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

Ortho Esters, Imidic Esters and Amidines. IV. The Mechanism of the Reaction of Aniline with Ethyl Orthoformate[1]

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Claisen described the "mechanism" of this reaction in terms of the two steps, equations 1 and 2. According to this, N,N'-diphenylformamidine (I) is an intermediate in the formation of II. We believe that although this represents the sequence of events observed in the laboratory preparation of II, the true mechanism of the reaction involves the operation of the reversible reactions of equations 3 and 4. By means of ultraviolet absorption spectrophotometry and high dilution techniques we have now completed the demonstration of all four of the reactions of equations 3 and 4 and have indicated the sequence they take in producing the over-all changes of equations 1 and 2. A unique feature of this work is the demonstration that II is actually intermediate to I rather than *vice versa*, as has been thought. An explanation is offered for the different courses taken by the reaction of aniline with ethyl orthoformate and by the reaction of formimidic esters with aromatic amines in the presence of and absence of catalytic amounts of acids.

Claisen first prepared ethyl N-phenylformimidate (II) from aniline and ethyl orthoformate.[2] He claimed that the "mechanism" of the reaction consisted of two steps.

$$2C_6H_5NH_2 + (C_2H_5O)_3CH \longrightarrow \underset{\text{I}}{C_6H_5N{=}CH{-}NHC_6H_5} + 3C_2H_5OH \quad (1)$$

$$\underset{\text{I}}{C_6H_5N{=}CH{-}NHC_6H_5} + (C_2H_5O)_3CH \longrightarrow 2\underset{\text{II}}{C_6H_5N{=}CH{-}OC_2H_5} + C_2H_5OH \quad (2)$$

According to this scheme, N,N'-diphenylformamidine (I) is an intermediate in the formation of ethyl N-phenylformimidate (II). In practice this was undoubtedly true, since I was isolated in good yield from mixtures of aniline and ethyl orthoformate which had been heated a short time, and lengthy heating of I with excess ethyl orthoformate gave a poor yield of II.

It has been shown[3] that the reaction of I with ethyl orthoformate is dependent on acid catalysis and that high yields of II may be obtained by use of an acid catalyst with these reactants, or with aniline and ethyl orthoformate. It was proposed in a later publication[4] that II is actually produced directly from aniline and ethyl orthoformate and that I is produced by subsequent reaction of II with a second molecule of aniline. A mechanism of aminolysis analogous to acid-catalyzed hydrolysis of ortho esters was proposed for these reactions (Fig. 2 of ref. 4). The conversion of II into I was described in terms of the same mechanism. Although all of the reactions of the ortho esters, imidic esters and amidines discussed in these papers could be correlated well by means of this mechanism, no real proof of its correctness was available then. We are now able to report definite proof of the sequences most in doubt.

Simplification of the mechanism originally outlined by elimination of all unstable intermediates leads to a rather surprising result: All of the reactions between aniline, ethyl orthoformate, ethyl N-phenylformimidate (II) and N,N'-diphenylformamidine (I), can be represented by two reversible equations

$$C_6H_5NH_2 + (C_2H_5O)_3CH \underset{\text{r}}{\overset{\text{f}}{\rightleftharpoons}} \underset{\text{II}}{C_6H_5N{=}CH{-}OC_2H_5} + 2C_2H_5OH \quad (3)$$

$$\underset{\text{II}}{C_6H_5N{=}CH{-}OC_2H_5} + C_6H_5NH_2 \underset{\text{r}}{\overset{\text{f}}{\rightleftharpoons}} \underset{\text{I}}{C_6H_5N{=}CH{-}NHC_6H_5} + C_2H_5OH \quad (4)$$

(in the following discussion, f and r are used to designate the forward and reverse reactions of equations 3 and 4).

Addition of equations 3f and 4f gives equation 1. The fact that I is the first isolatable product may be attributed to reactions 3f and 4f being consecutive, and 4f being faster than 3f. We believe that Claisen's second reaction (2) is also complex, and consists of two steps: first, alcoholysis of I to produce aniline and one molecule of II (4r); second, reaction of the aniline with ethyl orthoformate to produce a second molecule of II (3f). The ethanol required for the initial alcoholysis may be present in the ortho ester as an impurity or may be produced by reaction with the acid catalyst.[4] Theoretically, only one molecule is necessary to start the process, since two molecules are produced by 3f while only one is used up by 4r. Thus, addition of equations 4r and 3f gives equation 2.

