acetic acid, and 3.3 g (0.051 g-atom) of zinc powder, 0.25 g (38.5% yield) of 10 was obtained.

Acknowledgment.—The authors wish to thank Mr. T. Morofushi for his technical assistance.

Registry No.—**5a**, 24454-33-9; **5b**, 36287-24-8; **5c**, 37150-25-7; **6**, 37150-26-8; **7**, 80-71-7; **8**, 37160-44-4; **9a**, 37164-08-2; **9b**, 37164-09-3; **9c**, 37164-10-6; **10**, 21834-98-0.

Mono- and Di-2,2,2-trichloroethyl Acetals as Protecting Groups

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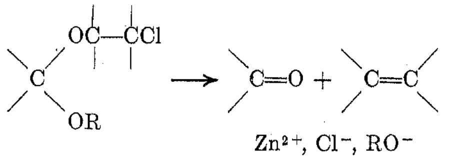
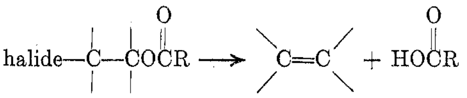
Mono- and di-2,2,2-trichloroethyl acetals have been selectively prepared in good yields by acid-catalyzed alcohol exchange with 2,2,2-trichloroethanol and dimethyl or diethyl acetals. A nonacidic and aprotic reductive cleavage using activated zinc dust in ethyl acetate or THF regenerates the carbonyl.

In connection with other synthetic work in these laboratories it was desirable to have available a protecting group for aldehydes that could be removed in a mild, selective, and nonacidic manner. The title compounds were therefore developed on the basis that the known reductive elimination of β-alkoxy halides[1] could, in the case of acetals, regenerate the carbonyl (eq 1). Reduction has previously been used



(1)

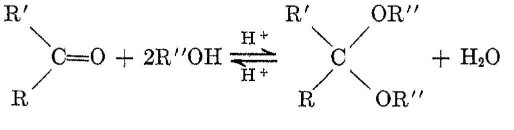
effectively in the removal of the 2-haloethyl carbonate (carbamate) protecting group from alcohols (amines), and the removal of the 2-haloethyl group from esters (eq 2).[2]



(2)

We would like to report the success of this overall design whereby a convenient, general synthesis of both the mono- and bis-2,2,2-trichloroethyl acetals has been developed and the optimum conditions for removal of the protecting group have been determined for a variety of systems.

Traditionally, an acetal is most expeditiously prepared from the aldehyde or ketone by treatment with the corresponding alcohols and a strong acid under conditions which would favor the equilibrium shown below (eq 3). Such methods as the use of excess al-

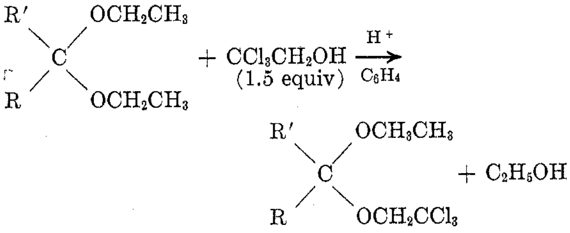


(3)

cohol, the use of a water scavenger such as triethyl orthoformate, or the azeotropic removal of water have all been employed.[3] These published techniques were found to be unsatisfactory with trichloroethanol, however, presumably due to the inductive (−*I*) effect of the trichloromethyl group which makes trichloroethanol less nucleophilic and less able to stabilize any intermediate carbonium ion. The use of tris-2,2,2-trichloroethyl orthoformate as a water scavenger was considered impractical due to its difficulty in preparation and its great stability to acid.[4]

