SYNTHESIS AND ISOMERIC CONVERSIONS OF SEVERAL 2-SUBSTITUTED 1,4-DIHYDRO-4-OXO-3-QUINOLINECARBOXYLIC ACID DERIVATIVES

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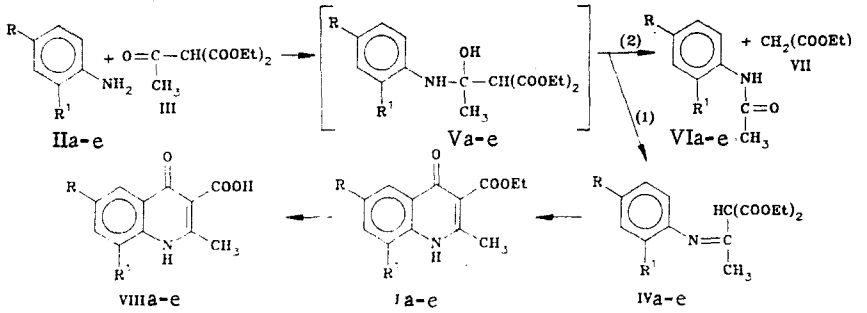
Ethyl ester derivatives of 6- and 8-substituted 2-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been synthesized by treatment of the diethyl ester of acetylmalonic acid with 2- or 4-substituted anilines. Condensation of these newly synthesized quinolinecarboxylic acid derivatives with 4-nitrobenzaldehyde resulted in the formation of 6- and 8-substituted 2-[2-(4-nitrophenyl)-vinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids and ethyl esters of 6- and 8-substituted 2-[2-(4-nitrophenyl)vinyl]-4-acetoxy-3-quinolinecarboxylic acids. The tautomeric and conformational transformations of these newly synthesized compounds have also been investigated, using IR, NMR, and UV spectroscopy.

Several methods are known for the preparation of benzene-ring substituted 2-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid ethyl esters (I), which are used in the synthesis of biologically active compounds [1-11].

In order to synthesize the desired quinolines I we selected a method based on reaction of the substituted aniline II with diethyl acetylmalonate at 40°C in the absence of solvent, which was followed by cyclization of the intermediate Schiff base IV via brief heating at 200°C [1-4]. The necessary ester starting material III was synthesized according to a published method [12-14].



I—VIII a,e R=H, b R=Br, c R=Cl, d R=CH_3O; a-d R^1=H, e R^1=F

In addition to quinolines I, acetanilides VI and diethyl malonate (VII) were also isolated from the reaction mixtures. The amount of compounds VI and VII formed depends on the nature of the substituents R and R^1. It should be noted that acetanilide VIa was detected among the reaction products of compounds IIa and III as far back as 1888.

The results obtained in these studies led us to conclude that the intermediate condensation products are aminoalcohols V, which can then decompose either via elimination of water (pathway 1) or of diethyl ester VII (pathway 2), depending on the nature of the aromatic radical. Comparison of the pK_a values of anilines IIa-e with the amount of water and ester VII formed upon reaction of compound III with anilines IIa-e reveals (Fig. 1a, b) that the lower limit of aniline basicity (pK_a) at which they no longer interact with the acetyl group in III is equal to 3.0; in the pK_a range 4.0-5.5 conversion of the aminoalcohol V occurs primarily along pathway 1, while at pK_a values above 5.5 direction 2 predominates. These results explain the failure of attempts to prepare 4-hydroxy-3-naphthyridinecarboxylic acid ethyl ester derivatives via condensation of compound III with 2-, 3-, or 4-aminopyridines. The high basicity of the latter compounds (pK_a values 6.86, 5.98, and 9.17, respectively)

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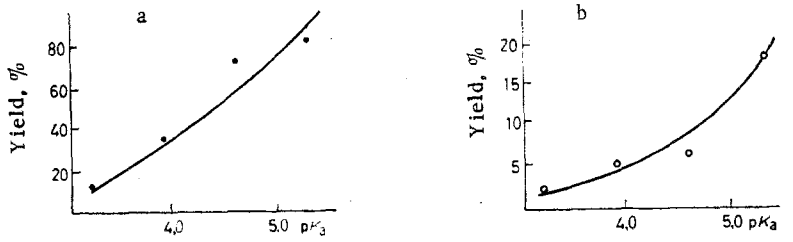


Fig. 1. Effect of aniline basicity IIa, b, d, and e on the yield of water (a) and of ester VII (b) upon condensation with diethyl acetylmalonate (III) in refluxing benzene.

