


Summary

The absorption spectra of eighteen compounds of the type A——B have been measured in which A is amino or alkyl substituted amino and B is one of six different electron attracting groups. The spectra of the compounds are very similar, being characterized by two bands, a long wave length band of high extinction and a short wave length band of low extinction.

It has been found for thirteen of the compounds (all those without nitro groups) that the ratios of the frequencies of the two bands are a linear function of the wave length of the main bands. These compounds fulfill the criteria for x' bands and it is concluded the two bands are x and x' bands. The ratio of the frequencies of the short to the long wave length band $\bar{\nu}'/\bar{\nu}$ is less than two and increases in the series as λ increases. The ratio of the extinction coefficients ϵ'/ϵ decreases as $\bar{\nu}'/\bar{\nu}$ increases.

The nitro compounds are anomalous, the second bands coming at too short a wave length and having too high an extinction to fit in the series. It

is proposed that the second band in these compounds is a combination of the x' band and the "partial" due to the nitro group.

A change in solvent results in a big shift in λ with some of these compounds. The shift is correlated with the ability to form hydrogen bonds with the solvent and the possibility of dipole interactions between solvent and solute.

The basicity of the A group is related to λ and ϵ , the more basic this group the higher λ and ϵ . This fact is correlated with resonance.

Substitution of an alkyl group for hydrogen in the A group results in an average shift in λ of 11 m μ toward longer wave length.

The relative chemical reactivity of some of the compounds bears a relation to where they absorb and both observations have been correlated with resonance.

Three new compounds, *p*-ethylaminoacetophenone, *p*-dimethylaminobenzenesulfonamide and *p*-diethylaminobenzenesulfonamide, have been made.

SAN FRANCISCO, CALIF.

RECEIVED MARCH 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SIENA HEIGHTS COLLEGE]

The Spectrophotometric Estimation of Methoxy-cinchona Alkaloids¹

BY MIRIAM MICHAEL STIMSON AND MARY AGNITA REUTER²

In the past, spectra of various cinchona alkaloids in ethanol, ether or dilute acid solutions have been reported³ in the range 2250–4000 Å. To facilitate the estimation of methoxyl cinchona alkaloids in crude extracts the spectra of the four common natural occurring alkaloids and some related compounds have been measured over a pH range 1–10.

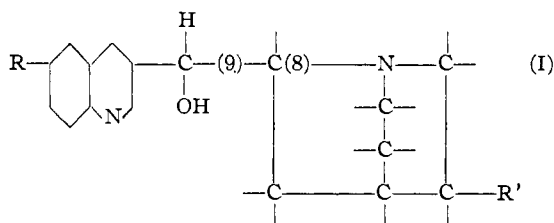
Discussion

The general uniformity of the spectra of quinine (Fig. 1), quinidine (Fig. 2), epiquinine (Fig. 3), epiquinidine (Fig. 4), dihydroquinine (Fig. 5) and dihydroquinidine (Fig. 6) indicates that there is little effect on the spectrum if the group substituted at R' in (I) is varied because the contribution of R' is isolated from the aromatic ring system by the spectroscopically ineffective piperidine ring, thus preventing either conjugation or interaction through resonance. The changes observed in the spectra of these alkaloids are

(1) This work was conducted as part of the research program of Institutum Divi Thomae, with which this Laboratory is affiliated.


(2) Sister Miriam Michael Stimson, O. P., and Sister Mary Agnita Reuter, O. P.

(3) Fischer, "Die physikalische Chemie in der gerichtlichen Medizin und in der Toxikologie mit spezieller Berücksichtigung der Spectrographie und der Fluorescenz-Methoden," Zurich, 1925; Manta, *Z. physik. Chem.*, **B22**, 465 (1933); Heidt and Forbes, *THE JOURNAL*, **56**, 2701 (1933); Fuchs and Kamptisch, *Sci. Pharm.*, **6**, 125 (1935); Carol, *J. Off. Agri. Chem.*, **26**, 238 (1943); Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).



thus attributed to changes in electronic configuration of the quinoline ring, either by introduction of an auxochrome, by weighting, or by variation in the average planarity of the molecules as controlled by epimerism at C₈ and C₉, or at C₆.

