[CONTRIBUTION FROM NEW PRODUCT DEVELOPMENT LABORATORY, GENERAL ELECTRIC COMPANY, CHEMICAL DIVISION]

Hydroxymethylphenols

BY R. W. MARTIN[1]

RECEIVED DECEMBER 6, 1951

p-Hydroxybenzyl alcohol, 2,4-di-(hydroxymethyl)-phenol and 2,4,6-tri-(hydroxymethyl)-phenol have been obtained as crystalline solids by reaction of phenol with formaldehyde. The compounds were separated by fraction distillation of their trimethylsilyl derivatives.

Phenol is capable of reacting with formaldehyde under alkaline conditions to form two mono-, two di- and one tri-(hydroxymethyl)-phenols depending on the amounts of formaldehyde that combine with the phenol.[2,3]

Only the two mono-(hydroxymethyl)-phenols had been reported[4,5] until recently when Carpenter and Hunter[6] reported the preparation of 2,4,6-tri-(hydroxymethyl)-phenol by an indirect procedure.

Herein is described the preparation and separation of *p*-hydroxybenzyl alcohol, 2,4-di-(hydroxymethyl)-phenol and 2,4,6-tri-(hydroxymethyl)-phenol by reaction of two moles of formaldehyde with a mole of phenol under alkaline conditions. The phenol alcohols were separated as their trimethylsilyl derivatives by fractional distillation, the derivatives being obtained by treatment of the phenol–aldehyde reaction products with trimethylchlorosilane in the presence of pyridine. Hydrolysis of the trimethylsilyl derivatives gave the phenol alcohols which were identified by the preparation of suitable derivatives for two of the alcohols and by infrared and mixed melting point data on the third.

The ease with which the trialkylsilyl derivatives of alcohols and phenols are prepared, their excellent thermal stability and resistance to air oxidation, combined with their ease of hydrolysis under neutral conditions make them ideal for use in the purification or separation of hydroxy compounds sensitive to heat, acids, alkalies, air oxidation, etc. The trimethylsilyl derivatives are, in general, low viscosity liquids, a very desirable property when running a distillation. The by-products of the hydrolysis of the trimethylsilyl derivatives are neutral compounds, trimethylsilanol and hexamethyldisiloxane,[7] and do not interfere with the purification of the hydroxy compounds.

Experimental

Reaction of Phenol with Formaldehyde.—Two hundred and eighty-two grams of phenol was dissolved in a solution containing 198 g. of 83% potassium hydroxide and 100 ml. of water. The phenate solution was cooled to 40° and 500 g. of 36.3% formalin, cooled to 17°, was added. The reaction mixture was kept at 25–35° for 48 hours. Approximately 300 ml. of water was distilled at a pressure of 15–20 mm. The pot temperature was not allowed to exceed 50° and for the most part was kept well below this temperature.

Preparation of Trimethylsilyl Derivatives.—The product obtained above was suspended in 1600 ml. of dry pyridine and stirred vigorously while trimethylchlorosilane was slowly added until an excess was indicated. The end-point can be determined by noting when further addition of trimethylchlorosilane does not cause a noticeable rise in the temperature of the reaction mixture. The chlorosilane was added at such a rate and with cooling so that the temperature of the reaction mixture in no case exceeded 55° and generally was kept below 45°. The pyridine hydrochloride and sodium chloride were filtered off, rinsed with benzene and then discarded. The filtrate and benzene washings were combined. The benzene and excess pyridine were distilled off by heating to a pot temperature of 160°. The residue was then separated into ten fractions by distillation through a three-bulb Snyder column.

Since time did not permit study of each fraction, fractions III, VI and VIII were selected, on basis of silicon content, as being likely to give mono-, di- and tri-(hydroxymethyl)-phenols on hydrolysis.

Hydrolysis of Fraction III.—Eleven grams of fraction III (b.p. 90–140° (15 mm.) Si, 21.5, 22.0) was boiled several minutes with 2 ml. of water and sufficient alcohol to give a homogeneous solution. Benzene was then added and the excess water removed by distilling off the benzene–water–alcohol azeotrope. On cooling, snow-white crystals, m.p. 114–115°, separated from the solution. The product was recrystallized from 3:1 benzene–alcohol, m.p. 119–120°. Melting points reported for *p*-hydroxybenzyl alcohol are 121°[8] and 124–125°.[9] The compound was shown to be *p*-hydroxybenzyl alcohol by comparison of its infrared absorption spectrum with that for an authentic sample of the compound.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.94, 67.99; H, 6.54, 6.59.

