parison with material prepared by a conventional synthesis involving the cyclization of *m*-hydroxyhydrocinnamic acid. Condensation of 2-hydroxymethylene-5-methoxyhydrindone-1 with hydroxylamine hydrochloride in acetic acid yields, instead of the expected nitrile, a dimolecular condensation product which is probably bis-(5-methoxy - 1 - keto - 2 - hydrindylidenemethyl) - hydroxylamine. Alkaline hydrolysis of the latter in the presence of hydroxylamine gives β-(2-carboxy-5-methoxyphenyl)-propionic acid. This acid is also obtained on alkaline cleavage of 2-cyano-5-methoxyhydrindone-1 which can be prepared from 5-methoxyhydrindone-1 through the 2-bromo derivative.

Oxidation of 6-methoxytetralin with lead tetraacetate gives the 1-acetoxy derivative in 62% yield. The latter readily loses the elements of acetic acid to form 7-methoxy-1,2-dihydronaphthalene which forms a crystalline dimer in the presence of hydrobromic acid. Oxidation of the monomeric substance gives β-(2-carboxy-5-methoxyphenyl)-propionic acid.

MADISON, WISCONSIN RECEIVED NOVEMBER 1, 1943

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[CONTRIBUTION NO. 501 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH; AND FROM THE MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

# Morpholinomethyl Derivatives of Urea and Substituted Ureas[1]

BY WELCOME I. WEAVER,[2] J. K. SIMONS[2] AND WILMER E. BALDWIN

The aminomethylation of active hydrogen compounds by primary or secondary amines and formaldehyde has received considerable attention. The work with active methylene compounds, the Mannich reaction, has been reviewed recently,[3] while that with nitrogen compounds has been reported in a number of investigations of amines,[4] imides,[5] amides[6] and thiourea.[7] Einhorn and Spröngerts[8] described the reaction products of diethylaminomethanol and piperidinomethanol with urea. Later Einhorn[9] patented the reaction products of these alcohols with isovalerylurea. More recently there has appeared a patent[10] on the use of several bis-(dialkylaminomethyl)-ureas including bis-(morpholinomethyl)-urea.

The object of the present work was to prepare morpholinomethyl derivatives of urea and a number of substituted ureas and to investigate their behavior under conditions which would bring about cleavage, *e. g.*, reduction, treatment with acid anhydrides, picric acid or alkali.

Monomorpholinomethyl- and bis-(morpholinomethyl)-urea were prepared in yields of 85–95% by the reaction of urea with one or two equivalents of morpholinomethanol in aqueous solution or with paraformaldehyde and morpholine in dioxane. The reaction of dimethylol urea and morpholine gave the bis derivative in a yield of 60%. Methylene-bis-morpholine and urea produced monomorpholinomethylurea in a yield of 33%.

Hydrolysis of these compounds in hot alkaline solution yielded morpholine quantitatively. Zinc and hydrochloric acid reduction of either compound produced N-methylmorpholine. Catalytic reduction of monomorpholinomethylurea under non-hydrolyzing conditions described in the experimental part yielded urea and the calculated anount of N-methylmorpholine.

Monomorpholinomethylurea treated with an excess of acetic anhydride yielded N-acetylmorpholine and a white solid which was provisionally identified by analysis as polymeric dimethylene urea $(-CH_2NCONCH_2-)_x$. Butyric anhydride and monomorpholinomethylurea produced a similar product.

The reaction of picric acid and the morpholinomethylureas in ethanol or water solution formed impure products. Recrystallization progressively changed the melting points until they were near that of morpholine picrate. The hydrolysis indicated by this result is similar to the reported behavior of the morpholinomethyl derivatives of ketones and phenylacetonitrile.[11] It was found that the picrates of both mono- and bis-(morpholino-methyl)-urea could be prepared in glacial acetic acid.

Monomorpholinomethyl derivatives of 18 different substituted ureas were prepared. The N-morpholinomethyl-N′-acetylurea was more stable to hydrolysis than any other urea derivative studied. It formed a picrate stable in water, ethanol and glacial acetic acid, which could be recrystallized without decomposition. Acetic or butyric anhydrides reacted to form N-acetoxymethyl-N′-acetylurea and N-butyroxymethyl-N′-acetylurea, respectively. The acylmorpholine was formed simultaneously.

(1) From a thesis submitted by Welcome I. Weaver in partial fulfillment of requirements for the degree of Doctor of Philosophy, University of Pittsburgh, 1943.

