

described. The sulfonic acid group in each of these sulfonations enters the 3-position of the pyridine nucleus.

The structures of the picoline sulfonic acids were determined by conversion to the correspond-

ing nitriles and the hydrolysis of these compounds to the known methylnicotinic acids.

Nicotinonitrile was obtained from sodium pyridine-3-sulfonate in 46% yields.

MADISON, WISCONSIN

RECEIVED AUGUST 5, 1943

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

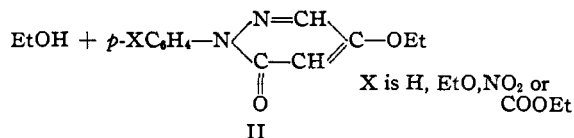
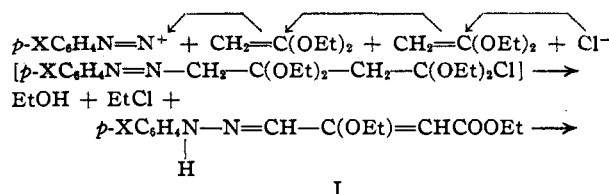
Ketene Acetals. XII. The Reaction of Ketene Diethylacetal with Diazonium Salts

BY S. M. McELVAIN AND ARTHUR JELINEK¹

In previous papers² from this Laboratory the reactions of a variety of cationoid reagents with the anionoid center of ketene acetal have been described. It seemed that a continuation of this study with the very reactive diazonium cation as the reagent would be of interest, particularly since it would make possible a comparison of the behavior of ketene acetal with other types of compounds, such as β -ketoesters, phenols and aromatic amines, of lower anionoid reactivity which react quite readily with diazonium compounds.

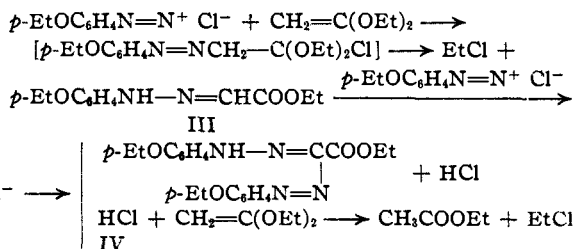
This paper describes the course of the reaction of ketene acetal with four representative diazonium salts, phenyl-, *p*-ethoxyphenyl-, *p*-nitrophenyl- and *p*-carbethoxyphenyldiazonium chlorides. Since the acetal reacts rapidly with water and other hydroxylic compounds, these reactions were carried out with the dry diazonium salt in the presence of an excess of the acetal. In some exploratory experiments, in which a 10:1 ratio of reactants was used, it was found that for each mole of diazonium salt 5 moles of ketene acetal were consumed in reactions with the salt and with such reaction products as alcohol and hydrogen chloride; the remaining 5 moles of acetal were recovered unchanged. Consequently a 5:1 molar ratio of the acetal to the diazonium salt was used in subsequent reactions.

In each case the main reaction product was a 1-phenyl-4-ethoxy pyridazine-6 (II) the formation of which may be rationalized as a cyclization of the phenylhydrazone (I) that is formed by the addition of the diazonium salt—the cation of which is in the resonance form,³ $\text{ArN}=\text{N}^+$ —across two molecules of ketene acetal, thus



The yields of the pyridazines (II) were 25–35% of the theoretical and in each case they dropped to about one-half of these values if the reaction was carried out in pyridine in which both reactants are soluble. With none of the diazonium salts was the yield of nitrogen more than 20% of the theoretical, a fact that indicates that no more than this amount of the salt underwent decomposition to produce free radicals.⁴

In addition to the pyridazine (II) varying quantities of products, the formation of which requires the addition of the diazonium salt to a single molecule of ketene acetal, were isolated from the reaction of all of the diazonium salts except phenyldiazonium chloride. The largest yield of such a product was obtained with *p*-ethoxyphenyldiazonium chloride. This compound, which was identified as ethyl *p,p'*-diethoxydiphenylformazyl formate (IV), was obtained as beautiful dark red leaflets in 27% yields. Its formation is the result of coupling of the diazonium compound with the hydrazone (III) that is formed by the addition of the diazonium salt to a single molecule of ketene acetal, thus



Both the pyridazine (II, X is H) and the formazyl compound (IV) are described in the literature. Sonn⁵ prepared the former compound by the ethylation of 1-phenyl-4-hydroxypyridazine-6 (VI, X is H) which was obtained through the following sequence of reactions starting with phenyl-

(1) Wisconsin Alumni Research Foundation Research Assistant, 1941–.