Although the effect is slight it will be noted that in quinine and its three epimers there is some variation in the effect of pH on the 2800 Å. maximum. In the case of quinine all indications of an absorption band have disappeared and a well-defined minimum appeared at pH 4. In quinidine this becomes evident at pH 3, while in both epiquinine and epiquinidine no clear cut minimum is observed until pH 1.0. It is of interest also to note that though both epiquinine and epiquinidine have lower over-all absorption curves than the parent compounds, epiquinidine

with the same quinoline ring  arrangement

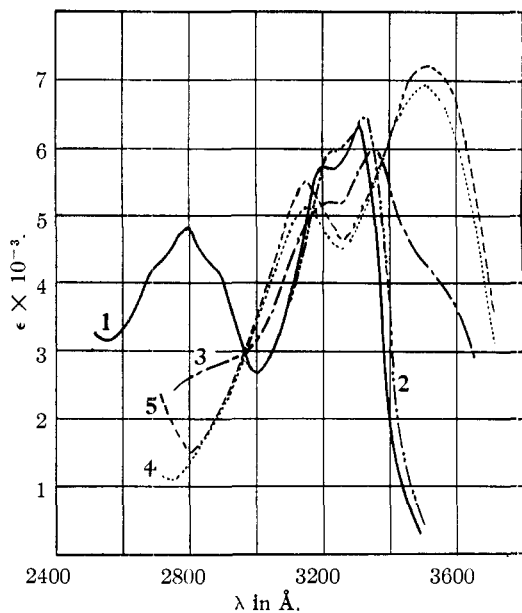


Fig. 1.—Quinine: 1, pH 's 9.5, 7.5; 2, pH 6.0; 3, pH 4.0; 4, pH 1.0; 5, pH 0.5.

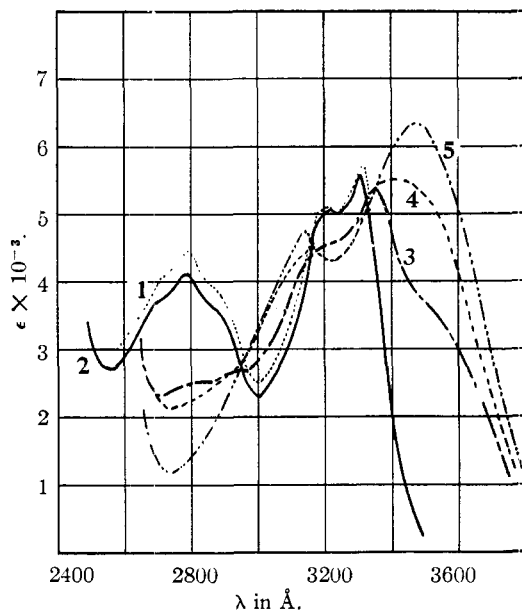


Fig. 2.—Quinidine: 1, pH 8.0; 2, pH 6.0; 3, pH 4.0; 4, pH 3.0; 5, pH 1.0.

as quinine, absorbs more strongly than epiquinine by about the same amount as quinine does more than quinidine.

This same uniformity in the spectral pattern is seen in the case of cinchonine and related compounds (Figs. 7-10). Cinchonidine and dihydrocinchonidine have slightly stronger absorption maxima than have cinchonine and dihydrocinchonine, respectively.

Moreover, it will be noted that the well defined invariant point of the levo-base, quinine,

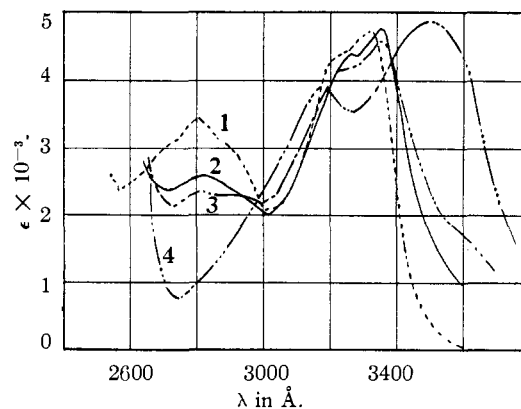


Fig. 3.—Epiquinine: 1, pH 8.2; 2, pH 5.2; 3, pH 3.0; 4, pH 1.0.