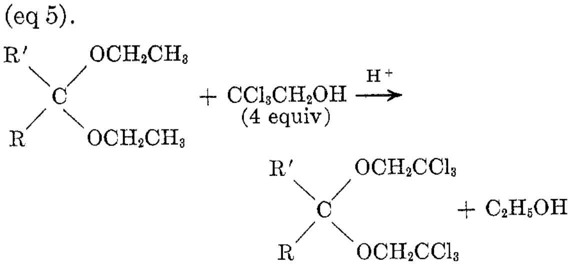
The method of choice for the preparation of trichloroethyl acetals proved to be a *p*-toluenesulfonic acid catalyzed alcohol exchange of a diethyl (or dimethyl) acetal with trichloroethanol in benzene or xylene. In this conversion, commerically available dimethyl or diethyl acetals were used whenever possible. However, in the majority of cases the free aldehyde or ketone was converted into the diethyl acetal with triethyl orthoformate and used without isolation in the subsequent alcohol exchange with trichloroethanol.

In the synthesis of the trichloroethyl acetals shown in Table I, advantage was taken both of the high boiling point of trichloroethanol, which allowed continuous removal of ethanol as an azeotrope, and of the acid stability of trichloroethyl ethers, which permitted the introduction of either one or two trichloroethoxy groups. For example, the use of 1.5 equiv of trichloroethanol in benzene gave the mixed acetal almost exclusively (eq 4), while the use of 4 equiv of trichloroethanol in



(4)

xylene gave good yields of the bistrichloroethyl acetals (eq 5).



(5)

A systematic search for the best experimental conditions for elimination soon focused on the use of ac-

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[1] See, for example, O. Grummitt, *et al.*, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 748, and references cited therein.

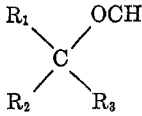
[2] E. Kasafirek, *Tetrahedron Lett.*, **20**, 2021 (1972); M. F. Semmelhack and G. E. Heinsohn, *J. Amer. Chem. Soc.*, **94**, 5139 (1972), and references therein.

[3] C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley, New York, N. Y., 1970, Chapter 9.

[4] A. Kankaanpira and M. Lahti, *Suom. Kemistilehti B*, **42**, 406 (1969).

TABLE I

TRICHLOROETHYL ACETALS

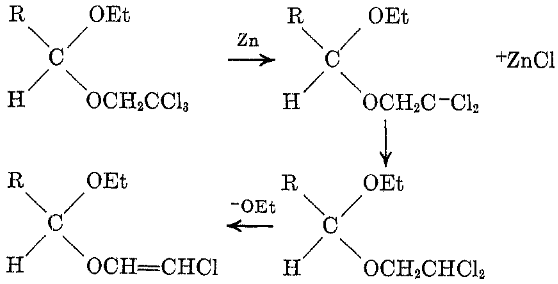


								Zinc elimination			Acid hydrolysis[k]	
No.	R_1	R_2	R_3	Registry no.	Yield,[b] %	Method	Mp or bp (mm), °C	Nmr shift (τ),[g] $-OCH_2CCl_3$	Solvent	Reflux time, hr	Yield,[i] %	Solvent[l]	Time,[m] min
1	$PhCH_2-$	H	OCH_3	37150-37-1	60	A[c]	114 (0.6)	5.95 (AB)[h]	EA	7	40	THF	180
2	$CH_3(CH_2)_6-$	H	OC_2H_5	37150-38-2	81	A	88 (0.5)	5.88 (S)	EA	12	90	THF	5
3	$CH_3(CH_2)_6-$	H	OCH_3CCl_3	37150-39-3	72	A	120 (0.5)	5.78 (S)	EA	11	70	THF	n
4	$-(CH_2)_4-$		OC_2H_5	37150-40-6	72	B	77 (13)	6.03 (S)	THF	18	100	Dioxane	5
5	$-(CH_2)_4-$		OCH_2CCl_3	37150-41-7	52	A	70–72°[d]	7.52 (S)	THF	11	85	Dioxane	60
6	Ph-	H	OC_2H_5	37150-42-8	65	B	79 (0.4)	6.04 (AB)	THF	11	100	THF	5
7	Ph-	H	OCH_2CCl_3	37150-43-9	43	B	145 (0.2)	5.80 (S)	THF	11	100	THF	60
8	$[CH_3]_2C{=}CHCH_2CH_2$	CH_3	OC_2H_5	37150-44-0	50	B	100 (0.1)	6.00 (S)	THF	12	96	Dioxane	5
9		H	OC_2H_5	37150-45-1	78	B	95–100 (0.4)	5.95 (AB)	EA	4	83	THF	5
10	$PhC{\equiv}C-$	H	OCH_3	37150-46-2	50	B	141–145 (1.5)	5.71 (AB)	THF	5	40	Dioxane	120
11	Ph-	Ph	OCH_3	37150-47-3	84	A[c]	128–129[e]	6.10 (S)	EA	3	86	THF	10
12	n-C_3H_7-	n-C_3H_7	OCH_2CCl_3[a]	37406-78-3	76	B	99–100[f]	5.85 (S)	EA	3	100	Dioxane	70
13	$PhCH{=}CH-$	H	OC_2H_5	37150-48-4	50	B	138 (0.2)	5.88 (S)	EA	3	62	THF	5
14	$PhCH{=}CH-$	H	OCH_2CCl_3	37150-49-5	49	B	170 (0.1)	5.72 (S)	EA	4	73	THF	90
15	$CH_3C(OCH_3)HCH_2$	H	OCH_3	37150-50-8	53	A[c]	113 (10)	5.90 (S)	EA	12	j	Dioxane	25

