Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 6.[1] Revision of the Structure of the Reaction Product of Cyclohexane-1,3-dione and Dimethyl β-Ketoglutarate and Conversion to 4-Substituted 5,6,7,8-Tetrahydro-5-oxo-2-quinolones

James Oehldrich and James M. Cook*

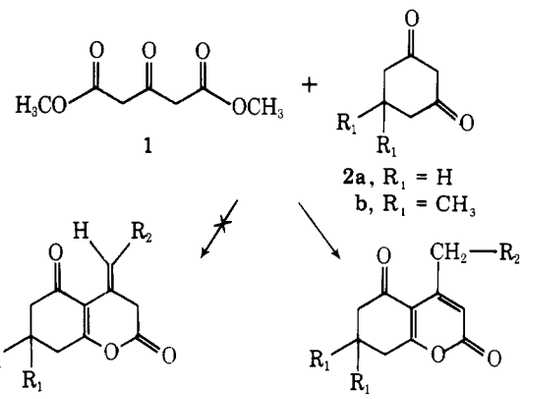
Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

Received August 6, 1976

In our first report concerning the reactions of 1,2- and 1,3-dicarbonyl compounds with dimethyl β-ketoglutarate (1), we proposed structure **3a** for the product obtained from reaction of cyclohexane-1,3-dione (**2a**) with 1 at pH 6.8. This structure has now been revised to methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a**) based on UV and ^{13}C NMR data. In addition, the tetrahydro-5-oxocoumarin derivatives **4a** and **4b** were converted to the corresponding 5,6,7,8-tetrahydro-5-oxo-2-quinolones **10a, 11a, 10b,** and **11b,** respectively, by reaction with *N*-benzylamine or ammonia. The ^{13}C NMR spectra of these 2-quinolones are presented and discussed.

During studies on the reaction of dicarbonyl compounds[1,2a-c] with dimethyl β-ketoglutarate (1) we reported, in preliminary form,[3] that stirring cyclohexane-1,3-dione (**2a**) with 1 at pH 6.8 provided the lactone **3a.** We would now like to revise the structure of this reaction product to the α-pyrone derivative, methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a**),[4] based on analogies between the UV and ^{13}C NMR spectra of **4a** with the spectra of 4-methyl-5,6,7,8-tetrahydro-5-oxocoumarin (**4c**).[5,6]

Scheme I



1

2a, R_1 = H
b, R_1 = CH_3

3a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3

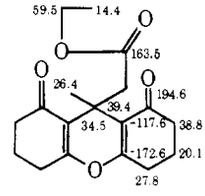
4a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3
c, R_1 = R_2 = H
d, R_1 = CH_3; R_2 = H

In the UV spectrum of the compound in question (**3a** or **4a,** λ_{max} 260 nm, log ε 4.06; 295 nm, sh, log ε 3.74) the shoulder at 295 nm was nearly obscured by the intense absorption at 260 nm and this led to the initial assignment (**3a**).[3] However, on closer examination of this spectrum, a shoulder (295 nm) was observed and in fact the spectrum was very similar to that of the known 5-oxocoumarin (**4c,** λ_{max} 261 nm, log ε 3.99; 299 nm, sh, log ε 3.63) and to that of the 7,7-dimethyl analogue (**4d**)[6] as illustrated in Table I. In addition, the band at 295 nm in the spectrum of **4a** has ε almost identical with that of α-pyrones[7] such as **5,** but much different from the oxo-enol ether system **6**[8] or the keto lactone **7.**[7]

It was felt, at this point, that the structure of the reaction product of 1 and **2a** was **4a**[4] and not the previously reported **3a.**[3] While IR and ^1H NMR favored structure **4a,** they were not very useful in distinguishing unambiguously between the two possibilities. However, the ^{13}C NMR spectra of **4c** and the reaction product (**4a**) were almost identical, when the difference between the group ($CH_2CO_2CH_3$ vs. CH_3) attached to C-4 of the heterocyclic ring was taken into consideration (see Table II). Furthermore, the absorption (169.3 ppm) due to the ester carbonyl in the ^{13}C NMR spectrum of the reaction product clearly eliminated the possibility of the α,β-unsaturated ester function, which would be present in **3a.** Saturated methyl ester carbonyls appear at 169–170 ppm in ^{13}C NMR spectra while their α,β-unsaturated counterparts are found at 163–164 ppm.[9] All of the compounds (α-pyrones and α-pyridones), whose spectra are illustrated in Table II, have signals in their ^{13}C NMR spectrum in the range of 169–170 ppm, and are certainly due to saturated methyl ester functions. This evidence, taken together with UV data, rules out structure **3a** as the product from reaction of 1 with **2a** and confirms the assignment of this derivative as **4a.** By analogy, stirring dimedone (**2b**) with 1 (at pH 6.8) furnished the 7,7-dimethyl analogue **4b.** The model compound, 4-methyl-5,6,7,8-5-oxocoumarin (**4c**), was prepared in several ways: by acid-catalyzed hydrolysis and decarboxylation of **4a;** by *heating* the reaction mixture of **2a** and 1 to 70 °C at pH 6.8; and also by reacting ethyl acetoacetate (8) and **2a** in pyridine.[5]

In addition, stirring the 1,3-dione (**2a**) with 8 at room temperature (pH 6.8) resulted in production of a small amount of **4c** along with larger amounts of ethyl 1,2,3,4,5,6,7,8-octahydro-9-methyl-1,8-dioxoxanthen-9-yl acetate (**9a**). The structure of the xanthene derivative was determined by comparing the spectral properties of **9a** to those of 9,9-dimethylxanthene (**9b**).[10] The structure of **9a** was further corroborated by comparison of its ^{13}C NMR spectrum (see Chart I) to the spectra of model compounds (see ref 11, 12). A set of

Chart I. ^{13}C NMR Chemical Shifts[a,b] for Xanthene (**9a**)



