Reactions of Some Acylquinolones with Diazomethane[1]

J. W. HUFFMAN AND J. H. CECIL[2]

Department of Chemistry and Geology, Clemson University, Clemson, South Carolina 29631

Received November 19, 1968

Several acylquinolones have been treated with diazomethane and the products characterized principally by spectroscopic means. 3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) gave 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**), 1-methyl-2-isobutyryl-4,8-dimethoxy-2-quinolone (**9**), and 3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6a**). 3-Isovaleryl-4-hydroxy-8-methoxy-2-quinolone (**2b**) gave 3-(2-oxo-3-methylpentyl)-4,8-dimethoxy-2-quinolone (**3b**), 3-(2-oxo-3-methylpentyl)-2,4,8-trimethoxyquinoline (**11**), and 3-isobutyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6b**). 3-Isobutyryl-4-hydroxy-2-quinolone (**2d**) gave 3-(2-oxo-3-methylbutyl)-4-ethoxy-2-quinolone (**3c**), 3-isobutyryl-4-methoxy-2-quinolone (**4b**), 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone (**6c**), and 3-isopropyl-3-hydroxy-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**13**). Treatment with hydrochloric acid gave 3-isopropylfuro[2,3-*b*]-4-quinolone (**14**) from **13**, and **3b** from **11**.

In previous work directed toward a general synthesis of furoquinoline alkaloids such as lunacrine (**1**), the reactions of the 3-acylquinolones **2a** and **2b** with diazomethane have been reported to give **3a** and **3b** (Chart I), the result of insertion into the side chain in addition to O methylation.[1] Reduction of these quinolones and cyclization leads to isobutyl furoquinolines rather than the desired isopropyl derivatives. In an attempt to take advantage of this homologation reaction, the 3-isobutyryl-4-hydroxy-2-quinolones **2c** and **2d** were treated with diazomethane, in the expectation that suitable precursors to the lunacrine alkaloids could be obtained.

Treatment of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with ethereal diazomethane gave a mixture from which two compounds, A and B, were isolated. Compound A, $C_{15}H_{17}NO_4$, shows a split carbonyl band in the infrared with absorption at 5.98 and 6.20 μ. The 6.20-μ absorption is at somewhat longer wavelength than that generally associated with 2-quinolones[3] (6.02–6.10 μ), however, the nmr spectrum is lacking the resonances due to the deshielded C-5 proton in a 4-quinolone.[4,5] This spectrum is essentially the same as that of the starting quinolone (**2c**), with a barely resolved pair of singlets centered about 4.01 ppm in place of the methoxyl singlet at 4.00 ppm. On the basis of these data, A must be 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**), the result of simple O methylation.

Compound B has an empirical formula of $C_{16}H_{17}NO_3$ and the infrared spectrum shows carbonyl absorption at 6.11 μ, at somewhat lower wavelength than that generally associated with 4-quinolones (6.13–6.17 μ),[3] however the nmr spectrum has the highly deshielded C-5 proton resonance at 8.10 ppm indicative of a 4-quinolone.[4,5] This C-5 proton is the X portion of the ABX multiplet, (J_{ortho} = 8 Hz and J_{meta} = 2 Hz) and in addition to the AB multiplet at 6.95–7.30 ppm, the balance of the nmr spectrum of B shows a vinyl doublet (J = 1 Hz) at 6.95 ppm, a methoxyl singlet, an N-methyl singlet, the typical isopropyl pattern with a methyl doublet (J = 7 Hz) at 1.35 ppm, and a rather deshielded methine multiplet centered about 3.32 ppm. Irradiation of the methine multiplet collapsed the doublet at 6.95 to a singlet, indicating that the isopropyl group is adjacent to the vinyl proton. The ultraviolet spectrum of B is virtually identical with that reported for anhydrobalfouridine; which has been shown to have the assigned structure (**5**) by its reduction to lunacrine (**1**).[6] Although the melting points of B and anhydrobalfouridine only differ by 1°, the mixture melting point[7] of the two is depressed, the infrared spectra are not identical and on the basis of these data B is assigned the structure 3-isopropyl-8-methoxy-9-methylfuro-[2,3-*b*]-4-quinolone (**6a**). It was originally thought that **6a** may have been anhydrobalfouridine on the basis of the chemical shift (6.95 ppm) of the furyl proton. It has been suggested that α protons of furoquinolones of general structure **7** have a chemical shift of 7.20–7.24 ppm while the β protons are in the range 6.98–7.01 ppm. The synthesis of the furoquinolone (**6a**) with α-proton resonance at 6.95 ppm indicates that these assignments are probably reversed. Apparently, in these 4-quinolone systems, the β protons are deshielded very strongly by the 4-carbonyl, while the α protons are in the normal range for those in simple furans.

