Preparative Buffered Formolysis of 1-ONs.—To 30 ml of 0.103 *M* potassium formate–formic acid solution, which had been prepared and kept in a nitrogen atmosphere, was added 82 mg (0.247 mmol) of 1-ONs. The solution was placed in a constant-temperature bath at 60.00 ± 0.05° for 20 hr (approximately 10 $t_{1/2}$). It was then cooled and placed in a separatory funnel with 50 ml of ether. The ether solution was washed with four 20-ml portions of water, two 10-ml portions of 7% sodium bicarbonate solution, and 25 ml of water and dried (Na_2SO_4). Removal of solvent gave a residue which was short-path distilled [40–45° (10^{-3} mm)] yielding 40.5 mg (97%) of 2-O_2CH: ir (thin film) 1720 cm^{-1} (C=O); nmr (CCl_4, internal TMS) τ 1.95 (s, O_2CH, 1), 2.65–3.05 (m, aromatic H's, 4), 5.1–5.2 (d, CHO_2CH, 1), 6.4–6.6 (m, *exo*-methylene H, 1), 6.75 (d, bridgehead H's, 2), and 7.5–7.7 (t, *endo*-methylene H, 1); the chemical shifts and peak multiplicities agree closely with those of 2-OAc.[5]

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.70; H, 5.81.

Formolysis Stability Check of 2-O_2CH.—To a 25-ml solution of 0.0103 *M* potassium formate–formic acid in a 50-ml round-bottom flask was added 40 mg (0.225 mmol) of 2-O_2CH. The solution was placed in a constant-temperature bath at 60.00 ± 0.06° for 20 hr (approximately 10 $t_{1/2}$). At the end of 20 hr, the solution was placed in a separatory funnel with 50 ml of ether, and was washed with five 25-ml portions of water, 10 ml of saturated sodium bicarbonate, and 20 ml of water and dried ($MgSO_4$). Removal of solvent gave a 39.7-mg (99%) recovery of 2-O_2CH, as shown by ir and nmr spectroscopy.

Formolysis Stability Check of 1-O_2CH.—To a solution of 30 ml of 0.0103 *M* potassium formate–formic acid in a 50-ml round-bottom flask was added 43 mg (0.244 mmol) of 1-O_2CH. It was placed in a constant-temperature bath at 60.00 ± 0.06° for 20 hr (approximately 10 $t_{1/2}$). The cooled solution was placed in a separatory funnel with 50 ml of ether, and was washed with five 25-ml portions of water, 15 ml of saturated sodium bicarbonate, and 25 ml of water and dried ($MgSO_4$). Removal of the solvent gave 36.3 mg of product. The isolated product was dissolved in 1.0 ml of absolute ethanol and cooled to 5°. To this solution at 5° was added 0.15 ml of a 5% potassium hydroxide in absolute ethanol. The mixture was stirred and warmed to room temperature over 14 hr. The reaction mixture was transferred to a separatory funnel with 20 ml of ether and enough 10% hydrochloric acid to acidify the resulting aqueous solution. This mixture was washed with five 15-ml portions of water, 10 ml of saturated sodium bicarbonate, and 15 ml of water and dried ($MgSO_4$). Removal of solvent gave 28 mg of material which was chromatographed on activity II–III, basic alumina where petroleum ether eluted 5 mg of naphthalene and methylene chloride eluted 22 mg of 1-OH.

Thermal Stability of 1-ONs.—A solution of 40 mg (0.12 mmol) of the title compound in 15 ml of benzene (thiophene-free benzene distilled from sodium) was placed in a round-bottom flask and set in a constant-temperature bath at 70.00 ± 0.05° for 5 hr (approximately 10 $t_{1/2}$). Removal of solvent by short-path distillation gave 40 mg (100%) of recovered 1-ONs.

