Synthesis of 5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepine and some of its Derivatives related to Anthramycin

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ANTHRAMYCIN (I)[1] is an anti-tumour antibiotic possessing the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine skeleton.

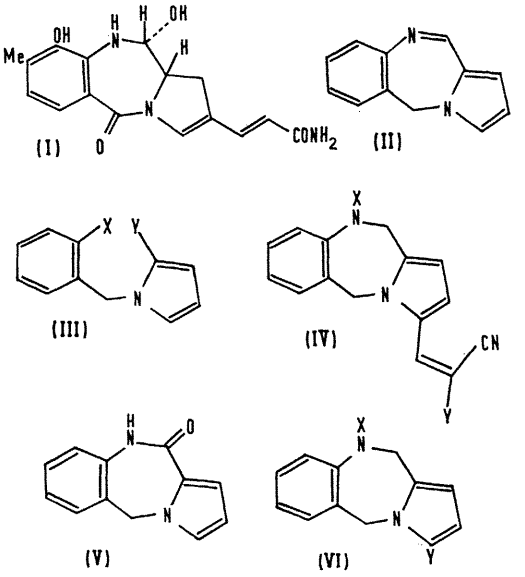
We report a general synthetic pathway leading to the parent nucleus (II) and to various derivatives of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (IV), (V), and (VI).

We used as starting material 1-(2′-nitrobenzyl)pyrrole-2-carbaldehyde (III; X = NO_2, Y = CHO).[2]

Reduction with hydrogen on PtO_2 catalyst of its oxime (III; X = NO_2, Y = CH:NOH; m.p. 130—132° from aqueous ethanol) afforded the corresponding 1-(2′-aminobenzyl)pyrrole-2-carbaldoxime (III; X = NH_2, Y = CH:NOH; m.p. 140—141° from ethanol), which was hydrolysed in acidic medium to give the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (II; m.p. 95—96° from petroleum b.p. 75—120°).

Attempts to prepare the parent heterocycle from 1-(2′-nitrobenzyl)pyrrole-2-carbaldehyde by catalytic hydrogenation on Pd–C failed, the only material formed being the 10,11-dihydro-derivative of (II). This compound [VI; X = Y = H; m.p. 152—154° (dec.) from ethanol] after acetylation (VI; X = Ac, Y = H; m.p. 154—155° from ethyl acetate–petroleum b.p. 40—70°) was submitted to Vilsmeier–Haack formylation, giving 10-acetyl-10,11-dihydro-2-formyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (VI; X = Ac, Y = CHO; m.p. 104—105° from benzene–petroleum b.p. 40—70°). This was converted into derivatives containing the acrylic group by reaction with ethyl cyanoacetate and cyanoacetamide to give, respectively, (IV; X = Ac, Y = $CONH_2$; m.p. 259—262° from ethanol) and (IV; X = Ac, Y = CO_2Et; m.p. 248—250° from *NN*-dimethylformamide).

By treatment with acetic anhydride 1-(2′-nitrobenzyl)-pyrrole-2-carbaldoxime was converted into 1-(2′-nitrobenzyl)pyrrole-2-carbonitrile (III; X = NO_2, Y = CN; m.p. 92—93° from ethanol) which was then hydrogenated in the presence of Pd–C to yield 1-(2′-aminobenzyl)pryyole-2-carbonitrile (III; X = NH_2, Y = CN; m.p. 59—60° from benzene–petroleum b.p. 40—70°). Hydrolysis of this compound in alkaline medium furnished 10,11-dihydro-11-oxo-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (V; m.p. 223—224° from aqueous ethanol).



All the compounds reported gave satisfactory elemental analyses; n.m.r. and i.r. data will be reported elsewhere.

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