Pyrrolo[1,2-*a*]quinolines. A Re-investigation

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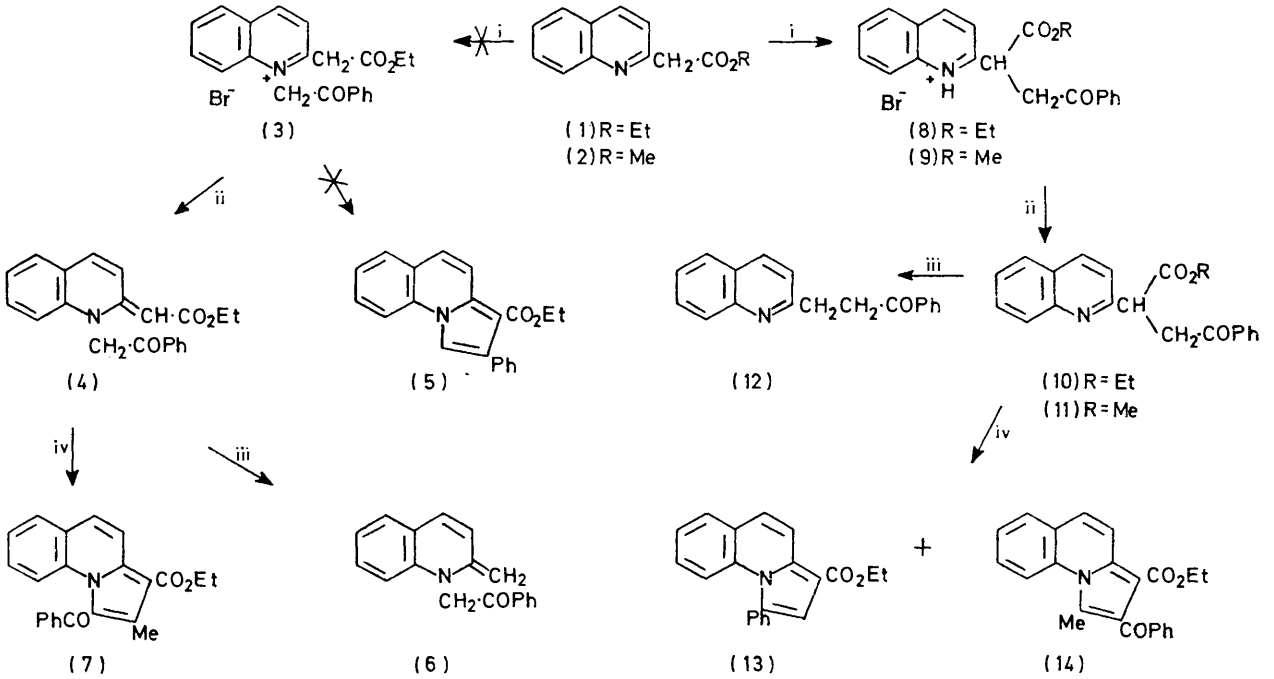
The reaction between ethyl 2-quinolylacetate and phenacyl bromide has been re-investigated and is now shown to proceed *via* *C*-alkylation to yield 2-(1-benzoyl-2-ethoxycarbonylethyl)quinoline. Treatment of this compound with acetic anhydride yielded 2-benzoyl-3-ethoxycarbonyl-1-methylpyrrolo[1,2-*a*]quinoline and 3-ethoxycarbonyl-1-phenylpyrrolo[1,2-*a*]quinoline.