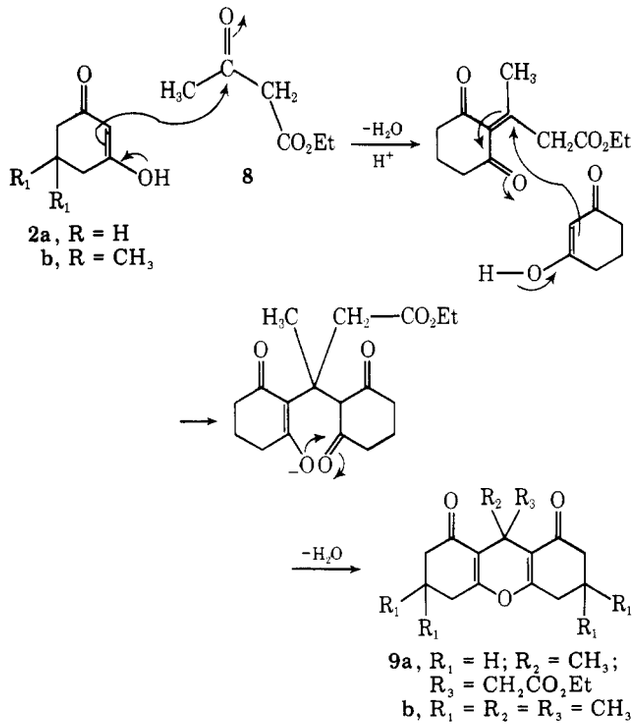
9a[c]

[a] Solvent $CDCl_3$. [b] $(CH_3)_4Si$ as internal standard. [c] Some of the methylene carbon assignments of 9a are tentative, their signals being too close to permit distinction between similar carbon atoms.

steps depicting a rational pathway to **9a** is outlined in Scheme II.[13]

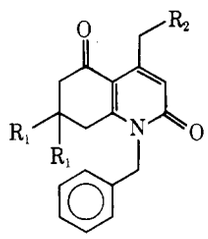
Synthesis of 5-hydroxy-5,6,7,8-tetrahydrocarbostyrils and 5-hydroxy-5,6,7,8-tetrahydro-2-quinolines[14a] have not re-

Scheme II

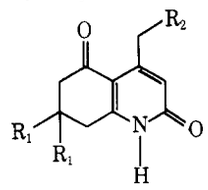


ceived much attention in the past; however, reports of the activity of bis-5-hydroxycarbostyrils against allergic asthma have stimulated new interest in this area.[14b] Since conversion of α-pyrones to α-pyridones is well known,[15] it was felt that reaction of the 5-oxocoumarin derivatives (**4a–d**) with amines might provide a facile route to 5,6,7,8-tetrahydro-5-oxo-2-quinolones, which could be converted (via the acetic acid function) to a variety of C-4 (alkyl) substituted-2-quinolones and quinolines.

In general, heating **4a** or **4b** in benzene with benzylamine gave poor yields of the corresponding tetrahydro-5-oxo-2-quinolones **10a** and **10b,** respectively. In the case of **4b,** a small amount of the amide (**10c**) was also obtained. However, when **4a** and benzylamine were stirred at room temperature in methanol for several days, there appeared to be one major

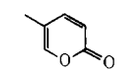
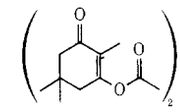
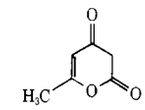


10a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3
c, R_1 = CH_3; R_2 = CONHBz
d, R_1 = R_2 = H



11a, R_1 = H; R_2 = COOH
b, R_1 = CH_3; R_2 = COOH HCl
c, R_1 = H; R_2 = $COONH_4$
12a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3

Table I. Ultraviolet[a] Spectra of 4a and Related Model Compounds

Compd	λ, nm	ε	Log ε
4a	260	11 430	4.06
	295	5 540	3.74
4b	263	9 375	3.97
	299	5 280	3.71
4c	261	9 780	3.99
	299	4 279	3.63
4d	262[b]	12 100	4.08
	296	5 960	3.76
5 	300[c]	5 000	3.69
6 	263[d]	28,024	4.45
7 	271[e]		

[a] Solvent CH_3OH. [b] Reference 10. [c] Reference 7. [d] Authentic sample provided by Professor Clayton Heathcock. See *J. Org. Chem.*, 41, 636 (1976). [e] Reference 7.

compound (**10a**), isolated in 80% yield, with only traces of **4a** remaining.

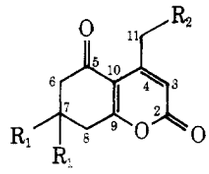
Slightly different behavior was observed on reaction of **4a** with anhydrous ammonia. Initially, ammonia was bubbled into a methanolic solution of **4a,** but yields of 5-oxo-2-quinolone **11a** were quite low. However, when the same transformation was carried out in a solution of 1:1 methanol/ether, a 92% yield of the quinolone carboxylic acid derivative (**11a**) precipitated as a white solid. The salt, 5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-ylacetic acid hydrochloride (**11b**), was prepared by treating **4b** with ammonia in much the same manner as the preparation of 5,6,7,8-tetrahydro-5-oxo-2-quinolon-4-ylacetic acid (**11a**). Treatment of a solution of **4a** in methanol with ammonium hydroxide again caused reaction at both oxygen-substituted carbonyls to generate, in this case, the ammonium salt (**11c**). This appears to be the first route to tetrahydro-5-oxo-2-quinolones with the 4 position of the heterocyclic ring available for further functionalization. Both **11a** and **11b** were esterified to generate the methyl esters **12a** and **12b,** respectively, in excellent yield.

The ^{13}C NMR spectra of the 5,6,7,8-tetrahydro-5-oxocoumarins and the 5,6,7,8-tetrahydro-5-oxo-2-quinolones, mentioned above, have been obtained. A summary of the chemical shifts is presented in Table II.

