[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Absorption Spectra of Heterocyclic Compounds. VI.[1] Some Polysubstituted 4-Aminoquinoline Derivatives

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

The emphasis which was placed upon 4-aminoquinoline derivatives during wartime research on potential antimalarials led to our interest in the absorption spectra of these types, both from the standpoint of further characterization and the possibility of correlating structure and activity. In previous contributions, simple aminoquinolines,[3] bz-halo-4-aminoquinolines,[4] and certain 7-alkoxy and aryloxy 4-aminoquinolines[5] have been considered. The present paper contains data relating to the absorption spectra of a number of 4-aminoquinoline derivatives bearing a chlorine atom in position 7, with another substituent in position 6 or with a second halogen atom in position 3, all of the bz-dichloro types, and some 3-methyl-4-aminoquinolines having a bz-methyl or alkoxy substituent. Attempts have been made to interpret certain features of the absorption spectra on the basis of structure. All of the compounds employed in these studies were prepared in these laboratories by use of the well-known Conrad–Limpach method.[6-11] Most of the 4-aminoquinolines were tested for antimalarial activity in conjunction with the program of the Office of Scientific Research and Development.[12]

The fact that the most satisfactory schizontocides among 4-aminoquinolines bear a halo substituent in position 7[12] led us to study the influence of halogens upon the absorption spectra of such types.[4] It seemed of interest to investigate further certain 4-amino-7-chloroquinolines bearing a substituent in position 6. Since the variations in the side-chain have been found to cause little change in the absorption spectra of 4-dialkylaminoalkylaminoquinolines,[4] 6,7-dichloro-4-(3-diethylamino-2-oxypropylamino)-quinoline was compared with 7-chloro-4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline and the corresponding 6-methyl compound (Fig. 1). The patterns of the spectral curves of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-6-methylquinoline and of the related compound having the nuclear alkyl group in position 3 (SN 6911,[12] Fig. 3 of the fourth contribution of this series[4]), both in 0.01*N* HCl, are quite closely related. This is, apparently, indicative of the relatively slight influence of the position of the alkyl group upon the enamine-ketimine tautomerism of the 4-aminoquinolines. This matter is of importance, for the introduction of the methyl group into the nucleus of the 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline molecule results in considerable alteration of both antimalarial activity and absorption spectrum.[4,13] Change of the position of the alkyl group, however, not only does not lead to much variation in spectrum, but also does not cause appreciable modification of the activity of the compounds (*cf.* ref. 8). It is indeed surprising that the differences between the 3- and the 6-methyl-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinolines should prove to be of relatively minor nature despite earlier studies concerning simple hydroxy[14] and amino derivatives.[3] It appears that the replacement of the 6-methyl grouping by a methoxy rest causes relatively little modification in the spectrum save for a slight bathochromic shift. These findings may be explained on the basis of the greater nucleophilic behavior of the alkoxy group in 7-chloro-4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline as compared with the nuclear alkyl group in the 6-methyl base. Interestingly, the spectrum of 6,7-dichloro-4-(3-diethylamino-2-oxypropylamino)-quinoline in 0.01 *N* HCl exhibits greater similarity to the form of the other two 6,7-disubstituted 4-aminoquinolines than to the 7-chloro type.[4]

The spectral curves for three 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinolines bearing different halogens in position 3 are shown in Fig. 2. It is readily noted that the alteration of the halogen from chlorine to iodine produces a bathochromic shift, but that there is a concomitant de-intensification through most of the spectrum. This feature is more or less similar, in its general aspects, to the effects produced upon varying the 7-halo substituent while maintaining a 3-methyl group.[4] The presence of but one flat maximum in the 340–360 region of the spectrum of 7-chloro-4-(3-diethylamino-2-oxypropylamino)-3-iodoquinoline may well be the result of steric effects of the iodine atom upon the enamine-ketimine tautomerism.

In the consideration of the bz-dichloro-4-

(1) Previous contribution of this series: Steck, Ewing and Nachod, THIS JOURNAL, **71**, 238 (1949).

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

(3) Steck and Ewing, THIS JOURNAL, **70**, 3397 (1948).