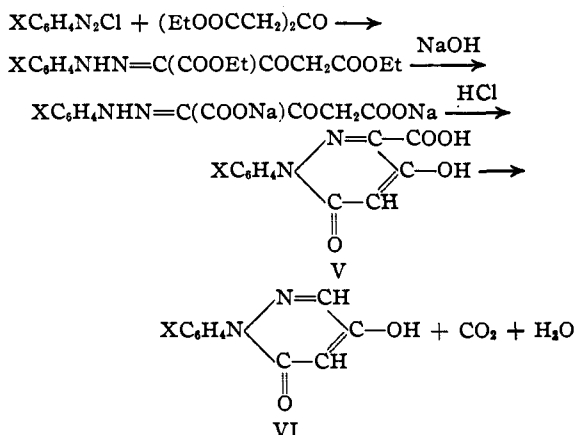
(2) (a) McElvain, *et al.*, *THIS JOURNAL*, **60**, 2210 (1938); (b) **62**, 1281 (1940); (c) **64**, 254 (1942); (d) **64**, 260 (1942).

(3) *Cf. Hauser and Breslow, ibid.*, **63**, 418 (1941).

(4) *Cf. Ann. Rep.*, **37**, 278 (1940).

(5) *Sonn, Ann.*, **318**, 290 (1935).

diazonium chloride and ethyl acetonedicarboxylate



The properties of the pyridazone (II, X is H) correspond to the product obtained by the ethylation of VI and a sample of this latter compound, prepared by Sonn's procedure, corresponds in its properties to acid obtained from the saponification of II. Sonn's method for the preparation of 4-hydroxypyridazones is quite general and is probably the more satisfactory method of preparing these compounds. However, the reaction of ketene acetal with the diazonium salt seems to be the more convenient procedure for the preparation of the 4-ethoxypyridazones. The hydroxypyridazones (VI) are fairly strong acids that give good neutral equivalents on titration with alkali. The 1-(*p*-aminophenyl)-4-hydroxypyridazone (VI, X is NH₂), obtained from the corresponding nitro compound that was prepared by Sonn's procedure⁶ has the high melting point and water solubility characteristic of a zwitterion.

The formazyl compound (IV) has been prepared by Pechmann and Wedekind⁷ by coupling *p*-ethoxyphenyldiazonium chloride with the sodium enolate of acetoacetic ester. A sample prepared by this procedure was found to be identical with the product (IV) obtained in the present work from ketene acetal and the diazonium salt.

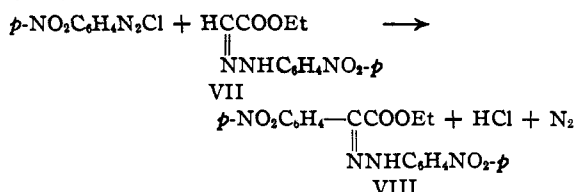
Along with the pyridazone (II, X is NO₂) a small amount of a product that appears to have formed from a hydrazone corresponding to III was isolated. This compound is an amorphous rust-red solid which could not be satisfactorily purified

(6) Before Sonn's work Bülow and Höpfner, *Ber.*, **34**, 71 (1901) had prepared the dibasic acid V (X is NO₂) from the interaction of *p*-nitrophenyldiazonium chloride and ethyl acetonedicarboxylate, but they assigned to it the 4-membered ring structure, $\text{p-NO}_2\text{C}_6\text{H}_4\text{-N-N}=\text{C}(\text{COOH})\text{C}=\text{CHCOOH}$ in order to

account for its dibasic acid character. In the present work this same dibasic acid has been prepared and decarboxylated to the monobasic hydroxypyridazone and this latter compound ethylated (see Experimental Part). The fact that this ethylated product was identical with the ethoxypyridazone (II, X is NO₂) obtained in the present work confirms Sonn's contention that Bülow and Höpfner's acid had the structure V instead of the 4-membered ring structure which the latter workers assigned to it.

