Anal. Calcd. for $C_{22}H_{29}O_3N_2Cl$: C, 65.2; H, 7.2; N, 6.9; Cl, 8.8. Found: C, 65.1; H, 7.3; N, 7.0; Cl, 8.6.

L-Phenylalanyl-L-leucine.—A water solution of the above ester hydrochloride (2.0 g., 0.005 mole) was hydrogenated as usual in the presence of palladium black as a catalyst. Upon concentrating to a volume of 20 ml. and adjusting the *p*H to 6.2, the peptide precipitated in form of needles; yield 1.2 g. (88%), m.p. 258–260° (reported[11] for D-phenylalanyl-D-leucine 262°), $[\alpha]^{20}D$ +4.5° (*c* 9.3%, in 0.3 *N* hydrochloric acid).

Anal. Calcd. for $C_{15}H_{22}O_3N_2$: C, 64.7; H, 7.9; N, 10.0. Found: C, 64.05; H, 7.8; N, 10.1.

L-Glutaminyl-L-leucine.—Using N-trityl-L-glutamine diethylammonium salt (4.6 g., 0.01 mole) as the starting material, N-trityl-L-glutaminyl-L-leucine benzyl ester was prepared in the same manner as was described for the phenylalanine derivative. The sirupy coupling product was detritylated[5] and debenzylated in one operation by hydrogenation in water–methanol (1:5) solution with palladium black as a catalyst. Part of the triphenylmethane precipitated during the hydrogenation and was removed together with the catalyst by filtration. The filtrate was evaporated to dryness *in vacuo*. Upon adding acetone, the free peptide precipitated while the triphenylmethane remained in solution. The peptide was recrystallized from water–alcohol; yield 0.8 g. (31%), m.p. 204–205°, $[\alpha]^{20}D$ −34.4° (*c* 2.6%, in 0.1 *N* hydrochloric acid).

Anal. Calcd. for $C_{11}H_{21}O_4N_3$: C, 59.5; H, 8.2; N, 16.2. Found: C, 59.4; H, 8.3; N, 16.3.

N-Trityl-L-asparaginylglycine Ethyl Ester.—To a solution of 1.4 g. (0.01 mole) of glycine ethyl ester hydrochloride in 25 ml. of anhydrous pyridine, cooled to 0°, was added dropwise 0.45 ml. of phosphorus trichloride, with cooling and vigorous shaking. After 3 minutes, 3.7 g. (0.01 mole) of trityl-L-asparagine was added and the solution kept at room temperature for 10 minutes and then at 80° for 3–4 hours. The solution was then poured into 250 ml. of cold 10% acetic acid and extracted three times with ether. The ether layer was washed successively with dilute acetic acid, potassium hydrogen carbonate and water, dried over sodium sulfate, and finally concentrated to 40 ml. On cooling, 1 g. (22%) of product was obtained; needles, m.p. 182°, $[\alpha]^{25}D$ −67.9° (*c* 5.7%, in chloroform).

Anal. Calcd. for $C_{27}H_{29}O_4N_3$: C, 70.6; H, 6.3; N, 9.1. Found: C, 70.5; H, 6.4; N, 9.2.

L-Asparaginylglycine.—To a suspension of 2.3 g. (0.005 mole) of the above ester in 5 ml. of ethanol was added 5.5 ml. of *N* sodium hydroxide. After 15 minutes, the solution was diluted with water and then acidified with acetic acid. The precipitate (trityl-L-asparaginylglycine, m.p. 205–207°) was detritylated with acetic acid as described[5] to yield 0.72 g. (80%) of free peptide; prisms, m.p. 215–217°, $[\alpha]^{20}D$ +54.2° (*c* 5%, in water).

Anal. Calcd. for $C_6H_{11}O_4N_3$: C, 38.4; H, 5.8; N, 22.2. Found: C, 38.5; H, 6.0; N, 22.1.

N-Tritylglycyl-L-phenylalanylglycine Ethyl Ester.—To a solution of 4.6 g. (0.01 mole) of tritylglycyl-L-phenylalanine[6] and 1.03 g. of glycine ethyl ester, in 30 ml. of tetrahydrofuran, was added 2.2 g. of N,N′-dicyclohexylcarbodiimide. The urea derivative began to precipitate within a few minutes and was filtered off (2.2 g.) after the solution had been left at room temperature for 12 hours. The filtrate was evaporated to dryness, the residue dissolved in ethyl acetate and the solution washed successively with 5% sodium carbonate, dilute acetic acid, sodium hydrogen carbonate and water, dried over sodium sulfate and evaporated to dryness. Ether was added and 4.4 g. (80%) of product obtained from the cooled solution; prisms, m.p. 140°. This same product, when prepared previously by the mixed anhydride procedure, was obtained as a sirup.[5]

Anal. Calcd. for $C_{34}H_{35}O_4N_3$: C, 74.3; H, 6.4; N, 7.6. Found: C, 74.5; H, 6.5; N, 7.7.

Glycyl-L-phenylalanylglycine.—The above product was saponified and then detritylated with acetic acid, as described,[5] to yield 1.1 g. (80%) of the free peptide with $[\alpha]D$ +15.7° (*c* 5.6%, 0.2 *N* hydrochloric acid).

Anal. Calcd. for $C_{13}H_{17}O_4N_3$: N, 14.9; NH_2/N, 5.0. Found: N, 14.9; NH_2/N, 5.2.

The specific rotation observed (+15.7°) is exactly one-half that which was previously reported for the peptide prepared by the mixed anhydride procedure.[5] In order to ascertain whether racemization had occurred or if an error was involved we have repeated our former experiment[5] and we have found $[\alpha]D$ +15.5°. Furthermore, we have prepared the peptide by a third method, namely, by the carbobenzoxy method. Carbobenzoxyglycyl-L-phenylalanylglycine ethyl ester[12] (m.p. 117–118°, $[\alpha]D$ −12.4° in ethanol) yielded on saponification carbobenzoxyglycyl-L-phenylalanylglycine, m.p. 168°, and after hydrogenation the free peptide, which exhibited $[\alpha]D$ +15.5°. Both these values are identical with that reported here and we must therefore conclude that the previously reported[5] value of $[\alpha]D$ +30.9° was in error.

(11) C. S. Smith and A. E. Brown, THIS JOURNAL, **63**, 2605 (1941).

