the peaks in the spectra do not seem to support such an acceleration of the rate, and this explanation appears less acceptable to us as a result. It would be helpful to have the results of ^{13}C labeling in both the fundamental and the phenylated systems to answer this new question.

It is interesting that I loses H easily in its mass spectral fragmentation, a route not found in the other compounds. Perhaps the loss of larger groups is made less favorable by the higher degree of substitution of the more stable pyridine ring in I, and the only important route available remains the loss of H. It would be of some interest to know the origin of this hydrogen, or the extent of hydrogen scrambling before the loss, but the technique applied here does not permit an answer at the moment.

Experimental Section

General.—Melting points, reported uncorrected, were recorded on a Thomas–Kofler apparatus. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. High-resolution mass-spectrometric elemental analyses were obtained on an MS-902 instrument at the Research Triangle Institute, Research Triangle Park, N. C.

3,5-Diphenyl-2,4,6-tris(*p*-fluorophenyl)pyridine (I) was prepared from *p*-fluorobenzaldehyde (Aldrich Chemical Co.) and 4′-fluorodeoxybenzoin (Aldrich) by the method of Weiss.[17] The crystals which separated from the reaction mixture were recrystallized from acetic acid–methanol, mp 215–217°.

Anal. Calcd for $C_{35}H_{22}F_3N$: C, 81.86; H, 4.32; monoisotopic mol wt, 513.1704. Found: C, 81.72; H, 4.29; mol wt, 513.1701.

2,5-Bis(*p*-fluorophenyl)-3,6-diphenylpyrazine (II).—Crude 4′-fluorobenzoin, prepared from 4′-fluorodeoxybenzoin by a standard procedure,[18] was heated with ammonium acetate according to Japp and Wilson's procedure.[19] The product was recrystallized from acetone, mp 248–248.5°.

Anal. Calcd for $C_{28}H_{18}F_2N_2$: C, 79.98; H, 4.31; monoisotopic mol wt, 420.1437. Found: C, 80.11; H, 4.20; mol wt, 420.1433.

5,6-Diphenyl-3-*p*-fluorophenyl-1,2,4-triazine (III) was prepared from benzil, *p*-fluorobenzhydrazide, and ammonium acetate by a literature procedure[20] and recrystallized from ethanol, mp 144.5–145.5°.

Anal. Calcd for $C_{21}H_{14}FN_3$: C, 77.05; H, 4.31; monoisotopic mol wt, 327.1170. Found: C, 76.93; H, 4.20; mol wt, 327.1170.

Mass Spectra.—The mass spectra were recorded on an AEI MS-902 instrument at the Research Triangle Institute and a Hitachi RMU-6E instrument at the University of North Carolina. The approximate resolution was 800 for the MS-902 and 500 for the RMU-6E. The samples were introduced by the direct probe at temperatures of 150, 170, and 120° for compounds I, II, and III, respectively.

Registry No.—I, 22158-33-4; II, 22158-34-5; III, 22158-35-6.

Acknowledgment.—This work was partially supported by the University of North Carolina Materials Research Center through Contract SD-100 with the Advanced Research Projects Agency. The MS902 mass spectrometer was purchased through funds made available by the Special Research Resources Branch of the National Institutes of Health. Spectra on this instrument were obtained by Dr. David Rosenthal and Mr. Fred Williams, to whom we express our thanks for their kind assistance.

(17) M. Weiss, *J. Amer. Chem. Soc.*, **74**, 200 (1952).

(18) W. S. Ide and J. S. Buck, *Org. Reactions*, **4**, 269 (1948).

(19) F. R. Japp and W. H. Wilson, *J. Chem. Soc.*, **49**, 829 (1886).

(20) P. V. Laakso, R. Robinson, and H. P. Vandrawela, *Tetrahedron*, **1**, 103 (1957).