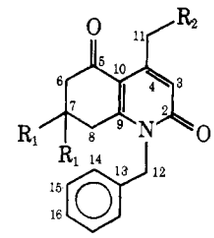
From examination of the data in Table II, it can be seen that the carbonyl carbon at position 5 is the signal which appears at lowest field (δ 195 ppm) and which undergoes the smallest change on transformation of the 5-oxocoumarin chromophore to the 5-oxo-2-quinolone moiety. The methyl ester carbonyl was more strongly deshielded than either the coumarin (δ 159 ppm) or the 2-quinolone (δ 162 ppm) carbonyl. These trends are in complete agreement with the chemical shifts of a number of α-pyridones, α-pyrones, and coumarins which have been reported recently in the literature.[11,12,16] Further support for the assignments made in Table II was obtained by examination of the partially proton coupled spectra of **4b** and **10b;** the multiplicities observed in the carbon spectra were exactly those predicted for methyl, methylene, and methine carbon atoms contained in heterocycles such as **4b** and **10b.**

The magnitude of the chemical shift at carbon 9 upon going from 5-oxocoumarin to 5-oxo-2-quinolone derivatives (i.e., **4a** → **10a,** Δ 17 ppm), as illustrated in Chart II, indicated that this position was a more sensitive probe for predicting the presence

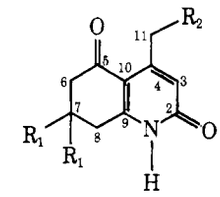
Table II. ^{13}C NMR Chemical Shifts[d]



4a, R_1 = H; R_2 = $COOCH_3$
b, R_1 = CH_3; R_2 = $COOCH_3$
c, R_1 = R_2 = H



10a, R_1 = H; R_2 = $COOCH_3$
b, R_1 = CH_3; R_2 = $COOCH_3$
d, R_1 = R_2 = H

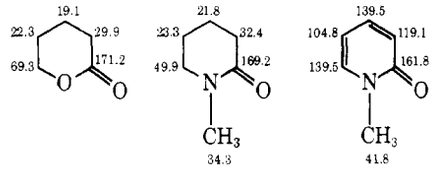


12a, R_1 = H;
R_2 = $COOCH_3$

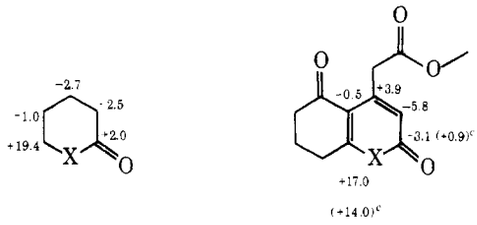
	4a	4b[b]	4c	10a	10b[b]	10d	12a[c]
2	159.1	159.4	159.5	162.2	162.3	162.0	164.7
3	115.4	115.1 d	113.0	121.2	120.8 d	118.9	120.7
4	150.4	150.2	156.2	146.5	146.2	151.9	149.5
5	195.4	195.4	195.4	195.5	195.5	195.5	195.2
6	38.0	51.9 t	38.6	37.7	51.2 t	38.2	38.7
7	19.6	31.8	19.7	20.8	31.9	20.8	20.8
R_1 = CH_3		28.0 q			27.9 q		
8	29.0	42.6 t	29.1	28.2	41.6 t	28.2	28.2
9	175.2	173.7	174.7	158.2	156.7	157.7	157.4
10	114.0	113.1	114.8	114.5	113.6	115.3	114.0
11	40.3	40.2 t	22.7	41.5	41.3 t	23.4	41.3
C=O, ester	169.2	169.7		170.8	170.6		170.6
OCH_3	52.1	52.1 q		51.9	51.8 q		52.0
12				47.2	46.9 t	46.8	
13				135.4	135.5	135.7	
14				126.3	126.0	126.1	
15				129.1	128.9	128.8	
16				127.8	127.6	127.6	

[a] $CDCl_3$ solvent, $(CH_3)_4Si$ internal standard. [b] Partially proton coupled multiplicities. [c] This spectrum courtesy of Professor Hutchinson, University of Wisconsin, School of Pharmacy. [d] Registry no.: **4a**, 61062-39-3; **4b**, 610 62-4-6; **4c**, 3265-68-7; **10a**, 61062-41-7; **10b**, 61062-42-8; **10d**, 61076-92-4; **12a**, 61062-43-9.

Chart II. ^{13} C NMR Chemical Shifts



13[a] **14**[a] **15**[b]



$\Delta(\delta)$ X = O ⟶ X = NCH_3 $\Delta(\delta)$ X = O ⟶ X = NBz
13 **14** **4a** **10a**

[a] See ref 12. [b] See ref 16. [c] The shifts for carbon atoms 2 and 9 in **10a** are very close and could be interchanged. The numbers in parentheses reflect this possibility: (+) upfield shift, (−) downfield.

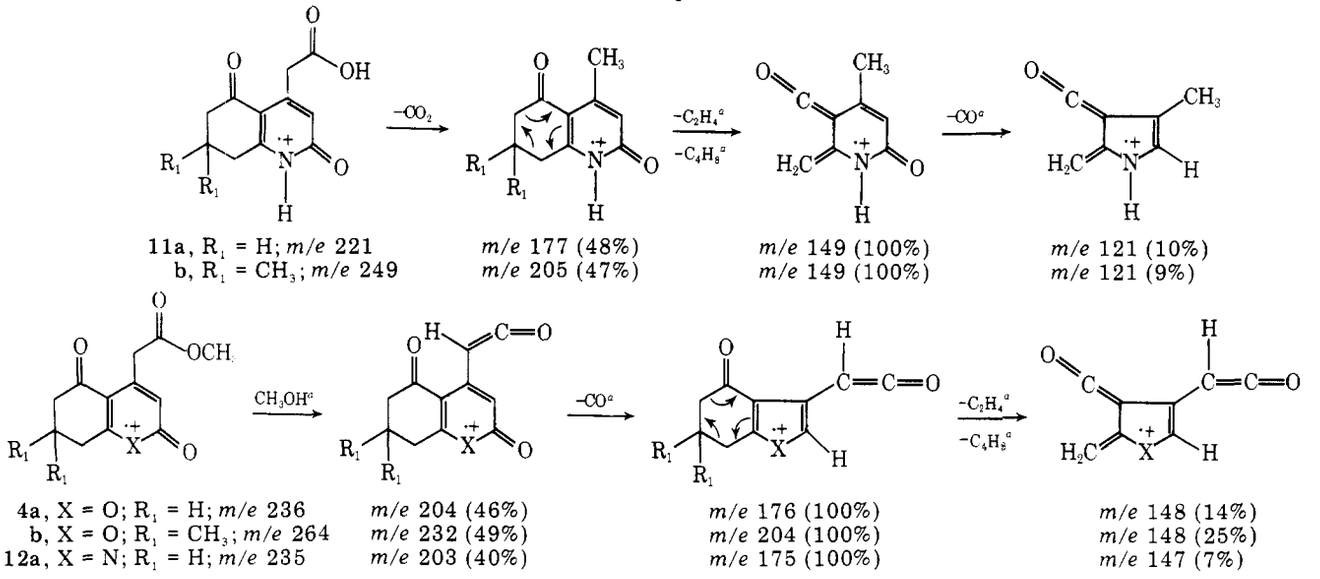
of nitrogen than either the change in carbonyl chemical shift at carbon 2 (3.1 ppm) or the change in the methine chemical shift at carbon 3 (5.8 ppm).