THE Chichibabin synthesis of indolizines uses the quaternisation of derivatives of α-picoline with α-halogenocarbonyl compounds and treatment of the salts with sodium hydrogen carbonate to yield the bridgehead compounds.[1] Few pyrrolo[1,2-*a*]quinolines (benzindolizines) have been reported [2] and unsuccessful attempts to extend the Chichibabin synthesis to this system have been reported.[3] It has been claimed previously that the quaternisation of ethyl 2-quinolylacetate (1) with phenacyl bromide yielded 2-ethoxycarbonylmethyl-1-phenacylquinolinium bromide (3) which failed to yield the expected pyrrolo[1,2-*a*]quinoline (5) and gave instead 1,2-dihydro-2-ethoxycarbonylmethylene-1-phenacylquinoline (4) *via* an elimination of hydrogen bromide. It was further suggested that hydrolysis and decarboxylation of this exo-methylene derivative (4) yielded 1,2-dihydro-2-methylene-1-phenacylquinoline (6).[3] Treatment of the ethoxycarbonylmethylene compound (4) with acetic anhydride, a method developed for the synthesis of indolizines *via* 2,3-bond formation, successfully yielded a bridgehead derivative which was formulated as 1-benzoyl-3-ethoxycarbonyl-2-methylpyrrolo[1,2-*a*]quinoline (7).[4] A re-examination of these reactions particularly on the basis of ^{1}H n.m.r. spectra has led us to propose isomeric structures for all of the above compounds.



Reagents: i, $PhCO{\cdot}CH_2Br$; ii, $NaHCO_3$; iii, NaOH; iv, Ac_2O.

Treatment of ethyl 2-quinolylacetate with phenacyl bromide yielded an oily hydrobromide which was converted into a crystalline hydrochloride salt on trituration with HCl. Basification of this product yielded the free base, previously formulated as the methine (4). The u.v. spectrum of this compound was essentially quinoline-like showing long-wavelength fine structure and maxima at 234 (ε $4{\cdot}24 \times 10^4$) and 317 nm ($4{\cdot}54 \times 10^3$). The ^{1}H n.m.r. spectrum showed clearly the presence of quinoline and phenyl ring protons and the ethyl ester group, but gave no indication of the olefinic or methylene signals expected for a methine structure. Instead, a

[1] D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 1962, 2627; 1963, 3277; *J. Chem. Soc.* (*C*), 1966, 2120; T. Melton and D. G. Wibberley, *ibid.*, 1967, 983 and references therein.

[2] W. L. Mosby in 'Heterocyclic Systems with Bridgehead Nitrogen Atoms,' ed. A. Weissberger, part I, Interscience, New York, 1961, p. 335.

[3] J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 1965, 2948.

[4] T. Melton, J. Taylor, and D. G. Wibberley, *Chem. Comm.*, 1965, 151.

triplet at τ 5·2 (1H, J 6·5 Hz) was observed together with an apparent two-proton multiplet at τ 5·95 which overlapped the ester methylene absorption at τ 5·73. To aid the spectral analysis in this region the above reaction sequence was repeated using methyl 2-quinolylacetate (2) which yielded the methyl ester analogue. The ^{1}H n.m.r. spectrum of this compound also showed a one-proton triplet at τ 5·18 (J 6·5 Hz) but the remaining protons were now exposed as an ABX multiplet at τ 6·04. Further simplification of the spectrum was obtained by treatment with D_2O which removed the absorption at τ 5·18 and thereby caused the remainder of the system to collapse to a quartet (J 19 Hz) characteristic of geminal coupling. A similar effect was noted in the case of the ethyl ester analogue.

We interpret this as suggesting that the initial alkylation proceeds *via* attack at carbon, rather than attack at nitrogen which is characteristic of ethyl 2-pyridylacetate, to produce the *C*-phenacyl hydrobromides [(8) and (9)] which yield 2-(1-benzoyl-2-ethoxycarbonylethyl)quinoline (10) and the methyl homologue (11), respectively, on treatment with base. In support of this is the fact that ethyl 2-quinolylacetate exchanges the methylene protons for deuterium rapidly when shaken with D_2O only at room temperature, whereas ethyl 2-pyridylacetate does not. Such behaviour may be due in part to the extra stability of exocyclic methine forms in the quinoline series over those in the pyridine series [5] which may increase the acidity of the 2-methylene protons, and hence increase the nucleophilicity of that carbon atom, and also to some extra steric restrictions to approach by the bulky phenacyl group.

