *dl*-tryptophan via several steps by Yoneda[6] was submitted to ketone fission in AcOH-conc HCl to furnish ketone **5**. The latter was then treated with dimethyloxosulfonium methylide[7] in anhydrous DMSO according to Corey. The oxirane (**6**) thus obtained in nearly quantitative yield, could also be prepared with dimethylsulfonium methylide as well according to the same author.

When treated with mixed hydride $HAlCl_2$[8] (prepared from $AlCl_3$: LAH = 4:1) at room temperature, the oxirane ring of **6** was reductively cleaved to furnish the objective primary alcohol (**7**)* in 72% yield, which was characterized as its crystalline acetate, m.p. 129–130°. For the best result the ethereal solution of $HAlCl_2$ should be added to the ethereal solution of the oxirane; reverse addition resulted in predominant formation of undesired tertiary alcohol.

To extend the above-obtained experimental result to our ultimate purpose graft of —CH(Et)·CN-side chain at the active α-methylene group of the ketone **6** was essential. After numbers of fruitless attempts we finally succeeded in aldol-type condensation followed by dehydration of **5** with n-propanal to give **8** in 54% yield, in which triton B was found to be a condensation agent of choice. Olefinic proton at 3·2 τ (tr in $CDCl_3$) in **8** supports its structure. This ketone (**8**) underwent a smooth hydrocyanation reaction with KCN-NH_4Cl[9] giving ketonitrile (**9**) in ca. 70% yield. Judging from its behaviour on TLC this hydrocyanation reaction appeared to have proceeded with high stereoselectivity.

Conversion of **9** to the corresponding oxirane (**10**) was carried out with dimethyloxosulfonium methylide as above, but the oxirane ring cleavage by means of $HAlCl_2$ carried out as in the foregoing fashion resulted in the formation of the objective primary alcohol (**11**) only in 20% yield accompanied with a considerable quantity (ca. 24%) of the undesired tertiary alcohol as a by-product. Aluminium hydride in boiling ether, however, was found to give better result (yield of **11** was raised to 54%), leaving CN-group intact.

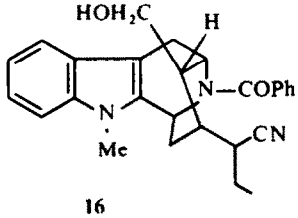
* Support of this structure was provided by oxidation of **7** with MnO_2 or DMSO-Ac_2O to give the corresponding aldehyde (NMR_{CDCl_3}, 0·35 τ), which isomerized with silicagel or alumina in benzene to give an equilibrium mixture of two aldehydes (NMR_{CDCl_3}, 0·35 τ and 0·48 τ).



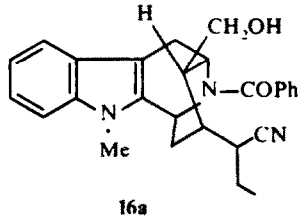
This alcohol was then reductively debenzylated to form **12**, which was benzoylated with benzoyl chloride-pyridine as usual yielding 0,N-dibenzoyl derivative **13**. When the latter was treated with 1% methanolic NaOH solution for a short time there was obtained N-benzoyl derivative (**14**), which also could be prepared directly through selective N-benzoylation of **12**.

When oxidized by means of DMSO-Ac_2O[10] the alcohol **14** furnished the corresponding aldehyde **15** in 80% yield, whose NMR (C<u>H</u>O-proton) appeared at 0·2 τ in $CDCl_3$. On being treated with alumina in benzene according to Masamune's method this aldehyde suffered partial isomerization to yield **15a** (C<u>H</u>O 0·5 τ in $CDCl_3$), giving an equilibrium mixture of **15**:**15a** $\doteqdot$ 2:3, which ratio is just a reverse of that in the ajmaline series. Further remarks upon this point will be made later. The isomeric aldehydes could not be separated, but the corresponding mixture of the isomeric alcohols prepared by $NaBH_4$ reduction could be separated into its components **14** and **14a**, the former of which was identical with the original **14**.