Hydrolysis of Fraction VI.—Ten grams of fraction VI (b.p. 115–125° (0.05 mm.) Si, 23.2) was hydrolyzed by boiling with 3 g. of water in sufficient methanol to give a clear solution. After concentrating the solution to a fairly small volume, ethyl acetate was added and the solution boiled until free of water. It is very important that the solution be anhydrous otherwise the product will not crystallize. The boiling point of the solution can be used to indicate when the solution is dry. On cooling the solution, snow-white crystals, m.p. 91–92°, were obtained. Upon recrystallization from ethyl acetate the crystals melted at 93–94°, uncorrected. The elemental analysis of the compound indicated that it was a di-(hydroxymethyl)-phenol.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.18; H, 6.52. Found: C, 62.22, 62.33; H, 6.84, 6.94.

The compound was shown to be the 2,4-isomer by conversion to the known 2,4-bis-(hydroxymethyl)-anisole by treatment with dimethyl sulfate in strong alkaline solution. The compound obtained melted at 100–101° and showed no depression in melting point when mixed with an authentic sample of 2,4-bis-(hydroxymethyl)-anisole, m.p. 101°.[10]

Hydrolysis of Fraction VIII.—Twenty-five grams of fraction VIII (b.p. 135–145° (0.03–0.05 mm.) Si, 23.4, 24.2) was dissolved in acetone containing several grams of water. The solution was warmed for 10 minutes and then filtered through a bed of Drierite to remove the bulk of the unreacted water. The solution was concentrated at room temperature to a small volume whereupon crystals separated. The product was recrystallized from ethyl acetate giving snow-white crystals, m.p. 84°. The elemental analysis of the compound indicated that the compound was tri-(hydroxymethyl)-phenol.

---

(1) Shell Development Co., Emeryville, California.

(2) (a) K. H. Meyer, *Trans. Faraday Soc.*, **32**, 345 (1936). (b) G. R. Sprengling and J. H. Freeman, THIS JOURNAL, **72**, 1982 (1950).

(3) R. W. Martin, Preprint Bulletin, Div. of Paint, Varnish and Plastics Chem., Chicago Meeting, Sept., 1950, pp. 68–72.

(4) L. Lederer, *J. Prakt. Chem.*, [2] **50**, 223 (1894).

(5) O. Manasse, *Ber.*, **27**, 2409 (1894).

(6) A. T. Carpenter and R. F. Hunter, *Plastics*, 287 (1950); *J. Applied Chem.*, **1**, 217 (1951).

(7) R. O. Sauer, THIS JOURNAL, **66**, 1707 (1944).

(8) I. W. Ruderman, *Ind. Eng. Chem., Anal. Ed.*, **18**, 753 (1946).

(9) R. Mozingo and K. Folkers, THIS JOURNAL, **70**, 229 (1948).

(10) R. Quelet and M. Anglade, *Compt. rend.*, **203**, 262 (1936).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.67, 58.68; H, 6.58, 6.50.

This was confirmed by conversion of the compound to the known 2,4,6-tri-(acetoxymethyl)-phenyl acetate[11] by the action of acetic anhydride in pyridine. The ester boiled at 172–175° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.45; H, 5.72; sapn. equiv., 88.08. Found: C, 57.89, 57.75; H, 5.83, 5.98; sapn. equiv., 87.3, 91.6.

A sample of the compound was also converted to the known sodium tri-(hydroxymethyl)-phenate[3] by dissolving in alcohol and treating with a slight excess of alcoholic sodium hydroxide. The sodium tri-(hydroxymethyl)-phenate precipitated from the alcohol solution as a dry white powder upon the addition of a little butanol, and was collected and dried; calcd. for neut. equiv., 206.2; found: neut. equiv., 204.5, 203.9.

PITTSFIELD, MASS.

---

[11] H. A. Bruson and C. W. Macmullen, THIS JOURNAL, **63**, 270 (1941).