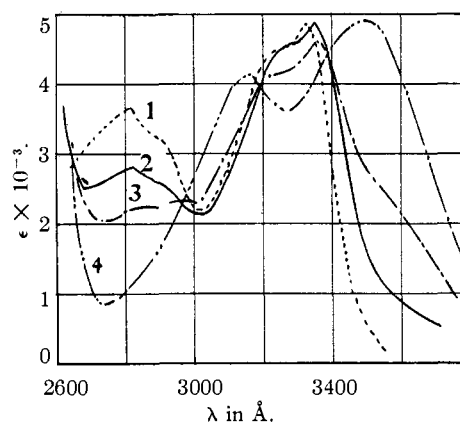


Fig. 4.—Epiquinidine: 1, pH 8.2; 2, pH 4.8; 3, pH 2.0; 4, pH 1.0.

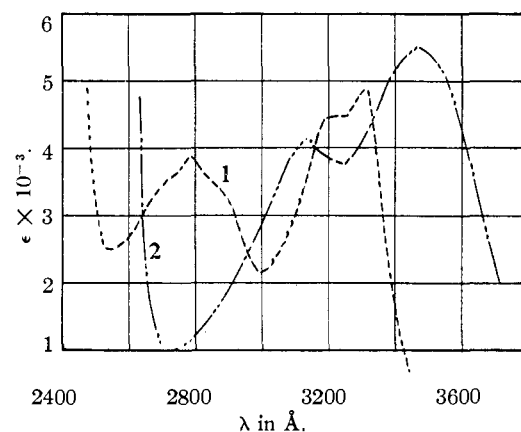


Fig. 5.—Dihydroquinine: 1, pH 6.0; 2, pH 2.0.

is also apparent in the levo-base, cinchonidine, indicating that possibly this may be related to the optical configurations of these compounds and that the energy distributions accountable for the appearance of these isobestic points are destroyed by epimerism at either or both C_8 and C_9 .

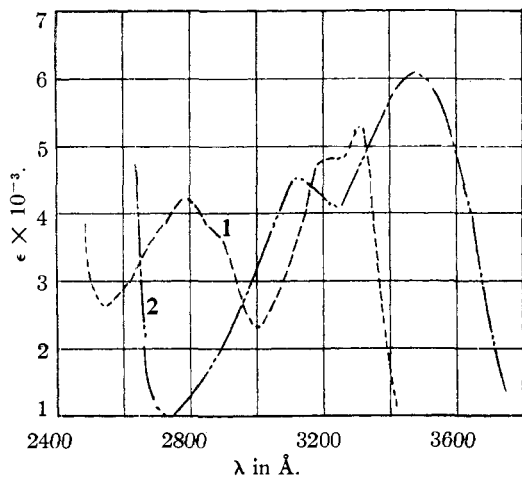


Fig. 6.—Dihydroquinidine: 1, pH 6.0; 2, pH 2.0.

In the broader aspects there is sufficient difference in these two classes of spectra—the quinine type (Q) and the cinchonidine type (C) to permit estimation of one in the presence of the other, as will be seen in Fig. 11, which shows the absorption curves of a number of mixtures of the two types. Although spectra of type (Q) are given by quinine, its epimers and derivatives, in routine assay of cinchona barks and crude extracts an estimation of the amount of quinine present can be rapidly made using the spectral characteristics, especially since the amounts of quinidine encountered represent but a very small percentage of the whole⁴ and practically all the

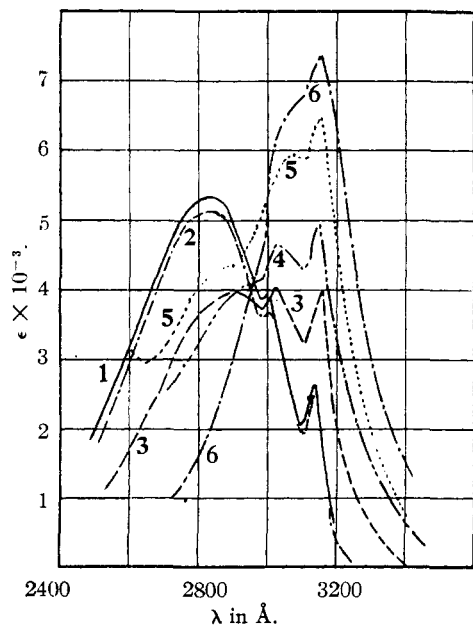


Fig. 7.—Cinchonine: 1, pH 8.0; 2, pH 6.0; 3, pH 4.0; 4, pH 3.5; 5, pH 3.0; 6, pH 1.0.

(4) Henry in "Allen's Commercial Organic Analysis," Vol. VII, fifth edition, The Blakiston Co., Philadelphia, Pa., 1929.

