Found: total halogen, 51.72 (silver halide calcd. as Ag_2BrCl).

Hydrogenation of 3-Amino-5-bromo-6-chloro-2-picoline and of 3-Amino-6-chloro-2-picoline.—A solution of 0.53 g. of 3-amino-5-bromo-6-chloro-2-picoline in 10 cc. of ethanol was hydrogenated at atmospheric pressure in the presence of palladium supported on charcoal as a catalyst. The hydrogenation was stopped when the calculated quantity of hydrogen necessary to remove one halogen had been absorbed. After filtration to remove the catalyst, the solvent was evaporated under reduced pressure. Extraction of the residue with ether yielded only a minute amount of material; so, the residue was treated with water which changed the insoluble material noticeably. The insoluble material was then removed by extraction with ether, and the residue from evaporation of the dried ether extracts consisted of 0.20 g. (38%) of colorless crystals, m. p. 161–163°, which did not depress the melting point of 3-amino-5-bromo-6-chloro-2-picoline.

The aqueous layer was made alkaline with dilute sodium hydroxide and evaporated at room temperature to dryness. The residue was extracted with chloroform, and the chloroform extracts were evaporated to obtain 0.10 g. (39%) of crystalline material which after sublimation and two recrystallizations from benzene–petroleum ether melted at 114–116°; picrate, m. p. 236° with decomposition. This material corresponded in properties to the 3-amino-2-picoline of Dornow.[10]

Hydrogenation of 48 mg. of 3-amino-6-chloro-2-picoline was carried out in ethanol at atmospheric pressure in the presence of palladium-on-charcoal as the catalyst. Following removal of the catalyst by filtration, the solvent was removed under reduced pressure. The residue was dissolved in a small amount of water, made alkaline and extracted with chloroform. The chloroform extracts were dried with anhydrous sodium sulfate and evaporated to dryness. The residue, m. p. 112–114°, amounted to 13 mg. or 37% of the theoretical yield. After recrystallization from benzene containing a small amount of petroleum ether the material melted at 114–116° and did not depress the melting point of the analogous product obtained on reduction of 3-amino-5-bromo-6-chloro-2-picoline.

Acknowledgment.—The authors gratefully acknowledge financial aid from the Pittsburgh Coke and Chemical Co., Pittsburgh, Pa., and the aid of Gwyn White Shive who carried out some of the analyses.

Summary

1. 5-Hydroxy-2-picoline has been synthesized from 6-amino-2-picoline and found to be identical with the hydroxy-2-picoline obtained by alkali fusion of the sulfonation product of 2-picoline.

2. 6-Chloro-5-hydroxy-2-picoline has been prepared from 6-amino-2-picoline and shown to be identical with the chloro-5-hydroxy-2-picoline obtained by nitration of 5-hydroxy-2-picoline and treatment of the nitro-5-hydroxy-2-picoline with concentrated hydrochloric acid.

3. Catalytic reduction of 3-amino-5-bromo-6-chloro-2-picoline with an equimolecular amount of hydrogen resulted in a mixture of the original compound and 3-amino-2-picoline in approximately equal amounts.

4. A number of substituted 2-picolines have been synthesized from 6-amino-2-picoline and characterized.

NEW ORLEANS, LA. RECEIVED SEPTEMBER 3, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PITTSBURGH]

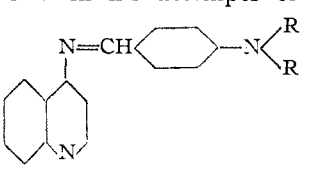
Studies in the Quinoline Series. VI. Synthesis of Certain 4-Substituted Quinoline Derivatives[1]

BY VIRGINIA G. RAMSEY,[2] WILMER E. BALDWIN AND R. STUART TIPSON

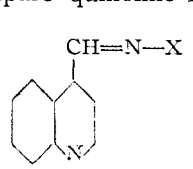
The extensive work of Browning, *et al.*,[3] on the chemotherapeutic properties of "anil quinolinium salts" suggested to us the desirability of preparing some of the related quinoline bases for testing as antimalarial agents.

