Experimental[23]

I. Preparation of Benzimidazoles.—Benzimidazole was obtained by the method of Phillips,[15] m. p. 170.5–171° (lit. m. p. 170°); the 5(6)-chloro analog was made similarly, m. p. 121–121.5° (lit.[24] m. p. 125°).

Anal. Calcd. for $C_7H_5ClN_2$: N, 18.34. Found: N, 18.24.

2-Chloromethylbenzimidazole[2,15] and the related 5(6)-chloro compound were formed by the Phillips synthesis. The properties of the latter substance were closely akin to the parent, the chloro group attached to position 2 showing allylic character (*cf.* ref. 16). When 5(6)-chloro-2-chloromethylbenzimidazole was boiled in water, a titration of the resulting chloride ion indicated that *ca.* 98% of the halogen in position 2 had been liberated.

Anal. Calcd. for $C_8H_6Cl_2N_2$: Cl (one), 17.64. Found: Cl, 17.34.

The several 2-dialkylaminomethylbenzimidazoles which were required were prepared from the 2-chloromethyl compound and a secondary amine in ethereal alcoholic solution.[2] Purification of the products was markedly facilitated by passage of their solutions through a column of activated alumina.[25] 2-Dimethylaminomethylbenzimidazole was most tedious of purification and it seemed of interest to study it microscopically.[26] The compound crystallizes in the form of blades which show oblique extinction; it is dimorphic and both the stable and unstable forms show anomalous polarization colors; the refractive index varies considerably with the wave length of light used.

(23) The melting points reported are not corrected for stem emergence.

(24) O. Fischer, *Ber.*, **37**, 556 (1904).

(25) Purchased from Aluminum Ore Co., East St. Louis, Ill., Grade F20, −80 mesh.

(26) Dr. Robert L. Clarke of this Institute was kind enough to carry out the microscopic studies here reported.

2-Aminobenzimidazole and its 5(6)-chloro analog were synthesized by the method of Pierron.[17,18]

The data pertinent to the new compounds are summarized in Table I.

II. Absorption Spectra.—The absorption spectra were all determined with a Beckman Quartz Spectrophotometer, Model DV, Serial No. D-377, as described in the first paper of this series.[27] All solvents herein employed met the conditions earlier noted.

Acknowledgments.—The authors wish to express their appreciation to Mrs. M. Becker and Mr. M. Priznar for their aid in the spectrophotometric studies, and to Mrs. B. Beecher for the careful plotting of the results. Most of the analyses have been due to the efforts of the group under the direction of Mr. M. E. Auerbach of this Institute.

Summary

1. Several new 2-dialkylaminomethyl benzimidazole type compounds have been prepared. 2-Diethylaminomethylbenzimidazole, earlier reported as a colored substance, has been obtained white when pure.

2. The absorption spectra of a number of benzimidazoles have been determined in alcohol, 0.01 *N* hydrochloric acid and 0.01 *N* sodium hydroxide. Certain features of the results obtained were emphasized due to bearing upon the structures involved.

(27) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Absorption Spectra of Heterocyclic Compounds. IV. Some Bz-Halo-4-aminoquinoline Derivatives[1]

BY EDGAR A. STECK, GALEN W. EWING[2] AND FREDERICK C. NACHOD

Introduction

The interest in 4-aminoquinoline types was heightened markedly when tablets of an antimalarial drug, seized during the North African campaign of the World War II, were found to contain the methane bis-1,1′-(2-hydroxy-3-naphthoate) of 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline.[3] These laboratories participated in the program of the Office of Scientific Research and Development[4] in this field, which led to the production of Aralen[5] (Chloroquine,[6] 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline,[7] (SN 7618[8]). The present contribution commenced as an adjunct in the characterization of 7-halo-4-aminoquinolines and their congeners, and expanded with the scope of the program of research in this Institute to include some theoretical aspects. A portion of the investigation was co-extensive with that of Irvin and Irvin,[9] who employed some compounds submitted by us to the OSRD. All compounds herein discussed have one halogen attached to the benzenoid moiety of a 4-aminoquinoline derivative. In the instance of the 3-methyl series, the 5-iodo compound is the only missing member of

(1) This paper was presented before the 113th meeting of the A. C. S. in Chicago, April 19–23, 1948.

(2) Present address: Department of Chemistry, Union College, Schenectady 8, N. Y.