House, *et al.*,[8] have reported the use of both methanol and boron trifluoride as catalysts for the diazomethane homologation of ketones. These catalysts were therefore employed in the reaction of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with diazomethane. Large volumes of methanol gave a mixture, from which, after repeated chromatography on alumina, were isolated two compounds. One of these was 3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6a**), while the second compound, $C_{16}H_{19}NO_4$, shows carbonyl absorption in the infrared at 5.95 and 6.20 μ. The ultraviolet spectrum of this compound is similar to that of 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**); however, the spectrum shifts in neither acid or base, while that of **4a** shifts in base (Scheme I). The nmr spectrum has a pair of singlets at 3.92 ppm with an area corresponding to nine protons, whereas **4a** has a pair of singlets at 4.01 ppm with an area corresponding to six protons. This methanol catalyzed product must therefore be 1-

(1) This work was supported in part by Grant GM-08731 and Research Career Program Award 1-K3-GM-5433 from the National Institute of General Medical Sciences, and should be considered as paper IV in a series "The Furanoquinoline Alkaloids." Previous paper: J. W. Huffman, S. P. Garg, and J. H. Cecil, *J. Org. Chem.*, **31**, 1276 (1966).

(2) Abstracted in part from a dissertation presented by J. H. Cecil in partial fulfillment of the requirements for the Ph.D. degree, Clemson University, Dec 1968.

(3) (a) M. F. Grundon, N. J. McCorkindale, and M. N. Rodgers, *J. Chem. Soc.*, 4282 (1955); (b) M. F. Grundon and N. J. McCorkindale, *ibid.*, 2177 (1957).

(4) S. Goodwin, J. H. Shoolery, and L. F. Johnson, *J. Amer. Chem. Soc.*, **81**, 3065 (1959).

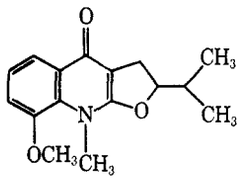
(5) A. V. Robertson, *Aust. J. Chem.*, **16**, 451 (1963).

(6) H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, **82**, 4395 (1960).

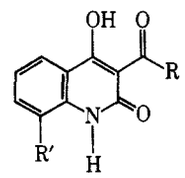
(7) Appreciation is expressed to Dr. Henry Rapoport for a sample of anhydrobalfouridine.

(8) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

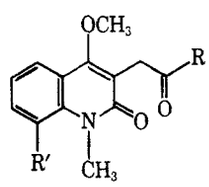
CHART I



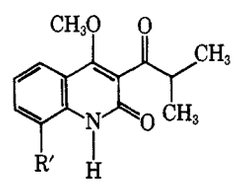
1



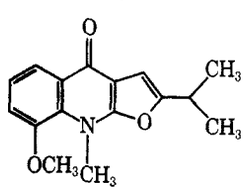
2a, R = *i*-Bu; R¹ = H
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = OCH_3
d, R = *i*-Pr; R¹ = H



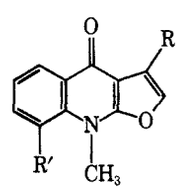
3a, R = *i*-Bu; R¹ = H
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = H



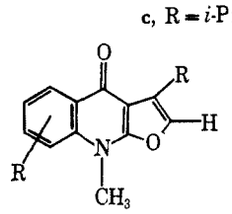
4a, R = OCH_3
b, R = H



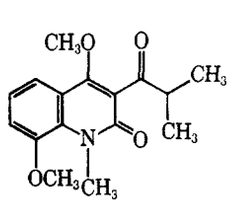
5



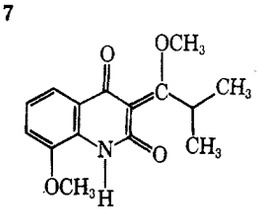
6a, R = *i*-Pr; R¹ = OCH_3
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = H



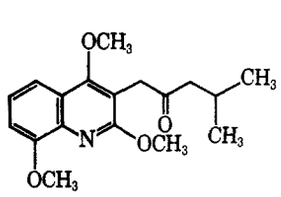
7



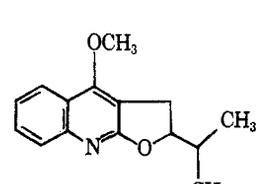
9



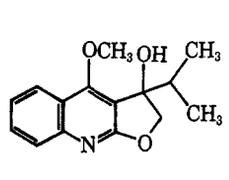
10



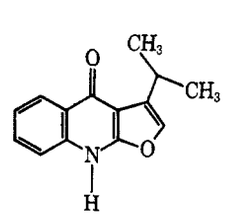
11



12



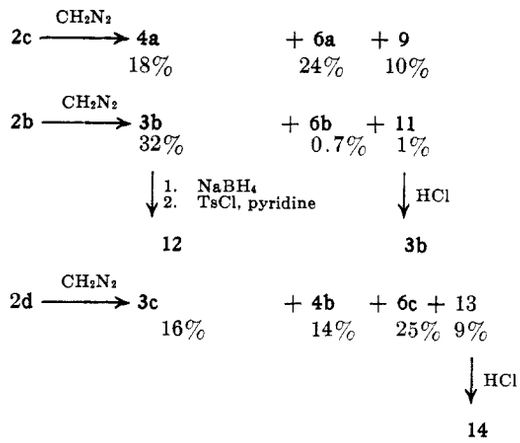
13



14

methyl-2-isobutyryl-4,8-dimethoxy-2-quinolone (**9**), the result of N,O dialkylation.