The 4-aminoquinolines used in the formation of several 4-(*p*-dialkylaminobenzylidene)-aminoquinolines (I) were obtained by well-established procedures mentioned in the experimental section and their condensation with the respective aldehydes conducted at 120–125° in the presence of piperidine as catalyst. The resulting azomethines were readily hydrolyzed to the parent aldehyde and amine by hydrolysis with 10% hydrochloric acid at 100°. Since few, if any, 4-benzylaminoquinolines appear to have been examined for antimalarial activity, a series of corresponding 4-(*p*-diethylaminobenzylamino)-quinolines was prepared from the benzylidene-amino compounds by reduction of the azomethine double bond with hydrogen under pressure, in the presence of Adams catalyst.

Quinoline-4-azomethines (II) of another type were prepared by causing quinoline-4-aldehyde to react with selected amines; in II, X was *p*-hydroxyphenyl, *p*-dimethylaminophenyl, or diethylaminoethyl. In agreement with the experience of Work[4] in his attempts to prepare quinoline-4-



(I)



(II)

(1) Based on a thesis submitted by Virginia G. Ramsey to the Graduate School of the University of Pittsburgh, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1946. Contribution No. 617 of the Department of Chemistry, University of Pittsburgh.

(2) Present address: Mellon Institute of Industrial Research, Pittsburgh, Pennsylvania.

(3) Browning, Cohen, Ellingworth and Gulbransen (a) *J. Path. Bact.*, **27**, 121 (1924); (b) **29**, 317 (1926); (c) *Proc. Roy. Soc.* (London), **B103**, 404 (1928); (d) **B105**, 99 (1929).

(4) Work, *J. Chem. Soc.*, 429 (1942).

TABLE I

PROPERTIES AND ANALYSES OF SOME 4-SUBSTITUTED QUINOLINE DERIVATIVES

Compound	SN[a]	Appearance	Solvent[b]	M. p., °C.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4-(*p*-Diethylaminobenzylidene)-aminoquinoline										
Unsubstituted	9,863	Yellow needles	M	177.4–178.4	79.20	6.98	13.82	79.03	7.02	14.15
2-Phenyl-	10,536	Yellow crystals	M-T	161.8–162.4	82.30	6.64	11.07	82.22	7.22	10.90
2-Methyl-	10,538	Yellow crystals	I	139.6–140.6	79.45	7.30	13.24	79.53	7.87	13.26
2-Methyl-6-methoxy-	10,263	Yellow crystals	I	145–145.8	76.05	7.26	12.10	75.82	7.34	12.00
6-Methoxy-	14,370	Yellow powder	I	131–131.4	75.65	6.95	12.60	75.78	7.10	12.41
4-(*p*-Dimethylaminobenzylidene)-aminoquinoline										
2-Methyl-6-methoxy-	10,264	Brown-yellow crystals	I	153–155	75.20	6.63	13.16	75.23	6.63	13.02
4-(*p*-Diethylaminobenzylamino)-quinoline										
Unsubstituted	14,037	Creamy-white crystals	X	133.2–134.6	78.65	7.59	13.76	78.68	7.79	13.76
2-Phenyl-	10,743	White crystals	T	159.4–160.4	81.83	7.13	11.01	81.77	7.02	11.42
2-Methyl-	10,742	Creamy-white powder	M	129.6–131.6	78.95	7.89	13.16	79.00	8.15	13.11
2-Methyl-6-methoxy-	11,802	Creamy-white crystals	M	132.4–134.4	75.61	7.79	12.03	75.94	7.91	12.15
6-Methoxy-		White crystals	E	143–145	75.20	7.51	12.53	75.41	7.47	12.37
Quinoline-4-aldehyde Derivatives										
Quinoline-4-aldehyde-*p*-dimethylaminoanil		Red platelets	M	156.2–157.2	78.51	6.23	15.27	78.19	6.42	15.66
Quinoline-4-aldehyde *p*-hydroxyanil	12,604	Fine orange crystals	M	198.0–198.8	77.40	4.87	11.29	77.10	5.02	11.38
Lepidal-*unsym*-diethylethylene-di-amine	12,569	Yellow-red oil		[180[e]]			16.46			16.60
7-Methylquinoline Derivatives										
4-Cyano methiodide		Orange platelets	M	213–214						
4-Cyano	8,713	Buff needles	I	101.6–102.2	78.55	4.79	16.66	78.50	4.74	16.26
4-Carboxylic acid		Tan powder	Et	264.8–267.8[d]	70.60	4.85	7.49	70.71	4.99	7.44
4-Ethyl carboxylate		Colorless liquid		[146[e]]	72.56	6.09	6.51	72.53	6.43	6.65
4-Carboxylic acid amide		Fine white needles	Et	216	70.95	5.41	15.04	71.22	5.80	15.25
4-Amino		White crystals	T	163.2–164.6	75.90	6.37	17.71	76.08	6.47	17.74

