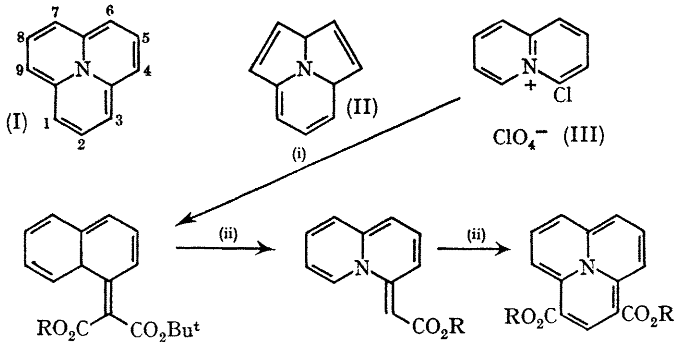
Synthesis of Pyrido[2,1,6-*de*]quinolizine (Cycl[3,3,3]azine)

By D. FARQUHAR and D. LEAVER*

(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh,* 9)

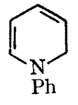
PYRIDO[2,1,6-*de*]QUINOLIZINE (I), otherwise known[1] as cycl[3,3,3]azine, has been the subject of theoretical studies[1,2] which have predicted a resonance energy greater than that of the highly stable and well-known[1,3] compound pyrrolo[2,1,5-*cd*]indolizine (cycl[3,2,2]azine) (II). Despite considerable effort,[4] however, the synthesis of the pyridoquinolizine has not hitherto been accomplished.† We now report the synthesis of this ring-system, from 4-chloroquinolizinium perchlorate (III,[6] by the route outlined below.



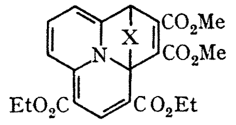
Reagents: (i) $NaCH(CO_2R)\cdot CO_2Bu^t$–THF; (ii) HCl–PhH (for R=Et) or $PhSO_3H$–AcOH (for R=Bu^t), NaOH; (iii) $HC{:}C\cdot CO_2R$–$PhNO_2$ at 210°.

Evidence for the structure of the diester (IV; R = Et) was provided by its ^1H n.m.r. spectrum which showed the following signals: τ 2·84 (s, 1H, 2–H) 3·86 (t, 2H, 5–H and 8–H) 3·23 (dd, 2H, 4–H and 9–H), and 4·77 (dd, 2H, 6–H and 7–H). The coupling constants were $J_{4,5} = J_{5,6}$ = 8·1 and $J_{4,6}$ = 1·7 Hz.

The brown, crystalline esters (IV) were stable in the solid state but their solutions, particularly those in hydroxylic solvents, rapidly changed from bright yellow (λ_{max} 453 nm. in EtOH) to dark brown. Hydrolytic procedures were therefore precluded and, in order to obtain the parent compound (I), it was necessary to heat the di-t-butyl ester (IV; R = Bu^t) in a sealed, evacuated tube at 250—300° for 5 min. The tube was then opened and the product was recovered from it by vacuum sublimation.

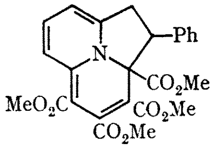


(V)



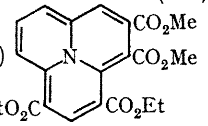
(VIa) X=–CH:CH–

(VIb) X=–$CH_2\cdot CH_2$–

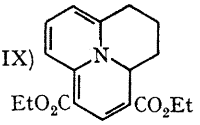


(VII)

(VIII)



(IX)



The pyridoquinolizine (I) was a brown, crystalline solid that gave bright yellow solutions (λ_{max} 458 nm. in cyclohexane) in ethers or hydrocarbons; it was stable in nitrogen but decomposed within minutes when exposed to air or when dissolved in $CHCl_3$, CCl_4, or hydroxylic solvents. The n.m.r. spectrum‡ of compound (I), in bis(trimethylsilyl) ether, showed a triplet centred at τ 6·35 (protons 2, 5, and 8) and a doublet of twice the intensity centred at τ 7·93 (protons 1, 2, 4, 6, 7, and 9), the coupling constant being *ca.* 8 Hz. These signals are respectively 2·2 and 2·8 p.p.m. upfield of their counterparts in the spectrum of the 1,2-dihydropyridine (V)[7] and the τ-values are among the highest yet reported for protons joined to trigonal carbon. We regard this high degree of shielding as evidence of a paramagnetic ring-current[8] in the peripheral, non-aromatic system of 12 π-electrons. The contrast with the typically aromatic pyrroloindolizine (II), which contains

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† Cyclopenta[*cd*]cycl[3,3,3]azines are known[5] but their properties cannot be expected to reflect those of the parent, tricyclic ring-system.

‡ The spectrum also indicated contamination by a trace of t-butyl pyrido[2,1,6-*de*]quinolizine-1-carboxylate, a compound that may be obtained in the pure state by pyrolysing the di-t-butyl ester under less vigorous conditions.

10 peripheral π-electrons and gives proton resonances[9] in the range τ 2·1—2·8, is striking.

We have not yet investigated the chemical properties of the parent compound (I) but those of the diester (IV; R = Et) show further evidence of lack of aromatic character. Thus the ester reacted with dimethyl acetylenedicarboxylate, in boiling benzene, to give a red Diels–Alder adduct (VIa), the structure of which follows from the resemblance of its u.v.-visible spectrum to that of the 4*H*-quinolizine (VII)[10] and from its ready conversion into a dihydro-derivative (VIb) that lost ethylene above 220° to give the tetracarboxylic ester (VIII). Catalytic hydrogeneration of the diester (IV; R = Et) proceeded readily, at room temperature and atmospheric pressure, to give a red tetrahydro-derivative (IX), the u.v. visible spectrum of which was closely similar to that of the adduct (VIa).

Despite its lack of aromatic character according to the foregoing criteria, the diester (IV; R = Et) participated in substitution reactions with certain electrophilic reagents (notably tetranitromethane, *NN*-dimethylformamide–phosphoryl chloride, and acetyl chloride). We do not accept these reactions as evidence of aromaticity but prefer to regard them as analogous to those of a typical enamine.

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