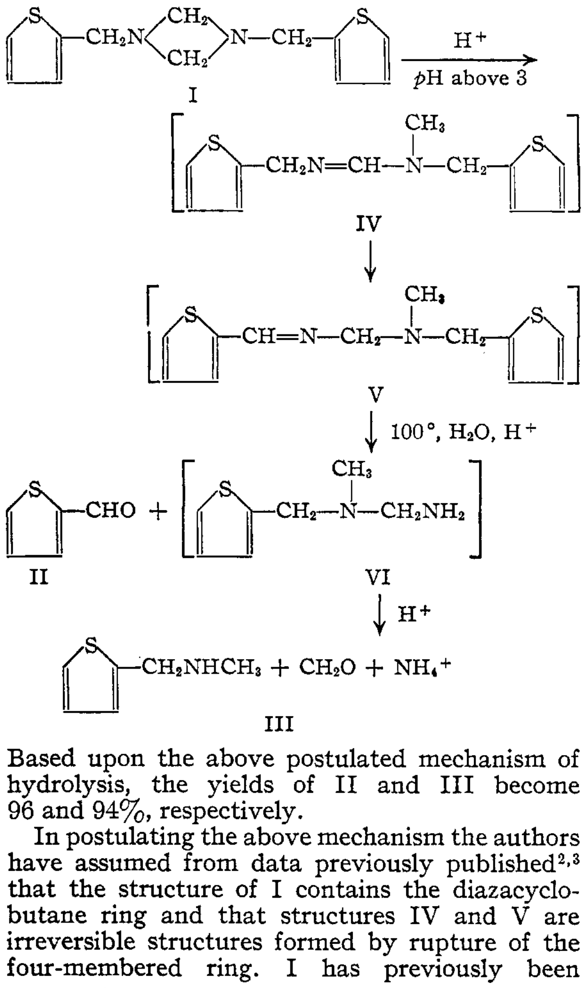
[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Aminomethylation of Thiophene. IV. Preparation of 2-Thiophenaldehydes from the N-(2-Thenyl)-formaldimines

BY HOWARD D. HARTOUGH AND JOSEPH J. DICKERT, JR.

Prior articles in this series[1,2,3] have dealt with reaction factors in the aminomethylation of thiophene, with preparation of the N-(2-thenyl)-formaldimines and with their reactions.

It has now been found that N,N′-di-(2-thenyl)-1,3-diazacyclobutane, I, can be hydrolyzed in dilute acid solution at a *p*H of 3 to 6.8 to give a 48% yield of 2-thiophenealdehyde, II, and a 47% yield of N-methyl-2-thenylamine, III. Ninety-five per cent. of the sulfur in I appears in the two products. At a lower *p*H than 3, formaldehyde is evolved and resinification occurs; at a *p*H above 7, no hydrolysis occurs. The hydrolysis of I is best expressed by the equation



Based upon the above postulated mechanism of hydrolysis, the yields of II and III become 96 and 94%, respectively.

In postulating the above mechanism the authors have assumed from data previously published[2,3] that the structure of I contains the diazacyclobutane ring and that structures IV and V are irreversible structures formed by rupture of the four-membered ring. I has previously been shown to exist in a dynamic equilibrium with N-(2-thenyl)-formaldimine, VII. The actual form depends upon the *p*H of the solution. At *p*H of 1 to 2, the existence of the monomer, VII, has been demonstrated.[3] Above *p*H of 3, I appears to exist and it has been isolated directly from a solution of *p*H 6 by extraction with ether.

Further positive evidence that I is the active intermediate in the hydrolysis to II and III is indicated by the fact that N,N′,N″-tris-(5-methyl-2-thenyl)-tetrahydro-1,3,5-triazine, VIII, does not yield 5-methyl-2-thiophenealdehyde under hydrolytic conditions. The dimeric form of N-(5-methyl-2-thenyl)-formaldimine corresponding to I could not be isolated in a prior work.[2]

A number of possible reaction courses are conceivable in this hydrolysis and should be considered. Analogy with the mechanism proposed by Sommelet[4] for production of benzaldehyde would suggest that VII was the active intermediate and a prototropic shift occurred in that compound to form N-methyl-2-thenaldimine, IX, which would subsequently be hydrolyzed to II. However, this mechanism does not account for the formation of III. IX has been prepared and characterized to substantiate that it could not be isolated in these hydrolysis experiments. Its inherent instability, however, would militate against its isolation under the drastic hydrolysis conditions applied.