SCHEME I



The use of boron trifluoride as a catalyst for the reaction of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with diazomethane gave a bright yellow solid, which, when dissolved in methanol, gave a yellow solution that turned colorless as it was warmed. From this colorless solution, only the starting quinolone (**2c**) could be obtained. Moreover, while the ultraviolet spectra in methanol of **2c** and the diazomethane product were identical, the infrared spectra were not. Owing to the instability of this material it could not be characterized completely; however, it appears that this compound is the enol ether (**10**).

Since the isobutyrylquinolones did not give homologation to any appreciable extent, it was felt that a repetition of the reaction of 3-isovaleryl-4-hydroxy-8-methoxy-2-quinolone (**2b**) with diazomethane might lead to the simple O-alkylated acylquinolone. However, the major product of the treatment of **2b** with ethereal diazomethane was the inserted quinolone (**3b**), identical with that previously reported.[1]

Two other compounds, C and D, were also isolated in small quantity from this reaction. Compound C has an empirical formula of $C_{17}H_{19}NO_3$ and its infrared, ultraviolet, and nmr spectra were quite similar to those of the furoquinolone (**6a**). Compound C is thus assigned the structure 3-isobutyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6b**). The nmr spectrum of C is in complete agreement with this assignment, showing in addition to a vinyl proton multiplet at 7.02 ppm, the typical isobutyl pattern of a broadened doublet at 2.71 ppm, a multiplet at 1.8–2.5 ppm, and a doublet at 0.97 ppm. These are assigned, respectively, to the methylene, methine, and methyl protons of the isobutyl group.

The infrared spectrum of D has absorption at 5.87 μ assigned to the side chain carbonyl, and medium intensity absorption at 6.15 μ which is probably due to aromatic absorption, since the nmr spectrum shows no evidence supporting a 4-quinolone structure. The ultraviolet spectrum of D has much the same shape as that of the 2-quinolone (**3b**), but is altered on acidification and does not shift in basic solution. The nmr spectrum of D shows singlets at 3.82, 3.93, 4.05, and 4.10 ppm with an area ratio equivalent to eleven protons. These data, particularly the shift of the ultraviolet spectrum in acidic solution, suggests that D is a trimethoxyquinoline. Treatment of D with hydrochloric acid gives the 2-quinolone (**3b**), and consequently D must be 3-(2-oxo-3-methylpentyl)-2,4,8-trimethoxyquinoline (**11**).

In order to explore further the nature of these reactions of 3-acylquinolones, 3-isobutyryl-4-hydroxy-2-quinolone (**2d**) was also treated with diazomethane to give a mixture from which two compounds, E and F, were isolated. Compound E has an empirical formula of $C_{15}H_{15}NO_2$, and the infrared spectrum has the medium intensity carbonyl absorption at 6.15 μ typical of a 4-quinolone. The nmr spectrum of E is the same as that of furoquinoline (**6a**), however the methoxyl singlet is absent. Compound E is therefore 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone (**6c**).

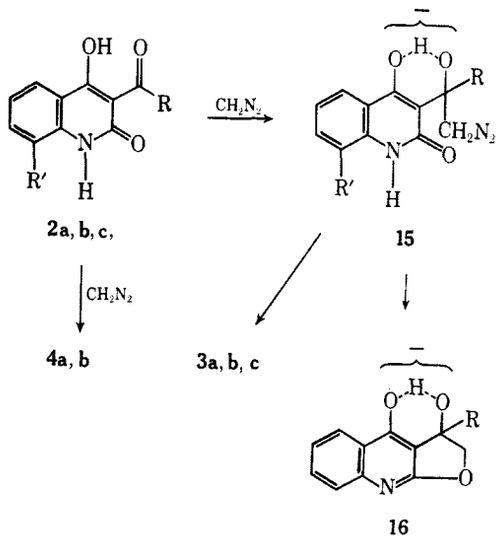
Compound F has the empirical formula $C_{15}H_{17}NO_3$, corresponding to the addition of two methylene units. The infrared spectrum shows strong 2-quinolone carbonyl absorption at 6.0 μ and nonconjugated carbonyl absorption at 5.85 μ. The nmr spectrum has a three-proton methoxy singlet at 3.92 ppm and a two-proton methylene singlet at 3.88 ppm in addition to aromatic and isopropyl signals. On the basis of these data F is assigned the structure 3-(2-oxo-methylbutyl)-4-methoxy-2-quinolone (**3c**), the result of both homologation and O methylation. Reduction of **3c** with sodium borohydride afforded the corresponding alcohol which on treatment with *p*-toluensulfonyl chloride–pyridine gave 2-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]-quinolone (**12**), by analogy with the synthesis of the isobutyl analog.[1] The spectral data for both these compounds (see Experimental Section) were in agreement with the assigned structures. There was insufficient material to complete the synthesis of demethoxylunacrine, and attempts to repeat this sequence gave variable results (*vide infra*).