For structure elucidation of **14** and **14a** reference compounds were needed. Thus alcohol **16a** and **16** having the same plane structures as **14** and **14a** were prepared from natural ajmaline by the known method. When compared directly, a pair of **14**

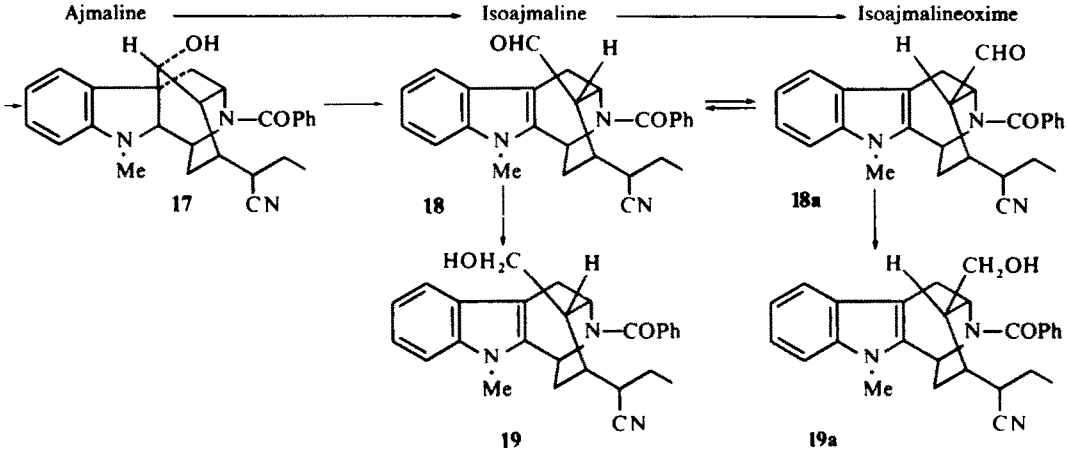


16



16a

and **16a**, and another pair of **14a** and **16** gave very similar IR absorption spectra, but they could not be assumed to have the same stereostructure when judged from their different behaviour on TLC. Thus the synthetic alcohols (**14** and **14a**) appeared to belong to isoajmaline series.



In order to provide support for the above assumption, isoajmaline oxime was prepared from ajmaline via isoajmaline, followed by treatment with benzoyl chloride–pyridine, all according to the known method. On being hydrolyzed partially with MeOH-KOH, N-benzoyl alcohol **17** was produced, which was then converted to aldehyde **18** by the agency of $Pb(OAc)_4$ in AcOH.* When a benzene solution of **18** was allowed to stand with alumina overnight partial isomerization to give **18a** took place, yielding an equilibrium mixture of **18**:**18a** ≒ 3:2. This mixture was inseparable, but when reduced with $NaBH_4$ a mixture of the corresponding alcohol **19** and **19a** were obtained, which now could be separated.

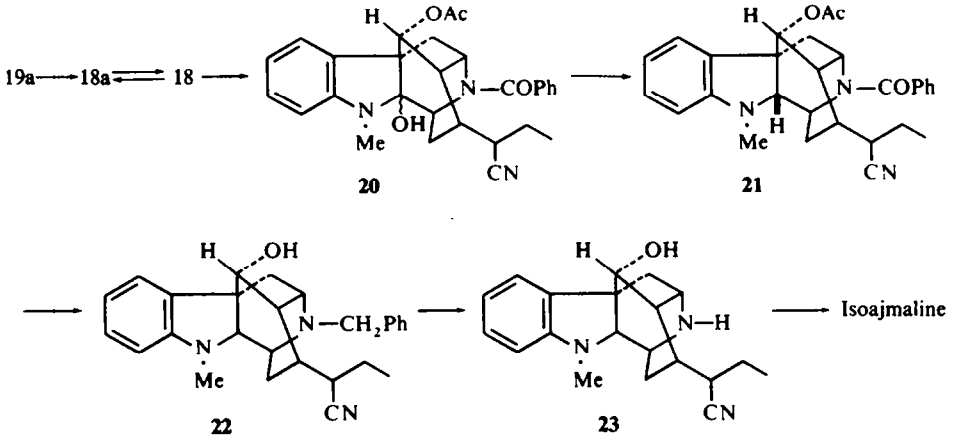
Through direct comparison of four kinds of alcohol (**14**, **14a**, **19** and **19a**) thus obtained, it was made clear that **14** and **14a** are identical with **19a** and **19** respectively, based on the identical IR and TLC data. Moreover all four alcohols gave molecular ion peak at *m/e* 427 in mass spectrum analysis. Total synthesis of isoajmaline thus became feasible using **19** or **19a** as a relay substance.

* The same type of conversion in ajmaline series proceeded smoothly in benzene, which is a poor solvent in the present case to allow the reaction to go favourably.

Based on the above-mentioned fact it could be assumed that the hydrocyanation reaction of enone **8** proceeded with a high degree of stereoselectivity to afford the nitrile **9** belonging to isoajmaline series. On the other hand in the course of Masamune's total synthesis of ajmaline introduction of an Et group to the α-position of —CH_2—CN side chain is said to take place stereoselectively to furnish ajmaline series of compound only.*

It is therefore of interest that we can control the synthesis to lead either to ajmaline† by Masamune's method or to isoajmaline by our present method to be described later. Another fact is the equilibrium ratio of α- and β-aldehyde in ajmaline and isoajmaline series. In the former the ratio of α (**18**) to β (**18a**) is 3:7, whereas in the latter α (**15a**), in which CHO-group is favourably disposed for further cyclization, predominates over β-aldehyde (**15**). This remarkable fact is probably due to stereorelationship between -CHO and -CN groups.