Since this article was originally submitted for publication, Angyal and Rassack[5] have briefly reported a study of the reaction of benzylamine hydrochloride and formaldehyde to form benzaldehyde, N-methylbenzylamine and ammonia. A thiophene, formaldehyde and ammonium chloride mixture will form a 2-thenylamine[1] and, therefore, a reaction similar to that proposed by Angyal and Rassack should be considered. Their mechanism would postulate the reaction of formaldehyde with the 2-thenylamine to form the formaldimine and subsequent reaction of equimolar amounts of the amine and the formaldimine to yield the 2-thiophenealdehyde, ammonia and an N-methyl-2-thenylamine. It will be noted that this mechanism gives the same products and in the same ratios as that involving the dimer, I, of the formaldimine as a reactant. Angyal and Rassack[5] discuss oxidation of benzylamine by formaldimine, $CH_2{=}NH$ (from hexamethylenetetramine), to yield benzaldehyde, methylamine and ammonia. Graymore and Davies[6] describe

---

(1) Hartough, Lukasiewicz and Murray, THIS JOURNAL, **70**, 1146 (1948).

(2) Hartough, Meisel, Koft and Schick, *ibid.*, **70**, 4013 (1948).

(3) Hartough and Meisel, *ibid.*, **70**, 4018 (1948).

(4) Sommelet, *C. R. Acad. Sci., Paris*, **157**, 852 (1913).

(5) Angyal and Rassack, *Nature*, **161**, 723 (1948).

(6) Graymore and Davies, *J. Chem. Soc.*, 293 (1945).

the similar oxidation of benzylformaldimine, and assume aminomethyl alcohol (from hexamethylenetetramine) to be the oxidizing agent. If such reactions occur in the thiophene series they produce one mole of 2-thiophenealdehyde from each mole of amine or formaldimine—twice the amount resulting from the mechanisms above. In addition to this oxidizing action, formaldehyde may cause a stepwise reduction of formaldimines to secondary or tertiary amines.[5,7]

Related to the hydrolysis of I is the treatment of 2-thenylamine and N-(2-thenyl)-formaldimine with hexamethylenetetramine, X, and hydrochloric acid. Angyal and Rassack[5] discussed treatment of benzylamine with X to form benzaldehyde, and Graymore and Davies[6] described the similar reaction of benzylformaldimine with X, with suitable concentrations of hydrochloric acid, to give the aldehyde. By analogy, similar reactions might be expected with thiophene isologs. When carefully acidified 2-thenylamine (sufficient acid to form the hydrochloride was employed) was added to X, the aldehyde, II, was formed. The reaction was not allowed to go to completion and the results definitely indicated that I was an intermediate since it was isolated by extraction with ether from the hydrolysis mixture at a *p*H of 4. Therefore, it appears that the mechanism of Angyal and Rassack[4] is not applicable to the present case.

2-Thiophenealdehyde, II, can also be obtained in 20–25% yield by warming I with formaldehyde and ammonium chloride. The remainder of I presumably reacts with formaldehyde and ammonium chloride to give a product containing a greater percentage of nitrogen than I. The product probably contains about 50% of bis-2,5-(methyleneiminomethyl)-thiophene, since it can be oxidized to a mixture of 2,5-thiophenedicarboxylic acid and 2-thiophenecarboxylic acid.

The formation of II and III does not require the prior separation of I. If the reaction mixture of thiophene, formaldehyde and ammonium chloride having a *p*H of 1.5 is adjusted to a *p*H of 3 to 6.8 and the mixture steam distilled, II can be obtained in 35–45% yield and III in 10–25% yield. If the *p*H is left at 1.5, only a trace of II is obtained. The *p*H dependence is probably associated with the fact[2] that I exists as the monomeric hydrochloride in solutions of *p*H 1 to 2 and as the dimer in more alkaline solutions. The yields of III were lower at higher *p*H values and the residual high boiling amines increased substantially. One would anticipate that at the lower *p*H value of about 6, the compound VI would hydrolyze more slowly to III.