When, however, the diazomethane reaction with 3-isobutyryl-4-hydroxy-2-quinolone (**2c**) was repeated under apparently identical conditions, the inserted quinolone (**3c**) could not be isolated although both thin layer chromatography and spectral measurements indicated that it was present. However, a third compound, G, was obtained. The empirical formula of G is $C_{14}H_{15}NO_3$, corresponding to the addition of one methylene group, and the infrared spectrum is almost identical with that of quinolone (**3c**), having peaks at 5.87 and 6.1 μ. The nmr spectrum, however, shows only one singlet at 4.04 ppm with an area corresponding to three protons plus aromatic and isopropyl resonances, and compound G is therefore 3-isobutyryl-4-methoxy-2-quinolone (**4b**), the result of simple O methylation.

In other reactions of **2c** with diazomethane, again under apparently identical conditions, neither the inserted nor the noninserted quinolones were isolated; however, the furoquinolone (**6c**) and another new compound, H, could be obtained. Compound H has an empirical formula of $C_{15}H_{17}NO_3$, indicating addition of two methylene units, and the infrared spectrum has strong hydroxyl absorption at 3.13 μ. The ultraviolet spectrum of H shifts in acid, but not in base, and the nmr spectrum does not have the deshielded C-5 proton multiplet, ruling out a 4-quinolone structure and suggesting that H is a quinoline. There is also present in the nmr a broadened singlet due to the hydroxyl proton at 5.45 ppm, which is removed by shaking with D_2O. The presence of a one-proton multiplet at 2.7 ppm and two doublets (J = 7 Hz) at 1.10 and 0.76 ppm indicates the presence of an isopropyl group attached to an asymmetric center. A simple AB quartet (J = 13 Hz) at 4.33 ppm with a superimposed methoxyl singlet at 4.22 ppm suggests that H is 3-hydroxy-3-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**13**). Confirmation of this structural assignment was accomplished by the conversion of **13** by treatment with dilute hydrochloric acid into 3-isopropylfuro[2,3-*b*]-4-quinolone (**13**).[9] The nmr spectrum of **13** is identical with that of 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone **6c**, with the exception of the absence of the N-methyl singlet.

The product distributions obtained in these reactions of 3-acyl-4-hydroxy-2-quinolones are summarized in Scheme I, and although the above data indicate that their course is quite complex, the observed products may all be explained in terms of the generally accepted mechanism for the reaction of diazomethane with aryl alkyl ketones.[8] In Scheme II the over-all course of

SCHEME II



these reactions is summarized and several generalizations may be made concerning the interaction of these quinolones with diazomethane. First, direct O methylation is competitive with the addition of diazomethane to the carbonyl group in the case of the 3-isobutyryl compounds (**2c, d**). However, in the reactions of the 3-isovaleryl ketones (**2a, b**),[1] only the homologated ketones could be isolated. This is easily explained in terms of steric hindrance in the vicinity of the carbonyl group caused by the α-isopropyl group in **2a** and **b**, as opposed to the methylene group in **2c** and **d**.[10]

In the intermediate (**15**) arising from the addition of diazomethane to the carbonyl group, hydrogen bonding between the C-4 hydroxyl and the alkoxide moiety in the side chain must be invoked in order to explain the exclusive formation of linear furoquinolones in these reactions since it has been observed that nucleophilic displacement reactions of this type normally give the angular isomer.[11] Intermediate **15** may decompose by one of two paths, either migration of the aryl residue to give the homologated ketone[8] or cyclization to afford an intermediate (**16**) which may then give rise to the

(9) E. A. Clarke and M. F. Grundon [*J. Chem. Soc.*, 438 (1964)] have carried out similar reactions in this series.

(10) The possibility that O methylation precedes addition to the carbonyl group seems remote in view of the work of M. E. C. Biffin, L. Crombie, and J. A. Eldridge, *J. Chem. Soc.*, 7500 (1965).