TABLE 1. Characteristics of Newly Synthesized Compounds

Compound	mp, °C*	Found, %			Molecular formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ia	231...232 (232 [3])								61
Ib	270...271 (271—272 [3])								33
Ic	265...267	58,9	4,6	5,1	$C_{13}H_{12}ClNO_3$	58,8	4,5	5,3	32
Id	265...266 (263...265 [3])								50
Ie	205...206	62,6	4,8	5,8	$C_{13}H_{12}FNO_3$	62,6	4,8	5,6	2,5
VIIIa	212...213 (243...244 [6])	64,9	4,7	6,8	$C_{11}H_9NO_3$	65,0	4,5	6,9	92
VIIIb	295	46,7	2,7	4,7	$C_{11}H_8BrNO_3$	46,8	2,9	5,0	93
VIIIc	320 (315 [8])	55,8	3,5	6,1	$C_{11}H_8ClNO_3$	55,6	3,4	5,9	93
VIIId	285	61,9	5,0	5,9	$C_{12}H_{11}NO_4$	61,8	4,7	6,0	89
VIIIe	237	59,8	3,6	6,2	$C_{11}H_8FNO_3$	59,7	3,6	6,3	93
IXa	320	64,2	3,7	8,1	$C_{18}H_{12}N_2O_5$	64,3	3,6	8,3	50
IXb	295	52,1	2,6	6,6	$C_{18}H_{11}BrN_2O_5$	52,1	2,7	6,7	94
IXc	290	58,4	3,0	7,7	$C_{18}H_{11}ClN_2O_5$	58,3	3,0	7,6	72
IXd	285	62,3	3,8	7,6	$C_{19}H_{14}N_2O_6$	62,3	3,8	7,6	60
IXe	290	61,0	3,0	8,2	$C_{18}H_{11}FN_2O_5$	61,0	3,1	7,9	53
Xa	300	64,8	4,5	6,9	$C_{22}H_{18}N_2O_6$	65,0	4,5	6,9	52
Xb	243	54,2	3,3	5,8	$C_{22}H_{17}BrN_2O_6$	54,4	3,5	5,8	63
Xc	254	60,0	3,8	6,2	$C_{22}H_{17}ClN_2O_6$	59,9	3,9	6,3	65
Xd	254	62,7	4,5	6,3	$C_{23}H_{20}N_2O_7$	63,3	4,6	6,4	59
XIIa	210	71,3	4,6	8,4	$C_{20}H_{16}N_2O_5$	71,4	4,8	8,3	40
XIV	255	47,3	2,4	7,0	$C_{16}H_9BrN_2O_5$	47,4	2,2	6,9	55
XV	225	53,3	2,7	7,8	$C_{16}H_9ClN_2O_5$	53,3	2,5	7,8	58

*Compounds VIIIb-e, IXa-e, Xa, c, d, XIIa, XIV, and XV melted with decomposition.

would be expected to facilitate the formation, primarily, of ester VII and acetylated 2-, 3-, or 4-aminopyridines; this was, in fact, verified experimentally by analysis of the corresponding reaction mixtures.

Attempted bromination of the methyl group in the 2 position of quinoline Ia with bromine led to the formation of the 6-bromo derivative Ib, which is substituted in the aromatic ring.

It is known that the methyl group in quinoline Ia condenses with 5-nitro-2-furfural [3, 15]. Extension of this reaction to 6-chloro- and 6-bromoquinolines (Ib, c) made it possible to synthesize their derivatives XIV and XV for the first time.