(4) Steck, Ewing and Nachod, *ibid.*, **70**, 3410 (1948).

(5) Nachod, Steck and Ewing, *ibid.*, **70**, 3954 (1948).

(6) Steck, Hallock and Holland, *ibid.*, **68**, 129, 132 (1946).

(7) Steck, Hallock, Holland and Fletcher, *ibid.*, **70**, 1012 (1948).

(8) Steck, Hallock and Suter, *ibid.*, **70**, 4063 (1948).

(9) Steck and Hallock, *ibid.*, in press.

(10) Surrey and Hammer, *ibid.*, **68**, 1244 (1946).

(11) Surrey and Cutler, *ibid.*, **68**, 2570 (1946).

(12) All compounds tested under the OSRD were assigned Survey Numbers (SN). Data relating to such studies are tabulated in a monograph "Antimalarial Drugs, 1941–1945," edited by F. Y. Wiselogle, Edwards Bros., Ann Arbor, Mich., 1946.

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

(14) Ewing and Steck, *ibid.*, **68**, 2181 (1946).

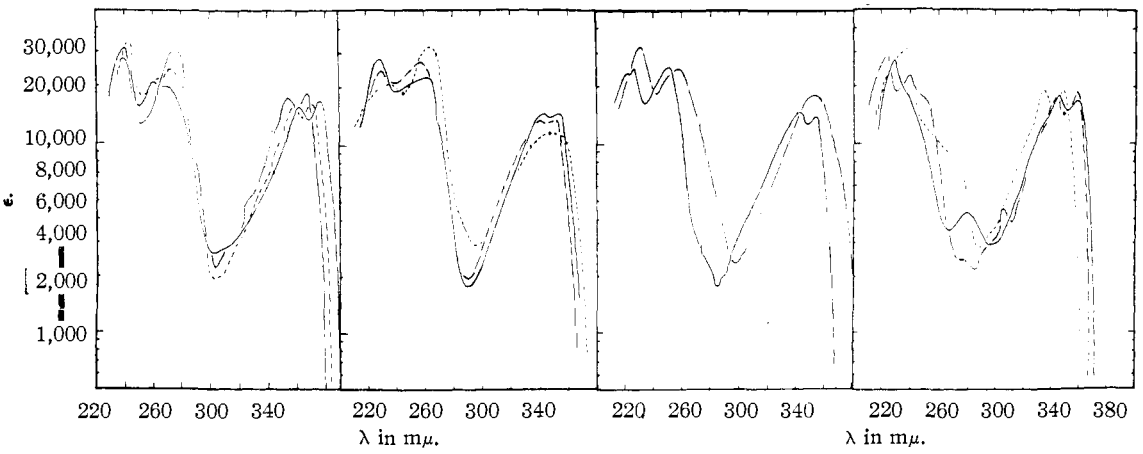

Fig. 1.—6-Methoxy-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline; —— 6-methyl-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline; - - - - -, 6,7-dichloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline.

Fig. 2.—3,7-Dichloro-4-(4-diethylamino-1-methylbutylamino)-quinoline; —— 3-bromo-7-chloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline; - - - - 3-iodo-7-chloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline.

Fig. 3.—5,6-Dichloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline; —— 5,7-dichloro-4-(4-diethylamino-1-methylbutylamino)-quinoline.

Fig. 4.—5,8-Dichloro-4-(4-diethylamino-1-methylbutylamino)-quinoline; —— 6,8-dichloro-4-(4-diethylamino-1-methylbutylamino)-quinoline; - - - - - 7,8-dichloro-4-(2-hydroxy-3-diethylaminopropylamino)-quinoline.