In a recent study, Hirsch[12] examined the ^{13}C NMR chemical shifts for the carbon atom α to the heteroatom in 1-hetero-2-cyclohexanones by comparison of the spectra of **13** and **15** with that of cyclohexanone.[12] He reported that the effect of a nitrogen heteroatom on the electron density of the carbon atoms in a six-membered heterocycle is best described as a through-bond inductive effect,[12,17,18] although the effect could also be explained from dipole-induced σ-polarization in combination with changes in nitrogen hybridization.[12] The magnitude of the substituent effect on the α carbon was O ≫ NCH_3 > NBz > NH. In the series of compounds described in Table II the substituent effect was O ≫ NBz > NH, which is in accord with the results for the saturated system.[12] This must indicate that a similar effect is influencing the electron density at the α-carbon atom (carbon 9) in the coumarin and 2-quinolone derivatives. The shifts outlined in Chart II demonstrate, at least qualitatively, that the changes in chemical shift α and β to the heteroatom in the saturated (**13** ⟶ **15**) and unsaturated (**4a** ⟶ **10a**) systems agree reasonably well.

The mass spectra of the tetrahydro-5-oxocoumarin and tetrahydro-5-oxo-2-quinolones showed a unique substituent effect on the mode of fragmentation of these heterocycles. The initial decomposition of the parent ion proceeded from the side chain attached to carbon 4. When the free acid was present (see Scheme III), as in **11a** or **11b**, the molecular ion lost the elements of carbon dioxide to provide a 4-methyl-α-pyridone (*m/e* 177, from **11a**) which then underwent a retro-Diels–Alder reaction to yield the base peak at *m/e* 149.[19] Extrusion of carbon monoxide, typical of α-pyridones,[20] then furnished the ion found at *m/e* 121 mass units.

When the side chain was substituted as a methyl ester, as in **4a**, **4b**, or **12a**, the parent ion decomposed to furnish what can best be described as a ketene intermediate by loss of methanol in either a concerted or two-step elimination process. The new fragment (from the loss of methanol) then preferentially lost the carbonyl group at C-2 to give an ion represented by the furan (*m/e* 176) in the case of **4a**, or the pyrrole (*m/e* 175) in the case of the 2-quinolone (**12a**). The tetrahydrofuran and pyrrole species then underwent a retro-Diels–Alder reaction to provide the five-membered

Scheme III. Mass Spectral Fragmentation Scheme for the Tetrahydro-5-oxocoumarin and Tetrahydro-5-oxo-2-quinolone Derivatives



11a, R_1 = H; *m/e* 221 — *m/e* 177 (48%) — *m/e* 149 (100%) — *m/e* 121 (10%)
b, R_1 = CH_3; *m/e* 249 — *m/e* 205 (47%) — *m/e* 149 (100%) — *m/e* 121 (9%)

4a, X = O; R_1 = H; *m/e* 236 — *m/e* 204 (46%) — *m/e* 176 (100%) — *m/e* 148 (14%)
b, X = O; R_1 = CH_3; *m/e* 264 — *m/e* 232 (49%) — *m/e* 204 (100%) — *m/e* 148 (25%)
12a, X = N; R_1 = H; *m/e* 235 — *m/e* 203 (40%) — *m/e* 175 (100%) — *m/e* 147 (7%)

[a] Metastables were observed.

heterocyclic ions at *m/e* 148 (from **4a** or **4b**) or at *m/e* 147 (from **12a**).

The interesting feature of the mass spectra of these tetrahydro-5-oxo compounds was the observed order of fragmentation. Thus, the 4-methyl-5-oxo-2-quinolones (formed from the free acids) lost the 2-keto group after the retro-Diels–Alder reaction in ring A, while the ketene derivatives (formed from the methyl esters) first extruded the carbonyl group and then underwent the retro-Diels–Alder reaction.

The reaction of cyclohexane-1,3-dione with dimethyl β-ketoglutarate (**1**), followed by treatment of the product with amines, furnishes a general route to 5,6,7,8-tetrahydro-5-oxo-2-quinolones, with the possibility of further functionalization via the acetic ester group at carbon atom 4. No other sequence found in the literature offers this possibility. The symmetry of dimethyl β-ketoglutarate permits this procedure to be carried out with few side products, in contrast to similar reactions performed with ethyl acetoacetate. The sequence described here appears to be a useful procedure to obtain 4-alkyl carbostyrils and work is in progress to convert the tetrahydro-5-oxo compounds to 4-alkyl-5-hydroxycarbostyrils.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and CFT-20 spectrometers with $(CH_3)_4Si$ internal standard. All mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or AEI MS 902 instrument. Infrared spectra were obtained on a Beckman IR-8 in either chloroform or KBr. Analytical TLC was performed on EM precoated sheets, silica gel F-254, 0.25 mm thickness while column chromatography was carried out with Baker Analyzed silica gel 60–200 mesh.

Dimedone, cyclohexane-1,3-dione, dimethyl β-ketoglutarate, and *N*-benzylamine were purchased from Aldrich Chemical Co. The citrate–phosphate buffer (pH 6.8) was prepared by dissolving $Na_2HPO_4 \cdot 7H_2O$ (2.60 g) and citric acid (0.82 g) in water (200 ml).