Alcoholysis of 4-Chloroquinolines to 4(1H)-Quinolones[1]

NED D. HEINDEL AND STEPHEN A. FINE

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

Received August 6, 1969

4-Chloroquinolines bearing a carbethoxy or nitro substituent in the 3 position have been found to undergo "alcoholysis" to 4-quinolones. The intermediacy of a 4-alkoxyquinoline has been indicated. Both the initial substitution of the 4-chloroquinoline and the cleavage of the 4-alkoxyquinoline have been found to be acid-catalyzed.

During our studies on the preparation of some 4-chloroquinolines, required as intermediates in the synthesis of potential antimalarial agents, it was discovered that purification of the crude halo heterocycles by recrystallization from alcohols often resulted in the generation of 4-(1H)-quinolones, even when thoroughly anhydrous alcohols were employed as solvents.[2] Nucleophilic displacement of "activated" halo heterocycles was originally demonstrated by Banks to be an acid-catalyzed process presumably proceeding *via* a protonated iminium salt.[3–5] Although a few particularly reactive substrates are known which undergo noncatalyzed ethanolysis,[4,6] the overall conversion of a 4-Cl into a 4-quinolone in pure alcohol appears to be without precedent.

As we have noted,[7] 4-chloroquinolines lacking special electron-withdrawing functions at C-3 are totally inert to alcoholysis unless traces of HCl are present, in which case excellent yields of 4-alkoxyquinolines are obtained. However, with more activated halo heterocycles, such as 3-carbethoxy-4-chloro- and 3-nitro-4-chloroquinolines, one might anticipate an autocatalyzed displacement of halogen by alcohol. Several examples are known where autocatalytic attack of ROH has been indicated.[4,6] That the formation of quinolones from our chloroquinolines is definitely an acid-autocatalyzed effect has been established by experiments in which 1 equiv of tertiary amine base was added as proton

(1) Supported in part by Contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command. This paper represents Contribution No. 723 from the Army Research Program on Malaria.

(2) Alcohols are often recommended as solvents for recrystallization of haloquinolines. See, for example, H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heyningen, *J. Amer. Chem. Soc.*, **69**, 371 (1947).

(3) C. K. Banks, *ibid.*, **66**, 1127 (1944).

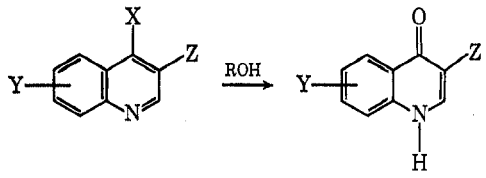
(4) G. Illuminati, *Advan. Heterocycl. Chem.*, **3**, 295 (1963).

(5) An excellent review of the entire field of displacements from azines is found in R. G. Shepherd and J. L. Fedrick, *ibid.*, **4**, 145 (1965).

(6) N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1194 (1954).

(7) N. D. Heindel and S. A. Fine, *J. Heterocycl. Chem.*, **6**, 961 (1969).

TABLE I



Run	Benzenoid substituents	Registry no.	X	Z	ROH	Time of reflux, hr	Quinoline product
1	6-OMe	22931-71-1	Cl	COOEt[a]	EtOH	24	84[b]
2	6-OMe		Cl	COOEt	EtOH	2	55[c]
3	6-OMe		Cl	COOEt	EtOH + 1 equiv Et_3N	24	No reaction
4	6-OMe	22931-72-2	OEt	COOEt	EtOH	24	No reaction
5	6-OMe		OEt	COOEt	EtOH + 1 equiv HCl	24	77
6	6-OMe		OEt	COOEt	EtOH + 0.1 equiv HCl	24	18
7	6-OMe, 7-Cl	22931-73-3	Cl	COOEt	EtOH	2	70[d]
8	7-Cl	22931-74-4	Cl	NO_2[e]	EtOH	1	100[e]
9	7-Cl		Cl	NO_2	*i*-PrOH	6	94
10	7-Cl	19499-19-5	Cl	COOEt[a]	EtOH	5	93[f]
11	7-Cl		Cl	COOEt	MeOH	3	90
12	7-Cl		Cl	COOEt	*i*-PrOH	3	87[g]
13	7-Cl	86-98-6	Cl	H	EtOH (or MeOH)	24	No reaction
14	7-Cl		Cl	H	EtOH + 0.05 equiv HCl	24	*h*

