

corresponding primary amines in good yields by methods involving the use of acidic solvents and palladium or platinum type catalysts.

The hydrogenation with Raney nickel in the presence of ammonia, however, results in the

formation of primary amines in nearly quantitative yields. Compounds hydrogenated include pyrimidine, piperidine, pyridine, thiazole and aliphatic basic nitriles.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Tris-(hydroxymethyl)-aminomethane Derivatives. I. Polyhydroxyamines^{1,2}

BY J. STANTON PIERCE AND JOHN WOTIZ³

Polyfunctional compounds are of particular interest as they afford opportunities for the synthesis of substances with varied properties, many of which are of practical importance. The ethanolamines have been found to be particularly useful, due to their solubility properties, ease of preparation and low cost. A large and interesting field for the synthesis of more highly polar amino alcohols than the ethanolamines was opened by the recent commercial synthesis of tris-(hydroxymethyl)-aminomethane, $(\text{HOCH}_2)_3\text{CNH}_2$,⁴ (A). In 1897, Piloty and Ruff⁵ prepared (A) by the reduction of tris-(hydroxymethyl)-nitromethane which had been prepared two years previously by Henry,⁶ by the reaction of nitromethane and formaldehyde.

Various investigators have combined two primary or secondary amino groups by reaction with epichlorohydrin,⁷ α,ω -dihalohydrins⁸ or α,ω -dihalogenalkanes.⁹ This paper takes up the synthesis of polyhydroxyamines by the union of two molecules of (A), mainly through methylene or methylene and hydroxymethylene groups, by the union of (A) with other amino alcohols through methylene and hydroxymethylene groups, and by the alkylation of (A) with chlorohydrins. A subsequent paper will take up the preparation of alkyl and alkaryl derivatives of (A).

The symmetrical polyhydroxydissecondary amines described in this paper usually were prepared by heating (A) with an α,ω -dihalide, in most cases the bromide. The reactions were carried out under reflux, with no solvent or with alcohol as solvent, and in sealed tubes, with alcohol as solvent. The asymmetrical diamines, all of

which are derivatives of 2-propanol, were prepared by treating a secondary amine with epichlorohydrin at a temperature not exceeding 30° and by the reaction of the product thus formed with (A) at elevated temperature, with alcohol as solvent. Also, two molecules of (A) reacted with epichlorohydrin, to form a symmetrical derivative. Monoalkylation products of (A) were prepared by reaction with halohydrins.

The greatest difficulty in the preparation of the polyhydroxyamines described in this paper was their isolation and purification. Since the free bases, as obtained, showed no tendency to crystallize, they were converted to hydrobromides or hydrochlorides for identification and analysis. A typical mixture in the preparation of a symmetrical dissecondary amine likely contained dihalide, (A), the monoalkylation product of (A) and the desired dissecondary amine, the latter three compounds being present both as the free bases and as the halogen acid salts. Usually, excess halogen acid was added to convert all of the free bases to their salts. The unreacted alkylene dihalide was removed by evaporation or extraction with ether. Finally, purification was effected by fractional crystallization or by selective extraction with two solvents, evaporation of the solvent, if necessary, and trituration of the oily residue with alcohol or acetone or a mixture of the two solvents. Since this purification involved so much loss of material, the yield is given only in the case of 1,3-bis-[tris-(hydroxymethyl)-methylamino]-2-propanol, the compound which was studied most fully.

The polyhydroxyamines described in this paper are characterized by their very high water solubility, both as the free bases and in the form of their salts with hydrochloric or hydrobromic acid. Some of these derivatives of (A) have a great tendency to hold ferric hydroxide, bismuth hydroxide and some other metallic hydroxides in solution. The solubilizing action of the derivatives of (A) is being studied with the view to technical and pharmaceutical applications and will be reported elsewhere. Each of these compounds has one or two secondary amino groups. The high proportion of hydroxyl groups and likely their spatial arrangement makes difficult some of the reactions

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(3) Taken from the thesis submitted by John Wotiz in partial fulfillment for the degree of Master of Science. Present address, Department of Chemistry, The Ohio State University, Columbus, Ohio.

(4) C. L. Gabriel, *Ind. Eng. Chem.*, **32**, 891 (1940).

