SYNTHETIC STUDIES ON MITOMYCINS. AN ALTERNATIVE SYNTHESIS OF 2,3-DIHYDRO-1H AND 9H-PYRROLO[1,2-a]INDOLES BY TRANSANNULAR RING CLOSURE

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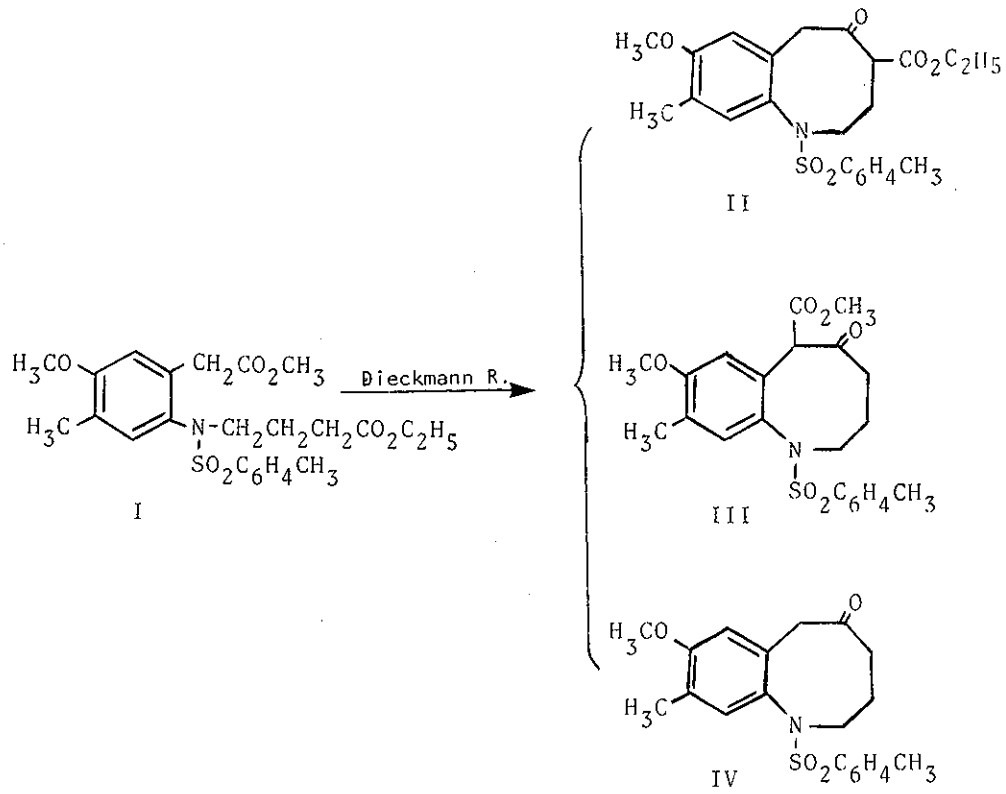
The synthesis of substituted 1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-ones and their conversion via transannular ring closure to the 2,3-dihydro-1H and 9H-pyrrolo[1,2-a]indole ABC parent ring system of the antitumor antibiotic mitomycin C is described.