Methyl 5,6,7,8-Tetrahydro-5-oxocoumarin-4-yl Acetate (4a). Cyclohexane-1,3-dione (**2a,** 22.4 g, 0.20 mol) was dissolved in citrate–phosphate buffer (400 ml, pH 6.8) and stirred for 10 min. To this solution dimethyl β-ketoglutarate (**1**, 104.4 g, 0.60 mol) was added and after 20 min the cloudy solution became clear. The reaction mixture was stirred at room temperature for 60 days. After 20 days the mixture was seeded with **4a** and crystals precipitated from the solution. The white solid was filtered off and the filtrate allowed to stir for the remaining 40 days. Crystals were again filtered from the reaction at the end of the 60-day period. The combined precipitates were recrystallized from methanol to furnish **4a** (26.0 g) in 55% yield. An additional 7 g of **4a** could be obtained by extraction of the filtrate with chloroform, concentration to small volume, and column chromatography of the residue on silica gel: overall yield 33.0 g, 70% yield; mp 123–125 °C; UV λ_{max} (CH_3OH) 260 nm (log ε 4.06), 295 (3.74); IR ($CHCl_3$) 1739 (s), 1682 (s), and 1628 cm^{-1} (w); NMR ($CDCl_3$) δ 2.16 (m, 2 H, *J* = 6 Hz), 2.53 (t, 2 H, *J* = 6 Hz), 2.90 (t, 2 H, *J* = 6 Hz), 3.72 (s, 3 H, OCH_3), 3.80 (s, 2 H), and 6.03 (s, 1 H); mass spectrum (80 eV) *m/e* 236 (M^+, 12), 208 (6), 205 (22), 204 (46), 177 (22), 176 (100), 152 (10), 149 (18), 148 (14), 120 (6).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.28; H, 5.28.

Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxocoumarin-4-yl Acetate (4b). Dimedone (**2b,** 10.0 g, 0.071 mol), tetrahydrofuran (150 ml), methanol (20 ml), and **1** (26.5 g, 0.154 mol) were dissolved in citrate–phosphate buffer (200 ml, pH 6.8). The solution was stirred for 44 days at room temperature and then extracted with chloroform (4 × 200 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. After the chloroform solution was cooled for several days, a white, crystalline solid (**4b,** 5.41 g) precipitated and was filtered from the solution. The filtrate was concentrated under reduced pressure and the residue chromatographed on silica gel (Skelly B, benzene, ethyl acetate, gradient elution) to provide an additional 5.16 g of **4b:** combined yield of **4b** 10.57 g (56%); mp 115–116 °C (recrystallized from benzene); UV λ_{max} (CH_3OH) 263 nm (log ε 3.97), 299 (3.72); IR ($CHCl_3$) 1739 (s), 1680 (s), and 1630 cm^{-1} (w); NMR ($CDCl_3$) δ 1.12 (s, 6 H), 2.36 (s, 2 H), 2.75 (s, 2 H), 3.65 (s, 3 H), 3.80 (s, 2 H), and 5.98 (s, 1 H); mass spectrum (80 eV) *m/e* 265 (3), 264 (M^+, 15), 236 (7), 233 (13), 149 (5), 148 (25), 93 (8).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.35; H, 6.16.

4-Methyl-5,6,7,8-tetrahydro-5-oxocoumarin (4c). Cyclohexane-1,3-dione (**2a,** 20.0 g, 0.18 mol) and **1** (93.4 g, 0.53 mol) were dissolved in citrate–phosphate buffer (400 ml, pH 6.8) and the mixture was stirred at room temperature for 64 h. The reaction mixture was then heated for 21 h, after which time it was cooled and extracted with chloroform (3 × 300 ml) followed by reextraction of the aqueous layer with benzene (3 × 300 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The oily residue was chromatographed on silica gel (Skelly B, benzene, ethyl acetate, gradient elution) to provide **4a** (10.6 g, 25%) and **4c** (6.4 g, 20%). The oil (**4c**) was dissolved in water from which white crystals precipitated: mp 98–99.5 °C (lit.[5] 98 °C); UV λ_{max} (CH_3OH) 261 nm (log ε 3.99), 299 (3.63); IR ($CHCl_3$) 1739 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (m, 2 H, *J* = 6 Hz), 2.45 (s, superimposed on a triplet, 5 H), 2.85 (t, 2 H, *J* = 6 Hz), and 5.96 (s, 1 H); mass spectrum (80 eV) *m/e* 178 (M^+, 43), 150 (72), 122 (100).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.67. Found: C, 67.42; H, 5.97.

Conversion of 4a to 4c by Acid Hydrolysis. Methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a,** 5.0 g, 0.021 mol) was dissolved in a solution of hydrochloric acid (12 N, 40 ml) and glacial acetic acid (50 ml) and the solution was refluxed for 24 h. The acidic solution was made basic (pH 8) with sodium hydroxide (3 N) and then extracted with chloroform (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to yield **4c** (1.5 g, mp 98 °C, 41% yield), identical in all respects with **4c** isolated in the previous experiment.

Preparation of Ethyl 1,2,3,4,5,6,7,8-Octahydro-9-methyl-1,8-dioxoxanthen-9-yl Acetate (9a) and (4c) from Ethyl Acetoacetate (8) and Cyclohexane-1,3-dione at pH 6.8. Cyclohexane-1,3-dione (60 g, 0.54 mol) was dissolved in citrate–phosphate buffer (1200 ml, pH 6.8). To the resulting cloudy solution, **8** (200 g, 1.54 mol) was added over a 2-min period. The turbid solution became clear and the mixture was allowed to stir at room temperare for 45 days. TLC indicated the presence of **4c** after 1 day. A small portion (200 ml) of the reaction mixture was taken out after 3 days and extracted with chloroform to furnish, after chromatography, a small amount of **4c,** mp 98 °C. The remainder of the mixture was allowed to stir until the 45-day period had ended. Crystals of **9a,** which formed in the reaction after 30 days, were filtered from the solution and were recrystallized from methanol: mp 160 °C; UV λ_{max} (CH_3OH) 304 nm (log ε 3.67), 229 (4.17); IR (KBr) 1730 (s), 1668 (s), 1610 (m), and 1125 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7 Hz), 1.63 (s, 3 H), 1.98 (m, 4 H, J = 6 Hz), 2.37 (q, 8 H, J = 6 Hz), 3.33 (s, 2 H), and 3.97 (q, 2 H, J = 7 Hz); mass spectrum (80 eV) m/e 318 (M^+, 1). The yield was 50% and no attempt has been made to maximize it.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.95; H, 7.18.

