The Synthesis of 1-Alkyl-1,4-dihydro-4-quinolone-2-carboxylic Acids

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A general method for the preparation of 1,4-dihydro-4-quinolone-2-carboxylic acids, especially those which carry alkyl substituents on the ring *N*-atom, is described.

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There has been considerable interest for a number of years in 1,4-dihydro-4-quinolone-2- or 3-carboxylic acids as potential therapeutic agents. This interest has been extended, in the case of the 3-carboxy series, to *N*-alkyl analogues (Ia), but little has been reported to date on the synthesis of *N*-alkyl derivatives in the 2-carboxy series (IIa). We have recently been involved in the study of these little described compounds.

Our initial synthetic approach to the required products was *via* an analogous method to that used to prepare *N*-alkyl derivatives in the 3-carboxy series. Such derivatives have been extensively obtained *via* standard alkylation conditions from esters of the parent acids (Ib) (1). Under these conditions, the *N*-alkyl compounds are generally obtained free from contamination with the isomeric *O*-alkyl derivatives (III). Baker and Bramhall (2) have reported that, in a similar manner, alkylation of 1,4-dihydro-4-quinolone-2-carboxylic acid (IIb) gave the *N*-methyl derivative (IIc). However, these workers gave no spectral data to support their assigned structure, and their reported melting point of 145-146° for the product was very close to that reported by Späth (3) (148-149°) for the isomeric *O*-methyl derivative (IV). We have repeated Baker and Bramhall's work and shown that the product obtained under these conditions is indeed the ether (IV). The structure of IV was assigned on the basis of spectroscopic evidence, which is discussed later in this paper and in the experimental section. In addition to this alkylation study, we also found that acylation of the ethyl 2-quinolinecarboxylate (Va) with acetic anhydride gave the *O*-acetyl derivative (Vb), rather than an *N*-acylated product. Whilst preparing the manuscript for this paper we noted some recently published work on the methylation of ethyl 1,4-dihydro-4-quinolone-2-carboxylate, where the major product isolated was the *O*-methyl derivative, though these workers did also obtain a low yield of the *N*-methyl isomer (4).

Two further studies on the alkylation of compounds of the general formula II (R = H) have been reported (5,6), but both of these successful reactions appeared to us to represent specialised cases and we sought a more general synthetic approach.

It is known that esters of 1,4-dihydro-4-quinolone-2-carboxylic acids may be prepared by the thermal cyclisation of anilinofumarate esters (VIa) (7). This route could also yield, unequivocally, the *N*-alkyl derivatives (*e.g.* IIc) if *N*-substituted anilinofumarates (*e.g.* VIb) could be readily obtained. However, Gudi, *et al.* (8), in reviewing six separate studies on the nucleophilic addition of amines to dimethyl acetylenedicarboxylate, concluded that, in general with primary amines, fumarate esters (VIa) are the major products but that maleate esters (VIIa) predominate when secondary amines are used. In one of these studies Huisgen, *et al.* (9), reported that with secondary amines, yields of the fumarate derivatives (VIa) could be increased if the reactions were carried out in a polar protic solvent such as methanol.

On repeating the condensation of *N*-methylaniline with dimethyl acetylenedicarboxylate in methanol, we obtained approximately a 1:1 mixture of the Z (fumarate) and E (maleate) isomers, VIc and VIIb, respectively. The composition of the mixture was determined by integration of the signals due to the vinylic protons in its nmr spectrum. Chromatography of this mixture on a silica column gave initially a mixture of the Z and E isomers which was rich in the Z component: further elution gave the pure E isomer, but the amount of this isomer obtained, was vastly in excess of that expected from the initial nmr analysis of the original reaction product. It would appear that the fumarate isomerised to the maleate during the chromatographic process. We did not isolate a pure sample of the Z isomer.