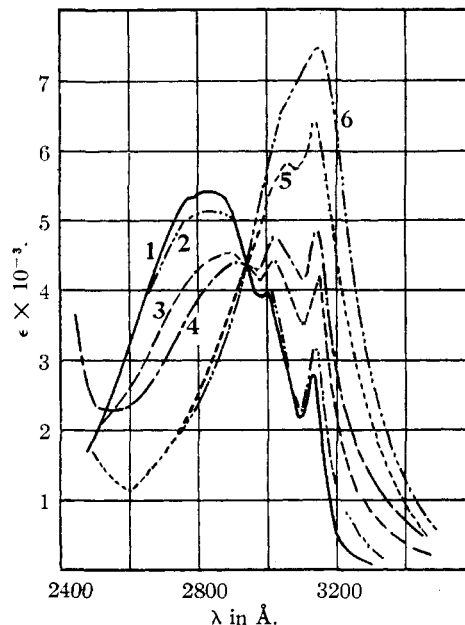


Fig. 8.—Cinchonidine: 1, pH 8.0; 2, pH 6.0; 3, pH 5.0; 4, pH 4.0; 5, pH 3.0; 6, pH 1.0.

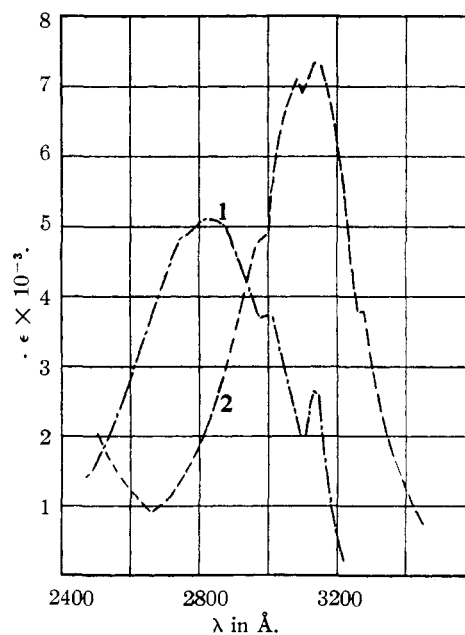


Fig. 9.—Dihydrocinchonine: 1, pH 6.0; 2, pH 1.

(Q) type absorption is due to quinine. Moreover, the spectral differentiation between the cinchona and the methoxyl-cinchona alkaloids permits the detection and estimation of cinchonidine in commercial quinine, in which, because of double salt formation of the sulfates, it is a common contaminant.

Figure 12 represents the dependence at 3310 Å. of $E_{1\text{cm}}^{1\%}$ on the weight of quinine-quinidine (Q) in g./l. and also on the % (Q). It is seen

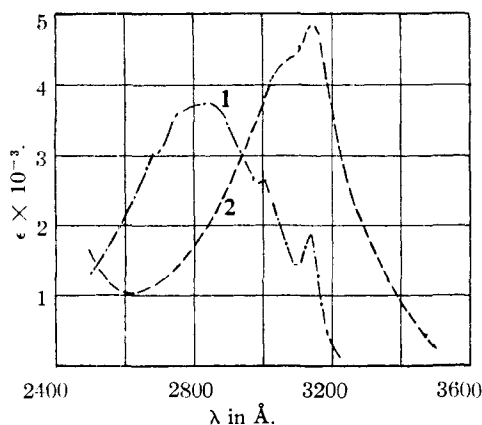


Fig. 10.—Dihydrocinchonidine: 1, pH 6.0; 2, pH 3.0.

that the values of $E_{1\text{cm.}}^{1\%}$ (calculated on the basis of total alkaloid) is a linear function of % (Q). Extrapolation to 0% (Q) gives an $E_{1\text{cm.}}^{1\%}$ of 3.4, of which 0.16 is due to the cinchonine-cinchonidine absorption and the remainder represents the error of the method which is approximately 2% (Q), or about 0.5–0.1 mg. of (Q)/l. in a sample of

TABLE I

DATA FOR 3310 Å.		
Log I_0/I	Concn. (alkaloid) g./l.	Concn. (quinine) g./l.
0.360	0.0427	0.0208
.286	.0385	.0166
.231	.0352	.0133
.189	.0325	.0106
.152	.0304	.0085
.123	.0287	.0068
.101	.0273	.0054

totaquine. However, in view of the assumptions concerning the presence of the isomers of quinine, this is not an unreasonable error and the loss of accuracy over some of the chemical methods is often justified in the saving of time, since an approximation of % (Q) can be finished in fifteen to twenty minutes. Figures 1–10 show that pH has a marked effect on the position and strength of the maxima of these alkaloids, hence to obtain reliable data the pH should be between 6.0–8.0. In routine work this can be obtained readily by preparing a stock solution of 95% ethanol at about pH 7.0–7.5. Table I gives the experimental data used in the construction of Fig. 12.