The alcohol **19a**, which was prepared as described above, was readily obtained in pure crystalline state and was chosen as a relay substance for the synthesis of isoajmaline. Thus this was oxidized by means of DMSO-Ac_2O to yield the corresponding aldehyde (**18a**), which was equilibrated with alumina in benzene. In the product the presence of α-aldehyde (**18**) was ascertained on TLC and NMR.



A larger quantity of the latter aldehyde needed for further work was again prepared from natural ajmaline. This aldehyde was dissolved in Ac_2O-AcOH and the resultant solution was saturated with HCl gas to produce **20**, which was reduced over Adams Pt-catalyst in 6N HCl solution. The reduction product was purified through silica-gel chromatography, when **21** was obtained in 10% yield.

For the best result to convert **21** to **23** we took a detour via **22** instead of direct hydrolysis. Thus, after several fruitless attempts **21** was first treated with the Meerwein reagent ($Et_3O^+BF_4^-$)[11] in CH_2Cl_2, followed by reduction with $NaBH_4$ in ethanol to yield N-benzyl-alcohol (**22**) in 85% yield, CN-group remained intact during this reaction. Reductive debenzylation over 10% Pd-C proceeded readily to give **23** in an

* We are grateful to Prof. S. Masamune for this communication.

† Ajmaline now became accessible along the line presented above (*vide infra*). Our synthesis of ajmaline will appear in a forthcoming paper elsewhere.

excellent yield, the structure of which was corroborated through the identical IR spectra ($CHCl_3$), $[\alpha]_D$ and undepressed mixed m.p. test with an authentic specimen.

Conversion of **23** into isoajmaline had already been described by Sir Robert Robinson *et al.*, thus our present work links to a total synthesis of isoajmaline.

Finally some remarks will be made on the isomerization of isoajmaline-ajamaline series.

16a ⇌ **19a**; **16** ⇌ **19**

13 ⟶ *dl*-**16a**

When **19a**, dissolved in a 1% MeOH-NaOH solution, was allowed to stand overnight, partial isomerization to **16a** took place affording an equilibrium mixture of **19a** and **16a** and *vice versa*. When similarly treated **13** also isomerized partially with simultaneous loss of the ester-type benzoyl group to afford a compound corresponding to a racemic form of **16a**. This fact means that our present synthesis of isoajmaline may also be construed as a total synthesis of ajmaline.

On the contrary **16** and **19** were found to be quite stable under the above-mentioned isomerization conditions.

EXPERIMENTAL

All m.ps are uncorrected. Optical activities were measured with Yanagimoto OR-20. IR spectra were taken on a Hitachi EP-G2 ($CHCl_3$) or JASCO IR-E (Nujol), UV spectra on a Hitachi EPS-2U, NMR spectra on a JEOL C-60 and Mass spectra on a Hitachi RMS-4.

5-Methyl 9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]*indole* (5). Compound **4** (50 g) was added to mixture of conc HCl (300 ml) and AcOH (300 ml) and refluxed for 6 hr. After removal of the solvent *in vacuo*, the residue was basified with 10% NaOH and extracted with benzene. The benzene extract was washed with water, dried and evaporated. The solid residue obtained was recrystallized with AcOEt to form colourless plates, m.p. 131·5–133°, yield 38 g (89%); IR ν_{max}^{Nujol} (cm^{-1}): 1700 (C=O). (Found: C, 80·03; H, 6·81; N, 8·38. $C_{22}H_{22}ON_2$ requires: C, 79·97; H, 6·71; N, 8·48%).

5-Methyl-12-benzyl-6,7,8,9,10,11-hexahydro-oxiranospiro[2,9]*-6,10-imino-5H-cyclooct*[*b*]*indole* **6**. To NaH (72% oil dispersion 2·2 g, 66 mmole, previously washed with hexane to remove the mineral oil), trimethyloxosulfonium iodide (14·5 g, 66 mmole) was added, followed by anhyd DMSO (100 ml). After standing for 0·5 hr **5** (10 g, 33 mmole) in anhyd DMSO (100 ml) was added and the mixture was stirred at room temp for 2 hr. The mixture was poured into ice-water and the oxirane was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and the solvent was removed. The residue was purified with alumina and then by distillation (b.p.$_{0\cdot01}$ 207–210°) to form a faint yellow viscous oil, yield 9·9 g (96 g (96%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 910 (oxirane). This base was so unstable that none of its derivatives could be prepared.

