Tetra- and Hexa-dehydroyohimbane Synthesis by an Intermolecular Cycloaddition of *o*-Quinodimethane

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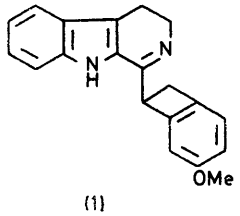
The thermolytic intermolecular cycloaddition reaction of 3,4-dihydro-β-carboline (9) with 1,2-dihydro-5-methoxybenzocyclobutene-1-carbonitrile (6) gave 15,16,17,18,19,20-hexahydro-17-methoxy-yohimbane-14-carbonitrile (3) which was converted into the decyano-derivative (2) and tetradehydroyohimbane (12) by Birch reduction. Xylopinine (8) has been synthesised by a novel decyanation reaction, and 18-methoxyhexadehydroyohimbane (4) has been obtained from 1-(1,2-dihydro-5-methoxybenzocyclobuten-1-yl)-3,4-dihydro-β-carboline (1).

PREVIOUSLY we reported a new synthesis of the 17-methoxyhexadehydroyohimbane (2) by an intramolecular cycloaddition of the *o*-quinodimethane generated by thermolysis of the 1-benzocyclobutenyl-3,4-dihydro-β-carboline (1) hydrochloride, followed by reduction of the rearranged product.[1] Recently we have developed a

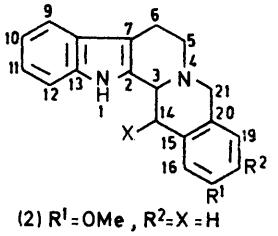
[1] T. Kametani, M. Kajiwara, and K. Fukumoto, *Chem. and Ind.*, 1973, 1165.

novel synthesis of the berbine ring system (7) by intermolecular cycloaddition of a benzocyclobutene-1-carbonitrile to a 3,4-dihydroisoquinoline derivative,[2] in which regioselectivity is controlled by a substituent on the cyclobutene ring.[3] We have been investigating the application of this type of reaction to the synthesis of the natural products, and here report a simple synthesis of the yohimbane ring system by intermolecular cycloaddition of an *o*-quinodimethane to 3,4-dihydro-β-carboline (9), and a synthesis of xylopinine (8) by a novel decyanation of the berbine-13-carbonitrile (7). We also describe the formation of 15,16,17,18,19,20-hexadehydro-18-methoxy-yohimbane (4), an isomer of (2), from (1).

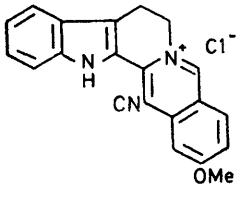
An equimolar amount of a mixture of 3,4-dihydro-β-carboline (9) and 1,2-dihydro-5-methoxybenzocyclobutene-1-carbonitrile (6)[1] was heated at 140—150° without solvent for 2 h in a current of nitrogen to give the cycloaddition product (3), *m/e* 329 (M^+), which was unstable and easily oxidised by air. The crude product



(1)



(2) R^1=OMe, R^2=X=H
(3) R^1=OMe, R^2=H, X=CN
(4) R^1=X=H, R^2=OMe



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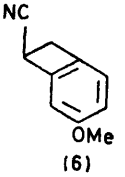
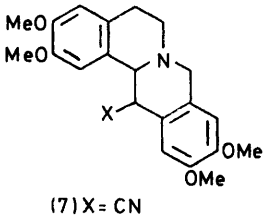
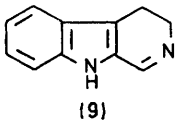


(6)

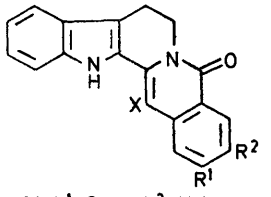


(7) X=CN
(8) X=H

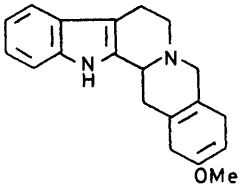
showed i.r. Bohlmann bands at 2850—2750 cm^{-1} and the n.m.r. spectrum revealed one of the C(21)H_2 signals at δ 4·10 as an AB type doublet (*J* 15·0 Hz). This suggested that the cycloaddition proceeded regioselectively to form the 15,16,17,18,19,20-hexadehydroyohimbane-14-carbonitrile (3). Moreover, dehydrogenation of the condensation product with iodine, followed by treatment of the resulting decadehydroyohimbane (5) with alkali, gave the lactam (10); this fact also indicated that the cyano-group was at C-14.