[a] SN (survey number) is an identifying number for compounds which will appear in a forthcoming monograph entitled, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor. [b] M, methanol; T, toluene; I, *i*-propyl alcohol; X, xylene, E, ether, Et, ethanol. [c] Anschütz thermometers used for m. p. determinations. [d] Decomposes. [e] Boiling point at 2 mm.

aldehyde from quinoline-4-aldehyde anil and quinoline-4-carboxylic acid anilide, respectively, these azomethines were very stable as shown by their resistance to acid hydrolysis. However, reductive hydrolysis by Clemmensen's method gave lepidine plus the corresponding original amine.

We take this occasion to record the preparation and some properties of 7-methyl-4-aminoquinoline. It was obtained by an extension of the method of Ainley and King[5] to the formation of ethyl 7-methylquinoline-4-carboxylate; conversion to the amide and treatment by the Hofmann reaction gave rise to the desired aminoquinoline. Although it has been mentioned in the patent literature,[6] no physical properties of the compound had been recorded.

(5) Ainley and King, *Proc. Roy. Soc.* (London), **B125**, 60 (1938).

(6) Andersag, Breitner and Jung, U. S. Patent 2,233,970 (1941); *C. A.*, **35**, 3771 (1941).

The analyses and some of the properties of these compounds are given in Table I.

Experimental

4-Aminoquinolines.—4-Aminoquinoline was synthesized from cinchoninic ester[5] through the amide, utilizing the Hofmann reaction.[7] **2-Phenyl-4-aminoquinoline** was prepared from cinchophen according to the procedures of Rosenmund,[8] and Dohrn and Zöllner.[9] **2-Methyl-4-aminoquinoline** and **2-methyl-4-amino-6-methoxyquinoline** were obtained by the Conrad and Limpach[10] synthesis from aniline and *p*-anisidine, respectively, each being carried through the usual reactions to obtain the corresponding 4-chloro-quinolines which, in turn, were converted

(7) Renshaw and Friedman, THIS JOURNAL, **61**, 3320 (1939).

(8) Rosenmund, *Ber.*, **54**, 2893 (1921).

(9) Dohrn and Zöllner, German Patent 375,715 (1923); *Chem. Zentr.*, **95**, I, 967 (1924).

(10) Conrad and Limpach, (a) *Ber.*, **20**, 944 (1887); (b) **21**, 1649 (1888).

by amination[11] to the 4-amino analogs. In preparing **6-methoxy-4-aminoquinoline**, the method described by Rubtsov and Lizgunova[12] was applied to the formation of 6-methoxy-4-chloroquinoline, with conversion to the amine in the usual way.[11]

4-(*p*-Dialkylaminobenzylidene)-aminoquinolines.—Equimolar amounts of *p*-dialkylaminobenzaldehyde and the respective 4-aminoquinoline, plus 10 drops of piperidine as catalyst, were dissolved in toluene and the solution heated under reflux at 120–125° (internal temperature) for about four hours. The water evolved was collected under toluene in a Stark and Dean trap and its amount indicated the extent of the reaction. The reactions usually became very slow when about half of the aminoquinoline had been utilized. The yield of product could be increased (from 40–50%) to 85–95% by re-treating the residue from crystallization of the product with an amount of dialkylaminobenzaldehyde equivalent to the unchanged 4-aminoquinoline. In each preparation, the structure of the resulting compound was proved by hydrolysis with 10% hydrochloric acid at 100° and identification of the products.