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Registry No.—1-OH, 33905-59-8; 1-OAc, 41562-89-4; 1-OTs, 41562-90-7; 1-ONs, 41562-91-8; 1-O_2CH, 41562-92-9; 2-O_2CH, 41562-93-0; Δ^2-cyclobutenyl acetate, 27238-02-4; benzenediazonium 2-carboxylate, 1608-42-0; 3-phenyl-Δ'-cyclobutenyl acetate, 41562-96-3; 4-phenyl-Δ^2-cyclobutenyl acetate, 41562-97-4; tosyl chloride, 98-59-9; nosyl chloride, 122-04-3; cyclohexyl tosylate, 953-91-3.

Notes

The Preparation of 2-Alkylamino-1,3,4-thiadiazoles

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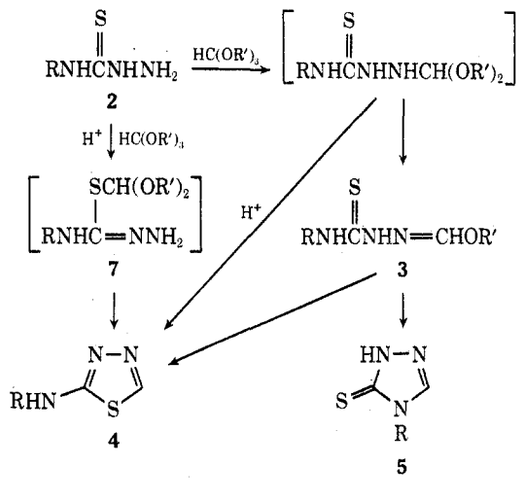
Investigation of the chemical and antimicrobial properties of mesoionic 8-alkyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-5,7-diones[1,2] required the preparation of 2-alkylamino-1,3,4-thiadiazoles, unsubstituted in the 5 position, as intermediates. We wish to report an improved procedure for the preparation of these thiadiazole derivatives.

Although 5-substituted 2-acylamino-1,3,4-thiadiazoles can be conveniently reduced to the corresponding amines with lithium aluminum hydride, the 5-unsubstituted amides are base sensitive and undergo extensive decomposition.[3] Formamidate esters undergo thermal rearrangement to *N*-alkylformamides which can be subsequently hydrolyzed to alkylamines.[4] Treatment of 2-amino-1,3,4-thiadiazole with a tenfold excess of trimethyl orthoformate gave as the sole product *N*,*N'*-bis(1,3,4-thiadiazol-2-yl)formamidine (**1**), instead of the desired methyl *N*-(1,3,4-thiadiazol-2-yl)-formamidate. Therefore, this method appears unsuitable for the preparation of the desired 2-alkylaminothiadiazoles.

2-*sec*-Amino-1,3,4-thiadiazoles have been prepared by the treatment of 4-substituted thiosemicarbazides **2** with triethyl orthoformate.[5a-e] Although this is a satisfactory method in the preparation of 2-arylamino derivatives,[5d] 2-alkylamino derivatives are obtained in low yield accompanied by nearly equivalent amounts of 4-alkyl-1,2,4-triazoline-3-thione (**5**). Thus treatment of **2** (R = CH_3) with a twofold excess of triethyl orthoformate results in the formation of both **4** (R = CH_3) and **5** (R = CH_3) in 39 and 34.5% yield, respectively. Heating of the presumed intermediate,[5a,b] ethyl formate 4-methylthiosemicarbazone (**3**, R =

(1) R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.*, **10**, 487 (1973).
(2) R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, in press.
(3) E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.*, **88**, 1272 (1958); J. Sandstrom, *Advan. Heterocycl. Chem.*, **9**, 165 (1968).
(4) R. M. Roberts and P. J. Vogt, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 420.
(5) (a) C. Ainsworth, *J. Amer. Chem. Soc.*, **78**, 1973 (1956); (b) M. Kanaoka, *J. Pharm. Sci. Jap.*, **75**, 1149 (1955); (c) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **77**, 5872 (1955); (d) B. Stanovnik and M. Tisler, *J. Org. Chem.*, **25**, 2234 (1960); (e) J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956).