(12) G. W. Anderson and R. W. Young, *ibid.*, **74**, 5307 (1952); J. C. Sheehan and I. I. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

ATHENS, GREECE

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Hypotensive Agents. I. The Effect of Hydrogen Bonding in Some 4-Dialkylaminoalkylaminoquinolines

BY ALEXANDER R. SURREY, GEORGE Y. LESHER, J. RICHARD MAYER AND WILLIAM G. WEBB

RECEIVED JULY 29, 1958

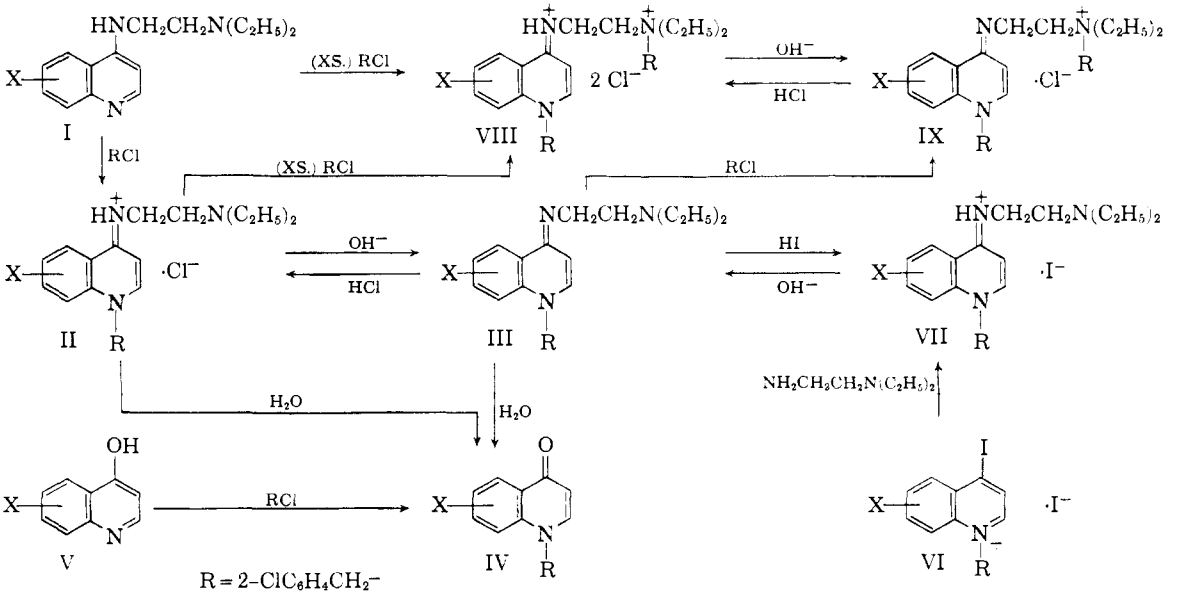
The reaction of a variety of 5-chloro- and 7-chloro-4-dialkylaminoalkylaminoquinolines with 2-chlorobenzyl chloride has been investigated. In many instances the use of one equivalent of the alkylating agent gave a 1-(2-chlorobenzyl)-quinoline derivative. Evidence for intramolecular hydrogen bonding in many of these 4-dialkylaminoalkylaminoquinolines as well as in the corresponding 1-(2-chlorobenzyl)-quinolinium derivatives is presented. This phenomenon appears to be responsible for the marked steric hindrance associated with the terminal nitrogen atom in the side chain and for the ease of hydrolysis of the 1-quinolinium derivative to the corresponding 4-quinolones.

In the course of our continuing investigation of quinoline chemistry we have prepared some mono- and bis-quaternary salts of a variety of 4-dialkylaminoalkylaminoquinolines. Most of these compounds as well as their pharmacology will be reported in other papers. The present communication deals mainly with some of our observations using 2-chlorobenzyl chloride as the quaternizing agent.

From the reaction of one equivalent of 2-chlorobenzyl chloride with 7-chloro-4-(2-diethylaminoethylamino)-quinoline (Ib)[1] (see Chart I) in acetonitrile a solid product was obtained which gave the correct analysis for a monoquaternary salt. When this material, which was soluble in water to only about one per cent., was dissolved in

(1) The 5-chloro compounds are designated by a and the 7-chloro compounds by b.

CHART I



warm water and the solution treated with dilute alkali, a solid base separated. Analysis of this new product indicated a loss of one mole of hydrogen chloride from the original compound. The latter could be regenerated from the base by the addition of a mole of hydrogen chloride.[2,3]

On the basis of pK_a values observed for compound Ib, 8.3[4] and 6.6, one might, as a first approximation, anticipate that quaternization of a 4-dialkylaminoquinoline such as I would occur first on the terminal nitrogen atom. From the above results it would appear, however, that the reaction of the 2-chlorobenzyl chloride had occurred on the ring-nitrogen atom.[5] Evidence for a 1-substituted quinoline derivative was obtained by hydrolysis of the base IIIb in aqueous alcohol solution to give 7-chloro-1-(2-chlorobenzyl)-4-quinolone (IVb). The latter compound was also formed by alkylation of 7-chloro-4-hydroxyquinoline (Vb) with 2-chlorobenzyl chloride. It follows, therefore, that the structure of IIIb must be 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline. Hydrolysis of the initial product IIb, designated in Chart I as the hydrochloride of the imino base, similarly resulted in the formation of the quinolone IVb.

Additional evidence for the reaction of 2-chlorobenzyl chloride with the 1-nitrogen atom was obtained by the interaction of 7-chloro-1-(2-chlorobenzyl)-4-iodoquinolinium iodide (VIb) with 2-diethylaminoethylamine. The product, 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydroiodide (VIIb), was identical with that obtained from the imino base IIIb on treatment with one equivalent of hydrogen iodide.

When a solution of the base Ib in acetonitrile was refluxed with a large excess of 2-chlorobenzyl chloride, a 53% yield of the colorless bis-quaternary ammonium salt (designated in Chart I as an imino-quaternary salt VIIIb) was isolated along with a 23% yield of the yellow imino hydrochloride IIb. This bis-quaternary VIIIb could also be prepared from the reaction of the imino salt IIb with an excess of 2-chlorobenzyl chloride. It would appear, therefore, that IIb is an intermediate in the formation of the bis-quaternary compound. Furthermore, the imino base IIIb reacts with 2-chlorobenzyl chloride to yield 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline-ω-(2-chlorobenzyl chloride)(IXb), which on treatment with alcoholic hydrogen chloride gave the bis-quaternary VIIIb. The imino-quaternary IXb could be regenerated by removal of hydrogen chloride from VIIIb with dilute alkali.