(3) The identification was made November 12, 1943, by Mr. Irwin S. Shupe, now Assistant Director of Control, Winthrop-Stearns, Inc. Each tablet contained 3.25 grains of the salt or 1.5 grains of base.

(4) *Cf.* Elderfield, *Chem. Eng. News*, **24**, 2598 (1946).

(5) Registered mark of Winthrop-Stearns, Inc., for its brand of Chloroquine.

(6) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(7) (a) Andersag, Breitner and Jung, U. S. Patent, 2,233,970; (b) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(8) This code number was assigned by the OSRD, Survey of Antimalarial Drugs. Data relating to the testing of the compounds are tabulated in a monograph "Antimalarial Drugs, 1941–1946," edited by Wiselogle, Edwards Bros., Ann Arbor, Mich., 1946.

(9) Irvin and Irvin, THIS JOURNAL, **69**, 1091 (1947).

the sixteen possible bz-halo-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinolines, this being due to preparative inaccessibility.

Preparation of Quinoline Derivatives

The preparation of all compounds herein studied was based upon the method of Conrad and Limpach.[10] In this synthesis, the azomethine resulting from the condensation of an aniline and a β-oxo ester was pyrolytically cyclized to produce a 4-hydroxyquinoline type. The interaction of the latter with phosphorus oxychloride readily gave the corresponding 4-chloro derivative, which could be caused to react with amines in phenol (as solvent) to produce the desired compounds. When the Conrad–Limpach synthesis was applied to *o*- or *p*-substituted anilines, only 8- or 6-substituted quinolines resulted. On the other hand, it was rare when only one quinoline derivative was obtained from a *m*-substituted aniline, for both possible isomers (*viz.*, 5- and 7-compounds) were formed upon cyclization. We have discussed the synthesis in detail in previous contributions[7b,11–14] from these laboratories.

Discussion

In order that this paper should not be burdened with an undue number of spectral curves, we have resorted to the tabulation of much data, just as in our most recent contribution of this series.[15] Only where particular emphasis is laid upon structural relationships within homologous groups is there a preference for graphical representation.

In Table I are to be found data relating to the spectral characteristics of fifteen of the sixteen possible bz-halo-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinolines in 0.01 *N* hydrochloric acid. The 5-iodo compound could not be prepared due to lability of the halogen during the synthesis.[13d] It is to be noticed that, in general, the alteration of the halogen from chlorine to bromine in position 7 results in less change in spectral character than to fluorine or iodine, as graphically shown in Fig. 1. As might be expected from the first member of a group, the fluoroquinoline shows exceptional behavior. The chlorine and bromine compounds show nearly the same spectral pattern, from which the iodoquinoline derivative varies in the form of a marked bathochromic and hyperchromic shift. There is ample evidence from other studies to indicate that the iodine atom does have greater auxochromic influence on spectra than chlorine or bromine. In

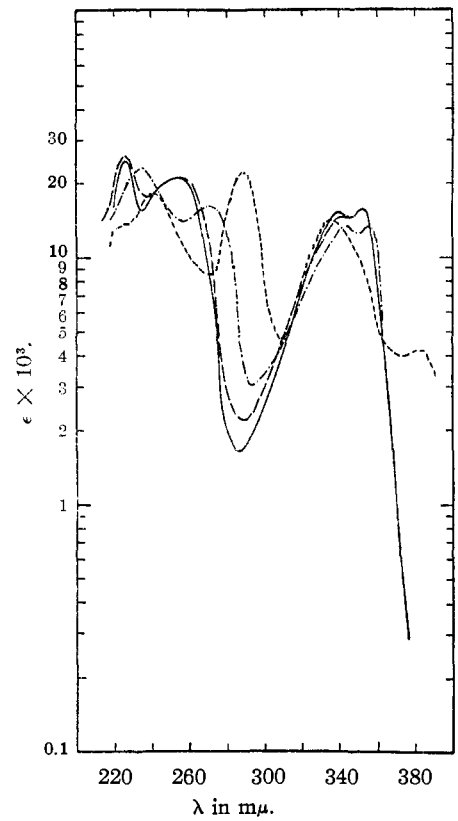


Fig. 1.—Spectra of the 7-halo-3-methyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline in 0.01 *N* hydrochloric acid: ...., fluoro-; —, chloro-; — —, bromo-; -·-, iodo compounds.