(9)



(10) R^1=OMe, R^2=H, X=CN
(11) R^1=X=H, R^2=OMe



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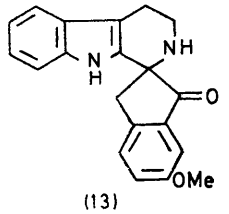

(13)

A reductive decyanation[4] of the nitrile (3) with lithium and liquid ammonia in the presence of propan-2-ol afforded the hexadehydroyohimbane (2) in 61% yield, which was identical with an authentic sample[1] prepared by a standard method (m.p. and spectral comparison). The formation of (2) from the cycloaddition product also indicated that the cyano-group in (3) is at C-14, thus showing that the cycloaddition proceeded regioselectively. The reaction of (3) with a large excess of lithium in liquid ammonia and propan-2-ol gave, in 33% yield, the tetradehydroyohimbane (12) by decyanation, followed by Birch reduction. The structure (12) was established by comparison with an authentic specimen prepared from the hexadehydroyohimbane (2) by normal Birch reduction.[5]

Similar treatment of the berbine-13-carbonitrile (7)[2] with lithium and liquid ammonia in the presence of propan-2-ol gave xylopinine (8), which was identical with an authentic sample[6] (spectral comparison).

The hydrochloride of the 1-benzocyclobutenyl-3,4-dihydro-β-carboline (1)[1] was stable at room temperature, but the free base was unstable in air. The free base (1) was converted into the spiro-[β-carboline-1,2′-inden]one (13) in chloroform or acetone–methanol by aerial oxidation with subsequent rearrangement at room temperature during 6 days.[7] The structure of this product was apparent from its u.v. [$\lambda_{max.}$ (MeOH) 290 and 280 nm], i.r. ($\nu_{max.}$ 1705 cm^{-1}) and n.m.r. [δ 3·20 and 3·64 (each d, *J* 16 Hz, $ArCH_2 \cdot C\leqslant$)] spectra. Irradiation of compound (13) with a Hanovia 450 W mercury lamp for 2·5 h in tetrahydrofuran at 25° gave the known lactam (11) [$\nu_{max.}$ 1645 (lactam CO) and 1615 (double bond)], which was converted by Naito

[2] T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, 1974, **39**, 447.
[3] T. Kametani, Y. Kato, and K. Fukumoto, *J.C.S. Perkin I*, 1974, 1712.
[4] P. Radrick and L. R. Brown, *J. Org. Chem.*, 1973, **38**, 3413.
[5] G. A. Swan, *J. Chem. Soc.*, 1950, 1534.
[6] T. Kametani, K. Ogasawara, and T. Takahashi, *Tetrahedron*, 1973, **29**, 73.
[7] T. Kametani, Y. Hirai, H. Takeda, M. Kajiwara, T. Takahashi, F. Satoh, and K. Fukumoto, *Heterocycles*, 1974, **2**, 339.

into the hexadehydro-18-methoxy-yohimbane (4), by a standard method.[8]

It is noteworthy that the starting material (1) could be converted into either of the position isomers (2) and (4) by virtue of the different stabilities of the free base and the hydrochloride.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 grating spectrophotometer and u.v. spectra with a Hitachi 124 spectrophotometer. N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with JNM-PMX60 and Hitachi H-60 instruments. Mass spectra were measured with a Hitachi RMU-7 spectrometer.

15,16,17,18,19,20-Hexadehydro-17-methoxy-yohimbane-14-carbonitrile (3).—A mixture of 3,4-dihydro-β-carboline (9) (1·0 g) and 1,2-dihydro-5-methoxybenzocyclobutene-1-carbonitrile (6) (0·9 g) was heated at 140—150° for 2 h in a current of nitrogen. The mixture was washed with ether to give the yohimbane (3) as a brown powder (1·6 g, 84·1%), $\nu_{max.}$ ($CHCl_3$) 3475 (indole ring NH), 2850—2750 (Bohlmann bands), and 2240 cm^{-1} (CN); $\lambda_{max.}$ (MeOH) 291 and 283 nm; δ ($CDCl_3$) 4·10 (1H, d, *J* 15 Hz, 21-H) and 3·71 (3H, s, OMe); *m/e* 329 (M^+) and 169 ($M^+ - 160$), which decomposed during attempted recrystallisation and was used without purification.