5-Methyl-9-hydroxymethyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[*b*]*indole* **7**. 75 ml of $HAlCl_2$ in ether [prepared from $AlCl_3$ (5·83 g, 43·8 mmole), LAH (0·42 g, 10·9 mmole) and anhyd ether (100 ml)] was added to **6** (3 g, 8·77 mmole) in anhyd ether (100 ml) and stirred at room temp for 3 hr. After being basified with NH_4OH, the ethereal layer was separated and aqueous layer was extracted with $CHCl_3$. The organic extracts were washed with water, dried, combined and evaporated. The residue was chromatographed on silica gel to give 7 as a yellow oil, yield 1·97 g (72%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}); 3200 (OH).

Acetate: Colourless prisms (from ether), m.p. 129–130°; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1720 ($OCOCH_3$). (Found: C, 77·16; H, 7·12; N, 6·83. $C_{25}H_{28}O_2N_2$ requires: C, 77·29; H, 7·29; N, 7·21%).

5-Methyl-8-n-propylidene-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[*b*]*indole* **8**. Triton-B (40% in MeOH, 3·6 ml) was added to **5** (19·8 g, 60 mmole) dissolved in 80% aq-THF (300 ml). To this solon was now added n-propanol (10·4 g, 180 mmole) in 80% aq-THF (100 ml) during 3·5 hr with stirring at room temp. After being stirred overnight the second portion of triton-B was added followed by dropwise addition of n-propanal in 80% aq. THF. After 3 hr this procedure was repeated for the third time and the whole was stirred overnight. Then the last portion of triton-B (0·6 ml) and n-propanal (3·5 g, total 0·6 mole) in 80% aq-THF (30 ml) were added. After 1 hr's stirring the solvent was removed *in vacuo* and the resultant residue was added with water and extracted with benzene, washed, dried, and evaporated to leave a solid,

which was purified from benzene to form colourless powder, m.p. 114–125°, yield 12·1 g (54%); IR ν_{max}^{Nujol} (cm^{-1}): 1680 (C=O), 1610 (C=C); NMR ($CDCl_3$): 3·2 τ (1H, tr, —CO—C(=)CH—CH_2—CH_3). (Found: C, 82·32; H, 7·21; N, 6·84. $C_{25}H_{26}ON_2$.2/3 C_6H_6 requires: C, 82·43; H, 7·16; N, 6·63%).

α-*Ethyl*-5-*methyl*-9-*oxo*-12-*benzyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[*b*]*indole*-8-*acetonitrile* **9**. A mixture of **8** (5·7 g, 15·4 mmole), KCN (4 g, 61·6 mmole), NH_4Cl (2·5 g, 46·2 mmole), DMF (250 ml) and water (31 ml) was heated at 100° for 2·5 hr with occasional shaking. After cooling the solvent was removed *in vacuo*, water was added and the product was extracted with benzene. The benzene extract was washed with water and dried. Evaporation of benzene *in vacuo* gave a yellow oil, which solidified on standing. This was recrystallized from benzene to give colourless crystalline powder, m.p. 186–189° (dec), yield 3 g (50%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1715 (C=O). (Found: C, 78·63; H, 6·96; N, 10·43. $C_{26}H_{27}ON_3$ requires: C, 78·56; H, 6·85; N, 10·57%).

α-*Ethyl*-5-*methyl*-12-*benzyl*-6,7,8,9,10,11-*hexahydro*-*oxirano*-*spiro*[2,9]-6,10-*imino*-5H-*cyclooct*[*b*]*indole*-8-*acetonitrile* **10**. To NaH (72% oil dispersion 253 mg, 7·6 mmole, previously washed with hexane to remove the mineral oil), was added trimethyloxosulphonium iodide (1·67 g, 7·6 mmole), followed by anhyd DMSO (13 ml). After 0·5 hr, **9** (1.52 g, 3·8 mmole) dissolved in a mixture of anhyd DMSO (16 ml) and anhyd. THF (12 ml) was added to the above DMSO solon and stirred at room temp for 4 hr. The reaction mixture was poured into ice-water, extracted with $CHCl_3$, washed with water and dried. After removal of the solvent, the residue was purified with alumina to give a yellow caramel, yield 0·78 g (50%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 910 (oxirane).

Picrate: yellow needles (from MeOH), m.p. 164–166° (dec). (Found: C, 61·70; H, 5·04; N, 12·99. $C_{33}H_{32}O_8N_6$ requires: C, 61·87; H, 5·04; N, 13·12%).

