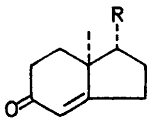
Total Synthesis of the Alkaloid (±)-Dendrobine

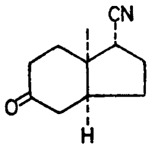
By YASUO INUBUSHI,* TOHRU KIKUCHI, TOSHIRO IBUKA, KIYOSHI TANAKA, IKUTARO SAJI, and KAZUO TOKANE
(*Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*)

Summary Dendrobine, an alkaloid from *Dendrobium* species, has been synthesised.

DENDROBINE (**20**) was first isolated from the Chinese drug Chin-Shih-Hu by Suzuki *et al.*[1] in 1932 and its structure was



(1) R = OH
(2) R = OTs
(3) R = CN



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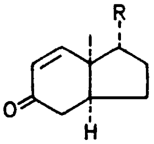
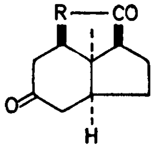
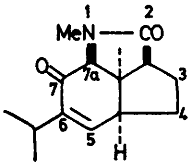


(5) R = CN
(6) R = CO_2H



(7) R = O
(8) R = NMe



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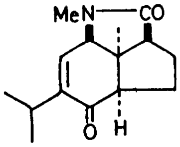

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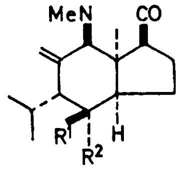
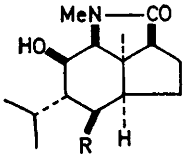
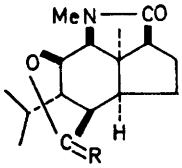


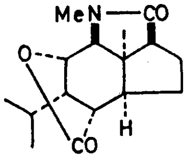
(11) R^1 = H, R^2 = CN
(12) R^1 = CN, R^2 = H
(13) R^1 = CO_2Me, R^2 = H



(14) R = CN
(15) R = CO_2Me



(16) R = NH
(17) R = NTs
(18) R = O



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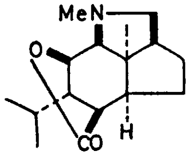

(20)

established independently by three groups[2] in 1964. There has been some interest[3] in its synthesis but the complication of asymmetry (seven centres) has prevented a successful synthesis. We report here a complete synthesis of (±)-dendrobine.

The ketol (**1**)[4] was converted into the tosylate (**2**), m.p. 110°, which was treated with NaCN in DMSO to give the keto-nitrile (**3**), m.p. 71—73° (80%). Hydrogenation of (**3**) over 5% $Pd–SrCO_3$ afforded the saturated keto-nitrile (**4**), m.p. 76° (93%). Treatment of (**4**) with Br_2 (1 equiv.), followed by dehydrobromination provided the enone (**5**), m.p. 89°, and the keto-nitrile (**3**) (ratio, 1 : 3—4). After acetalisation, compound (**5**) was refluxed in $KOH–HO{\cdot}CH_2{\cdot}CH_2{\cdot}OH–H_2O$ (2 : 4 : 1) and deacetalisation of the product with dilute HCl gave the keto-acid (**6**), m.p. 150—152°, and the keto-lactone (**7**), m.p. 95°. When refluxed in $HO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ with 25% H_2SO_4, compound (**6**) gave more keto-lactone (**7**). The overall yield of (**7**) from (**5**) was > 55%. Compound (**7**) was heated with aq. $MeNH_2$ in the presence of HCl to give the lactam (**8**), m.p. 105°, (> 80%) and this lactam was then successively treated with Pr^iMgBr, $KHSO_4$, $I_2–AcOAg–AcOH–H_2O$,[5] $H_2O–MeOH–KOH$, and CrO_3–pyridine to afford the enone (**9**), oil, [δ ($CDCl_3$) 3·57 (s, 7a-H) and 6·61 (q, J 1 and 5 Hz, 5-H) p.p.m.] and the enone (10), m.p. 83° [δ ($CDCl_3$) 3·82 (q, J 1 and 4 Hz, 7a-H) and 6·46 (q, J 4 and 1 Hz, 7-H) p.p.m.] in 10 and 20% yield, respectively. Hydrocyanation of (**9**) with Et_2AlCN[6] gave three isomeric cyano-ketones (**11**), m.p. 199—200° [δ ($CDCl_3$) 3·36, (q, J 1 and 4·5 Hz, 5-H_{eq}) p.p.m.], (**12**), m.p. 133°, [δ ($CDCl_3$) 3·22 (q, J 3·5 and 10 Hz, 5-H_{ax}) p.p.m.], and a compound, m.p. 123°, in which the configurations of the isopropyl and cyano-group is not certain in 18, 29, and 20% yield, respectively. Reduction of (**11**) with $NaBH_4$, followed by hydrolysis with aq. KOH and acidification with dilute HCl, yielded (±)-oxodendrobine (**18**), m.p. 183—184°, and its isomer (**19**), m.p. 182°, in 25 and 50% yield, respectively. Alternatively, (±)-oxodendrobine alone was obtained in 40% yield from (**12**) *via* the methyl ester (**13**), m.p. 145—146°, and the hydroxy-ester (**15**), m.p. 170—171°. (±)-Oxodendrobine was also obtainable from (**12**) *via* the hydroxy-nitrile (**14**), the imino-lactone (**16**), and the *N*-tosylate (**17**). Reduction of (±)-oxodendrobine by Borch's method[7] gave (±)-dendrobine (**20**), m.p. 131—132°, identical with an authentic sample of natural dendrobine in all respects except the specific rotation.

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[1] H. Suzuki, I. Keimatsu, and K. Ito, *J. Pharm. Soc., Japan*, 1932, **52**, 1049.

[2] (a) T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem.* and *Pharm. Bull.* (*Japan*), 1964, **12**, 506; (b) S. Yamamura and Y. Hirata, *Tetrahedron Letters*, 1964, 79; (c) Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konida, J. Matsumoto, E. Katarao, and J. Nakano, *Tetrahedron*, 1964, **20**, 2007.

[3] Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, 1971, **27**, 5157; K. Yamamoto, I. Kawasaki, and T. Kaneko, *Tetrahedron Letters*, 1970, 4859.

[4] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 1960, 4547.

[5] R. B. Woodward and F. V. Brutcher, *J. Amer. Chem. Soc.*, 1958, **80**, 209.

[6] W. Nagata and M. Yoshioka, *Tetrahedron Letters*, 1966, 1913.

[7] R. F. Borch, *Tetrahedron Letters*, 1968, 61.