15,16,17,18,19,20-Hexadehydro-17-methoxy-yohimbane (2).—A mixture of the nitrile (3) (1·6 g) and propan-2-ol (3·0 g) was dissolved in liquid ammonia (*ca.* 300 ml) in a Dewar vessel. Lithium (98·1 mg) was then added with occasional stirring in three portions during 30 min. The reaction was continued until the i.r. spectrum showed no cyano-absorption. Ammonium chloride (5·0 g) was added carefully, the excess of ammonia was evaporated off, and the product was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a syrup, which was crystallised from benzene to give the decyanated product (2) (0·9 g, 61·0%), m.p. 169° (sinters at 150°), identical (i.r. spectrum) with an authentic sample;[1] $\nu_{max.}$ ($CHCl_3$) 3480 (NH) and 2850—2760 cm^{-1} (Bohlmann bands); $\lambda_{max.}$ (MeOH) 290sh and 282 nm; δ ($CDCl_3$) 3·72 (3H, s, OMe) and 4·00 (1H, d, *J* 15 Hz, 21-H; the higher field portion of this AB quartet was obscured), *m/e* 304 (M^+), 169, 144, and 134.

Birch Reduction of the Hexadehydroyohimbane (2).—A mixture of the hexadehydroyohimbane (2) (1·2 g), propan-2-ol (2·5 g), and tetrahydrofuran (2·5 g) was dissolved in liquid ammonia (*ca.* 300 ml). Lithium (200 mg) was then added with occasional stirring in four portions during 30 min and the mixture was set aside for 2 h. Ammonium chloride (5·0 g) was added and the excess of ammonia was evaporated off. The residue was treated with water (100 ml) and extracted with benzene (100 ml). The organic layer was washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to give crystals (1·0 g, 83·0%); recrystallisation from chloroform–methanol gave 15,17,18,20-tetradehydro-17-methoxy-yohimbane (12) as leaflets, m.p. 188° (lit.,[5] 188°) (Found: C, 78·1; H, 7·3; N, 9·0. Calc. for $C_{20}H_{22}N_2O$: C, 78·4; H, 7·25; N, 9·15%), $\nu_{max.}$ ($CHCl_3$) 3480 (NH), 2850—2750 (Bohlmann bands), and 1705 and 1670 cm^{-1} (C:C·OMe); $\lambda_{max.}$ (MeOH) 291sh, 282, and 275 nm; δ ($CDCl_3$) 2·05—2·40 (2H, m, $ArCH_2{\cdot}CH_2$), 2·78 (4H, s, 16- and 19-H_2), 3·55 (3H, s, OMe), and 4·62br (1H, s, 18-H), *m/e* 306 (M^+), 291 ($M^+ - 15$), 276 ($M^+ - 30$), 184, 170, 169, and 141.

Birch Reduction of the Nitrile (3).—A mixture of the nitrile (3) (1·3 g) and propan-2-ol (2·0 g) was dissolved in liquid ammonia (300 ml). Lithium (0·5 g) was added with occasional stirring in four portions during 30 min. The mixture was set aside for 2 h. More lithium (0·5 g) was added during 1 h, then ammonium chloride (10 g) was added and the excess of ammonia was evaporated off. Water was added to the residue and the mixture was extracted with benzene (100 ml). The organic layer was washed with saturated sodium chloride solution, dried (Na_2SO_4), and distilled. The product was purified by silica gel chromatography [chloroform–methanol (9 : 1)] to give the enol ether (12) as crystals (0·45 g, 33·0%), m.p. 188° (from chloroform–methanol), identical (i.r. spectrum) with an authentic sample.[5]

1,2,2′,3,3′,4-Hexahydro-6′-methoxyspiro-[β-carboline-1,2′-inden]-1′-one (13).—(*a*) A solution of the hydrochloride (2·0 g) of (1) in 10% ammonia (pH 10) was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and then kept at room temperature for 6 days. The solvent was removed and the residue was recrystallised from ethanol to give orange *prisms* (13) (1·5 g, 80%), m.p. 238—242° (decomp.) (Found: C, 75·65; H, 5·6; N, 8·8. $C_{20}H_{18}N_2O_2$ requires C, 75·45; H, 5·7; N, 8·8%), $\nu_{max.}$ ($CHCl_3$) 3460 (NH) and 1705 cm^{-1} (C=O), $\lambda_{max.}$ (MeOH) 346, 332, 290sh, 280sh, and 259 nm; δ [$CDCl_3$–$(CD_3)_2SO$] 2·63—3·08 (4H, m, $ArCH_2{\cdot}CH_2$), 3·20 and 3·64 (each 1H, d, *J* 16 Hz, 3′-H_2), 3·82 (3H, s, OMe), 6·83—7·83 (7H, m, 7 × ArH), and 9·96br (1H, s, indole NH); *m/e* 318 (M^+) and 290 ($M^+ - 28$).