Figure 13 indicates the absorption spectrum of a typical sample of Totaquine USP XII. From Fig. 12 the 3310 Å. band corresponds to 25% (Q) which is in agreement with the values based on a typical analysis.⁵

(5) A. A. Hamilton, "Malaria and Anti-malarials," Board of Economic Warfare and Department of Commerce, Washington, D. C.

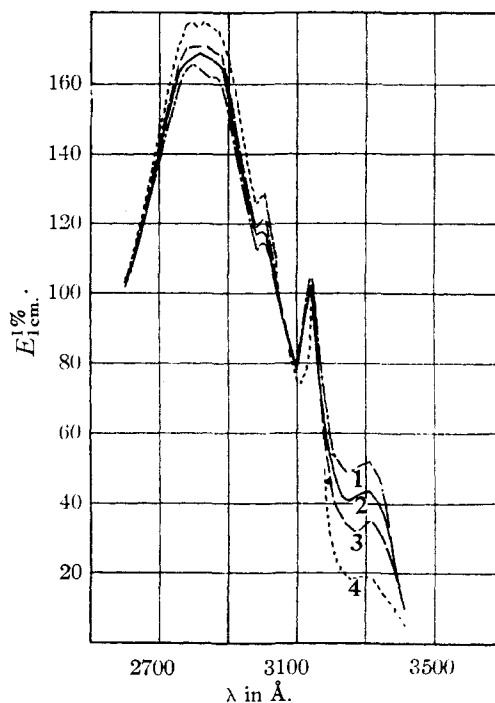


Fig. 11.—Cinchonidine-quinine mixtures: 1, 30% quinine; 2, 25% quinine; 3, 20% quinine; 4, 10% quinine.

Experimental

Method.—Weigh out accurately approximately 0.1 g. of totaquine and dissolve in ethanol to make 100 ml. of solution. Dilute 1 ml. of the above solution to 10 ml. and determine $E_{1\text{cm.}}^{1\%}$. The % (Q) can be read from the curve (Fig. 12).

Material.—The samples of quinine, quinidine, cinchonidine and cinchonine were recrystallized from hot alcohol to constant extinction. Because

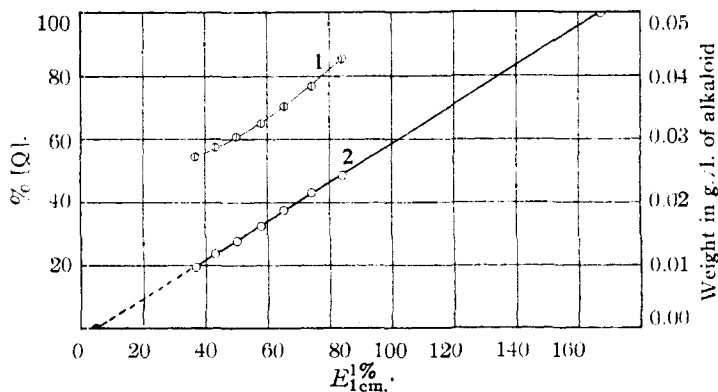


Fig. 12.—Dependence of $E_{1\text{cm.}}^{1\%}$ on concentration of alkaloid.

of the paucity of material no attempt was made to further purify the other samples.

The solutions were made either in ethanol-hydrochloric acid mixtures or ethanol-sodium hydroxide mixtures and the pH's were determined colorimetrically.

