NOTES

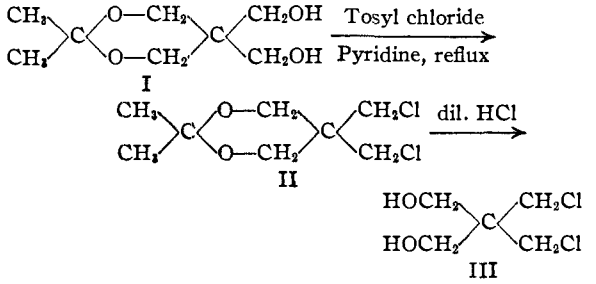
Pentaerythritol Dichloride

BY H. RAPOPORT[1]

Previous workers have prepared pentaerythritol dichlorohydrin (III) from pentaerythritol, with the mono-, tri- and tetra-analogs and other products, by the action of sulfur monochloride,[2] concentrated hydrochloric acid in a sealed tube,[3] and thionyl chloride and pyridine.[4]

During the course of some work on the chlorine substitution products of pentaerythritol, we prepared the dichlorohydrin (III) by a method which prevented the formation of any mono-, tri- or tetrachloro compound, and found that (III) melted at 79–80°, uncor. This is in close agreement with the value reported by Mooradian and Cloke[4] (83° cor.) but differs significantly from those of Bougault[2] (65°) and Fecht[3] (95°), who probably did not have the pure compound.

In our preparation of (III) 2,2-dimethyl-5,5-bis-(hydroxymethyl)-1,3-dioxane[5] (I) was refluxed



I

II

III

in pyridine with *p*-toluenesulfonyl chloride to give 2,2-dimethyl-5,5-bis-(chloromethyl)-1,3-dioxane (II), which on warming with dilute hydrochloric acid gave (III).

Experimental[6]

2,2-Dimethyl-5,5-bis-(chloromethyl)-1,3-dioxane (II).—To a cooled solution of 13.4 g. (0.07 mole) of *p*-toluenesulfonyl chloride (purified) in 30 ml. of pyridine (dried over potassium hydroxide) was added slowly with shaking 6.2 g. (0.035 mole) of 2,2-dimethyl-5,5-bis-(hydroxymethyl)-1,3-dioxane (I), m. p. 126–127°,[5] so that the internal temperature did not rise above 35°. After the addition was completed, the solution was refluxed for sixteen hours, cooled, the precipitated pyridinium *p*-toluenesulfonate filtered with suction and washed with 5 ml. of dry pyridine, and the combined filtrate and washings evaporated under reduced pressure. The residual magma was dissolved in 100 ml. of chloroform, and the chloroform solution was washed with dilute sulfuric acid, saturated aqueous sodium bicarbonate, and distilled water. The crystalline solid remaining after evaporation of the chloroform was recrystallized from methanol–water using decolorizing carbon and dried over sulfuric acid. The yield was 3 g. of II, 40%. A sample, after sublimation at 35–40° at 1 mm., had a m. p. of 48–49°.

Anal.[7] Calcd. for $C_7H_{14}O_2Cl_2$: Cl, 33.30; mol. wt., 213. Found: Cl, 33.42, 33.36; mol. wt., 203, 210 (Rast).

Pentaerythritol Dichlorohydrin (III).—A suspension of 1.5 g. (0.007 mole) of 2,2-dimethyl-5,5-bis-(chloromethyl)-1,3-dioxane (II) in 25 ml. of 0.5 *N* hydrochloric acid was heated on the steam-bath, and the effluent was bubbled through a solution of iodine in 10% sodium hydroxide in order to observe the evolution of acetone (by iodoform formation). After fifteen minutes, a heavy cloudiness appeared in the iodine solution, and after fifty minutes (total time on steam-bath) the hydrolysis appeared to be complete. The acid solution was now evaporated under reduced pressure to a sirupy residue which crystallized on cooling. Recrystallization first from water and then from benzene gave 0.5 g., 41%, of pentaerythritol dichlorohydrin (III). A sample after sublimation in high vacuum melted at 79–80°.