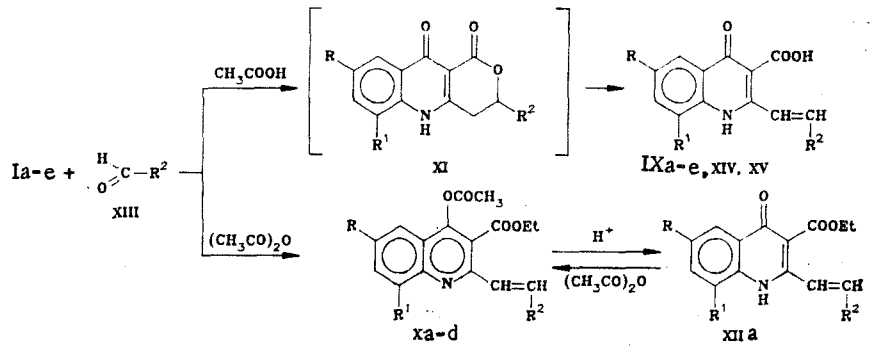
When the analogous condensations of quinolines Ia-e with 4-nitrobenzaldehyde (XIII) were carried out in glacial acetic acid, 6- and 8-substituted 2-[2-(4-nitrophenyl)vinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (IX) were formed; in acetic anhydride, in contrast, substituted 2-[2-(4-nitrophenyl)vinyl]-4-acetoxy-3-quinolinecarboxylic acid ethyl ester derivatives (X) were formed (see scheme on following page).

Cleavage of the ester linkage upon condensation in glacial acetic acid, as well as in its mixture with acetic anhydride, appears to be an intramolecular process, occurring via intermediate lactone XI (the formation of a similar type of compound has been reported previously [16]). However, it was not possible to detect lactone XI with $R = R^1 = H$ in the reaction mixture, using NMR spectroscopy, apparently because of its rapid decomposition.

TABLE 2. IR Spectra of Substituted Ethyl Esters of 2-[2-(4-Nitrophenyl)vinyl]-4-acetoxy-3-quinolinecarboxylic Acids (Xa-d) in Nujol Suspensions

Compound	ν, cm⁻¹					
	CH arom	C=O acetyl	C=O ester	condensed aromatic ring	as-NO_2	s-NO_2
Xa	3080 w	1765 s	1730 s	1640 w, 1620 w, 1595 m, 1555 w	1510 s	1345 s
Xb	3080 w	1770 s	1730 s	1640 w, 1610 w, 1595 m, 1580 s, 1545 w	1530 s	1340 s
Xc	3080 w	1775 s	1730 s	1640 w, 1595 m, 1580 s	1525 s	1340 s
Xd	3110 w 3080 w	1765 m	1735 s	1620 m, 1600 m, 1560 w	1520 s	1340 s

The acetoxy group in ethyl 2-[2-(4-nitrophenyl)vinyl]-4-acetoxy-3-quinolinecarboxylate (Xa) can be selectively hydrolyzed in the presence of catalytic amounts of hydrochloric acid. Upon brief heating in acetic anhydride ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate (XIIa) is converted to the starting material Xa.



IX—XII a R=H, b, e R=Br, c R=Cl, d R=CH_3O; a-e; R^1=H; R^2=*p*-$C_6H_4NO_2$; XIV R=Br, XV R=Cl; XIV, XV R^1=H; R^2= 5-nitro-2-furyl

The possibility of hydrogen atom migration in these synthesized compounds, from the nitrogen heteroatom to the oxygen in the 4 position of the quinoline (quinoline–quinolone isomerism) [1] explains the necessity of carrying out special spectroscopic studies, directed to finding the most favored isomeric forms for each case.