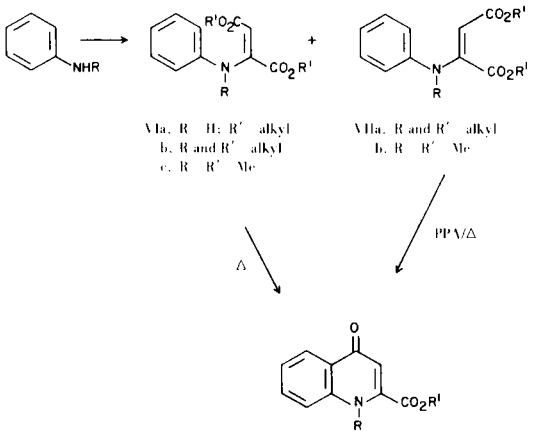
Interestingly we noted that the E isomer very slowly isomerised to the Z isomer when left on the laboratory bench, exposed to a mixture of normal sunlight and artificial lighting. The degree of isomerisation was markedly enhanced by subjecting either the solid E isomer, or a solution of it in methanol, to ultra-violet light. However, once again a pure sample of the Z isomer was not obtained, as decomposition of the materials occurred under the influence of the uv light before complete isomerisation had occurred.

Attempts to thermally cyclise either the mixture of Z and E isomers or the pure E isomer itself by heating in refluxing diphenyl ether to give the *N*-alkyl quinolone derivative (IIc) were unsuccessful. This was not too surprising, since *prima facie* one would not have expected the E isomer to cyclise, unless it had first thermally isomerised to the Z isomer under the reaction conditions. We detected no evidence of a thermal isomerisation of this type. This finding contrasts somewhat with the conclusions of Hall, *et al.* (10), who found, that in the case of *N-H* anilino-fumarate/maleate mixtures, thermal treatment produced cyclisation to the *N-H* quinolones,

and they suggested that their maleate isomers were rearranging to the fumarate intermediates under these conditions.

A consideration of the enaminic nature of the anilinomaleate derivative (VIIb) led us to speculate that the compound should isomerise fairly readily under acidic conditions. Thus a solution of VIIb in polyphosphoric acid was heated at 80° for 2 hours, and the product isolated, with total consumption of the starting maleate ester, proved to be the cyclic methyl quinolone-2-carboxylate (IIc) (Scheme). The time course, the temperature dependence and the nature of the inorganic acid required for this isomerisation-cyclisation reaction were studied in some further detail. In polyphosphoric acid at room temperature no chemical change occurred over a 30 minute period, but at 80° the maleate was completely consumed in 30 minutes. Identical results were obtained with concentrated sulphuric acid, but neither concentrated hydrochloric acid nor monophosphoric acid produced the cyclic quinolone to any significant extent, even at 80°. Further studies with polyphosphoric acid revealed that at 80°, the cyclisation reaction is indeed complete within 5 minutes. This new acid catalysed method of quinolone formation is particularly advantageous over the diphenyl ether thermal cyclisation procedure for the preparation of compounds bearing heat sensitive substituents. Using this technique we also found that it was not necessary to separate the initial fumarate-maleate mixture obtained from the addition of the *N*-methylaniline to dimethyl acetylenedicarboxylate, since the mixture itself readily yielded the methyl quinolone-2-carboxylate directly when heated with polyphosphoric acid.

Scheme

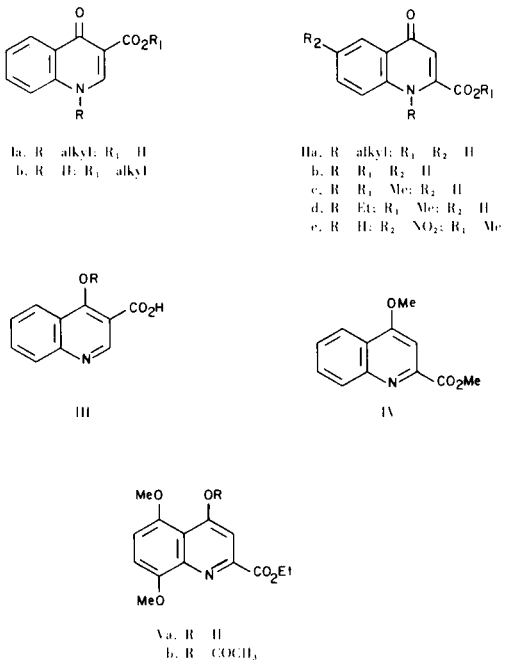


II

The ir and nmr spectra of the products discussed in this paper were entirely consistent with the assigned structures. Thus in its ir spectrum, the *N*-methyl ester IIc had a strong ester C=O stretching frequency at 1725 cm^{-1}, together with an equally strong absorption at 1615 cm^{-1} assigned to the C=O stretch of the 4-oxo group (vinylogous amide). This contrasted with the ir spectrum of its isomeric 4-methoxyquinoline derivative (IV) which had an ester carbonyl absorption at 1710 cm^{-1}, but no amide absorption.