[a] Monotrichloroethyl acetal could not be purified. [b] Yield after distillation. [c] Commercially available. [d] Recrystallized from hexane. [e] Recrystallized from acetone–water. [f] Recrystallized from acetone–water and sublimed [95° (0.2 mm)]. [g] Nmr taken in $CDCl_3$ or CCl_4. [h] In all cases where an AB pattern was displayed, $J/\Delta\nu$ 2–4. [i] Yield based on product judged better than 90% pure by nmr. [j] Aldehyde formation but with unidentified by-product. [k] Water–THF–p-toluenesulfonic acid. [l] Dioxane was used whenever necessary for nmr clarity. [m] Time required for better than 95% hydrolysis by nmr. [n] No reaction after 30 hr.

tivated zinc dust in ethyl acetate or tetrahydrofuran (THF). It can be seen from Table I that refluxing zinc in ethyl acetate works well for both the formation of aldehydes and ketones, while THF is best suited for those eliminations producing ketones. No decomposition was observed when solutions of the acetals in THF or ethyl acetate were refluxed in the absence of zinc. A comparison of activated zinc with a zinc-copper couple indicated that activated zinc was superior.

While the use of activated zinc in ethyl acetate or THF produced only aldehydes or ketones, several additional products were observed when other solvents were used. For example, acetic acid rapidly consumed the activated zinc with no recognizable carbonyl products produced. Moreover, the acetals **1**, **2**, and **10** when treated with zinc in ethanol gave only small amounts of reduction products **16** and **17** (eq 6).



17 **16** (6)

The use of acetone as solvent gave improvements in yields of aldehydes from **1**, **2**, and **10**, but generated significant amounts of diacetone alcohol.

The stability of 2-chloroethyl ethers to acid has been previously observed.[4,5] Comparisons were therefore made between the rates of hydrolysis for trichloroethyl acetals and those for the corresponding diethyl or dimethyl acetals. When p-toluenesulfonic acid in THF–water was used all of the monotrichloroethyl acetals hydrolyzed noticeably although not appreciably slower than the coresponding diethyl or dimethyl systems. However, significant rate differences were observed for the bistrichloroethyl acetals such that the acid stability might be used as an additional option in synthetic design.

The procedure as outlined above offers a new method for the protection of aldehydes and ketones or, alternatively, for the hydrolysis of an ordinary acetal under nonaqueous conditions by alcohol exchange with trichloroethanol and subsequent zinc reduction.

Experimental Section

All boiling points and melting points are uncorrected. All of the trichloroethyl acetals are new compounds and gave satisfactory (±0.4%) analyses for carbon and hydrogen.