Using IR spectroscopy, the ν_{COO}, ν_{NH}, and $\nu_{C=C}$ group stretching frequencies in the synthesized compounds (Tables 2-4) were compared with the analogous data for 2-mercaptoalkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid esters, which were analyzed in a previous study [17]. The fact that the frequencies and intensities of the bands at 1705-1725 and 1630-1645 cm^{-1} overlap one another in these two series of compounds being compared provides evidence for the presence of two carbonyl groups, located β to one another, in compounds I and XII; one of these carbonyl groups is found in an ester functional group, while the other is located in the 4 position of the quinoline ring. In the IR spectra of carboxylic acids IX and VIII, these groups gave rise to bands at 1670-1720 and 1630-1645 cm^{-1}, respectively (see Tables 3 and 4). An increase in the frequency of the carbonyl group absorption band for a dilute solution of compound VIIIa in acetonitrile, from 1685 to 1715 cm^{-1} is indicative of a dimeric structure for 6-substituted 2-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (VIIIa-d) in the crystalline state. Inversely, the decrease in the frequency of the corresponding absorption band for a dilute solution of compound IXb in acetonitrile (addition of HCl to the solution does not affect the frequency of the carbonyl absorption band), from 1720 to 1680 cm^{-1}, makes it possible to explain the appearance of two absorption bands for the carboxyl group in compounds IXa-d and XV (Table 5) as a consequence of existence of the latter in two conformational states A and B.

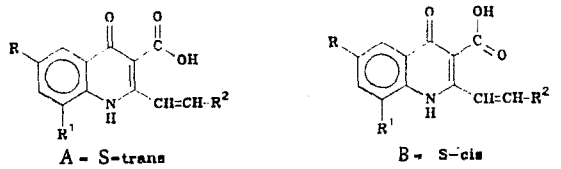


TABLE 3. IR Spectra of Substituted 2-Methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids and Their Ethyl Esters (Ia-e, VIIIa-e) in Nujol Suspensions

Compound	ν, cm⁻¹					
	NH	CH arom	C=O ester	C=O carboxyl	C=O quinoline	condensed aromatic ring
Ia	3280 m, 3240 w	3100 w, 3060 w	1720 s	—	1640 s, 1610 m	1585 m, 1550 m, 1510 s
Ib	3280 m, 3220 m, 3160 m	3100 w, 3060 m	1710s	—	1640 m, 1610 w	1580 m, 1550 s
Ic	3280 w, 3220 w, 3160 w	3060	1705 s	—	1640 m, 1610 w	1580 w, 1550 s, 1510 s
Id	3240 m, 3110 w	3100 m	1725 s	—	1620 m	1590 m, 1550 s, 1520 s
Ie	3280 w, 3220 w, 3160 w	3080 w	1720 s	—	1645 s, 1610 w	1590 s, 1550 s, 1510 s
VIIIa	3360 w, 3280 w, 3220 m	3060 m	—	1685 s	1640 s, 1615 m	1575 m, 1530 m
VIIIb	3260 w, 3200 w,	3060 m	—	1680s	1640 s, 1610 m	1575 m, 1520 m
VIIIc	3280 w, 3210 m	3080 m	—	1680 s	1640 s, 1610 m	1575 m, 1525 s
VIIId	3290 w, 3220 w	3090 w, 3070 w	—	1665s	1645 m, 1625 s	1530 s, 1495 s
VIIIe	3220 w, 3160 w	3080 w	—	1700 s	1640 m, 1620 m	1595 m, 1520 m

TABLE 4. IR Spectra of 2-Methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Derivatives (IXa-d, XIIa, XV) in Nujol Suspensions

Compound	ν, cm⁻¹							
	NH	CH arom	C=O ester	C=O, C=O COOH	C=O quinoline	condensed aromatic ring	as-NO_2	s-NO_2
IXa	3200 w	3100 w, 3080 w	—	— 1675 m	1640 s	1600 s 1560 w	1520 s	1350 s
IXb	3260 w	3080 w	—	1720 s, —	1630 s	1595 m	1510 s	1350 s
IXc	3260 w, 3200 w	3090 w, 3060 w	—	1700 s, 1670 s,	1630 m	1610 s, 1595 w, 1540 w	1510 s	1350 s
IXd	3120 w	3080 w	—	1710 s —	1635 m	1620 m, 1600 m	1510 s	1360 s
XV	3170 w,	3080 w,	—	1720 m, 1670 s	1630 m	1610 m, 1570 w,	1510s	1360s
XIIa	3260w, 3200 w, 3160 w, 3120 w	3100 w, 3080 w	1735 s	— —	1645 m, 1630 m	1550 w, 1610 m, 1570s, 1550 s	1520s	1360 s