the case of the fluorine compound, the bifurcation in the 320–360 mμ region, which is noted in the other 7-halo compounds, is modified markedly. It is difficult to say whether the steep maximum at 288 mμ or the minor one at 382 mμ might have the greater significance, but it does appear that the latter is the result of degenerative effects of the resonance of the fluoroquinoline. The antimalarial activity of the 7-halo-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinolines was, in general, considerably greater than that of the other isomers. The electrophilic halogen in the 7 position is so situated on the quinoline nucleus that it can cause a weakening of the reactions of the basic nitrogen attached to position 4 as well as the ring nitrogen (*cf.* ref. 9). It is not, however, only the nature of the basic side chain attached to position 4 which modifies the antimalarial activity of the quinoline nucleus through influence upon the basicity of the compound, for there are a number of inactive substances which have *pK* values approximating those of effective antimalarials.[16] The effects of variation of the halogen in position 7 might be expected to show greatest influence upon resonance hybrids in the quinoline derivative, extending from the weakest to the strongest

(10) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Limpach, *ibid.*, **64**, 969 (1931).

(11) Huber, Bair and Laskowski, THIS JOURNAL, **67**, 1619 (1945).

(12) Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(13) Steck, Hallock and Holland, *ibid.*, **68** (1946): (a) p. 129, (b) p. 132, (c) p. 380, (d) p. 1241.

(14) (a) Steck, Hallock, Holland and Fletcher, *ibid.*, **70**, 1012 (1948); (b) Steck, Hallock, and Suter, forthcoming publication.

(15) Steck, Nachod, Ewing and Gorman, THIS JOURNAL, **70**, 3496 (1948).

(16) Christopher, *Trans. Faraday Soc.*, **39**, 333 (1943).

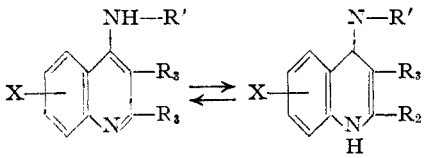
TABLE I

SPECTRAL CHARACTERISTICS OF Bz-HALO-4-(4′-DIETHYLAMINO-1′-METHYLBUTYLAMINO)-3-METHYLQUINOLINES IN 0.01 *N* HYDROCHLORIC ACID

Bz-Halo group	SN[a]	Maxima, wave length in mμ, ε × 10³				
Fluoro 5-F	8798	222(19.1)	242(18.5)	288(4.9)	340(13.3)	346(13.2)
6-F		215(24.0)	245(26.2)		340–355(13.6)[b]	
7-F	8797		240(18.5)	288(22.2)	336(13.8)	382(4.2)
8-F		220(20.6)	241(23.5)		338–342(14.8)[b]	351(15.2)
Chloro 5-Cl	8138	228(20.0)	250(19.4)	348(13.3)	360(11.5)	
6-Cl	9905	220(27.0)	230(29.0)	344(14.0)	360(13.0)	
7-Cl	6911	225(25.0)	255(21.1)	340(14.9)	352(15.5)	
8-Cl	10452	225(19.7)	240(20.8)	345(15.7)	360(15.6)	
Bromo 5-Br	10652	225(21.7)	260(18.4)	340(12.7)	350(12.8)	
6-Br	12486	220(29.0)	252(32.3)	345(13.5)	358(14.3)	
7-Br	7284	226(26.2)	258(21.7)	340(14.6)	352(14.9)	
8-Br	12160	222(19.0)[c]	242(24.0)	350(15.5)	360(14.5)[c]	
Iodo 6-I		221(24.6)	254(27.2)	349(14.4)		
7-I	9904	232(23.1)	268(16.0)	342(13.1)	354(13.2)	
8-I		243(27.3)		349(16.6)		

[a] Survey Number, *cf.* ref. 8. [b] The extinction coefficient remained constant over this range. [c] Inflection point.

electrophilic of these. It does appear that not only is the nature of the group in position 7 responsible for a modification of the resonance structures possible, but also for the dipole moments thereto associated. There seem to be few conclu-



Where X is a halogen, R_2 and R_3 a hydrogen or alkyl, R′ a basic side chain

sions which may be drawn as to the extent to which the several effects must be interrelated for production of maximum activity as antimalarials. It may be noted, however, that the chemical behavior of the fluoro and iodo series both differed quite noticeably from the related chloro- and bromo-3-methylquinolines.