CH_3; R′ = C_2H_5), obtained in high yield by reducing the reaction period to 1 hr, gave **4** (R = CH_3) and **5** (R = CH_3) in 24.3 and 27.8% yields, respectively.



It was found that the addition of a small amount of concentrated hydrochloric acid to the reaction of 4-alkylthiosemicarbazides with orthoformate esters gives **4** in high yield with no triazolethione **5** as by-product. Table I gives the yields obtained from the reaction of

TABLE I

ACID-CATALYZED REACTION OF 4-ALKYLTHIOSEMICARBAZIDES (2) WITH TRIETHYL ORTHOFORMATE

Compd	R	Mp of product 4, °C	Yield of 4, %	Lit. mp of thione 5, °C
2a	CH_3	66–67[a]	71.7	168[d]
2b	C_2H_5	71–72[b]	92.6	96–97[e]
2c	*n*-C_3H_7	42–43	91.0	74–75[f]
2d	CH_2Ph	106–107[c]	87.3	121–122[g]
2e	*t*-C_8H_{17}	127–128	92.1	182–184[f]
2f	1-Adamantyl	155–155.5	80.9	

[a] Lit. mp 65–66°: G. Werber and F. Massio, *Ann. Chim. (Rome)*, **51**, 944 (1961); *Chem. Abstr.*, **56**, 7305 (1962). [b] Lit.[5c] mp 70°. [c] Lit.[5d] mp 109°. [d] C. F. Kruger, W. Sattler, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 121 (1961). [e] M. Freund, *Chem. Ber.*, **29**, 2487 (1896). [f] S. A. Greenfield, M. C. Seidel, and W. C. Von Meyer, German Patent 1,943,915 (1970); *Chem. Abstr.*, **72**, 100713 (1970). [g] H. Saikachi and M. Kanaoka, *Yakugaku Zasshi*, **81**, 1333 (1961); *Chem. Abstr.*, **56**, 7304 (1962).

4-alkylthiosemicarbazides **2a–f** with triethyl orthoformate in ethanol with an acid catalyst present. The yields of the desired products, **4a–f**, ranged from 72 to 93% and were not affected by the amount of added acid. In addition, it was found that the reaction time could be shortened from 20–36 hr without acid catalyst to 2 hr for the acid-catalyzed reaction.

The use of trimethyl orthoformate in methanol with an acid catalyst was found to give results similar to those described for the acid-catalyzed reactions employing triethyl orthoformate. The reaction was extended to the use of triethyl orthoacetate with **2a** to give, under acid-catalyzed conditions, a 78% yield of 2-methylamino-5-methyl-1,3,4-thiadiazole (**6**).

The thiadiazoles **4a–e** may be distinguished from the previously reported triazoles **5a–e** by a band at 1530–1570 cm^{-1} generally present in the thiadiazoles and absent in the triazoles. In no case could **5** be detected *via* tlc analysis of the reaction product mixtures.

When intermediate **3** (R = CH_3; R′ = C_2H_5) was heated in ethanol with or without added acid, slow conversion to a mixture of **4a** and **5a** was observed, leading to the conclusion that **3** is not the intermediate leading to the formation of **4a** in the reaction of **2a** and triethyl orthoformate under acid catalysis.

Although it is possible that under acid catalysis 2-alkylamino-1,3,4-thiadiazole is produced *via* 4-alkylthiosemicarbazide 1-acetal, a reviewer has suggested that a different point of attack, possibly by the dialkoxy carbenium ion, on the thiosemicarbazide leads to the formation of **7** which can cyclize only to the observed product. Tlc analysis of the reaction mixture, involving **2a**, prior to heating shows the disappearance of **2a** and the formation of an intermediate (not formed in the absence of ortho ester). During attempted isolation, this intermediate reverts to the thiosemicarbazide following addition of weak base ion-exchange resin and solvent removal *in vacuo*. This behavior is more easily rationalized for the more labile suspected intermediate **7**.

