Transformations in the 2-Quinolone Series

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The treatment of 1-substituted-1,2-dihydro-4-hydroxy-2-oxo-3-quinoline carboxylic acid esters and 4-hydroxy-1-methyl-3-nitro-2-(1*H*)quinolinone with phosphorus oxychloride resulted in the formation of the corresponding 4-chloro-2-quinolones. Their reactions with a variety of carbon, nitrogen, oxygen, and sulfur nucleophiles is described.

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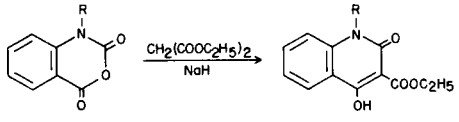
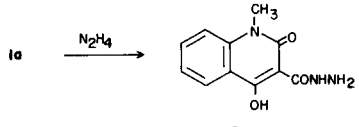
In previous papers (1,2) we have reported the synthesis of a variety of substituted 2- and 4-quinolones. In a continuing search for compounds possessing interesting pharmacological activity, the functional transformations of some of these compounds was investigated. An interesting candidate for such manipulations is 1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic acid ethyl ester (**1a**). Its synthesis may be readily accomplished by the reaction of *N*-methylisatoic anhydride with diethyl malonate in the presence of sodium hydride (1,3).



1a (R=CH_3)

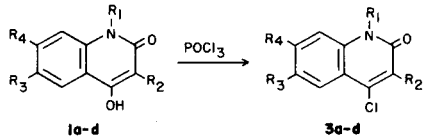
The reaction of **1a** with hydrazine resulted in the isolation of the hydrazide **2** in quantitive yield.



2

For a reaction to occur at the 4-position rather than on the ester, a functionality more reactive than the hydroxy would have to be present. It was decided that a chlorine atom at this position, which would be doubly activated by the aromatic ring and the ester, would fulfill this criterion.

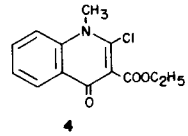
The conversion of 4-hydroxy-*N*-methylcarbostyrils into their 4-chloro derivatives has been reported to proceed in moderate yields by treatment with phosphorous oxychloride at elevated temperatures (4). When **1a** was refluxed with phosphorus oxychloride for 3 hours, the resulting 4-chloroquinoline (**3a**) was isolated in 78% yield. Similar treatment of analogous 4-hydroxyquinolines (**1b-1d**) (2) furnished the corresponding 4-chloro compounds (**3b-3d**).



1a-d **3a-d**

	R_1	R_2	R_3	R_4
a	CH_3	$COOC_2H_5$	H	H
b	$CH_2CH=CH_2$	$COOC_2H_5$	OCH_3	OCH_3
c	CH_3	$COOC_2H_5$	O-CH_2-O	
d	CH_3	NO_2	H	H

Although chlorination is assumed to take place at the 4-position, the unlikely possibility of formation of the 2-chloro-4-quinoline (**4**) cannot be ruled out. As far as we are able to ascertain, there is no chemical precedent for structures of type **4**. As previously described, the reported chlorination of 4-hydroxy-*N*-methylcarbostyril with phosphorous oxychloride resulted in the formation of 4-chloro-1-methylcarbostyril. The introduction of chlorine into the 2-position required the use of phosphorus pentachloride at high temperatures (4). These conditions resulted in demethylation, and 2,4-dichloroquinoline was isolated in low yield.



4

However, further evidence of the 2-quinolone structure **3** was desired. Infrared studies of 2- and 4-quinolones indicated in general that 2-quinolones absorb at 1660-1650 cm^{-1} while 4-quinolones at 1630-1620 cm^{-1} (5,6,7), although exceptions to the rule are known and compounds have been reported to absorb in the 1647-1631 cm^{-1} region (5,8,9). The amide absorption of chloro compounds **3** is observed between 1660 and 1645 cm^{-1} with **3b** absorbing at 1630 cm^{-1}. Although this evidence suggests the 2-quinolone structure, it is not conclusive.