The influence of a halo substituent in position 5 may be compared with that of one in position 7 of a 4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline in Table I. It is to be seen that the fluoro compound is aberrant from the bathochromic and hypsochromic shiftings in the case of the chloro and bromo derivatives as brought out in Figs. 2 and 4. The influence of the mildly auxochromic halogen upon the resonance in the 4-aminoquinoline system is thus less when present in the 5- rather than 7-position. This is quite in harmony with the general conclusions of Irvin and Irvin.[9]

It is of interest to consider in more detail the influence of the 3-methyl group upon the spectrum of 4-(4′-diethylamino-1′-methylbutylamino)-quinoline derivatives in acid medium. Irvin and Irvin have compared only 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline (SN 7618) and its 3-methyl analog (SN 6911). They conclude that the alkyl group causes a marked change in the resonance of the molecule due to the polar and steric effects of the group. In Fig. 2 it is to be seen that the 3-methyl group does indeed cause a bathochromic and hypsochromic shift in the 5- and 7-chloro series. Of particular importance may be the influence of the 3-methyl grouping upon the resonance conditions which result in the appearance of the maximum at 236 mμ in the case of the 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline (SN 7618). Figure 3 serves to compare the parent compounds of each series represented in Fig. 2. The spectral curve for 4-(4′-diethylamino-1′-methylbutylamino)-quinoline shows a definite bathochromic shift through the entire region examined upon introduction of a methyl group in position 3. Only in the second maximum is there no hypsochromic effect in the latter case. These are the same characteristics to be noted when there is a chloro group in the 5- or 7-position. The unique character of the maximum at 236 mμ in the instance of SN 7618 is further emphasized. It may very well be the combination of factors contributing to the resonance hybrids and the dipoles of this compound which render outstanding the extent of its antimalarial activity.

Table II further serves to emphasize the complexity of the problem of deciding the origin of influences of structural modification upon the resonance within molecules. It does, nonetheless,

TABLE II

SPECTRAL CHARACTERISTICS OF SOME Py-ALKYL-Bz-CHLORO-4-(4′-DIETHYLAMINO-1′-METHYLBUTYLAMINO)-QUINOLINES IN 0.01 *N* HYDROCHLORIC ACID

Compound	Maxima wave length in mμ, ε × 10³			
2-Methyl-7-chloro[a]	222(30.2)	250(19.6)	326(16.9)	338(17.4)
3-Propyl-5-chloro	225(28.3)	240(35.1)		340(15.2)
3-Propyl-7-chloro	226(28.8)	244(24.5)		341(12.7)

SN 7135 (*cf.* ref. 8).

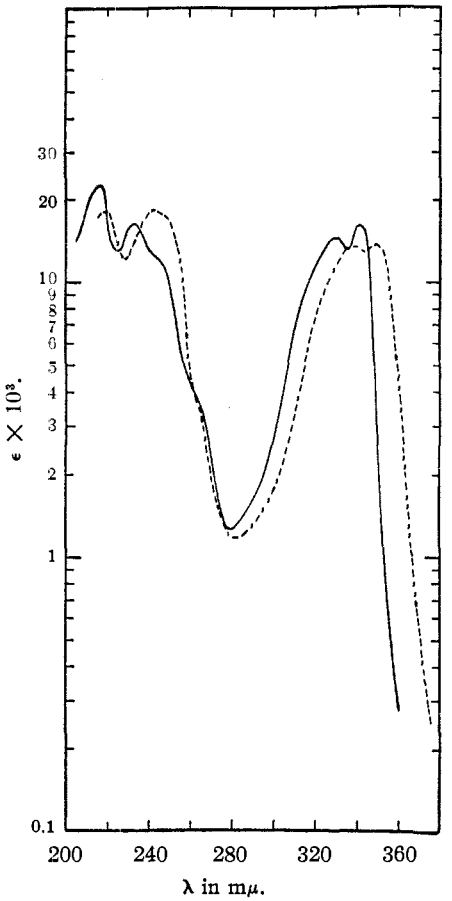


Fig. 2.—Influence of methyl substitution on spectra of: ..., 3-methyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline; —, 4-(4′-diethylamino-1′-methylbutylamino)-quinoline in 0.01 *N* hydrochloric acid.