Experimental Section

Nmr spectra were obtained on a Varian T-60 spectrometer and chemical shifts are reported relative to TMS. Infrared spectra were recorded by a Perkin-Elmer Model 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points were determined by a Mel-Temp melting point apparatus and are uncorrected.

***N,N′*-Bis(1,3,4-thiadiazol-2-yl)formamidine** (1).—2-Amino-1,3,4-thiadiazole (3.0 g, 30 mmol) and trimethyl orthoformate (31.8 g, 0.3 mol) were heated on an oil bath (120°) for 1 hr. The crystalline material, obtained upon cooling the reaction mixture, was collected and recrystallized from dimethylformamide to yield 2.2 g (94.4%) of 1 as off-white crystals, mp 238–240° dec (lit.[5a] mp 240° dec). The same product was obtained in comparable yield when methanol was employed as a reaction solvent.

4-(*tert*-Octyl)thiosemicarbazide (2e).—Hydrazine (0.64 g, 20 mmol) was added dropwise with stirring to a solution of *tert*-octyl isothiocyanate (3.42 g, 20 mmol) in anhydrous ether (25 ml) at 0°. After the reaction mixture was stirred for 3 hr at room temperature, the solvent was removed *in vacuo* to yield a colorless oil which crystallized upon standing. Recrystallization from an ethyl acetate–petroleum ether (bp 30–60°) mixture gave 3.3 g (81.3%) of **2e**: mp 94–95°; ir ($CHCl_3$) 3390 and 3300 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (s, 9 H), 1.6 (s, 6 H), 2.0 (s, 2 H), 3.8 (broad signal, 2 H), 7.6 (broad signal, 1 H), and 7.8 (broad signal, 1 H).

Anal. Calcd for $C_9H_{21}N_3S$: C, 53.16; H, 10.41; N, 20.66; S, 15.77. Found: C, 53.33; H, 10.51; N, 20.52; S, 15.52.

The 4-alkylthiosemicarbazides **2a–d** were prepared according to the method of Jensen, *et al.*,[6] and **2f** according to Oliver and Stokes.[7]

Reactions of 4-Methylthiosemicarbazide (2a) **and Ethyl Orthoformate.** A.—4-Methylthiosemicarbazide (**2a**) (1.0 g, 10 mmol) and triethyl orthoformate (3.0 g, 20 mmol) were heated on an oil bath (120°) for 20 hr. Upon cooling, a crystalline product was collected and recrystallized from ethanol to yield 0.38 g (34.5%) of 4-methyl-1,2,4-triazoline-3-thione (**5a**), mp 167–168° (lit.[8] mp 168°). The reaction mother liquid was evaporated *in vacuo* to yield a colorless oil, which was distilled, bp 130–132° (0.35 mm), to give a colorless oil which crystallized

(6) K. A. Jensen, V. Anthoni, B. Kagi, C. Larsen, and C. Pedersen, *Acta. Chem. Scand.*, **22**, 1 (1968).

(7) J. E. Oliver and J. B. Stokes, *J. Med. Chem.*, **13**, 779 (1970).

(8) C. F. Kroger, W. Sattler, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 121 (1961).

upon standing. Recrystallization from ethyl acetate gave 0.42 g (39%) of 2-methylamino-1,3,4-thiadiazole (**4a**), mp 65° (lit.[9] mp 65–66°).

B. Ethyl Formate 4-Methylthiosemicarbazone (3, R = CH_3; R′ = C_2H_5).—The above reaction was repeated but the period of heating was 1 hr. At this time, the reaction flask was cooled in an acetone–Dry Ice bath and a white, crystalline product was obtained. Recrystallization from ethyl acetate gave 1.5 g (93.3%) of ethyl formate 4-methylthiosemicarbazone (**3**, R = CH_3; R′ = C_2H_5): mp 100–101°; ir ($CHCl_3$) 3375, 1645, 1550, 1180 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (t, 3 H), 3.5 (d, 3 H), 4.45 (q, 2 H), 6.8 (s, 1 H), 7.6 (broad signal, 1 H), 9.2 (broad signal, 1 H).

