A TOTAL SYNTHESIS OF (±)-YOHIMBINE

Tetsuji Kametani,* Masahiro Kajiwara, Tamiko Takahashi, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

A total synthesis of (±)-yohimbine (8) from 1,2,3,4,5,6,7,-12b-octahydroindolo[2,3-a]quinolizin-2-one (5) has been achieved through 15,16-dehydroyohimbinone (6) and yohimbinone (7). Two kinds of novel syntheses of (5) are also reported.

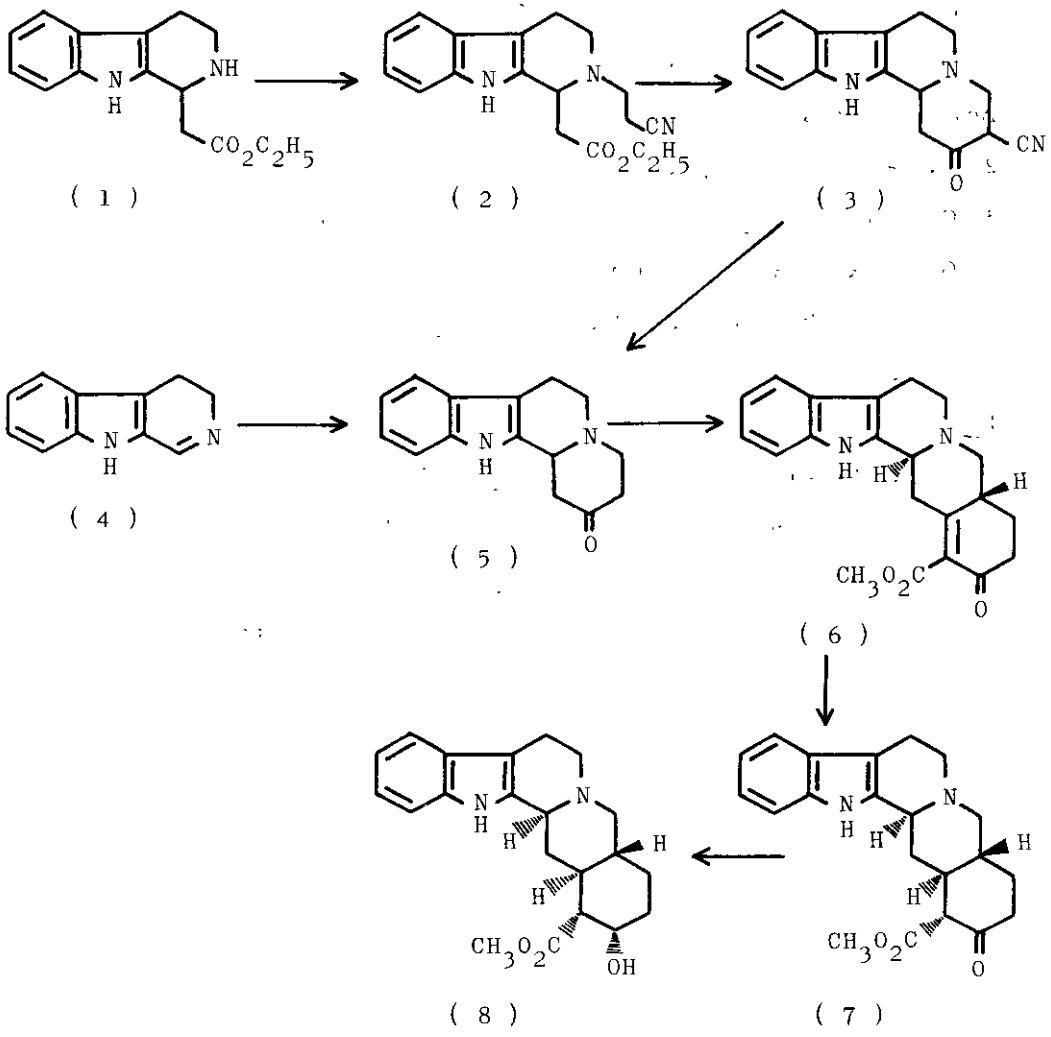
The yohimbane-type alkaloids[1] have been subjected to more studies than those of the other alkaloids in the indole series, because of the pharmacological activity of yohimbine (8) and reserpine. We are currently investigating the synthesis of alkaloids of the yohimbane group[2] and here wish to report a total synthesis of yohimbine (8).