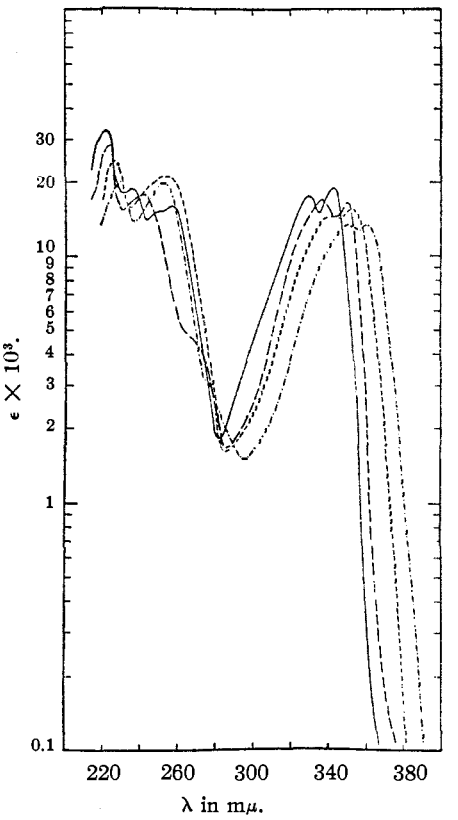


Fig. 3.—Spectra of: —, 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline; — —, 5-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline; – – –, 7-chloro-3-methyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline; –·–·, 5-chloro-3-methyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline; all in 0.01 *N* hydrochloric acid.

show that with a simple alkyl substituent (nucleophilic) in position 2 of the quinoline nucleus there is a less marked influence than when that group is in position 3, in accord with the conclusions of Irvin and Irvin.[9]

While it would be expected that the same general behavior of the 5- and 7-chloro compounds would hold for the 3-propyl series as for the 3-methyl, the results are reversed. An extraordinarily high peak at 240 mμ is to be found in the 5-chloro-4-(4′-diethylamino-1′-methylbutylamino)-3-propylquinoline. This apparent discrepancy cannot be explained at this time.

The influence of the halogen substituent in position 6 of the 4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline nucleus is indicated in Table I and also Fig. 4. In the latter, all of the possible bz-bromo compounds are contrasted in the form of spectral curves. The behavior of the 6-fluoro-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline in the 340–355 mμ region is outstanding in its unusual character. This does not appear to be the more readily understood despite the fact that the fluorine is the first member of the halogens and is a less complex electrophilic group than the others. Here again a knowledge of the dipole moments involved would probably aid in explaining this behavior. Bathochromic shifts are observable throughout the spectral region studied upon passage from the chloro to iodo group in position 6. The heights of the maxima do not appear in a uniform pattern and little may be gleaned from attempts to interpret it. Absence of a fourth maximum in the case of the 4-(4′-diethylamino-1′-methylbutylamino)-6-iodo-3-methylquinoline contrasts sharply with the related 7-iodo compound, in which there is a maximum, even as in the case of the other 7-halo derivatives.

Once again the case of the fluorine derivative of 4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline in position 8 shows anomalous behavior. As indicated in Table I, this compound has a rather constant value for the extinction coefficient in the 338–342 mμ region, much after the pattern of the 6-fluoro type, but there is a final maximum at 351 mμ in this instance. The related compounds containing chlorine or bromine are rather closely related in showing maxima in the

TABLE III

EFFECT OF VARIATION OF THE SIDE CHAIN ON THE SPECTRAL CHARACTERISTICS OF 4-AMINOQUINOLINE DERIVATIVES IN 0.01 *N* HYDROCHLORIC ACID

Compound[a]	SN[b]	Maxima, wave length in mμ, ε × 10³				
Parent Type 4-Aminoquinoline Derivatives						
R = I	6732	232(18.9)	330(18.8)	340(18.5)		
3-Methyl-4-aminoquinoline Derivatives						
R = I	6733	220(21.0)	242(22.8)	338(14.8)	350(15.1)	
7-Chloro-4-aminoquinoline Derivatives						
R = I	7618	221(33.0)	236(19.0)	256(16.0)	330(18.0)	343(19.0)
R = II	8136	220(33.0)	235(19.0)	256(16.2)	330(17.5)	342(18.3)
R = III	8137	220(31.0)	235(21.7)	256(16.0)	328(17.1)	340(17.3)
R = IV	12309	220(30.0)	234(26.0)	254(14.0)	325(14.2)	338(14.0)
R = V	11628	222(30.0)	235(25.5)	248(15.8)	326(18.1)	338(18.1)
R = VI	11166	220(31.2)	235(19.7)	255(15.7)	330(17.3)	342(18.3)
R = VII	10651	220(32.6)	235(18.2)	255(15.2)	330(16.8)	340(16.7)
3-Methyl-7-chloro-4-aminoquinoline Derivatives						
R = I	6911	225(25.0)	255(21.1)	340(14.9)	352(15.5)	
R = II	7718	224(30.4)	254(24.5)	339(15.4)	351(15.6)	
R = III	6945	224(25.5)	248(21.7)	338(13.1)	350(13.0)	
R = IV		225(29.0)	244(25.0)	336(14.2)	348(13.5)	
R = VI	9853	225(27.8)	252(23.3)	340(14.8)	350(15.1)	
R = VII	10650	224(29.0)	255(24.0)	340(15.4)	350(15.4)	
R = VIII		224(29.0)	255(25.0)	338(15.5)	350(15.5)	

