A FACILE SYNTHESIS OF 2,3-DIHYDRO-1H-PYRROLO[1,2-a]INDOLES

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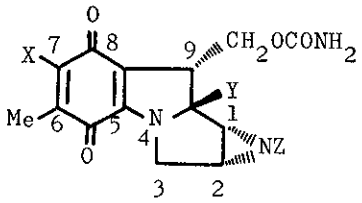
Cyclisation of α-(2-bromophenyl)-$\Delta^{2,\alpha}$-pyrrolidineacetonitriles (4 and 13) with sodium hydride and cuprous bromide in dimethylformamide gave quantitatively the corresponding pyrrolo[1,2-a]indoles (5 and 14), which were converted into the aldehydes (6 and 15).

Mitomycins (1), isolated from Streptomyces cultures, have been found to be active against bacteria and in cancer chemotherapy. Although considerable efforts had been made in the synthetic approach of mitomycins[1], most of the published routes were concerned with the formation of tricyclic pyrrolo[1,2-a]indole system, but their yields did not seem to be satisfactorily high. Here we wish to report a facile synthesis of a pyrrolo[1,2-a]indole ring system, which also constitutes a formal synthesis of 7-methoxymitosene (2), an antibacterial agent.

As a preliminary experiment, a cyclisation of α-(2-bromo-4,5-dimethoxyphenyl)-$\Delta^{2,\alpha}$-pyrrolidineacetonitrile (4), m.p. 173°, which was prepared by a condensation of the nitrile (3) with O-methyl-

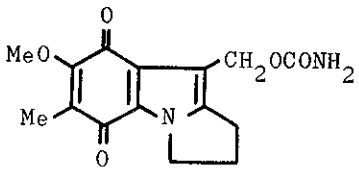
pyrrolidone in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) or triethylamine[2] at 110° in 79 % yield, was examined under various conditions. The structure of 4 including the geometry was deduced by comparison of its i.r. [$\nu_{max}^{CHCl_3}$ 3450 (NH) and 2180 cm^{-1} (CN)] and n.m.r. spectra [$\delta(CDCl_3)$ 1.90 - 2.40 (2H, m, 4-CH_2), 2.95 (2H, t, J 6 Hz, 3-CH_2), 3.50 (2H, t, J 6 Hz, 5-CH_2), 3.82 (6H, s, 2 x OMe), 4.80 (1H, broad s, NH), 6.80 and 7.00 p.p.m. (each 1H, each s, 2 x ArH)] of 4 with the reported data of α-phenyl-$\Delta^{2,\alpha}$-pyrrolidineacetonitrile.[3] When the cyclisation was carried out by refluxing with sodium hydride in dimethylformamide and by a reaction under $S_{RN}1$ condition,[4] the desired pyrrolo[1,2-a]indole (5), m.p. 203°, was obtained in 60 - 70 % and 2 % yield, respectively. Finally, a treatment of 4 with sodium hydride in the presence of cuprous bromide[5] in dimethylformamide for 1 hr at 80° afforded 5 in 93 % yield, which showed the i.r. [$\nu_{max}^{CHCl_3}$ 2210 cm^{-1} (CN)], n.m.r. [$\delta(CDCl_3)$ 3.85 (6H, s, 2 x OMe), 6.62 and 7.00 p.p.m. (each 1H, each s, 2 x ArH)] and mass [m/e 242 (M^+)] spectra. In the above reactions, a benzyne mechanism is not probable because α-(3-bromo-4,5-dimethoxyphenyl)-$\Delta^{2,\alpha}$-pyrrolidineacetonitrile (7) did not give 5 under the above reaction conditions. Refluxing the nitrile (5) with nickel-aluminium alloy and 50 % aqueous acetic acid[6] gave the aldehyde (6), m.p. 211°, in 91 % yield, whose n.m.r. [$\delta(CDCl_3)$ 3.85 and 3.90 (each 3H, each s, 2 x OMe), 6.72 and 7.60 (each 1H, each s, 2 x ArH) and 9.75 p.p.m. (1H, s, CHO)], i.r. [$\nu_{max}^{CHCl_3}$ 1640 cm^{-1} (C=O)] and mass spectra [m/e 245 (M^+)] supported the above structure.