[a] Starting material prepared as described in ref 7. [b] Reported in C. F. Geschicter and L. M. Rice, U. S. Patent 2,719,848 (1955); *Chem. Abstr.*, **50**, 12119 (1956). [c] In addition, 12% ethyl 4-ethoxy-6-methoxy-3-quinolinate and 33% recovered starting material were obtained. [d] Reference 2. [e] Quinolone and chloroquinoline were prepared as described in A. R. Surrey and R. A. Cutler, *J. Amer. Chem. Soc.*, **73**, 2413 (1951). [f] Prepared by the method of C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946). [g] Also isolated were 59% isopropyl chloride, 38% diisopropyl ether, and 40% HCl; see Experimental Section for details. [h] Only isolated product was 84% 4-ethoxy ether.

scavenger. Thus, although 24-hr reflux in anhydrous, acid-free ethanol resulted in an 84% conversion of ethyl 4-chloro-6-methoxy-3-quinolinate into the quinolone (see Table I, run 1), the same procedure carried out with 1 equiv of triethylamine present resulted in complete recovery of starting material.

In a related study, Cutler and Surrey[8] have shown that 4,7-dichloroquinoline and anhydrous glacial acetic acid undergo an acid-catalyzed conversion into quinolone and acetic anhydride. The authors obtained indirect evidence that the mechanism involved the intermediacy of a 4-acetoxyquinolinium species, which underwent attack by solvent (HOAc) at the carbonyl carbon to expell the protonated quinolone leaving group and produce Ac_2O.

Similarly, a 4-alkoxyquinoline seems to be the most probable transient in our solvolysis of 4-haloquinolines. It is recognized that such alkyl heterocyclic ethers are readily cleaved by dilute aqueous hydrochloric acid,[9] and the claim has been made,[10] although it rests on tenuous experimental grounds, that the alkyl fragment is evolved as RCl. On short contact with refluxing ethanol, a low yield of the ether could indeed be isolated (run 2) and converted upon further heating into the quinolone if a proton source were present (see runs 4–6). Undoubtedly, the best synthesis of these alkyl heterocyclic ethers is the sodium alkoxide reaction with the halo substrate.[11]

The data indicate that proton availability is a requirement for both the formation and for the cleavage of the 4-alkoxyquinolines. Thus, with the less activated 4,7-dichloroquinoline (runs 13 and 14), no ether results unless a trace of HCl is present. The acid necessary to produce ethers is apparently available by an autocatalytic effect for the more activated 3-substituted haloquinolines (runs 1 and 3), and these ethers require acid, although not in stoichiometric amounts, to experience fragmentation. It is worthy of note that, in run 6, 0.10 equiv of HCl promoted the formation of almost 0.2 equiv of quinolone. Under these reaction conditions (refluxing anhydrous alcohol), the ethers of 4,7-dichloroquinoline are stable to at least a 5-equiv excess of HCl.

Two principle mechanisms have been recognized for cleavage of alkoxy heterocycles: nucleophilic attack at the saturated carbon with concomitant alkyl oxygen cleavage or nucleophilic attack at hetero ring site ("addition–elimination") with cleavage of the aryl–oxygen bond.[12] Obviously, with aqueous acid cleavage these pathways are not easily distinguishable. With aryl thiols as nucleophiles, Illuminati and Gilman[13] reported that, although the quinolones were formed in both cases, 2-ethoxyquinoline experienced alkyl–oxygen scission (forming EtSAr), but 4-ethoxyquinoline underwent ring-carbon attack (generating EtOH).