4-(*p*-Diethylaminobenzyl)-aminoquinolines were prepared from the corresponding benzylidene-aminoquinolines by hydrogenation of the azomethine double bond. This was accomplished by shaking a 4 to 10% suspension of benzylidene compound in methanol with 0.2–0.4 g. of platinum oxide (Adams catalyst) in the presence of hydrogen at 2–3 atmospheres at room temperature. The yields ranged from 80 to 95%. The absence of hydrolysis of these compounds under the conditions which cause fission of their parent benzylidene compounds was considered proof of the position at which hydrogenation took place.

Quinoline-4-aldehyde was prepared by the action of selenium dioxide on lepidine, using the procedure of Hamilton.[13]

Quinoline-4-aldehyde *p*-Hydroxyanil.—*p*-Aminophenol (6.97 g.) was dissolved in absolute ethanol (150 cc.) under reflux, the hot solution filtered, and a solution of quinoline-4-aldehyde (10 g.) in absolute ethanol (15 cc.) was added to the filtrate. The mixture was refluxed for eighteen hours, cooled, allowed to crystallize and filtered. The product was purified by recrystallization from dioxane (8 volumes); yield of purified material, 80%.

Quinoline-4-aldehyde *p*-Dimethylaminoanil.—Equimolar amounts of quinoline-4-aldehyde and *p*-dimethylaminoaniline were heated together in an open flask for one hour at a bath temperature of 100–105°. The product was purified by extraction with, and crystallization from, methanol; yield of purified product, 94%.

Lepidal-*unsym*-diethylethylenediamine.—Quinoline-4-aldehyde (7.8 g.) and *unsym*-diethylethylenediamine (5.8 g.) were mixed in a Claisen flask, heated in a bath at 105–110° for one hour, the evolved water removed under reduced pressure, and the residue fractionated. A constant-boiling fraction was collected and redistilled from a Claisen flask possessing a 7-inch Vigreux side arm to give a fraction (5.3 g.) which boiled at 180° at 2 mm.

A picrate was obtained by mixing alcoholic solutions of picric acid and lepidal-diamine (in slight excess). After recrystallization from ethanol (10 volumes) it melted at 133°.

Anal. Calcd. for $C_{16}H_{21}N_3 \cdot C_6H_3O_7N_3$: C, 54.52; H, 4.99. Found: C, 54.67; H, 4.94.

4-Cyano-7-methylquinoline Methiodide.—7-Methylquinoline was converted successively to 7-methylquinoline methosulfate, 1,7-dimethyl-4-cyanoquinolane, and 4-cyano-7-methylquinoline methiodide by application of the procedure of Ainley and King[5] for the preparation of ethyl cinchoninate from quinoline. It was not found possible, however, to crystallize 1,7-dimethyl-4-cyanoquinolane. Because of the known instability of quinolanes, the crude 1,7-dimethyl-4-cyanoquinolane was transformed, without prolonged attempts at purification, to 4-cyano-7-methylquinoline methiodide. The over-all yield, on the basis of the 7-methylquinoline taken, was 40%.

Anal. Calcd. for $C_{12}H_{11}N_2I$: I, 40.93. Found: I, 41.60.

4-Cyano-7-methylquinoline.—Ethyl benzoate (100 cc.) and 4-cyano-7-methylquinoline methiodide (75 g.) were mixed in a flask equipped for the removal of methyl iodide by distillation, and the mixture heated in a bath at 230° for three hours. An ether solution of the products was extracted exhaustively with portions of 3 *N* hydrochloric acid and the acid extracts made just alkaline to congo red with ammonium hydroxide. The precipitate was filtered off, washed, and dried at 60°; yield, 97%.

7-Methylquinoline-4-carboxylic acid was obtained from 4-cyano-7-methylquinoline by direct application of Ainley and King's[5] method for the preparation of cinchoninic acid from 4-cyanoquinoline; yield, 92%.