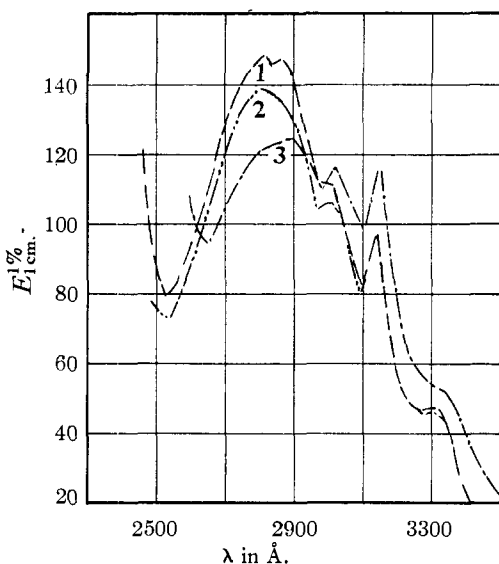


Fig. 13.—Totaquine U.S.P. XII: 1, pH 6.0; 2, pH 5.0; 3, pH 4.0.

Acknowledgments.—The bulk of the alkaloids was kindly furnished by Dr. Randolph T. Major of Merck and Company. The samples of epiquinidine hydrochloride and epiquinine hydrochloride were supplied, through the kindness of Dr. Leonard H. Cretcher and Mr. R. S. Tipson of Mellon Institute. We are also indebted to Mr. J. A. Oliva of the New York Quinine and

TABLE II

MELTING POINTS AND CRYSTAL HABIT		
Compound	M. p., °C. ^a	Crystal habit
Quinine	174.5	Soft rosetts
Quinidine	173	Monoclinic crystals, 2 mm. on major axis
Cinchonidine	205.5	Hexagonal plates, 2-3 mm. along major axis
Cinchouine	263 ^b	Very fine rhombohedra or spherulites
Dihydroquinine	171.5
Dihydroquinidine	168.4
Dihydrocinchonine	273
Dihydrocinchonidine	235 ^c

^a All melting points corrected. ^b To avoid decomposition the bath was preheated to 255°. ^c 229°, uncor.; the literature gives 229° for m. p.

Chemical Works for the sample of totaquine. It is a pleasure to acknowledge the discussions with Dr. E. S. Cook of Institutum Divi Thomae and Dr. J. M. Vandenberg of Parke, Davis & Company.

Summary

The spectra of a number of cinchona alkaloids have been reported together with a method for spectrophotometrically estimating the amount of the methoxy-alkaloids in crude materials with special reference to quinine-quinidine in totaquine.

ADRIAN, MICHIGAN

RECEIVED⁶ MARCH 20, 1946

(6) Original manuscript received April 7, 1945.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Allylic Chlorides. II. Catalytic Hydrolysis and Characterization of 1,3-Dichloropropene¹

BY LEWIS F. HATCH AND GEORGE B. ROBERTS

Although 1,3-dichloropropene has become readily available through the development of the high temperature substitutive chlorination of propylene,^{2,3} the two geometrical isomers (*cis* and *trans*) have not as yet been characterized as to their geometrical configuration. The present investigation was undertaken to effect this characterization.

A reaction mechanism has recently been proposed for the cuprous chloride catalyzed hydrochloric acid hydrolysis of allyl chloride which postulates that the ionization step of the hydrolysis is accelerated by the cuprous chloride-chloride ion complex forming an intermediate association complex or transition state with the double bond.⁴ If this hypothesis were valid, the actual

rate determining step would be the involvement of the cuprous chloride complex with the double bond, and any difference in the relative reaction rates of the two isomers of 1,3-dichloropropene in a similar hydrolysis would be related to geometrical configuration. The relationship between relative reactivity and geometrical configuration in reactions involving the double bond is well established. For example, Wright⁵ has reported that *cis*-methyl cinnamate mercurated about three times as fast as the *trans* isomer and *cis*-stilbene mercurated readily while the *trans* form did not mercurate. Thomas and Wetmore⁶ mercurated the isomeric 2-butenes and on the basis of reaction rates assigned the *trans* configuration to the isomer which reacted more slowly.

The results of a number of hydrolyses of 1,3-dichloropropene using a hydrochloric acid solution of cuprous chloride are given in Fig. 1.

(1) Presented in part at the Texas Regional Meeting of the American Chemical Society, Austin, Texas, December 8, 1945.

(2) Williams, *Trans. Am. Inst. Engrs.*, **37**, 157 (1941); *Chem. Met. Eng.*, **47**, 834 (1940).

(3) Groll and Hearne, *Ind. Eng. Chem.*, **31**, 1530 (1939).

(4) Hatch and Estes, *THIS JOURNAL*, **67**, 1730 (1945).

(5) Wright, *ibid.*, **57**, 1993 (1935).

(6) Thomas and Wetmore, *ibid.*, **63**, 136 (1941).