Reaction 4f is well known[4-6]; it is immeasurably fast if more than a trace of acid is present.[4] There seems little doubt that reaction 3r occurs. Knott[7] reported that when II is treated with a carboxylic acid or sulfonic acid in alcoholic solution, ethyl orthoformate and a salt of I are formed. We have obtained similar results using hydrochloric and picric acids. These reactions must involve alcoholysis of II (3r), the aniline reacting as fast as it is formed with the remaining II according to equation 4f.

The present investigation was undertaken to seek experimental evidence for the occurrence of reactions 3f and 4r. Since it was thought that both of these reactions, under the conditions favoring their occurrence, are followed by rapid consecutive reactions, it was recognized that it would be difficult or impossible to demonstrate them in the

(1) Presented at the Regional Conclave of the Southwest and Southeast Sections of the American Chemical Society, New Orleans, La., December 11, 1953.

(2) L. Claisen, *Ann.*, **287**, 362 (1895).

(3) R. M. Roberts, THIS JOURNAL, **71**, 3848 (1949).

(4) R. M. Roberts, *ibid.*, **72**, 3603 (1950).

(5) H. L. Wheeler and T. B. Johnson, *Ber.*, **32**, 35 (1899).

(6) E. B. Knott and R. A. Jeffreys, *J. Org. Chem.*, **14**, 879 (1949).

(7) E. B. Knott, *J. Chem. Soc.*, 685 (1945).

classical manner, *i.e.*, by isolating the primary products of the reactions. However, high dilution techniques in conjunction with ultraviolet absorption spectrophotometry seemed to offer promise of success.

Experimental

Materials.—Heptane obtained from Phillips Petroleum Co. was stirred with two portions of concentrated sulfuric acid, fuming sulfuric acid, distilled water and 10% sodium hydroxide solution in that order, dried over potassium hydroxide and distilled through a 100-cm. packed column; the distillate used boiled at 97.1–97.8°.

Ethyl orthoformate from Kay-Fries Co. was shaken with 5% sodium hydroxide, dried over potassium hydroxide and distilled from sodium through a 20-cm. Vigreux column; b.p. 144°.

Aniline was redistilled just before use.

Ethyl N-phenylformimidate (II) was prepared as before[3] and redistilled through a 20-cm. Vigreux column just before use.

N,N'-Diphenylformamidine (I), prepared according to Claisen,[2] was recrystallized from a mixture of isopropyl alcohol and petroleum ether and a second time from a mixture of benzene and petroleum ether; m.p. 139–140.5°.

Ethanol was commercial absolute alcohol, used just after opening. Acetic acid was commercial glacial. Sodium *t*-butoxide was prepared from clean sodium and *t*-butyl alcohol, dried at 100° (20 mm.) before use.

All solutions for spectrophotometric determinations were prepared by dissolving the materials in heptane and diluting volumetrically to the desired concentrations.

Procedure.—Absorption spectra were determined using a Beckman Model DU spectrophotometer with 1-cm. silica cells at 29 ± 3°.

Absorption Spectra of Pure Compounds.—The absorption spectra of heptane solutions of N,N'-diphenylformamidine, aniline and ethyl N-phenylformimidate which were 1.93×10^{-5}, 5.17×10^{-5} and 4.61×10^{-5} *M*, respectively, were determined (Fig. 1). The absorption spectra of these compounds in heptane solutions containing about 4% ethyl orthoformate by volume were found to be practically identical with the spectra determined in pure heptane.