(11) J. W. Huffman and L. E. Browder, *J. Org. Chem.*, **29**, 2598 (1964).

various furoquinolones obtained from these reactions. The former path appears to be favored when R = isobutyl and the latter when R = isopropyl, and these differences must be caused by subtle differences in the conformation of intermediate **15** caused in turn by differences in the bulk of the isopropyl and isobutyl groups.

Experimental Section[12]

3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) was prepared by the method reported earlier for the synthesis of 3-isovaleryl-8-methoxy-2-quinolone[1] (**2b**). From 12.0 g of 4-hydroxy-8-methoxy-2-quinolone and 25.0 ml of isobutyryl chloride was obtained 12.33 g (75.2%) of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**). Recrystallization from methylene chloride–hexane gave white needles: mp 166–167°; ir 6.05 μ; uv max, neutral and acid, 248 mμ (log ϵ = 4.30), 308 (4.12), 316 (4.13), base, 242 (4.49), 267 sh (4.03), 310 (3.96); nmr δ 7.0–7.9 m (Aryl H), *ca.* 4.3 m (CH), 4.00 s (OCH_3), 1.22 d (J = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane, mp 169–170°.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.53; H, 5.67; N, 5.28.

Reaction of 3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone with Diazomethane. A.—To a slurry of 5.00 g of the above quinolone (**2c**) in 100 ml of absolute ether was added 100 ml of a solution of diazomethane in dry ether made from 8.00 g of nitrosomethylurea. A trace of methanol was added and the slurry stirred overnight at room temperature. Reducing the volume of solution gave 1.31 g of recovered starting material. Boiling the solution to dryness gave a red glass which was chromatographed on Merck acid-washed alumina.

Elution with methylene chloride–hexane 1:1 gave 0.93 g (24.3%) of **3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone** (**6a**), recrystallized from methylene chloride–hexane as colorless needles: mp 130–131°, a mixture melting point with anhydrobalfouridine[7] was 110–120°; ir 6.11 μ (C=O); uv max, neutral and base, 235 mμ (log ϵ = 4.40), 241 sh (4.45), 247 (4.53), 262 sh (3.86), 295 sh (3.66), 303 (3.73), 327 sh (3.80), 339 (3.98), 354 (3.93), acid, 248 (4.59), 303 (3.60), 328 sh (3.71), 340 (3.88), 354 (3.88); nmr δ 8.10 q (J_{ortho} = 8 Hz, J_{meta} = 2 Hz, C-5 H), 6.95–7.30 (Ar H), 6.95 d (J = 1 Hz =CH),4.01 s (OCH_3), 3.83 s (NCH_3), *ca.* 3.3 m (CH), 1.35 d (J = 7 Hz, isopropyl). Irradiation of the multiplet at 3.3 collapsed the doublet at 6.95 to a singlet. The analytical sample was recrystallized from methylene chloride–hexane, mp 130.0–130.5°.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.21; N, 5.07.

Elution with methylene chloride gave 0.68 g (17.5%) of **3-isobutyryl-4,8-dimethoxy-2-quinolone** (**4a**), crystallized from methylene chloride–hexane: mp 183–186°; ir 5.98 (C=O) and 6.20 μ (amide C=O); uv max, neutral and acid, 225 mμ (log ϵ = 4.10), 253 (4.22), 287 (3.69), base 253 (4.36), 275 sh (3.84); nmr δ 7.0–7.8 (Ar H), 4.01 (OCH_3, six protons), 3.50 m (CH), 1.27 d (J = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane as colorless plates, mp 189–191°.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.31; H, 6.23; N, 5.08.

B.—The diazomethane reaction was repeated with 7.00 g of quinolone (**2c**) in 100 ml of methanol and 100 ml of an ether solution of diazomethane from 20.0 g of nitrosomethylurea. Boiling the solution to dryness gave a red glass which, after being chromatographed three times on Merck acid-washed alumina, gave 0.77 g (10.0%) of **1-methyl-3-isobutyryl-4,8-dimethoxy-2-quinolone** (**9**). Crystallization from hexane gave white needles: mp 61–63°; ir 5.95 (C=O) and 6.20 μ (amide C=O); uv max neutral, acid, base, 232 mμ (log ϵ = 4.55), 258 (4.41), 291 (3.93); nmr δ 7.1–7.6 (Ar H), 3.92, 3.92 s (NCH_3, OCH_3, nine protons), 3.28 m (CH), 1.22 d (J = 7 Hz, isopropyl). The analytical sample was recrystallized from hexane as colorless plates, mp 68–69°.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.24; H, 6.72; N, 4.82.