This fact, coupled with the claim that alkoxypyridines bearing additional conjugated electron-withdrawing functions such as cyano and nitro fragment by aryl–oxygen cleavage owing to the enhanced electrophilicity of the hetero ring carbon,[12] might suggest that this mechanism should operate in our 4-ethoxy 3-substituted quinolines. Indeed, electronic effects in the parent 4-chloroquinolines which appear to facilitate their conversion into quinolones are in the direction of enhancing ring-carbon electrophilicity. Thus the greater electron–withdrawing effect of $-NO_2$ than of

(8) R. A. Cutler and A. R. Surrey, *J. Amer. Chem. Soc.*, **72**, 3394 (1950).

(9) R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, p 153.

(10) T. Sandmeyer, *Chem. Ber.*, **19**, 2655 (1886).

(11) W. J. Adams and D. H. Hey, *J. Chem. Soc.*, 1521 (1951).

(12) H. Meislich in "Pyridine and Derivatives," part 3, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 678–680.

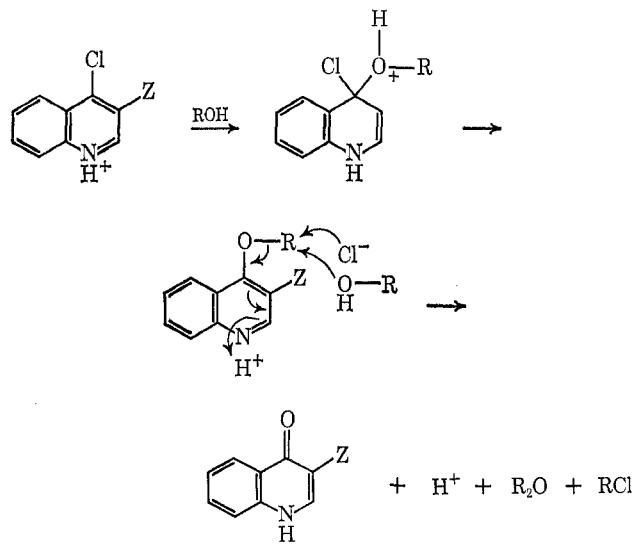
(13) G. Illuminati and H. Gilman, *J. Amer. Chem. Soc.*, **71**, 3349 (1949).

–COOEt[14] is reflected in the more facile quinolone production seen in run 8 *vs.* run 10. Similarly, under identical conditions the 6-methoxy-7-chloro system (run 7) results in a greater conversion into quinolone product than the 6-methoxy substrate (run 2).

Vapor phase chromatographic analysis of the mother liquors of these ethanolysis experiments invariably displayed the presence of the alkyl chloride and the dialkyl ether. Since initial displacement of the 4-Cl by alcohol must produce 1 equiv of HCl, it might be argued that alkyl chloride and ether detected in the medium result from a postdisplacement reaction of HCl with the solvent. This possibility was rigorously tested by a "blank" run.

The alcoholysis of ethyl 4,7-dichloro-3-quinolinate with 2-propanol was monitored by vpc analysis and by titration (run 12). In addition to 87% quinolone product, 59% isopropyl chloride, 38% isopropyl ether, and 40% HCl were detected. As a blank run, a solution of dry HCl gas in 2-propanol was prepared at 1.2 times the concentration of HCl which would have been present if all of the 4-Cl in the alcoholysis experiment were evolved into the medium. This blank was heated under the same conditions of temperature and time as the product run, and, although vpc analyses showed the presence of some alkyl chloride and dialkyl ether, the amounts were low in comparison with the product run. The data given in Table I for run 12 have been corrected for "blank" results.

It would therefore appear that a logical mechanism for the solvolysis of 4-chloroquinolines by anhydrous alcohols involves displacement of the 4 halogen by solvent and subsequent nucleophilic attack of Cl^- or alcohol at the alkyl carbon of the protonated heterocyclic ether. It is apparent that the electron-withdrawing substituents at C-3 function primarily to make the protonated quinolyl fragment a better leaving group



in the alkyl–oxygen ether cleavage. Since 4-chloroquinolines lacking pyridine ring substituents can still undergo ether formation if traces of HCl are present,[7] these C-3 substituents are obviously not necessary to permit nucleophilic attack at C-4. The COOEt and NO_2 undoubtedly assist in halide ion displacement, since no added acid is necessary in these systems to effect ether formation.