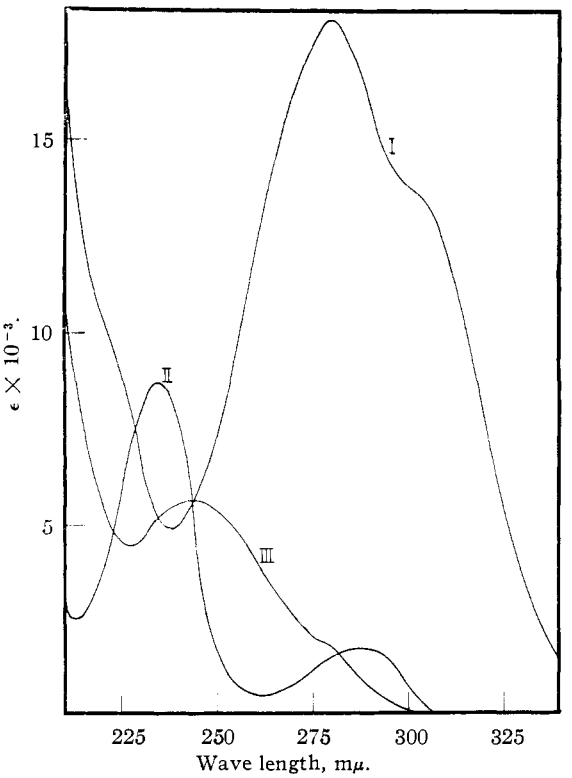

Fig. 1.—Ultraviolet absorption spectra: I, N,N'-diphenylformamidine; II, aniline; III, ethyl N-phenylformimidate (in heptane).

Reaction of Aniline with Ethyl Orthoformate.—A heptane solution which was 6.00×10^{-5} *M* in aniline and contained about 4% by volume of ethyl orthoformate was prepared. A blank solution having the same ethyl orthoformate concentration as the reaction solution was made up. The absorption spectrum of the reaction solution was determined two hours after mixing the solution and found to be qualitatively identical with that of aniline. The solution was allowed to stand for 48 hours at room temperature and its absorption curve redetermined; both of the absorption maxima were lower than before, but the curve still resembled that of aniline. Both the reaction solution and blank were then placed in an oven at 85° for 12 hours. The absorption spectrum of the reaction solution after this treatment was qualitatively identical with that of ethyl N-phenylformimidate and entirely different from that of aniline. The absorption curves for this solution when first prepared and after being heated are shown in Fig. 2. These curves show that aniline is converted into ethyl N-phenylformimidate under the conditions of the experiment, and that no detectable amount of N,N'-diphenylformamidine is formed.

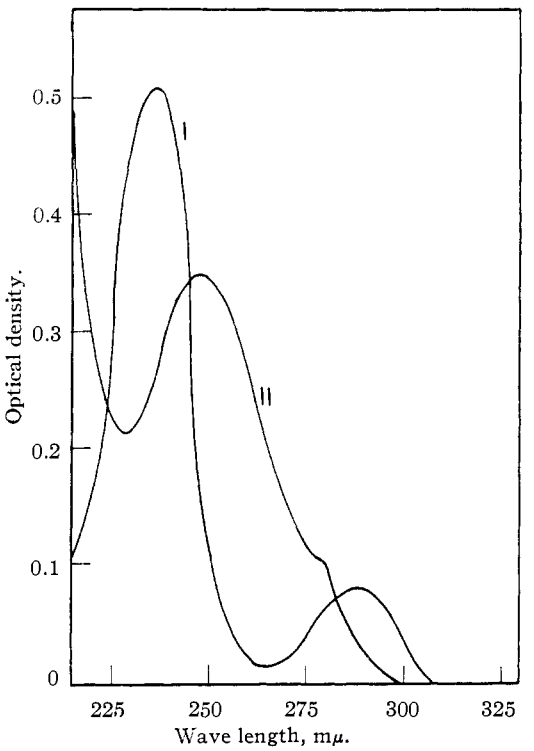

Fig. 2.—Reaction of aniline with ethyl orthoformate: I, absorption spectrum of solution before heating; II, absorption spectrum after heating.

The experiment was repeated to check the reproducibility of the results obtained. The results were similar to those described above except that the reaction went to completion in 12 hours at room temperature. To check the possibility that the reaction may be catalyzed by traces of acidic substances adsorbed on the walls of the flask which contained the solution, a third experiment was performed which was identical with the ones just described except that the reaction was carried out in a flask which had been rinsed with ammonium hydroxide and dried shortly before use. Instead of going to completion in 12 hours at room temperature, the reaction was far from complete after 24 hours at room temperature. Heating the solution for 12 hours at 85° converted the aniline to ethyl N-phenylformimidate.

An experiment was performed which was identical with those described above, except that both the reaction solution and blank solution contained approximately 8 parts per million of acetic acid by volume. The absorption spec-

trum of the reaction solution was determined after about 1.5 hours standing at room temperature and was found to be qualitatively identical with that of ethyl N-phenylformimidate. This indicates that aniline is converted into ethyl N-phenylformimidate in less than 1.5 hours in the presence of a trace of acid.