(7) Pechmann and Wedekind, *ibid.*, **30**, 1688 (1895).

by recrystallization. The nitrogen and ethoxyl content indicate that it is the *p*-nitrophenylhydrazone of ethyl *p*-nitrobenzoylformate (VIII) which was formed by the loss of nitrogen during the coupling of the diazonium salt with the hydrazone (VII), thus



Busch and collaborators⁸ have shown that certain aryl-diazonium salts couple with the *syn* forms of the arylhydrazones of methyl glyoxalate to yield a formazyl compound such as IV but react with the isomeric *anti* form with the loss of nitrogen to yield a hydrazone of the type represented by VIII.

A small yield (1.2%) of the hydrazone resulting from the addition of the diazonium salt to one molecule of ketene acetal and similar in structure to III and VII was isolated along with the pyridazone II when *p*-carbethoxyphenyldiazonium chloride was used. Associated with this hydrazone were traces of a deep red crystalline material which was, in all probability, the corresponding formazyl compound, but there was not sufficient of this material to permit identification.

It is apparent from the reactions that are described above that ketene acetal reacts with diazonium salts by direct addition followed by elimination of simpler molecules (alcohol and ethyl chloride) and rearrangement to yield hydrazones. In so far as this addition involves only a single molecule of the acetal the reaction shows some resemblance to the reaction of the enolic forms of 1,3-diketones and β -ketoesters with the diazonium salts to produce hydrazones of aldehydes and ketones. However, the most general behavior of ketene acetal with these salts involves the addition of the salt across two molecules of the acetal and in taking this course the reaction follows the same pattern that was observed when bromine,^{2a} acids^{2c} and maleic anhydride^{2d} were added to ketene acetal.

Experimental Part

Reaction of Phenyldiazonium Chloride with Ketene Acetal.—A mixture of ether-moist phenyldiazonium chloride (prepared from 14.0 g. (0.11 mole) of aniline hydrochloride and 17.0 g. of amyl nitrite⁹) and 58.0 g. (0.50 mole) of ketene diethylacetal was placed in a 200-ml. flask fitted with a reflux condenser. The top of this condenser was connected through a dry-ice trap to a 1-liter aspirator bottle arranged to collect and measure any evolved nitrogen. The mixture was heated in a warm water-bath at 50° until incipient reaction, as evidenced by the development

(8) Busch, *et al.*, *J. prakt. Chem.*, [2] **92**, 25 (1915); *Ber.*, **58**, 442 (1925).

(9) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," The Macmillan Company, New York, N. Y., 1937, p. 286.

of a deep red coloration and the evolution of gas bubbles; whereupon, the water-bath was removed. It usually was necessary to cool the reaction mixture in an ice-bath in order to control the highly exothermic reaction that then occurred. After this initial reaction had subsided, the mixture was heated in an oil-bath at 85° for two hours. The collected nitrogen amounted to 155 ml. (7%). Fractionation of the material in the cold trap yielded 4.0 g. (62%) of ethyl chloride, b. p. 12°.

After standing overnight a solid crystallized from the reaction mixture and after cooling to -70° it was filtered off. This crude 1-phenyl-4-ethoxy-pyridazine-6 (II, X is H) so obtained weighed 7.8 g.; after one recrystallization from petroleum ether (b. p. 90-100°) the resulting white product weighed 7.6 g. (35%) and melted at 125-126°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.7; H, 5.6; N, 13.0; C_2H_5O , 20.8. Found: C, 66.6; H, 5.6; N, 13.2; C_2H_5O , 21.0.

A 1.0-g. sample of this pyridazine was saponified by refluxing for eight hours with a 5% solution of sodium hydroxide in 75% alcohol. The resulting 1-phenyl-4-hydroxypyridazine-6 melted at 229-230° and had a neutral equivalent of 185 (calcd. 188). Sonn⁸ reported the 1-phenyl-4-ethoxy- and the 1-phenyl-4-hydroxypyridazine-6 as melting at 124-125° and 221-222°, respectively. A sample of the 4-hydroxypyridazine prepared by Sonn's procedure melted at 228-229° and when mixed with the product obtained from the saponification of the 4-ethoxy-pyridazine melted at 228-229°. The product obtained by the ethylation of the sodium salt of the 4-hydroxypyridazine with ethyl iodide melted either alone or when mixed with the 4-ethoxy-pyridazine (II, X is H) at 125-126°.