C.—The diazomethane reaction was repeated with a solution of 2.00 g of the quinolone (**2c**) and 1 ml of boron trifluoride etherate in 50 ml of methylene chloride. To this solution was added diazomethane from 4.0 g of nitrosomethylurea in 40 ml of dry ether. The solution was allowed to stir overnight, washed with sodium bicarbonate and water, dried, and boiled to dryness, giving 1.97 g (93.6%) of the cross-conjugated *enol ether* (**10**). attempted recrystallization of this yellow compound from methanol gave colorless solutions on warming, from which only the starting quinolone (**2c**) could be obtained. All other attempts to purify this compound gave only **2c**: ir 6.10 μ (C=O); nmr δ 7.1–7.3 m (Ar H), 4.00, 4.10 (OCH_3), 1.34 d (J = 6 Hz, isopropyl).

Reaction of 3-Isovaleryl-4-hydroxy-8-methoxy-2-quinolone with Diazomethane.—To a solution of 4.00 g of the above quinolone (**2b**) in 100 ml of absolute ether was added a trace of methanol and 150 ml of an ether solution of diazomethane from 8.00 g of nitrosomethylurea. The solution was allowed to stir overnight. Filtration gave 0.42 g of **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**), identical with an authentic sample.[1] Boiling the solution to dryness gave a red glass which was chromatographed on Merck acid-washed alumina.

Elution with methylene chloride gave 0.17 g of solid material. Dissolving this material in hexane and cooling to 5° gave 0.025 g (0.6%) of 9-methyl-8-methoxy-3-isobutylfuro[2,3-*b*]-4-quinolone (**6b**): mp 125–127°; ir 6.15 μ (C=O); uv max, neutral and base, 235 mμ (log = ϵ 4.40), 241 sh (4.45), 247 (4.53), 262 sh (3.86), 295 sh (3.66), 303 (3.73), 327 sh (3.80), 339 (3.98), 354 (3.93), acid, 248 (4.59), 303 (3.60), 328 sh (3.71), 340 (3.88), 354 (3.88); nmr 8.16 m (C-5 H), 7.1–7.4 m (Ar H), 7.02 m (=CH), 4.12 s (OCH_3), 3.90 s (NCH_3), 2.71 d (J = 7 Hz, CH_2), 1.8–2.5 m (CH), 0.97 d (J = 6 Hz, isopropyl). The analytical sample recrystallized from hexane as colorless needles, mp 126–127°.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.61; H, 6.84; N, 4.85.

Cooling the hexane mother liquors from the above crystallizations to −15°, followed by immediate filtration, gave 0.045 g (1.0%) of **3-(2-oxo-4-methylpentyl)-2,4,8-trimethoxyquinoline** (**11**): mp 62–64; uv max, neutral and base, 246 mμ (log ϵ = 4.66), 247 sh (3.73), 280 (3.73), 290 (3.65), 315 (3.35), 328 (3.28), acid 247 (4.58), 257 sh (4.29), 283 (3.70), 315 (3.62), 333 (3.46); nmr 6.9–7.7 m (Ar H), 4.10, 4.05, 3.93 s (OCH_3), 3.82 s (=CCH_2CO), 1.8–2.5 m (CH_2CH), 0.95 d (J = 7 Hz, isopropyl). The analytical sample recrystallized from hexane as colorless needles, mp 62–63°.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.95; H, 7.18; N, 4.34.

Heating this 2-methoxyquinoline (**11**) on a steam bath with 10% hydrochloric acid gave **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**).

Further repeated chromatography of the remaining material from the diazomethane reaction gave only an additional 0.97 g (31.6% total) of **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**).

3-Isobutyryl-4-hydroxy-2-quinolone (**2d**) was prepared in the same manner as the 8-methoxy analog (**2c**). From 15.0 g of 4-hydroxy-2-quinolone and 35.0 ml of isobutyryl chloride there was obtained 12.7 g (59%) of a white solid, mp 198–201°. Recrystallization from ethyl acetate–cyclohexane gave light yellow needles: mp 221–224° (lit.[13] mp 222–224°); ir 6.0 μ; uv max, neutral and acid, 220 mμ (log ϵ 4.25), 237 (4.44), 306 (4.04).

Reaction of 3-Isobutyryl-4-hydroxy-2-quinolone with Diazomethane. A.—To a slurry of 4.72 g of the above quinolone (**2d**) in 75 ml of absolute ether at 0–5° was added 100 ml of a solution of diazomethane in dry ether made from 8.00 g of nitrosomethylurea. A trace of methanol was added and the slurry stirred overnight at room temperature. Reducing the volume of solution gave 1.15 g of recovered starting material. Boiling the solution to dryness gave a red glass which was chromatographed on 80 g of Merck acid-washed alumina.

(12) Melting points were determined on a Kofler hot stage or a Hershberg melting point apparatus and are uncorrected. Infrared spectra were taken as potassium bromide disks using a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were taken in methanol, using a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using deuteriochloroform as a solvent unless otherwise noted, and tetramethylsilane as an internal reference. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) N. S. Vul'fsan and R. B. Zhurin, *Zh. Vses. Khim. Obshch. im D. I. Mendeleeva*, **5**, 352 (1960); *Chem. Abstr.*, **54**, 24733 (1960).

