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SYNTHESIS OF 13-AZAEQUILENIN ANALOGS FROM 1,2-DIHYDRO-4-METHYL-BENZ(f)ISOQUINOLINES

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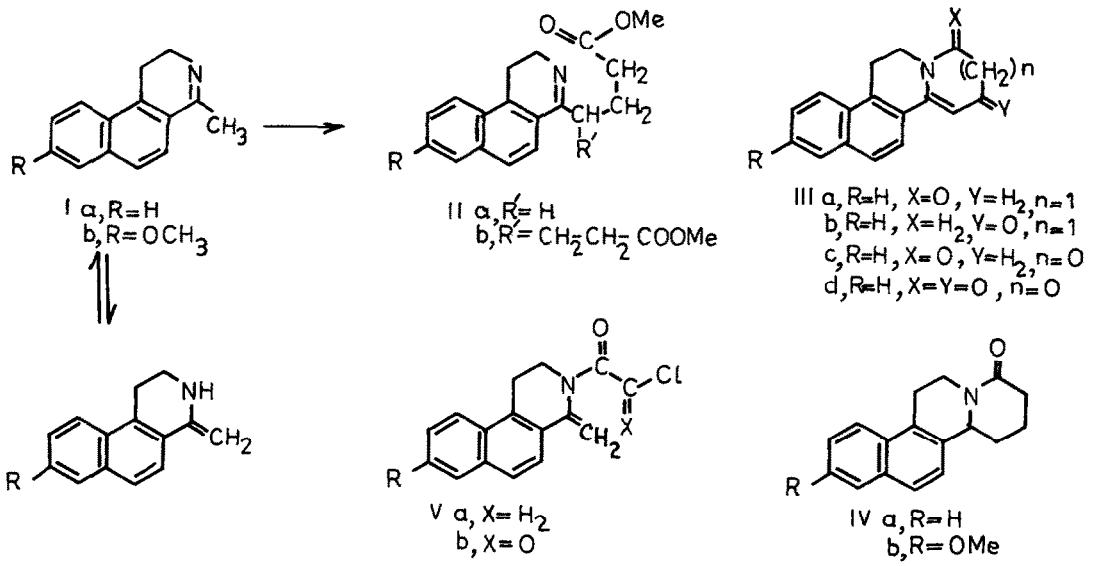
Abstract: Reaction of 1,2-dihydro-4-methyl-benz(f)isoquinolines with methyl acrylate and oxalyl chloride gave the corresponding tetracyclic compounds, while with chloroacetyl chloride an enamide was obtained which could not be cyclised thermally.

The ability of harmaline to act as a 1,3-dinucleophile[1] has been exploted for synthesis of eburane alkaloids.[2] Similar reactions of dihydro-benz(f) isoquinolines(I) can lead to 13-azaequilenin analogs.[3] Also, a comparative study of N vs C attack in this system is of interest.[4]

Dissolving the compound Ia in CD_3OD caused a slow collapse of the C-methyl PMR signal at δ2.5, persumably because of deuterium exchange through imine-enamine tautomerism. However, on treatment with methyl acrylate (2.0 mole) in benzene-methanol (1:1) at room temperature, Ia was recovered unchanged (72 hrs), indicating a lower reactivity than the indole compounds.[1] Refluxing for 120 hrs. gave a mixture which on silica gel chromatography afforded IIa (34%, $C_{18}H_{19}NO_2$, m.p.74-75°), IIb (30%, $C_{22}H_{25}NO_4$,m.p.51-52°) and IIIb (30%,$C_{17}H_{15}NO$,m.p. 161-162°). The amide IIIa could be obtained by heating (48 hrs, xylene) IIa or by employing acrylic acid, instead of the methyl ester, in the original reaction. The tetracyclic compounds IIIa and IIIb can be distinguished on the basis of IR, UV and PMR spectra.[2] The olefinic proton signal (a singlet at δ 5.95 in IIIb and a triplet at δ 5.83 in IIIa) is specially diagnostic. The compound IVa ($C_{17}H_{17}NO$, m.p. 149-150°) was secured (90%) by sodium borohydride reduction of IIa in methanol. Essentially similar results were obtained in the methoxy series and (±) 13-aza-D-homo-18-norequilenin methyl ether[5] [IVb,$C_{18}H_{19}NO_2$,m.p.174-175°, m/e 281 (M^+), 280,266,236,211] was obtained in 26% yield starting from Ib.[6]



To append a five membered ring, Ia was treated with chloroacetyl chloride in pyridine. The enamide Va($C_{16}H_{14}NOCl$, m.p.121-122°) was the only product and all attempts at its thermal cyclisation were unsuccessful. However, reaction of Ia with oxalyl chloride gave the 16-oxo compound IIId [$C_{16}H_{11}NO_2$, m.p.219-220°, PMR ($CDCl_3$) δ 3.6(t,2H,C_{11}), 4.01(t,2H,C_{12}), 5.95(s,1H,C_{15}) and 7.8(m,6H, Ar); m/e 249 (M^+), 221,193] . Ring closure of Va and Vb to IIIc and IIId involves a weakly nucleophilic enamide system but seems favoured in terms of Baldwin rules[7] (5-Exo-Tet). However, models reveal that in Va the terminal olefinic π orbital is not appropriately positioned for backside attack on the chlorine bearing carbon atom. In Vb, on the other hand, its lateral overlap with the acyl π orbital can initiate a bonding interaction.

References and Notes

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6. 1,2-dihydro-4-methyl-8-methoxy benz(f)isoquinoline (Ib,$C_{15}H_{15}NO$, m.p.91-92°) was secured through acylation and B.N.cyclisation of 2-(6-methoxy-1-naphthyl)ethylamine, which was prepared according to S.V.Kessar, Manmehar Singh, V.K.Ahuja and A.K.Lumb, J.Chem.Soc.(c),262(1971).
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