The products obtained by hydrolysis of a reaction mixture from 2-methylthiophene, formaldehyde and ammonium chloride are not strictly analogous to those from thiophene. While 5-methyl-2-thiophenealdehyde, XI, was recovered it was not possible to isolate any N-methyl-5-methyl-2-thenylamine or, for that matter, any amine but the unhydrolyzed N-(5-methyl-2-thenyl)-formaldimine. The formaldimine produced from the reaction of 2-methylthiophene, formaldehyde and ammonium chloride[2] is a trimer of N-(5-methyl-2-thenyl)-formaldimine, VIII. Attempts to hydrolyze an isolated sample of VIII gave no aldehyde, XI. Polymerization of VIII occurred. The experimental observations might well be explained by the Sommelet mechanism, assuming that the formaldimine reacts as the monomer in acid solution. There is no experimental evidence of the existence of a dimer when 2-methylthiophene is employed.[2] Graymore and Davies[6] decided that, in the case of benzylformaldimine, trimerization to tribenzyltrimethylenetriamine precluded the prototropic shift and subsequent reaction and, to obtain the aldehyde, conditions avoiding polymerization were required.

When a reaction mixture obtained from 3-methylthiophene is hydrolyzed, products corresponding to those from thiophene are obtained at a *p*H of about 3 but at a *p*H of 6 no N-methyl-3-methyl-2-thenylamine was isolated. Instead, the amine N,N-dimethyl-3-methyl-2-thenylamine was isolated in low yield. Similarly, 2-chlorothiophene and *t*-butylthiophene produced N,N-dimethylamines but no N-methyl-2-thenylamines were isolated. Experimental work was not sufficiently extensive in these cases nor in the case of 2-methylthiophene to define the reaction courses. Formation of the N,N-dimethyl derivatives may take place stepwise through the reducing action of formaldehyde on the formaldimine.[5,7]

Experimental

The purity of thiophene, 2- and 3-methyl-, and 2-chlorothiophene, as determined by infrared analysis, was greater than 99 mole per cent. The *t*-butylthiophene used was later found to contain almost equimolar portions of 2-*t*-butyl- and 3-*t*-butylthiophene.[8] All melting points are corrected; boiling points are uncorrected.

General Procedure.—To the aqueous reaction mixture containing the N-(2-thenyl)-formaldimines as described in prior references[2,3] was added enough 10% sodium hydroxide solution to raise the *p*H of the solution to about 6 as determined by Hydrion paper. Normally a heavy oil separated from the reaction mixture. The well-stirred mixture was steam distilled (still temperature 105–110°) until no trace of the characteristic odor of thiophenealdehydes was noted in the distillate. The distillate, slightly basic, was neutralized with a little hydrochloric acid and extracted three times with ether. The extract was dried over anhydrous calcium sulfate, the ether evaporated and the product distilled *in vacuo*.

In the case of 5-chloro-2-thiophenealdehyde and the *t*-butyl-2-thiophenealdehyde the products were not sufficiently volatile with steam to be collected readily in that

---

(7) Werner, *J. Chem. Soc.*, 111, 844 (1917).

(8) This material was previously thought to be pure 2-*t*-butylthiophene but was reinvestigated after Appleby, Sartor, Lee and Kapranos reported formation of isomers in alkylation of thiophene at the 112th Meeting of the American Chemical Society, New York City, September, 1947. This information was later published: This Journal, 70, 1552 (1948).

TABLE I

2-THIOPHENEALDEHYDES

Substituent	Yield, %	B. p. °C.	Mm.	$n^{20}D$	Acid M. p., °C.	Semicarbazone M. p., °C.	Semicarbazone Formula	Semicarbazone Calcd.	Semicarbazone Found
....	45	72.5	7.0	1.5920	....	223–224	$C_6H_7N_3OS$	N, 24.85	N, 25.24
5-Methyl	37	52.5	0.7	1.5742	137–138[a]	207–208	$C_7H_9N_3OS$	S, 17.5	S, 17.4
3-Methyl[c]	42	65	2.2	1.5860	147–148[a]	211–212	$C_7H_9N_3OS$	N, 22.93	N, 22.54
5-Chloro	48	63–64	0.7	1.5942	151.5–152.5[a]	218–219	$C_6H_6ClN_3OS$	N, 20.59	N, 20.51
t-Butyl	44	155–162	1.0	1.5356[b]	128–128.5[a]	212–214	$C_{10}H_{15}N_3OS$	S, 14.23	S, 14.16

[a] Mixed melting point with an authentic sample[10] of acid showed no depression. [b] Refractive index at 30°. [c] No trace of 4-methyl-2-thiophenecarboxylic acid could be detected on oxidation. This is consistent with the data presented in ref. 3. It appears then that the aminoalkylation reaction takes place exclusively at the 2-position.