[a] The grouping in position 4 is designated by numerals: I, $NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$; II, $NHCH_2CH_2CH_2CH_2N(C_2H_5)_2$; III, $NHCH_2CH(OH)CH_2N(C_2H_5)_2$; IV, $NHCH_2CH_2NHCH_2CH_2OH$; V, $NHCH_2CH_2N(C_4H_{13})_2$; VI, $NHCH_2CH_2SCH_2CH_2N(C_2H_5)_2$; VII, $NHCH_2CH_2CH_2SCH_2CH_2N(C_2H_5)_2$; VIII, $NHCH_2CH_2CH_2N(C_2H_5)_2$. [b] Survey Number, *cf.* ref. 8.

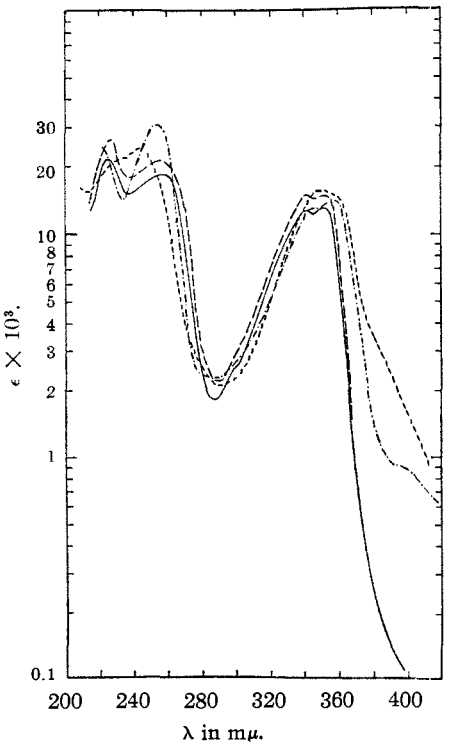


Fig. 4.—Influence of position of halo-substituent on spectra of 3-methyl-*n*-bromo-4-(4′-diethylamino-1′-methylbutylamino)-quinolines in 0.01 *N* hydrochloric acid: —, 5; – – –, 6; — —, 7; –·–·, 8-compound.

same general regions, as might be expected. 4-(4′-Diethylamino-1′-methylbutylamino)-8-iodo-3-methylquinoline, even as an outer member of a series, behaves surprisingly. The first maximum (in the 220 mμ region) is absent, but may possibly be present below 209 mμ, at which wave length observation was begun, and indicated a descending slope. This 8-iodoquinoline derivative also fails to exhibit more than two maxima in the range studied. The lability of the iodine in the 5-substituted series (*cf.* ref. 13d) precluded the possibility of study of that base, hence we find that only the 7-iodo compound shows maxima at four positions, more after the pattern of the chloro and bromo derivatives. Some of the observed effects in the 8-halogen compounds are probably the result of the proximity of that grouping to the ring nitrogen. In our previous work[17,18] we have also noted the deviation of the 8-substituted hydroxy and amino quinolines (bearing no other substituents on the pyridinoid or benzenoid cycles) from the other bz-substituted compounds. The size as well as the nature of the group in 8-substituted quinolines most probably influences the polarity of the molecule. It might be noted that the large iodine atom may have considerable steric effects.

The influence of the variation of the side-chain in position 4 of the quinolines can be studied in Table III. The bathochromic and hyperchromic influences of the 3-methyl grouping are once again

(17) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).
(18) Steck and Ewing, *ibid.*, **70**, 3397 (1948).