A carbon-13 nmr study was therefore undertaken on **3a**. Comparison of the carbon shifts in the heterocyclic ring with a variety of model compounds **5-9** (Table 1) show that the shifts of **3a** more closely resemble a 2-quinolone system rather than a 4-quinolone.

Based on the carbon-13 data, the infrared absorptions, and lack of chemical precedent for the formation of **4**, the structures of the chlorinated quinolones are believed to be **3**.

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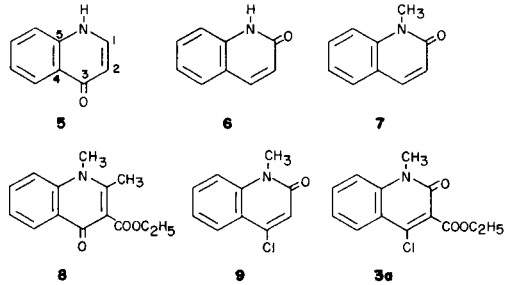
Table 1

Carbon-13 NMR Shift Data For Model Compounds and **3a** (a)



Compound No.	1	2	3	4	5
5	139.5	108.8	177.2	125.9	140.1
6	162.0	121.7	140.1	119.1	139.0
7	162.6	121.9	139.2	120.8	140.2
8	149.5	118.5	174.3	126.4	141.2
9	160.8	120.9	144.2	119.1	139.7
3a	158.2	126.6	140.9	118.1	139.2

(a) Shift data for **5** and **6** (10). Shift data for **7** (11). Synthesis of **8** (2). Synthesis of **9** (4).

With compounds of type **3** in hand, their reaction with amines was investigated. When **3a** was allowed to react with various amines in refluxing toluene, the 4-amino compounds **10** were isolated in good yields (Table 2). The reaction with dimethylamine was performed at 60° in a steel vessel. Analogous reactions with **3d** furnished the corresponding 4-amino-3-nitroquinolones **10g** and **10h**.

In contrast with the formation of **2**, the reaction of **3a** with *N*-methylhydrazine resulted in the formation of the pyrazolo[4,3-*c*]-quinoline **12** (12).

The chlorine in **3a** is readily displaced by a variety of nucleophiles, reaction with cuprous cyanide in refluxing

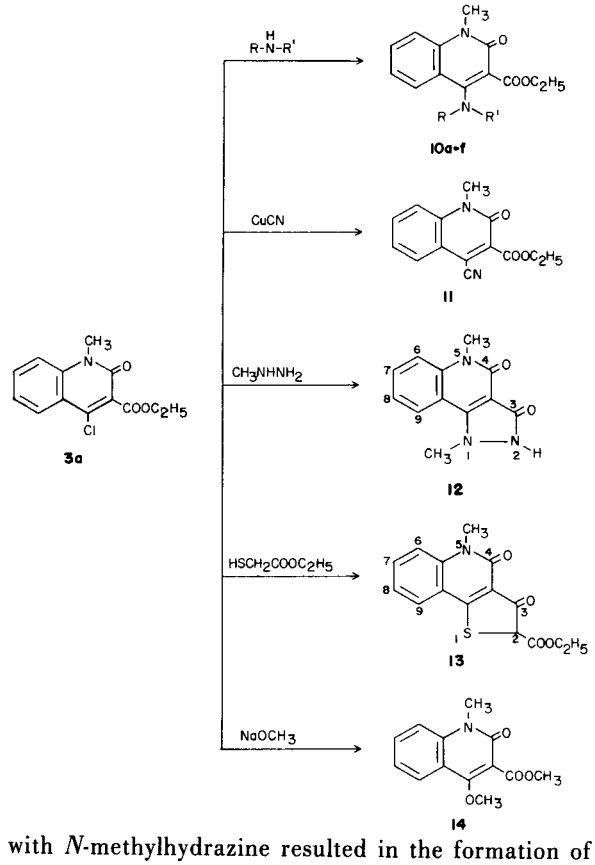
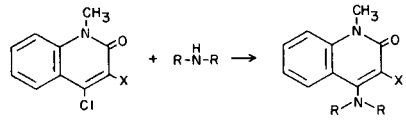


