Acetal Preparation in Sulfuric Acid

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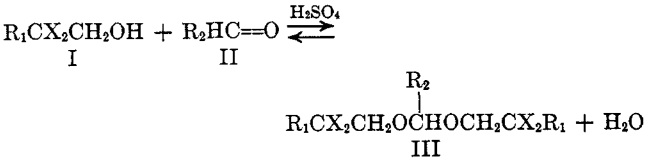
Negatively substituted alcohols such as 2,2,2-tribromoethanol, 2,2,2-trinitroethanol, and 2,2-dinitropropanol produce good yields of formals by reaction with formaldehyde in concentrated sulfuric acid. Negatively substituted diols produce the corresponding dioxanes with formaldehyde, chloral, and glyoxal.

A common method for preparing simple acetals involves acid or metal halide catalysis of the reaction of an alcohol and aldehyde with removal of the water as formed, in order to shift the equilibrium toward formation of the product. With negatively substituted alcohols, however, acetal formation is difficult to achieve by normal synthetic methods. A recent study showed that esters of halogen-substituted alcohols and phenols were not completely protonated or cleaved by sulfuric acid and that these esters could be prepared by transesterification from other, more easily cleaved, esters in concentrated sulfuric acid solvent.[2] We wish to report that bis(2,2,2-trinitroethyl) formal and bis-(2,2,2-tribromoethyl) formal are also incompletely cleaved in strong sulfuric acid and, indeed, have been prepared by the reaction of the corresponding alcohols with formaldehyde in strong sulfuric acid. This new method of acetal preparation has been extended to the synthesis of acetals of other negatively substituted alcohols, such as the 2,2,2-trihaloethanols, 2,2-dinitropropanol, and some 2-nitro diols.



$$\underset{\text{I}}{R_1CX_2CH_2OH} + \underset{\text{II}}{R_2HC{=}O} \xrightleftharpoons{H_2SO_4} \underset{\text{III}}{R_1CX_2CH_2O\overset{R_2}{\overset{|}{C}}HOCH_2CX_2R_1} + H_2O$$

R_1 = alkyl, chlorine, bromine, or nitro; X = chlorine, bromine, or nitro; R_2 = H, $-CCl_3$, or –CHO

Results

In general, the reaction consists of adding paraformaldehyde to a solution of a negatively substituted alcohol in concentrated sulfuric acid, at room temperature or below. The product begins to separate almost immediately, and only a small part of the total product remains dissolved in the reaction solution. After a reaction period of 1 hr or less, the acetal is isolated either directly from the reaction mixture by filtration, or by pouring the mixture onto ice. The results of various preparations are summarized in Table I.

The structure of the alcohol, I, and of the aldehyde reactants, II, markedly influence the degree of conversion to acetal product. Aliphatic alcohols, such as propanol, 2,2-dimethyl-1-propanol, and 1,3-propanediol, which do not have negative substituents, do not react. In contrast, good yields of formals are obtained from the β-trihaloethanols, β-nitroethanols and -propanols, and 2-halo- or 2-nitropropanediols. The aldehyde reactant must either be formaldehyde or a negatively substituted aldehyde; for example, an acetal does not form from acetaldehyde or dimethyl acetal. Aldehydes with negative substituents, as exemplified by chloral and glyoxal, form acetals with 2-methyl-2-nitropropanol and 2-methyl-2-nitropropane-1,3-diol.

The degree of conversion to acetal was very sensitive to the conditions under which the reaction was run. Sulfuric acid concentration, concentration of reacting species in the acid, and temperature all influenced the yields of products, with the optimum set of conditions dependent upon the structure of alcohol and aldehyde reactants. The reaction exhibited the normal characteristics of an equilibrium process; an excess of either the alcohol or aldehyde shifted the equilibrium to the right and increased the yield of product, III, over that obtained from stoichiometric equivalents. The alcohol, I, could be recovered from a solution of the acetal, III, which at equilibrium was largely hydrolyzed. For example, in a saturated solution of bis(tribromoethyl) formal in 90% sulfuric acid, only 2.7% remained uncleaved; the same amount was found when the saturation was obtained by the reaction of tribromoethanol and paraformaldehyde.