Ethyl 7-Methylquinoline-4-carboxylate.—7-Methylquinoline-4-carboxylic acid (23.2 g.), absolute ethanol and concentrated sulfuric acid were mixed in the proportions described for cinchoninic acid[5] and refluxed for ten hours. The excess ethanol was removed under reduced pressure and the residue poured onto ice in a separatory funnel and made alkaline with ammonium hydroxide. The solution was extracted with chloroform, the extracts washed and dried, and the chloroform removed under reduced pressure. Upon distillation of the residue at 6–8 mm., a fraction (18.5 g.) boiling at 166–169° was collected; yield, 70%. A portion of this material was redistilled at 2 mm. for analysis. The ester crystallized after keeping at room temperature for approximately three weeks.

7-Methylquinoline-4-carboxylic Acid Amide.—Anhydrous methanol was prepared as described by Fieser.[14] Through anhydrous methanol (125 cc.) in a pressure bottle, dry ammonia was passed, with cooling, until 21 g. had been absorbed. Ethyl 7-methylquinoline-4-carboxylate (17 g.) was added, the bottle stoppered, and the mixture allowed to stand at room temperature for seventeen days. The ammonia and alcohol were then evaporated off and the residue washed with ether; yield, 96%. The amide was used for the next step without further purification.

4-Amino-7-methylquinoline.—A solution of potassium hypobromite was prepared by dissolving 85% potassium hydroxide (2.9 g.) and bromine (1.6 g.) in water (85 cc.). The solution, cooled to 4°, was added with stirring to 7-methylquinoline-4-carboxylic acid amide (1.7 g.) suspended in water (20 cc.). A temperature of 4° was maintained until only a trace of the amide remained undissolved (approximately thirty minutes). A purer product was obtained if the amide was slightly in excess of the hypobromite.

The unreacted amide (0.15 g.) was removed by filtration, the temperature of the filtrate gradually raised to 75° during some fifteen minutes, and then maintained at 75–80° for the remainder of the reaction. Material (0.026 g.) which precipitated during the first ten minutes was filtered off and discarded, and heating then continued for seventy-five minutes. After chilling, the precipitated amine was filtered off; yield, 70%. Heating the filtrate for a further two hours gave no increase in yield of amine.

Acknowledgment.—The authors are grateful to Dr. Leonard H. Cretcher, Head of the Department of Research in Pure Chemistry of the Mellon Institute, for his interest in the work, and to Dr. Alice G. Renfrew of the same department for many suggestions made during the course of the investigation.

Summary

Several new 4-(*p*-dialkylaminobenzylidene)-aminoquinolines have been prepared; from certain

(11) Eisleb, German Patent 540,699 (1931); *Chem. Zentr.*, **103, I**, 1804 (1932).

(12) Rubtsov and Lizgunova, *J. Gen. Chem.* (U. S. S. R.), **13**, 697 (1943); *C. A.*, **39**, 704 (1945).

(13) Private communication from C. S. Hamilton.

(14) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 360.

of these, the corresponding 4-(*p*-diethylaminobenzylamino)-quinolines were obtained by hydrogenation of the azomethine double bond.

Three new azomethines of quinoline-4-aldehyde are also described; it was found that they resist acid hydrolysis.

A series of reactions is given for the preparation of 4-amino-7-methylquinoline from 7-methylquinoline.

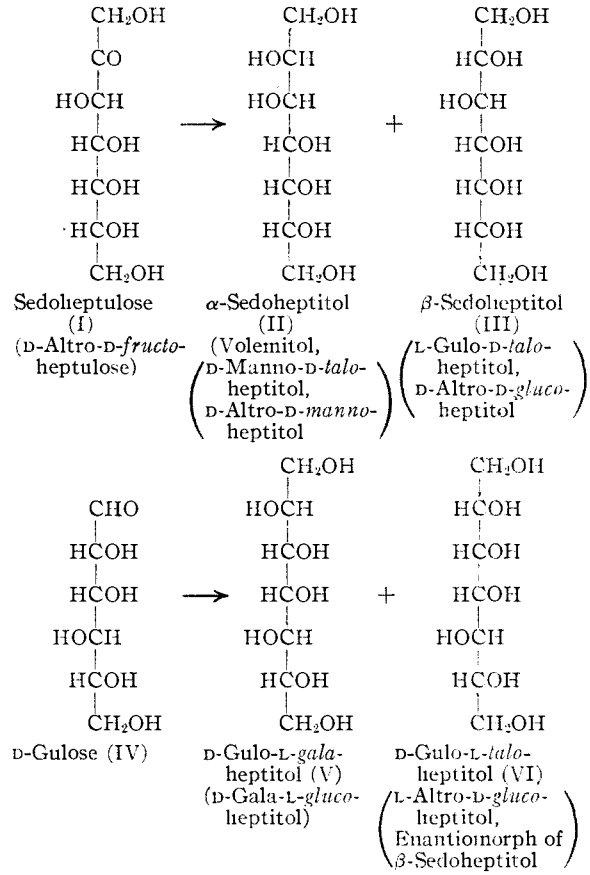
PITTSBURGH 13, PA. RECEIVED SEPTEMBER 7, 1946