Anal.[7] Calcd. for $C_5H_{10}O_2Cl_2$: Cl, 41.00; OH, 19.65. Found: Cl, 41.36, 41.10; OH, 19.5.

Purification of Pyridinium *p*-Toluenesulfonate.—The pyridinium *p*-toluenesulfonate isolated from the reaction of 2,2-dimethyl-5,5-bis-(hydroxymethyl)-1,3-dioxane (I) with *p*-toluenesulfonyl chloride in pyridine was twice recrystallized from an ethanol–ether mixture and, after drying *in vacuo* at 65°, had a m. p. of 118–119°.[8]

Anal. Calcd. for $C_{12}H_{13}O_3SN$: S, 12.75; neut. equiv., 251. Found: S, 12.62, 12.53, neut. equiv., 253 (by titration with 0.1 *N* sodium hydroxide).

(1) Present address: National Institute of Health, Bethesda, Md.

(2) Bougault, *Compt. rend.*, **123**, 187 (1896).

(3) Fecht, *Ber.*, **40**, 3888 (1907).

(4) Mooradian and Cloke, THIS JOURNAL, **67**, 942 (1945).

(5) Orthner, *Ber.*, **61**, 116 (1928).

(6) All melting points are uncorrected.

(7) Microanalyses by Dr. Carl Tiedcke, 366 Fifth Ave., New York, N. Y.

(8) Gebauer-Fülnegg and Riesenfeld, *Monatsh.*, **47**, 185 (1926), reported m. p. 113–115° for this compound obtained by heating *p*-toluenesulfonyl chloride and pyridine in a sealed tube at 140–150°.

HEYDEN CHEMICAL CORPORATION
GARFIELD, NEW JERSEY RECEIVED OCTOBER 3, 1945

The Heparin of Pig Tissue

BY WILLIAM C. RISSER

Heparin, the blood anticoagulant, has been found in most tissues and organs of the animal body.[1] Highly vascular tissues and organs such as lung and liver contain this substance in greatest quantity. Charles and Scott[2] first isolated crystalline barium acid heparinate from ox lung. Jaques, Waters and Charles[3] have isolated the crystalline barium acid salt of heparin from the lungs of the pig and sheep and from the liver of dogs. They found that the biological activity of the heparin salts from the different species varied widely; the potencies of the acid barium salts expressed in Toronto units per mg. were reported to be: dog 240, beef 100, pig 44 and sheep 23. No significant differences in chemical analy-

(1) A. F. Charles and D. A. Scott, *J. Biol. Chem.*, **102**, 431 (1933).

(2) A. F. Charles and D. A. Scott, *Biochem. J.*, **30**, 1927 (1936).

(3) L. B. Jaques and E. T. Waters, *J. Physiol.*, **99**, 454 (1941); L. B. Jaques, *Science*, **92**, 488 (1940); L. B. Jaques, E. T. Waters and A. F. Charles, *J. Biol. Chem.*, **144**, 229 (1942).

sis or rotatory power of the barium acid heparinates from the different species could be detected.

Very recently Wolfrom[4] and co-workers have reported that the crystalline barium acid salt of heparin from dog liver has the *same* biological activity as the beef heparin barium salt, in contrast to the claims of Jaques and co-workers.

We have prepared the pure amorphous sodium salt of heparin from pig liver by a procedure similar to that of Charles and Scott.[1,2] The biological activity of this material was determined by two different methods. The first assay method used was that of Charles and Scott[2] which employs freshly drawn cat's blood. This method was described in greater detail by Jaques and Charles.[5] The second method of assay used was the excellent method of Kuizenga, Nelson and Cartland.[6] By both methods of assay, the anticoagulant potency of the amorphous sodium salt of heparin isolated from pig liver was found to be 110–120 Toronto units per milligram,[7,8] which is the same as the anticoagulant potency reported for the pure amorphous sodium salt of heparin isolated from beef tissue.