(2) Present address: Plaskon Division, Libbey-Owens-Ford Glass Company, Toledo, Ohio.

(3) Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303–341.

(4) Henry, *Bull. soc. chim.*, **13**, 157 (1895).

(5) (a) Sach, *Ber.*, **31**, 1230 (1898); (b) Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925); (c) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(6) Einhorn, *Ann.*, **342**, 269 (1905).

(7) Morgan and Wells, German Patent 575,114; *C. A.*, **27**, 3483 (1933).

(8) Einhorn and Spröngerts, *Ann.*, **361**, 113 (1908).

(9) Einhorn, German Patent 248,440; *Frdl.*, **12**, 702 (1915).

(10) Burke and Peters, U. S. Patent 2,281,410.

(11) Zief and Mason, *J. Org. Chem.*, **8**, 1 (1943).

Monomorpholinomethylthiourea was prepared from thiourea and one equivalent of the aminomethanol. Succinimide and phthalimide yielded N-(morpholinomethyl)-succinimide and N-(morpholinomethyl)-phthalimide. The N-morpholinomethyl derivatives of benzenesulfonamide and *p*-toluenesulfonamide were prepared.

The symmetrical structure suggested by Einhorn[9] for the piperidinomethyl derivative of isovalerylurea has been assigned to bis-(morpholinomethyl)-urea and to the monomorpholinomethyl derivatives of the substituted ureas. Morpholinomethanol reacts only with an amido group ($-NH_2$) of a urea where that group is not substituted. Thus symmetrical diphenyl- and dibutylurea failed to react with morpholinomethanol under the same experimental conditions as phenyl- and butylurea. Normal butylurea yielded only a monomorpholinomethyl derivative even though it reacted with an excess of the aminomethanol. Urea formed only bis-(morpholinomethyl)-urea where two, three or four equivalents of morpholinomethanol were allowed to react with urea.

Dimethylol urea, which is the symmetrical derivative, reacted with morpholine to form a bis-(morpholinomethyl)-urea which was identical with the product formed from two (or more) moles of morpholinomethanol.

N-Carbamylmorpholine is an example of a urea in which both hydrogens of one amido group are substituted. It readily formed a monomorpholinomethyl derivative which must have the symmetrical structure.

## Experimental Part

**General and Preparations of Materials.**—Morpholinomethanol was prepared according to the general procedure of Henry.[4] The unpurified product was used directly. Some of the substituted ureas were commercially available, others were prepared by reported methods.[12] β-Benzoyloxyethylurea, a new substituted urea, was prepared as follows: β-benzoyloxyethylamine hydrochloride[13] from benzoyl chloride and ethanolamine hydrochloride was heated with an equivalent of urea at 130–140°; the product was isolated by washing with water and purified by recrystallizing from ethanol. The melting point was 122–124°; yield, 36%.

*Anal.* Calcd. for $C_{10}H_{12}N_2O_3$: N, 13.5. Found: N, 13.6.

All melting points were determined with an Anschütz thermometer and were not corrected for stem immersion.

**Monomorpholinomethylurea.**—A mixture of urea (0.5 mole) and an aqueous solution of morpholinomethanol (0.5 mole) was heated to 80–90°. After the vigorous exothermic reaction took place, the mass was cooled to precipitate a white crystalline solid; yield of crude product was 92%. It was obtained in needle crystals, m. p. 162–163°, by recrystallization from a mixture of ethanol and acetone.

Combination of equivalent quantities of urea, morpholine and paraformaldehyde in boiling dioxane gave the same product in 84% yield. Interaction of methylene-bismorpholine[5e] and urea in boiling dioxane yielded only 33% of the theoretical monomorpholinomethylurea.

**Bis-(morpholinomethyl)-urea.**—Urea (0.25 mole) and two equivalents of aqueous morpholinomethanol were heated until the mixture boiled. On cooling there was obtained a 95% yield of crude product which was purified by crystallization from a mixture of ethanol and acetone. It was obtained in platelets melting at 163–164°. The mixed melting point with monomorpholinomethylurea was slightly lower, 157–159°.

Interaction of urea with two equivalents each of paraformaldehyde and morpholine in boiling dioxane gave the bis derivative in 90% yield. By evaporation of a mildly refluxed solution of dimethylol urea (0.063 mole) and morpholine (0.2 mole) in 50 cc. of water a crude product was obtained, which yielded 60% of the theoretical quantity of bis-(morpholinomethyl)-urea.