Based on the results of an analogous study [18], the band at 1670-1675 cm^{-1} is assigned to conformer A with the double bond of the carboxyl group oriented trans- with respect to the double bond in the quinoline ring, while the band at 1700-1720 cm^{-1} is assigned to conformer B, with a cis-orientation of the carbonyl group. The presence of NH absorption bands in the 3100-3300 cm^{-1} region in the IR spectra of compounds I, VIII, IX, and XII, which are absent in the IR spectra of compounds X containing an acetylated hydroxyl group (see Table 3), provides additional evidence to support the existence of these compounds in the quinolone isomeric forms.

The PMR spectra of these newly synthesized compounds are summarized in Table 5.

Additional information obtained from an analysis of the ^{13}C-NMR spectra of these compounds makes it possible to solve the question of quinoline–quinolone isomerism. It is known that the $C_{(4)}$ carbon atom signal in quinolones occurs at 174 ppm, and that it is shifted downfield (163-161 ppm) [19, 20] in the ^{13}C-NMR spectra of substituted 4-hydroquinolines. It follows, therefore, that the signals observed at 173.5 and 173.9 ppm in the spectra of compounds Ia and XIIa reflect the existence of quinolone isomeric structures. In compound Xa, which contains a quinoline structure, the $C_{(4)}$ signal occurs at 153.2 ppm (see Table 6).

It is known that, in contrast to the spectra of 4-quinolones, the UV spectra of 4-hydroxyquinolines contain intense absorption bands in the 260-290 nm region, and do not contain absorption bands in the 310-360 nm region [18, 21-23]. The UV spectrum of compound Ia thus reflects its quinolone structure (see Fig. 2). An increase in the length of the conjugation chain due

TABLE 5. PMR Spectra of Newly Synthesized Compounds

Compound	Chemical shifts, δ, ppm (in DMSO-D_6)*						
	$COOC_2H_5$	CH_3	OCH_3	COOH	NH	$C_9H_3R(R^1)N$	$C_9H_3R(R^1)N$, CH=CH, C_6H_4
Ia	1,26; 4,22	2,48	—	—	11,80	7,20—7,80	—
Ib	1,26; 4,24	2,37	—	—	11,95	7,44—8,13	—
Ic	1,29; 4,27	2,39	—	—	11,87	7,51—8,04	—
Id	1,26; 4,24	2,38	3,82	—	11,87	7,24—7,62	—
Ie	1,29; 4,25	2,44	—	—	11,78	7,20—7,93	—
VIIIa	—	2,26	—	9,10	12,11	7,07—8,02	—
VIIIb	—	2,88	—	9,42	12,17	7,67—8,31	—
VIIIc	—	2,91	—	9,39	11,91	7,69—8,13	—
VIIId	—	2,88	3,83	8,84	12,11	7,40—7,84	—
VIIIe	—	3,00	—	9,40	12,64	7,42—8,11	—
IXa	—	—	—	—	12,53	—	7,49—8,52
IXb	—	—	—	—	12,60	—	7,53—8,60
IXc	—	—	—	—	11,93	—	7,46—8,51
IXd	—	—	3,93	—	12,42	—	7,46—8,53
IXe	—	—	—	—	11,90	—	7,44—8,44
Xa	1,38; 4,53	—	—	—	—	—	7,69—8,42
Xb	1,38; 4,53	—	—	—	—	—	7,69—8,46
Xc	1,38; 4,47	—	—	—	—	—	7,56—8,36
Xd	1,38; 4,38	—	3,93	—	—	—	7,56—8,36
XIIIa	1,30; 4,38	—	—	—	11,91	—	7,31—8,44
XIV	—	—	—	—	12,70	—	—
XV	—	—	—	—	12,42	—	—

*For the acetoxy groups in compounds Xa-d the chemical shift values are equal to 2.6 ppm, and are thus overlapped by the proton signals due to DMSO-D_6. In the case of the $C_9H_3R(R^1)N$, CH=CH, and C_4H_2O groups, their chemical shift values are 7.33-8.53 (for XIV), and 7.28-8.39 ppm (for XV).