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

L-Gulo-D-*talo*-heptitol (β-Sedoheptitol) and its Enantiomorph

BY ALICE T. MERRILL, W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

LaForge and Hudson[1] showed that the reduction of sedoheptulose, the seven-carbon ketose that occurs in the free state in *Sedum spectabile* Bor. and many related plants,[2] yields two heptitols which they named α- and β-sedoheptitol. It was found later[3] that α-sedoheptitol is identical with volemitol, a heptitol which occurs in the mushroom *Lactarius volemus* Fr. and in several species of *Primula*,[4] but the configuration of this heptitol remained unknown until Ettel[5] proved that volemitol (*syn.*, α-sedoheptitol) is D-manno-D-*talo*-heptitol (II). It then became evident that if the configuration of β-sedoheptitol could be determined, the configuration of sedoheptulose would become established. LaForge and Hudson[1] had reported that β-sedoheptitol melts at 127–128° and shows no rotation in water or in borax solution; these data did not correspond with the properties of any known heptitol, a fact which led LaForge[6] to synthesize the two D-guloheptitols from D-gulose (IV) through the epimeric D-guloheptoses. One D-guloheptitol proved to be identical with D-gala-L-*gluco*-heptitol and was therefore D-gulo-L-*gala*-heptitol (V); accordingly the other D-guloheptitol could be assigned the epimeric configuration that is represented by the name D-gulo-L-*talo*-heptitol (VI). LaForge reported that D-gulo-L-*talo*-heptitol melted at 128–129° and that it showed no rotation in borax solution, even though the configuration, which is unsymmetrical, represents a substance that should possess some rotatory power; its rotation seemed to be so small that it remained undetected. When Ettel proved that volemitol and α-sedoheptitol are D-manno-D-*talo*-heptitol it became evident to him from configuration II that β-sedoheptitol could not be LaForge's D-gulo-L-*talo*-heptitol (VI) but might be the enantiomorph, namely, L-gulo-D-*talo*-heptitol (III). The melting points of these possible enantiomorphs were alike and if one of them fortuitously exhibited no detected rotation the other would also show no rotation under like conditions of observation. Ettel therefore concluded from LaForge's data that β-sedoheptitol is L-gulo-D-*talo*-heptitol and therefore that sedoheptulose has the configuration I. Conclusive and independent evidence that the ketose possesses this configuration was obtained subsequently by Richtmyer, Hann and Hudson[7] through the oxidative degradation of sedoheptulose to D-altronic acid, which was identified by its characteristic crystalline calcium salt. The work that is reported in the present article was undertaken for the purpose of deciding whether



(1) LaForge and Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

(2) References concerning its wide occurrence in the *Crassulaceae* can be found in the review article by N. K. Richtmyer in "Advances in Carbohydrate Chemistry," Academic Press, Inc., New York, 1945, Vol. I, p. 47.

(3) LaForge, *J. Biol. Chem.*, **42**, 375 (1920); LaForge and Hudson, *ibid.*, **79**, 1 (1928).

(4) References concerning volemitol can be found in the review article by C. S. Hudson in "Advances in Carbohydrate Chemistry," Vol. I, p. 13 (1945).

(5) Ettel, *Collection Czechoslov. Chem. Commun.*, **4**, 504 (1932).

(6) LaForge, *J. Biol. Chem.*, **41**, 251 (1920).

(7) Richtmyer, Hann and Hudson, THIS JOURNAL, **61**, 343 (1939).