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A Contribution to the Synthesis of Ajmaline[1]

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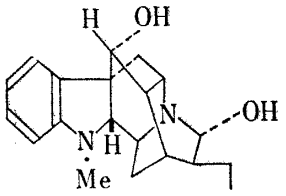
5-Methyl-9β-benzoyloxymethyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5-*H* cyclooct[*b*]indole-8-acetonitrile (**8**) is a key intermediate in the synthesis of ajmaline (**1**) by Masamune, *et al.* We report here an alternate synthesis of this important compound starting from the easily accessible (**3**), whose preparation has been described in the foregoing paper.

It was in 1967 when Masamune, *et al.*[3] first reported their brilliant total synthesis of ajmaline (**1**), in which 5-methyl-9β-benzoyloxymethyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (**2**) was a key intermediate.



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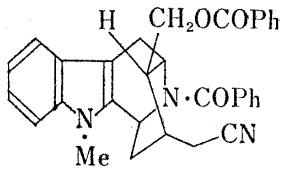

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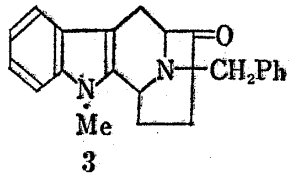
We now succeeded to synthesize this intermediate compound from the readily accessible 5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**3**), which



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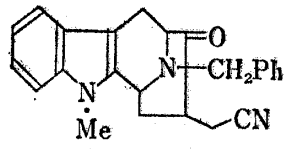

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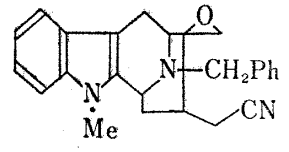

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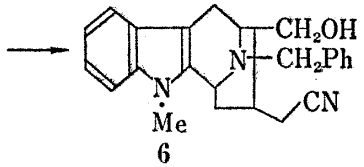

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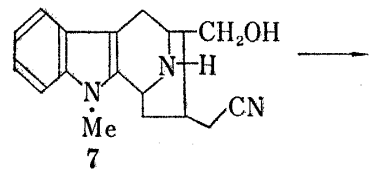

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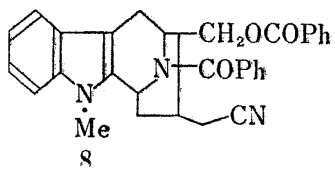

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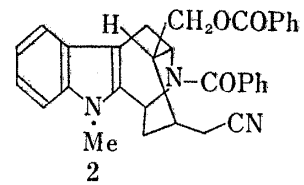

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1) For preliminary communication, see *Tetrahedron Letters*, **1969**, 905.
2) Location: *Toda, Saitama.*
3) S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar and Y. Yasunari, *J. Am. Chem. Soc.*, **89**, 2506 (1967).

also was the starting material in our synthesis of isoajmaline, as was described in the related paper.[4]

Pyrrolidine–enamine of this ketone (**3**) was alkylated with chloroacetonitrile in dioxane solution to afford the objective 5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (**4**) in 65% yield, which was characterized as its crystalline picrate of mp 203—205°. On being treated with dimethyloxosulfonium methylide in dimethyl sulfoxide (DMSO) according to Corey,[5] **4** yielded the expected 5-methyl-12-benzyl-6,7,8,9,10,11-hexahydro-oxiranospiro-[2,9]-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (**5**), mp 165—166°, which was dissolved in benzene and treated with an ethereal solution of $HAlCl_2$[6] to furnish 5-methyl-9β-hydroxymethyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (**6**) in 80% yield after chromatography, which gave a single spot in thin-layer chromatography and O-benzoyl derivative melting fairly sharply at 198—201°. From these facts it could be assumed that oxirane ring cleavage occured stereoselectively to yield a single hydroxymethyl derivative (**6**) in good yield.

This alcohol was then reductively debenzylated and the resultant secondary base, 5-methyl-9β-hydroxymethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (**7**), was treated with benzoyl chloride–pyridine to give O,N-dibenzoyl derivative (**8**). The latter was repeatedly purified from ethyl acetate, when two kinds of solid were obtained: the one formed prisms of mp 140—145° and the other was crystalline powder of mp 202—204°. They both analysed correctly for **8** and are interconvertible by regulating the amount of recrystallization solvent. They gave different infrared (IR) spectra in nujol mull, but in chloroform solution their IR spectra are superposable, supporting their being dimorphous. Moreover the IR spectrum (chloroform) and nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of **8** tallied completely with those of the compound (**2**), from which Masamune, *et al.*[3] had already synthesized ajmaline.

In recent years ajmaline has been utilized as anti-arrhythmic drug and we are now making effort to synthesize ajmalinelike structures along the line mentioned above.

Experimental

All melting points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 ($CHCl_3$) or a JASCO IR-E (Nujol) spectrometer and NMR spectra were taken on a JEOL C-60.

5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (4)——Pyrrolidine-enamine of the ketone (3) [from 3 (20 g, 60 mmole), pyrrolidine (42 g) and benzene (400 ml)] was dissolved in dioxane (200 ml) and to this solution was added chloroacetonitrile (6 g, 72 mmole). After being refluxed for 2 hr, the reaction mixture was added to water (100 ml) and stirred overnight at room temperature. After evaporating the solvent *in vacuo*, the residue was extracted with $CHCl_3$. From the $CHCl_3$ extract, there was obtained a yellow viscous oil, yield 14.3 g (65%) after chromatography. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1720 (C=O).