The distinguishing feature between the nmr spectra (deuteriochloroform) of the *O*-methyl and *N*-methyl derivatives lay in the chemical shifts of the H_3-proton singlets. In the *O*-methyl compound (IV) this signal was in the aromatic region of the spectrum at δ = 7.6 ppm, but in the *N*-methyl compound (IIc) it was at considerably higher field, δ = 6.6 ppm.

That the procedure is likely to be of general synthetic usefulness for the preparation of quinolone-2-carboxylates was demonstrated by the preparation of the derivatives IId and IIe from *N*-ethylaniline and *p*-nitroaniline, respectively.



EXPERIMENTAL

Melting points (uncorrected) were determined on a Büchi melting point apparatus. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU 6 spectrometer. Infrared spectra were recorded on Perkin-Elmer 257 and 457 instruments using potassium bromide discs, unless otherwise stated, and a Perkin-Elmer 402 spectrometer was used to obtain ultraviolet spectra. Pmr spectra were determined in deuteriochloroform, unless otherwise stated, at 60 MHz on a Perkin-Elmer R12 spectrometer with TMS providing an internal lock signal.

Methyl 4-Methoxyquinoline-2-carboxylate (IV).

The procedure of Baker and Bramhall (2) was followed; the product isolated was assigned structure IV on the basis of the following spectral data; pmr: δ 4.07 and 4.09 two x (s, 3, OCH_3), 7.59 (s, 1, H_3), 7.29 to 8.35 ppm (complex splitting pattern, 4, aromatic protons); ir (nujol): 1710 cm^{-1} (ester C=O) (this is

the only absorption in the carbonyl region).

Ethyl 4-Acetoxy-5,8-dimethoxyquinoline-2-carboxylate (Vb).

A mixture of ethyl 4-hydroxy-5,8-dimethoxyquinoline-2-carboxylate (11) (2.63 g.), acetic anhydride (10 ml.) and concentrated sulphuric acid (0.5 ml.) was heated under reflux for 2 hours. The hot solution was then poured into ice-water and the precipitated yellow solid was crystallised from ethyl acetate, with charcoaling, as yellow needles (2.2 g.), m.p. 167-168°; pmr: δ 1.45 (t, 3, ester CH_3), 2.35 (s, 3, acetyl CH_3), 3.86 and 3.98 two x (s, 3, OCH_3), 4.48 (q, 2, ester CH_2), 6.92 (q, J = 9 Hz, 2, aromatic AB), 7.84 ppm (s, 1, H-3); ir (nujol): 1780 (acetoxy C=O), 1740 cm^{-1} (ester C=O).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.2; H, 5.4; N, 4.4. Found: C, 60.6; H, 5.7; N, 4.2.

Condensation of *N*-Methylaniline with Dimethyl Acetylenedicarboxylate (VIc and VIIb).

Benzyltrimethylammonium hydroxide (triton B, 40% aqueous solution, 5 ml.) was added, at room temperature, to a stirred solution of *N*-methylaniline (10.7 g.) and dimethyl acetylenedicarboxylate (14.2 g.) in methanol (75 ml.). The reaction mixture was heated under reflux for four hours and the solvent was removed *in vacuo* to leave a reddish brown oil (23.2 g.). Tlc examination (silica gel plates: ether-petroleum ether 1:1) revealed that the oil was principally a mixture of two components and pmr analysis revealed the presence of an isomeric mixture of dimethyl *N*-methylanilinofumarate (VIc) and dimethyl *N*-methylanilinomaleate (VIIb) in the percentage ratio of 54:46. This ratio was determined from the integration of the peaks in the pmr spectrum of the two vinylic protons at δ 6.1 (*Z* isomer) and 4.76 (E isomer) and of the NCH_3 protons at δ 3.29 (*Z* isomer) and 3.14 (E isomer).