Thereafter 9-formyl-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo-

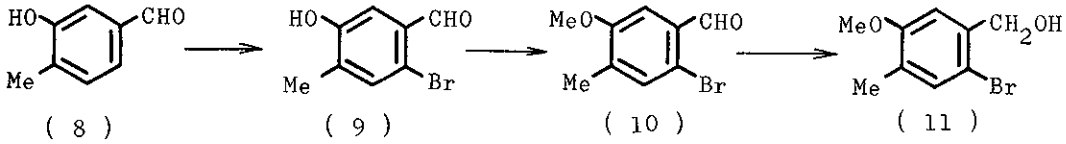


(1)

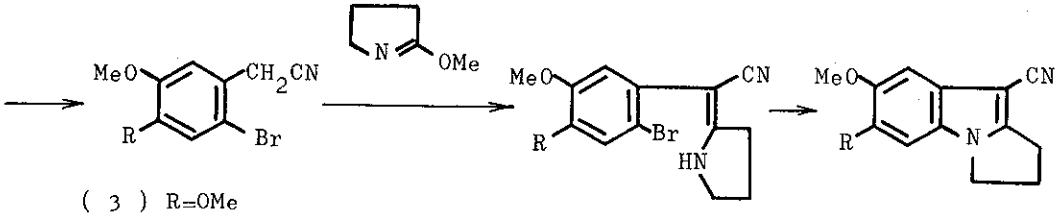
	X	Y	Z
Mitomycin A	MeO	MeO	H
Mitomycin B	MeO	HO	Me
Mitomycin C	NH_2	MeO	H
Porfiromycin	NH_2	MeO	Me



(2)



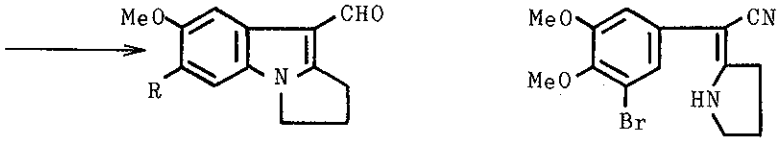
(8) (9) (10) (11)



(3) R=OMe
(12) R=Me

(4) R=OMe
(13) R=Me

(5) R=OMe
(14) R=Me



(6) R=OMe
(15) R=Me

(7)

1,2-a]indole (15) was synthesised as follows. Bromination of 3-hydroxy-4-methylbenzaldehyde (8)[7] yielded the bromide (9), m.p. 159 - 160°, in 80 % yield, which was then methylated with dimethyl sulphate to give the aldehyde (10), m.p. 95 - 96°, in 94 % yield. Reduction of 10 with sodium borohydride, followed by chlorination of the resulting alcohol (11), m.p. 94°, and successive cyanation, gave the nitrile (12), m.p. 108 - 110°, in 68 % yield from 10. Heating the nitrile (12) and O-methylpyrrolidone with DBU at 120° gave the pyrrolidine (13), m.p. 143° [$\nu_{max}^{CHCl_3}$ 3450 (NH) and 2180 cm^{-1} (CN); $\delta(CDCl_3)$ 2.15 (3H, s, Me), 3.80 (3H, s, OMe), 6.75 and 7.30 p.p.m. (each 1H, each s, 2 x ArH)]. Treatment of 13 with sodium hydride and cuprous bromide in dimethylformamide afforded the pyrrolo[1,2-a]indole (14), m.p. 174° (lit.,[1a] 173.5°), m/e 226 (M^+), in 93 % yield, which was further transformed to the aldehyde (15), m.p. 187° (lit.,[1a] 190°), m/e 229 (M^+), in 89 % yield as mentioned above. The data of i.r. and n.m.r. spectra of 14 and 15 were identical with the reported ones.[1a] The latter aldehyde (15) had been already converted into 7-methoxymitosene (2).[1b]

Thus a facile synthesis of 7-methoxymitosene has been accomplished.

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