(14) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1968, p 241.

Experimental Section[15]

Ethyl 4,7-Dichloro-6-methoxy-3-quinolinate.—A mixture of 0.24 mol of ethyl 7-chloro-4-hydroxy-6-methoxy-3-quinolinate[2] and phosphorus oxychloride (67 g, 0.43 mol) was heated on a steam bath for 1.5 hr, allowed to cool, and added with stirring to 1200 g of crushed ice and 120 ml of concentrated NH_4OH. The mixture was extracted thoroughly with chloroform and the extract was washed with water. Evaporation of solvent from the dried ($MgSO_4$) chloroform extract followed by recrystallization of the crude product from cyclohexane afforded pale yellow crystals (44 g, 66%), mp 114–116°. Another recrystallization from cyclohexane furnished the analytical sample, mp 116–117°.

Anal. Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.69; Cl, 23.62. Found: C, 52.23; H, 3.79; Cl, 23.78.

The other 4-chloroquinolines used in this study have been prepared previously (see Table I for references).

Ethyl 4-Ethoxy-6-methoxy-3-quinolinate.—Ethyl 4-chloro-6-methoxy-3-quinolinate (8.0 g, 0.029 mol) was added to a solution prepared by dissolving 0.60 mol of sodium in 50 ml of absolute ethanol. The stirred mixture was refluxed for 2 hr, cooled, and poured into 300 ml of water. The mixture was extracted with ether, and the ethereal extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual orange oil was distilled *in vacuo* to yield 55% pale yellow oil: bp 160° (0.05 mm); ir (neat) 1722 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 0.95 (s, 1, H_2), 2.03 (q, 1, J_o = 8 Hz, J_p = 1.5 Hz, H_8) 2.10 (m, 2, H_5 and H_6), 5.62 (two q, 4, $OCH_2CH)_3$, 6.08 (s, 3, OCH_3), and 8.52 (two t, 6, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.70; H, 6.24; N, 5.36.

Reaction of 4-Chloroquinolines with Alcohols. General Procedure.—A solution of the chloroquinoline (1.0 g) in the appropriate absolute alcohol (40 ml) was refluxed (see Table I for reaction times). The reaction mixture was cooled and the insoluble quinolone was collected by suction and washed with the same alcohol used as solvent. The products were identified by melting point, mixture melting point with authentic samples of the quinolones, and comparison of the ir spectra. In every case the infrared spectrum of the product was superimposable on a spectrum of the corresponding authentic quinolone.

The same reaction conditions were utilized with the 4-ethoxy compound (runs 6–8).

All of the quinolones have been prepared previously (see Table I for references).

Reaction of Ethyl 4,7-Dichloro-3-quinolinate with 2-propanol. Vpc Analysis of Reaction Mixture.—A solution of ethyl 4,7-dichloro-3-quinolinate (1.0 g, 3.7 mmol) in 40 ml of reagent grade 2-propanol was refluxed for 3 hr and then cooled in an ice bath. After the quinolone precipitate had settled, a portion of the supernatant was withdrawn and the remainder of the reaction mixture was worked up as above.

Vpc analysis[16] of the supernatant revealed the presence of isopropyl chloride (59%) and diisopropyl ether (38%). Yields are based on the initial amount of halo quinoline and are corrected for isopropyl chloride and diisopropyl ether formed by the reaction of HCl with 2-propanol in a "blank run."

Titration of the supernatant with standardized sodium hydroxide solution showed the presence of hydrogen chloride (40%).

(15) Nmr spectra were obtained on a Varian A-60 spectrometer and are expressed in τ units with TMS = 10. Infrared spectra were run as mulled samples in Nujol on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were provided by Dr. George I. Robertson, Florham Park, N. J.

(16) Vpc analyses were obtained on a 15-ft 20% Carbowax 20M column. Authentic samples of isopropyl chloride and diisopropyl ether were used for comparison.