Anal. Calcd for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06; S, 19.89. Found: C, 37.44; H, 7.05; N, 26.10; S, 20.09.

This compound (1.6 g, 10 mmol) was heated (neat) at 190° for 5 min. The resultant oil was dissolved in hot absolute ethanol and, upon cooling, 0.32 g (27.8%) of **5a** was obtained, mp 166–167°. The filtrate was evaporated *in vacuo* and the product was distilled to give 0.28 g (24.3%) of **4a** as an oil which crystallized upon standing, mp 63–64°. Similar yields of both products were obtained when ethanol was used as a reaction solvent, with and without acid catalyst. In these cases, the reaction mixture was refluxed for 20 hr.

C. 2-Methylamino-1,3,4-thiadiazole (4a).—Triethyl orthoformate (3.0 g, 20 mmol) and **2a** (1.0 g, 10 mmol) were added to absolute ethanol (10 ml). Concentrated hydrochloric acid (0.05 ml) was added and the suspension was stirred until solution was complete (1 hr). After the solution had been refluxed for 1 hr, the solvent was evaporated *in vacuo* and the crystalline product was dissolved in chloroform (10 ml). This solution was filtered and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from ethyl acetate gave 1.65 g (72%) of **4a** as white needles, mp 66–67°.

The 2-alkylamino-1,3,4-thiadiazoles **4b–f** were prepared in the same manner as **4a**, part C, using 10 mmol of 4-alkylthiosemicarbazide, 20 mmol of triethyl orthoformate, and 0.05 ml of concentrated HCl.

2-*n*-Propylamino-1,3,4-thiadiazole (4c).—The product **4c** was obtained as low-melting white crystals, mp 37–40°. Distillation, bp 136–138° (0.3 mm), gave a sample which melted at 42–43°: nmr ($CDCl_3$) δ 1.01 (t, 3 H), 1.76 (m, 2 H), 3.36 (t, 2 H), 7.33 (broad s, 1 H), 8.50 (s, 1 H); ir (neat) 3226 and 1530 cm^{-1}; hydrochloride salt mp 127–128°.

Anal. Calcd for $C_5H_9N_3S \cdot HCl$: C, 33.43; H, 5.61; N, 23.39; S, 17.85; Cl, 19.73. Found: C, 33.58; H, 5.57; N, 23.43; S, 17.92; Cl, 19.66.

2-*tert*-Octylamino-1,3,4-thiadiazole (4e).—The product **4e** was recrystallized from ethyl acetate: mp 127–128°; ir ($CHCl_3$) 3400, 1570 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (s, 9 H), 1.6 (s, 6 H), 1.8 (s, 2 H), 6.9 (broad signal, 1 H), 8.55 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}N_3S$: C, 56.30; H, 8.98; N, 19.70; S, 15.03. Found: C, 56.28; H, 8.84; N, 19.60; S, 14.96.

2-(1-Adamantylamino)-1,3,4-thiadiazole (4f).—The product **4f** was recrystallized from ethanol: mp 155–155.5°; ir ($CHCl_3$) 1570 cm^{-1}; nmr (DMSO-d_6) δ 1.6–2.2 (m), 8.95 (s, 1 H).

Anal. Calcd for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85; S, 13.62. Found: C, 61.52; H, 7.41; N, 17.94; S, 13.69.

2-Methylamino-5-methyl-1,3,4-thiadiazole (6).—A mixture of 4-methylthiosemicarbazide (0.79 g, 7.5 mmol), triethyl orthoacetate (2.43 g, 15 mmol), and 0.05 ml of concentrated hydrochloric acid in ethanol (10 ml) was stirred at room temperature for 1 hr. The resulting clear solution was refluxed for 1 hr and the solvent was removed *in vacuo*. Recrystallization of the residue from ethyl acetate gave 0.75 g (78.1%) of **6** as white crystals, mp 111–112° (lit.[10] mp 112°).