**Morpholinomethyl Derivatives of Substituted Ureas.**—These compounds were prepared from the substituted urea by interaction with one equivalent of morpholinomethanol in aqueous solution (see Table I for several exceptions). In a few cases sufficient ethanol was added so that a homogeneous solution was obtained as the mixture was brought to a boil. The morpholinomethyl derivatives usually crystallized on cooling; a few were obtained by concentrating the solution *in vacuo* and then cooling, while others crystallized after standing for several days in a cold room (0°).

The morpholinomethyl derivatives of *s*-hexylurea and *as*-dimethylurea crystallized at 0° but melted below room temperature and were not purified. The derivative of *as*-diethylurea failed to crystallize after six months.

The preparative and analytical data for the morpholinomethyl derivatives of urea and substituted ureas are listed in Table I.

**Symmetrical Disubstituted Ureas and Morpholinomethanol.**—*sym*-Diphenylurea (0.1 mole) was refluxed for five minutes with one equivalent of morpholinomethanol in 50 cc. of ethanol. Ninety-five per cent. of the original weight of diphenylurea was recovered unchanged and no evidence of reaction was observed.

*sym*-Di-*n*-butylurea was heated with one and with two equivalents of morpholinomethanol in dilute ethanol solution. Only unreacted dibutylurea was recovered from the mixture.

Experiments with urea and 2, 3 and 4 equivalents of morpholinomethanol yielded only bis-(morpholinomethyl)-urea in yields of 95, 78 and 63%, respectively. Formation of no other product was indicated.

*n*-Butylurea and different excess amounts of morpholinomethanol yielded only the mono derivative.

**Morpholinomethanol with Thiourea, Imides and Sulfonamides.**—These compounds combined readily with morpholinomethanol in dioxane, water or aqueous alcohol by refluxing for thirty minutes. The data are summarized in Table II.

**Hydrolysis of Monomorpholinomethylurea.**—Monomorpholinomethylurea (0.05 mole) in 100 cc. of 10% sodium hydroxide was steam distilled. The distillate was acidified and concentrated. The concentrated solution by treatment with benzenesulfonyl chloride and 20% alkali yielded 11.7 g. of N-benzenesulfonylmorpholine (m. p. 118–119°). This accounted for 97% of the calculated amount of morpholine present.

**Reductions of Monomorpholinomethylurea.**—Zinc dust (4 equivalents) was added in small portions to a mildly refluxing hydrochloric acid solution (10%) of the urea derivative. After complete solution of the zinc, the reaction was made alkaline and steam distilled. Organic base in the distillate was determined by titration and identified as methylmorpholine by conversion to picrate, m. p. 224–226°. Morpholine was proved to be absent by testing with benzenesulfonyl chloride; yield of methylmorpholine, 79%. By the same procedure bis-(morpholinomethyl)-urea and morpholinomethanol gave, respectively, 70 and 57% yields of methylmorpholine.

In order to eliminate the probability that morpholinomethanol was first formed by hydrolysis and then reduced, the hydrogenation of monomorpholinomethylurea was

(12) (a) Davis and Blanchard, THIS JOURNAL, **51**, 1790 (1929); (b) "Organic Syntheses," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1923, pp. 95–97; (c) Rudqvist, *Arch. Pharm.*, **236**, 452 (1898); (d) Harvey and Caplan, U. S. Patent 2,247,495.

(13) Mannich, *Arch. Pharm.*, **272** 341 (1934).