Reaction of N,N'-Diphenylformamidine with Ethyl Orthoformate. A. In the Absence of Catalysts.—A 2.40×10^{-5} *M* heptane solution of N,N'-diphenylformamidine containing about 4% by volume of ethyl orthoformate and a blank solution having the same concentration of ethyl orthoformate were prepared. The absorption spectrum of the N,N'-diphenylformamidine solution was determined about two hours after preparing the solution and found to be qualitatively identical with the spectrum of N,N'-diphenylformamidine in pure heptane. The solution and blank were allowed to stand for 72 hours at room temperature and were then heated for 11 hours at 85°. The absorption spectrum of the solution was redetermined and found to be unchanged.

B. **In the Presence of Acetic Acid.**—A 4.20×10^{-5} *M* heptane solution of N,N'-diphenylformamidine containing about 4% by volume ethyl orthoformate and about 16 parts per million by volume of acetic acid and a blank solution having the same content of ethyl orthoformate and acetic acid were prepared. The absorption spectrum of the solution containing N,N'-diphenylformamidine was determined and was found to be qualitatively similar to that of N,N'-diphenylformamidine in pure heptane, except that in place of the shoulder at 300 mμ there was a small peak, possibly caused by interaction of N,N'-diphenylformamidine with the acetic acid in the solution (a separate determination on a solution containing the same concentrations of N,N'-diphenylformamidine and acetic acid, but no ethyl orthoformate, gave a spectrum qualitatively identical with the one under discussion). The spectrum of the solution was redetermined after heating the solution for 48 and 144 hours at 65° and was found to be almost unchanged.

C. **In the Presence of Acetic Acid and Ethanol.**—A 4.20×10^{-5} *M* heptane solution of N,N''-diphenylformamidine which contained about 4% by volume of ethyl orthoformate, about 16 parts per million by volume of acetic acid and 1.6% by volume of ethanol and a blank having the same concentrations of ethyl orthoformate, acetic acid and ethanol were prepared. The absorption spectrum of the N,N'-diphenylformamidine solution was determined soon after preparing the solution and was found to resemble that of N,N'-diphenylformamidine in heptane containing 16 parts per million of acetic acid. The spectrum was redetermined after heating the reaction solution and blank for 70 hours at 65°, and was found to have changed considerably from the initial spectrum. The altered spectrum did not resemble that of either ethyl N-phenylformimidate or N,N'-diphenylformamidine. When 0.42 × (initial absorption curve) was subtracted from the curve obtained after heating the reaction solution for 70 hours, the curve which remained was qualitatively identical with that of ethyl N-phenylformimidate. (The factor 0.42 represents the fraction of N,N'-diphenylformamidine remaining unreacted, estimated from absorption in the region beyond 320 mμ.)

The reaction solution and blank were heated for another 70 hours at 65° and the absorption spectrum of the reaction solution redetermined. This time the curve was qualitatively quite similar to that of ethyl N-phenylformimidate (minimum at 225, maximum at 240, and shoulder at 275 mμ), although the amount of absorption past 300 mμ indicates that some unreacted N,N'-diphenylformamidine was still present in the solution. The absorption curves for this solution before heating and after heating for 140 hours are shown in Fig. 3.

The absorption of this solution after heating (presumably due principally to ethyl N-phenylformimidate) is somewhat greater in comparison to its absorption before heating than would be expected from the absorption curves of N,N'-diphenylformamidine and ethyl N-phenylformimidate in pure heptane. This may be due to interaction of N,N'-diphenylformamidine with the acid catalyst, which would be expected to reduce its absorption. Ethyl N-phenylformimidate, being a weaker base, would be less affected.

