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SYNTHETIC STUDIES ON MITOMYCINS

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

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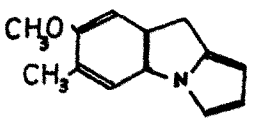
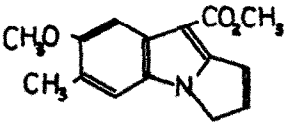
We reported the systhesis of N-methoxycarbonyl-aziridino-pyrrolo(1,2-a) indoles, having the same ring system of dehydroxy mitomycin A [1]. However, during further investigation, these tetracyclics thus obtained proved not to have aziridine ring but to be oxazoline.

We now wish to report the revised synthesis of aziridino-pyrrolo (1,2-a) indole (V). 9H-pyrrolo (1,2-a) indole (I) [1] was converted with dimethlcarbonate and potassium tert-butoxide to 3H-pyrrolo(1,2-a) indole (II) (m.p. 151-155°C, ν_{max}(nujol) 1680, 1130 cm^{-1}, λ_{max}(EtOH) 230, 257, 334 mμ, τ ($CDCl_3$) 7.20 (3H.s. C-6 CH_3) 6.14 (6H.s. CH_3O, CO_2CH_3) 5.60 (2H, apparent triplet C-3) 3.42(1H.d-t. J=6.0, 2.0 cps. C-1) 3.05 (1H.s. C-5) 3.00 (1H.d-t. J=6.0, 2.0 cps. C-2) 2.50 (1H.s. C-8))which was functionalized by iodine-azide addition to iodo-azide (III) (m.p. 124-134°C, ν_{max}(nujol) 2130, 1685, 1547, 1284 cm^{-1}). Catalytic hydrogenation of iodo-azide with palladium-charcoal in ethylacetate and methanol containing hydrogen chloride gave iodo-amine hydrochloride (IV) (free amine ; m.p. 124-134°C, ν_{max}(nujol) 3375, 3325, 1687, 1550 cm^{-1}).

Cyclization of iodo-amine or its hydrochloride with sodium methoxide in boiling methanol afforded crystalline mixture which was treated with methylchloroformate and triethylamine to N-methoxycarbonyl-aziridino-pyrrolo(1,2-a) indole (V) (m.p. 144-146°C and remelted at 199-206°C ν_{max}($CHCl_3$) 1728, 1702, 851 cm^{-1}, λ_{max}(EtOH) 242, 295 mμ, τ ($CDCl_3$) 7.70 (3H.s. C-6) 6.45 (3H.s.) 6.13 (3H.s.) 6.05 (3H.s.) ; OCH_3 and two CO_2CH_3, 5.45-6.00(4H.m. C-1,C-2, C-3) 3.07 (1H.s. C-5) 2.50 (1H.s. C-8)). And preparative thin layer chromatography of this mother liquor afforded the other two compounds ; (VI)(m.p. 176.0-178.2°C, ν_{max}(nujol) 3400, 1710, 1693, 1525 cm^{-1}.λ_{max} (EtOH)245, 295 mμ, τ (CD_3COCD_3 and $DMSO_{d-6}$) 7.75 (3H.s. C-6 CH_3) 6.63 (3H.s)6.40 (3H.s.) 6.20 (6H.s.) ; two OCH_3 and two CO_2CH_3, 5.05-6.10 (4H.m. C-1, C-2, C-3) 2.75 (1H.s. C-5) 2.53 (1H.s. C-8) 2.45 (1H.-NH-), which is presumably formed by ring opening of aziridine by nucleophilic attack of



I



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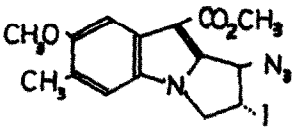

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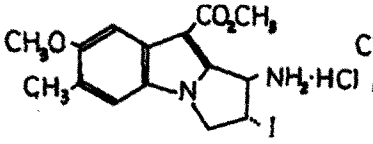

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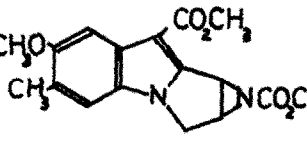

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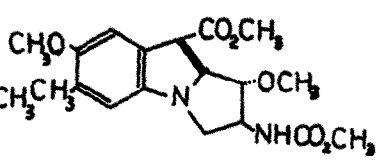