Fractionation of the filtrate from which the above pyridazine was filtered yielded the following: (a) 9.0 g. of diethyl ether, (b) 2.3 g. of ethyl acetate, (c) 30.3 g. of ethyl orthoacetate, (d) 3.9 g. of ethyl *o*-ethylacetate,²⁰ b. p. 70-75° (10 mm.), (e) 8.0 g. of a mixture of the dimer and trimers of ketene acetal, b. p. 105-128° (0.3 m.), and (f) 6.2 g. of an undistillable residue.

Reaction of Other Diazonium Salts with Ketene Acetal.

p-Ethoxyphenyl-, *p*-nitrophenyl- and *p*-carbethoxyphenyldiazonium chlorides each were mixed with ketene acetal in the same molar amounts and ratio that were used in the above reaction with phenyldiazonium chloride. With each of the substituted diazonium salts, however, the reaction with ketene acetal was spontaneous and consequently the initial warming was unnecessary. In fact, it was necessary to cool the reaction mixture from the start in order to keep the highly exothermic reaction under control. After the initial spontaneous reaction had subsided the reaction mixture was heated for two to three hours at 70°. The yields of nitrogen and ethyl chloride were 15-20% and 40-50%, respectively.

The solid that separated from the reaction mixture in which *p*-ethoxyphenyldiazonium chloride was used was a light tan powder mixed with deep red crystals. These two reaction products were separated in the following manner. The solid, which weighed 11.9 g., was extracted with 900 ml. of a boiling 25% alcohol solution and filtered through a steam-jacketed funnel. The deep red crystalline product that collected on the filter was practically pure ethyl *p,p'*-diethoxydiphenylformazyl formate (IV). It weighed 4.1 g. and, after recrystallization from ethyl alcohol, melted at 130-131° and showed no depression in melting point when mixed with a sample of ester prepared by the procedure of Pechmann and Wedekind.⁷ Cooling of the filtrate from which the formazyl compound was filtered caused 6.1 g. of 1-(*p*-ethoxyphenyl)-4-ethoxypyridazine-6 (II, X is EtO), m. p. 157-159°, to crystallize from solution. Recrystallization of this product from a 25% alcohol solution gave a perfectly white product that melted at 159-160°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: C, 64.6; H, 6.2; N, 10.8; C_2H_5O , 34.6. Found: C, 64.4; H, 6.3; N, 11.1; C_2H_5O , 34.4.

Distillation of the filtrate from the initial filtration of the reaction mixture yielded similar fractions to those obtained

from the reaction of phenyldiazonium chloride. If the distillation were interrupted after the removal of the ethyl orthoacetate, and the undistilled material cooled, more solid material could be filtered off. When this was separated as described above, an additional 1.0 g. of the formazyl compound (IV) and 0.4 g. of the pyridazine were obtained. Thus the total yields of these products were 5.1 g. (27%) and 6.5 g. (25%), respectively.

From the reaction mixture in which *p*-nitrophenyldiazonium chloride was used a red solid that weighed 12.0 g. separated on cooling. Trituration of this solid with three 50-ml. portions of acetone dissolved the red material and left undissolved 5.6 g. of 1-(*p*-nitrophenyl)-4-ethoxypyridazine-6 (II, X is NO₂), a lemon yellow solid that melted at 245-247°. Upon evaporation of the acetone solution to about 30 ml. an additional quantity of this product separated. After filtration and washing with a little cold acetone this product melted at the point of the undissolved pyridazine. Total yield 7.0 g. (25%). Recrystallization from dioxane raised the melting point to 249-250°.

Anal. Calcd. for $C_{12}H_{11}O_4N_3$: N, 16.1; C_2H_5O , 17.2. Found: N, 16.2; C_2H_5O , 17.2.