(*b*) The free base (1) (563·2 mg) was kept at room temperature for 3 days in methanol–acetone (1 : 1) (60 ml). The solvent was removed and the residue was recrystallised from ethanol to give (13) as orange prisms (400 mg, 67·5%), m.p. 238° (decomp.), identical with the sample prepared by method (*a*).

3,4,14,15,16,17,18,19,20,21-Decadehydro-17-methoxy-21-oxo-yohimbane-14-carbonitrile (10).—To a solution of the nitrile (3) (1·0 g) in ethanol (200 ml) was added iodine (3·08 g), and the mixture was heated under reflux for 4·25 h. The solvent was evaporated off and the excess of iodine was decomposed by dropwise addition of 10% sodium thiosulphate solution. An insoluble substance was collected by filtration and then washed with ether on the filter. The resulting iodide (1·03 g) was dissolved in ethanol (250 ml) and to the solution was added sodium hydroxide (1·9 g). After stirring for 46·5 h at room temperature, the ethanol was evaporated off. The product was extracted with methylene chloride and then benzene. The organic layers were combined and evaporated and the residue was washed with n-hexane to afford compound (10) (729·7 mg, 94·1%) as a yellow *powder*, m.p. 137—138° (decomp.) (Found: C, 74·75; H, 5·75. $C_{21}H_{15}N_3O_2{\cdot}0{\cdot}5C_6H_{14}$ requires C, 75·0; H, 5·5%), $\nu_{max.}$ ($CHCl_3$) 3460 (indole ring NH), 2190 (CN), and 1650 cm^{-1} (C=O), $\lambda_{max.}$ (MeOH) 386, 367, 310sh, 292sh, and 254 nm; δ ($CDCl_3$) 0·88br (3H, s, 0·5 × $CH_3{\cdot}[CH_2]_4{\cdot}CH_3$), 1·25br (4H, s, 0·5 × $CH_3{\cdot}[CH_2]_4{\cdot}CH_3$), 3·86 (3H, s, OMe), and 9·5br (1H, s, NH); *m/e* 341 (M^+), 326 ($M^+ - 15$), 268, and 159.

[8] T. Naito and O. Nagase, *J. Pharm. Soc. Japan*, 1960, **80**, 629.

(±)-*Xylopinine* (8).—To liquid ammonia (*ca.* 300 ml) under nitrogen a solution of the berbinecarbonitrile (7) (1·4 g) in propan-2-ol (1·5 g) was added. Lithium (50 mg) was then added within 1·5 h and the reaction was continued until the i.r. spectrum showed no cyano-absorption. The mixture was carefully decomposed with ammonium chloride (5·4 g) and the excess of ammonia evaporated off overnight. The product was diluted with water (80 ml) and extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried (K_2CO_3), and evaporated to give (±)-xylopinine (8) as a pale orange crystalline mass (1·1 g, 84·6%), m.p. 145—148° (lit.,[9] 147—148°; lit.,[10] 145—145·5°; lit.,[6] 150—151·5°; lit.,[11] 151·5—152·5°), identical (i.r. spectrum) with an authentic sample.[6]

3,4,14,15,16,17,18,19,20,21-*Decadehydro*-18-*methoxyyohimban*-21-*one* (11).—A solution of the spiro-[β-carboline-1,2′-inden]one (13) (718 mg) in dry tetrahydrofuran (700 ml) was irradiated with a Hanovia 450 W mercury lamp in a current of nitrogen at 25° for 2·5 h. The solvent was then distilled off *in vacuo* to give a crude brown powder, which was purified by silica gel chromatography [chloroform–methanol (9 : 1)] to give the lactam (11) (150 mg, 21%) as yellow prisms, m.p. >300° (lit.,[8] 327—328°), $\lambda_{max.}$ (MeOH) 370, 340, and 331sh nm; $\nu_{max.}$ ($CHCl_3$) 1645 (lactam C=O) and 1615 cm^{-1} (C=C), δ ($CDCl_3$) 3·90 (3H, s, OMe) and 7·0—7·9 (8H, m, 8 × ArH), *m/e* 316 (M^+) and 301 ($M^+ - 15$), identical with an authentic sample (spectral comparison).

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[4/1817 *Received*, 3*rd September*, 1974]

[9] M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan*, 1969, **80**, 1238.

[10] T. Kametani and M. Ihara, *J. Pharm. Soc. Japan*, 1967, **87**, 174.

[11] E. Späth and F. Kruta, *Monatsh.*, 1928, **50**, 341.