hydrogen bromide and hydrogen chloride in ether is not caused by a reaction of hydrogen bromide with the solvent, forming ethanol and ethyl bromide. Such a reaction should be more rapid with hydrogen bromide, but it is not thought to be a probable cause of the difference. The observations of Hantzsch and Weissberger[1a] and of Dörken[2] call for a more thorough investigation and for comparative measurements of the conductivity of the two hydrogen halides in ether. None of this work is planned by the author. The above scant data and discussion may serve to draw attention to a rather interesting problem of acid catalysis.

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ROCHESTER 4, N.Y. RECEIVED JUNE 21, 1945

Acetates, Propionates and Butyrates of Simple Saccharides

BY IVAN A. WOLFF

The lower saturated fatty acid esters of carbohydrates are usually prepared by acylation with a mixture of pyridine and the anhydride of the acid. After reaction is complete, the mixture is customarily poured onto ice and the ester is separated either by filtration or by solvent extraction of the aqueous medium. An alternative isolation procedure, which has apparently been used very little, involves separation of the ester by vacuum distillation of excess reactants and volatile products after esterification. This method has been applied to the preparation of starch esters by Mullen and Pacsu[1] and of pentapropionylglucose and pentabutyrylglucose by Hess and Messmer.[2]

The general applicability of this latter procedure is shown by the results presented here. It has been found that the sugar esters can be obtained in quantitative yield by concentration of the reaction mixture *in vacuo* after the esterification process is complete. The excess pyridine, anhydride and fatty acid formed, are removed,[3] leaving the ester in a good state of purity. Further appropriate purification procedures can then be applied if desired, depending on the properties of and intended uses for the particular ester. This method of operation has the following advantages: (1) ease of operation with a minimum of manipulative steps, and (2) increased yields of esters in many cases. It is particularly useful as compared to the conventional procedure when the desired ester is moderately water soluble (*e.g.*, levoglucosan triacetate).

By use of the procedure described, the acetates, propionates and butyrates of sucrose, diacetone D-glucose α-methyl-D-glucoside, D-sorbitol, levoglucosan and D-glucose have been prepared. Properties of the products are listed in Table I.

TABLE I

PROPERTIES OF THE SUGAR ESTERS[a]

Substance	Color	State	M. p., °C.	Rotation measurements $[\alpha]^{25}D$	in $CHCl_3$	Conen.	% Acyl- Calcd.	Found[f]
Sucrose octaacetate crude[b]	White	Crystals	84–86	+ 60.6		3	50.7	50.8
Sucrose octapropionate crude	White	Crystals	44–46	+ 52.7		1	57.7	57.7
Sucrose octabutyrate[c] crude	Brown	Sirup	.....	+ 46.5		3	63.0	63.0
Diacetone D-glucose monoacetate crude	Off white	Crystals	51–58	− 34.3		2	14.2	15.6
Diacetone D-glucose monoacetate recryst.	White	Crystals	57–61.5	− 36.9		1	14.2	14.6
Diacetone D-glucose monopropionate[c] crude	Yellow	Sirup	.....	− 32.2		2	18.0	19.7
Diacetone D-glucose monopropionate[c] distil.	Water-white	Sirup	120.5–123[d]	− 35.1		1	18.0	18.4
Diacetone D-glucose monobutyrate[c] crude	Yellow	Sirup	.....	− 31.3		2	21.5	23.5
Diacetone D-glucose monobutyrate[c] distil.	Water-white	Sirup	121[d]	− 33.3		1	21.5	21.9
α-Methyl-D-glucoside tetraacetate crude	White	Crystals	98–102	+130.4		3	47.5	47.3
α-Methyl-D-glucoside tetrapropionate[c] crude	Viscous	Sirup	.....	+114.5		3	54.5	54.8
α-Methyl-D-glucoside tetrabutyrate[c] crude	Brown fluid	Sirup	.....	+102.6		2	59.9	60.1
D-Sorbitol hexaacetate crude	Slightly yellow	Crystals	91–97	+ 12.3		3	59.4	58.8
D-Sorbitol hexaacetate recryst.	White	Crystals	97–98.5	+ 10.6		3	59.4	59.2
D-Sorbitol hexapropionate[c] crude	Slightly yellow	Sirup	.....	+ 14.1		4	66.0	65.6
D-Sorbitol hexabutyrate[c] crude	Brown	Sirup	.....	+ 17.4		3	70.8	70.2
Levoglucosan triacetate crude	White	Crystals	107–110	− 61.5		1	44.8	44.2
Levoglucosan tripropionate[c] distil.	White	Crystals	37–38	− 56.8		2	51.8	52.0
Levoglucosan tributyrate[c] distil.	Colorless	Sirup	170[d]	− 34.5[e]		2	57.2	57.3
Pentaacetyl-D-glucose crude	White	Crystals	93–100	+ 73.2		1	55.1	54.9
Pentapropionyl-D-glucose crude	V. visc. lgt. yellow	Sirup	.....	+ 53.7		2	62.0	61.6
Pentabutyryl-D-glucose crude	Visc. lgt. brown	Sirup	.....	+ 44.5		2	67.0	67.0

