

TABLE I

Compound	M. p., °C.	Yield, %	Formula	Calcd.	Nitrogen, % Found
2-Fluoro-4-methylpyridine	^a	36	C ₆ H ₈ NF	12.6	12.8
2-Fluoro-6-methylpyridine	^b	34	C ₆ H ₈ NF	12.6	12.8
2-Fluoro-4-pyridinecarboxylic acid	195-197 ^c	34	C ₆ H ₄ O ₂ NF	9.93	9.69, 9.88
2-Fluoro-6-pyridinecarboxylic acid	135-137	50	C ₆ H ₄ O ₂ NF	9.93	9.77, 9.86
Methyl 2-fluoro-4-pyridinecarboxylate	^d	84	C ₇ H ₈ O ₂ NF	9.03	8.93
Methyl 2-fluoro-6-pyridinecarboxylate	53-54.5	76	C ₇ H ₈ O ₂ NF	9.03	9.05
2-Fluoro-4-pyridinecarboxamide	173-174	100	C ₆ H ₅ ON ₂ F	20.00	20.14
2-Fluoro-6-pyridinecarboxamide	134-135	100	C ₆ H ₅ ON ₂ F	20.00	19.83, 19.81

^a Liquid, b. p. 157°; *n*_D²⁵ 1.4690; *d*₄²⁵ 1.0805. ^b Liquid, b. p. 142°; *n*_D²⁵ 1.4673; *d*₄²⁵ 1.0762. ^c Taken in the usual manner, the material contracted sharply at 188°, but no definite transition to the liquid state was observed upon further heating. If the bath were pre-heated to 195-197° the material when inserted melted quickly to a liquid, but re-solidified at once. ^d Liquid, b. p. 91° at 13 mm.; *n*_D²⁵ 1.4843.

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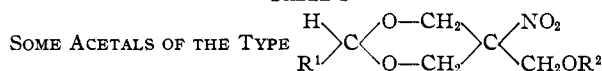
Some Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane and their Derivatives

BY ALLEN SCATTERGOOD AND ALAN L. MACLEAN¹

The cyclic acetals derived from tris-(hydroxymethyl)-nitromethane and five different aldehydes have been reported by Senkus² who prepared them by the azeotropic removal of water from equimolar quantities of the nitro triol and the aldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid. These cyclic acetals are the 5-nitro-5-(hydroxymethyl)-2-alkyl-1,3-dioxanes and should theoretically be capable of existing in both *cis* and *trans* forms. Although *cis-trans* isomers of cyclic acetals of tris-(hydroxymethyl)-nitromethane have never been obtained,

employed in the acid catalyzed formation of cyclic acetals of carbohydrates or their derivatives in aqueous solution. Accordingly this triol was allowed to react with several aldehydes in an aqueous medium that was two molar in both reactants and also in hydrochloric acid. Three of the aldehydes formed crystalline acetals under these conditions. Two of these crystalline acetals were derived from aldehydes previously employed by Senkus. However, these acetals melted at higher temperatures than the acetals obtained by Senkus. It is probable that the compounds isolated by Senkus are *cis-trans* isomers of the ones prepared by us. We have demonstrated the presence of a free hydroxyl group in all of our acetals by the formation of their crystalline benzoates. We have also secured one *p*-toluenesulfonate and a cyanoethylation product. The properties of the new compounds are given in Table I.

TABLE I



R ¹	R ²	Yield, %	Solvent	M. p. (cor.), °C.	Empirical formula	Calculated, C	Calculated, H	Calculated, N	Analysed, C	Analysed, H	Analysed, N
C ₆ H ₅	H	74	Ethanol-water	124.8	C ₁₁ H ₁₃ O ₅ N	55.2	5.44	5.85	55.19	5.48	6.04
C ₆ H ₅	C ₆ H ₅ CO	90	Isobutyl alcohol	116.2	C ₁₈ H ₁₇ O ₆ N	63.1	4.96	4.08	63.11	4.96	4.25
C ₆ H ₅	SO ₂ C ₆ H ₄ CH ₃	90	Isobutyl alcohol	143.3	C ₁₈ H ₁₅ O ₇ NS	54.9	4.83	3.56	54.61	4.96	3.68 ^d
<i>n</i> -C ₃ H ₇	H	81	<i>n</i> -Hexane	100.2 ^a	C ₈ H ₁₅ O ₅ N	46.8	7.31	6.82	46.93	7.47	6.83
<i>n</i> -C ₈ H ₇	C ₆ H ₅ CO	..	Isobutyl alcohol	107.0	C ₁₅ H ₁₉ O ₆ N	58.2	6.15	4.53	57.94	6.14	4.59
(C ₂ H ₅) ₂ CH	H	65	<i>n</i> -Hexane	81.2 ^b	C ₁₀ H ₁₅ O ₅ N	51.5	8.15	6.01	51.5	8.21	6.28
(C ₂ H ₅) ₂ CH	C ₆ H ₅ CO	..	<i>n</i> -Hexane	63.1	C ₁₇ H ₂₃ O ₆ N	60.5	6.82	4.15	60.40	6.88	4.26
C ₆ H ₅	CH ₂ CH ₂ CN	..	<i>n</i> -Hexane	77.7	C ₁₄ H ₁₆ O ₅ N ₂	57.5	5.48	9.6	58.5	5.47	9.60