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (1)[3] was condensed with acrylonitrile on a water bath for 20 hr to give in 97.6 % yield the corresponding 2-cyanoethyl derivative (2), mp 126 - 136° [ν max ($CHCl_3$) 3340 (indole NH), 2245 (CN) and 1710 (CO) cm^{-1}; λ max (MeOH) 291, 282 - 280 and 275^{sh} nm; m/e 311 (M^+); δ($CDCl_3$) 0.94 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 2.4 - 3.33 (10H, m, 5 x CH_2), 4.2 (3H, q, J 7 Hz, OCH_2CH_3 and ArC$\underline{H}$N), 7.0 - 7.6 (4H, m, ArH) and 8.36 (1H, broad s, NH)], which was subjected to Dieckmann cyclisation in the presence of sodium hydride in boiling benzene for 2 hr to afford 3-cyano-1,2,-

3,4,5,6,7,12b-octahydroindolo[2,3-a]quinolizin-2-one (3) in 87.9 % yield [m/e 265 (M^+); ν max ($CHCl_3$) 2250 (CN) and 1720 (CO) cm^{-1}]. Treatment of (3) with 10 % sulphuric acid for 24 hr under reflux yielded the decyanated indolo[2,3-a]quinolizin-2-one (5), mp 177 - 180° (lit.,[3] mp 180 - 181°) in 70 % yield [m/e 240 (M^+); ν max ($CHCl_3$) 3475 (NH), 2760 - 2850 (Bohlmann bands), and 1717 (CO) cm^{-1}; $\delta(CDCl_3)$ 8.07 (NH)]. This compound was also obtained in poor yield by Robinson annelation of 3,4-dihydro-β-carboline (4) with methyl vinyl ketone in methanol at room temperature for 1 hr and identical with the authentic sample, prepared by the known methods,[3] in ir and nmr spectral comparisons.

Reaction of the pyrrolidine enamine of this ketone (5) with methyl 3-oxo-4-pentenoate in boiling benzene for 10 min by Stork's method[4] gave the 15,16-dehydroyohimbinone (6) in 25 % yield, after separation and purification on silica gel column chromatography and tlc, mp 189° (lit.,[5] mp 188 - 189°)[m/e 350 (M^+); ν max ($CHCl_3$) 3475 (NH), 2760 - 2850 (Bohlmann bands), 1725 and 1675 (CO), and 1625 (C=C); λ max (MeOH) 291, 283, and 274 nm; δ ($CDCl_3$) 3.93 (3H, s, $CO_2C\underline{H}_3$)], which was hydrogenated on 30 % palladium-carbon[5] in methanol to give the yohimbinone (7) in 60 % yield, mp 239° (lit.,[5] mp 238 - 239°)[m/e 352 (M^+, 100 %), 351, 321, 320, 319, 294, 293, 291, 237, 235, 223, 221, 184, 170, 169, 156, 155 and 141], whose ir [ν max ($CHCl_3$) 3480 (NH), 1740 (CO_2CH_3), and 1150 cm^{-1}] and nmr [δ ($CDCl_3$) 3.83 (3H, s, $OC\underline{H}_3$)] spectra were superimposable on those of the authentic sample (7).[6] Yohimbinone (7) has already been correlated with yohimbine (8) by Szántay and co-workers[7] and Ziegler and Sweeny.[8]

Thus we have accomplished a total synthesis of (±)-yohimbine (8) from 3,4-dihydro-β-carboline (4) in four steps.



(1) (2) (3)

(4) (5) (6)

(8) (7)

REFERENCES

1 H. J. Monteiro, "The Alkaloids", ed. by R. H. F. Manske, Vol. XI, pp. 145, Academic Press, New York, 1968.

2 T. Kametani, M. Kajiwara, and K. Fukumoto, Tetrahedron, 1974, 30, 1053.

3 G. B. Kline, J. Amer. Chem. Soc., 1959, 81, 2251.

4 G. Stork and R. N. Guthikonda, J. Amer. Chem. Soc., 1972, 94, 5109; K. Mori, I. Takemoto, and M. Matsui, Agr. Biol. Chem., 1972, 36, 2605.

5 Cs. Szántay, K. Honty, L. Töke, A. Buzas, and J. P. Jacquet, Tetrahedron Letters, 1971, 4871.

6 J. D. Albright and L. Goldman, J. Amer. Chem. Soc., 1965, 87, 4214.

7 L. Töke, K. Honty, and Cs. Szántay, Chem. Ber., 1969, 102, 3248.

8 F. E. Ziegler and J. G. Sweeny, J. Org. Chem., 1969, 34, 3545.

Received, 16th December, 1974