Elution with absolute ether yielded 0.96 g (25.0%) of **9-methyl-3-isopropylfuro[2,3-*b*]-4-quinolone** (**6c**), recrystallized from methylene chloride–hexane as colorless needles: mp 139.0–139.7°; ir 6.15 μ (C=O); uv max, neutral and base, 240 mμ (log ϵ = 4.23), 252 (4.20), 260 (4.23), 285 (3.23), 295 (3.23), 328 sh (3.67), 339 (3.79), 353 sh (3.71), acid *ca.* 243 (4.57), 257 sh (3.88), 305 (3.47), 318 (3.69), 333 sh (3.74), 343 (3.82), 355 sh (3.77); nmr ($CDCl_3$), δ 8.45 m (C-5 H), 7.1–7.75 (Ar-H), 6.98 d (J = 1 Hz, =CH), 3.72 s (NCH_3), 3.34 *m* (**CH**), 1.38 d (*J* = 7 Hz, isopropyl); nmr (d_6-DMSO) δ 8.28 m, 7.2–7.8 m, 7.41 s, 3.85 s, 3.25 m, 1.31 d (*J* = 6.5 Hz). The analytical sample was recrystallized from methylene chloride–hexane, mp 140.0–140.5°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.49; H, 6.40; N, 5.83.

Elution with methylene chloride–isopropyl alcohol 20:1 gave 0.65 g (16.2%) of **3-(2-oxo-3-methylbutyl)-4-methoxy-2-quinolone** (**3c**). Crystallization from methylene chloride–hexane gave white needles: ir 5.85 μ (C=O) and 6.0 μ (amide C=O); uv max, neutral and acid, 231 mμ (log ϵ = 4.28), 245 sh (3.80), 264 (3.59), 271 (3.70), 279 (3.65), 314 (3.44), 324 (3.61), 336 (3.55); nmr δ 7.2–7.9 m (Ar H), 3.92 s (OCH_3), 3.88 s (Ar **CH_2**), 2.89 m (**CH**), 1.25 d (*J* = 7 Hz, isopropyl). Recrystallization from methylene chloride–hexane gave the analytical sample, mp 182–183°.

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.18; H, 6.39; N, 5.68.

B.—The diazomethane reaction was repeated with 10.00 g of the quinolone (**2d**) and diazomethane from 20.00 g of nitrosomethylurea. Reducing the volume of solution gave 3.80 g of recovered starting material and a red glass which was chromatographed on Merck acid-washed alumina. Elution with methylene chloride gave 0.59 g (9.9%) of the furoquinolone (**6c**). Elution with methylene chloride–isopropyl alcohol 20:1 gave 1.50 g of a white solid which by tlc was a mixture of the inserted and noninserted acylquinolones. Several recrystallizations from methylene chloride–hexane gave 0.91 g (13.8%) of **3-isobutyryl-4-methoxy-2-quinolone** (**4b**): ir 5.87 μ (C=O) and 6.1 μ (amide C=O); uv max, neutral and acid, 228 mμ (log ϵ = 4.40), 273 (3.70), 278 (3.71), 328 (3.63), base 236 (4.41), 273 sh (3.69), 338 (3.50); nmr δ 7.1–8.1 m (Ar H), 4.04 s (OCH_3), 3.40 m (**CH**), 1.31 d (*J* = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane, mp 158–160°.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71: Found: C, 68.79; H, 6.18; N, 5.65.

C.—The diazomethane reaction was repeated with 3.00 g of the quinolone (**2d**) and diazomethane from 6.00 g of nitrosomethylurea, followed by chromatography on Merck acid-washed alumina. Elution with benzene gave 0.56 g (17.9%) of the furoquinolone (**6c**). Elution with benzene–isopropyl alcohol 100:1 gave 0.31 g (9.2%) of **3-hydroxy-3-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline** (**13**). Crystallization from methylene chloride–hexane gave a white amorphous solid: mp 157–159°; ir 3.13 μ (OH); uv max, neutral and base, 228 mμ (log ϵ = 4.52), 239 sh (4.45), 264 (3.67), 274 (3.73), 285 (3.67), 305 sh (3.41), 314 (3.63), 328 (3.67), acid 238 (4.49), 293 (3.87), 314 sh (3.77); nmr δ 7.2–8.1 m (Ar H), 5.45 s (**OH**), 4.33 AB (*J* = 13 Hz, OCH_2), 4.22 s (OCH_3), 2.7 m (**CH**), 1.10 d (*J* = 7 Hz, isopropyl), 0.76 d (*J* = 7 Hz, isopropyl). Recrystallization from methylene chloride–hexane gave the analytical sample, mp 158–159°.