Attempts to prepare the corresponding 5-chloro derivative VIIIa either directly from 5-chloro-4-(2-diethylaminoethylamino)-quinoline(Ia) or from the imino salt IIa were unsuccessful. In contrast, the base Ia reacts readily with 2 moles of *benzyl chloride* to give the expected bis-quaternary ammonium salt. Furthermore, it was found that with 5-chloro-4-(2-*dimethylamino*ethylamino)-quinoline, quaternization with 2 moles of 2-chlorobenzyl chloride also gave a bis-quaternary com-

(2) The reversible elimination of HX from 1-quinolinium salts has been demonstrated by others. For example, J. B. Cohen, K. E. Cooper and P. G. Marshall, *Proc. Roy. Soc.* (*London*), **B108**, 130 (1931), have reported that 2-(2-methoxyanilino)-1-methylquinolinium iodide loses HI on treatment with alcoholic ammonia to yield 1-methyl-2(2-methoxyphenylimino)-1,2-dihydroquinoline.

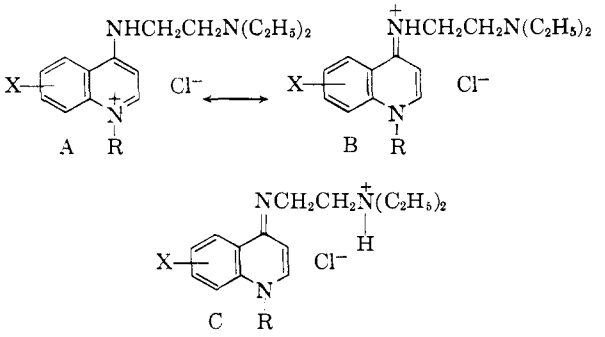
(3) A. Albert and B. Ritchie, *J. Chem. Soc.*, 458 (1943), have shown that 9-amino-10-methylacridinium iodide is reversibly converted to the corresponding 9-iminodihydroacridine on treatment with base.

(4) (a) The pK_a values in the present work were determined in 50% aqueous alcohol essentially according to the procedure given by T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1945); (b) J. L. Irvin and E. M. Irvin, THIS JOURNAL, **69**, 1091 (1947); **72**, 2743 (1950), have shown that the first proton is accepted by the dialkylamino nitrogen atom in 4-(4-diethylaminobutylamino)-quinoline. We have found this also to apply to 7-chloro-4-(2-diethylaminoethylamino)-quinoline.

(5) H. C. Brown and N. R. Eldred, *ibid.*, **71**, 445 (1949), have investigated the reaction of alkyl halides with bases of different strengths and steric requirements. The activation energy increases more rapidly for the base of higher steric requirements as the alkyl halide becomes bulkier. In the reaction of tertiary amines with a large group such as 2-chlorobenzyl chloride one would therefore expect the steric factor to be the predominant one on the rates of reaction.

pound. Even with one mole of 2-chlorobenzyl chloride a mixture was obtained whose analysis indicated a preponderance of the bis-quaternary salt. From these results it would appear that the steric hindrance associated with the terminal nitrogen atom in the side chain is the determining factor in the quaternization reactions. This will be discussed in more detail below.

Having determined the structure for the imino base III, which may be considered as a vinylog of an amidine,[6] it seemed of interest to see whether it was possible to determine the position of the proton in II. The following structures can be written for



II, A ⟷ B, a resonance hybrid in which the proton is associated with the aromatic system and C in which the proton is attached to the terminal nitrogen atom in the side chain.

As mentioned in the above discussion, the imino base IIIb as well as its hydrochloride IIb could be hydrolyzed in aqueous solution to the corresponding quinolone IVb. However, attempted hydrolyses of the bis-hydrochloride salt of IIIb in aqueous solution or of IIIb in 6 *N* hydrochloric acid were unsuccessful. The starting material could be recovered unchanged even after prolonged heating. This appeared to indicate that hydrolysis in aqueous solution may require the presence of a non-protonated doubly bonded nitrogen atom in the 4-position and structure C would then be favored. However, if one considers the observed basicity associated with the terminal nitrogen atom (pK_a 7.3) and that associated with the aromatic nucleus (pK_a 11.7)[7] in the imino base IIIb, then one would expect the latter to accept the first proton and structure A ⟷ B would be favored.

In an attempt to obtain information regarding the structure of II, a study was made of the ultraviolet absorption spectra of several of the compounds described in Chart I. The spectrum of the imino base IIIb was compared with that of its hydrochloride IIb in 95% alcohol and in 95% alcohol containing dilute hydrochloric acid (Fig. 1). In alcohol the curves for IIb and IIIb are identical: λ_{max} 337, 349 mμ (log ε 4.32, 4.36).

However, in absolute alcohol we have observed only one peak in this region (λ_{max} 352 mμ). The double peak develops as water is added to this alcoholic solution. Apparently the imino base IIIb becomes protonated in the presence of water. As might be expected the curves for IIb and IIIb

(6) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).

(7) This value is in good agreement with that reported for 1-methyl-4-imino-1,4-dihydroquinoline (pK_a 12.4, ref. 6).

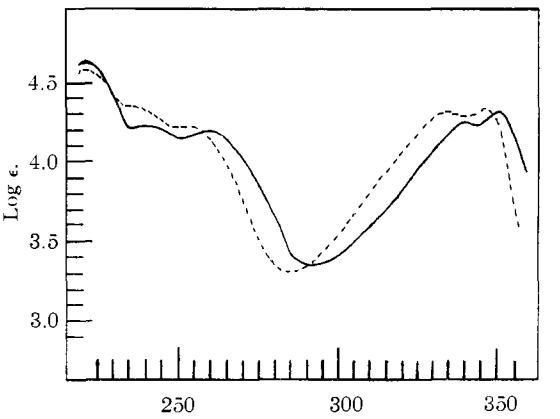


Fig. 1.—The ultraviolet absorption spectrum of 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline (IIIb) and of its hydrochloride salt IIb in 95% ethanol, ———, and in 0.01 *N* ethanolic HCl, – – – –.

in acid solution were identical: μ_{max} 333, 347 mμ (log ε 4.32). The bis-quaternary ammonium salt VIIIb, which undoubtedly possesses essentially the same resonance as in A ⟷ B, shows λ_{max} 333, 348 mμ (log ε 4.33, 4.34).

In 95% alcohol solution the base Ib, 7-chloro-4-(2-diethylaminoethylamino)-quinoline, exhibited only one maximum (λ_{max} 328 mμ, log ε 408) in the 320–360 mμ region of the spectrum (Fig. 2).