α-*Ethyl*-5-*methyl*-9β-*hydroxymethyl*-12-*benzyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8-*acetonitrile* (**11**). A solution of AlH_3 in anhyd ether [prepared from $AlCl_3$ (230 mg, 1·7 mmole), LAH (171 mg, 4·5 mmole) and anhyd ether (10 ml)] was added to the boiling ethereal solon (13 ml) of **10** (780 mg, 1·9 mmole) and stirred for 2 hr under reflux. After adding $NaHCO_3$aq, the reaction mixture was extracted with benzene. The benzene extract was washed with water, dried and evaporated. The residue was chromatographed on silicagel to give **11** as a solid, which was recrystallized from benzene–n-hexane to form faint yellow prisms, m.p. 137–139°, yield 420 mg (52·8%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3200 (OH), 2250 (CN). (Found: C, 78·13; H, 7·60; N, 9·93. $C_{27}H_{31}ON_3$ requires: C, 78·41; H, 7·56; N, 10·16%).

α-*Ethyl*-5-*methyl*-9β-*hydroxymethyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8-*acetonitrile* (**12**). A solon of **11** (2·43 g, 5·8 mmole) and conc HCl (0·7 ml) in EtOH (100 ml) was shaken in H_2 atmosphere over 10% Pd-C catalyst (1·3 g) at room temp, 1·2 molar equiv H_2 (170 ml) being absorbed. The catalyst was filtered off and washed with EtOH. The combined ethanolic solon was evaporated *in vacuo* to leave a residue, which was dissolved in $CHCl_3$, washed with $NaHCO_3$, followed with water, dried and evaporated to leave a caramel. This was crystallized with benzene and then from EtOH to give colourless prisms, m.p. 212·5–213·5° (dec), yield 1·25 g (67%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3250 (OH, NH), 2250 (CN). (Found: C, 70·90; H, 7·55; N, 12·30. $C_{20}H_{25}ON_3 \cdot H_2O$ requires: C, 70·35; H, 7·97; N, 12·31%).

α-*Ethyl*-5-*methyl*-9β-*benzoyloxymethyl*-12-*benzoyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]-*indole*-8-*acetonitrile* (**13**). To a solon of **12** (0·94 g, 2·9 mmole) in pyridine (20 ml) benzoyl chloride (1·26 g, 9 mmole) was added with stirring and ice-cooling. Stirring was continued overnight at room temp. The mixture was poured into ice-water and extracted with benzene. The benzene extract was washed with water, dried and evaporated to leave a faint yellow caramel (1·62 g), which was triturated with i-PrOH to form crystals. These were recrystallized from i-PrOH to give colourless plates, m.p. 106–107·5°, yield 1·31 g (85%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1720 (OCOPh), 1635 (NCOPh), 3400 (OH). (Found: C, 75·28; H, 6·90; N, 7·20. $C_{34}H_{33}O_3N_3 \cdot$ i-C_3H_7OH requires: C, 75·10; H, 6·98; N, 7·10%).

α-*Ethyl*-5-*methyl*-9β-*hydroxymethyl*-12-*benzoyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8-*acetonitrile* (**14**). 1. *From* **13**. Dibenzoate **13** (500 mg, 0·9 mmole) was added to a solon of NaOH (250 mg, 6·2 mmole) in MeOH (35 ml) and the resulting mixture was stirred at room temp for 50 min. After evaporation of MeOH *in vacuo* and addition of water, the solid separated was extracted with benzene-AcOEt. The organic extract was washed with water, dried and the solvent was removed. The residue was chromatographed on silicagel to give a colorless caramel, yield 360 mg (90%). This was crystallized with i-PrOH and again from i-PrOH-n-hexane to form minute colorless prisms, m.p. 204–206° (dec); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3380 (OH), 2250 (CN), 1615 (NCOPh); Mass spectrum: *m/e* 427 (molecular ion). (Found: C, 75·29; H, 7·08; N, 10·10. $C_{27}H_{29}O_2N_3$ requires: C, 75·85; H, 6·84; N, 9·83%).

2. *From* **12**. To a solon of **12** (100 mg, 0·3 mmole) in $CHCl_3$ (2 ml) and benzene (8 ml) basified with 1% NaOH (5 ml) was added dropwise benzoyl chloride (90 mg, 0·6 mmole) in benzene (5 ml) with ice-cooling and stirring. After 4 hr the organic layer was separated and aqueous layer was extracted with benzene. The combined extracts were washed with water, dried, and the solvent removed. The residual colorless caramel (140 mg) could not be induced to crystallize after silicagel chromatography, yield 100 mg (78%), which was identified with the foregoing specimen through IR absorption data ($CHCl_3$).