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.77; H, 6.68; N, 5.32.

3-Isopropylfuro[2,3-*b*]-4-quinolone (**14**).—To 0.140 g of 3-hydroxy-3-isopropyl-4-methoxy-2, 3-dihydrofuro [2,3-*b*] quinoline (**13**) was added 20 ml of 10% hydrochloric acid. After 1.5 hr of heating on a steam bath, the solution was cooled, filtered, and the solid recrystallized from methanol–water yielding 0.050 g (41.0%) of colorless cubes: mp 245–258°; ir 6.12 μ; uv max, neutral, 238 mμ (log ϵ = 4.42), 249 (4.36), 257 (4.39), 282 (3.40), 294 (3.40), 320 sh (3.80), 332 (3.92), 340 sh (3.84), acid, 241 (4.68), 257 sh (4.10), 286 (3.33), 299 sh (3.57), 318 sh (3.78), 334 (3.88), 342 sh (3.80), base 232 (4.29), 255 sh (4.52), 262 (4.59), 307 sh (3.53), 320 sh (3.70), 331 sh (3.82), 342 (3.93), 355 (3.85); nmr (d_6-DMSO) δ 8.33 m (C-5 H), 7.2–7.8 m (Ar H), 7.41 d (*J* = 1 Hz, =CH), 3.28 m (**CH**), 1.33 d (*J* = 6 Hz, isopropyl). The analytical sample was recrystallized from methanol–water, mp 245–247°.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.09; H, 5.90; N, 6.02.

3-(2-Hydroxy-3-methylbutyl)-4-methoxy-2-quinolone.—To a solution of 0.22 g of **3c** in 50 ml of 95% ethanol was added 2.00 g of sodium borohydride. The solution was heated at reflux 5 hr, concentrated to about one-half its volume, and diluted with water. The aqueous suspension was extracted with four portions of methylene chloride, the extracts were combined and dried, and the solvent was removed. Crystallization from hexane–ethyl acetate gave 0.14 g (63%) of colorless needles: mp 156–157°; ir 6.10 μ (C=O); uv max, neutral acid, base and 231 mμ (log ϵ = 4.39), 245 sh (3.98), 272 (3.82), 280 (3.77), 311 sh (3.63), 324 (3.76), 336 sh (3.63); nmr δ 7.2–7.9 (ArH), 4.02 s (**OH**), 4.00 s (OCH_3), 3.90 t (CH_2), 3.69 (**CH**OH), *ca.* 1.8 m (**CH**-$(CH_3)_2$), 1.05 d (*J* = 7 Hz, isopropyl). The analytical sample, mp 166–167°, was crystallized from hexane–ethyl acetate.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.35; N, 5.36. Found: C, 69.24; H, 7.50; N, 5.20.

2-Isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**12**).—To a solution of 0.170 g of 3-(2-hydroxy-3-methylbutyl)-4-methoxy-2-quinolone in 3 ml of dry pyridine was added 0.70 g of *p*-toluenesulfonyl chloride. The reaction mixture stood at room temperature 72 hr, was diluted with water, and the precipitated solid collected. The filtrates were made strongly basic with 10% sodium hydroxide and extracted with four portions of methylene chloride. The organic extracts were dried and the solvents removed at reduced pressure leaving a brown oil which was combined with original precipitate, dissolved in 1:1 hexane–methylene chloride and chromatographed on Merck acid-washed alumina. Elution with the same solvents gave 0.050 g (32%) of **12**; uv, neutral and base, 229 mμ (log ϵ = 4.56), 232 sh (4.44), 252 (3.74), 262 (3.75), 272 (3.78), 283 (3.70), 309 (3.48), 323 (3.51), acid 216 (4.44), 234 (4.47), 239 sh (4.45), 293 (3.93), 304 (3.88), 317 (3.76); nmr δ 7.1–8.1 (ArH), 4.40 m (**OCH**), 4.10 (OCH_3), 3.35 m (CH_2), 195 m $(CH_3)_2$, 0.98 d (*J* = 7 Hz, isopropyl). Recrystallization from hexane–methylene chloride gave the analytical sample, mp 125–126°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.85; H, 7.21; N, 5.93.

Registry No.—Diazomethane, 334-88-3; **2c**, 19765-48-1; **3c**, 19765-49-2; **4a**, 19779-44-3; **4b**, 19765-50-5; **6a**, 19765-51-6; **6b**, 19765-52-7; **6c**, 19765-53-8; **9**, 19765-54-9; **11**, 19765-55-0; **12**, 19765-56-1; **13**, 19765-57-2; **14**, 19765-58-3; 3-(2-hydroxy-3-methylbutyl)-4-methoxy-2-quinolone, 19765-59-4.