^a Senkus² reported a melting point of 69.8° for the acetal prepared by his method. ^b Senkus² reported a melting point of 70.3° for the acetal prepared by his method. ^c The microanalyses were performed by Mr. S. M. Nagy and Mrs. Louise W. Spencer. ^d Calcd. for C₁₈H₁₅O₇NS: S, 8.14. Found: S, 8.19.

Senkus³ has prepared two sets of *cis-trans* isomers of cyclic acetals of a nitro glycol.

It seemed possible that tris-(hydroxymethyl)-nitromethane might serve as a model polyol useful in exploring conditions that could be

(1) The material in this note is taken in part from a thesis submitted to the Massachusetts Institute of Technology by Alan L. MacLean in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemical Engineering.

(2) Senkus, THIS JOURNAL, **63**, 2635 (1941).

(3) Senkus, *ibid.*, **65**, 1658 (1943).

Experimental

Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane.—One-tenth mole (15.1 g.) of tris-(hydroxymethyl)-nitromethane (supplied by the Commercial Solvents Corporation, Terre Haute, Indiana), 10 cc. of water, 8 cc. (0.1 mole) of concentrated hydrochloric acid and 10 cc. of methyl cellosolve (to act as a mutual solvent, omitted in the case of *n*-butyraldehyde) and 0.1 mole of the aldehyde were mixed, and the volume of the mixture (which may be two phase) was made up to 50 ml. with water. Thus the mixture was two molar in each of the reactants and also in hydrochloric acid. Homogeneous mixtures were allowed

to stand at room temperature until the bulk of the product had crystallized, while two phase mixtures were shaken by machine at room temperature until formation of product was complete. After several days at room temperature, the solid product was filtered off, washed with water until neutral, and air-dried. The solid products were recrystallized to constant melting point. The solvent, melting point and analytical data for each acetal are given in Table I. No solid acetals were obtained from the reaction of tris-(hydroxymethyl)-nitromethane and the following aldehydes under our conditions: propionaldehyde, isobutyraldehyde, α -ethyl-*n*-hexaldehyde, *n*-heptaldehyde and α -ethyl- β -*n*-propyl-acrolein.

Benzoates and Tosylates of Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane.—One-tenth mole of each acetal was dissolved or suspended in 0.2 mole of purified pyridine and 0.1 mole of benzoyl chloride or *p*-toluenesulfonyl chloride was added all at once. If the temperature went above 50° the reaction mixture was cooled until the temperature had gone below this figure. After twenty-four hours at room temperature, the reaction mixtures were poured into water, and the solid products were removed by filtration and washed with additional water. The solvents used in recrystallization together with the melting points and analytical data are listed in Table I.

2-Phenyl-5-nitro-5-(β -cyanoethoxymethyl)-1,3-dioxane.—One-tenth mole of the benzaldehyde acetal of tris-(hydroxymethyl)-nitromethane was dissolved in 65 cc. of dioxane containing 5.3 g. (0.1 mole) of acrylonitrile, and 0.4 g. of sodium hydroxide dissolved in a little water was added. After standing overnight, the solution was concentrated and the viscous residue was extracted with hot *n*-hexane. After recrystallization from *n*-hexane the substance melted at 77.7°. The analytical data are recorded in Table I.

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Side Reaction in the Hydrogenation of 4-Nitro-2-chlorobenzoic Acid and Its Esters

BY ANNA WEIZMANN

In attempts to prepare diethylaminoethyl 4-amino-2-chlorobenzoate,¹ the catalytic hydrogenation of the corresponding 4-nitro-acid, its ethyl and its β -diethylaminoethyl ester was studied. A number of side reactions were observed which made the method impractical from a preparative point of view.

In some cases, incomplete reduction resulted, leading to hydroxylamino- and azoxybenzene derivatives, in others the chlorine atom was lost—this occurred in hydroxylic solvents, not in ethyl acetate. Sometimes, β -diethylaminoethyl 4-nitro-2-chlorobenzoate suffered hydrogenolysis to give ethyl esters; in one case even a methyl ester was formed, before the nitro group was attacked. These hydrogenolytic reactions are somewhat unusual; they recall similar, very recent observations of Metayer.²

Experimental

4-Nitro-2-chlorobenzoic acid is best prepared by the method of Cohen and McCandlish³ with some modifications: a mixture of 2 g. of 4-nitro-2-chlorotoluene and 6

liters of 33.5% nitric acid (1.32) is heated (autoclave) at 120° for eight hours. While 1010 g. of the starting material remains unattacked, 1090 g. of the desired acid is obtained; m. p. 138–139°; conversion, 49.5%; yield, 93.6%. *Ethyl ester*, b. p. 188° (24 mm.); 145–147° (3 mm.); 122–123° (0.2 mm.).