(5) O. Piloty and O. Ruff, *Ber.*, **30**, 1665, 2062 (1897).

(6) Henry, *Bull. soc. chim.*, [3] **13**, 1001 (1895).

(7) O. Eisleb, U. S. Patent 1,790,042 (1931); Groggins and Stirton, *Ind. Eng. Chem.*, **29**, 1359 (1937).

(8) J. F. Olin, U. S. Patent 2,042,621 (1936); V. Kartaschoff, U. S. Patent 2,149,527 (1939).

(9) I. G. Farbenindustrie A. G., British Patent 459,746 (1937).

of amino nitrogens. However, in some cases it is possible to get an amino group to react and a study is being made to utilize these polyhydroxyamines for the preparation of various polyfunctional compounds.

Experimental

1,3-Bis-[-tris-(hydroxymethyl)-methylamino]-propane Dihydrobromide, $(\text{HOCH}_2)_3\text{CNHCH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HBr}$.—A solution of 24 g. of (A) (0.2 mole) and 10 g. of trimethylene bromide (0.05 mole) in 150 ml. of alcohol was heated under reflux on a water-bath for six hours. On standing overnight, needle-like crystals of (A)·HBr were formed. These crystals were filtered off and the filtrate was made distinctly acidic with hydrobromic acid. The acidic solution was evaporated to low volume to remove most of the water. The gummy residue was dissolved in hot absolute alcohol and the solution was treated with an equal volume of anhydrous acetone. Two layers were formed. The lower layer was separated and triturated with a mixture of equal volumes of absolute alcohol and anhydrous acetone; until crystalline. The solid, 1,3-bis-[-tris-(hydroxymethyl)-methylamino]-propane dihydrobromide, on three recrystallizations from alcohol, melted at 170–171°.

1,2-Bis-[-tris-(hydroxymethyl)-methylamino]-ethane Dihydrobromide, $(\text{HOCH}_2)_3\text{CNHCH}_2\text{CH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HBr}$.—This product was made and purified by practically the same procedure as the compound above.

1,6-Bis-[-tris-(hydroxymethyl)-methylamino]-hexane Dihydrobromide, $(\text{HOCH}_2)_3\text{CNH}(\text{CH}_2)_6\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HBr}$.—A mixture of 48.4 g. of (A) (0.4 mole) and 24.4 g. of hexamethylene bromide (0.1 mole) was refluxed with mechanical stirring until a homogeneous mixture was obtained. The brown glue thus formed was dissolved by refluxing with 300 ml. of 95% alcohol. The alcoholic solution was made strongly acidic with hydrobromic acid and most of the alcohol was evaporated. The residue was treated with absolute alcohol and anhydrous acetone to yield crystals of impure (A)·HBr, melting at 128–132°. The filtrate was treated with three volumes of anhydrous acetone. An oily layer was formed. This lower layer was triturated with absolute alcohol and anhydrous acetone, yielding a solid melting at 150–155°. On recrystallization from 95% alcohol and anhydrous acetone, the product melted at 160.5–162°.

1,3-Bis-[-tris-(hydroxymethyl)-methylamino]-2-propanol Dihydrochloride, $(\text{HOCH}_2)_3\text{CNHCH}_2\text{CHOHCH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HCl}$.—Glyceroldichlorohydrin was heated with two molar quantities of (A) at 100° for three hours with no solvent and with frequent stirring. The yellow glue formed was dissolved in hot alcohol and the solution was acidified with hydrochloric acid. The precipitate which formed, on cooling, was recrystallized from aqueous alcohol.

Better results were obtained by the following procedure: 242 g. of (A) (2.0 moles) and 92.5 g. of epichlorohydrin (1.0 mole) were mixed with 200 ml. of alcohol and heated on a boiling water-bath under reflux for five hours. The viscous brown liquid was treated with 100 ml. (appreciable excess) of concentrated hydrochloric acid, with stirring. The reaction mixture was cooled and filtered with suction. On one recrystallization from an alcohol-water solution, there was obtained 190 g. (51%) of the dihydrochloride of 1,3-bis-[-tris-(hydroxymethyl)-methylamino]-2-propanol, m. p. 185–187°.