TABLE IV

SPECTRAL CHARACTERISTICS OF SOME 4-AMINOQUINOLINE DERIVATIVES IN ALCOHOLIC SOLUTION

Compound[a]	SN[b]	Maxima, wave length in mμ, ε × 10³				
Parent Type 4-Aminoquinoline Derivatives						
R = I	6732	215(31.4)	234(14.3)	328(12.2)		
7-Chloro-4-aminoquinoline Derivatives						
R = IV	12309	220(35.0)	250(15.2)	255(15.6)	328(11.6)	338(10.0)[c]
3-Methyl-7-chloro-4-aminoquinoline Derivatives						
R = IV		222(38.0)	252(21.0)	338(9.3)	350(6.7)[c]	
R = VIII		223(36.0)	255(22.0)	335(8.9)		
3-Methyl-5-chloro-4-aminoquinoline Derivatives						
R = II	9299	226(29.7)	244(23.0)	334(9.9)		

[a] The side-chains have been given the same numbers as in Table III. [b] Survey Number, *cf.* ref. 8. [c] Inflection point.

TABLE V

SPECTRAL CHARACTERISTICS OF SOME 4-AMINOQUINOLINE DERIVATIVES IN 0.01 *N* SODIUM HYDROXIDE

Compound[a]	SN[b]	Maxima, wave length in mμ, ε × 10³			
Parent Type 4-Aminoquinoline Derivatives					
R = I	6732		235(14.1)[c]	325(10.9)	
7-Chloro-4-aminoquinoline Derivatives					
R = I	7618		254(17.8)	330(12.0)	334(11.5)[c,d]
R = IV	12309	220(34.0)	252(16.0)	324(9.6)	
7-Chloro-3-methyl-4-aminoquinoline Derivatives					
R = IV		225(37.0)	255(18.0)[c]	328(6.8)	
R = VIII		225(36.0)	245(21.0)[c]	330(7.4)	
5-Chloro-4-aminoquinoline Derivatives					
R = I	12158	220(30.0)	246(16.0)	332(12.5)	
5-Chloro-3-methyl-4-aminoquinoline Derivatives					
R = II	9299	227(30.0)	250(15.0)[c]	330(6.5)	
6-Chloro-3-methyl-4-aminoquinoline Derivatives					
R = I	9905		242(23.5)	320(6.5)	
8-Bromo-3-methyl-4-aminoquinoline Derivatives					
R = I	12160	230(31.0)		325(7.8)	

[a] The side-chains have been numbered as in Table III. [b] Survey Number, *cf.* ref. 8. [c] Inflection point. [d] *Cf.* Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946), also ref. 9.

to be noted when the basic chain is varied. Even a terminal secondary amine chain, or a sulfur-interrupted chain do not alter this characteristic effect. Variation in the chain does not markedly influence the spectral characteristics in an homologous series.

The effects of the variation of *p*H upon the spectra of a number of these compounds have also been studied. Results of this work are in general agreement with those reported by Irvin and Irvin.[9] In Tables IV and V it can be seen that the 7-chloro - 4′ - [2′ - (2′ - hydroxyethylamino) - ethylamino]-quinoline; the related 3-methyl compound; 5-chloro-4-(4′-diethylaminobutylamino)-quinoline; 7-chloro-4-(3′-diethylaminopropylamino)-3-methylquinoline; and also the 6-chloro and the 8-bromo-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline all show hypsochromic shifts as there is an increase in *p*H. This is in complete agreement with the results shown in Figs. 2–7 of the contribution of Irvin and Irvin.[9] Furthermore, the bifurcation in the 330–350 mμ range which is apparent at *p*H 1 is degenerated with increasing *p*H and the second maximum becomes an inflection point at *p*H 7–8, finally disappearing entirely in the alkaline range.

Experimental

I. **Preparation of Quinoline Derivatives.**—All of the 4-aminoquinoline derivatives which were here studied have formed the basis of separate contributions from these laboratories.[7b,11-14] The samples employed were ordinarily from batches submitted for testing under auspices of the Office of Scientific Research and Development and given SN designation.[8]

II. **Absorption Spectra.**—The spectrophotometric studies were all carried out with a Beckman Quartz Spectrophotometer, Model DV, Serial No. D-377. The method and solvents employed were as described in earlier contributions of this series.[17,18]

Acknowledgment.—The authors wish to express their gratitude to a number of co-workers for the efforts which have led to this contribution. To Drs. Suter and Buck we owe much for

their helpful counsel through the entire program of research relating to antimalarials. The compounds, all prepared in this Institute, were the result of patience as well as skill on the part of many, who are indicated in references. The careful spectrophotometric studies have been due, in the main, to Mrs. E. Faulkner, Mrs. M. Becker, Mrs. K. Grant and Miss J. Gould. We are further indebted to Mrs. B. Beecher for her patient and meticulous efforts in plotting the curves.