α-*Ethyl-5-methyl-9β-formyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct*[b]*indole-8-acetonitrile* (**15**). Ac_2O (0·2 ml) was added to a solon of **14** (50 mg) in DMSO (2 ml) and the resulting solon was stirred overnight at room temp. The reaction mixture was poured into ice-water and extracted with benzene. The benzene extract was washed with water, dried and benzene was removed *in vacuo*. The residue was chromatographed on silicagel to give a colorless caramel, yield 40 mg (80%); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2730 (CHO), 2250 (CN), 1725 (CHO), 1630 (NCOPh). NMR ($CDCl_3$): 0·2 τ (1H, CHO).

α-*Ethyl-5-methyl-9α-hydroxymethyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct*[b]*indole-8-acetonitrile* (**14a**) *and* 9β-*isomer* (**14**). To a solon of **15** (295 mg) in benzene (30 ml) was added alumina (3 g) and the mixture was allowed to stand overnight at room temp. Alumina was removed by filtration and the filtrate was concentrated *in vacuo* to give a colorless caramel (180 mg). This was a mixture of **15** and **15a**, and the ratio of **15** to **15a** was ca. 2:3 judging from NMR measurement; NMR ($CDCl_3$): (15), 0·2 τ (β-CHO); (15a), 0·5 τ (α-CHO).

The above mixture (180 mg, 0·4 mmole) was dissolved in EtOH (3 ml) and MeOH (6 ml) and reduced with $NaBH_4$ (80 mg, 2·1 mmole). After removal of the solvent, the residue was mixed with water and extracted with benzene-AcOEt. The extract was washed with water, dried and the solvent removed *in vacuo*. The residue was chromatographed on silicagel to give **14** (40 mg) and **14a** (88 mg), the former of which was identical with the original **14**. Compound, **14a**, colorless caramel, was crystallized with i-PrOH and recrystallized from i-PrOH–n-hexane to form colorless minute needles, m.p. 201·5–203° (dec); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3380 (OH), 2250 (CN), 1630 (NCOPh): mass spectrum: *m/e* 427 (molecular ion). (Found: C, 75·89; H, 6·97; N, 9·74. $C_{27}H_{29}O_2N_3$ requires: C, 75·85; H, 6·84; N, 9·83%).

N(b)-*Benzoyl-anhydroisoajmalineoxime* (**17**). A mixture of isoajmalineoxime (1·6 g, 4·6 mmole), benzoyl chloride (5 ml) and pyridine (15 ml) was heated at 120–130° for 2·5 hr. The mixture was poured into ice-water, basified with 10% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave a syrup, which was heated with 10% MeOH-NaOH (15 ml) at 85° for 3 min. After cooling, water was added to the mixture and this was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and the solvent was removed to give powder, which was recrystallized from MeOH to form colorless prisms, m.p. 252·5–255° (dec), yield 1·06 g (53%); $[\alpha]_D^{20}$ +21·2° (*c* = 2, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1625 (NCOPh). (Found: C, 75·82; H, 6·99; N, 9·84. $C_{27}H_{29}O_2N_3$ requires: C, 75·85; H, 6·84; N, 9·83%).

α-*Ethyl-5-methyl-9α-formyl-12-benzoyl-6,7,8,9,10,11,-hexahydro-6,10-imino-5H-cyclooct*[b]*indole-8-acetonitrile* (**18**). 70% $Pb(OAc)_4$ (2·1 g, 3·3 mmole) was added to a solon of **17** (1·28 g, 3 mmole) in AcOH (100 ml) and the mixture was stirred at room temp for 20 mins and poured into ice-water (800 ml). The solid that separated was collected, washed with water and dried. A faint brown powder was obtained, yield 1·16 g (91%); $[\alpha]_D^{20}$ +51·3° (*c* = 2, AcOH); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2730 (CHO), 2250 (CN), 1725 (CHO), 1635 (NCOPh); NMR ($CDCl_3$): 0·5 τ (1H, CHO).