TABLE I

MORPHOLINOMETHYL DERIVATIVES OF UREA AND SUBSTITUTED UREAS RNHCONHCH$_2$N$\langle$CH$_2$CH$_2$$\rangle$O CH$_2$CH$_2$

| R | Yield, %[a,b] | M. p., °C.[c] | Empirical formula | Analyses: Nitrogen, % Found | Nitrogen, % Calcd. | Neut. equiv. Found | Neut. equiv. Calcd. |
|---|---|---|---|---|---|---|---|
| Hydrogen- | 92 | 162.0–163.0[e] | $C_6H_{13}N_3O_2$ | 26.44 | 26.41 | 160.2 | 159.1 |
| Methyl- | 44 | 124.4–125.4[h] | $C_7H_{15}N_3O_2$ | 24.25 | 24.27 | 175.0 | 173.1 |
| Ethyl- | 77 | 109.6–110.8[f] | $C_8H_{17}N_3O_2$ | 22.28 | 22.45 | 188.8 | 187.2 |
| *n*-Propyl- | 57 | 89.2– 90.0[i] | $C_9H_{19}N_3O_2$ | 20.81 | 20.89 | 202.7 | 201.2 |
| Isopropyl- | 80 | 126.8–128.0[j] | $C_9H_{19}N_3O_2$ | 20.70 | 20.89 | 202.8 | 201.2 |
| Allyl- | 85 | 104.0–105.0[h] | $C_9H_{17}N_3O_2$ | 21.08 | 21.10 | 198.7 | 199.2 |
| *n*-Butyl- | 70 | 109.0–109.6[j] | $C_{10}H_{21}N_3O_2$ | 19.37 | 19.53 | 215.5 | 215.2 |
| Isobutyl- | 74 | 112.0–112.6[j] | $C_{10}H_{21}N_3O_2$ | 19.46 | 19.53 | 214.4 | 215.2 |
| *s*-Butyl- | 75 | 111.0–112.0[j] | $C_{10}H_{21}N_3O_2$ | 19.50 | 19.53 | 214.0 | 215.2 |
| *t*-Butyl | 54[d] | 137.8–138.8[i] | $C_{10}H_{21}N_3O_2$ | 19.33 | 19.53 | 213.4 | 215.2 |
| *s*-Amyl | 83 | 107.0–108.4[h] | $C_{11}H_{23}N_3O_2$ | 18.34 | 18.33 | 229.7 | 229.3 |
| *t*-Amyl | 68 | 107.4–109.0[f] | $C_{11}H_{23}N_3O_2$ | 18.39 | 18.33 | 231.5 | 229.3 |
| Cyclohexyl- | 64 | 138.0–139.0[f] | $C_{12}H_{23}N_3O_2$ | 17.38 | 17.42 | 241.3 | 241.1 |
| Phenyl- | 97 | 149.4–150.0[k] | $C_{12}H_{17}N_3O_2$ | 17.80 | 17.87 | 234.3 | 235.2 |
| Benzyl- | 67 | 149.3–149.8[l] | $C_{13}H_{19}N_3O_2$ | 16.88 | 16.87 | 248.4 | 249.1 |
| Acetyl- | 87[d] | 161.0–161.8[g] | $C_8H_{15}N_3O_3$ | 20.91 | 20.89 | 201.8 | 201.1 |
| β-Hydroxyethyl- | 82[d] | 118.0–119.8[f] | $C_8H_{17}N_3O_3$ | 20.61 | 20.69 | 203.1 | 203.2 |
| β-Benzoyloxyethyl- | 52 | 125.4–127.6[k] | $C_{16}H_{21}N_3O_4$ | 13.60 | 13.68 | 310.9 | 307.2 |
| N-Carbamyl morpholine[m] | 63 | 131.6–133.0[f] | $C_{12}H_{19}N_3O_3$ | 18.37 | 18.34 | 225.8 | 229.2 |
| Morpholinomethyl- | 95 | 163.0–164.0[l] | $C_{11}H_{22}N_4O_3$ | 21.48 | 21.70 | 131.2 | 129.1 |

[a] Yield based on crude products. [b] Yield of compound prepared in aqueous solution unless otherwise designated. [c] Melting points on purified products. [d] Yield of compound prepared in dioxane. [e] Crystallized from ethanol–acetone. [f] Crystallized from acetone. [g] Crystallized from acetone–dioxane. [h] Crystallized from methyl isobutyl ketone. [i] Crystallized from benzene–ligroin. [j] Crystallized from methyl ethyl ketone. [k] Crystallized from ethanol–water. [l] Crystallized from ethanol. [m] This is the complete name for this compound.

TABLE II

MONOMORPHOLINOMETHYL DERIVATIVES OF THIOUREA, IMIDES AND SULFONAMIDES

| Compound | Yield, %[a,b] | M. p., °C.[c] | Empirical formula | Analyses: Nitrogen, % Found | Nitrogen, % Calcd. | Neut. equiv. Found | Neut. equiv. Calcd. |
|---|---|---|---|---|---|---|---|
| Thiourea | 71 | 141.4–142.0[d] | $C_6H_{13}N_3OS$ | 23.98 | 23.99 | 175.8 | 174.2 |
| Succinimide | 67 | 109.6–110.4[e] | $C_9H_{14}N_2O_3$ | 14.12 | 14.14 | 197.9 | 198.1 |
| Phthalimide | 81 | 117.8–118.8[e] | $C_{13}H_{14}N_2O_3$ | 11.37 | 11.38 | 246.8 | 246.1 |
| Benzenesulfonamide | 81 | 81.6– 82.6[f] | $C_{10}H_{16}N_2O_3S$ | 10.86 | 11.01 | 254.5 | 256.2 |
| *p*-Toluenesulfonamide | 90 | 109.6–111.2[g] | $C_{11}H_{18}N_2O_3S$ | 10.26 | 10.37 | 272.6 | 270.2 |