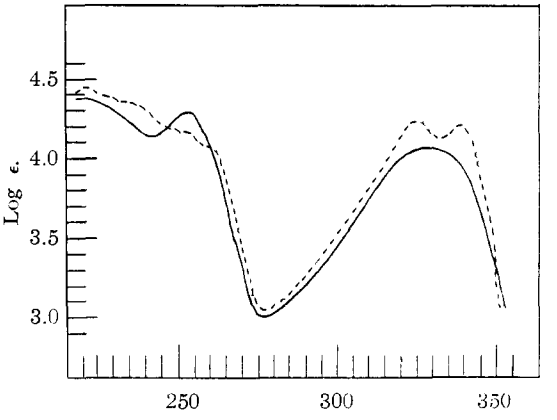


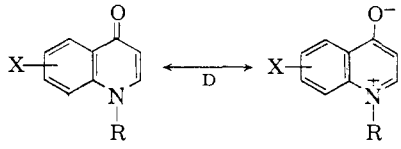
Fig. 2.—The ultraviolet absorption spectrum of 7-chloro-4-(2-diethylaminoethylamino)-quinoline (Ib) in 95% ethanol, ———, and in 0.01 *N* ethanolic HCl, – – – –.

However, in dilute hydrochloric acid a double peak was observed: λ_{max} 325, 339 mμ (log ε 4.23, 4.23). In acid solution a resonance hydrid of the type A ⟷ B (R = H) has been proposed for 4-dialkylaminoalkylquinolines.[8]

(8) (a) A. Albert and R. Goldacre, *Nature*, **153**, 467 (1944), have attributed the high basicity of 4-aminoquinoline to this type of resonance hydrid. (b) The same conclusions were reached by J. L. Irvin and E. M. Irvin, ref. 4, in their investigation of some 4-dialkylaminoalkylaminoquinolines. These authors have shown that the first proton is accepted by the terminal nitrogen atom and the second by the aromatic system to give a resonating system as in D. The ultraviolet absorption spectrum of the monoprotonated compound is similar to the base itself, whereas the addition of the second proton results in a different absorption curve. (c) N. L. Drake, H. J. Creech, D. Draper, J. A. Garman, S. Haywood, R. M. Peck, E. Walton and J. O. Van

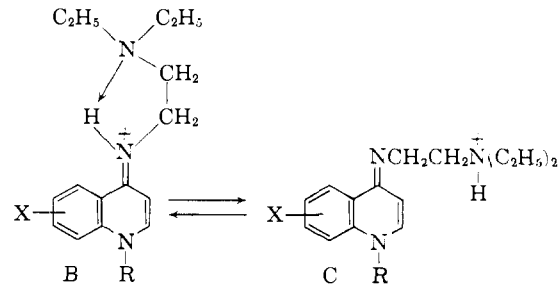
In the above examples, a reversible shift of electrons between the ring nitrogen and the 4-amino nitrogen atoms is involved. *It would appear that this resonance is responsible for the double peak observed in the ultraviolet absorption spectrum in the 320–360 mμ region for the 4-aminoquinolinium compounds as well as for the 4-aminoquinoline salts.*

A similar situation exists with 7-chloro-1-(2-chlorobenzyl)-4-quinolone (IVb) which exhibits a double peak in alcohol or in acid solution; λ_{max} (alcohol) 324, 338 (log ϵ 4.15, 4.23); λ_{max} (acid) 323, 337 mμ (log ϵ 4.15, 4.17). This may be accounted for by the resonance hybrid D, which is analogous to the 4-amino derivatives.



It is interesting to note that in acid solution a compound such as 7-chloro-4-[(2-diethylaminoethyl)-methylamino]-quinoline, which has a tertiary nitrogen atom at the 4-position, shows only one distinct high intensity peak (λ_{max} 350 mμ, log ϵ 4.20) in the 320–360 mμ region. This is also true for 7-chloro-4-piperidino-1-methylquinolinium iodide - (Xb) (λ_{max} 367 mμ, log ϵ 4.27).[9] Apparently in these instances there is a steric inhibition of resonance, which could account for the absence of a double peak in the 320–360 mμ region.[10]

Although the ultraviolet absorption studies offered excellent confirmatory evidence for the position of the 2-chlorobenzyl group in II, they did not appear to give any information regarding the position of the proton. Assuming on the basis of the observed pK_a values of the basic centers in IIIb, that structure A ⟷ B is the preferred representation for the salt IIb, then an explanation for the hydrolysis to the quinolone IVb must be presented. A possible mechanism for the transfer of a proton from N(4) in A ⟷ B to the terminal nitrogen atom to give a non-protonated nitrogen atom at position 4 could be pictured as



The presence of hydrogen bonding in II could also account for the marked steric hindrance associated with the terminal nitrogen atom, especially in the case of the 5-chloro compound IIa.[11] In connection with this work, 7-chloro-4-(2-diethylaminoethylamino)-quinoline(Ib) was examined for evidence of hydrogen bonding.[12] A comparison of the infrared absorption spectra, dipole moments and nuclear magnetic resonance of compound Ib with 4-butylamino-7-chloroquinoline (XIb) did indeed indicate the presence of intramolecular hydrogen bonding in Ib.

In view of these results, several additional compounds were investigated in the 3-μ region of the infrared spectrum to determine whether intramolecular hydrogen bonding could be detected. The wave lengths of N–H absorption for these compounds are given in Table I. The observed value for the 4-butylamino compound in each series XIb and XVIa in which no intramolecular bonding is possible was used as the reference.

In the 7-chloro series the diethylaminoethylaminoquinoline and the diethylaminopropylaminoquinoline compounds Ib, XIIb and IIb show evidence of intramolecular N—H----N bonding. The diethylaminopropyl compound XIIb showed the greatest increase in wave length for the N–H stretching vibration over the reference compound XIb. This is in contrast to the 5-chloro series where the observed N–H wave lengths indicate that intramolecular bonding is present only in those compounds having two methylene groups between N(4) and the terminal nitrogen atom in the side chain. Apparently the presence of the 5-chlorine atom in these diethylaminopropylamino compounds inhibits the formation of a six-membered bridged ring. The wave length observed for 5-chloro-4-(3-diethylaminopropylamino)-quinoline (XIIa) is similar to the one for diethylaminohexylamino compound XIIIb.

This steric hindrance is probably also responsible for the absence of intramolecular bonding in the

Hook, THIS JOURNAL, **68**, 1214 (1946), observed double peaks in the 320–360 mμ region for salts of all the 4-aminoquinolines which they examined, and attributed this absorption to a similar resonating system.