1,3-Bis-[-tris-(hydroxymethyl)-methylamino]-2-propanol, $(\text{HOCH}_2)_3\text{CNHCH}_2\text{CHOHCH}_2\text{NHC}(\text{CH}_2\text{OH})_3$.—The free base, mixed with a little sodium chloride, was prepared by treatment of the dihydrochloride, in methyl alcohol, with the calculated quantity of sodium methylate, refluxing, filtering and evaporating the methyl alcohol solution. Also, the free base, free of inorganic impurities, was obtained from the dihydrochloride by prolonged heating of an aqueous solution with excess silver carbonate, removal of dissolved silver with hydrogen sulfide and removal of colored impurities by repeated solution in absolute alcohol

and treatment with anhydrous acetone. Finally, by evaporation of the oily lower layer, the free base was obtained as an oil. Calcd. for $\text{C}_{11}\text{H}_{27}\text{O}_7\text{N}_2$: nitrogen, 9.40. Found: N, 9.41.

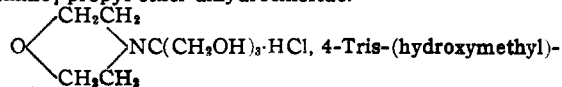
1-Diethanolamino-3-tris-(hydroxymethyl)-methylamino-2-propanol Dihydrochloride, $(\text{HOCH}_2\text{CH}_2)_2\text{NCH}_2\text{CHOHCH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HCl}$.—A mixture of 10.5 g. of diethanolamine (0.1 mole) and 9.5 g. of epichlorohydrin (0.1 mole) was stirred well, the temperature being kept around 30°. After the initial exothermic reaction ceased, the mixture was left overnight at room temperature. The clear viscous liquid was extracted with ether. The ether insoluble product was added to 12 g. of (A) (0.1 mole) and 50 ml. of alcohol and the mixture was heated under reflux for six hours on a water-bath. The reaction mixture was acidified with concentrated hydrochloric acid. An oil was thrown out by the addition of absolute alcohol, acetone and ether. This oil was converted to a semi-solid by solution in aqueous alcohol, treatment with anhydrous acetone and by allowing the lower layer, after evaporation, to stand in a vacuum desiccator. Finally, purification was effected by extraction with hot absolute alcohol.

1,3-Di-(diethanolamino)-2-propanol Dihydrochloride, $(\text{HOCH}_2\text{CH}_2)_2\text{NCH}_2\text{CHOHCH}_2\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2 \cdot 2\text{HCl}$.—The condensation product of diethanolamine and epichlorohydrin was prepared to compare it with the product formed by the reaction of epichlorohydrin with one molecule each of diethanolamine and (A).

10.5 g. of diethanolamine (0.1 mole) and 9.3 g. of epichlorohydrin (0.1 mole) were mixed by shaking and cooling below 30°. After the exothermic reaction ceased, a clear viscous liquid resulted. An additional 10.5 g. of diethanolamine was added and the liquid was heated on a water-bath for eight hours. The product then was acidified with concentrated hydrochloric acid and was extracted with acetone. The lower layer was recrystallized from absolute alcohol.

1-Ethylethanolamino-3-tris-(hydroxymethyl)-methylamino-2-propanol Dihydrochloride, $\text{HOCH}_2\text{CH}_2(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CHOHCH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HCl}$.—Ethylaminoethanol was treated with an equimolar quantity of epichlorohydrin at a temperature below 30°. After the exothermic reaction ceased, the viscous liquid was left at room temperature overnight. The condensation product thus formed was heated with an equimolar amount of (A) for eight hours on a water-bath and the mixture was acidified with hydrochloric acid. Repeated attempts to recrystallize from alcohol failed to yield a solid but the light pink colored glue analyzed satisfactorily.