Saponification of the ethoxypyridazine (II, X is NO₂) yielded a liquid reaction product from which it was not possible to isolate the corresponding 4-hydroxypyridazine. However, this latter compound was prepared by the decarboxylation of Bülow and Höpfner's dibasic acid (*cf.* ref. 6) and ethylated by Sonn's procedure—using only one equivalent of sodium ethoxide with an excess of ethyl iodide—to the same ethoxypyridazine as was obtained from the reaction of ketene acetal with the diazonium salt.

The red material dissolved in the acetone was precipitated by the addition of several volumes of ether. The resulting rust-red compound when heated began to darken at 150° and decomposed at 183-185°. Attempts to recrystallize it from a number of different solvents yielded only oils. It could be precipitated from a solution in ethyl acetate by the addition of ether, but this treatment did not appreciably change the decomposition point. Analyses of this material indicated that it contained 17.2% of nitrogen and 12.4% ethoxy. These values correspond most closely to the ethyl *p*-nitrobenzoylformate *p*-nitrophenylhydrazone (VIII) the nitrogen and ethoxyl content of which are 15.6 and 12.6%, respectively.

The solid that separated from the reaction mixture in which *p*-carbethoxyphenyldiazonium chloride was used was light yellow in color, weighed 12.7 g. and contained a few deep red crystals scattered through it. The yellow material was evidently a mixture since it melted over a range of 110-116° even after recrystallization from alcohol. This material was heated in a sublimation apparatus at 90-110° under 0.2 mm. pressure, whereupon 0.4 g. of a product that melted at 88-91° sublimed. Resublimation of this product yielded 0.3 g. (1.2%) of ethyl glyoxalate *p*-carbethoxyphenylhydrazone, a light yellow solid that melted at 92-93°.

Anal. Calcd. for $C_{15}H_{15}O_4N_2$: N, 10.6; C_2H_5O , 34.1. Found: N, 10.3; C_2H_5O , 33.8.

Recrystallization from alcohol of the residue from which this hydrazone had been sublimed gave 9.5 g. (33%) of 1-(*p*-carbethoxyphenyl)-4-ethoxypyridazine-6 (II, X is COOEt) which melted at 130-131°. A second recrystallization from this solvent gave a lemon yellow product that melted at 131-132°. Further recrystallizations failed to change the melting point or color of this compound.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: N, 9.7; C_2H_5O , 31.2. Found: N, 9.9; C_2H_5O , 31.1.

1-(*p*-Nitrophenyl)-4-hydroxypyridazine-6.—In a 250-ml. long-neck flask was placed 23.5 g. of 1-(*p*-nitrophenyl)-3-carboxy-4-hydroxypyridazine-6 (prepared by the procedure of Bülow and Höpfner*) and 90 g. of diphenyl ether. The mixture was heated to 250° in a metal bath until the evolution of carbon dioxide ceased. After cooling, the mixture was treated with 2.0 liters of a 3% aqueous sodium hydroxide solution and the aqueous portion extracted several times with diethyl ether in order to remove the diphenyl ether. Then the aqueous alkaline solution

was acidified with hydrochloric acid, and, after cooling, the precipitated pyridazone filtered. After washing with several liters of hot distilled water the 1-(*p*-nitrophenyl)-4-hydroxypyridazone-6 weighed 15 g. (76%) and melted with decomposition at 298–299°. Recrystallization from an alcohol-water mixture only raised the melting point of this product to 299–300°. Its neutral equivalent was 226 (calcd. 233).

Anal. Calcd. for $C_{10}H_7O_4N_2$: N, 18.0. Found: N, 17.9.

1-(*p*-Aminophenyl)-3-carboxy-4-hydroxypyridazone-6 and 1-(*p*-aminophenyl)-4-hydroxypyridazone-6.—These amino compounds were prepared by shaking a solution (or suspension) of 0.03 mole of the sodium salt of the corresponding nitro compounds in 125 ml. of water with 1 g. of Raney nickel at 500 lb. pressure of hydrogen. The reductions proceeded rapidly at 50°. A 65% yield of 1-(*p*-aminophenyl)-3-carboxy-4-hydroxypyridazone-6, that melted at 297–299° with the evolution of carbon dioxide and had a neutral equivalent of 126 (calcd. 123.5), was obtained.