α-*Ethyl-5-methyl-9α-hydroxymethyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct*[b]*indole-8-acetonitrile* (**19**) *and* 9β-*isomer* (**19a**). To a solon of **18** (900 mg) in benzene (40 ml) was added alumina (10 g) and the mixture was allowed to stand overnight at room temp. Alumina was removed by filtration and the filtrate was concentrated *in vacuo* to give a faint yellow caramel (700 mg). This was a mixture of **18** and **18a** in the ratio of ca. 3:2 judging from NMR measurement [NMR ($CDCl_3$): **18**, 0·5 τ (α-CHO); **18a**, 0·2 τ (β-CHO)], which (650 mg, 1·5 mmole) was dissolved in a mixture of EtOH (10 ml) and MeOH (20 ml) and reduced with $NaBH_4$ (110 mg, 3 mmole). After working up a colorless caramel was obtained (660 mg) and chromatographed on silicagel to give **19** (370 mg) and **19a** (90 mg). Compound **19**: colorless needles (from i-PrOH–n-hexane), m.p. 126 – 128° (dec); $[\alpha]_D^{20}$ −24·5° (*c* = 2, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3380 (OH), 2250 (CN), 1630 (NCOPh); mass spectrum: *m/e* 427 (molecular ion). (Found: C, 76·31 H, 7·99; N, 8·27. $C_{27}H_{29}O_2N_3 \cdot 2/3\ C_6H_{14}$ requires: C, 76·78; H, 8·11; N, 8·64%). Acetate: colorless caramel, IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1740 ($OCOCH_3$), 1630 (NCOPh); NMR: 8·12 τ (3H, $OCOCH_3$) in $CDCl_3$; 8·17 τ (3H, $OCOCH_3$) in d_6-DMSO. Compound **19a**: colorless prisms (from benzene), m.p. 231–233° (dec); $[\alpha]_D^{26}$ −4·5° (*c* = 1·1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3380 (OH), 2250 (CN), 1615 (NCOPh); mass spectrum: *m/e* 427 (molecular ion). (Found: C, 75·99; H, 6·91; N, 9·49. $C_{27}H_{29}O_2N_3$ requires: C, 75·85; H, 6·84;

N, 9·83%). Acetate: colorless caramel; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1740 ($OCOCH_3$), 1630 (NCOPh); NMR: 8·32 τ (3H, $OCOCH_3$) in $CDCl_3$; 8·32 τ (3H, $OCOCH_3$) in d_6-DMSO.

α-*Ethyl*-5-*methyl*-9β-*formyl*-12-*benzoyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8-*acetonitrile* (**18a**). Ac_2O (0·2 ml) was added to a solon of **19a** (59 mg) in DMSO (2 ml) and the mixture was stirred overnight at room temp. The reaction mixture was poured into ice-water and extracted with benzene. The benzene extract was washed with water, dried and evaporated *in vacuo* to leave a yellow caramel, which was chromatographed on silicagel to give a colorless caramel, yield 30 mg (50%); $[\alpha]_D^{20}$ −56° (*c* = 0·3, AcOH); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2730 (CHO), 2250 (CN), 1725 (CHO), 1630 (NCOPh); NMR ($CDCl_3$): 0·2 τ (1H, CHO).

α-*Ethyl*-5-*methyl*-9α-*formyl*-12-*benzoyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8-*acetonitrile* (**18**) *and* 9β-*isomer* (**18a**). To a solon of **18a** (85 mg) in benzene (20 ml) was added alumina (0·5 g) and the mixture was allowed to stand overnight at room temp. Alumina was removed by filtration and the filtrate was concentrated *in vacuo* to give a colorless caramel (60 mg). This was a mixture of **18** and **18a** in the ratio of ca. 3:2 judging from NMR measurement; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2730 (CHO), 2250 (CN), 1725 (CHO), 1635 (shoulder), 1630 (NCOPh); NMR ($CDCl_3$): (**18**), 0·5 τ (α-CHO), (**18a**), 0·2 τ (β-CHO).

2-*Hydroxy*-4-*benzoyl*-17-*O*-*acetyl*-*anhydroisoajmalineoxime* (**20**). A solon of **18** (1·16 g) in a mixture of Ac_2O (4·5 ml) and AcOH (10 ml) was saturated with dry HCl gas at 15°. After standing for 2·5 hr at room temp, the mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave a brown caramel, which was chromatographed on silicagel to give a faint yellow caramel, yield 390 mg (30%). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3520 (OH), 2250 (CN), 1740 (OAc), 1630 (NCOPh). UV: λ_{max}^{EtOH} 292, 244 mμ (ε = 2500, 13700); $\lambda_{max}^{6N\text{-}HCl}$ 294, 243, 234 mμ (ε = 3000, 10800, 13500).

4-*Benzoyl*-17-*O*-*acetyl*-*anhydroisoajmalineoxime* (**21**). The above-obtained **20** (200 mg, 0·4 mmole) suspended in 6N-HCl (21 ml) was shaken in H_2-atmosphere over PtO_2 catalyst (100 mg) at room temp, 1·6 molor equiv H_2 (15·4 ml) being absorbed. The catalyst was filtered off and water was added to the filtrate, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated *in vacuo* to leave a faint yellow caramel, which was chromatographed on silicagel to give a colorless caramel, yield 20 mg (10%). This was crystallized with i-PrOH to form colorless minute needles, m.p. 204–206° (dec). $[\alpha]_D^{20}$ −27·4° (*c* = 1·5, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2250 (CN), 1730 (OAc), 1630 (NCOPh).

