

SYNTHESIS OF ISOAJMALINE

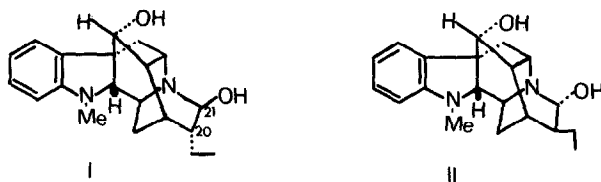
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Total synthesis of ajmaline (II) was first reported in 1967 by S. Masamune et al.¹⁾ In the present communication we wish to describe the first synthesis of isoajmaline (I), a natural base, which is stereoisomeric with ajmaline at C₂₀ and 21.



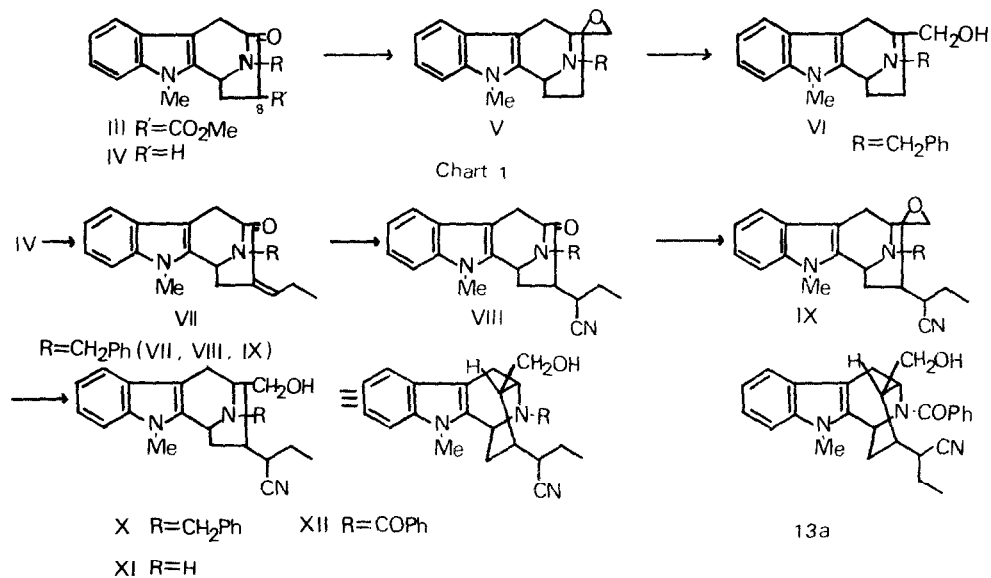
As the preliminary for our ultimate purpose we attempted to synthesize (VI), having fundamental molecular framework of both ajmaline and isoajmaline.

Thus the compound (III), whose preparation from tryptophan had already been recorded by N. Yoneda²⁾ in our laboratory, was subjected to ketone fission reaction by heating with acetic-hydrochloric acid mixture to give ketone (IV) (mp. 133°, IR_{nujol} 1700cm⁻¹(C=O), yield 80%). This was treated either with dimethyloxosulfonium methylide or dimethylsulfonium methylide³⁾ in DMSO according to Corey to furnish the corresponding oxirane derivative (V) (yellow oil bp_{0.01} 207-210°, IR* 910cm⁻¹(oxirane), yield 96%).

On being treated with HAlCl₂⁴⁾ in anhydrous ether the oxirane ring in (V) was reductively cleaved yielding (VI) in 72% yield. (IR 3200cm⁻¹(OH), O-acetyl mp. 129-130°) (Chart 1).

In order to extend the above reaction sequence to the synthesis of ajmaline type of compound we undertook to graft -CH(C₂H₅)CN side chain at 8-position

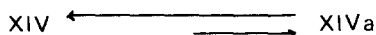
*The IR spectra were taken in CHCl₃ unless stated otherwise.



of (IV). After numbers of fruitless experimentation we succeeded to condense the ketone (IV) with *n*-propanal by means of triton-B to obtain the propylidene derivative (VII) in 54% yield, (mp. 114-125°, IR_{nujol} 1680cm⁻¹(C=O), 1610cm⁻¹(C=C), NMR_{CDCl₃} olefin-H 3.2 τ triplet), which underwent smooth hydrocyanation reaction with KCN-NH₄Cl⁵⁾ to furnish (VIII) (mp. 186-189°(decompd.), IR 2250 cm⁻¹(CN), 1715cm⁻¹(C=O), yield 54%). The latter was now converted to oxirane (IX) (IR 2250cm⁻¹(CN), 910cm⁻¹(oxirane), yield 50%, picrate mp. 164-166° (decompd.)) as before, followed by reductive cleavage of the oxirane ring with AlH₃⁴⁾ in anhydrous ether. The resultant carbinol (X) (mp. 137-139°, IR 3200 cm⁻¹(OH), 2250cm⁻¹(CN), yield 54%) was submitted to hydrogenolysis over 10% Pd-C to give the debenzylated base (XI) (mp. 212.5-213.5°(decompd.), IR 3250 cm⁻¹(OH,NH), 2250cm⁻¹(CN), yield 58%), of which dibenzoyl derivative (mp. 106-108°) was prepared with an excess of benzoyl chloride-pyridine. When the latter was subjected to brief treatment with CH₃ONa in methanol, *O*-benzoyl group was selectively removed to yield (XII) (mp. 202.5-205.5°(decompd.), IR 3380cm⁻¹(OH), 1615cm⁻¹(N-COPh)). (Chart 2)