Methyl 1-Benzyl-5,6,7,8-tetrahydro-5-oxo-2-quinolon-4-yl Acetate (10a). In a round-bottom flask (100 ml) equipped with a magnetic stirrer, Dean-Stark trap, and condenser were placed **4a** (3.0 g, 0.013 mol), benzylamine (13.6 g, 0.13 mol), and dry benzene (30 ml). The reaction mixture was refluxed for 17 h, cooled, and then extracted with hydrochloric acid (3 × 50 ml of 10%), aqueous potassium carbonate (3 × 50 ml), and water (2 × 50 ml), respectively. The organic phase was dried (K_2CO_3) and filtered over Norit (1 g) and the solvent was removed under reduced pressure to provide a brown oil. The oil was chromatographed over silica gel (benzene, methanol, gradient elution) to yield **10a** (1.70 g, 45% yield): mp 106.5–110.0 °C (from Skelly B–ethyl acetate, 1:1); UV λ_{max} (CH_3OH) 282 nm (log ε 4.09), 3.08 (sh), 322 (sh); IR ($CHCl_3$) 1739 (m) and 1664 cm^{-1} (s); NMR ($CDCl_3$) δ 2.05 (m, 2 H, J = 6 Hz), 2.43 (t, 2 H, J = 6 Hz), 2.87 (t, 2 H, J = 6 Hz), 3.70 (s, 3 H), 3.83 (s, 2 H), 5.36 (s, 2 H), 6.37 (s, 1 H), and 7.23 (m, 5 H); mass spectrum (80 eV) m/e (rel intensity) 326 (44), 325 (M^+, 100), 324 (15), 294 (37), 293 (31), 266 (16), 265 (35), 235 (7), 234 (36), 219 (14).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.84; H, 5.69; N, 4.24.

The yields in refluxing benzene were generally quite low; however, merely stirring a 1:1 mixture of **4a** and benzylamine at room temperature in methanol for 6 days, followed by column chromatography on silica gel, provided 65–80% yield of **10a.** Some starting material was also recovered.

Methyl 1-Benzyl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-yl Acetate (10b). This reaction was carried out in refluxing benzene (15 ml) with **4b** (3.83 g, 0.014 mol) and benzylamine (3.10 g, 0.029 mol) under analogous conditions to that described in the previous experiment. A red oil was obtained which was chromatographed on silica gel (benzene, methanol gradient elution) to furnish **10b** (2.22 g, 45%) and **10c** (0.407 g, 8.5%).

The quinolone derivative (**10b**) was obtained as a white, crystalline solid: mp 141–143 °C (from Skelly B–ethyl acetate, 1:1); UV λ_{max} (CH_3OH) 282 nm (log ε 4.29), 308 (sh), and 323 (sh); IR ($CHCl_3$) 1739 (m) and 1662 cm^{-1} (s); NMR ($CDCl_3$) δ 0.93 (s, 6 H), 2.32 (s, 2 H), 2.72 (s, 2 H), 3.68 (s, 3 H), 3.88 (s, 2 H), 5.40 (s, 2 H), 6.38 (s, 1 H), and 7.25 (m, 5 H); mass spectrum (80 eV) m/e 353 (M^+, 100); CI mass spectrum (NH_3) m/e (rel intensity) 371 (M + 18, 1.9), 356 (7), 355 (30), 354 (M + 1, 100), 353 (2.5), 297 (26), and 296 [(M + 1) − 58, 45].

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.57; N, 3.66.

The structure of **10c** was deduced by comparison of the ^1H NMR with that of **10b** and the mass spectrum of **10c:** m/e (rel intensity) 429 (12), 428 (M^+, 35), 413 (4), 410 (4), 395 (7), 323 (8), 322 (25), 321 (53), 307 (4), 306 (12), 295 (14), 294 (8), 293 (15), 280 (8), 204 (8), 107 (3), 106 (20), 92 (12), 91 (100).

1-Benzyl-4-methyl-5,6,7,8-tetrahydro-5-oxo-2-quinolone (10d). *N*-Benzylamine (0.61 g, 0.0057 mol) and **4c** (1.01 g, 0.0057 mol) were dissolved in benzene (30 ml) and the resulting solution was refluxed for 24 h. The water was removed by means of a Dean-Stark trap. The reaction mixture was cooled and an additional amount of benzylamine (0.63 g) was added. The reaction mixture was refluxed for another 6 h and cooled and the benzene removed under reduced pressure. A red oil remained, which was subjected to column chromatography on silica gel (benzene, methanol, gradient elution) to remove decomposition products. The yellow glassy oil was rechromatographed on silica gel (CH_2Cl_2) to remove **4c** and then distilled, bp 119 °C (0.1 Torr), to provide **10d** (1.13 g, 74% yield) which later crystallized from methanol: mp 81–83 °C; UV λ_{max} (CH_3OH) 281 nm (log ε 4.2); IR ($CHCl_3$) 1680 (s) and 1660 cm^{-1} (s); NMR ($CDCl_3$) δ 1.90 (m, 2 H, J = 6 Hz), 2.43 and 2.50 (overlapping triplet and singlet, 5 H), 2.82 (t, 2 H, J = 6 Hz), 5.36 (s, 2 H), 6.33 (s, 1 H), and 7.23 (m, 5 H); Mass spectrum m/e 267 (M^+).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.35; H, 6.30; N, 5.04.