[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

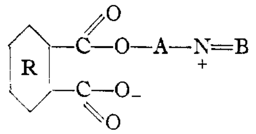
Dialkylaminoalkyl Acid Esters and Salts as Hypotensive Agents[1a,1b]

BY LEONARD M. RICE,[2] ANTOINETTE POPOVICI, MARTIN RUBIN, CHARLES F. GESCHICKTER AND E. EMMET REID[3]

RECEIVED DECEMBER 10, 1951

A series of dialkylaminoalkyl half esters was prepared by the reaction of the appropriate dialkylaminoalkyl alcohol with an anhydride. These compounds have been found to possess hypotensive action.

As part of a research program directed toward the finding of clinically useful hypotensive agents, the investigation of a series of half esters of dialkylaminoalkyl alcohols and some of the corresponding magnesium salts of the structural type illustrated was undertaken.



Representative compounds in which the cyclic nucleus was phenyl, 3-nitrophenyl, *cis*-Δ^4-cyclohexene and 3,6-endomethylene-*cis*-Δ^4-cyclohexene have been prepared. In these compounds the side chains have been varied so that the –A– grouping represents two or three methylene carbon atoms while the –B– grouping represents alkyl groups in the range of methyl to butyl as well as cyclic systems such as the morpholino, pyrrolidino and phthalimido rings. In general these materials have been prepared by the reaction of the appropriate anhydride and amino alcohol in anhydrous acetone. The reactions were exothermic and the product usually separated in crystalline form on standing.

Aqueous 20% solutions of the alkyl amino acid esters have a *p*H of 6.6–7.0 when measured on the Beckman *p*H meter. This neutrality shows that the carboxyl group is not free and that the compound probably exists as a zwitterion. This contention is further supported by the high water-solubility of the compounds. In a similar manner the insolubility in such solvents as benzene, petroleum ether, chloroform and ether is in keeping with the zwitterion formulation.

As the basicity of the nitrogen in the side chain of the molecule decreased, the products became less water-soluble. In the compounds where 2-(β-hydroxyethyl)-pyridine was the alcohol used in the esterification there is a marked decrease in solubility of the product. When the basicity of the nitrogen is further decreased, as in the compound containing the N-(β-ethyl)-phthalimide grouping, the solubility is further decreased.

In the series of compounds derived from 3-nitrophthalic acid it has been shown that the alkylamino group enters the 2-position.[4] These compounds have lower water-solubilities than the other series.

As a variation of the nitrogen-containing portion of the molecule, the *cis*-Δ^4-tetrahydrophthalamic acids shown in Table V were prepared[5] and characterized.

From such a large group of compounds of similar structure it is possible to draw some conclusions as to the relation of structure and activity of these materials. When screened in normotensive dogs it could be established that the most active compounds are those characterized by the alicyclic nucleus such as *cis*-Δ^4-tetrahydrophthalic and the endomethylene *cis*-Δ^4-tetrahydrophthalic. The maximal activity and least toxicity appeared in the compounds where –A– was an ethyl substituent in common with many similar pharmacologically active materials.

In the –B– portion of the molecule lower alkyl groups such as methyl and ethyl showed the most activity. The amic acid class did not show comparable activity. In all cases conversion to the magnesium salts potentiated the hypotensive action of the products.

It is interesting to note that bis-(β-diethylaminoethyl) *cis*-Δ^4-tetrahydrophthalate is a powerful hypotensive compound.

A much more complete report of the pharmacological properties of these compounds will be published elsewhere.

---

[1] (a) Presented at the XIIth International Congress of Pure and Applied Chemistry, Medicinal Section, New York, N. Y., September, 1951. (b) Supported (in part) by a research grant from the National Heart Institute, U. S. Public Health Service, and the Geschickter Fund for Medical Research, Inc.

[2] Abstracted in part from the thesis submitted to Georgetown University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] Professor Emeritus, Johns Hopkins University, Balitmore, Md.

[4] Blicke and Otsuki, THIS JOURNAL, **63**, 1945 (1941).

[5] L. M. Rice, M. Rubin, Jean Scholler and E. E. Reid, *J. Org. Chem.*, **16**, 501 (1951).