Table 2

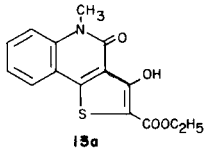


Compound No.	X	R-N-R	M.p., °C	Yield, %	Amide C=O cm^{-1}	Molecular Formula	Analysis Calcd. (Found) C	H	N	
10a	$COOC_2H_5$	$N(CH_3)_2$	73-76	68	1615	$C_{15}H_{18}N_2O_3$	65.7	6.6	10.2	
							(65.7	6.6	10.1)	
10b	$COOC_2H_5$	HN⌒N$(CH_3)_2$	64-68	50	1610	$C_{17}H_{23}N_3O_3$	64.3	7.3	13.7	
							(64.3	7.1	13.3)	
10c	$COOC_2H_5$	$N(CH_2CH=CH_2)_2$	oil	79	1615	$C_{19}H_{22}N_2O_3$	69.9	6.7	8.6	
							(69.7	7.0	8.6)	
10d	$COOC_2H_5$	N⬡	93-96	70	1620	$C_{18}H_{22}N_2O_3$	68.8	7.1	8.9	
							(68.5	7.2	8.5)	
10e	$COOC_2H_5$	N⬡O	133-136	63	1625	$C_{17}H_{20}N_2O_4$	64.6	6.4	8.9	
							(64.5	6.4	9.0)	
10f	$COOC_2H_5$	N⬡N-CH_3	133-137	39	1610	$C_{18}H_{23}N_3O_3$	65.6	7.0	12.8	
							(65.5	6.9	12.5)	
10g	NO_2	$HNCH_2COOC_2H_5$	170-173	55	1635	$C_{14}H_{15}N_3O_5$	55.1	5.0	13.8	
							(55.5	5.0	13.5)	
10h	NO_2	N⬡N-CH_3	209-212	45	1640	$C_{15}H_{18}N_4O_3$	59.6	6.0	18.5	
							(59.3	5.5	18.4)	(a)

(a) Reanalysis did not improve the value.

dimethylformamide furnishes **11** in 73% yield. The action of sodium methoxide on **3a** produces the 4-methoxyquinoline **14** in which transesterification subsequently occurs resulting in the formation of a methyl ester in the 3-position. The intereaction of **3a** with ethyl 2-mercaptoacetate in the presence of sodium hydride furnishes the thieno[3,2-*c*]quinoline (**13**). This product can be rationalized as forming by the initial displacement of the 4-chlorine by the thiolate anion followed by a Dieckmann cyclization.

Compound **13** is believed to exist in the 3-keto tautomer due to the observance of three distinct infrared carbonyl absorptions (1720, 1680 and 1645 cm^{-1}). However, when the nmr spectrum of **13** in trifluoroacetic acid was analyzed, the proton at the 2-position could not be found. It is believed that in this solvent, **13** exists in the enolized form (**13a**) with the enolic proton being hidden by the acid protons of the trifluoroacetic acid.



13a

The reaction of **3a** with additional nucleophiles is currently being investigated.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60 and A-60 spectrometers using tetramethylsilane as an internal reference. chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. General nmr spectral and instrumental parameters employed were: internal deuterium lock to the solvent; spectral width of 5120 Hz; a pulse width 25 μs, corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra 8K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ± 0.05 ppm.

Unless otherwise stated, all solutions of organic compounds were washed with aqueous saturated sodium chloride solution and dried over sodium sulfate. No attempt had been made to optimize the yields of the described reactions.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Hydrazide (2).

To a solution of 4.0 g of **1a** (1,2) in 40 ml of ethanol was added 0.55 g of anhydrous hydrazine and the mixture was refluxed for 18 hours. After cooling, the resulting precipitate was filtered and washed with ethanol then ether to give 3.5 g (100%) of **2**, m.p. 243-245°; ir (Nujol): 3330, 3240, 1645 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.6; H, 4.7; N, 18.0. Found: C, 56.8; H, 5.1; N, 17.9.

4-Chloro-1,2-dihydro-1-methyl-2-oxo-3-quinoline carboxylic Acid Ethyl Ester (**3a**).