TABLE II

N-METHYL-2-THENYLAMINES

-2-Thenylamines	B. p. °C.	Mm.	$n^{20}D$	Derivatives Compound	M. p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Sulfur Calcd.	Sulfur Found
N-Methyl-[a]	41–42	1.2	1.5369	Phenylthiourea	127–128	$C_{13}H_{14}N_2S_2$	10.68	10.49	...	...	24.42	24.26
				Hydrochloride	195.5–196 dec.	$C_6H_{10}ClNS$	8.56	8.74	...	...	19.56	19.51
				Picrate[f]	181.5–182 dec.	$C_{12}H_{12}N_4O_7S$	15.73	16.00	40.45	39.70	9.00	9.06
N-Methyl-3-methyl-[b]				Phenylthiourea	148–149	$C_{14}H_{16}N_2S_2$	10.15	9.38[c]	...	...	...	...
N,N-Dimethyl-3-methyl-	61	2.5	1.5386	Methiodide[g]	179.5–180.5	$C_9H_{16}INS$	4.71	4.76	36.36	35.86	10.8	10.8
N,N-Dimethyl-5-chloro-[d]	42–44	0.5	1.5335	Methiodide[h]	193.5–194.5	$C_8H_{13}ClINS$	4.40	4.38	30.18	30.15	...	...
N,N-Dimethyl-*t*-butyl-[d,e]				Methiodide	193–194 dec.	$C_{12}H_{22}INS$	4.13	4.50	...	...	...	...

[a] Yield from hydrolysis of pure IV was 48%. Yields from hydrolysis of reaction mixtures generally ranged from 10–25%. [b] Isolated from the reaction mixture as the amine hydrochloride, m. p. 196–199° dec., by extracting the concentrated steam hydrolysate with chloroform. [c] Sample lost before check analyses could be obtained. [d] Obtained in low yields—generally below 10%. [e] Product not distilled. Identified as the methiodide. [f] Calcd.: H, 3.37. Found: H, 3.37. [g] Calcd.: H, 5.39. Found: H, 5.42. [h] Calcd.: H, 4.09. Found: H, 3.80.

manner. The hydrolysate, after boiling for two hours, was cooled and extracted with ether. After drying, the aldehydes were obtained by distillation *in vacuo*.

Isolation of the amine fraction was carried out in the following manner. Any oily or semi-resinous water-insoluble material was separated by decantation and discarded. The aqueous layer was neutralized with 40% sodium hydroxide, the amines were extracted with ether and dried, the ether was evaporated, and the amines were distilled *in vacuo* from a Claisen flask. Higher boiling complex amine mixtures were also noted from continued distillation but no simple products could be isolated.

Distillation of the insoluble oil obtained by the decantation step above, which normally was discarded, yielded, in the case of thiophene, only a small amount of aldehyde and higher boiling complex oxygen-containing products containing no active alcohol, aldehyde or acid components. These materials resinified in concd. hydrochloric acid indicating them to be methylene thenyl ethers. One relatively pure product from thiophene, b. p. 110° at 0.5 mm., $n^{20}D$ 1.5780, analyzed as follows: C, 55.65; H, 5.65; S, 26.78. These analyses indicate an empirical formula of $C_{11}H_{13}O_2S_2$. The product was oxidized with alkaline permanganate to 2,5-thiophenedicarboxylic acid, m. p. 358.5–359.5° (sealed tube on melting point block). No simple structure that oxidizes to this acid can be reconciled with the empirical formula $C_{11}H_{13}O_2S_2$.

Any significant departure from the above general procedure can be found in footnotes to the tables.

Hydrolysis of N,N′-Di-(2-thenyl)-1,3-diazacyclobutane, I.—To 21 g. (0.164 mole) of I obtained by a method previously described,[2] was added 12 g. of concd. hydrochloric acid in 200 ml. of water. This mixture was heated at the reflux temperature for one hour and then steam distilled. 2-Thiophenealdehyde, 9.0 g. (48%), was obtained by extraction of the distillate with ether. Caustic neutralization of the hydrolysate mixture, followed by ether extraction, yielded 10.0 g. (47%) of N-methyl-2-thenylamine, b. p. 184–185° (uncor.).