[a] Yield based on crude product. [b] Yield of compound prepared in aqueous solution. [c] Melting points on purified products. [d] Crystallized from ethanol. [e] Crystallized from acetone. [f] Crystallized from benzene. [g] Crystallized from ethanol–water.

attempted under conditions where hydrolysis was unlikely.

**Catalytic Reduction of Monomorpholinomethylurea.**—Monomorpholinomethylurea (0.0094 mole) in absolute ethanol was hydrogenated at room temperature and atmospheric pressure using a platinum catalyst (0.1056 g.).[14] One molecular equivalent of hydrogen was absorbed. A quantitative yield of methylmorpholine was isolated as its picrate (m. p. 224–226°). Urea was identified as the other hydrogenolysis product by formation of characteristic crystals of urea nitrate.

Exactly similar results were obtained by hydrogenation in glacial acetic acid.

**Acid Anhydride and Monomorpholinomethylurea.**—Monomorpholinomethylurea did not react with cold (0–5°) acetic anhydride. At steam-bath temperature reaction took place and an insoluble solid was formed. This product was washed in turn with alkali, alcohol and ether to obtain material, m. p. 235–236°, with fairly reproducible nitrogen values. Found: N, 33.29, 33.21, 33.94. Acetylmorpholine was obtained in 62% yield from the acetic anhydride mother liquors.

Monomorpholinomethylurea and butyric anhydride at steam-bath temperatures yielded the same white insoluble solid, m. p. 233–236°. The mixture of this compound with the preceding product melted at 235–236°. Found: N, 33.69, 33.94. The identity of this solid product is not known, but it may be some urea-formaldehyde condensation product, *e. g.*, $(-CH_2NCONCH_2-)_x$; calcd.: N, 33.3.

**N-Acetoxymethyl-N'-acetylurea.**—Morpholinomethylacetylurea (0.05 mole) and acetic anhydride (0.39 mole) were heated on the steam-bath for three hours. Solution occurred slowly and cooling yielded a white crystalline product. Crystallization from ethyl acetate yielded 5.5 g. (64%) of material with m. p. 144.6–145.2°. Its saponification equivalent indicated that under the conditions used[15] the acetylurea part of the molecule was saponified also. This conclusion was substantiated by a blank with acetylurea.

*Anal.* Calcd. for $C_6H_{10}N_2O_4$: N, 16.09; saponification equivalent, 87. Found: N, 16.07; saponification equivalent, 87.

(14) Thanks are owed R. P. Mariella, Carnegie Institute of Technology, who prepared the catalyst and carried out the hydrogenation.

(15) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 21–22.

Distillation of the acetic anhydride mother liquors yielded 4.6 g. (72%) of acetylmorpholine, b. p. 230–240°.

**N-Butyroxymethyl-N'-acetylurea.**—Morpholinomethylurea (0.05 mole) and butyric anhydride (0.31 mole) were heated on the steam-bath for two and one-half hours. A clear solution formed within five minutes and on cooling yielded 8.5 g. (84%) of plate-like crystals which, crystallized from ethyl acetate, melted at 116.8–117°.

*Anal.* Calcd. for $C_8H_{14}N_2O_4$: N, 13.85; saponification equivalent, 101. Found: N, 13.80; saponification equivalent, 100.

**Picrates of Morpholinomethyl Derivatives.**—Mono- and bis-(morpholinomethyl)-urea formed unstable picrates (m. p. 140–160°) from alcohol and water solutions. In contrast to these results stable picrates were prepared from glacial acetic acid solutions in a yield expected for a one to one molecular combination from mono- and bis-(morpholinomethyl)-urea. They melted at 162.0–163.3° and 163–164°.

Morpholinomethyl derivatives of alkylureas did not form picrates in glacial acetic acid solutions. In alcohol and water solutions unstable picrates were obtained which on purifying yielded morpholine picrate (m. p. 148.8–149.2°).

