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1-ALKYL-1,6-DIHYDRO-1-BENZAZOCINE DERIVATIVES THROUGH RING EXPANSION OF 1-ALKYL-1,4-DIHYDROQUINOLINES

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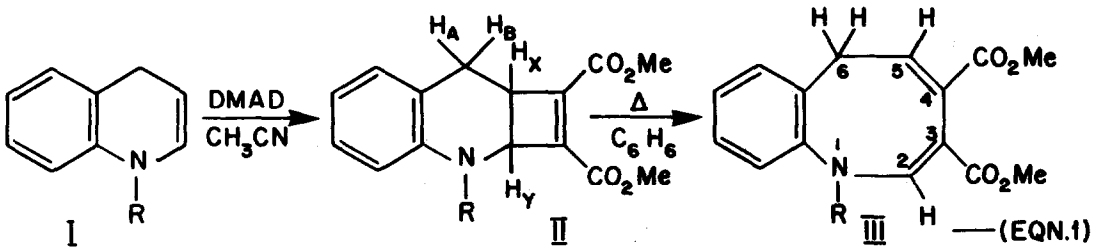
Cyclic enamines react with electrophilic alkynes (non-concerted 1,2-cyclo-addition) to form cyclobutene adducts which undergo step-wise ring opening under mild thermal conditions to afford ring expanded dienamines.[1] Some heterocyclic enamines, e.g. 3-pyrrolidino-2,5-dihydrofuran[2] and 1-acetyl-3-piperidinoindole[3] and compounds which can apparently behave as such, e.g. 2-ethoxy-1-methylindole[4] and 1-methylindole,[5] react with dimethyl acetylenedicarboxylate (DMAD) to give ring expanded heterocyclic products. However, the cyclobutene adducts from certain 1,3-disubstituted-1,4-dihydropyridines and DMAD do not undergo thermal ring expansion.[6]

The cycloaddition of DMAD to 1-alkyl-1,4-dihydroquinolines[7] to form isolable cyclobutene adducts susceptible to thermal ring expansion, is now reported. This sequence (eqn. 1) constitutes a new and direct synthesis for derivatives of the 1,6-dihydro-1-benzazocine ring system.[8]



—(EQN.1)

Reaction of 1-methyl-1,4-dihydroquinoline[7] (I, R = Me) with DMAD (1 mole) in acetonitrile under nitrogen followed by chromatography on alumina gave the cyclobutene adduct (II, R = Me) m.p. 42.5-43°. This structure is supported by spectra: p.m.r. (100 MHz, $CDCl_3$, TMS) δ 7.22-6.63, m (4H) aromatic; 4.24, d (1H) H_Y; approx. 3.74, m (1H) H_X; 3.73, s (3H) OMe; 3.68, s (3H) OMe; 3.03, s (3H) NMe; 2.96, d of d (1H) H_A: 2.77, d of d (1H) H_B; J_{AX} = 3 Hz; J_{BX} = 5 Hz; J_{AB} = 15 Hz; J_{XY} = 5 Hz. Decoupling: irradiation of H_X caused the 8 line AB

part of the ABX system to collapse to 4 lines. Simultaneously, the H_Y doublet collapsed to a singlet. I.r. (nujol) 1690, 1625, 1593 cm^{-1}. U.v. (ethanol, λ_{max} nm, log ε) 290 (3.35), 246 (4.04), 232 (4.06).

Cyclobutene adduct (II, R = Me), obtained in the same way but not purified, was heated under reflux in dry benzene for 8 hr. Chromatography on alumina gave 1-methyl-3,4-dicarbomethoxy-1,6-dihydro-1-benzazocine* (III, R = Me) as an oil, which crystallised (77.9%) in ether, m.p. 132-133°. P.m.r. (as above): δ 6.79, s (1H) H_2; 7.30-6.82, m (5H) aromatic + H_5; 3.91, br.d (2H) H_6, $J_{5,6}$ = 8 Hz; 3.64, s (3H) OMe; 3.61, s (3H) OMe; 3.41, s (3H) NMe. Decoupling: H_5 was obscured by the aromatic multiplet but was located (approx. δ 7.1) by irradiating the H_6 doublet. Irradiation of H_5 then resulted in the collapse of the H_6 doublet to a singlet. I.r. (nujol) 1708, 1690, 1630, 1600, 1590, 1570 cm^{-1}. U.v. (as above) 355 (3.67), 298 (3.96), 276 (4.18), 250 (4.16).

Dienamines of type (III) do not add DMAD but do give conjugate addition products resulting from nucleophilic attack at C_5.

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* Satisfactory microanalysis obtained.