Reaction of I with Formaldehyde and Ammonium Chloride.—To 25 g. of N-(2-thenyl)-formaldimine dimer, I, were added 13 g. of ammonium chloride and 42 g. of 36% formaldehyde. The temperature fell to 18° and then slowly rose to 40°. I dissolved in the aqueous solution during the temperature rise. When the heat of reaction was no longer noticeable the reaction mixture was warmed to 70–80° for two hours. After cooling, 5.5 g. (20%) of 2-thiophenealdehyde was extracted from the mixture with ethyl ether and identified as the semicarbazone, m. p. 223–224°.

The amine portion of the reaction product, obtained in the usual manner by caustic neutralization,[2] contained 13.63% nitrogen. A 5-g. sample slurried with 10 g. of sodium hydroxide in 125 ml. of water was oxidized slowly by adding 10 g. of potassium permanganate in 150 ml. of water at 40° to the slurry. After obtaining the crystalline acids (3.2 g.) in the conventional manner, there were obtained 2.2 g. of 2,5-thiophenedicarboxylic acid, m. p. 358.5–359.5° and 1.0 g. of 2-thiophenecarboxylic acid, m. p. 128–129°. These acids are conveniently separated by digesting in benzene, the 2,5-thiophenedicarboxylic acid being very insoluble.

N-Methyl-2-thenaldimine was prepared by a modification of the method used for the preparation of N-methylpyrrolaldimine.[9] To 36 g. (0.3 mole) of 25% ethylamine was added with stirring 34 g. (0.3 mole) of 2-thiophenealdehyde during the course of one hour. The temperature rose to 35° after the addition was completed following which the mixture was heated at a temperature of 60° for two hours.

The mixture was then washed three times with 50-ml. portions of water. About 120 ml. of 17% hydrochloric acid was added and the mixture extracted with ether. Evaporation of the ether layer yielded 21 g. of unreacted 2-thiophenealdehyde. The residue was neutralized with caustic and the imine extracted with ether. The ether solution was dried and the ether was removed by evaporation; the residue of N-methyl-2-thenaldimine (9 g.) boiled at 48–49° (1.5 mm.); $n^{20}D$ 1.5864.

---

[9] Emmert, Diehl and Gollwitzer, *Ber.*, **62**, 1733 (1929).

[10] Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947).

Anal. Calcd. for C_6H_7NS: N, 11.2; S, 25.6. Found: N, 11.4; S, 26.0.

This compound must be analyzed immediately since it is hydrolyzed rapidly by the moisture in the air. One sample which was allowed to stand for two days had only 9.73% nitrogen. This same sample was allowed to stand for several weeks and at that time had only 5.07% nitrogen.

An attempt to prepare a picrate of this compound gave only the picrate of methylamine, m. p. and mixed m. p. 209–211° uncor.

Anal. Calcd. for $C_7H_8N_4O_7$: C, 32.31; H, 2.96. Found: C, 32.01; H, 3.07.

Reaction of 2-Thenylamine Hydrochloride and Hexamethylenetetramine.—One mole (140 g.) of hexamethylenetetramine in 500 ml. of water was heated to boiling in a flask equipped for distillation. To this boiling mixture, one mole, 113 g., of 2-thenylamine[3] in 100 g. of 36% hydrochloric acid and 200 ml. of water was added dropwise over a period of approximately ninety minutes. 2-Thiophenealdehyde, 15 g., was obtained from the distillate after this period of time. The reaction was stopped at this point, not because the aldehyde formation had stopped, but in order that the insoluble yellow oily layer could be investigated. The *p*H of the reaction mixture was approximately 6 at this point as determined by Hydrion paper. After cooling to 20°, 150 ml. of concd. hydrochloric acid was added. The *p*H changed from 6 to approximately 4 during this addition but the yellow oil did not dissolve. Extraction with ether yielded 90 g. of a bright yellow oil which when distilled gave 10 g. of 2-thiophenealdehyde. The remaining material, b. p. 116–124.5 (0.8 mm.), was identified as I, N,N′-di-(2-thenyl)-1,3-diazacyclobutane.[2]

Acknowledgment.—The authors are grateful to Dr. D. E. Badertscher for his advice and interest in this problem and to Dr. Seymour L. Meisel for the preparation of N-methyl-2-thenaldimine and determination of its properties in connection with another phase of this problem.

Summary

A convenient synthesis of several 2-thiophenealdehydes is described in which the aminomethylation intermediates, the N-(2-thenyl)-formaldimines, undergo a prototropic shift and are hydrolyzed to the corresponding aldehydes. The reaction is complicated by side reactions and N-methyl- and N,N-dimethyl-2-thenylamines are also isolated.