The above structures are also supported by the i.r. spectrum [ν(CO_2Et) 1725, ν(PhCO) 1685 cm^{-1}] and by the mass spectrum particularly in the presence of the quinolyl ion (*m/e* 128). Further chemical evidence for the position of alkylation was provided by the basic hydrolysis of the products [(10) and (11)] which yielded 2-benzoylethylquinoline (12). The ^{1}H n.m.r. spectrum of this compound showed a multiplet centred at τ 6·5 due to the overlapping of signals due to the interaction of two methylene groups. The mass spectrum was also consistent with this formulation and again showed the quinolyl ion at *m/e* 128.

When 2-(1-benzoyl-2-ethoxycarbonylethyl)quinoline (10) was treated with acetic anhydride two products were isolated. One (m.p. 116—117°) was obtained from a light petroleum extract while the other (m.p. 187—188°), which was obtained *via* crystallisation from ethanol, was identical with the compound previously described as 1-benzoyl-3-ethoxycarbonyl-2-methylpyrrolo[1,2-*a*]quinoline (7). The reformulation of (4) as (10) for the starting material, the expectation that the course of this reaction proceeds *via* cyclisation at the acetyl rather than benzoyl function,[4] and the ^{1}H n.m.r. spectrum, particularly the presence of the methyl resonance at τ 7·10 which is close to the value for a ring substituent (τ 7·3) but is too deshielded to indicate an acetyl group (τ 7·9), suggest that this compound is better formulated as 2-benzoyl-3-ethoxycarbonyl-1-methylpyrrolo[1,2-*a*]quinoline (14). The lower melting product did not contain an acetyl residue and showed the presence of a singlet at τ 2·92 due to a free pyrrole proton and could thus be identified as 3-ethoxycarbonyl-1-phenylpyrrolo[1,2-*a*]quinoline (13).

EXPERIMENTAL

N.m.r. spectra were measured in deuteriochloroform solution using a Varian A-60A spectrometer, with tetramethylsilane as internal standard. I.r. spectra were recorded with a Unicam SP 200 spectrophotometer. Mass spectra were obtained using an A.E.I. MS9 instrument with direct insertion into the heated inlet system at 200°.

Ethyl and methyl 2-quinolylacetate were prepared from 2-quinolylmethyl-lithium and diethyl or dimethyl carbonate according to published methods.[6] However, yields were generally poor and small improvements were obtained by a reverse addition of the reagents; the bulk of the product was diacylated. Thus 2-quinolylmethyl-lithium [from quinoline (20 g) and dimethyl carbonate (10 g)] yielded *dimethyl 2-quinolylmalonate* (6·9 g, 19%) as orange plates, m.p. 108—109° (from light petroleum) (Found: C, 65·1; H, 5·2; N, 5·6. $C_{14}H_{13}NO_4$ requires C, 64·9; H, 5·0; N, 5·4%), $\nu_{max.}$ 1690 cm^{-1} (C=O), *m/e* 259 (M^+).