(9) R. U. Schock, THIS JOURNAL, **79**, 1570 (1957).

(10) Some interesting results were obtained with 6- and 8-methoxy-4-(2-diethylaminoethylamino)-quinoline (I, X = 6-OCH_3, 8-OCH_3). In *alcohol solution* both bases exhibited a double peak in the ultraviolet absorption spectrum I (X = 6-OCH_3), λ_{max} 326, 339 (log ϵ 3.87, 3.88); I (X = 8-OCH_3), λ_{max} 319, 328 (log ϵ 4.17, 4.17). This is contrary to the results observed with I (X = H, 5-Cl, 7-Cl, 3-CH_3). It would appear that the methoxy group in the 6- and 8-positions has a marked influence on the resonance of the aromatic system which results in the appearance of the double peak in the neutral solution.

In all other respects the 6-methoxy compound is similar to the other 4-aminoquinoline derivatives. In acid solution it exhibits a double peak: λ_{max} 336, 348 (log ϵ 4.05, 4.05). Its 1-(2-chlorobenzyl)-chloride derivative shows λ_{max} (alcohol) 3.48, 362 (log ϵ 4.20, 4.24); λ_{max} (HCl) 3.46, 357 (log ϵ 4.17, 4.18).

The 8-methoxy compound (I, X = 8-OCH_3) is quite unique. In alcohol solutions as mentioned above it shows a double peak; in acid solution only one high intensity peak was observed in the 320–360 mμ region: λ_{max} 333 (log ϵ 4.12). The 1-(2-chlorobenzyl)-chloride derivative also gave one peak in this region: λ_{max} 345 (log ϵ 4.24).

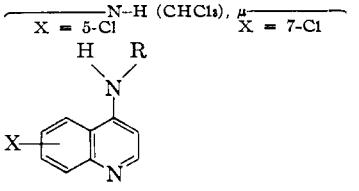
This unusual behavior may be due to a field effect exerted by the 8-methoxy group which could interfere with the resonating system by favoring that structure which places a positive charge on the nitrogen atom.

(11) (a) According to L. N. Short, *J. Chem. Soc.*, 4584 (1952), very little is apparently known regarding the N—H—N bonds. He was able to demonstrate the existence of intramolecular hydrogen bonding in 4-aminoacridine and 8-aminoquinoline. In both cases hydrogen-bond formation involves a five-membered ring rather than the more usual six-membered ring and the calculated bond angle for N—H---N was considerably less than 180°. (b) E. D. Bergmann, E. Gil Av and S. Pinchas, THIS JOURNAL, **75**, 68 (1953), have reported on the presence of intramolecular bonds of the type OH--N involving five-membered rings with some 2-aminoalkanols. These authors have estimated the strength of the intramolecular hydrogen bond at 8 kcal./mole. (c) Evidence for intramolecular hydrogen bonding involving five-membered rings has recently been reported by G. M. Badger and R. G. Buttery, *J. Chem. Soc.*, 614 (1956), with 5-phenylazo-8-hydroxyquinoline.

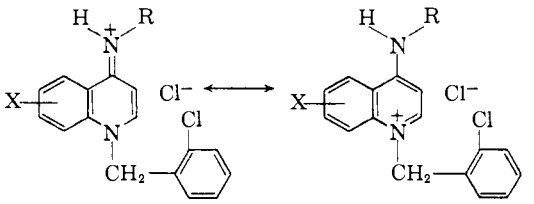
(12) F. C. Nachod, A. R. Surrey, G. Y. Lesher, C. M. Martini, J. R. Mayer, M. Priznar and W. G. Webb, THIS JOURNAL, **81**, 2897 (1958).

TABLE I

WAVE LENGTHS FOR N–H STRETCHING VIBRATIONS



R	X = 5-Cl		X = 7-Cl	
$(CH_2)_3CH_3$	...		XIb	2.903[a]
$(CH_2)_2N(C_2H_5)_2$	Ia	2.964	Ib	2.971
$(CH_2)_3N(C_2H_5)_2$	XIIa	2.883	XIIb	3.065
$(CH_2)_6N(C_2H_5)_2$	...		XIIIb	2.885
$(CH_2)_2NC_4H_8O$[b]	XIVa	2.935	...	
$(CH_2)_2NC_5H_{10}$[c]	XVa	2.977	...	



$(CH_2)_3CH_3$	XVIa	2 920	...	
$(CH_2)_2N(C_2H_5)_2$	IIa	3.027	IIb	3.04
$(CH_2)_3N(C_2H_5)_2$	XVIIa	2.941	...	
$(CH_2)_3N(CH_2)_2$	XVIIIa	2.978	..	
$(CH_2)_2NC_4H_8O$	XIXa	3.025	XIXb	2.965

[a] Determined in CS_2, it shows a peak at 3.05μ which disappears upon dilution. [b] NC_4H_8O = morpholino. [c] NC_5H_{10} = piperidino.

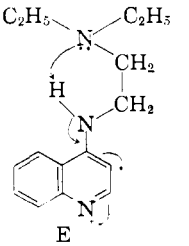
corresponding compound, 5-chloro-1-(2-chlorobenzyl) - 4 - (3 - diethylaminopropylimino) - 1,4 - dihydroquinoline hydrochloride (XVIIa). Lowering the steric requirements at the terminal nitrogen atom in compound XVIIa by replacing diethyl with dimethyl (XVIIIa) results in an increase in the N–H wave length which is indicative of hydrogen bridging.

The effect of intramolecular hydrogen bonding on steric hindrance at the terminal nitrogen atom in 5-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydrochloride (IIa) is readily observed with atomic models (Courtauld). This phenomenon could explain our unsuccessful attempts to quaternize IIa with 2-chlorobenzyl chloride. The desired bis-quaternary ammonium salt VIIIa was finally prepared by converting the salt IIa to the corresponding imino base which on treatment with 2-chlorobenzyl chloride yielded the imino quaternary compound IXa. When the latter was treated with an equivalent of alcoholic hydrogen chloride, 5-chloro-4-(2-diethylaminoethylamino)-quinoline bis-(2-chlorobenzyl chloride) (VIIIa) was obtained.

The existence of intramolecular hydrogen bonding in the 4-aminoquinoline bases may be important in influencing reactivity at the 1-position by enhancing the nucleophilic character of the 1-nitrogen atom.

The usual attraction of electrons by the ring nitrogen would be favored by a concerted electron shift due to N → H bonding as represented in E.