PAULSBORO, N. J. RECEIVED SEPTEMBER 10, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. III. Synthesis of Cyclobutanone, Cyclobutanol, Cyclobutene and Cyclobutane[1]

BY JOHN D. ROBERTS AND CHARLES W. SAUER[2,3]

The formation of methylenecyclobutane from the reaction of pentaerythrityl bromide with zinc represents one of the simplest methods for the synthesis of a cyclobutane derivative in good yield from readily available starting materials. This reaction, which was discovered by Gustavson[4] and studied by a large number of other investigators,[5] gives methylenecyclobutane along with lesser amounts of 2-methyl-1-butene and spiropentane. Derfer, Greenlee and Boord[6] have extended the scope of the reaction considerably by showing that 1,1,1-tri-(bromomethyl)-alkanes react with zinc to give alkenyl- and alkylidenecyclobutanes.

Methylenecyclobutane has been converted to cyclobutanone in 30–36% yield by ozonization[7] and in small yield by oxidation with potassium permanganate in aqueous acetone[8] or *via* reduction of the corresponding nitrosite.[9] Other methods for the preparation of cyclobutanone, with the exception of the reaction of ketene with diazomethane,[10] involve at least five steps from available starting materials and give over-all yields of less than 10%.[11]

In the present work, methods for the preparation of cyclobutanone from methylenecyclobutane were investigated. Ozonization was not attempted because of the relative difficulty of adapting this procedure to large-scale laboratory operation. Satisfactory yields of cyclobutanone were obtained from methylenecyclobutane by oxidation to 1-(hydroxymethyl)-1-cyclobutanol and cleavage of the glycol with lead tetraacetate. Gustavson[4] has previously obtained 1-(hydroxymethyl)-1-cyclobutanol in 40% yield by oxidation of methylenecyclobutane with dilute aqueous potassium permanganate. In the present investigation, 80–83% yields were achieved by performic acid oxida-

---

(1) Earlier papers in this series, THIS JOURNAL, **67**, 1281 (1945); **68**, 843 (1946).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

(3) Present address: Arthur D. Little, Inc., Cambridge, Mass.

(4) Gustavson, *J. prakt. Chem.*, [2] **54**, 97, 104 (1896); Gustavson and Bulatoff, *ibid.*, [2] **56**, 93 (1897).

(5) See Marrian, *Chem. Rev.*, **43**, 149 (1948), for a number of leading references.

(6) Derfer, Greenlee and Boord, THIS JOURNAL, **67**, 1863 (1945); **71**, 175 (1949).

(7) Bauer and Beach, *ibid.*, **64**, 1142 (1942), cite unpublished work by Whitmore and Williams; *cf.* Williams, Ph.D. Thesis, Pennsylvania State College, 1941, and Krimmel, Ph.D. Thesis, Pennsylvania State College, 1945.

(8) Filipow, *J. Russ. Phys.-Chem. Soc.*, **46**, 1141 (1914); *J. prakt. Chem.*, [2] **93**, 162 (1916).

(9) Demjanow, *Ber.*, **41**, 915 (1908); Demjanow and Dojarenko, *J. Russ. Phys.-Chem. Soc.*, **49**, 193 (1917); *Ber.*, **55**, 2727 (1922).

(10) (a) Lipp and Köster, *Ber.*, **64**, 2823 (1931); (b) Lipp, Buchkremer and Seeles, *Ann.*, **499**, 1 (1932); (c) Benson and Kistiakowsky, THIS JOURNAL, **64**, 80 (1942).

(11) (a) Kishner, *J. Russ. Phys.-Chem. Soc.*, **37**, 106 (1905); (b) **39**, 922 (1907); (c) Demjanow and Dojarenko, *Ber.*, **40**, 4393 (1907); (d) **41**, 43 (1908); (e) **55**, 2737 (1922); (f) Demjanow, *J. Russ. Phys.-Chem. Soc.*, **61**, 1861 (1929); (g) Demjanow and Shuikina, *J. Gen. Chem. (USSR)*, **5**, 1213 (1935); (h) Demjanow and Telnow, *Bull. acad. sci. URSS, Classe sci. math. nat. sci. chim.*, 529 (1937); (i) Curtius and Grandel, *J. prakt. Chem.*, [2] **94**, 359 (1916); (j) Wagner, Ph.D. Thesis, Pennsylvania State College, 1941.