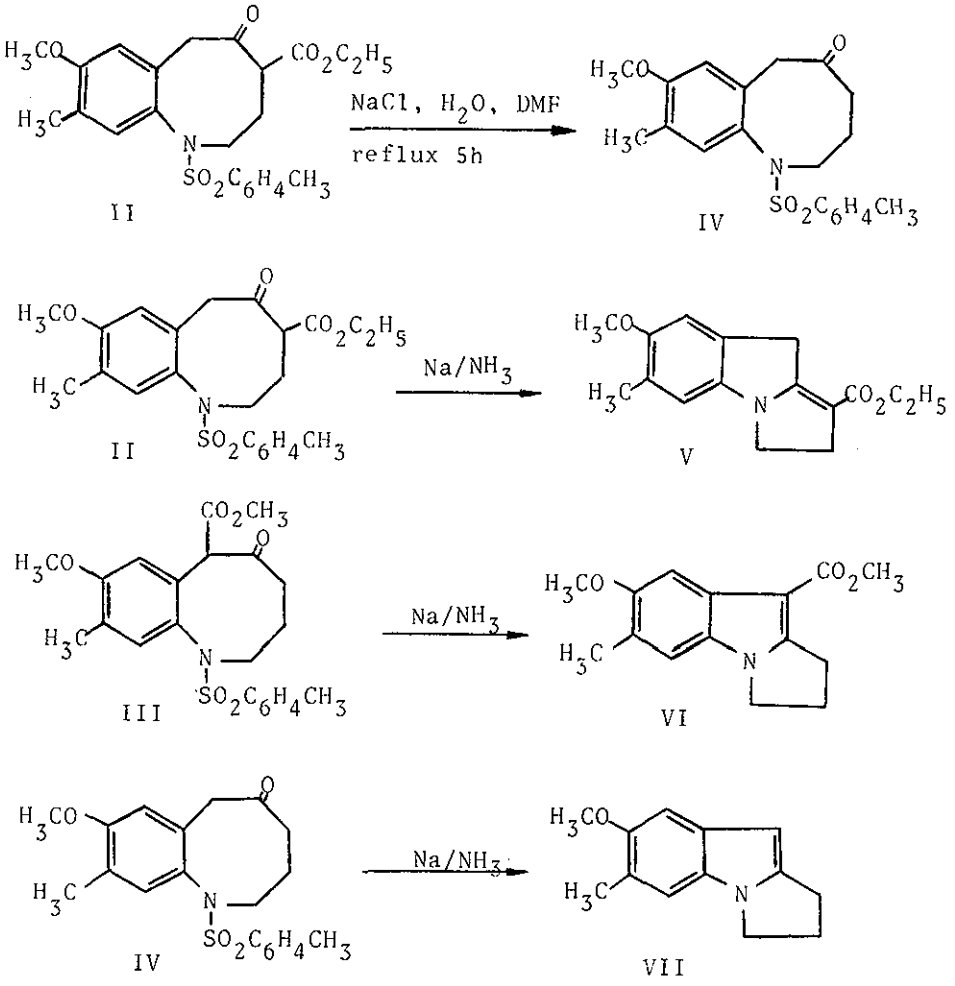
In the previous paper of this series[1] we demonstrated that certain hexahydrobenzazocines (II, III and IV), obtained by the Dieckmann reaction on methyl 5-methoxy-4-methyl-2-[N-(3-ethoxycarbonylpropyl)]-p-toluenesulfonamidophenylacetate (I), could serve as key intermediates in the biogenetic type synthesis of an antitumor antibiotic, mitomycin C.

In this paper, we wish to report that a slight modification of the Dieckmann condensation on I (mp 59° from methanol) gives a better yield of the products with completely different distribution. When the reaction was carried out in boiling toluene the major product, isolated as an oil, was 8-methoxy-9-methyl-N-p-toluenesulfonyl-1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-one(IV) (24.6%)[1]. While in benzene using the high dilution method of Leonard[2] the major product obtained, after column chromatographic



separation on silica gel with benzene as eluent followed by crystallization of the fractions n-hexane, was ethyl 8-methoxy-9-methyl-N-p-toluenesulfonyl-1,2,3,4,5,6-hexahydro-2,3-benzazocin-5-one-2-carboxylate (II) (32%) together with the 6-carboxylate (III) (trace) and IV (1%) (mp 140°).

We also found that compound II could be converted quantitatively into IV by de-ethoxycarbonylation[3] with sodium chloride (slightly more than one equivalent of II) in aqueous dimethylformamide.



II IV V III VI IV VII

All the hexahydrobenzazocines (II, III and IV) were treated separately with sodium in liquid ammonia[1] to give the corresponding 2,3-dihydro-7-methoxy-6-methylpyrrolo[1,2-a]indoles (V, VI and VII), the parent ring system of mitomycin C. The structures of V and VII were established by direct comparison with authentic samples[1,4]. Structure VI[2,3-dihydro-1-methoxycarbnyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole] was assigned to the product(mp 89° from methanol) from III on the basis of its spectral data: Mol. wt. Anal. Calcd. for $C_{15}H_{17}NO_3$: 259.1208, Found: 259.1214 (mass spectrum). $\nu_{max}^{CHCl_3}$: 1680 cm^{-1}(α,β-unsaturated carbonyl -CH=CHCO-), Nmr ($CDCl_3$); (δ) 2.33 (s, 3H,CH_3), 2.68 (m, 2H,methylene), 3.26 (t, 2H, methylene), 3.87 (s, 3H, CH_3), 3,91 (s, 3H, CH_3), 4.06 (t, 2H, methylene), 6.40 (s, 1H, 5 or 8H), 7.00(s, 1H, 8 or 5H).

REFERENCES

1 J. W. Lown and T. Itoh, Canad. J. Chem., 1975, 53, 960.

2 N. J. Leonard and R.C. Sentz, J. Amer. Chem. Soc., 1952, 74, 1704.

3 A. P. Krapcho and A. J. Lovey, Tetrahedron Letters, 1973, 957.

4 G. R. Allen, J. F. Poletto, and M. J. Weiss, J. Org. Chem., 1965, 30, 2897.

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