Stable picrates of morpholinomethyl derivatives of acetylurea (m. p. 195°), phenylurea (156–158°), phthalimide (205°), and succinimide (188–189°) were prepared in either water, alcohol or glacial acetic acid solutions.

## Summary

Mono- and bis-(morpholinomethyl)-urea were prepared and described. These compounds were cleaved by hydrolysis, reduction, and acetic anhydride to yield morpholine, methylmorpholine and acetylmorpholine.

Morpholinomethyl derivatives of 18 substituted ureas were prepared and characterized; N-morpholinomethyl-N'-acetylurea underwent reaction with acetic anhydride, yielding N-acetoxymethyl-N'-acetylurea and acetylmorpholine. Butyric anhydride gave the analogous butyroxymethyl derivative.

The morpholinomethyl derivatives of thiourea, succinimide, phthalimide, benzene- and *p*-toluenesulfonamide were prepared and characterized.

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[CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA]

# Kinetics of Reactions between Iodine and Histidine

BY CHOH HAO LI

Imidazole compounds react readily with iodine.[1] The imidazole containing amino acid, histidine, however, has not hitherto been iodinated. Bauer and Strauss[2] were not able to halogenate the histidine with ICl, but their results[3] with globin indicate the possibility of iodohistidine formation. On the other hand, Pauly[1b] succeeded in preparing benzoyldiiodo-histidine and tetraiodo-histidine anhydride. The fact that histidine cannot be iodinated in the free state but both its anhydride and its benzoyl derivative smoothly take up one mole of iodine (on the two C atoms of the imidazole ring) in a slightly alkaline solution has recently been confirmed by Bauer, Strauss and Maschmann.[4]

When histidine and iodine are allowed to react in a nearly neutral solution, the disappearance of iodine follows the rate law

$$dx/dt = (a - x)(b - 2x) \qquad (1)$$

where $a$ and $b$ are the initial concentrations of histidine and titratable iodine, respectively; $k_2$ is the specific rate constant and $x$ is the concentration of diiodo-histidine which is formed according to the reaction: histidine + 2 $I_2$ → di-iodohistidine + 2HI. The rate law (1) is identical with that found in the formation of diiodotyrosine.[5] Table I gives the values of $k_2$ in a typical run for successive time intervals by means of the integrated form of equation (1). The concentrations are in moles per liter and time in minutes. The bimolecular rate law is further verified when one varies the initial concentrations of iodine and histidine. The specific rate is not changed by the addition of neutral salts.

TABLE I

A TYPICAL KINETIC EXPERIMENT AT 25°

$b = 2a = 5.26 \times 10^{-3}m$, $(I^-) = 3.15 \times 10^{-2}m$, $p$H 7.21 citrate–phosphate buffer ($HPO_4^=$) = $3.50 \times 10^{-2}m$.

| $t$, min. | $(b)$ $10^3$ | $(x)$ $10^3$ | $k_2$ |
|---|---|---|---|
| 0 | (5.26) | | |
| 5.0 | 4.50 | (0.38) | (6.4) |
| 12.5 | 3.72 | .77 | 6.2 |
| 18.0 | 3.30 | .98 | 6.2 |
| 30.0 | 2.65 | 1.30 | 6.1 |
| 50.0 | 2.00 | 1.63 | 6.3 |
| | | | Av. 6.2 |

**The Rate as a Function of *p*H.**—The dependence of specific rate on $p$H of the environment is similar to that found for the iodine-phenol reaction,[5] *i. e.*, the reaction becomes slower as the acidity of the solution increases. Data, summarized in Table II, give a relationship

$$k_2 = 0.10 + (5 \times 10^{-8}/(H^+)) \qquad (2)$$

in citrate buffers containing $(I^-) = 3.15 \times 10^{-2}$.

(1) (a) H. Pauly and K. Gundermann, *Ber.*, **41**, 3999 (1909); (b) H. Pauly, *ibid.*, **43**, 2243 (1910); (c) H. Pauly and E. Arauner, *J. prakt. Chem.*, **118**, 33 (1928).

(2) H. Bauer and E. Strauss, *Ber.*, **69B**, 245 (1936).

(3) H. Bauer and E. Strauss, *Biochem. Z.*, **284**, 197, 231 (1936).

(4) H. Bauer, E. Strauss and E. Maschmann, *Ber.*, **68B**, 1108 (1935).

(5) C. H. Li, THIS JOURNAL, **64**, 1147 (1942).