The red oil was chromatographed on a silica column. Using ether-petroleum ether (1:4) as eluent, a mixture of Z and E isomers was obtained which had a Z to E ratio of 71 to 29 (from pmr studies); 4.5 g. of this mixture were obtained. Increasing the polarity of the eluent to 1:1 ether-petroleum ether yielded colourless crystals of the E isomer (18 g.) as a single entity (tlc), m.p. 71-72°; pmr: δ 3.17 (s, 3, NCH_3), 3.59 and 3.62 two x (s, 3, OCH_3), 4.77 (s, 1, vinylic CH), 7.25 ppm (m, 5, aromatic H).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.5; H, 6.1; N, 5.6. Found: C, 62.6; H, 6.3; N, 5.6.

Thus, although the E isomer was the minor component in the original reaction product, it was by far the major constituent isolated by column chromatography. Therefore, there must have been a significant amount of isomerisation occurring on the column.

Cyclisation Reactions to Produce IIc.

(A) Diphenyl ether.

A mixture of VIc and VIIb (2.0 g.) was added to refluxing diphenyl ether (80 ml.) and heating was continued for a further 15 minutes. Subsequently the diphenyl ether was removed by azeotropic distillation and the resultant product was extracted into ethyl acetate. Tlc examination of this solution indicated a multi-component mixture and the reaction was abandoned. The above procedure was repeated using pure dimethyl *N*-methylanilinomaleate (0.5 g.) in refluxing diphenyl ether (20 ml.) and, with an identical work up, unchanged VIIb was recovered in almost quantitative yield.

(B) Polyphosphoric Acid.

A solution of VIIb (14 g.) in polyphosphoric acid (140 ml.) was heated at 80° for 2 hours. The reaction mixture was poured into water and neutralised by the addition of solid sodium bicarbonate and then extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulphate and the solvent was evaporated *in vacuo* to leave a brown solid which was crystallised from ethanol, with charcoaling, to give IIc as colourless needles (9.5 g.), m.p. 132-134°; pmr: δ 3.8 (s, 3, NCH_3), 3.96 (s, 3, OMe), 6.59 (s, 1, H_3), 7.55 (m, 3, H_6, H_7, H_8), 8.40 ppm (*ortho* and *meta* coupled d, 1, H_5); ir: 1725 (ester C=O), 1615 cm^{-1} (ring C=O); uv: 218 (ε = 23,544), 242 (ε = 18,445), 340 nm (ε = 9,765); ms: m/e 217 M^+ and base peak.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.0; N, 6.4. Found: C, 66.3; H, 5.2; N, 6.4.

Methyl 1-Ethyl-1,4-dihydro-4-quinolone-2-carboxylate (IId).

Triton B (5 ml.) was added to a stirred solution of *N*-ethylaniline (12.1 g.) and dimethyl acetylenedicarboxylate (14.2 g.) in methanol (100 ml.) and the reaction mixture was heated under reflux for eight hours. Removal of the solvent *in vacuo* yielded an oil (18 g.) which was heated at 80° with polyphosphoric acid (100 ml.) for two hours. The reaction mixture was poured into water, made neutral by the addition of solid sodium bicarbonate, and extracted with ethyl acetate. The organic phases were washed with water and dried over magnesium sulphate. The solvent was removed *in vacuo* and the product was crystallised from ethanol to give IId (4.0 g.) as light brown prisms, m.p. 107-109°; pmr (DMSO-d_6): δ 1.37 (t, 3, CH_2CH_3), 3.94 (s, 3, OCH_3), 4.27 (q, 2, CH_2CH_3), 6.33 (s, 1, H_3), 7.28-8.31 ppm (complex splitting pattern 4, aromatic protons); ir: 1725 (ester C=O), 1618 cm^{-1} (ring C=O); uv: 216 (ε = 25,680), 242 (ε = 20,888), 338 nm (ε = 11,304); ms: m/e 231 M^+ and base peak.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.7; H, 5.9; N, 6.4.

Methyl 6-Nitro-1,4-dihydro-4-quinolone-2-carboxylate (IIe).

Application of the polyphosphoric acid cyclisation described above gave the known IIe in 80% yield from dimethyl 4-nitroanilinofumarate, m.p. 296-298° (Lit. m.p. (10), 297-300°).

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