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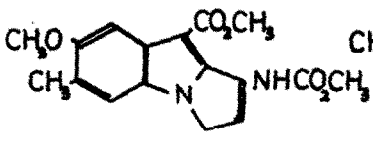

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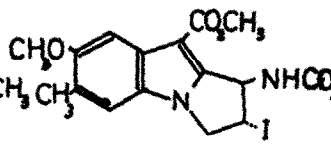
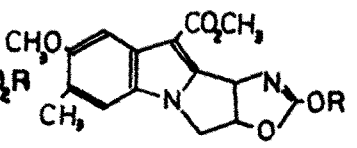


VIII

a R = CH_3

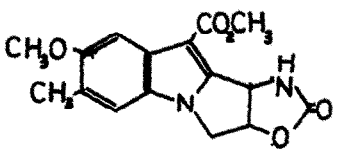
b R = $CH_2C_6H_5$



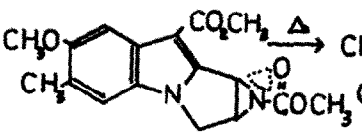
IX

a R = CH_3

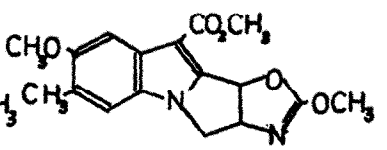
b R = $CH_2C_6H_5$



XI



V



X

methoxide anion and protection of resulted amino group by methylchloroformate, and (VII)(m.p. 184.5-186.5°C, ν_{max}(nujol) 3200, 1722, 1662 cm^{-1}, λ_{max}(EtOH) 246, 270, 320, 334(sh) mμ. τ ($CDCl_3$) 7.65 (3H.s. C-6 CH_3) 6.16 (3H.s.) 6.08 (3H.s.) 6.00 (3H.s.); OCH_3, two CO_2CH_3. 5.44 (2H.d. J=2.5 cps C-3) 3.33 (1H.t. J=2.5 cps C-2) 2.94 (1H.s. C-5) 2.60 (1H.s. C-8)).

Aziridino-pyrrolo (1,2-a) indole (V) is not so stable and changed by heating over 150°C to the compound having no carbonyl absorption over 1700 cm^{-1}, (m.p. 206-209°C, ν_{max}(nujol) 1690, 1670 cm^{-1}, λ_{max}(EtOH) 243, 295 mμ), presumed rearranged oxazoline (X).

Treatment of iodo-carbamate (VIII) with sodium methoxide in dimethoxyethane gave no aziridine compound but oxazoline[2] (IX) (IXa.m.p. 206.5-208.5°C, ν_{max}(nujol) 1690, 1665 cm^{-1} λ_{max}(EtOH) 243, 295 mμ, τ($DMSO_{d-6}$) 7.77(3H.s. C-6 CH_3), 6.21 (6H.s.) 6.23 (3H.s.) : OCH_3, two CO_2CH_3 5.67 (1H.q. J=3.0, 13.0 cps) 5.53 (1H.q. J=6.0, 13.0 cps.) these are nonequivalent geminal protons of C-3, 4.35 (1H.d. J=7.5 cps. C-1) 4.17(1H.m. C-2) 2.79 (1H.s. C-6) 2.59 (1H.s. C-8). picrate : ν_{max}(nujol) 1751, 1670 cm^{-1}; IXb m.p. 142.5-150°C, νmax(nujol) 1685, 1665 cm^{-1}, λ_{max}(EtOH) 242, 295 mμ). In boiling methanol with sodium methoxide, (VIII) afforded (VII) and (X) as main products.

Oxazoline structure of (IX) was confirmed by catalytic hydrogenation of (IXb) to oxazolidone (XI). (m.p. 279-300°C, ν_{max}(nujol) 3275, 3125, 1755, 1690 cm^{-1}, λ_{max}(EtOH) 242, 294 mμ) which was also prepared from (VIII) by pyrolysis in boiling acetic acid [3].

REFERENCES AND FOOTNOTES

Satisfactory analyses were obtained for all new compounds.

All m.p. 's are uncorrected.

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