γ,γ' -Bis-[-tris-(hydroxymethyl)-methylamino]-propyl Ether Dihydrochloride, $(\text{HOCH}_2)_3\text{CNHCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{CH}_2\text{OH})_3 \cdot 2\text{HCl}$.—A mixture of 17 g. of γ,γ' -dichloropropyl ether (0.1 mole) and 24 g. of (A) (0.2 mole) in 100 ml. of alcohol was heated in a sealed tube overnight at 110°. The alcoholic solution was acidified with hydrochloric acid and the precipitated (A)·HCl was filtered off. Repeated evaporations, solution in absolute alcohol, treatments with anhydrous acetone and finally treatments with anhydrous ether were necessary to remove all of the (A)·HCl. The oil finally obtained analyzed slightly low for γ,γ' -bis-[-tris-(hydroxymethyl)-methylamino]-propyl ether dihydrochloride.



methylmorpholine Hydrochloride.—Fourteen grams of β,β' -dichloroethyl ether (0.1 mole) and 24 g. of (A) (0.2 mole) were heated with 100 ml. of alcohol in a sealed tube overnight at 150°. On cooling, snow-white crystals of (A)·HCl were formed. The crystals were filtered off and the filtrate was acidified with hydrochloric acid. On partial evaporation, a solid was obtained. On recrystallization from alcohol, the 4-tris-(hydroxymethyl)-methylmorpholine hydrochloride melted at 184–185°. Calcd. for $\text{C}_8\text{H}_{15}\text{O}_4\text{NCl}$: Cl, 15.57. Found: Cl, 15.59.

A further concentration of the original filtrate yielded other crops of crystals, likely mainly (A)·HCl, judging

TABLE I
POLYHYDROXYAMINE HYDROHALIDES

Compounds	Empirical formula	M. p., °C. uncor.	Halogen analyses, %	
			Calcd.	Found ^b
(HOCH ₂) ₃ CNH ₂ ·HCl ^a	C ₄ H ₁₂ O ₃ ClN	149-150	22.50	22.58
(HOCH ₂) ₃ CNH ₂ ·HBr ^a	C ₄ H ₁₂ O ₃ BrN	133-134	39.55	39.52
(HOCH ₂) ₃ CNHCH ₂ CH ₂ NHC(CH ₂ OH) ₃ ·2HBr	C ₁₀ H ₂₆ O ₆ Br ₂ N ₂	205-206	37.16	37.09
(HOCH ₂) ₃ CNH(CH ₂) ₃ NHC(CH ₂ OH) ₃ ·2HBr	C ₁₁ H ₂₈ O ₆ Br ₂ N ₂	170-171	35.98	35.25
(HOCH ₂) ₃ CNH(CH ₂) ₄ NHC(CH ₂ OH) ₃ ·2HBr	C ₁₄ H ₃₄ O ₆ Br ₂ N ₂	160.5-162	32.87	32.10
(HOCH ₂) ₃ CNHCH ₂ CHOHCH ₂ NHC(CH ₂ OH) ₃ ·2HCl	C ₁₁ H ₂₆ O ₇ Cl ₂ N ₂	186-188	19.10	19.07
(HOCH ₂) ₃ CNHCH ₂ CHOHCH ₂ NHC(CH ₂ OH) ₃ ·2HBr	C ₁₁ H ₂₆ O ₇ Br ₂ N ₂	160-162	34.73	34.67
(HOCH ₂ CH ₂) ₂ NCH ₂ CHOHCH ₂ N(CH ₂ CH ₂ OH) ₃ ·2HCl	C ₁₁ H ₂₆ O ₅ Cl ₂ N ₂	98-100	20.90	20.97
(HOCH ₂ CH ₂) ₂ NCH ₂ CHOHCH ₂ NHC(CH ₂ OH) ₃ ·2HCl	C ₁₁ H ₂₆ O ₆ Cl ₂ N ₂	139-141	19.96	19.55
(HOCH ₂ CH ₂) ₂ (C ₂ H ₅)NCH ₂ CHOHCH ₂ NH(CH ₂ OH) ₃ ·2HCl	C ₁₁ H ₂₆ O ₅ Cl ₂ N ₂	Sirup	20.90	19.74
HOCH ₂ CHOHCH ₂ NHC(CH ₂ OH) ₃ ·HCl	C ₇ H ₁₈ O ₅ ClN	Sirup	15.31	14.90
HOCH ₂ CH ₂ NHC(CH ₂ OH) ₃ ·HCl	C ₆ H ₁₆ O ₄ ClN	Sirup	17.58	17.30
HOCH ₂ CH ₂ CH ₂ NHC(CH ₂ OH) ₃ ·HBr	C ₇ H ₁₈ O ₄ BrN	Sirup	30.72	30.18
(HOCH ₂) ₃ CNH(CH ₂) ₃ O(CH ₂) ₃ NHC(CH ₂ OH) ₃ ·2HCl	C ₁₄ H ₃₄ O ₇ Cl ₂ N ₂	Sirup	17.16	16.30

^a Compounds given for reference. ^b We are indebted to E. E. Bowden and Walter W. Haden for most of the halogen analyses in this work.

from the melting points. No β,β' -bis-[tris-(hydroxymethyl)-methylamino]-ethyl ether was isolated.