Reaction of Ethyl N-Phenylformimidate with Ethanol in the Presence of Hydrochloric Acid.—A solution of 1.49 g. (0.01 mole) of ethyl N-phenylformimidate and 5.8 ml. (0.10 mole) of ethanol in 25 ml. of dry ether was prepared. Dry hydrogen chloride was passed into the solution; within 30

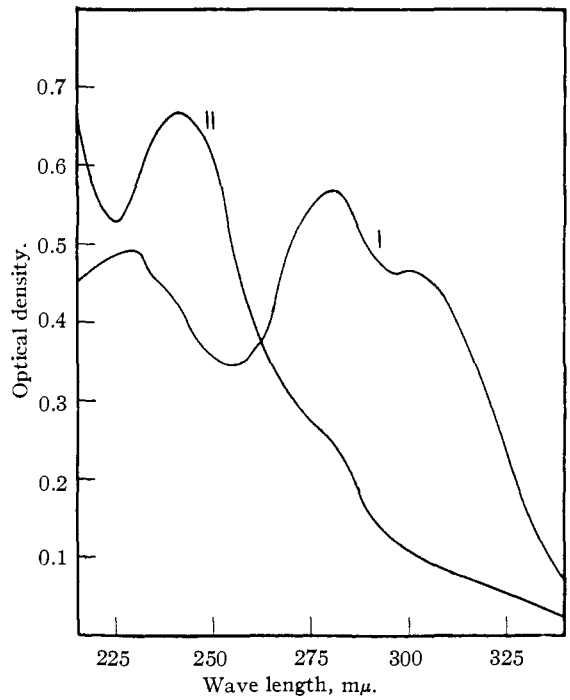

Fig. 3.—Reaction of N,N'-diphenylformamidine with ethyl orthoformate in the presence of ethanol: I, absorption spectrum of solution before heating; II, absorption spectrum of solution after heating.

seconds white crystals began to separate. The addition of hydrogen chloride was continued for 30 minutes; a reflux condenser protected by a calcium chloride tube minimized the loss of solvent. The crystals were collected on a filter, and, as more separated from the filtrate, these were collected and added to the first batch; total weight, 1.00 g. This product was stirred with concentrated ammonium hydroxide solution, collected again on a filter, washed with more ammonium hydroxide solution, dried and recrystallized from a mixture of dry benzene and petroleum ether. The needles of N,N'-diphenylformamidine thus obtained weighed 0.51 g.; m.p. 135–138°, not depressed by mixture with authentic material. Ethyl orthoformate cannot be isolated from this reaction because it is decomposed by hydrogen chloride.[8]

Reaction of Ethyl N-Phenylformimidate with Ethanol in the Presence of Picric Acid.—Picric acid (0.10 mole) was dissolved in 120 ml. of benzene, and the solution was dried by azeotropic distillation, distilling off one third of the benzene. Ethyl N-phenylformimidate (0.22 mole) was dissolved in 50 ml. of dry benzene. Fifteen milliliters of absolute ethanol was added to the picric acid solution, and the two solutions were mixed in a 250-ml. erlenmeyer flask. After a few seconds, a thick yellow mass of fine crystals formed in the reaction flask. The stoppered flask was cooled in an ice-bath and the liquid phase was separated from the N,N'-diphenylformamidine picrate (m.p. 189–192°) by suction filtration. The picrate weighed 28 g., about 70% of the theoretical yield.

The filtrate was transferred to a separatory funnel and extracted with three portions of concentrated ammonium hydroxide solution. The benzene solution was then extracted with two portions of 0.5 *N* sodium hydroxide, the second portion remaining colorless. The organic phase was then washed with water and dried over anhydrous potassium carbonate. The dry, colorless benzene solution was transferred to a 200-ml. round-bottomed flask and the flask was connected to a 12-plate vacuum-jacketed distilling column. When 100 ml. of distillate (b.p. 80.5°) had been collected, the solution remaining in the pot was transferred to a 100-ml. flask and distillation was resumed. After all of the benzene had been removed, about 3.5 ml. of distillate was col-

(8) See H. W. Post, "The Chemistry of the Aliphatic Orthoesters," Reinhold Publ. Corp., New York, N. Y., 1943, p. 59.

lected boiling between 143 and 144°. This liquid had the boiling point and the characteristic odor of ethyl orthoformate.

Discussion

Experiments involving reactions of aniline with ethyl orthoformate in heptane solutions which are very dilute with respect to aniline show conclusively that ethyl N-phenylformimidate (II) and not N,N'-diphenylformamidine (I) is the product of the reaction. Thus, reaction 3f has been demonstrated. With higher concentrations of aniline, I is formed by reaction of II with aniline. The possibility of II being formed by means of a two-step reaction involving I as an intermediate is ruled out by the fact that I does not react with ethyl orthoformate at an appreciable rate under the conditions of the experiment.

