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SYNTHESIS OF 1-SUBSTITUTED-7-METHOXYMITOSENES

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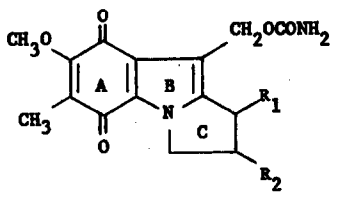
Several attempts toward the synthesis of the mitomycins have been reported. In 1965 G. R. Allen and co-workers reported the synthesis of 7-methoxymitosene (I), an analog active *in vivo* against gram (+) bacteria.[1,2] This analog lacked only the aziridine ring of 7-methoxy-1,2-aziridinomitosene (II), a mitomycin A derivative equal in anticancer and antibacterial activity to the parent compound.[3] Subsequently other interesting approaches to the synthesis of aziridinomitosenes were reported.[4,5,6] One of these resulted in the elaboration of the tetracyclic ring system of the mitomycins,[4] but in no case were the structures elaborated to the degree that they provided useful analogs.

Degradative studies on the mitomycins have shown that although the aziridine ring is an important contributor to the activity, it is not an absolute requirement. Analogs with suitable substituents on ring C (pyrrole ring) showed significant therapeutic ratios against experimental tumors in mice (eg., III).[7] Based upon these findings we have sought to establish synthetic routes to mitosenes with a variety of substituents on the C-ring. Analogs with good leaving groups at the 1-position are of particular interest, as they offer the possibility of two sites for alkylation of biological nucleophiles, and thus should closely parallel the action of the mitomycins. We report in this paper the synthesis of one such analog, 1-acetoxy-7-methoxymito-

sene (IV), and its conversion to 7-methoxy-1-oxomitosene (V), a degradation product of mitomycin A. The latter compound not only represents the first link between synthetic and degradative studies of the mitomycins, it also affords a versatile intermediate for the preparation of new C-ring analogs. In addition, we would note that our approach offers an efficient route to these analogs, and represents considerable improvement over the route used for the synthesis of 7-meth oxymitosene. The improvement was achieved primarily through the nitro derivative X, via reduction to amino derivative XI and direct Fremy's salt oxidation to quinone XII, a route which had been accomplished with simpler indole derivatives but which had not as yet been demonstrated with pyrroloindoles.[8]

The pyrroloindoloketone VI (prepared in nine steps from 2,5-xylenol)[2] was reduced using $NaBH_4$ to the alcohol VII (m.p. 148-149°) in 93% yield. The alcohol VII was acetylated with acetic anhydride to give the acetate VIII (m.p. 134-135°) in 97% yield. Formylation of VIII under Vilsmeier-Haack conditions provided aldehyde IX (m.p. 170-172°) in 75% yield, which was nitrated with 90% HNO_3 to give the nitro derivative X (m.p. 175-176°) in 60% yield. Reduction of X by iron in acetic acid afforded amino derivative XI which was oxidized directly to the quinone XII (m.p. 126-127°) by Fremy's salt in 50% yield (from X). Careful reduction of XII with $NaBH_4$, followed by $FeCl_3$ oxidation gave hydroxymethyl derivative XIII (m.p. 123-124°) in 59% yield. This reaction was accompanied by only a small amount of acetate hydrolysis. Conversion of XIII into the desired carbamate IV (m.p. 204-205° dec) was accomplished via phenylcarbonate XIV in an overall yield of 41%. Selective hydrolysis of IV using methanolic NH_3 gave 1-hydroxy analog XV (m.p. 195-196°) in 93% yield, which was readily oxidized with MnO_2 to the ketone V. This ketone was found to be identical with a sample (desammono-apo-mitomycin A) obtained from degradation of mitomycin A, via infrared and mass spectral comparison, and parallel and overspot TLC.[9,10]

All of the new compounds described above had infrared and nmr spectra consistent with their indicated structures, and gave correct microanalyses for C,H,N, except the phenylcarbonate XIV and the unstable amine XI, both of which were used without purification.



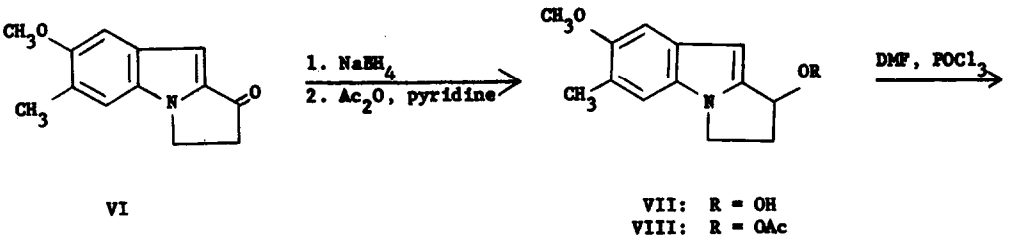
I: R_1, R_2 = H

II: R_1, R_2 = >NH

III: R_1 = OH; R_2 = NHAc

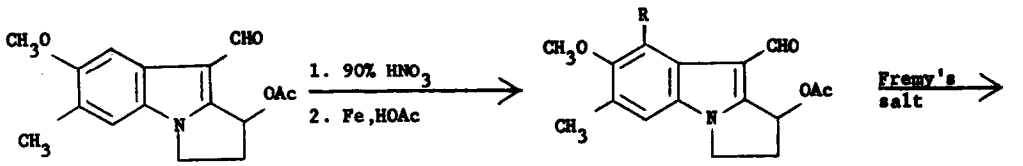
IV: R_1 = OAc; R_2 = H

V: R_1 = =O; R_2 = H



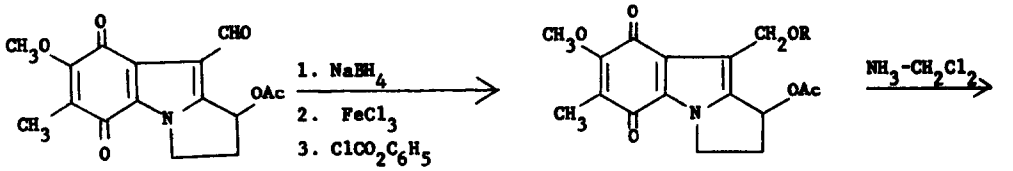
VI

VII: R = OH
VIII: R = OAc



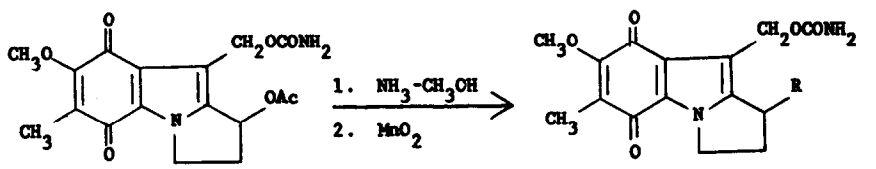
IX

X: R = NO_2
XI: R = NH_2



XII

XIII: R = H
XIV: R = $CO_2C_6H_5$



IV

XV: R = OH
V: R = =O

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10. We are grateful to Dr. J. S. Webb of the Lederle Laboratories Division, American Cyanamid Company, for supplying a sample of desammono-apo-mitomycin A.