Diethylaminoethyl 4-Nitro-2-chlorobenzoate.—A mixture of 23 g. of ethyl 4-nitro-2-chlorobenzoate and 26.4 g. of diethylaminoethanol was heated for six hours at 140–150° and the reaction product treated with water and ether and fractionated; b. p. 162–163° (0.18 mm.); 140° (0.02 mm.); yield, 16 g. (52%).

Anal. Calcd. for $C_{18}H_{17}O_4N_2Cl$: C, 52.0; H, 5.7; N, 9.3. Found: C, 51.8; H, 5.5; N, 9.0.

Hydrochloride from ethyl acetate, white needles, m. p. 144°.

Anal. Calcd. for $C_{18}H_{18}O_4N_2Cl_2$: C, 46.3; H, 5.3; N, 8.3; Cl, 21.1. Found: C, 46.6; H, 5.2; N, 8.2; Cl, 21.5.

Approximately the same yield (50%) was obtained when the reaction was carried out under reflux in dioxane as solvent (six hours, bath temperature 120°); *trans*-esterification in presence of toluene and aluminum isopropoxide as catalyst (150°, five hours, with continuous removal of the ethyl alcohol formed) gave a yield of 37.5%.⁴

Diethylaminoethyl Acetate.—Azeotropic esterification of 160 g. of ethylene chlorohydrin and 120 g. of acetic acid in 100 cc. of benzene took five hours, when 10 cc. of concentrated sulfuric acid was employed as catalyst. The resulting solution was washed with sodium carbonate and dried and the β -chloroethyl acetate purified by fractionation; b. p. 145–147° (760 mm.); 50° (18 mm.); yield, almost quantitative.⁵ The ester obtained (200 g.) was refluxed with an excess of diethylamine (250 g.) for eight hours, and after addition of another 125 g. of diethylamine for the same period again. The filtered solution was fractionated; b. p. 147°; yield, 130 g.

Hydrogenation of Diethylaminoethyl 4-Nitro-2-chlorobenzoate.—Three representative experiments are reported: (a) A solution of 9 g. (0.03 mole) of the nitro-ester in 50 cc. of anhydrous ethyl alcohol absorbed, at room temperature and in presence of 1 g. of palladium-barium sulfate catalyst, 2010 cc. of hydrogen (0.09 mole) within five and one-half hours. The oily residue of the filtered solution crystallized partly; trituration with cold chloroform gave a white solid which was recrystallized from butyl acetate and melted at 135°. Analysis and reducing properties pointed to the formation of diethylaminoethyl 4-hydroxylamino-2-chlorobenzoate, $HONH \cdot C_6H_3(Cl) \cdot COO \cdot CH_2CH_2N(C_2H_5)_2$.

Anal. Calcd. for $C_{18}H_{19}O_3N_2Cl$: C, 54.5; H, 6.6; N, 9.8; Cl, 12.2. Found: C, 54.3, 54.7; H, 6.9, 7.1; N, 9.8; Cl, 12.4.

Evaporation of the chloroform solution left a strongly basic oil of anesthetic properties which boiled at 130–135° (0.05 mm.) and gave, with alcoholic hydrogen chloride, crystals of ethyl 4-aminobenzoate hydrochloride, m. p. 210°, which were identified by analysis and mixed m. p.

Anal. Calcd. for $C_9H_{12}O_2NCl$: C, 53.7; H, 6.0. Found: C, 53.8; H, 5.9.

(b) When a solution of 6 g. (0.02 mole) of the nitro-ester in 30 cc. of diethylaminoethyl acetate was hydrogenated at room temperature in presence of 0.5 g. of the palladium catalyst, a thick precipitate appeared after the absorption of 500 cc. of hydrogen (0.02 mole), and no further absorption took place. Extraction of the solid phase with butyl acetate gave 2 g. of the above hydroxylamino-compound, m. p. 135°, while the liquid phase contained 3 g. of an oil which crystallized partly on standing. Recrystallization from methanol gave ethyl 4-amino-2-chlorobenzoate of m. p. 110°.¹

(1) Rubin, Marks, Wishinsky and Lanzilotti, *THIS JOURNAL*, **68**, 623 (1946).

(2) Metayer, *Bull. soc. chim.*, 1093 (1948).

(3) Cohen and McCandlish, *J. Chem. Soc.*, **87**, 1271 (1905).

(4) For a similar method, see Alix, French Patent 841,343; *C. A.*, **34**, 4077 (1940).

(5) For the usual acetylation of ethylene chlorohydrin, see "Beilstein," Vol. II, p. 128; 2nd suppl. Vol. II, p. 136.