Materials.—The following items were obtained from Aldrich Chemical Co., Milwaukee, Wis., trichloroethanol (98%, distilled prior to use), triethyl orthoformate, p-toluenesulfonic acid monohydrate, phenylacetaldehyde dimethyl acetal, benzophenone dimethyl acetal, and 3-methoxybutyraldehyde dimethyl acetal. Aldehydes and ketones were obtained from a variety of sources and distilled prior to use. The zinc used was Mallinckrodt reagent grade. Both ethyl acetate and THF were the best commercial grades and were used as received.

Preparation of Diethyl Acetals.—The diethyl acetal was prepared by refluxing the aldehyde or ketone (0.1 mol) with triethyl orthoformate (16.3 g, 0.11 mol), absolute ethanol (13.8 g, 0.3 mol), and a trace of anhydrous ferric chloride in benzene (150 ml). An overnight reflux (drying tube) was sufficient for all those acetals prepared in this manner. The solution was then neutralized with sodium ethoxide, filtered, concentrated, and distilled. The freshly distilled diethyl acetal was then subjected to method A.

Preparation of Monotrichloroethyl Acetals. Method A.—A solution consisting of the diethyl or dimethyl acetal (0.1 mol) in benzene (150 ml) was heated on a steam bath in an apparatus set up for simultaneous liquid addition and distillation. Trichloroethanol (17.9–22.4 g, 0.12–0.15 mol) dissolved in benzene (30 ml) was added to the dropping funnel. Benzene was allowed to distil until a steady boiling point of about 81° was obtained. Approximately 3 ml of the trichloroethanol–benzene solution was then added, followed by the addition of p-toluenesulfonic acid

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(5) T. Hara and J. Azizian, *Tetrahedron Lett.*, 4443 (1969).

monohydrate (25 mg). A drop of several degrees in the distillate temperature indicates removal of ethanol or methanol. Best results were obtained with a rapid distillation and a rate of addition of 1 drop/sec. Distillation was continued (additional benzene may be required) until the distillate temperature returned to 81°. Anhydrous sodium carbonate was then added, and the solution was filtered, concentrated, and distilled under vacuum through a 30-cm column packed with glass helices and heated with an electrical heating tape.

Method B.—The diethyl acetal was prepared as indicated above but was not neutralized with sodium ethoxide. Instead, the benzene was distilled off to remove ethyl formate and ethanol from the reaction mixture (more benzene may be required to bring the distillate temperature to 81°) and the crude residue was then subjected to method A.

Preparation of Bistrichloroethyl Acetals.—Either method A or B may be employed with the following modifications: (1) use 0.1 mol of the acetal and 0.4 mol (59.6 g) of trichloroethanol, (2) add the acetal in xylene to trichloroethanol in xylene, (3) distil until the boiling point of xylene is reached, then distil for one additional hour.

Zinc Elimination.—The trichloroethyl acetal (1.0 g) was refluxed in ethyl acetate or THF with zinc (2.0 g), previously activated by washing with 5% HCl, H_2O, ethanol, ether, and drying *in vacuo* over P_2O_5. The solution was then filtered, enriched with ether, washed with 1% HCl, 5% sodium bicarbonate, brine, dried (sodium sulfate), and evaporated to give the free aldehyde or ketone.

Acid Hydrolysis.—A solution consisting of the acetal (0.05 mol) THF or dioxane (9 ml) water (0.5 ml) and *p*-toluenesulfonic acid monohydrate (50 mg) was refluxed until the nmr of the reaction mixture indicated greater than 95% hydrolysis to the aldehyde or ketone.

Acknowledgment.—We gratefully acknowledge support of this work by the National Institutes of Health, Grant No. A1-10,597-01.