In a recent publication Schock[3] reported the preparation of 7-chloro-4-piperidino-1-methylquinolinium iodide (Xb) which was hydrolyzed in strong potassium hydroxide solution to 7-chloro-1-methyl-4-quinolone (XXb). In this case there can be no elimination of HX to give a C=N— linkage at the 4-position of the quinoline nucleus. It might appear therefore that an imino base is not essential for hydrolysis, although it has been well established that the true imino compounds are readily hydrolyzed. This hydrolysis is probably base catalyzed, the hydroxyl ions being generated in aqueous solution by the strong imino base itself.[13] In all instances the ease of hydrolysis is undoubtedly dependent upon low electron density at the carbon atom to which the amino group is attached.[6]



E

As mentioned above, the ultraviolet spectrum of the piperidino compound Xb shows only one peak in the 320–360 mμ region. It would appear therefore that this compound Xb is not stabilized to any great extent by resonance and its hydrolysis is probably similar to that of 9-dimethylaminoacridine.[13] The situation in the case of the 1-substituted-4-dialkylaminoalkyliminoquinolines is quite different. The monoprotonated species is very strongly stabilized by resonance and one would therefore expect greater difficulty in hydrolysis.

Actually, our observations are that in those cases where hydrogen bonding is indicated by infrared data, the hydrolyses are rapid, albeit, related to the basicity of the terminal nitrogen atom. For example, when the imino salt IIb is hydrolyzed by refluxing in 50% alcohol (*p*H of the solution was 8.8) for six hours, a 52% yield of the quinolone IVb was isolated. Under similar conditions (*p*H of solution was adjusted to 9 by addition of sodium hydroxide solution), 4-butylimino-7-chloro-1-(2-chlorobenzyl)-1,4-dihydroquinoline hydrochloride (XVIb), in which no intramolecular bonding is possible, failed to give any quinolone after 24 hours.

With 7-chloro-4-piperidino-1-methylquinolinium iodide (Xb), hydrolysis in aqueous alcohol at *p*H 9.2 was quite slow. The yield of 7-chloro-1-methyl-4-quinolone (XXb) was approximately 50% after five days as determined by ultraviolet absorption spectra.

By comparing the hydrolyses of IIb with 4-butylimino-7-chloro-1-(2-chlorobenzyl)-1,4-dihydroquinoline hydrochloride (XVIb) at identical *p*H's, it is apparent that the tertiary amino nitrogen in II is assisting in the reaction. In order to

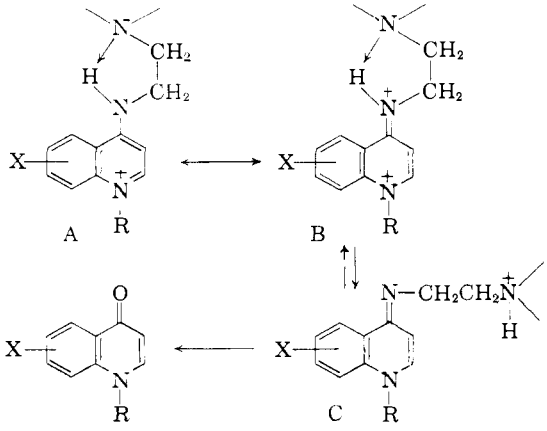
(13) Reference 3. 9-Amino-acridine, pK_a 9.5 is hydrolyzed in 80% alcohol at the rate of 1.25% per hour to the acridone. With 5 *N* potassium hydroxide the extent of hydrolysis is only increased to 11% in 2 hours. Under these conditions 9-dimethylaminoacridine is 68% hydrolyzed. This facile hydrolysis has been attributed to a relief of strain which is inherent in the tertiary amino compound.

see if this might be due to an inductive effect, hydrolysis of the bis-quaternary ammonium salt VIIIb was attempted at *p*H 9. If an inductive effect was involved then one would expect a quaternary nitrogen atom to be more effective than a tertiary nitrogen atom. Our results indicated that no detectable hydrolysis of VIIIb had occurred after refluxing for 17 hours.

The apparent relationship between intramolecular bonding and hydrolysis is supported by the following observations. The 4-(3-diethylaminopropylimino) compound XVIIa, in which no bonding is indicated by infrared studies, disproportionates when dissolved in water. A 30% yield of the imino base from XVIIa precipitated in a matter of seconds and a 40% yield of the bis-hydrochloride salt from XVIIa could be isolated from the filtrate. One might expect that in this case a maximum yield of about 50% of quinolone IVa would be obtained from hydrolysis of the imino base formed as a result of this disproportionation. When an aqueous alcohol solution of XVIIa was refluxed for 23 hours a 44% yield of the quinolone VIa was isolated. With the corresponding dimethylaminopropyl compound XVIIIa, which exhibits intramolecular hydrogen bonding, hydrolysis proceeded to an extent of 70% in 18 hours.

An attempt to hydrolyze 7-chloro-1-(2-chlorobenzyl)-4-(5-diethylaminopentylimino)-1,4-dihydroquinoline hydriodide by refluxing in aqueous alcohol solution (*p*H 10.6) for 22 hours was unsuccessful. Only starting material (86%) was recovered.

Further evidence supporting the intramolecular proton transfer *via* bonding was obtained by the hydrolysis of 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydrochloride (IIb) in high dilution. In six hours the latter was hydrolyzed at *p*H 9.2 to an extent of 60.5%. On diluting a second reaction mixture thirty-fold (*p*H 8.8) and refluxing for six hours, a 60.5% yield of quinolone IVb was isolated. The rate of the hydrolysis reaction would therefore appear to be independent of the concentration (pseudo first order) of the imino salt (A⟷B), and any equilibrium which leads to the protonated terminal nitrogen compound C is not seriously affected by dilution.



The equilibrium concentration of compound C is apparently dependent upon the basicity of the terminal amino group. In compounds XIXa and XIXb, 5-chloro-1-(2-chlorobenzyl)-4-(2-morpholinoethylimino)-1,4-dihydroquinoline hydrochloride and the corresponding 7-chloro derivative, which show intramolecular bonding (see Table I), the terminal amino groups are weak bases.[14]

One might anticipate that the rates of hydrolysis of these compounds would be very slow. When aqueous alcohol solution of XIXa (*p*H of solution was 7.2) was refluxed for 6.5 hours a 7.4% yield of 5-chloro-1-(2-chlorobenzyl)-4-quinolone (IVa) was isolated. An aqueous solution of XIXa (*p*H 7.4) gave 39% of the quinolone after 19.5 hours. Under similar conditions (*p*H 8.4) the 7-chloro compound XIXb gave 25% of the 7-chloroquinolone.