In the preparation of bis(2,2,2-tribromoethyl) formal, and in most of the other formal preparations, best results were obtained in 90% sulfuric acid; yields were somewhat diminished in 85, 80, and 70% acid at comparable alcohol concentrations. However, acetals of 2,2-dinitropropane-1,3-diol and 2-methyl-2-nitropropane-1,3-diol were exceptions. These alcohols formed the desired crystalline cyclic acetal in 96.4% sulfuric acid, but formed an oil in 90% acid. Reactions with trinitroethanol worked best in 96.4% sulfuric acid, and good yields were obtained even in 5% fuming sulfuric acid. For preparative purposes, optimum acid strength for good yield was achieved by careful addition of water to a homogeneous solution of the alcohol and aldehyde in a strong acid concentration until complete precipitation of the product had occurred. In a bis(tribromoethyl) formal preparation this procedure increased yield by 75% for only a 6% change in acid strength. Insolubility of the product in the acid medium was not always necessary for a good yield. 5-Methyl-5-nitro-1,3-dioxane, which formed in 70% yield in 90% sulfuric acid, remained in solution in equilibrium with its precursors. For the most part, however, it appears that precipitation of the product, III, from the reaction mixture was an important factor in obtaining good yields.

In systems of a given acid strength, optimum yields were obtained at alcohol concentrations near the saturation point. The solubility of the alcohols varied widely in 90% sulfuric acid at room temperature. In some cases it was necessary to warm the alcohol-acid mixture in order to obtain solution and to achieve the optimum concentration.

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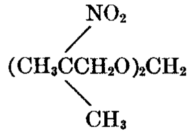
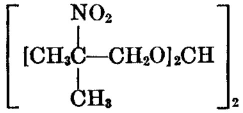
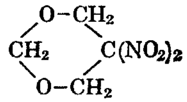
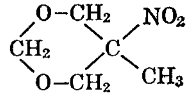
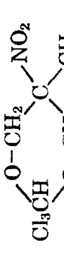
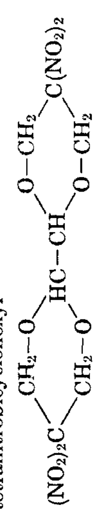
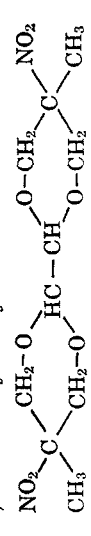
[2] M. E. Hill, *J. Am. Chem. Soc.*, **82**, 2866 (1960).

TABLE I
ACETAL PREPARATION IN SULFURIC ACID[a]

Product	Mp or bp (mm), °C	Initial H_2SO_4 concn, %	Moles of alcohol/ l. of acid[b]	% yield	Method of purification	Formula	Calcd, %			Found, %[c]		
							C	H	N	C	H	N
Bis(2,2,2-tribromoethyl) formal	71–72	96.4	4.0	10	Recrystn from pentane	$C_5H_6Br_6O_2$	10.31	1.04		10.50	1.11	
$(CBr_3CH_2O)_2CH_2$		89.6	4.0	87								
		89.6	2.0	74								
		89.6	0.5	13								
		85.2	2.0	80								
		80.0	0.5[d]	63								
		70.0	0.5[d]	5								
Bis(2,2,2-trichloroethyl) formal[e] $(CCl_3CH_2O)_2CH_2$	12.5 87 (1)	90	12	70	Distillation under reduced pressure	$C_5H_6Cl_6O_2$	19.30	1.90		19.56	1.98	
Bis(2,2,2-trifluoroethyl) formal[e] $(CF_3CH_2O)_2CH_2$	−28 31 (25)	96.4	12	68	Distillation under reduced pressure	$C_5H_6F_6O_2$	28.30	2.38		28.21	3.10	
Bis(2,2,3,3-tetrafluoropropyl) formal[e] $(HCF_2CF_2CH_2O)_2CH_2$	57–58 (5.5)	90	12	63.4	Distillation under reduced pressure	$C_7H_8F_8O_2$	30.42	2.92		30.75	3.02	
Bis(2-methyl-2-nitropropyl) formal[e] 	65–66	90	4	0	Recrystn from 70% CH_3OH-H_2O	$C_9H_{18}N_2O_6$	43.19	7.24	11.18	43.23	7.12	11.27
		90	8	10								
		90	12	45								
		90	12[f]	60								
		90	12[g]	78								
		96	12	0.4								
Bis(2,2-dinitropropyl) formal $[CH_3C(NO_2)_2CH_2O]_2CH_2$	33–33.5	96.4	12	70	Recrystn from 75% CH_3OH-H_2O	$C_7H_{12}N_4O_{10}$	26.93	3.87	17.94	26.95	3.68	17.73
		96.4	8	33								
		96.4	4	0								
Bis(2,2,2-trinitroethyl) formal $[(NO_2)_3CCH_2O]_2CH_2$	64–65	96	4	90	Recrystn from 50% $MeOH-H_2O$	$C_5H_6N_6O_{14}$	16.05	1.62	22.46	16.03	1.50	22.47
Tetra(2-methyl-2-nitropropyl) glyoxal acetal 	189–191	90	8	35	Recrystn from 70% γ-butyrolactone–H_2O	$C_{18}H_{34}N_4O_{12}$	43.40	6.88	11.23	43.59	6.90	10.23
5,5-Dinitro-1,3-dioxane 	53[h]	96	4	69	Recrystn from γ-butyrolactone–H_2O	$C_4H_6N_2O_6$	26.95	3.37	15.70	26.73	3.32	15.37
5-Methyl-5-nitro-1,3-dioxane[e,i] 	71[j]	90	4	70	Recrystn from 50% CH_3OH-H_2O	$C_5H_9NO_4$	40.81	6.16	9.52	41.14	6.24	
		96	4	68								
		96	8	75								