This was identified with the acetate of **17** through IR ($CHCl_3$), $[\alpha]_D$ and mixed m.p. Acetate of **17**: m.p. 204–206° (dec); $[\alpha]_D^{26}$ −30·8° (*c* = 2, $CHCl_3$). (Found: C, 74·24; H, 6·77; N, 8·89. $C_{29}H_{31}O_3N_3$ requires: C, 74·17; H, 6·65; N, 8·95%).

4-*Benzyl*-*anhydroisoajmalineoxime* (**22**). To a solon of Meerwein reagent [prepared from $BF_3 \cdot Et_2O$ (680 mg, 4·8 mmole), epichlorohydrin (330 mg, 3·6 mmole) and anhyd ether (25 ml)] in anhyd CH_2Cl_2 (10 ml) **21** (400 mg, 0·8 mmole) was added in anhyd CH_2Cl_2 (10 ml) and allowed to stand overnight at room temp. After evaporation of the solvent *in vacuo*, the residue was dissolved in anhyd. EtOH (12 ml) and reduced with $NaBH_4$ (280 mg, 7·2 mmole) with ice-cooling. After standing overnight at room temp, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave a syrupy residue, which was purified on silicagel to give a colorless caramel (380 mg). This was refluxed in 2% MeOH-NaOH (20 ml) for 10 min and evaporated to give a syrupy residue, which was dissolved in $CHCl_3$ and worked up as usual. A solid thus obtained was purified from i-PrOH to give colorless minute needles, m.p. 195–197°, yield 280 mg (85%); $[\alpha]_D^{22}$ +31·0° (*c* = 2, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3450 (OH), 2250 (CN). (Found: C, 78·64; H, 7·70; N, 10·23. $C_{27}H_{31}ON_3$ requires: C, 78·41; H, 7·56; N, 10·16%).

Anhydroisoajmalineoxime (**23**). A solon of **22** (200 mg) in a mixture of EtOH (20 ml) and dioxan (2 ml), acidified with conc HCl (1 ml), was shaken in H_2 atmosphere over 10% Pd-C catalyst (100 mg) at room temp, 1·5 molor equiv H_2 (17·6 ml) being absorbed. The catalyst was filtered off and washed with EtOH. The combined filtrates were evaporated *in vacuo* to leave a syrupy residue, which was basified with aq $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated to leave a solid (95 mg), which was crystallized with MeOH to form colorless needles, m.p. 214–216° (dec)*, yield 40 mg (25%); $[\alpha]_D^{22}$ +54·6° (*c* = 1·08, $CHCl_3$)*; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3560, 3440 (OH, NH), 2250 (CN).

Isomerization of **19a** to **16a**. β-alcohol **19a** (100 mg, 0·2 mmole) was dissolved in 1% MeOH-NaOH (10 ml) and stirred overnight at 27°. MeOH was then evaporated *in vacuo* at room temp and the residue obtained was mixed with water and extracted with benzene. The benzene extract was washed with water, dried and

* [lit[1]: m.p. 219–220°; $[\alpha]_D^{19}$ + 74° (*c* = 1·2, $CHCl_3$)).

evaporated to leave a colorless caramel (85 mg), which was chromatographed on silicagel to recover unchanged **19a** (30 mg) and isomerized **16a** (25 mg) as a colorless caramel. The latter thus obtained was identical in every respect with the authentic sample derived from ajmaline. **16a**: IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3390 (OH), 2250 (CN), 1615 (NCOPh).

Debenzoylation and isomerization of **13** *to* (dl-**16a**). The ester **13** (100 mg) was added to a solon of NaOH (50 mg) in MeOH (7 ml) and stirred overnight at room temp. After removal of MeOH *in vacuo* at room temp, the residue obtained was added with water and extracted with benzene. The benzene extract was washed with water, dried and evaporated to leave a colorless caramel (70 mg), which gave two main spots on TLC (silicagel; cyclohexane 1 : AcOEt 3), the one (R_f 0·49) corresponding to **14** and the other to *dl*-**16a**.

Isomerization of **16a** *to* **19a**. β-Alcohol **16a** (100 mg, 0·2 mmole) was dissolved in 1% MeOH-NaOH (10 ml) and stirred overnight at 27°. After removal of MeOH *in vacuo* at room temp, the residue obtained was added with water and extracted with benzene. The benzene extract was washed with water, dried and evaporated to leave a colorless caramel (75 mg), which was chromatographed on silicagel to give unchanged **16a** (22 mg) and isomerized **19a** (24 mg).

The latter thus obtained was crystallized with benzene to form colorless prisms, m.p. 224–227° (dec), yield 10 mg.

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