All in 0.01 *N* HCl solution.

aminoquinoline derivatives, it seems desirable to arrange the compounds into those bearing a 5-chloro group (Fig. 3) and those with that substituent in position 8 (Fig. 4). The 6,7-dichloro type was discussed with other 6,7-disubstituted 4-aminoquinolines. The absorption spectrum of 5,7 - dichloro - 4 - (4 - diethylamino - 1 - methylbutylamino)-quinoline in 0.01 *N* HCl (Fig. 3) may be compared with those of 5- and 7-chloro-4-(4 - diethylamino - 1 - methylbutylamino) - quinolines (Fig. 3 of paper IV of this series[4]). It appears that the curve for the dichloro compound is an envelope of the 5- and 7-chloro bases in the 340–360 mμ region with a super-position of the several maxima into one at 350 mμ. The intermingling of the influences of each of the chloro groups does not seem to occur as much in the spectrum of 5,6-dichloro-4-(3-diethylamino-2-oxypropylamino)-quinoline as it did in the instance of 5,7 - dichloro-4 - (diethylamino - 1-methylbutylamino)-quinoline. As earlier noted,[4] the variation in the side-chain is considered to have little influence on the spectral patterns of such types. The 5,6-dichloro compound shows considerable similarity to the 5-chloro base in the four maxima, with the bifurcation characteristic of the monosubstituted 4-aminoquinoline derivatives.

As shown in Fig. 4, the presence of a chlorine in position 8 of the bz-dichloro-4-aminoquinoline types evokes a variety of effects. The spectra of 5,8-, 6,8- and 7,8-dichloro-4-aminoquinoline derivatives in 0.01 *N* HCl are compared. Although the spectral pattern of 5,8-dichloro-4-(4 - diethylamino - 1 - methylbutylamino) - quinoline is more similar to other 4-aminoquinolines studied, showing four maxima (at 228, 280, 344 and 358 mμ), little more can be said. While the related 6,8-dichloro compound has five maxima (224, 239, 306, 342 and 358 mμ), the spectrum of 7,8-dichloro-4-(3-diethylamino-2-oxypropylamino)-quinoline has three, at 238, 334 and 348 mμ. These data make it appear that a 7-chloro grouping in the bz-dihalo-4-aminoquinolines leads to decrease in fine structure through its positional influences. The unique nature of this position has again been emphasized.

It seemed of interest to study certain bz-alkoxy 3-methyl-4-aminoquinolines and compare the spectra in 0.01 *N* HCl with related bz-halo-3-methyl-4-aminoquinolines.[4] The general form of the spectral curves of the 4-(4-diethylamino-1-methylbutylamino)-3-methylquinolines bearing a methyl group in position 6 or 8 was similar to

TABLE I

SPECTRAL CHARACTERISTICS OF CERTAIN 4-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO)-3-METHYLQUINOLINE DERIVATIVES IN 0.01 *N* HCl

Bz-Substituent Alkyl	Maxima: λ in mμ, ε × 10^{-3}			
6-Methyl	220(24.5)	250(33.0)	342(15.0)	350–356(14.0)[a]
8-Methyl		240(11.4)	341(6.7)	352(6.6)
5,6-Dimethyl	228(13.2)	256(31.5)	280(3.6)[b]	362(11.0)
6,7-Dimethyl	220(27.6)	250(33.7)	340(14.2)	350(14.5)
Alkoxy				
6-Methoxy	221(16.7)	255(29.3)	315(3.4)[b]	355–360(10.7)[a]
8-Methoxy	242(37.8)	285(3.9)	348(13.4)	
6-Ethoxy	220(11.6)	253(20.2)	315(2.5)[b]	359(7.9)
7-Ethoxy[c]	233(28.7)	259(17.8)	330(14.5)	
8-Ethoxy	245(41.1)	290(4.1)	346(14.9)	

[a] Plateau. [b] Inflection point. [c] Included here for purposes of comparison. Previously reported by Nachod, Steck and Ewing.[5]

that of the bases having an halogen in those positions, hence the data are presented in tabular form (Table I). The 8-substituted types exhibited greater similarity than did the corresponding 6-substituted compounds. A single nucleophilic alkyl group on the benzene moiety in general led to a de-intensification with little alteration in pattern. The presence of an additional methyl group in position 5 or 7 of the 6-substituted type resulted in more complex effects, as may be noted in Table I.