The pure amorphous sodium salt of heparin from pig liver was converted into the crystalline barium acid salt. This substance assayed 95 Toronto units per milligram by the cat blood method of Charles and Scott.[2] This, likewise, is in good agreement with the value reported for the crystalline barium acid heparinate of beef tissue.[3]

It has been shown that the anticoagulant potencies of the sodium salt and crystalline barium acid salt of heparin from pig liver are identical to the anticoagulant potencies of these same salts of heparin from beef tissue. Thus within the limits of the bioassay procedures, the heparin of pig liver appears to be identical with heparin from beef tissue. Furthermore, since Wolfrom[4] has shown that heparin from dog liver is identical to heparin from beef tissue, it is apparent that the anticoagulant potencies of heparin from three different species—the dog, the pig and the ox—are identical.

These findings are therefore in disagreement with the claims of Jaques and co-workers[5] that the anticoagulant potency of beef heparin is twice that of pig heparin. Wolfrom and co-workers[4] have suggested that the observations of Jaques and co-workers on the variation of heparin potency with species source may have resulted from different degrees of inactivation by acid in preparing the crystalline barium acid salts from different species.

Three samples of crystalline barium acid salt of heparin from pig tissue supplied by this Laboratory were used by Copley and Whitney[9] in developing a colorimetric method of assay. Although it is doubtful whether reaction with toluidine blue parallels anticoagulant activity very closely, it is interesting to compare the reactivity to toluidine blue of heparin samples from pig tissue (Ba-1-PHi, Ba-3-PHi-II, Ba-2-PHi of Table V, in paper by Copley) and the remaining heparin samples, supplied by other laboratories, and of presumably different origin. No gross differences are apparent.[10]

(4) M. L. Wolfrom, J. V. Karabinos, C. S. Smith, P. H. Ohliger, J. Lee and O. Keller, THIS JOURNAL, **67**, 1624 (1945).

(5) L. B. Jaques and A. F. Charles, *Quart. J. Pharm. Pharmacol.*, **14**, 1 (1941).

(6) Marvin H. Kuizenga, John W. Nelson and George F. Cartland, *Am. J. Physiol.*, **139**, 612 (1943).

(7) The author is indebted to Mr. H. C. Spruth and his coworkers, Robert T. Olsen, Marguerite Tonyan and Melle Russell Cummings for the biological assays recorded herein.

(8) Dr. E. F. Cook, Chairman of the Committee of Revision of the Pharmacopoeia of the United States, has recently supplied a provisional International Standard sodium heparin which has been given the value 130 international units per mg. (approx. 130 Toronto u./mg.) Different batches of sodium heparin from pig liver, on the dry basis, assay 120 to 140 international u./mg.

(9) Alfred L. Copley and David V. Whitney, *J. Lab. Clin. Med.*, **28**, 762 (1943).

(10) The author is grateful to Dr. D. W. MacCorquodale for his interest and encouragement.

ABBOTT LABORATORIES
NORTH CHICAGO, ILLINOIS RECEIVED OCTOBER 8, 1945

2-Mercaptopyridine

BY JOHN R. THIRTLE

A recent paper[1] describing the use of mono-, di- or triethylene glycol as a reaction solvent to obviate the use of an autoclave or bomb-tube method prompts the report of a similar technique developed in this Laboratory.

2-Mercaptopyridine was prepared in 83–87% yield by the reaction of 2-bromopyridine with potassium hydrosulfide in propylene glycol. The crude product melts at 121–124° and is pure enough for most reactions. Crystallization from benzene with considerable loss raises the melting point to 128°. Previous methods made use of sodium[2] or potassium hydrosulfide[3] or thiourea.[4]

Procedure.—Hydrogen sulfide was passed into 1000 g. (15 moles) of potassium hydroxide (reagent grade, 85%) and 250 cc. of water until saturation was reached. A little ferrous sulfide which formed was removed by filtration and the filtrate was evaporated to dryness under vacuum by heating on an oil-bath at 100–170°. The white crystalline potassium hydrosulfide was dissolved in 2500 cc. of propylene glycol. The solution was heated at 170–175° under a reflux condenser while 790 g. (5 moles) of 2-bromopyridine[5] was added at such a rate that gentle refluxing occurred. Stirring and heating were continued for twenty hours at 150–175°. The potassium bromide was removed by filtration and washed with 1500 cc. of ethanol in portions. The filtrate, including washings, was

(1) Soffer, Soffer and Sherk, THIS JOURNAL, **67**, 1435 (1945).