Registry No.—**1**, 26907-35-7; **2a**, 6610-29-3; **2b**, 13431-34-0; **2c**, 13431-35-1; **2d**, 13431-41-9; **2e**, 41593-77-5; **2f**, 21126-27-2; **3** (R = CH_3; R′ = C_2H_5), 21304-97-2; **4a**, 38490-45-8; **4b**, 13275-68-8; **4c**, 41593-82-2; **4c** HCl, 41593-83-3; **4d**, 23289-12-5; **4e**, 41593-85-5; **4f**, 41593-86-6; **5a**, 24854-43-1; **5b**, 32362-78-0; **5c**, 41593-89-9; **5d**, 32362-84-8; **5e**, 41593-91-3; **6**, 38917-35-0; 2-amino-1,3,4-thiadiazole, 4005-51-0; trimethyl orthoformate, 149-73-5; *tert*-octyl isothiocyanate, 17701-76-7; triethyl orthoformate, 122-51-0.

(9) G. Werber and F. Massio, *Ann. Chim. (Rome)*, **51**, 944 (1961); *Chem. Abstr.*, **56**, 7305 (1962).

(10) C. Pulvermacher, *Chem. Ber.*, **27**, 613 (1894).

A Facile Synthesis of 2,2′-Bi-2-thiazolines and -thiazines

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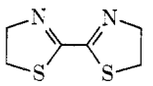
The first reports of the synthesis of 2,2′-bi-2-thiazolines appeared in 1954. In that year, two groups[1,2] discovered independently that the parent compound **1** could be prepared in poor to modest yield by the reaction of cyanogen with 2-mercaptoethylamine. Subsequent work by Woodburn, *et al.*,[3] has shown that **1** can also be prepared in very good yield by the reaction of dibutyloxamidine 2HCl with 2-mercaptoethylamine HCl. Preparation of its six-membered analogs, **2**,



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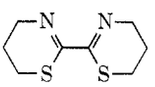

2

however, has been hindered in that necessary precursors were not readily available. To date, the synthesis of 2,2′-bi-2-thiazine, **2**, or its homologs has not yet been reported.

We wish to describe a general and facile synthesis of **1**, **2**, and their homologs based on the readily available precursors: dithiooxamide (rubeanic acid) and amino alcohols. Heterocycles **1** and **2** are of interest in that they have been found to form dications bearing charge on mutually attached carbon atoms when allowed to react with acylating agents[4a] or Brønsted acids.

The synthetic route involved stirring appropriate amino alcohols with dithiooxamide at room temperature until ammonia evolution ceased, using modified Wallach reaction conditions.[4b] Reaction of the resulting *N,N′*-bis(hydroxyalkyl)dithiooxamide with thionyl chloride produced the corresponding bithiazolinium or -thiazinium dications (**1′–4′**) in good to excellent yield. The free bases (**1–4**) were liberated by treatment with sodium bicarbonate since stronger bases generally led to hydrolysis products. (See Scheme I.)

The dications could be stored for several days under anhydrous conditions; however, exposure to moisture led to unidentified hydrolysis products. Samples of the free bases appeared to have long-term stability. The latter compounds were characterized by ir and nmr analyses as well as by elemental analyses.

Dication **5**, as well as its oxygen analog **6**, were of particular interest in that there are relatively few examples of dications bearing positive charges on mutually attached carbon atoms reported in the literature.[5] Dications **5** and **6** were prepared by addition of **1** or 2,2′-bi-2-oxazoline to neat FSO_3H. The proton chemical shift assignments for protons a and b were based

(1) R. Kuhn and F. Drawert, *Justus Liebigs Ann. Chem.*, **590**, 55 (1954).

(2) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(3) H. M. Woodburn and W. E. Hoffman, *J. Org. Chem.*, **23**, 262 (1958).

(4) (a) D. A. Tomalia, to be published; (b) O. Wallach, *Justus Liebigs Ann. Chem.*, **262**, 357 (1891).

(5) C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 376 (1972).