Glyoxal Derivatives. V. Reaction of Alcohols with Glyoxal[1]

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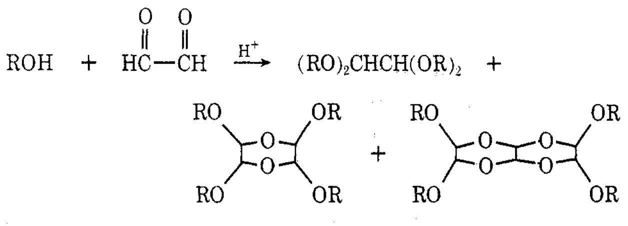
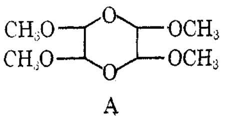
Aqueous glyoxal reacts with alcohols to give glycolates and acetal products consisting of 1,1',2,2'-tetraalkoxyethanes, 1,3-dioxolanes, and 1,3-bisdioxolanes. It is shown that the dioxolanes are, in fact, the structures which have heretofore been misassigned as dioxane and naphthodioxanes. The relative abundance of any of the acetal products depends on the initial glyoxal concentration as well as the initial ratio of alcohol to glyoxal in the reaction mixture. It is also shown that dioxolane formation can be rationalized not only by the reaction of alcohol with dimeric and trimeric glyoxal, but also *via* the direct reaction of glyoxal with any of the already formed acetals.

The observation that glyoxal reacts readily with alcohols under acid conditions to give 1,1',2,2'-tetraalkoxyethanes is well documented.[2-4] It has also been reported that higher molecular weight products are also afforded,[4,5] *i.e.*, the corresponding tetraalkoxydioxane and naphthodioxane derivatives.

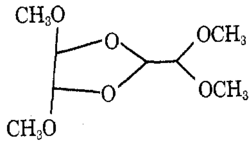


R = *i*-Pr,[5a] *n*-Bu,[5b,c] Et[5d]

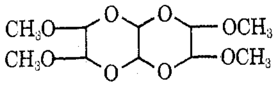
More recently, we demonstrated[1] that one of the products derived from methyl alcohol and glyoxal was not the expected *p*-dioxane derivative A, but was rather the 1,3-dioxolane derivative B, and that the product derived from glyoxal trimer was not the naphthodioxane product, C, but was, in reality, the bis-1,3-dioxolane, D.



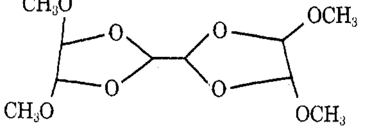
A



B



C



D

In this paper we shall present our findings on the general reaction of glyoxal with alcohols, as well as a partial insight into the equilibrium reactions of glyoxal with itself.

Results

We have found that, in general, the products of the reaction of glyoxal with alcohols include not only the bisacetals, but also glycolates, dioxolanes and bisdioxolanes (eq 1). The 1,3-dioxolane products were not isolated in addition to the previously presumed *p*-dioxane products, but, in fact, were the same compounds whose structures have been incorrectly assigned.[5]

Furthermore, the relative abundance of any of the acetal products (M, D, or T) depends on the initial

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(1) For previous paper, see J. M. Kliegman, E. B. Whipple, M. Ruta, and R. K. Barnes, *J. Org. Chem.*, **37**, 1276 (1972).

(2) C. B. Purves, U. S. Patent 2,194,405 (March 19, 1940).

(3) L. G. MacDowell and R. W. McNamee, British Patent 559,362 (Feb 16, 1944).

(4) Union Carbide Product Booklet, "General Chemistry of Glyoxal," F-41296, 1965.

(5) (a) O. C. Dermer and J. P. Yuk, *J. Amer. Chem. Soc.*, **77**, 1285 (1955); (b) B. DuVal, R. H. Hall, and B. K. Howe, *J. Appl. Chem.*, **2**, 546 (1952); (c) H. Fiesselmann and F. Horndler, *Chem. Ber.*, **87**, 906 (1954); (d) F. Chartrette, M. Chartrette, J. C. Duplan, and J. Delman, *Tetrahedron*, **27**, 5597 (1971).