[a] Melting points and boiling points are uncorrected. [b] The word "crude" is used in this table to indicate the whole of the ester fraction obtained as a residue upon distillation of the non-ester bodies. [c] These compounds are believed to be previously unreported in the literature. [d] Boiling point at <1 mm. pressure. [e] In methyl alcohol. [f] Average of duplicate determinations.

In the case of D-glucose a mixture of isomeric penta-esters was formed on acylation. A single product results whenever the hemiacetal hydroxyl group on carbon one is combined, so that change of configuration cannot occur.

Experimental

The general procedure used in preparing the esters was as follows: One-tenth mole of the sugar was mixed at room temperature with one and a half times the quantity of anhydride and two times the amount of dry pyridine

(1) Mullen and Pacsu, *Ind. Eng. Chem.*, **34**, 1209 (1942).

(2) Hess and Messmer, *Ber.*, **54**, 499 (1921).

(3) Gardner, *ibid.*, **23**, 1567 (1890).

theoretically required for complete esterification. Heating of the reaction mixture often occurred at this point. The mixture was allowed to stand at room temperature for twenty-four hours after all of the sugar was in solution. Stirring was helpful in accelerating the rate of solution of the sugar in certain cases, as with sucrose, in which an exothermic reaction does not occur. The reaction mixture was then concentrated *in vacuo* with a bath temperature of 50–80°. If the derivative was known to be crystalline, the sirupy residue was induced to crystallize by scratching or seeding. The crystals were then dried in a vacuum desiccator over solid sodium hydroxide and concentrated sulfuric acid and finally in a vacuum oven. When the ester was a sirupy liquid it was either purified directly by distillation or freed of traces of pyridine by drying in thin layers in a vacuum oven.

Acyl analyses, with the exception of those on the esters of D-glucose, were carried out by saponification at room temperature in acetone solution with either aqueous or alcoholic potassium hydroxide. The glucose esters were analyzed by a slight modification of the method of Elek and Harte.[4]

Acknowledgment.—Mr. C. H. Van Etten performed several of the acyl analyses listed in the table.

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PEORIA, ILLINOIS[5] RECEIVED JULY 7, 1945

(4) Elek and Harte, *Ind. Eng. Chem., Anal. Ed.*, **8**, 267–269 (1936).

(5) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

The Species Specificity of Heparin

BY M. L. WOLFROM,[1] J. V. KARABINOS,[1] C. S. SMITH,[2] P. H. OHLIGER,[2] J. LEE[3] AND O. KELLER[3]

Charles and Scott[4] demonstrated that a blood anticoagulant, presumably heparin, was widely distributed in various tissues of beef. It was found in greatest quantities in muscle, liver and lung; smaller quantities were obtained from heart, thymus, spleen and blood. Charles and Todd[5] proved the chemical and biological identity of the crystalline barium acid heparinate isolated from beef lung and beef liver. Jaques, Waters and Charles[6] isolated crystalline barium acid heparinate from the lungs of pork and sheep and from the liver of dogs. These workers found no significant chemical differences in the product from these sources and from beef but they claimed a wide variation in biological activity, the blood anticoagulant potencies being in the order 10:5:2:1 = dog:beef:pork:sheep.