The formation of the latter in 82% yield from compound XIXb by hydrolysis at *p*H 9.1 is evidence for the dependency of hydrolysis upon hydroxide ion concentration.

Experimental

7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline Hydrochloride (IIb).—A solution of 50.0 g. (0.180 mole) of 7-chloro-4-(2-diethylaminoethylamino)-quinoline (Ib) and 28.9 g. (0.180 mole) of 2-chlorobenzyl chloride in 250 ml. of acetonitrile was refluxed for 24 hours. Upon cooling in ice, bright yellow crystals appeared which were collected, washed with ethyl acetate, and dried to give 53.2 g. (67%) of product, m.p. 200–203°.

Anal. Calcd. for $C_{22}H_{26}Cl_3N_3$: N, 9.58; Cl^-, 8.08. Found: N, 9.63; Cl^-, 7.77.

7-Chloro-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline (IIIb).—A solution of 0.89 g. of 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydrochloride (IIb) in warm water was made basic with excess 10% sodium hydroxide solution to give a gum which slowly crystallized. Filtration gave 0.75 g. (92.1%) of a pale yellow solid. One recrystallization from hexane afforded 0.55 g. (67.6%) of pale yellow prisms, m.p. 107–108.8°.

Anal. Calcd. for $C_{22}H_{25}Cl_2N_3$: N_{AP}, 6.97; Cl_{DC}, 17.63. Found: N_{AP}, 7.03; Cl_{DC}, 17.66.

When 0.29 g. of the imino compound was treated with one equivalent of hydrogen chloride in methanol, the solvent removed, and the resulting oil triturated with ether, there was obtained 0.12 g. of yellow solid, m.p. 207–209°. The melting point was undepressed on admixture with authentic 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydrochloride (IIb).

7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline Hydriodide (VIIb).—Diethylaminoethylamine (2.5 g.) was added with stirring to a solution of 2.7 g. of 7-chloro-1-(2-chlorobenzyl)-4-iodoquinolinium iodide[15] in 30 ml. of absolute alcohol. There was an exothermal reaction and the reddish color of the solution gradually disappeared. After stirring for a few minutes, the product which separated was filtered off and recrystallized from ethyl alcohol yielding 2 g. melting at 195–200°. A mixed melting point determination with the product obtained from 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline on treatment with hydrogen iodide was not depressed.

Anal. Calcd. for $C_{22}H_{25}Cl_2N_3 \cdot HI$: I^-, 23.93. Found: I^-, 24.11.

7-Chloro-4-(2-diethylaminoethylamino)-quinoline Bis-(2-chlorobenzyl chloride) (VIIIb).—A solution containing 50 g. (0.18 mole) of 7-chloro-4-(2-diethylaminoethylamino)-quinoline and 100 g. (0.62 m.) of 2-chlorobenzyl chloride in 750 ml. of acetonitrile and 5 ml. of water was refluxed with stirring for 20 hours. Upon cooling, the product was filtered, washed with acetone and dried to give 57 g. of solid, m.p. 175–177°. Recrystallization from alcohol and ether gave colorless crystals, m.p. 170.5–171.5°.

(14) The pK_a values obtained for 5- and 7-chloro-4-(2-morpholinoethylamino)-quinoline are 7.2, 4.3 and 7.4, 4.9.

(15) See accompanying paper, part II, p. 2894.

The filtrate from the reaction mixture on standing afforded 18 g. (23%) of tan crystals, m.p. 190–205°, which was identified as the imino salt IIb.

Reaction of 7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline hydrochloride (IIb) with 2-Chlorobenzyl Chloride.—A solution of 5.0 g. of 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino-1,4-dihydroquinoline hydrochloride (IIb) and 7.35 g. of 2-chlorobenzyl chloride in 40 ml. of acetonitrile was refluxed for 24 hours. After removal of the solvent the residue was triturated with ether to give a crystalline solid. Recrystallization from acetonitrile gave 3.74 g. (55%) of colorless solid, m.p. 167.5–168.5°, mixed m.p. with the bis-quaternary compound VIIIb, 167–168.5°.

Reaction of 7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino-1,4-dihydroquinoline (IIIb) with 2-Chlorobenzyl Chloride.—A solution containing 3.0 g. (0.00748 mole) of the imino base IIIb and 1.17 g. (0.0073 mole) of 2-chlorobenzyl chloride in 25 ml. of acetonitrile was refluxed for 24 hours. The cooled reaction was diluted with five volumes of ethyl acetate and placed in the refrigerator. This gave 2.68 g. (64%) of pale tan needles, m.p. 126–142°. One recrystallization from alcohol–ethyl acetate gave 1.45 g. of golden-yellow prisms, m.p. 150.5–152.5° dec.

Anal. Calcd. for $C_{29}H_{31}Cl_4N_3$: Cl_{DC}, 25.17. Found: Cl_{DC}, 25.71.

This product was shown to be 7-chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino-1,4-dihydroquinoline-ω-(2-chlorobenzyl chloride) (IXb) by its conversion with isopropanolic hydrogen chloride to the bis-quaternary compound VIIIb, m.p. 167–169°.

A small quantity of the bis-quaternary VIIIb was treated with alcoholic potassium hydroxide, the solvent removed and the residue recrystallized from isopropyl alcohol to give a yellow crystalline solid (63%), m.p. 150–152°, mixed m.p. with the imino quaternary IXb, 148–150°.

Hydrolysis of 7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline (IIIb).—A solution of 0.4 g. of the imino compound IIIb in 20 ml. of alcohol and 50 ml. of water was refluxed for 7 hours. The reaction mixture was diluted with an equal volume of water and cooled in ice to give 0.24 g. (79%) of colorless product, m.p. 201–205°. Recrystallization from ethyl acetate yielded 0.2 g. of 7-chloro-1-(2-chlorobenzyl)-4-quinolone (IVb), m.p. 205.5–207°.

Anal. Calcd. for $C_{16}H_{11}Cl_2NO$: C, 63.17; H, 3.65; Cl_{DC}, 23.30. Found: C, 62.89; H, 3.90; Cl_{DC}, 23.21.

Preparation of 7-Chloro-1-(2-chlorobenzyl)-4-quinolone (IVb).—A solution containing 11.0 g. of 7-chloro-4-hydroxyquinoline (Vb), 2.24 g. of potassium hydroxide and 6.45 g. of 2-chlorobenzyl chloride in 100 ml. of alcohol was refluxed for 6 hours. The reaction mixture was poured into water to give 10 g. of colorless crystals. One recrystallization from ethyl acetate gave 4 g. of product, m.p. 207–208°. This material on admixture with hydrolysis product from IIIb gave no depression in melting point.