5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-ylacetic Acid (11a). Diethyl ether (100 ml), methanol (50 ml), and the 5-oxocoumarin derivative **4a** (11.31 g, 0.048 mol) were placed in a round-bottom flask (250 ml) equipped with magnetic stirrer, condenser, and gas inlet tube. Ammonia gas was bubbled into the solution for 15 min until a chalky white precipitate formed, at which time TLC indicated that starting material was no longer present. The white solid was filtered from the solution, washed with aqueous HCl (10%), and recrystallized from aqueous hydrochloric acid (10%) to provide white needles of **11a** (9.55 g, 90% yield): mp 272 °C dec; UV λ_{max} (CH_3OH) 280 nm (log ε 4.18) and 317 (sh); IR (KBr) 2985 (s), 1718 (s), 1639 (s), 1586 cm^{-1} (sh, m); mass spectrum (80 eV) m/e (rel intensity) 221 (M^+, 3), 205 (8), 203 (3), 177 (48), 176 (5), 175 (8), 150 (10), 149 (100), 121 (10), 94 (9), 93 (16), 44 (35).

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found C, 59.70; H, 5.07; N, 6.50.

5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-ylacetic Acid Hydrochloride (11b). The 7,7-dimethyl-5-oxocoumarin derivative **4b** (1.85 g, 0.007 mol) was dissolved in a solution of anhydrous ether (50 ml) and methanol (25 ml) in a setup analogous to the previous experiment. Ammonia (anhydrous) gas was bubbled in for 45 min at which time TLC indicated that **4b** had been completely consumed. A white precipitate was filtered from the reaction, dissolved in water, and reprecipitated by addition of aqueous, *concentrated* hydrochloric acid. The crystals of **11b** (1.38 g, 74% yield) resembled clear plates: mp 237 °C (changes from white to brown crystals which are stable to >289 °C); UV λ_{max} (CH_3OH) 282.5 nm (log ε 4.14) and 317 (sh); IR (KBr) 3479 (s), 3409 (sh, s), 2894 (s), 1716 (s), 1637 (s), 1496 (sh, s), 1466 (w); mass spectrum (80 eV) m/e (rel intensity) 249 (M^+, 3) 231 (3), 205 (49), 204 (6), 203 (10), 177 (6), 150 (11), 149 (100), 121 (9), 93 (12), and 44 (23).

Anal. Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64. Found: C, 54.50; H, 5.42.

Yields up to 80% were also obtained from this reaction.

This 2-quinolone was converted to its methyl ester (see below).

Methyl 5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-yl Acetate (12a). The acid **11a** (5.23 g, 0.024 mol) was dissolved in methanolic HCl and the solution refluxed for 20 h. The methanol was removed under reduced pressure and the residue was taken up in methylene chloride. The organic layer was washed with aqueous potassium carbonate (3 × 50 ml) and water (50 ml) and then dried ($MgSO_4$). The methyl ester (**12a**) crystallized from the solution as a white powder (2.92 g, 52% yield), mp 223–224 °C. An additional 2.2 g of **12a** could be obtained by column chromatography over silica gel: overall yield 92%; UV λ_{max} (CH_3OH) 281 nm (log ε 4.28), 303 (sh), and 317 (sh); IR (KBr) 3400 (broad), 1733 (s), 1632 (s), 984 (m), and 712 cm^{-1} (m); NMR ($CDCl_3$) δ 2.13 (m, 2.5 H, J = 6 Hz), 2.52 (t, 2 H, J = 6 Hz), 2.95 (t, 2 H, J = 6 Hz), 3.71 (s, 3 H), 3.85 (s, 2 H), 6.20 (s, 1 H), and 13.16 (0.5 H) (addition of D_2O reduced the integration of the signal at δ 2.13 to two protons and eliminated the signal at δ 13.16); mass spectrum (80 eV) m/e (rel intensity) 235 (M^+, 21), 204 (20), 203 (40), 176 (30), 175 (100), 149 (7), 148 (7), 147 (7), 120 (8), 119 (10).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.50; H, 5.31; N, 5.91.

Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-yl Acetate (12b). This reaction was run under the conditions described above with **11b** (0.650 g, 0.0026 mol) and methanolic HCl (40 ml). The same workup procedure provided **12b** as a white powder (0.416 g, 61% yield). The yield could be increased to 80% by chromatography of the mother liquors on silica gel. **12b:** mp 199–201 °C; UV λ_{max} (CH_3OH) 281 nm (log ε 4.22), 302 (sh), and 316 (sh); IR (KBr); 1730 (s), 1660 (very strong), 1606 (w), 1421 (s), and 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 6 H, also a broad band integrating for 1 H appeared in this region), 2.37 (s, 2 H), 2.83 (s, 2 H), 3.67 (s, 3 H), 3.84 (s, 2 H), and 6.22 (s, 1 H);

mass spectrum *m/e* (rel intensity) 263 (M^+, 20), 232 (27), 231 (73), 217 (27), 216 (94), 204 (27), 203 (100), 189 (13), 188 (73), 175 (20), 147 (10).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.05; H, 6.45; N, 5.21.

Registry No.—**1**, 1830-54-2; **2a**, 504-02-9; **2b**, 126-81-8; **8**, 141-97-9; **9a**, 61062-44-0; **10c**, 61104-46-9; **11a**, 61062-45-1; **11b**, 61062-46-2; **12b**, 61062-47-3.