Summary

The ultraviolet absorption spectra of thirty-five substituted quinolines have been reported.

Fifteen out of the sixteen possible bz-halo-3-methyl-4-(4′-diethylamino-1′-methylbutylamino)-quinolines have been studied and the influence of halo-substitution has been discussed critically.

Spectral changes due to the influence of the methyl or propyl groups in the 3- position, as well as the influence of the methyl group in position 2 has been pointed out.

The 4-diethylamino-1-methylbutylamino side chain has been replaced by eight other side chains and the resulting spectra have been discussed.

Finally the influence of *p*H on the resonance of these substituted quinolines has been investigated and compared with other data reported in the literature.

RENSSELAER, N. Y. RECEIVED MARCH 16, 1948

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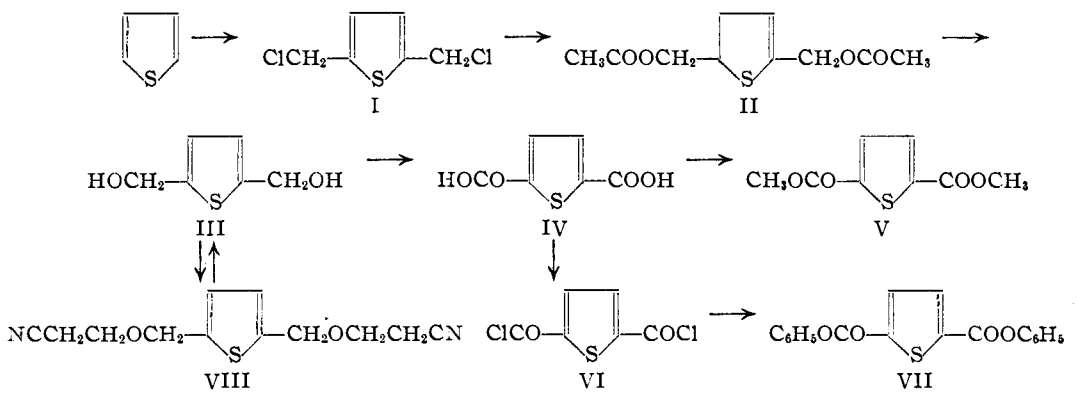
2,5-bis-(Chloromethyl)-thiophene and Some of its Derivatives

BY JOHN M. GRIFFING AND L. FRANK SALISBURY

Introduction

In the course of investigations of linear condensation polymers a number of difunctional intermediates containing the thiophene nucleus have been prepared. All were based on the intermediate, 2,5-bis-(chloromethyl)-thiophene, I, for which a simple method of preparation was developed. The preparation and properties of the new compounds are described in this paper.

The addition of thiophene to a mixture of formalin and strong hydrochloric acid in the absence of other catalysts gave I, together with some of the monofunctional derivative, 2-chloromethylthiophene, which has previously been described by Blicke and Zienty.[1] Treatment of I with potassium acetate in glacial acetic acid gave the diacetate, II, which was hydrolyzed to the glycol, III, not isolated in this instance, but oxidized directly to the dicarboxylic acid, IV. The diacid was converted to a dimethyl ester, V, the melting point (148.5–149.5°) of which corresponded to that of the dimethyl ester of thiophene-2,5-dicarboxylic acid (146–147°) reported by R. Bonz[2] who prepared the acid by a sodium amalgam condensation of 2,5-dibromothiophene and ethyl chlorocarbonate and esterified its silver salt with methyl iodide. The 2,3 isomer melts at 60°,[3] while the 2,4 isomer melts at 120–121°.[4] The positions on the thiophene nucleus occupied by the original chloromethyl groups are thus demonstrated, it having been shown that monochloromethylation occurs at the 2 position.[1] That the second chloromethyl group should enter the 5 position of thiophene is in agreement with observed reactions of thiophenes substituted in the 2 position by an electron donor.



Fusion of thiophene-2,5-dicarbonyl chloride, VI (from IV and thionyl chloride), with phenol

(1) F. F. Blicke and M. F. Zienty, THIS JOURNAL, **63**, 2945 (1941).

(2) R. Bonz, *Ber.*, **18**, 2305–2307 (1885).

(3) W. Grünewald, *ibid.*, **20**, 2585–2587 (1887).

(4) N. Zelinsky, *ibid.*, **20**, 2017–2035 (1887).