1,2-Dihydroxy-3-tris-(hydroxymethyl)-methylaminopropane Hydrochloride, HOCH₂CHOHCH₂NHC(CH₂OH)₃·HCl.—A mixture of 24 g. of (A) (0.2 mole) and 11 g. of glycerol monochlorohydrin (0.1 mole) was heated under reflux with 50 ml. of alcohol for five hours. The resulting liquid was acidified with hydrochloric acid, while hot. On cooling, crystals of (A)·HCl were obtained and filtered off. More (A)·HCl was obtained by concentration of the filtrate and treatment with dry acetone. This process was repeated until no crystals were obtained. The solution then was concentrated to a sirup which was completely miscible with absolute alcohol and dry acetone.

The sirup, while hot, was placed in a vacuum desiccator. After two days of drying, a satisfactory analysis for chloride was obtained.

Similar procedures were used for the reaction of ethylene chlorohydrin and trimethylene bromohydrin with (A) and for purification of the products formed.

Summary

A series of highly polar polyhydroxyamines have been made from tris-(hydroxymethyl)-aminomethane.

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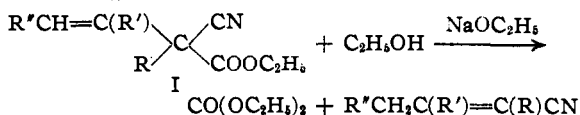
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Cleavage of (Dialkylvinyl)-alkylcyanoacetic Esters by Sodium Alkoxides¹

BY ELIZABETH M. OSMAN AND ARTHUR C. COPE

More or less extensive cleavage of (dialkylvinyl)-alkylcyanoacetic esters to unsaturated nitriles has been observed to occur as a side reaction during condensation of the esters with urea in the presence of sodium alkoxides.² This paper reports an investigation of the cleavage reaction, and its use in the preparation of certain α,β -unsaturated nitriles. The hydrolysis of the nitriles to acids has also been studied.

The products of cleavage are ethyl carbonate and an α,β -unsaturated nitrile



Similar cleavage of other cyanoacetic and malonic ester derivatives has been observed by several

investigators.³ The reaction proceeds readily at moderate temperature with disubstituted esters such as I which contain an α,β -unsaturated (electron attracting, or negative) group. Malonic ester derivatives which are not labilized by electron attracting substituents are cleaved in a similar manner at higher temperatures.^{3c}

Kandiah and Linstead⁴ have proposed a reaction mechanism for the cleavage in which the carbethoxyl group is removed by combination with ethoxide ion as ethyl carbonate, forming the anion of the nitrile. This ion acquires a proton from the solvent alcohol, producing the nitrile and reforming ethoxide ion. α,β - and β,γ -unsaturated nitriles are equilibrated rapidly in the presence of sodium ethoxide,⁴ so that

(1) Abstracted from a dissertation presented to the Faculty of the Graduate School of Bryn Mawr College by Elizabeth M. Osman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Cope and Hancock, THIS JOURNAL, 61, 776 (1939).

(3) Cf. (a) Rogerson and Thorpe, J. Chem. Soc., 87, 1702 (1905); Thole and Thorpe, *ibid.*, 99, 2191 (1911); Ingold and Thorpe, *ibid.*, 115, 143 (1919); Birch, Kon and Norris, *ibid.*, 123, 1369 (1923); Birch and Kon, *ibid.*, 123, 2440 (1923); (b) Kon and Narayanan, *ibid.*, 1536 (1927); (c) Cope and McElvain, THIS JOURNAL, 54, 4311, 4319 (1932).

(4) Kandiah and Linstead, J. Chem. Soc., 2139 (1929).