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INTERCONVERSION BETWEEN PYRROLO[1,2-a]INDOLES AND 2,3-BENZAZOCIN-5-ONES ——— A SYNTHETIC APPROACH TO MITOMYCINS

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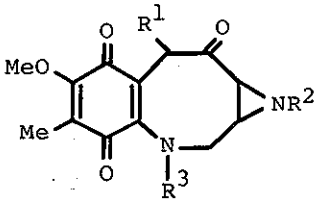
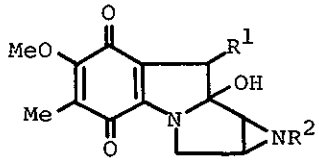
Pyrrolo[1,2-a]indoles (3 and 5) were converted to hexahydro-2,3-benzazocin-5-ones (10 and 11) by a novel sequence involving the reduction with sodium borohydride in acetic acid followed by von Braun reaction. The benzazocines 10 and 11 were recyclised to pyrrolo[1,2-a]indoles (4 and 5).

Recently we have reported a facile synthesis of 7-methoxy-mitosene[1] and desammonoapomitomycin[2] for the synthetic approach to mitomycins. The introduction of the oxo-substituent at the C_{9a} position seems to be one of the most difficult problems for the mitomycins. For this purpose, photooxygenation of 9-keto-9H-pyrrolo[1,2-a]indole has been studied and the required 9a-oxo-substituted compound has been obtained.[3] However the trans-annular cyclisation of an eight membered ketone (1) to 2 seems to be a promising approach for the synthesis of the natural products. Lown and Itoh synthesised hexahydro-2,3-benzazocin-5-

ones by the application of the Dieckmann condensation and then cyclised to pyrrolo[1,2-a]indoles.[4] Here we wish to report the conversion of pyrrolo[1,2-a]indoles, easily available by the known methods, to 2,3-benzazocin-5-ones, which were recyclised to the starting pyrroloindoles.[5]



(1)



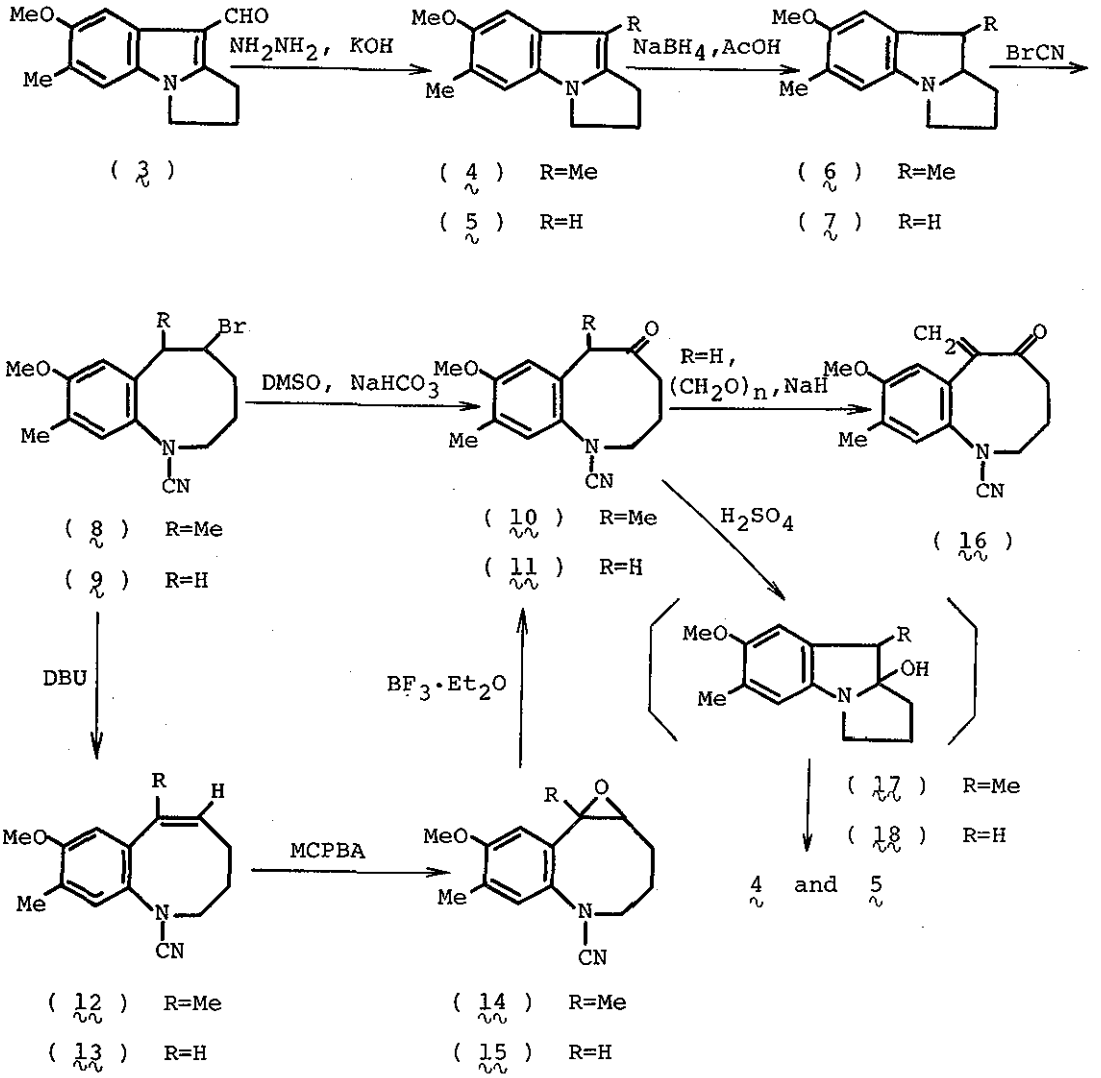
(2)