(2) Gastel and Wibaut, *Rec. trav. chim.*, **53**, 1031 (1934).

(3) Marckwald, Klemm and Trabert, *Ber.*, **33**, 1556 (1900).

(4) Phillips and Shapiro, *J. Chem. Soc.*, 584 (1942). This procedure, requiring no special equipment, involved the reaction of 2-bromopyridine with thiourea followed by decomposition of the isothiouronium salt with ammonium hydroxide. Yields (67.5%) and quality (m. p. 116–120°) are inferior to those of the product described here.

(5) The 2-bromopyridine was made in 92% yield by the method of Craig, THIS JOURNAL, **56**, 231 (1934); *cf.* Whitmore, Mosher, Goldsmith and Rytina, *ibid.*, **67**, 393 (1945).

distilled to dryness under a vacuum. The residue was dissolved in 1500 cc. of water and treated with 50 g. of Norite at the boiling point. The filtrate was carefully acidified with glacial acetic acid. The 2-mercaptopyridine formed in bright yellow crystals which were collected, after chilling to 5°, and washed with 2 liters of ice water. The dry product weighed about 400 g. and melted at 121–124°. A further 67–77 g. (m. p. 125–128°) was obtained by extraction of the filtrate and washings by chloroform, removing the latter by distillation and crystallizing the residue from benzene. The total yield was 461–483 g. (83–87%).

COMMUNICATION NO. 1014 FROM
KODAK RESEARCH LABORATORIES
ROCHESTER 4, NEW YORK RECEIVED OCTOBER 27, 1945

NEW COMPOUNDS

Derivatives of Mesitylene

Methyl 3,5-Dinitromesitoate.—Two grams of methyl mesitoate was added dropwise to an ice-cold mixture of 25 ml. of concentrated sulfuric acid and 25 ml. of fuming nitric acid at such a rate that the temperature did not rise above 10°. It was necessary to cool and stir continuously. The solution was kept cold for fifteen minutes and poured on cracked ice. The dinitro ester was recrystallized from methanol: yield 2.3 g. (m. p. 136–138.5°). The pure compound melted at 138.5–139.5°.

Anal. Calcd. for $C_{11}H_{12}O_6N_2$: N, 10.4. Found: N, 10.6.

α,α-Diphenylacetomesitylene. A. From the Acetone Derivative of Mesitylglycolic Acid.—A solution of 50 g. of the acetone derivative of mesitylglycolic acid[1] in 100 ml. of ether was added slowly to a solution of phenylmagnesium bromide containing approximately four times the theoretical amount of active reagent. The mixture was heated overnight under reflux and decomposed in the usual way. The product, presumably 1,1-diphenyl-2-mesitylethylene glycol, was an oil boiling at 190° (4 mm.). A 5-g. portion of the oil was heated under reflux for one hour with a mixture of 65 ml. of glacial acetic acid and 15 ml. of hydrochloric acid. When the mixture was poured on ice the α,α-diphenylacetomesitylene separated as a solid. It was recrystallized from ethanol; m. p. 152–153°; yield 4.5 g.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.70; H, 7.04.

B. From Diphenylacetyl Chloride.—Twenty-seven grams of anhydrous aluminum chloride was added portionwise over a period of twenty minutes to a mixture of 29.5 g. of diphenylacetyl chloride, 15.1 g. of mesitylene and 200 ml. of carbon disulfide. The mixture was kept in an ice-bath and was stirred continuously throughout the period of addition and for seventy minutes afterward. By pouring the reaction mixture on ice the α,α-diphenylacetomesitylene was precipitated as a solid melting at 148–150°; yield 83%. It was purified by repeated recrystallization from ethanol; m. p. 152–153°.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.50; H, 7.20.