References and Notes

(1) J. Oehldrich, J. M. Cook, and U. Weiss, *Tetrahedron Lett.*,in press.
(2) (a) S. Yang and J. M. Cook, *J. Org. Chem.*, **41**, 1903 (1976); (b) S. Yang, M. Mueller-Johnson, J. Oehldrich, D. Wichman, J. M. Cook, and U. Weiss, *ibid.*, in press; (c) J. Oehldrich and J. M. Cook, *Can. J. Chem.*, in press.
(3) D. Yang, D. Foerst, J. Oehldrich, and J. M. Cook, *J. Org. Chem.*, **41**, 743 (1976).
(4) J. Oehldrich, O. Campos, D. Foerst, and J. M. Cook, presented at the 10th Great Lakes Regional Meeting of the American Chemical Society, Evanston, Ill., June 1976, Abstract No. 179.
(5) H. J. Roth and G. Langer, *Arch. Pharm. (Weinheim, Ger.)*, **301**, 810 (1968).
(6) J. H. Sellstedt, *J. Org. Chem.*, **37**, 1337 (1972).
(7) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, Elmsford, N.Y., 1964, p 141.
(8) We wish to thank Professor Heathcock for a generous sample of **8**. See C. Heathcock et al., *J. Org. Chem.*, **41**, 636 (1976).
(9) G. C. Levy and G. L. Nelson in "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 119.
(10) J. H. Sellstedt *J. Org. Chem.*, **37**, 1337 (1972).
(11) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972, pp 357 and 333; S. G. Levine, R. E. Hicks, H. E. Gottlieb, and E. Wenkert, *J. Org. Chem.*, **40**, 2540 (1975); H. O. House, A. V. Prabhuand, and W. V. Phillips, *J. Org. Chem.*, **41**, 1209 (1976).
(12) J. A. Hirsch and E. Havinga, *J. Org. Chem.* **41**, 455 (1976).
(13) The harsh conditions (Δ, trifluoroacetic acid) employed in this reaction, when carried out by Sellstedt and co-workers (see ref 10), led to the 9,9-dimethylxanthene derivative (**9b**).
(14) (a) A. Curran, *J. Chem. Soc.*, 975 (1976), and references cited therein; (b) K. Nakawaga, S. Yoshizaki, N. Murakami, and M. Hideo, Japan Kokai 7570 374; *Chem. Abstr.*, **84**, 43878u (1976); K. Nakagawa and U. Minoru, Japan Kokai 7606 971; *Chem. Abstr.*, **84**, 180076v (1976).
(15) M. Guthzeit, *Chem. Ber.*, **26**, 2795 (1893); L. Smith and R. Kelly, *J. Am. Chem. Soc.*, **74**, 3300 (1952); R. Wiley, L. Knabeschick, A. Duchwall, and N. Smith, *ibid.*, **76**, 625 (1954), and references cited therein.
(16) V. Vogeli and W. von Phillipsborn, *Org. Magn. Reson.*, **5**, 551 (1973).
(17) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967).
(18) J. A. Hirsch, "Concepts in Theoretical Organic Chemistry", Allyn and Bacon, Boston, Mass., 1974, Chapters 4 and 6, and references cited therein.
(19) K. Biemann, "Mass Spectrometry", McGraw-Hill, New York, N.Y., 1962, p 106; H. E. Audier, S. Bory, M. Fetizon, and N. T. Anh, *Bull. Soc. Chim. Fr.*, 4002 (1966).
(20) D. M. Clugston and D. B. MacLean, *Can. J. Chem.*, **44**, 781 (1966).

Alkylations of 1-(4-Chlorophenyl)-3-ethoxy-1*H*-isoindole

Marcel K. Eberle,* Leszek Brzechffa, and William J. Houlihan

Department of Research, Sandoz Inc., East Hanover, New Jersey 07936

Received October 3, 1975

Abstraction of the benzylic proton from 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1a**) with sodium hydride gave the corresponding carbanion which was alkylated with a variety of alkyl halides to give the imino esters **1d–i**, **5** while oxidation yielded **1b**. Hydrolysis led to the lactams **2d–i**, **6** and 2-(4-chlorobenzoyl)benzoic acid ethyl ester, respectively. The tetrazolo compounds **4e–l** were prepared via the intermediates **3e–i**. Heating of **6** resulted in the formation of **7a** which could be reduced to the amine **7b**. From the imino ester **5** the triazole **9** was prepared.

Recently we have described the preparation of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1a**) and its conversion to 1-amino-4-(4-chlorophenyl)phthalazine[1] via reaction with hydrazine. As a continuation of our efforts to explore the synthetic usefulness of **1a** we have prepared[2] a variety of 3-alkylated derivatives and converted them to the novel tricyclic systems.

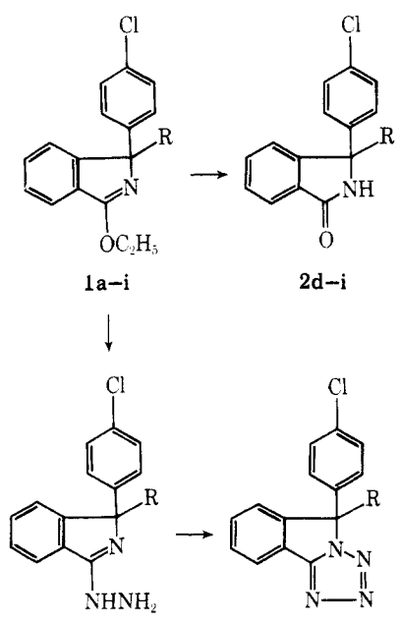
The proton of the benzylic position of **1a** was abstracted by sodium hydride in an aprotic solvent (DMF) to generate the corresponding carbanion of **1a**. Treatment of the carbanion with oxygen led to the crystalline hydroxy imino ester **1b** in 43% yield. For structure proof, **1b** was hydrolyzed to the known 2-(4-chlorophenyl)benzoic acid ethyl ester.[3] Spectral data indicated that **1b** exists in the cyclic form; no absorption for the open benzophenone tautomer was observed in the IR spectrum of **1b** (Nujol) in the region between 1650 and 1700 cm^{-1}. Furthermore, the UV spectrum of **1b** closely resembles that of the known methoxy homologue **1c**.[4]

The carbanion of **1a** on treatment with alkyl halides, e.g., methyl iodide, propargyl bromide, allyl bromide, isopropyl iodide, and benzyl chloride, gave the alkylated analogues **1e–i** (Tables II–IV). Reaction with methylene chloride led in good yield to **1d**, which was found to be inert in the presence of excess of carbanion.

The substituted 1-alkyl-1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindoles **1d–i** on treatment with hydrochloric acid in ethanol were hydrolyzed to the corresponding 1-alkyl-1-(4-chlorophenyl)phthalimidines **2d–i**.[5a,b]

While the reaction of 1-(4-chlorophenyl)-3-ethoxy-1*H*-

Scheme I



1a–i **2d–i**

3e–i **4e–i**

a, R = H
b, R = OH
c, R = OCH_3
d, R = CH_2Cl
e, R = CH_3
f, R = $CH_2C{\equiv}CH$
g, R = $CH_2CH{=}CH_2$
h, R = i-C_3H_7
i, R = $CH_2C_6H_5$