Tetrahedron Letters No.1, pp. 19-22, 1969. Pergamon Press. Printed in Great Britain.

SYNTHETIC STUDIES ON MITOMYCINS

SYNTHESIS OF AZIRIDINO-PYRROLO(1,2-a)INDOLES.

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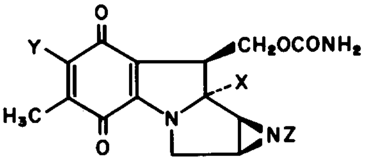
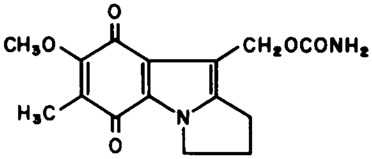
(Received in Japan 12 November 1968; received in UK for publication 22 November 1968)

Synthetic approaches toward mitomycins (I) (1) have been made energetically by a Lederle group and the synthesis of 7-methoxymitosene (II) was reported (2). However, their various efforts to build up the tetracyclics by attaching an aziridine moiety to the tricyclics were not fruitful (3).



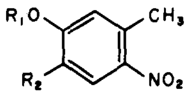
I



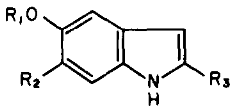
II

In the present paper, we wish to describe the first synthesis of those tetracyclics, aziridino-pyrrolo(1,2-a) indoles (XIII) having the complete ring system of mitomycins.

Esters (IV) (IVa, m.p. 155-156°; IVd, m.p. 141-142°; IVb, (2); IVc, (3a)) prepared from nitrocompounds (III) by modified Reissert's method (4) were reduced with $LiAlH_4$ to alcohols (V) (Va, m.p. 83.5-85.0°; Vb, m.p. 139-140°; Vc, m.p. 103-104°; Vd, m.p. 100-103°). Oxidation of alcohols (V) with potassium permanganate in acetone (5) afforded poor yields (10-20 %) of aldehydes (VI) (VIa, m.p. 136-137°; VIb, m.p. 172-173°; VIc, m.p. 178-179°; VId, m.p. 172-175°), but the yields were improved to 90 % by employing CrO_3-pyridine complex. On the treatment with sodium hydride and vinyltriphenyl phosphonium bromide (6) in tetrahydrofuran, aldehydes (VI) furnished 9H-pyrrolo (1,2-a) indoles (VII) (VIIa, m.p. 80-81°, λ_{max}(EtOH) 264, 301 mμ, τ. ($CDCl_3$) 6.25 (5H. S. OCH_3 and C-9 superimposed on it), 3.97 (1H. m. C-1), 3.70 (1H. apparent



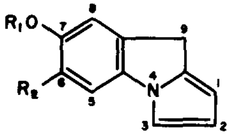
III a–d



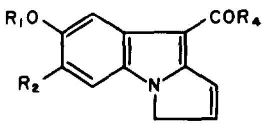
IV a–d $R_3 = CO_2C_2H_5$

V a–d $R_3 = CH_2OH$

VI a–d $R_3 = CHO$

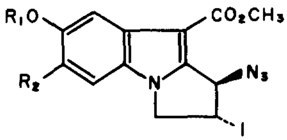


VII a–d

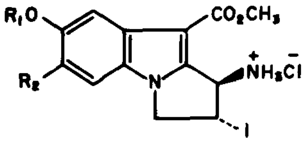


VIII a, c, d $R_4 = OCH_3$

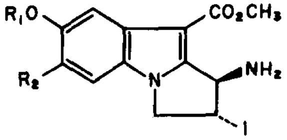
VIII a′, d′ $R_4 = H$



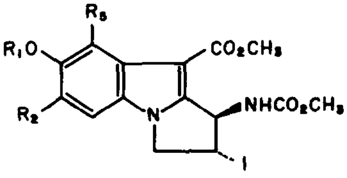
IX a, d



X a, d

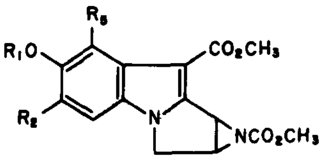


XI a, d



XII a, d $R_5 = H$

XII a′, d′ $R_5 = NO_2$



XIII a, d $R_5 = H$

XIII a′, d′ $R_5 = NO_2$

		R_1	R_2
a	:	CH_3	H
b	:	CH_3	CH_3
c	:	$C_6H_5CH_2O$	H
d	:	$C_6H_5CH_2O$	CH_3

triplet, C-2), 3.27 (1H. d-d. J=2, 7.5 cps, C-6), 3.10 (1H. d. J=2 cps. C-8), 3.07 (1H. C-3), 2.97 (1H. d. J=7.5 cps. C-5); VIIc, m.p. 96-98°; VIId, m.p. 88-89°) in 80-88 % yields (7).