Mesityl *p*-Phenylphenyl Ketone.—A solution of 9 g. of *p*-phenylbenzoyl chloride in 75 ml. of carbon disulfide was added slowly to a mixture of 5.5 g. of mesitylene, 6.5 g. of anhydrous aluminum chloride and 20 ml. of carbon disulfide. After the addition was completed the reaction mixture was stirred at room temperature for two hours. A portion of the solvent was evaporated and the residual mixture was poured into a mixture of ice and concentrated hydrochloric acid. The ketone, after one recrystallization from ethanol, melted at 108–110°; yield 80% of the theoretical. The melting point of the pure compound was 111–112°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.75; H, 6.77.

3,5-Dinitromesityl 4-Methyl-3-nitrophenyl Ketone.—Two grams of *p*-toluylmesitylene was dissolved in 8 ml. of concentrated nitric acid, and the mixture heated at 45° for ten minutes. The trinitro derivative, precipitated by pouring the reaction mixture on cracked ice, was recrystallized from 95% ethanol; m. p. 168–169°.

Anal. Calcd. for $C_{17}H_{15}N_3O_7$: C, 54.71; H, 4.02; N, 11.26. Found: C, 54.33; H, 4.09; N, 11.14.

THE NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

REYNOLD C. FUSON
M. D. ARMSTRONG
C. H. FISHER
NORMAN RABJOHN
G. E. ULLYOT
WM. E. WALLACE

RECEIVED NOVEMBER 2, 1945

Di-*o*-tolylglycolic Acid

A solution of the binary mixture, Mg–MgI_2,[1] was made from 6 g. of magnesium, 30.6 g. of iodine, 120 ml. of ether and 240 ml. of benzene. To this reagent was added a solution of 20 g. of *o*-toluyl chloride in 20 ml. of ether. The mixture was heated under reflux, with stirring, for eighteen hours and treated with an ice cold solution of 20 ml. of water in 200 ml. of acetic acid. The organic layer was washed successively with 5% sodium thiosulfate solution, 10% potassium bicarbonate solution and water. After the solution had been dried the solvent was evaporated. The residual oil was mixed with a solution of 35 g. of hydrated copper sulfate in 25 ml. of water and 20 ml. of pyridine. The mixture was heated under reflux, with stirring, for four hours. The yellow *o*-tolil was distilled at 140–170° (2 mm.). It solidified and was recrystallized from ethanol; m. p. 92–94° (cor.)[2]; yield 34%.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.98; H, 6.25.

o-Tolil was found to undergo the benzilic acid rearrangement. To a solution of 10 g. of *o*-tolil in 200 ml. of ether was added a solution of 5 g. of sodium ethoxide in 40 ml. of 95% ethanol. The container was stoppered tightly and allowed to stand for twenty-four hours. The solution was extracted with 200 ml. of water. Acidification of the aqueous solution precipitated 7 g. of the **di-*o*-tolylglycolic acid.** It was recrystallized from benzene; m. p. 162–163°; yield 65%. It gave a purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; neut. equiv., 256. Found: C, 74.85; H, 6.49; neut. equiv., 251.

THE NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

REYNOLD C. FUSON
A. I. RACHLIN

RECEIVED NOVEMBER 23, 1945

X-[N-(β-Acetamidoethyl)-N-methyl]-aminoazobenzene

Aniline (0.98 ml., 0.0108 mole) was dissolved in a mixture of 2.50 ml. (0.030 mole) of concentrated hydrochloric acid and about 8 ml. of water. The temperature was brought to 0° by adding ice, and the solution was diazotized at 0–5° by adding in the usual manner a solution of 0.77 g. (0.0108 mole) of 97% sodium nitrite in 1.5 ml. of water.

(1) Fuson and Rachlin, THIS JOURNAL, **64**, 1567 (1942).

(1) Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927).

(2) Since this work was done, *o*-tolil has been described by Kharasch, Nudenberg and Simons [THIS JOURNAL, **65**, 495 (1943)].