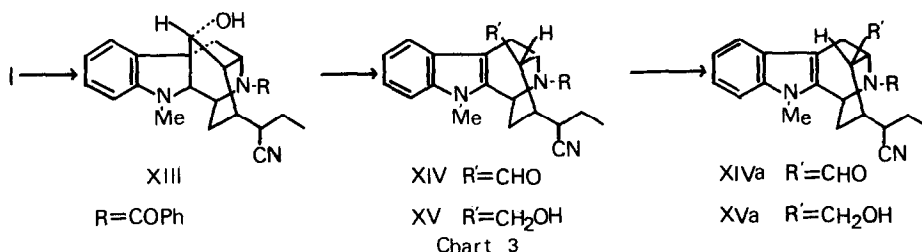
When compared with Masamune's compound 13a¹⁾ having same plane structure, our compound gave a similar IR chart, but they could not be regarded

identical as judged from their distinctly different behaviour on TLC, rendering probable that (XII) belongs to isoajmaline species.



Therefore, by the known method^{1,6)}, isoajmaline was converted into (XIV) (IR 2730cm^{-1} (CHO), 2250cm^{-1} (CN), 1725cm^{-1} (CHO), 1635cm^{-1} (N-COPh), $\text{NMR}_{\text{CDCl}_3}$ CHO 0.5 τ yield 80%) via several steps (Chart 3), which was reduced with NaBH_4 to furnish (XV) (mp. $125\text{-}127^\circ$).

On the other hand isomerization of (XIV) to (XIVa) ($\text{NMR}_{\text{CDCl}_3}$ CHO 0.2 τ) was effected by treating with alumina in benzene solution to give an equilibrium mixture of (XIV) and (XIVa) in an approximate ratio of 3 : 2. On being reduced with NaBH_4 (XIVa) gave the corresponding alcohol (XVa) (mp. $230\text{-}233^\circ$ (decompd.), IR 3380cm^{-1} (OH), 2250cm^{-1} (CN), 1615cm^{-1} (N-COPh)) in good yield, which was found to be identical with (XII) mentioned above. Synthesis of isoajmaline thus became feasible.



For isoajmaline synthesis (XVa) could now be used as a relay substance. This was oxidized with $\text{DMSO-Ac}_2\text{O}$ back to the aldehyde (XIVa) in 80% yield, which was equilibrated to give (XIV), followed by treatment with $\text{Ac}_2\text{O-AcOH}$ containing hydrogen chloride gas. The resultant compound (XVI) (IR 3520cm^{-1} (OH), 2250cm^{-1} (CN), 1740cm^{-1} (O-COCH₃), 1630cm^{-1} (N-COPh), UV $\lambda_{\text{max}}^{6\text{N.HCl}}$ 294, 243, 234 m ($\epsilon = 8000, 10800, 13500$), $\lambda_{\text{max}}^{\text{EtOH}}$ 292, 244 m ($\epsilon = 2500, 13700$), yield 30%) was subjected to hydrogenolysis over $\text{PtO}_2\text{-Pt}$ catalyst in 6N-HCl solution, affording (XVII) (mp. $204\text{-}206^\circ$, IR 2250cm^{-1} (CN), 1730cm^{-1} (O-COCH₃), yield 10%), of which N-CO-Ph was best reduced by treating first with the Meerwein reagent ($\text{Et}_3\text{O}^+\text{BF}_4^-$) followed by reduction with NaBH_4 ⁷⁾ to yield (XVIII) (mp. $195\text{-}197^\circ$, IR 3570cm^{-1} , 3400cm^{-1} (OH), 2250cm^{-1} (CN), yield 85%). Usual reductive debenzoylation converted

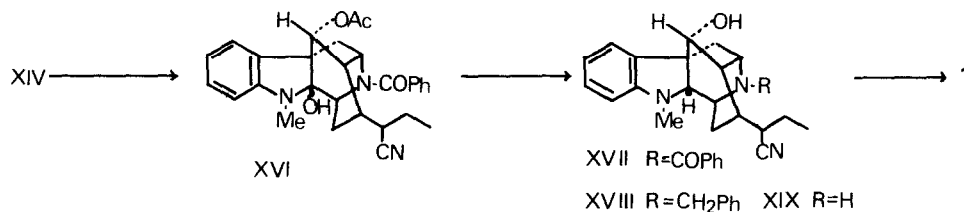


Chart 4

the latter into (XIX), whose m.p., $[\alpha]_D$ and IR data tallied with those of the authentic sample⁶⁾. Since the conversion of (XIX) into isoajmaline (I) has already been accomplished by Prof. Sir Robert Robinson et al⁶⁾, total synthesis of (\pm)-isoajmaline was now achieved by our present work. (Chart 4)

Remarks will be made on the results on isomerization experiments of some of the intermediate compounds.

When allowed to stand overnight in 1% MeOH-NaOH solution at 27°, about a half of (XVa) isomerizes to (13a) and vice versa to give an equilibration mixture of both compounds, while (XV) is stable under the above conditions.

Acknowledgement

We express our hearty gratitude to Professor Sir Robert Robinson for a generous donation of a large quantity of ajmaline, which enabled us to carry out the present work. Thanks are also due to Prof. emeritus S. Sugawara, Prof. Y. Ban and Dr. M. Kawanishi for their pertinent advice, and Mr. M. Yamazaki, head of this laboratory for his unfailing interest throughout this work.

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