Experimental Part

The requisite compounds were all available from researches carried out in these laboratories (refs. 6–11 inc.), and the spectrophotometric studies were made with aid of a Beckman Quartz Spectrophotometer, Model DU, Serial No. D-377 (*cf.* ref. 14).

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Summary

The ultraviolet absorption spectra of nineteen polysubstituted 4-dialkylaminoalkylaminoquinolines have been determined in 0.01 *N* hydrochloric acid.

The influence of various substituents upon the spectra of 4-amino-7-chloroquinoline derivatives has been studied. All of the possible bz-dichloro- and some 3-methyl-bz-alkyl or alkoxy 4 - (4 - diethylamino - 1 - methylbutylamino) - quinolines have been subjected to similar investigation.

It is concluded that little, if any, clear interrelation may be found between the absorption spectra here determined and antimalarial activity of 4-aminoquinoline types.

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Metal Fluorides as Fluorinating Agents[1]

BY CHARLES I. TEWKSBURY[2] AND HELMUT M. HAENDLER

Many recent studies on the fluorination of hydrocarbons and halogenated hydrocarbons have utilized the more active metal fluorides, such as cobalt(III) fluoride, manganese(III) fluoride, cerium(IV) fluoride, etc., in attempting to produce highly or completely fluorinated products.[3] Fowler, *et al.*,[4] have related, in a general way, the reactivity of these more active metal fluorides to the oxidation–reduction potential of the couple composed of the higher and lower valent ions of the respective metals.

The use of less reactive metal fluorides in the halogen exchange reaction has long been known. Antimony, mercury and silver fluorides are quite effective in this type of reaction and have been widely used. The use of cadmium,[5a] calcium,[5b] potassium,[5c] thallium,[5d] and zinc[5e] fluorides has also been reported.

In an attempt to relate the reactivity of some of the metal fluorides to other properties, a comparison of the reactivities of a number of fluorides was undertaken. The criterion was the relative effectiveness of the fluoride in the vapor phase conversion of benzotrichloride (α,α,α-trichlorotoluene) to benzotrifluoride (α,α,α-trifluorotoluene).

Experimental

Apparatus.—The electrically-heated reactor furnace was made from a 24-inch section of 2-inch copper pipe. It was fitted with a coaxial stirrer, passing through a Teflon-packed bearing and rotated at about 25 r. p. m. G-355 Silver Brazing Alloy (American Platinum Company) was used on internal joints.

The benzotrichloride was vaporized by dropping the liquid from a calibrated reservoir into a heated flask, connected to the reactor by a copper-to-glass seal. The product was collected in two copper traps, one cooled by ice–salt and the other by Dry Ice in trichloroethylene.

Procedure.—A stream of vaporized benzotrichloride, diluted with dry nitrogen, was passed through the continuously stirred mass of finely divided fluoride at 225°. The nitrogen space velocity (cc. of nitrogen/ml. of fluoride/hour) and the addition rate (ml. of benzotrichloride/hour) were held constant at 22 and 10, respectively, during the series of reactions.

The product in the traps was treated with 10% sodium hydroxide solution, washed with water, dried over Drierite, and fractionated through a 50-plate column packed with $^3/_{32}$" nickel helices and fitted with a semi-micro distilling head.[6] The benzotrifluoride was identified by boiling

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(2) This paper represents parts of theses presented by Charles I. Tewksbury to the University of New Hampshire in partial fulfillment of the requirements for the degrees of Bachelor of Science and Master of Science.

(3) Symposium on Fluorine Chemistry, *Ind. Eng. Chem.*, **39**, 236–434 (1947).

(4) Fowler, *et al.*, *ibid.*, **39**, 343 (1947).

(5) (a) Halbedel, Cardon and Schenk, U. S. Patent 2,442,290 (May 25, 1948); (b) E. I. du Pont de Nemours and Co., French Patent, 730,874 (1932); (c) Hoffmann, THIS JOURNAL, **70**, 2596 (1948); (d) Ray, *Nature*, **132**, 173 (1933); (e) Meslans, *Ann. chim. phys.*, [7] **1**, 411 (1894).

(6) Haendler, *Anal. Chem.*, **20**, 596 (1948).