A mixture of 25 g of **1a** (1,2) and 200 ml of phosphorus oxychloride was stirred at 95° for 3 hours. Excess phosphorus oxychloride was removed under reduced pressure and the residue was poured into cold water. The mixture was neutralized with 2*N* sodium carbonate solution and the resulting precipitate was filtered. The organic solid was dissolved in methylene chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the product crystallized from ether to give 20.9 g (78%) of **3a**, m.p. 97-98°; ir (chloroform): 1740, 1645 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (m,l), 7.9-7.1 (m,3), 4.5 (q,2), 3.7 (s,3), 1.45 (t,3); ms: (70 eV) molecular ion at m/e 265.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.8; H, 4.6; N, 5.3; Cl, 13.3. Found: C, 58.6; H, 4.3; N, 5.2; Cl, 13.4.

1-Allyl-4-chloro-1,2-dihydro-6,7-dimethoxy-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (**3b**).

The reaction using 1-allyl-1,2-dihydro-6,7-dimethoxy-4-hydroxy-2-oxo-3-quinolinecarboxylic acid ethyl ester (**1b**) (13) was performed similar to that of **3a** and the product, **3b**, was isolated in 38% yield, m.p. 93-96°; ir (chloroform): 1730, 1630 cm^{-1}; nmr (deuteriochloroform): δ 7.35 (s, 1), 6.8 (s, 1), 6.2-5.6 (m, 1), 5.45-4.85 (m, 4), 4.45 (q, 2), 3.9 (s, 6), 1.4 (t, 3); ms: (70 eV) molecular ion at m/e 351.

Anal. Calcd. for $C_{17}H_{18}ClNO_5$: C, 58.0; H, 5.2; N, 4.0; Cl, 10.1. Found: C, 58.2; H, 4.9; N, 3.9; Cl, 10.3.

4-Chloro-1,2-dihydro-6-7-methylenedioxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (**3c**).

The reaction using 1,2-dihydro-4-hydroxy-1-methyl-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylic acid ethyl ester (**1c**) (2) was performed similar to that of **3a** and the product, **3c**, was isolated in 61% yield, m.p. 163-166°; ir (chloroform): 1735, 1645 cm^{-1}; nmr (deuteriochlorform): δ 7.2 (s, 1), 6.8 (s, 1), 6.05 (s, 2), 4.45 (q, 2), 3.6 (s, 3), 1.4 (t, 3).

Anal. Calcd. for $C_{14}H_{12}ClNO_5$: C, 54.3; H, 3.9; N, 4.5. Found: C, 54.2; H, 4.3; N, 4.5.

4-Chloro-1-methyl-3-nitro-2-(1*H*)quinolinone(**3d**).

The reaction using 4-hydroxy-1-methyl-3-nitro-2-(1*H*)quinolinone (**1d**) (1) was performed similar to that of **3a** and the product, **3d**, was isolated in 41% yield, m.p. 224-247°; ir (Nujol): 1660 cm^{-1}; mnr (DMSO-d_6): δ 8.1-7.2 (m, 4), 3.65 (s, 3).

Anal. Calcd. for $C_{10}H_7ClN_2O_3$: C, 50.3; H, 3.0; N, 11.7. Found: C, 50.3; H, 3.2; N, 12.0.

Preparation of 4-Aminosubstituted-2-oxoquinolines **10** (Table 2).

A mixture of 0.02 mole of **3a** or **3d** and 0.025 mole of the appropriate amine in 100 ml of toluene was refluxed for 8 hours. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. The solution was washed with water, then saturated sodium chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from ether to give the product.

In the case of **10a**, 0.02 mole of **3a** and 5 ml of dimethylamine in 10 ml of toluene was heated at 60° in a steel vessel for 18 hours. The reaction was worked up as described above.

4-Cyano-1,2-dihydro-1-methyl-2-oxo-3-quinoinecarboxylic Acid Ethyl Ester (**11**).