In fact, the experiments indicate that I does not react directly with ethyl orthoformate at all. In the dilute heptane solutions, I is not converted into II unless ethanol is added, confirming the theory that alcoholysis (reaction 4r) is the first step in the conversion. It does not seem likely that the reaction in the presence of ethanol could be due to a change in the physical properties of the reaction medium, since it contained only 1.6% ethanol.

It has been shown previously[3] that the practical preparation of II from the reaction of I with ethyl orthoformate is completely dependent on acid catalysis. It has now been demonstrated that this process involves the two steps 4r and 3f. Reaction 3f seems to be somewhat less dependent on acid catalysis, since it was found to occur even when precautions were taken to remove all acids. So there is indication that reaction 4r is a step which is extremely dependent on and sensitive to acid catalysis. If we assume that this step is more dependent on acid catalysis than any of the other three steps of equations 3 and 4, we can give very satisfactory explanations to some problems which have puzzled the authors for several years.

There is a spectacular difference in the practical course taken by the reaction of aniline with ethyl orthoformate in the absence of or presence of acids, as far as products are concerned: in the absence of acids, only I can be isolated, no matter how large an excess of ethyl orthoformate is used; in the presence of acids, II can be isolated in good yields. Formerly we stated[4] that different mechanisms must operate in the absence of and presence of acids. Although still possible, this does not seem so likely now since the observed facts can be explained quite well in terms of the two reversible equations 3 and 4. In the presence of acid catalysts, II is obtained by the operation of the steps 3f, 4f (fast), followed by 4r, 3f (slow). The isolation of only I in the absence of acid catalysts is attributable to the fact that 4f is much faster than 3f, and to the inappreciable rate of 4r in the absence of acid.

There is also a spectacular difference in the course taken by the reaction of a formimidic ester such as I with an aromatic amine in the absence of or presence of acids, as far as products are concerned, *if the aromatic groups of the ester and amine are not identical:* in the absence of acids the unsymmetrical N,N'-diarylformamidine is obtained; in the presence of acids, a mixture of the unsymmetrical and the two corresponding symmetrical N,N'-diarylformamidines is obtained.[4] Formerly, we ascribed these results, too, to the operation of different mechanisms. Now they can be explained readily in terms of equations 3 and 4. A glance at the mechanisms proposed for acid-catalyzed disproportionation (Fig. 1 of ref. 4) will show that reversibility of the reaction is responsible for formation of the mixture of formamidines. The reverse reactions involved are of the type 4r, and these do not occur at an appreciable rate in the absence of acid catalysts. Hence, the formation of the unsymmetrical N,N'-diarylformamidine is essentially irreversible when acids are excluded, and disproportionation does not occur.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Polyamine Salts with Autonomic Blocking Properties[1]

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A series of tris-dialkylaminoalkylamine salts has been prepared and found to possess autonomic ganglionic blocking properties. Direct alkylation of appropriate dialkylaminoalkyl amines with dialkylaminoalkyl halides proved a convenient route to many of these substances.

The ability of certain polymethylene-bis-ammonium salts to effect ganglionic blockade is well known. The familiar "C_6" (hexamethylene-bis-trimethylammonium ion), for example, displays the highest order of potency among the members of that homologous series. The alkylene chain may be interrupted by a tertiary amine function, however, without detriment to its activity,[2] as demonstrated in a series of compounds prepared by Marxer and Miescher.[3]

In the course of our investigations into the properties of polyamines we had occasion to prepare substance I.

$N[CH_2CH_2N(C_2H_5)_2]_3$ (I) (a) trihydrochloride (b) trimethiodide

(1) Presented in part at the 121st meeting of the American Chemical Society, Milwaukee, Wisc., March 31, 1952. Publication was delayed in order to complete work which was in progress. Pharmacological work was presented by A. J. Plummer, J. A. Schneider and W. A. Barrett at the Pharmacology Section of the 19th International Congress, Montreal, September 5, 1953, and is in press, *Arch. intern. pharmacodynamie.*

(2) H. J. Bein and R. Meier, *Experientia*, **6**, 351 (1950); *Schweiz. med. Wochr.*, **81**, 446 (1951).

(3) A. Marxer and K. Miescher, *Helv. Chim. Acta*, **34**, 924 (1951).