TABLE 6. ^{13}C-NMR Spectra of 2-Methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Derivatives

Compound	^{13}C chemical shifts (ppm)									
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	other C atoms
Ia	148,9	114,8	173,5	125,0	123,5	132,0	117,9	139,2	124,7	18,0 ($2\text{-}CH_3$), 166,7 (COO), 60,2 (OCH_2), 14,0 (CH_3)
XIIa	144,7	115,3	173,9	125,0	124,0	132,7	118,6	139,5	124,9	134,7 (C_α), 147,5 (C_p), 124,2 (C_β), 166,2 (COO), 141,5 (C_i), 60,8 (CH_2), 128,4 (C_o), 14,2 (CH_3), 124,2 (C_m)
Xa	151,8	118,9	153,2	128,7	128,0	129,0	132,4	148,6	120,9	133,5 (C_α), 168,0 (COO), 122,5 (C_β), 62,1 (CH_2), 142,4 (C_i), 13,9 (CH_3), 128,4 (C_o), 164,3 (OCO), 123,9 (C_m), 20,3 ($COCH_3$), 147,2 (C_p)

to introduction of a 4-nitrophenylvinyl substituent in the 2 position of the quinoline ring increases the intensity (of this band) and also leads to the appearance of new absorption bands, so that the UV spectra of the quinoline and quinolone forms of compounds Xa and XIIa do not exhibit significant differences. The highly intense absorption band in the 300-340 nm region in the spectrum of compound XIIa also supports its existence in a quinolone structural form.

On the basis of IR, UV, and PMR spectroscopic analysis, compounds I, IX, XII, and VIII have been shown to exist in the form of 1,4-dihydro-4-oxoquinoline structures, rather than in the form of 4-hydroxyquinoline structures, as previously proposed for compounds of this type [3].

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer using suspensions in Nujol; UV spectra were obtained on a Specord UV-vis spectrophotometer using CH_3CN solutions. NMR spectra were recorded on a Bruker WH-90 spectrometer; ^1H-NMR spectra using DMSO-D_6 solutions (versus TMS as internal standard), ^{13}C-NMR spectra using DMSO solutions (versus C_6H_{12} as internal standard). Elemental analyses were performed on a Carlo Erba 1106 model apparatus.

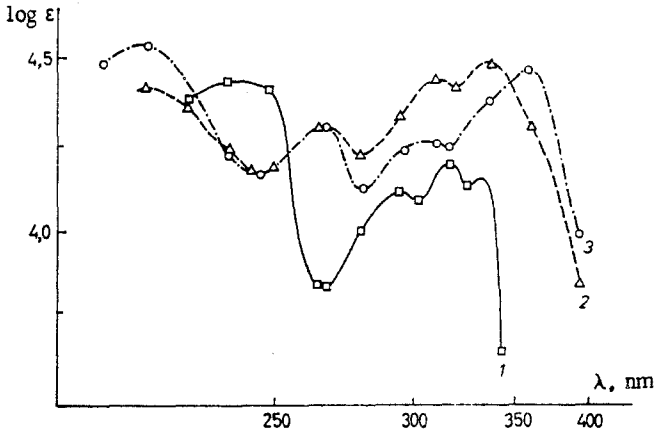


Fig. 2. UV spectra of 2-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid derivatives: 1) Ia; 2) XII; 3) Xa.

The course of the reactions and purity of newly synthesized compounds were monitored by TLC on Silufol UV-254 plates using two solvent systems: A (acetone–acetic acid, 95:5), and B (chloroform–hexane, 1:1). The characteristics of compounds I, VIII-X, XII, XIV, and XV are presented in Table 1.