Anal. Calcd. for $C_{11}H_9O_4N_2$: N, 17.0. Found: N, 16.8.

The yield of 1-(*p*-aminophenyl)-4-hydroxypyridazone-6 was 60% of the theoretical. This compound melted at 250–251° and had a neutral equivalent of 203 (calcd. 202).

Anal. Calcd. for $C_{10}H_9O_2N_2$: N, 20.8. Found: N, 20.5.

Summary

The products of reaction of ketene diethylacetal with phenyl-, *p*-ethoxyphenyl-, *p*-nitrophenyl- and *p*-carbethoxyphenyldiazonium chloride are reported. Regardless of the nature of the substituent in the aryl nucleus of the diazonium salt, the main reaction product is a 1-aryl-4-ethoxy-pyridazone-6 (II) which was obtained in 25–35% yields. The formation of this product involves the addition of the diazonium salt across two molecules of the acetal.

With the substituted phenyldiazonium salts products that indicate the addition of the salt to a single molecule of the acetal are formed. The most important of these is ethyl *p,p'*-diethoxydiphenylformazyl formate (IV) which was obtained in 27% yields from the reaction of *p*-ethoxyphenyldiazonium chloride with ketene acetal.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XIII. The Cyclic Trimerization of Ketene Diethylacetal by Hydrogen Fluoride: 1,1,3,3,5,5-Hexaethoxycyclohexane

BY S. M. McELVAIN AND J. W. LANGSTON¹

In the seventh paper² of this series the unusual behavior of ketene acetal with hydrogen fluoride was reported. This acid, instead of adding to one or two molecules of the acetal as did the other acids that were studied, caused a polymerization of the acetal. The nature of this polymeric product was not investigated but it appeared to consist of much more of the distillable liquid polymers of ketene acetal³ than were obtained when cadmium chloride was used to bring about the polymerization. This latter catalyst converted the acetal mainly to a solid polymer composed of chains containing, on an average, 22–23 ketene acetal units.⁴ However, it was possible to separate by distillation a small amount of liquid polymer from this solid polymer and then to separate further this liquid material into a dimer and a trimer fraction. Because of the fact that both γ -acetoacetic ester and 1,3,5-triethoxybenzene (I) were isolated from the trimer fraction, it appeared that it contained both the open chain trimer and the cyclic trimer, 1,1,3,3,5,5-hexaethoxycyclohexane (II).

Since hydrogen fluoride converted ketene acetal mainly into liquid polymers, it seemed advisable to study further this polymerization in the hope that the yield of the trimer fraction might be materially increased and that the hexaethoxycyclo-

hexane (II) could be isolated. The present paper is a report of the results of this investigation.

It is quite likely that one of the reasons that low molecular weight liquid polymers were obtained in the earlier work² with hydrogen fluoride was that the polymerization had occurred in an ethereal solution and that the separation of the monomer molecules by those of the solvent had favored the formation of these lower polymers. If this were true it appeared that the optimum yield of the trimer fraction would be dependent upon the nature of the reaction medium, the dilution and the ratio of the reactants. After a number of exploratory experiments it was found that diethyl ether was superior to such hydrocarbons as benzene and petroleum ether as a reaction medium and that about 5 mole per cent. of hydrogen fluoride gave the best yield of the distillable liquid polymers of ketene acetal. A 1% solution of the acetal in ether was found to be the concentration that gave the optimum yield of the trimer fraction; a 10% solution gave considerable of the solid polymer while with a 0.1% solution the amount of the trimer fraction was not substantially larger than that obtained with the 1% solution. From this latter dilution of ketene acetal in ether it was possible to obtain, with 5 mole per cent. of hydrogen fluoride, 12–14% of the weight of the acetal as a dimer fraction, which corresponded in properties to that previously reported,⁴ and 40–45% of the weight of the acetal as a trimer fraction that boiled at 105–110° (0.5 mm.).

(1) Harshaw Chemical Company Fellow, 1942–1944.

(2) McElvain and Kundiger, *THIS JOURNAL*, **64**, 254 (1942).

(3) D. G. Kundiger, Ph.D. Thesis, University of Wisconsin, 1942.

(4) Johnson, Barnes and McElvain, *THIS JOURNAL*, **63**, 964 (1940).