A mixture of 1.0 g of **3a** and 0.45 g of cuprous cyanide in 7 ml of dimethyformanide was refluxed for 4 hours. After cooling the reaction mixture was poured into a solution of hydrated ferric chloride (1.5 g ferric chloride, 0.33 ml concentrated hydrochloric acid, and 5 ml water) and the mixture was heated at 65° for 20 minutes. After cooling, the organic material was extracted into ethyl acetate and the solution was washed with 6*N* hydrochloric acid, 2*N* sodium hydroxide, and saturated sodium chloride. The solvent was removed under reduced pressure to give 0.7 g

(73%) of **11**. An analytical sample was crystallized from ether; m.p. 146-148°; ir (chloroform): 1740, 1655 cm^{-1}; nmr (deuteriochloroform): δ 8.1-7.2 (m, 4), 4.5 (q, 2), 3.5 (s, 3), 1.5 (t, 3); ms: (70 eV) molecular ion at m/e 256.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.7; N, 10.9. Found: C, 65.6; H, 4.9; N, 10.7.

1,5-Dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-3,4-(2*H*, 5*H*)dione (12).

A mixture of 6.0 g of **3a** and 2.2 g of methylhydrazine in 100 ml toluene was refluxed for 18 hours. After cooling, the precipitate was filtered and triturated with hot ethanol to give 3.5 g (67%) of **12**, m.p. > 300°; ir (Nujol): 3280, 1635, 1460 cm^{-1}; nmr (deuteriotrifluoroacetic acid): δ 8.4 (m, 1), 8.3-7.6 (m, 4), 4.55 (s, 3), 3.95 (s, 3).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.9; H. 4.8; N, 18.3. Found: C, 62.6; H, 4.8; N, 18.3.

2,3,4,5-Tetrahydro-5-methyl-3,4-dioxothieno[3,2-*c*]quinoline-2-carboxylic Acid Ethyl Ester (**13**).

To a solution of 3.5 g of ethyl 2-mercaptoacetate in 50 ml of dimethylacetamide was added 1.4 g of sodium hydride (50% in mineral oil, pentane washed) in portions. After stirring at room temperature for 30 minutes, a solution of 7.0 g of **3a** in 85 ml of dimethylacetamide was added. The mixture was stirred at 85° for 90 minutes. Then it was poured into 300 ml of water. The resulting precipitate was filtered, washed with water, ethanol, and ether to give 3.0 g. (37%) of **13**, m.p. 318° dec.; ir (Nujol): 1720, 1680, 1645 cm^{-1}; nmr (trifluoroacetic acid): δ 8.1-7.3 (m, 4), 4.5 (q, 2), 4.0 (s, 3), 1.55 (t, 3); ms: (70 eV) molecular ion at m/e 303.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.4; H, 4.3; N, 4.6; S, 10.6. Found: C, 59.1; H, 4.4; N, 4.5; S, 10.9.

1,2-Dihydro-4-methoxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Methyl Ester (**14**).

To 140 ml of methanol was added 1.1 g of sodium. When a clear solution formed, 10.0 g of **3a** was added and the mixture was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the produce, 6.0 g (65%) of **14**. An analytical sample was crystallized from ether, m.p. 92-95°; ir (chloroform): 1740, 1630 cm^{-1}; nmr (deuteriochloroform) δ 7.95 (m, 1), 7.7-7.0 (m, 3), 4.1 (s, 3), 4.0 (s, 3), 3.65 (s, 3); ms: (70 eV) molecular ion at m/e 247.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.1; H, 5.3; N, 5.7. Found: C, 62.8; H, 5.3; N, 5.5.

Acknowledgement.

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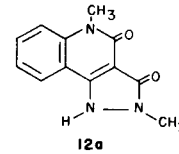
(12) The product is assumed to have arisen by initial displacement of the chlorine (as observed in compounds **10**) by the more basic methylated nitrogen of the methylhydrazine followed by ring closure, although the 2-methyl isomer, which may form as a result of initial attack at the ester or displacement of the chloring by the unsubstituted nitrogen, cannot be totally discounted. Spectrally, the observed nmr *N*-methyl signals (a singlet at δ 4.55 and a singlet at δ 3.95) favor structure **12** as drawn. The methyl group, being colinear with the aromatic ring, would be expected to produce a signal shifted downfield. The isomer *12a* would be expected to exhibit both methyl signals closer together.



12a

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