Species specificity is the rule with protein material but is unusual for carbohydrate principles. The heparin from dog liver, being reputedly of the highest activity, was of greatest interest and was accordingly prepared. The crude heparin (sodium heparinate) was isolated from the excised dog livers according to the general procedure of Charles and Scott.[7] The crude product was purified through the benzidine salt and converted into the amorphous sodium salt. This substance showed an anticoagulant potency[8] of 577 Roche anticoagulant units (ACU) per mg. (dry basis). The sodium salt was transformed into the crystalline barium acid heparinate which showed a potency of 600 Roche ACU per mg. (dry basis). These potencies are entirely within the normal range for beef heparin prepared by the same procedures. Had the potencies of the dog heparin been twice that of beef, values in the range of 1200 Roche ACU per mg. should have been found.

Our results therefore do not support the claim of Jaques and co-workers that a species variation exists between dog and beef heparin. It is possible that the variation in potencies found by these workers is to be ascribed to the sensitivity of the crystalline barium acid salt and the ease with which it is inactivated by mild acidity.[9]

(1) Department of Chemistry, The Ohio State University.

(2) Department of Physiological Chemistry, The Ohio State University.

(3) Scientific Department, Hoffmann-La Roche, Inc.

(4) A. F. Charles and D. A. Scott, *J. Biol. Chem.*, **103**, 431 (1933).

(5) A. F. Charles and A. R. Todd, *Biochem. J.*, **34**, 112 (1940).

(6) L. B. Jaques and E. T. Waters, *J. Physiol.*, **99**, 454 (1941); L. B. Jaques, *Science*, **93**, 488 (1941); L. B. Jaques, E. T. Waters and A. F. Charles, *J. Biol. Chem.*, **144**, 229 (1942).

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

(8) The bioassays were performed according to the procedure described by R. H. K. Foster, *J. Lab. Clin. Med.*, **27**, 820 (1942). We are indebted to Dr. R. H. K. Foster for the bioassays.

(9) M. L. Wolfrom and W. H. McNeely, THIS JOURNAL, **67**, 748 (1945).

NUTLEY, NEW JERSEY
COLUMBUS, OHIO RECEIVED JULY 7, 1945

NEW COMPOUNDS

p-Acetamino-(β-chloro-*t*-butyl)-benzene

The monoacetamino derivative of neophyl chloride was prepared by means of the general procedure previously described.[1] Recrystallization from dilute alcohol yielded nacreous flakes, m. p. 155–156°.

Anal. Calcd. for $C_{12}H_{16}ONCl$: Cl, 15.72. Found: Cl, 15.59.

No diacetamino derivative was isolated, presumably because of hindrance by the chlorobutyl group of nitration in the ortho position.

(1) V. N. Ipatieff and L. Schmerling, THIS JOURNAL, **59**, 1056 (1937); **60**, 1476 (1938).

RESEARCH LABORATORIES
UNIVERSAL OIL PRODUCTS COMPANY V. N. IPATIEFF
RIVERSIDE, ILLINOIS LOUIS SCHMERLING
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N,N-Dimethylphthalamidic Acid

The reaction of phthalic anhydride with dimethylamine gave a 71–75% yield of N,N-dimethylphthalamidic acid. In a 3-liter, two-necked, round-bottomed flask fitted with a reflux condenser and an inlet tube were placed 296.2 g. (2.0 moles) of phthalic anhydride and 1000 ml. of *dry* benzene. The mixture was heated to boiling and 90 g. (2.0 moles) of liquid dimethylamine was allowed to evaporate in a separate flask and bubble slowly through the inlet tube. (The dry amine was previously obtained by the