Refluxing the aldehyde 3[1] with hydrazine and potassium hydroxide in diethylene glycol for 6 hr afforded the 6,9-dimethyl-pyrrolo[1,2-a]indole (4), which was treated with sodium borohydride in glacial acetic acid[6] at 25 - 30° for 30 min to give the hexahydropyrrolo[1,2-a]indole (5) [nmr (CCl_4) δ : 1.26 (3H, d, J = 7 Hz, C_9-CH_3), 2.06 (3H, s, Ar-CH_3); m/e 217 (M^+)] in an excellent yield. Treatment of 5 with cyanogen bromide in benzene cleaved selectively the bond between the carbon at C_{9a} and nitrogen to furnish the benzazocin derivative (6)[7], mp 137 - 138° [nmr (CCl_4) δ : 1.44 (3H, d, J = 7 Hz, C_6-CH_3), 2.18 (3H, s, Ar-CH_3); ir $\nu_{max}^{CHCl_3}$ 2210 cm^{-1} (CN); m/e 324, 322 (M^+).] in a good yield. The oxidation of 6 was firstly carried out by heating with sodium hydrogen carbonate in dimethyl sulphoxide, but the

objective ketone 10, mp 147 - 149° [nmr ($CDCl_3$) δ 1.40 (3H, d, J = 7 Hz, C_6-CH_3), 2.15 (3H, s, Ar-CH_3); $\nu_{max}^{CHCl_3}$ 2210 (CN), 1705 cm^{-1} (C=O); m/e 258 (M^+)] was obtained in a rather poor yield. Thus the bromide 9 was converted to 10 by three steps as follows. Each reaction proceeded in a reasonable good yield. Dehydrobromination of 9 by heating with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) in tetrahydrofuran yielded the olefin 12 [nmr ($CDCl_3$) δ : 2.10 (3H, broad s, C_6-CH_3), 2.16 (3H, s, Ar-CH_3), 5.50 - 6.00 (1H, m, C_5-CH); ir $\nu_{max}^{CHCl_3}$ 2220 cm^{-1} (CN); m/e 242 (M^+)], which was stirred with m-chloroperbenzoic acid in methylene chloride to give the epoxide 14, mp 186 - 188° [nmr ($CDCl_3$) δ : 1.70 (3H, s, C_6-CH_3), 2.20 (3H, s, Ar-CH_3); $\nu_{max}^{CHCl_3}$ 2220 cm^{-1} (CN); m/e 258 (M^+)]. Treatment of 14 with boron trifluoride etherate in benzene at room temperature for 5 min provided the above ketone 10.

The tetrahydropyrrolo[1,2-a]indole (5)[8] was also converted into the ketone 11 in the similar manner as above. Thus reduction of 5 with sodium borohydride in acetic acid yielded quantitatively the amine 7, the von Braun reaction of which gave the bromide 9 [m/e 310, 308 (M^+)]. Treatment of 9 with DBU, followed by epoxidation of the resulting 13 [m/e 228 (M^+)] afforded 15 [m/e 244 (M^+)], which was transformed to the ketone 11 [nmr ($CDCl_3$) δ : 2.16 (3H, s, Ar-CH_3), 3.74 (2H, s, C_6-CH_2); ir $\nu_{max}^{CHCl_3}$ 2210 (CN), 1705 cm^{-1} (C=O), m/e 244 (M^+)]. The ketone 11 was also prepared by heating 9 with sodium hydrogen carbonate in dimethyl sulphoxide.

The ketones 10 and 11 were quantitatively converted to the


MeO
CHO
Me
N
NH_2NH_2, KOH
R
$NaBH_4$, AcOH
BrCN
(3)
(4) R=Me
(5) R=H
(6) R=Me
(7) R=H
Br
DMSO, $NaHCO_3$
CN
(8) R=Me
(9) R=H
(10) R=Me
(11) R=H
R=H,
$(CH_2O)_n$, NaH
CH_2
O
(16)
H_2SO_4
DBU
$BF_3 \cdot Et_2O$
H
MCPBA
OH
(12) R=Me
(13) R=H
(14) R=Me
(15) R=H
(17) R=Me
(18) R=H
4 and 5

pyrrolo[1,2-a]indoles (4 and 5) via the intermediates 17 and 18, by refluxing in ethanolic sulphuric acid. Reaction of 11 with paraformaldehyde in the presence of sodium hydride gave the methylene compound 16. The details of the above reactions will be published elsewhere.

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