2-(1-*Benzoyl-2-ethoxycarbonylethyl*)*quinoline* (10).—Ethyl 2-quinolylacetate [6] (2·15 g), phenacyl bromide (1·0 g), and acetone (5 cm^3) were heated together under reflux for 17 h. The solution was evaporated to dryness and the residue was triturated with dilute hydrochloric acid (10 cm^3) and ether (10 cm^3) to precipitate the *quinoline hydrochloride* (1·39 g, 38%), m.p. 181—182° (decomp.) (from ethanol) (Found: C, 68·2; H, 5·6; N, 3·7. $C_{21}H_{20}ClNO_3$ requires C, 68·2; H, 5·4; N, 3·8%). Basification of the acid layer yielded unchanged ethyl 2-quinolylacetate (1·1 g). A solution of the hydrochloride (1·2 g) in water was treated with aqueous sodium hydroxide (10%) to yield the *quinoline* (0·7 g, 65%) as needles, m.p. 64—65° (from ethanol), $\nu_{max.}$ 1725 (ester C=O) and 1685 cm^{-1} (ketone C=O), τ ($CDCl_3$) 8·79 (t, J 7 Hz, CH_3CH_2), 5·95 (d, J 6·5 Hz, $CHCH_2$), 5·73 (q, J 7 Hz, CH_3CH_2), 5·2 (t, J 6·5 Hz, $CHCH_2$), 1·8—2·55 (m, aromatic protons), and 1·72 (d, J 8·5 Hz, 4-H) (Found: C, 75·5; H, 5·7; N, 4·4. $C_{21}H_{19}NO_3$ requires C, 75·7; H, 5·7; N, 4·2%), *m/e* 333 (M^+). A similar reaction of methyl 2-quinolylacetate yielded the methyl ester analogue, τ ($CDCl_3$) 6·28 (s, CH_3), 6·07 (m, collapsing to q, J 19 Hz, on treatment with D_2O, $CHCH_2$), 5·18 (exchangeable t, $CHCH_2$), and 1·7—2·55 (m, aromatic protons).

2-(2-*Benzoylethyl*)*quinoline* (12).—2-(1-Benzoyl-2-ethoxycarbonylethyl)quinoline (0·2 g), sodium hydroxide (1 cm^3; 20%), and ethanol (10 cm^3) were heated together under reflux for 1·5 h. The solution was concentrated to low bulk, adjusted to pH 7·0 and extracted with ether. Evaporation of the ethereal extract yielded the *quinoline* (0·14 g, 88%) as needles, m.p. 78—80° (from ethanol), $\nu_{max.}$ 1685 cm^{-1} (C=O), τ ($CDCl_3$) 6·5 (m, CH_2CH_2), and 1·9—2·17 and 2·2—2·68 (m, aromatic protons) (Found: C, 82·3; H, 5·8; N, 5·6. $C_{18}H_{15}NO$ requires C, 82·7; H, 5·8; N, 5·4%), *m/e* 261.

[5] K. Winterfeld and K. Küllmar, *Arch. Pharm.*, 1958, **291**, 485.

[6] D. L. Hammick, E. Johnston, and E. D. Morgan, *J. Chem. Soc.*, 1957, 5074.

Pyrrolo[1,2-a]*quinolines from* 2-(1-*Benzoyl*-2-*ethoxycarbonylethyl*)*quinoline*.—2-(1-Benzoyl-2-ethoxycarbonylethyl)-quinoline (1 g) and acetic anhydride (10 cm^3) were heated together for 4 h. Ethanol was added to the dark solution which was then evaporated to dryness. Crystallisation of the residue from ethanol yielded 2-*benzoyl*-3-*ethoxycarbonyl*-1-*methylpyrrolo*[1,2-a]*quinoline* (14) (0·28 g, 26%) as pale yellow plates, m.p. 187—188° (Found: C, 77·4; H, 5·2; N, 3·9. $C_{23}H_{19}NO_3$ requires C, 77·3; H, 5·3; N, 3·9%), *m/e* 357 (M^+), τ ($CDCl_3$) 9·12 (t, *J* 7 Hz, CH_3CH_2), 7·1 (s, CH_3), 6·0 (q, *J* 7 Hz, CH_3CH_2), and 1·6—2·8 (m, aromatic protons). The ethanolic mother liquors were evaporated to dryness and extracted with light petroleum to yield 3-*ethoxycarbonyl*-1-*phenylpyrrolo*[1,2-a]*quinoline* (13) (0·19 g, 20%) as fawn needles, m.p. 116—117° (Found: C, 79·5; H, 5·2; N, 4·5. $C_{21}H_{17}NO_2$ requires C, 80·1; H, 5·4; N, 4·5%), *m/e* 315, τ ($CDCl_3$) 8·62 (t, *J* 7 Hz, CH_3CH_2), 5·62 (q, *J* 7 Hz, CH_3CH_2), 2·92 (s), and 1·8—2·9 (m, aromatic protons).

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