Acylation of 9H-pyrrolo (1,2-a) indoles (VII) with potassium tert. butoxide and dimethylcarbonate afforded the key intermediates 3H-pyrrolo (1,2-a) indoles (VIII) (8) in 60-80 % yields (VIIIa, m.p. 121-123°, ν_{max}(nujol) 1690, 1621 cm^{-1}, λ_{max}(EtOH) 229, 255, 339 mμ. τ.($CDCl_3$) 6.24, 6.25 (6H. two singlets : CO_2CH_3 and OCH_3), 5.58 (2H. diffused split, C-3), 3.34 (1H. d-t. J=6.25, 2 cps. C-2), 3.20 (1H. d-t. J=8.8, 2.6 cps. C-5) 2.95 (1H. d-t. J=6.25, 2cps. C-1), 2.92 (1H. d. J=8.8 cps. C-5), 2.33 (1H. d. J=2.6 cps. C-8); VIIIc, m.p. 122-123°; VIIId, m.p. 139-141°) and with ethylformate gave (VIII) (VIIIa', m.p. 135-141°(dec.); VIIId', m.p. 138-142°). Functionalization of the vinylic double bond of (VIII) for attachment of aziridine moiety was achieved by iodine-azide addition (9) giving iodo-azides (IX) in 74-75 % yields (IXa, m.p. 93.8-94.5°, ν_{max} (nujol) 2171(sh.), 2130, 1700 cm^{-1}, λ_{max}(EtOH) 242, 298 mμ. τ.($CDCl_3$) 6.13, 6.12 (6H. two singlets : CO_2CH_3 and OCH_3) 5.19-5.80 (3H. C-2, C-3), 4.35 (1H. s. C-1), 3.05 (1H. d-d. J=2.5, 9 cps. C-6), 2.87 (1H. d. J=9 cps. C-5), 2.32 (1H. d. J=2.5 cps. C-8); IXd, m.p. 171-179°).

Catalytic hydrogenation of (IX) with palladium-charcoal in methanol containing hydrogen chloride gave iodo-amine hydrochorides (X) in 60-90 % yields (Xa, m.p. $>300^{\circ}$, ν_{max}(nujol) 2770, 2600, 1670 cm^{-1}; Xd, m.p. $> 300^{\circ}$, ν_{max}2680, 2650, 1670 cm^{-1}), which on quick alkaline treatment afforded iodo-amines (XI) (XIa, no definite m.p. ν_{max}(nujol) 3340, 3440, 1680 cm^{-1}; XId, m.p. 135-141°(dec.) not clear, ν_{max}(nujol) 3390, 3300, 1680 cm^{-1}).

Direct aziridine cyclization from (XI) was examined by various methods but only intractable reaction mixture was resulted. Protection of amino group of (XI) with methylchloroformate furnished iodo-carbamates(XII) (XIIa, m.p. 160-162°, ν_{max}(nujol) 3350, 1708, 1695 cm^{-1};XIId, m.p. 183-184°). The last step for cyclization of (XII) to aziridine was achieved with such base as sodium methoxide in dimethoxyethane or tetrahydrofuran in 60-65 % yields. The products were (XIII) (XIIIa, m.p. 210.5-214.5°, ν_{max}(nujol) 1690, 1662 cm^{-1}, λ_{max}(EtOH) 243, 290 mμ. τ.($DMSO_{d-6}$+$CDCl_3$) 6.20 (3H. s.), 6.21 (6H. s.) : OCH_3 and two CO_2CH_3, 5.67 (1H. q. J=2.8, 12.8 cps), 5.50 (1H. q. J=5.8, 12.8 cps.) these are nonequivalent geminal protons of C-3, 4.34 (1H. d. J=7.7 cps. C-1), 4.20 (1H. m. C-2), 3.13(1H. q. J=2.8, 10.5 cps. C-6), 2.67 (1H. d. J=10.5 cps. C-5), 2.48 (1H. d. J=2.8 cps. C-8) ; XIIId, m.p. 219.5-221.5°).

Nitration of (XIIa) and (XIId) afforded 8-nitro derivatives (XIIa') (m.p. not clear, ν_{max} (nujol) 3380, 1701, 1540 cm^{-1}) and (XIId') (m.p. 192-199°), location of nitro group at C-8 is elucidated by n.m.r. spectra (10) (XIIa', τ.($DMSO_{d-6}$) 2.78 (1H. d. J=8.5 cps. C-6), 2.32 (1H.

d. J=8.5 cps. C-5) typical for ortho aromatic protons). Ring closure of (XIId') and (XIId') to aziridine (XIIIa') (m.p. 242-246°, ν_{max}(nujol) 1715, 1671, 1542 cm^{-1}) and (XIIId') (m.p. 232.0-233.5°, ν_{max}(nujol) 1710, 1675, 1540 cm^{-1}) was performed in the same work-up as mentioned above.

Entry of nitro group would be suitable for elaboration of quinone moiety.

Acknowledgment : We wish to acknowledge the encouragement of Dr. S. Wakaki, Kyowa Fermentation industry Co., Ltd.

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All m.p.'s are uncorrected. Satisfactory analyses were obtained for all compounds.

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