2-Methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Esters (Ia-e). A mixture of 0.1 mole of the appropriate aniline IIa-e, 20.2 g (0.01 mole) of acetylmalonic ester, and two drops of conc. HCl was stored in a vacuum drying cabinet over $CaCl_2$ at 45-50°C (20-100 mm Hg) for 16 h. The resulting mixture was then heated at 190-220°C for 0.5 h, until no more ethanol was liberated. At reduced pressure the low-boiling components were evaporated (10 mm Hg). The residue was diluted with ethanol and cooled. The resulting crystals of Ia-e which precipitated were filtered and recrystallized from ethanol.

The anilides IVa-e were isolated from the ethanol mother liquor after removal of the desired compounds above. The structures (of the anilides) were established based on their PMR spectral data and the absence of melting point depressions when mixed with authentic samples.

2-Methyl-6-bromo-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (Ib). To a solution of 0.4 g (1.7 mmole) ester Ia in 30 ml glacial acetic acid was added 0.26 ml (5.1 mmole) bromine, and the mixture was stirred at room temperature for 3 h. The resulting precipitate was removed by filtration to give 0.1 g 18%) of compound Ib. The identity of these two samples of Ib, prepared via the above two methods, was demonstrated based on their PMR spectral data and the absence of a melting point depression.

2-Methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids (VIIIa-e). A mixture of 1 N NaOH solution and 0.01 mole of the appropriate ester Ia–e was refluxed for 8 h, until no more starting material remained (according to TLC). The resulting solution was then cooled and filtered, and acidified with concentrated HCl to pH 6. The resulting precipitates of compounds VIIIa-e were removed by filtration and dried.

2-[2-(4-Nitrophenyl)vinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (IXa–e). To a solution of 0.01 mole of the appropriate ester Ia–e in 30 ml glacial acetic acid was added 0.01 mole 4-nitrobenzaldehyde, and the resulting mixture was refluxed for 8 h. The solution was cooled, and the resulting precipitate of compound IXa-e was removed by filtration and recrystallized from DMF.

2-[2-(4-Nitrophenyl)vinyl]-4-acetoxy-3-quinolinecarboxylic Acids, Ethyl Esters (Xa-d). To a solution of 0.01 mole of the appropriate ethyl ester Ia-d in 50 ml acetic anhydride was added 0.1 mole of 4-nitrobenzaldehyde, and the resulting mixture was refluxed for 8 h. The reaction mixture was cooled and the precipitate of compound Xa-d was removed by filtration and recrystallized from acetic anhydride.

2-[2-(4-Nitrophenyl)vinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (XIIa). A solution consisting of 50 ml ethanol, 1.6 g (3.9 mmole) ethyl 2-[2-(4-nitrophenyl)-vinyl]-4-acetoxy-3-quinolinecarboxylate, and 2 ml concentrated HCl was rapidly heated to its boiling point. When a precipitate appeared (after several minutes) heating was discontinued and the

mixture was cooled slowly to room temperature. The solution was filtered and precipitate XIIa was recrystallized from ethanol. Yield 0.5 g.

6-Substituted 2-[2-(5-Nitro-2-furyl)vinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids (XIV, XV). A mixture of 0.01 mole ester Ib or Ic and 0.01 mole 5-nitrofurfural in 80 ml glacial acetic acid was refluxed for 2 h, cooled, and the precipitate of compound XIV or XV was removed by filtration and recrystallized from DMF.

General Method for Determining the Amount (yield) of Water and Malonate Ester Displaced upon Reaction of Substituted Anilines (IIa, b, d, and e) with Diethyl Acetylmalonate (III). To a 250 ml flask was added 0.1 mole of the substituted aniline, 0.1 mole diethyl acetylmalonate, 50 ml absolute benzene, and 2 drops concentrated HCl. The mixture was refluxed with a condenser and an azeotropic distillation adapter until no more water was evolved (approximately 16 h). From the amount of water collected in this manner was subtracted the amount of water displaced in a blank experiment (refluxing aniline, benzene, and hydrochloric acid in the absence of diethyl acetylmalonate).

The quantitative amount of malonic ester present in the reaction mixture was determined by GLC (5% OV-17, T = 100-250°C, 20°C/min, P 1.8 atm).

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