2-Trichloromethyl-5-methyl-5-nitro-1,3-dioxane[e] 	195–196	90 96	1 2	35 71	Recrystn from 70% CH_3OH-H_2O	$C_6H_8Cl_3NO_4$	27.24	3.03	5.32	27.45	3.16	5.35
2,6,2′,6′-Tetraoxa-4,4,4′,4′-tetranitrobicyclohexyl[k] 	259–260 dec	96	1	59	Recrystn from 80% γ-butyrolactone–H_2O	$C_8H_{10}N_4O_{12}$	27.15	2.85	15.82	27.65	2.82	15.35
2,6,2′,6′-Tetraoxa-4,4′-dimethyl-4,4′-dinitrobicyclohexyl 	>300	90	4	34	Recrystn from 80% γ-butyrolactone–H_2O	$C_{10}H_{16}N_2O_8$	41.10	5.52		41.36	5.49	

[a] Reaction at room temperature of stoichiometric amounts of alcohol and aldehyde unless otherwise noted. [b] The percentages given for acid concentrations are for initial acid strength since water which forms in the reaction decreases the acidity; *e.g.*, in the reaction of 0.06 mole of 2,2,2-tribromoethanol in 5 ml of 96% sulfuric acid, 0.5 g of water is formed by complete reaction of the alcohol with formaldehyde, reducing the acid strength to 90% in the final reaction mixture. [c] Analyses are averages of two or more determinations. [d] Saturated solution of alcohol. [e] Initial reaction temperature of 0° with reverse addition of reactants. [f] Alcohol to aldehyde ratio = 1:1. [g] Alcohol to aldehyde ratio = 4:1 and yield is based on aldehyde. [h] M. H. Gold, E. E. Hamel, and K. Klager, *J. Org. Chem.*, **22**, 1665 (1957). [i] M. Senkus, *J. Am. Chem. Soc.*, **63**, 2635 (1940). [j] Product did not precipitate from acid medium. [k] Glyoxal bisulfite was used.

The 2,2,2-tribromo- and -trinitroethanols and 2,2-dinitropropyl alcohols reacted well at room temperature, but considerable discoloration occurred in the reaction mixtures containing the chlorine- and fluorine-substituted alcohols. 2-Methyl-2-nitropropanol, when dissolved in sulfuric acid at room temperature, rapidly darkened and fumed off. For the alcohols sensitive to sulfuric acid at room temperature, reverse addition of the reactants, *i.e.*, adding the alcohol to a sulfuric acid solution of paraformaldehyde at ice–water bath temperature, proved successful in avoiding undesirable side reactions. In the preparation of the cyclic acetals, the same variation in optimum temperature for the reaction was observed.