Picrate: Yellow prisms (from EtOH), mp 203—205°. *Anal.* Calcd. for $C_{30}H_{26}O_8N_6$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.25; H, 4.52; N, 13.64.

5-Methyl-12-benzyl-6,7,8,9,10,11-hexahydro-oxiranospiro[2,9]-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (5)——To NaH (64% oil dispersion 0.22 g, 8.9 mmole, previously washed with hexane to remove the mineral oil) was added trimethyloxosulfonium iodide (1.29 g, 8.9 mmole), followed by abs. DMSO (20 ml). The ketone (4) (2 g, 5.4 mmole) in abs. DMSO (25 ml) was added dropwise to the above solution at room temperature and stirred for 4 hr. The resulting mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried. After removal of $CHCl_3$ *in vacuo* and chromatography on alumina, the crude solid obtained was recrystallized from benzene to give colorless prisms, mp 165—166°, yield 1.49 g (70%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 905 (oxirane). *Anal.* Calcd. for $C_{25}H_{25}ON_3$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.57; H, 6.38; N, 10.74.

4) K. Mashimo and Y. Sato, *Tetrahedron*, in press.
5) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
6) M.N. Rerick and E.L. Eliel, *J. Am. Chem. Soc.*, **84**, 2356 (1962).

5-Methyl-9β-hydroxymethyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (6)——43.4 ml of $HAlCl_2$ in ether [prepared from $AlCl_3$ (3.08 g, 23 mmole), $LiAlH_4$ (0.217 g, 5.8 mmole) and abs. ether 93 ml] was added to the foregoing oxirane (**5**) (2.3 g, 4.6 mmole) in abs. ether (62 ml) with ice-cooling. After stirring at room temperature for 4 hr, the resulting mixture was basified with NH_4OH and the ethereal layer was separated and aqueous layer was extracted with $CHCl_3$. The organic layers were washed with water, dried, combined and evaporated.

The residue was chromatographed on silicagel to give primary alcohol (**6**) as colorless caramel, yield 1.84 g (80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250 (OH), 2250 (CN).

Benzoate: Colorless prisms (from AcOEt), mp 198—201°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2450 (CO_3), 2250 (CN), 1720 (OCOPh). *Anal.* Calcd. for $C_{32}H_{31}O_2N_3 \cdot H_2CO_3$: C, 71.85; H, 6.03; N, 7.62. Found: C, 72.46; H, 6.24; N, 8.16.

5-Methyl-9β-hydroxymethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (7)——A solution of the above-obtained alcohol (**6**) (180 mg) and conc. HCl (0.2 ml) in EtOH (10 ml) was shaken in H_2-atmosphere over 10% Pd–C catalyst (90 mg) at room temperature, 1 molar equivalent H_2 (11 ml) being absorbed. The catalyst was filtered off and washed with EtOH. The combined ethanolic solution was evaporated *in vacuo* to leave a residue, which was dissolved in $CHCl_3$, washed with dilute NH_4OH, followed with water, dried and evaporated to leave a solid residue. This was recrystallized from benzene to give colorless needles, mp 191—193°, yield 110 mg (80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—3200 (OH, NH), 2250 (CN). *Anal.* Calcd. for $C_{18}H_{21}ON_3$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.32; H, 7.23; N, 14.09.

5-Methyl-9β-benzoyloxymethyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-acetonitrile (8)——To a solution of the foregoing secondary base (**7**) (680 mg, 2.3 mmole) in pyridine (10 ml) was added a solution of benzoyl chloride (800 mg, 5.1 mmole) in pyridine (5 ml) with ice-cooling. After standing overnight in an icebox, $CHCl_3$ was added to the reaction mixture, which was washed with 10%-Na_2CO_3, then with water and dried. After removal of the solvent, the residual yellow caramel (1.1 g) was obtained, which was crystallized with AcOEt to form colorless prisms, mp 140—145°, yield 960 mg (83%).

On further recrystallization from AcOEt, the foregoing prisms separated in colorless powder of mp 202—204°. However, when the latter was dissolved in a large amount of AcOEt and allowed to stand overnight, there separated two kinds of solid, which were sorted manually to give colorless prisms of mp 140—145° and colorless crystalline powder of mp 202—204°. The IR data given below support their being dimorphous. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1720 (OCOPh), 1630 (NCOPh). IR ν_{max}^{Nujol} cm^{-1}: Prisms; 2260 (CN), 1710 (OCOPh), 1625 (NCOPh). Powder; 2260 (CN), 1710 (shoulder), 1700 (OCOPh), 1637 (shoulder), 1622 (NCOPh). *Anal.* Calcd. for $C_{32}H_{29}O_3N_3$: C, 76.32; H, 5.80; N, 8.35. Found: Prisms; C, 76.12; H, 5.89; N, 8.45. Powder; C, 76.58; H, 5.88; N, 8.33.

The IR spectrum ($CHCl_3$) and NMR spectrum ($CDCl_3$) of (**8**) tallied completely with those of the compound (**2**), which were kindly provided by Prof. S. Masamune.

Acknowledgement We are grateful to Prof. S. Masamune for providing us with IR and NMR spectra of his compound. Thanks are also due to Prof. emeritus S. Sugasawa, 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. The authors are indebted to the members of the Analytical Center of this company for IR and NMR spectral measurement and elementaly analyses.