Anal. Calcd. for $C_{16}H_{11}Cl_2NO$: Cl, 23.30. Found: Cl, 23.46.

Hydrolysis of 7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline Hydrochloride (IIb).—A suspension of 1.0 g. of IIb in 25 ml. of water was heated to boiling and refluxed for 7 hours. Upon cooling, 0.47 g. (67%) of colorless crystals separated, m.p. 195–203°. One recrystallization from ethyl acetate gave 0.38 g. (54%) of 7-chloro-1-(2-chlorobenzyl)-4-quinolone which melted at 203–205°.

Attempted Hydrolysis of 7-Chloro-4-(2-diethylaminoethylamino)-quinoline Bis-(2-chlorobenzyl Chloride) (VIIIb).—A solution of 1 g. of the bis-quaternary compound in 45 ml. of 33% alcohol was adjusted to *p*H 9.00 with 0.01 *N* sodium hydroxide and refluxed for 17 hours. Upon cooling (*p*H 8.8) and removal of the solvent, an oil was obtained which, after trituration with ether, gave 0.91 g. (91%) of starting material, m.p. 177–178°.

The Disproportionation and Hydrolysis of 5-Chloro-1-(2-chlorobenzyl)-4-(3-diethylaminopropylimino)-1,4-dihydroquinoline Hydrochloride (XVIIa).—One gram of XVIIa was added with stirring to 20 ml. of water. Immediately upon solution a colorless solid crystallized affording 0.15 g. (30%) of the imino compound from XVIIa, m.p. 113–114°. Evaporation of the solvent from the filtrate under reduced pressure gave a gummy material which upon crystallization from isopropyl alcohol–ethyl acetate yielded 0.43 g. (40%) of the bis-hydrochloride salt from XVII, m.p. 215–217°.

Anal. Calcd. for $C_{23}H_{27}Cl_2N_3 \cdot 2HCl.H_2O$: Cl^-, 13.97; N_K, 8.28; H_2O_{KF}, 3.55. Found: Cl^-, 13.80; N_K, 8.15; H_2O_{KF}, 3.59.

A solution containing 0.53 g. of 5-chloro-1-(2-chlorobenzyl)-4-(3-diethylaminopropylimino)-1,4-dihydroquinoline in 40 ml. of alcohol was treated with one equivalent of hydrochloric acid (12.7 ml. of 0.1 *N* HCl) and refluxed for 23 hours. Removal of the alcohol under reduced pressure gave 0.17 g. (44%) of the quinolone, m.p. 230–235°, mixed m.p. with authentic quinolone 232–237°.

The Hydrolysis of 5-Chloro-1-(2-chlorobenzyl)-4-(3-dimethylaminopropylimino)-1,4-dihydroquinoline Hydrochloride (XVIIIa).—A solution containing 1 g. of XVIIIa in 25 ml. of water (*p*H 10.1) was heated on the steam-bath for 18 hours. The yellow crystalline solid which separated was filtered (filtrate *p*H 8.8) to give 0.5 g. (70%) of product, m.p. 235–238°. A sample on admixture with authentic 5-chloro-1-(2-chlorobenzyl)-4-quinolone gave no depression in melting point.

The Attempted Hydrolysis of 1-(2-Chlorobenzyl)-4-(5-diethylaminopentylimino)-1,4-dihydroquinoline Hydroiodide.—A solution of 1 g. of the hydroiodide in 60 ml. of 50% alcohol (*p*H 10.6) was refluxed for 22 hours. Upon cooling, (*p*H 10.2) the precipitate was filtered to give 0.86 g. (86%) of starting material, m.p. 160–170°.

The High Dilution Hydrolysis of 7-Chloro-1-(2-chlorobenzyl)-4-(2-diethylaminoethylimino)-1,4-dihydroquinoline Hydrochloride (IIb). A.—A solution of 1 g. of IIb in 15 ml. of water containing 0.5% alcohol (*p*H 9.2) was refluxed for six hours, cooled in ice and the resulting precipitate was filtered and dried to give 0.42 g. (60.5%) of the corresponding quinolone, m.p. 204–206°.

B.—A solution of 1 g. of IIb in 2.9 l. of water and 15 ml. of alcohol (*p*H 8.8) was refluxed for six hours. Upon cooling in ice there was obtained 0.35 g. of colorless solid, m.p. 206–207°. The filtrate was acidified, concentrated to 100 ml., and cooled in ice to give 0.07 g. of solid, m.p. 190–195°. Both samples were undepressed in melting point on admixture with authentic 7-chloro-1-(2-chlorobenzyl)-4-quinolone.

The Hydrolysis of 5-Chloro-1-(2-chlorobenzyl)-4-morpholino-1,4-dihydroquinoline Hydrochloride (XIXa).—A solution containing 1 g. of XIXa in 80 ml. of 37% alcohol (*p*H 7.2) was refluxed for 6.5 hours. Evaporation of the alcohol gave 0.05 g. (7.4%) of 5-chloro-1-(2-chlorobenzyl)-4-quinolone, m.p. 231–234°.

When a solution containing 1 g. of XIXa was refluxed in 50 ml. of water (*p*H 7.4) for 19.5 hours, acidified with 6 *N* hydrochloric acid and cooled, there was obtained 0.26 g. (39%) of the quinolone IXa, m.p. 236–238°.

The Hydrolysis of 7-Chloro-1-(2-chlorobenzyl)-4-morpholinoethylimino-1,4-dihydroquinoline Hydrochloride (XIXb).—A solution containing 1 g. of XIXb in 50 ml. of water (*p*H 8.4) was refluxed for 19.5 hours. Upon cooling there was obtained 0.17 g. (25.3%) of 7-chloro-1-(2-chlorobenzyl)-4-quinolone, m.p. 203–206°.

Hydrolysis of 7-Chloro-1-methyl-4-(1-piperidyl)-quinolinium Iodide.—A solution of 1.94 g. of the methiodide in 50 ml. of ethyl alcohol and 50 ml. of distilled water was adjusted to a *p*H of 9.2 with 0.1 *N* sodium hydroxide and refluxed for five days. A comparison of the ultraviolet spectra of the product mixture with that of several synthetic mixtures of varying amounts of starting material and product indicated that hydrolysis had gone to an extent of 50%.

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