The sulfuric acid method of preparation of formals is also adaptable to a two-phase system. In this case a solution of the alcohol in a solvent such as methylene chloride is stirred vigorously with a sulfuric acid solution of paraformaldehyde. After a brief reaction period the product is isolated from the solvent phase.

Discussion

For negatively substituted alcohols converted to acetals in strong sulfuric acid, experimental data do not contraindicate a mechanism similar to the generally accepted mechanism for acetal formation and, conversely, hydrolysis. The reactants, intermediates, and product are, of course, in equilibrium with the acid medium, which acts as a dehydrating agent as well as solvent. Thus, a possible mode of reaction includes the initial formation of a hemiacetal, IV, which then ionizes to the transitory intermediate, V, and reacts with a second mole of alcohol to form the product, VII.

$$(HCHO)H^+ + ROH \rightleftharpoons \underset{\text{IV}}{ROCH_2OH_2^+} \qquad (1)$$

$$ROCH_2OH_2^+ \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \underset{\text{V}}{(ROCH_2)^+} + H_2O \qquad (2)$$

$$ROH + (ROCH_2)^+ \rightleftharpoons \underset{\text{VI}}{ROCH_2\overset{H}{O}R^+} \qquad (3)$$

$$\underset{\text{VI}}{ROCH_2\underset{H}{O}R^+} \rightleftharpoons \underset{\text{VII}}{ROCH_2OR} \text{ (un-ionized form)} \qquad (4)$$

Although the reaction is written here in the forward direction to represent the formation of the product, the reverse reaction is the familiar mechanism for the hydrolysis of simple acetals; this is supported by ample evidence and is reviewed by Taft[3] and Long and Paul.[4] The only difference between the simple acetal hydrolysis and the hydrolysis of the negatively substituted acetals and formals in sulfuric acid is the very much weaker basicity of the negatively substituted acetals and the very much stronger acidity of the hydrolyzing medium.[5]

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(3) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., p 636.

(4) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 965 (1957); see also J. M. O'Gorman and H. J. Lucas, *J. Am. Chem. Soc.*, **72**, 5489 (1950).

(5) If an attempt were made to hydrolyze bis(2,2,2-trichloroethyl) formal in 1 *M* acid, one would wait a very long time for reaction. Calculation of the rate from the relationship, log $(k/k_0) = \sigma^*\rho^*$, and values $\rho^* = 8.3$, $\sigma^* = 2.65$, and ref 3, Tables IX and XII, gives $k = 10^{-27}$; the rate relative to the hydrolysis of methylal is 10^{-18}.

The aldehyde reactants are largely in protonated form,[6] but the negatively substituted alcohols, as very weak bases, may exist partly un-ionized because of incomplete reaction with sulfuric acid. This view is

$$ROH + H_2SO_4 \rightleftharpoons ROH_2^+ + HSO_4^-$$

$$ROH_2^+ + H_2SO_4 \rightleftharpoons ROSO_3H + H_3O^+$$

supported by other work, in which cryoscopic measurements in 100% sulfuric acid gave "*i*" factors of 2.6 (instead of the expected 3.0) for an alcohol whose acidity becomes pronounced from the inductive effect of negative substituents, as in 2,2,2-trinitro-, trifluoroethanol, and 2,2-dinitropropanol.[7] Furthermore, in acid solution having up to 11% water, the equilibrium constant for the protonation reaction probably becomes very small—analogous to the small constant for protonation of the product acetals. Since the nonprotonated alcohol is the reacting species, the failure of these alcohols to protonate appreciably should help drive reaction 1 and the following reactions forward.

In strong sulfuric acid, the oxocarbonium ion, V, is due to the acid's extraction of water from the oxonium ion IV, eq 2. This step is analogous to numerous reported reactions[6] in sulfuric acid, in which dehydration is a principal step toward an eventual carbonium or oxocarbonium ion.[8] Such an ion is very strongly electrophilic and can exist only in a very weakly basic solvent such as sulfuric acid.[9] A reasonable concentration of the oxocarbonium ion, V, may be expected to exist because of such stabilization.

An important factor influencing the degree of conversion of alcohol and aldehyde to product is the strong acidity of the product conjugate acid, VI. The protonated product must be stable in the sulfuric acid in order that eq 3 may proceed to the right, and also must be acidic enough to give up its proton to base (bisulfate ion, eq 4) in the system, and produce the un-ionized form, VII, in equilibrium. Since 5-methyl-5-nitro-1,3-dioxane was obtained in high yield without precipitation, apparently it is only sufficient and necessary that VI be formed; this ion probably is in equilibrium with the un-ionized form. However, if the product, VII, is insoluble in the medium, its separation continues to upset the equilibrium as the alcohol and aldehyde decrease in concentration until they are no longer able to produce any product in excess of the saturation point. In very strong acid, the product solubility is much greater, as shown by the homogeneity of a 96.4% sulfuric acid solution of bis(tribromoethyl) formal, from which a 13% recovery was obtained, compared with 2.7% recovered from 90% sulfuric acid.

Experimental Section

Typical experiments are described below. The results of other preparations with condition variations are summarized in Table I. (*CAUTION:* The nitro alcohols and their derivatives are explosives; suitable care must be taken with their reactions.)

Bis(2,2,2-tribromoethyl) Formal.—Paraformaldehyde, 0.30 g (0.01 mole as HCHO), was added at room temperature to a solution of 5.66 g (0.02 mole) of 2,2,2-tribromoethanol in 5 ml of 89.6% sulfuric acid. Within 3 min the product began to separate as an oil which then crystallized to a thick mass of white crystals. After 30 min the viscous reaction mixture was poured into ice and water. The heavy white crude product was removed by filtration, washed with water, dried, and recrystallized from pentane. Bis(2,2,2-tribromoethyl) formal was obtained in 87% yield, mp 71–72° (Table I), mol wt 575[10] (calcd for $C_5H_6Br_6O_2$, 577.6).

Bis(2,2,2-trichloroethyl) Formal. Reverse Addition, Low-Temperature Reaction.—A solution of 2.0 g of paraformaldehyde (0.06 mole as HCHO) in 10 ml of 90% sulfuric acid was cooled to 0°, and 18.0 g (0.12 mole) of 2,2,2-trichloroethanol was added rapidly with stirring. The reaction mixture was stirred for 10 min and then at room temperature for 1 hr. A colorless oil separated on top of the orange-brown reaction mixture within a few minutes after addition of the alcohol. The colorless oil was separated and added to ice and water. This mixture was extracted with ethyl ether and dried over anhydrous magnesium sulfate, and the ether was removed by evaporation under reduced pressure. The crude product was distilled under reduced pressure; bis(2,2,2-trichloroethyl) formal, bp 87° (1 mm) (mp 12.5°), was collected in 70% yield (Table I).

Bis(2,2-dinitropropyl) Formal. Two-Phase System.—A solution of 6.0 g (0.04 mole) of 2,2-dinitropropanol in 10 ml of methylene chloride was prepared in a 50-ml round-bottom flask fitted with a mechanical stirrer. A solution of 0.60 g (0.02 mole as HCHO) of paraformaldehyde in 5 ml of 96% sulfuric acid was added, and the mixture was stirred vigorously at ambient temperature for 15 min. The methylene chloride layer was separated. The sulfuric acid solution was extracted with 2-ml portions of methylene chloride, and the extracts were added to the original methylene chloride layer. Methylene chloride was removed by evaporation under reduced pressure, leaving a residual oil which solidified on seeding with bis(2,2-dinitropropyl) formal. This product crystallized from 200 ml of a mixture of methanol and water (3:1) in glistening white leaflets. The yield was 4.35 g (70% based on unrecovered alcohol), mp 32.5–33° (Table I).

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[6] R. J. Gillespie and J. A. Leisten, *Quart. Rev.* (London), **8**, 40 (1954).

[7] M. E. Hill and A. Bradley, unpublished information.

[8] For example, the formation of NO_2^+ from the nitric acid, Ph_3C^+ from triphenylcarbonyl, and $Me_3C_6H_2CO^+$ from mesitoic acid.

[9] R. J. Gillespie and E. A. Robinson, *Advan. Inorg. Chem. Radiochem.*, **1**, 398 (1959).

[10] Determined by Dr. J. R. Holden, U. S. Naval Ordnance Laboratory, from measurement of unit cell volume.